ATTI DEL XI CONGRESSO NAZIONALE sismec2021

Società Italiana di Statistica Medica ed Epidemiologia Clinica

DATI, MODELLI, DECISIONI: METODI A SERVIZIO DELL'ORGANIZZAZIONE SANITARIA

Bari, 15-17 settembre 2021

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XI Congresso Nazionale
Bari,15-18 settembre 2021

Il Congresso nazionale della SISMEC è un'occasione per confrontarsi su temi metodologici applicati alla ricerca biomedica e all'assistenza sanitaria. La pandemia esplosa nel corso del 2020 ha rappresentato una sfida per entrambi gli ambiti: da una parte la necessità di utilizzare metodi innovativi per comprendere ed approfondire le dinamiche della diffusione del virus e della patologia da questo determinata, dall'altra le strategie organizzative per ridurre l'impatto della diffusione tra la popolazione al fine di mantenere le migliori condizioni di vita possibile

Si è ravvivato l'interesse per lo sviluppo di modelli di analisi e previsione della diffusione della patologia e sono stati sviluppati indicatori per il monitoraggio e l'orientamento delle scelte sanitarie e politiche. La ricerca scientifica si è sviluppata in questi settori fino a giungere ad un insieme di strumenti che sono in uso e che possono essere migliorati grazie alle occasioni di confronto e collaborazione scientifica tra studiosi, che questo incontro vuole offrire.

La ricerca, nel periodo pandemico, si è svolta con una rapidità che in epoche precedenti non sembrava possibile. Questo apre al dibattito sulla disponibilità di dati ed informazioni, sulla qualità della ricerca proposta, sugli strumenti adottati e sulle conseguenze in termini sia di beneficio che di rischi per coloro che usufruiscono dei risultati della ricerca. Politici, amministratori, e sopra tutti, i cittadini, in questo periodo diventati spesso "pazienti", vorrebbero tornare a condurre una vita "piena" e per questo contano sulla possibilità di usufruire dei risultati concreti della ricerca: disponibilità e sicurezza di farmaci e vaccini, nonché indicazioni su stili e norme di vita che tutelino la salute.

Il dibattito ha visto spesso i media impegnati nel trasmettere informazioni e divulgare conoscenza. I ricercatori di varie discipline sono usciti dal guscio delle proprie stime, più o meno precise, per confrontarsi con il pubblico, che, nella maggior parte dei casi, ha poca dimestichezza con gli aspetti metodologici. In riferimento a quella che è stata chiamata "Infodemia", questo congresso è un'occasione preziosa per discutere sugli strumenti informativi che siano strumenti per decisori e cittadini al fine di accrescere la capacità critica per effettuare scelte consapevoli.

Il comitato scientifico ed organizzatore auspicano di poter svolgere il congresso in presenza, ospitando tutti coloro che vorranno contribuire con la presentazione di un proprio lavoro, al fine di tener vivo il dialogo ed il confronto tra tutti i partecipanti, che è la migliore modalità per sviluppare la ricerca e la collaborazione.

Il congresso, qualora in presenza, si svolgerà nella cornice di una importante università del Sud Italia, in una regione che ha recentemente ricevuto riconoscimenti internazionali per l'ospitalità ed il turismo. Sarà così anche l'occasione per conoscere l'evoluzione di una città, già meta culturale e turistica, che ha saputo riqualificarsi e che dal punto di vista infrastrutturale si sta avvicinando agli standard delle grandi città europee.

È con queste premesse che il comitato scientifico ed organizzatore auspicano la partecipazione al XI Congresso della Società di Statistica Medica ed Epidemiologia Clinica nella sede di Bari.

Bari, 15 aprile 2021

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SEGRETERIA ORGANIZZATIVA

MEETING PLANNER SRL
Via Divisione Paracadutisti Folgore, 5
70125 Bari (Italia)
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SITO WEB DEL CONGRESSO

https://sismecbari2021.it/

SITO WEB DELLA SOCIETÀ ITALIANA DI STATISTICA MEDICA ED EPIDEMIOLOGIA CLINICA

https://www.sismec.info/

Mercoledì, 15 Settembre 2021

11.00-17.00 CORSO PRECONGRESSUALE
(Fuori attività formativa)

MACHINE LEARNING

Paola Berchialla
Università di Torino

Introduction to Machine Learning with Tidymodels
Alison Hill
Rstudio USA

17.00 Apertura del Congresso

Saluto delle autorità
Prof. Stefano Bronzini
Rettore Università degli Studi di Bari

Prof. Pier Luigi Lopalco
Assessore alla Sanità Regione Puglia

Prof. Loreto Gesualdo
Preside Facoltà di Medicina e Chirurgia

Prof. Salvatore Barbuti
Professore Ordinario, Decano di Igiene

18.30 Relazione di apertura
Il caso Covid-19: la metodologia e le decisioni. Come usare modelli e metodi per scegliere gli interventi di salute pubblica: l'esperienza della pandemia Covid19 e la futura preparazione dei metodologi
Giovanni Rezza
Direttore Generale della Prevenzione del Ministero della Salute

19.30 Modelling diseases: from situational awareness to forecast
Alessandro Vespignani
Network Science Institute, Northeastern University, Boston MA

20.10 Chiusura lavori prima giornata

Giovedì, 16 Settembre 2021

SESSIONE PLENARIA

MODELLI E STRATEGIE DI INTERVENTO IN SANITA' PUBBLICA: IL CASO COVID19 E LE FUTURE SFIDE

***Moderatori:* Alessio Farcomeni**
Università di Roma "Tor Vergata"
Rosa Prato
Università degli Studi di Foggia

09.20-10.00 L'organizzazione sanitaria alla prova della pandemia: la predittività dei modelli e le azioni concrete
Pier Luigi Lopalco
Università di Pisa

10.00-10.40 Modelli e indicatori per provvedimenti di sanità pubblica
Stefano Merler
Fondazione Bruno Kessler

SESSIONE PLENARIA

EMERGING ISSUES IN CAUSAL INFERENCE

***Moderatori:* Rino Bellocco**
Università degli Studi Milano Bicocca
Lorenzo Richiardi
Università degli Studi di Torino

11.30-11.50 Challenges in emulating target trials from observational studies
Bianca De Stavola
UCL GOS Institute of Child Health, United Kingdom

11.50-12.10 Transportability of results in an observational study setting
Ghislaine Scelo
Università di Torino

12.10-12.30 Causal inference for high-dimensional exposures
Andrea Bellavia
Harvard T.H. Chan School of Public Health, Boston

12.30 Discussione

14.00-16.00 **Sessioni Parallele *(Fuori attività formativa)***

AULA PLENARIA

Epidemiologia (generale e clinica)

Moderatori:* *Paolo Chiodini
Università degli studi della Campania "Luigi Vanvitelli"
Miriam Isola
Università degli Studi di Udine

AULA PARALLELA

Metodi Biostatistici

***Moderatori:* Clelia Di Serio**
Università Vita e Salute San Raffaele Milano
Giovanni Veronesi
Università degli Studi dell'Insurbia

16.00-17.00 Riunione dei professori ordinari e votazione

17.00-18.00 Assemblea dei professori e dei ricercatori MED01

Venerdì, 17 Settembre 2021

SESSIONE PLENARIA

LA RICERCA SCIENTIFICA ALLA PROVA DELL'EMERGENZA: COME CONCILIARE QUALITÀ E TEMPESTIVITÀ

Moderatrici: Flavia Carle
Università Politecnica delle Marche
Susanna Conti
Consigliera SISMEC

09.00-09.40 Strumenti e metodi per la ricerca nelle emergenze sanitarie: come conciliare qualità e tempestività
Salvatore Scondotto
Dipartimento attività sanitarie, Osservatorio Epidemiologico, Regione Sicilia

09.40-10.20 La gestione di una sorveglianza in una fase emergenziale: l'esperienza della sorveglianza Covid-19 in Italia
Antonio Bella
Istituto Superiore di Sanità

10.20-11.00 La cultura scientifica basata sui dati: proposte per un approccio ragionato alle banche dati nelle fasi di emergenza
Giovanni Corrao
Università di Milano Bicocca

SESSIONE PLENARIA
WORKSHOP

FRAGILITÀ: QUALE FUTURO

Moderatori: Paolo Trerotoli
Università degli Studi di Bari
Simona Villani
Università degli Studi di Pavia

11.00-11.20 Fragilità: che cosa è e come si misura
Giuseppe Bellelli
Dipartimento di Medicina e chirurgia, Università degli Studi di Milano-Bicocca

11.20-11.40 Fragilità: sfide cliniche e metodologiche
Graziano Onder
Dipartimento di malattie cardiovascolari, endocrino-metaboliche e invecchiamento - Istituto Superiore di Sanità

11.40-12.00 Il quadro epidemiologico della fragilità nell'anziano: indicazioni per il futuro
Lucia Galluzzo
Dipartimento di malattie cardiovascolari, endocrino-metaboliche e invecchiamento - Istituto Superiore di Sanità

12.00-12.20 Azioni di misurazione, valutazione e prevenzione della fragilità tra passato e futuro
Lucia Bisceglia
Area epidemiologia e care intelligence - Agenzia regionale strategica per la salute e il sociale, Regione Puglia

12.20-12.40 La fragilità: il punto di vista dei cittadini e dei pazienti
Paola Mosconi
Dipartimento di Ricerca Salute Pubblica - Istituto di Ricerche Farmacologiche Mario Negri (Milano)

12.40-13.10 Conclusioni

14.30-15.30 **Sessioni Parallele *(Fuori attività formativa)***

AULA PLENARIA

Metodi Biostatistici

Moderatori: Vincenzo Bagnardi
Università degli Studi Milano Bicocca
Marta Di Nicola
Università degli Studi "Gabriele d'Annunzio" Chieti

AULA PARALLELA

Epidemiologia (generale e clinica)

***Moderatori:* Domenica Matranga**
Università degli Studi di Palermo
Giuseppe Signoriello
Università degli studi della Campania "Luigi Vanvitelli"

15.30-17.00

SESSIONE PLENARIA
TAVOLA ROTONDA
COMUNICAZIONE SCIENTIFICA E INFODEMIA

Moderatrice: Annarita Vestri
Università di Roma La Sapienza

Clelia Di Serio
Università Vita e Salute San Raffaele, Milano

Alessio Farcomeni
Università di Roma "Tor Vergata"

Silvio Tafuri
Università degli Studi di Bari

Filippo Anelli
Presidente FNOMCEO

Francesca Russi
Ufficio Stampa Azienda Ospedaliera Policlinico Consorziale di Bari

17.00-19.00 Assemblea dei soci SISMEC

19.00 Chiusura del Congresso

POSTER CON VIDEO PRESENTAZIONE

METODI BIOSTATISTICI

https://youtube.com/playlist?list=PLtqc7yHg6SKHMhYykwBOdrXiEZsPdlTGG

EPIDEMIOLOGIA GENERALE

https://youtube.com/playlist?list=PLtqc7yHg6SKFz6lUnM0m0XYx41eov-XXJ

EPIDEMIOLOGIA CLINICA

https://youtube.com/playlist?list=PLtqc7yHg6SKFxaUs1c-hvccEqxjcPT5Dh

POSTER

EPIDEMIOLOGIA (GENERALE E CLINICA)

POSTER

METODI BIOSTATISTICI

ATTI DEL
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ed Epidemiologia Clinica

Giovedì 16 settembre 2021

AULA PLENARIA

EPIDEMIOLOGIA (GENERALE E CLINICA)

Valutazione della effectiveness vaccinale del vaccino Pfizer/BioNTech (Comirnaty) nel personale dell'AOUC Policlinico Bari.

Autori: Francesco Paolo Bianchi[1], Paolo Trerotoli[1] , Silvio Tafuri[1]
[1]Dipartimento di Scienze Biomediche e Oncologia Umana, Università degli Studi di Bari

Introduzione

Il COVID-19 è una malattia infettiva causata da SARS-CoV-2, la cui diffusione a partire da febbraio 2020 ha avuto uno sviluppo pandemico, con centinaia di milioni di casi e milioni di morti a livello globale [1]. Il 27/12/2020 è stata avviata una campagna di vaccinazione di massa in Europa. L'Italia ha scelto di dare priorità alla vaccinazione degli operatori sanitari (OS), una decisione in linea con le raccomandazioni del Center for Disease Control and Prevention [2]. Il prodotto disponibile per immunizzare gli OS era il vaccino BNT162b2 mRNA COVID-19 (Comirnaty), indicato per individui di età pari o superiore a 16 anni e somministrato in due dosi ad almeno 21 giorni di distanza [3].

I trial pre-licensure hanno evidenziato un'efficacia vaccinale del 95% nella prevenzione del COVID-19, incluse le manifestazioni gravi [4]. I susseguenti studi osservazionali hanno riportato una effectiveness vaccinale (VE) >90% anche nella prevenzione dell'infezione [5-7]; la metodologia di questi studi, tuttavia, non permette la valutazione della VE nel medio-lungo termine.

Obiettivi

L'obiettivo dello studio è quello di valutare l'incidenza cumulativa di casi COVID-19 e la VE di vaccino Comirnaty in un campione di OS dell'AOUC Policlinico Bari.

Materiale e Metodi

Il periodo di studio è stato compreso tra il 27/12/2020 e il 31/05/2021, considerando quale soglia di vaccinazione con prima dose il 31/03/2021. Le informazioni dello status vaccinale sono state ricavate dalla piattaforma Giava vaccini. Le informazioni relative alla infezione da Sars-CoV-2 e eventuali sintomi (nel periodo compreso tra il 27/12/2020 e il 31/05/2021) sono state ricavate dalla piattaforma GIAVACOVID-19. Dall'analisi sono stati esclusi gli OS per cui risultava essere stata diagnosticata una infezione da Sars-CoV-2 nel periodo 01/02/2020-26/12/2020 e quelli che non avessero completo il ciclo basale di Comirnaty (se non per diagnosi di infezione).

Il periodo di follow-up per i soggetti vaccinati inizia a partire dalla data della dose I di vaccino e termina alla diagnosi di infezione o alla fine del periodo di osservazione; il periodo di follow-up per i soggetti non vaccinati inizia il 27/12/2020 e termina alla diagnosi di infezione, alla somministrazione della dose I di vaccino o alla fine del periodo di osservazione.

L'hazard cumulativo di infezione nei due gruppi (vaccinati vs. non vaccinati) è stato descritto mediante lo stimatore di Nelson-Aalen; il log-rank test è stato utilizzato per confrontarlo tra gruppi. Sono stati considerati quattro periodi temporali: 1) 14-34 giorni dalla dose I; 2) 14-41 giorni dalla dose II; 3) 42-69 giorni dalla dose II; 4) >69 giorni dalla dose II. Per ogni periodo, è stato calcolato il Risk Ratio (RR) di infezione come rapporto tra il rischio nei vaccinati e quello nei non vaccinati; la VE è stata stimata come 1 – RR, con l'indicazione dell'intervallo di confidenza al 95% (95%CI).

Per tutti i test è stato considerato significativo un valore di p-value<0,05.

Risultati

Il campione in studio è costituito da 6.136 OS, di cui 5.351 (87,2%) vaccinati con almeno una dose di Comirnaty e 787 (12,8%) non vaccinati. Le caratteristiche del campione, per gruppo, sono descritte in tabella 1. Il valore mediano del tempo intercorso tra dose I e II è pari a 23 giorni (range IQR=22-23).

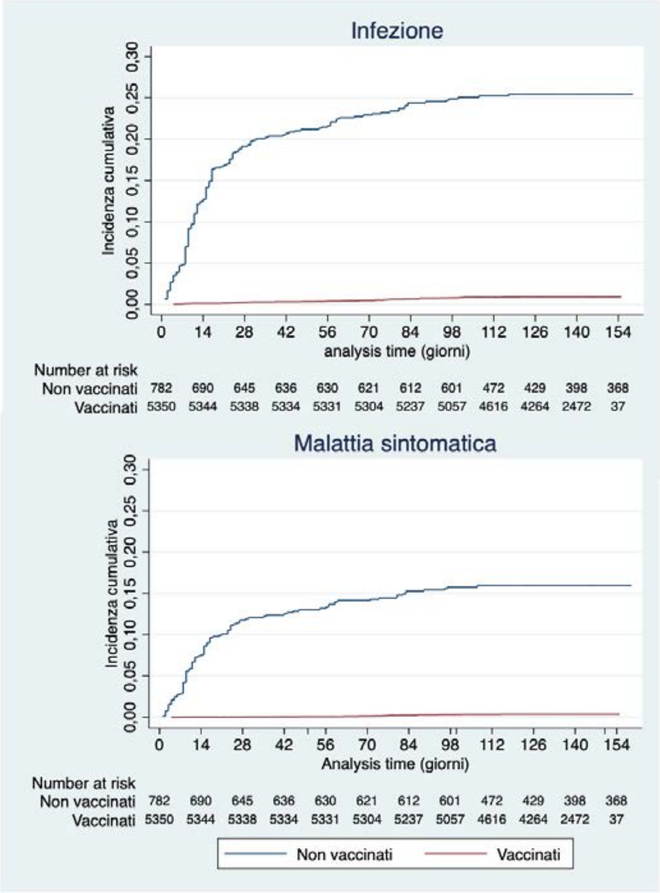
Tabella 1. Caratteristiche del campione, per gruppo.

Caratteristica	Non vaccinati (n=787)	Vaccinati (n=5.351)	Totale (n=6.136)	p-value
Femmine; n (%)	489 (62,3)	3.181 (59,5)	3.670 (59,8)	0,129
Età; mediana; range IQR (range)	44; 31-54 (21-70)	47; 32-56 (22-70)	46; 32-56 (21-70)	<0,001
Mansione; n (%)				<0,0001
• Medici	159 (20,3)	1.898 (35,5)	2.057 (33,5)	
• Infermieri	275 (35,0)	1.647 (30,8)	1.922 (31,3)	
• Ausiliari/OSS	204 (26,0)	888 (16,6)	1.092 (17,8)	
• Altro sanitario	147 (18,7)	918 (17,1)	1.065 (17,4)	

In un periodo di follow-up mediano pari a 139 giorni (range IQR=135-143) sono stati riscontrati 227 (3,7%) casi di infezione (incidenza cumulativa: 2,8x10.000 giorni-persona), pari a 19,9x10.000 giorni-persona nei non vaccinati e a 0,7x10.000 giorni-persona nei vaccinati; l'Incidence Rate Ratio (IRR) è pari a 0,03 (95%CI=0,02-0,05; p<0,0001). Sono stati riscontrati 131 (2,1%) casi di malattia sintomatica (incidenza cumulativa: 1,6x10.000 giorni-persona), pari a 12,4x10.000 giorni-persona nei non vaccinati e 0,3 x10.000 giorni-persona nei vaccinati; l'IRR è pari a 0,02 (95%CI=0,01-0,04; p<0,0001).

La figura 1 descrive l'incidenza cumulativa di infezione e malattia sintomatica nei due gruppi (log-rank p-value<0,0001).

Figura 1. Incidenza cumulativa di infezione e malattia sintomatica, per gruppo (vaccinati vs. non vaccinati).



La VE nei confronti dell'infezione è 97,7% (95,4-99,0%) a 14-34 giorni dalla dose I, 94,8% (87,0-97,8%) a 14-41 giorni dalla dose II, 83,0% (65,0-92,0%) a 42-69 giorni dalla dose II e 81,0% (42,0-94,0%) a >69 giorni dalla dose II. La VE nei confronti della malattia sintomatica è 99,2% (96,4-99,8%) a 14-34 giorni dalla dose I, 97,2% (90,3-99,2%) a 14-41 giorni dalla dose II, 85,0% (63,0-94,2%) a 42-69 giorni dalla dose II e 88,0% (42,0-97,6%) a >69 giorni dalla dose II.

Conclusioni

La VE nei primi 2 mesi dalla somministrazione della dose I è ˜95%, in linea con le evidenze già riportate in letteratura [5-7]; nelle settimane successive, si osserva una diminuzione (˜85%). Nonostante questo calo, i dati sono coerenti con l'assoluta efficacia del vaccino nella prevenzione dell'infezione/malattia sintomatica da SARS-CoV-2. Questi risultati potrebbero migliorare la compliance vaccinale negli OS , poiché un vaccino che conferisce la prevenzione delle malattie può essere considerato una forma di dispositivo di protezione individuale. Inoltre, un vaccino che previene l'infezione nel medio termine potrebbe limitare drasticamente la circolazione del virus in ambito ospedaliero.

Bibliografia

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INVESTIGATING THE CAUSAL ROLE OF INFLAMMATION ON PARKINSON'S DISEASE BY A BI-DIRECTIONAL MENDELIAN RANDOMIZATION APPROACH

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Introduction

In the last decades, several observational studies suggested that inflammatory processes may influence the pathogenesis of Parkinson's disease (PD) [1,2]. The central nervous system has been hypothesized to be the origin of inflammation through microglia activation, which leads to the production of proinflammatory cytokines, such as interleukin (IL) 6, and tumor necrosis factor-α (TNF-α) [3]. Several studies found increased levels of proinflammatory cytokines in both cerebrospinal fluid and blood in PD patients [4–6]. However, previous findings from observational studies are well known to be prone to many sources of bias, such as confounding, measurement error, and reverse causation.

Mendelian randomization (MR) is an instrumental variable (IV) approach, that is used to assess the causal role of exposure on disease outcomes [7]. MR uses genetic variants as instruments of a modifiable exposure (e.g. a lifestyle risk factor), or a more general biomarker that could be targeted by a drug (e.g. a specific protein). Since genetic variants are randomly inherited at conception and, thus, are likely to be unaffected by environmental factors or disease processes, MR may greatly diminish the risk of confounding bias and potentially avoids the problem of reverse causation [8]. Reliability and robustness of MR studies rely on three assumptions on the genetic variant: (i) relevance: it should be strongly associated with the exposure; (ii) exchangeability: it should be not associated with possible unmeasured confounders of the exposure and the outcome; (iii) exclusion restriction: it should with the disease outcome only through the exposure of interest (absence of pleiotropy) [9].

Objectives

In this study, a two-sample MR design was used to evaluate the causal relationship between inflammation and PD risk and its age at onset (AAO) by leveraging information from large genome-wide association studies (GWAS) on inflammatory biomarkers, PD, and AAO.

Methods

C-reactive protein (CRP), interleukin 1 receptor-antagonist (IL-1ra), IL-6, and TNF-α were considered as inflammatory markers and used as exposures in MR analysis. Genetic instruments were identified using summary-level data from different GWAS on European ancestry participants (from 27,185 to 204,402 participants). Genetic association data on PD and its AAO were obtained from the International Parkinson's Disease Genomics Consortium (IPDGC) (1,456,306 participants). A bi-directional two-sample MR approach was used to estimate causal associations [10]. From each GWAS, we selected IVs that were strongly associated with the exposure (p<5x10-8; F-statistic>10) and highly independent from each other, using a conservative r^2 threshold (<0.001) to handle linkage disequilibrium [11]. In the primary analysis, the Wald ratio method was used to assess the causal association for each exposure. When more than one IV was identified, results were pooled using the fixed effects inverse variance weighted (IVW) estimator. The presence of horizontal pleiotropy, i.e. genetic variants that influence the outcome independently of the hypothesized causal pathways, was assessed using Q-statistic and I^2 index, measures of heterogeneity when multiple genetic instruments were selected [12]. Sensitivity analyses were performed with two-sample MR methods robust to the presence of horizontal pleiotropy [13]. All the analyses were performed for each GWAS of inflammatory biomarkers to check the findings' consistency. The MR estimates are expressed as odds ratio (OR) (for PD outcome) or mean difference (MD) (for AAO outcome) for a 1-unit increase in the log concentration of the exposures along with 95% confidence intervals (CIs). All the analyses were performed with R software for statistical computing using *MendelianRandomization* and *TwoSampleMR* packages.

Results

Considerable statistical evidence in support of reduced AAO of PD (MD: -2.011; 95% CI: -3.706, -0.317]) was observed and associated with higher IL-6 concentration, whereas less evidence was found for risk of PD (OR: 1.152; 95% CI: 0.900, 1.475). Regarding CRP, there was limited statistical evidence of an association with PD (OR: 1.020; 95% CI: 0.914, 1.139) and AAO (MD: 0.446; 95% CI: -0.875, 1.767). Limited statistical evidence was also observed for IL-1ra (OR: 0.973; 95% CI: 0.872, 1.085 and MD: -0.182; 95% CI: -0.982, -0.563) and TNF-α (OR: 1.41; 95% CI: 0.709, 2.807 and MD: -3.03; 95% CI: -7.692, 1.633). Low values of Q-statistic and I^2 index suggest that no strong horizontal pleiotropic effects were present. Sensitivity analyses further strengthened the hypothesis of the absence of horizontal pleiotropy. No evidence of reverse causation, i.e. PD influencing inflammatory biomarkers levels, was observed. Results were also consistent across the inflammatory biomarkers GWAS datasets.

Conclusions

In the present study, the causal effect of inflammation on PD and its age at onset were evaluated with an MR approach. Supportive evidence for a causal pathway between inflammation and PD was found for IL 6, whereas limited evidence was observed for remaining inflammatory biomarkers considered as exposures. Results from these MR analyses could provide new insights into the context of anti-inflammatory therapeutic strategies for disease prevention, suggesting potential targets for drug development.

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MATERNAL DIETARY PATTERNS DURING BREASTFEEDING AND HUMAN MILK COMPOSITION: RESULTS FROM THE MEDIDIET STUDY

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Introduction

Human milk of healthy and well-nourished mothers is the optimal nutrition for infants [1]. It includes several bioactive compounds contributing to the gastrointestinal tract, immune system and neurological development of the infant [2-4]. The World Health Organization encourages mothers to exclusively breastfeed their infants up to 6 months of life, and thereafter to continue breastfeeding with adequate complementary food up to 2 years old or beyond [1].

Human milk fatty acid (FA) composition has been related to maternal diet, while other milk components, including macronutrients, appear less sensitive to maternal dietary habits [5,6]. Most published studies have analysed the association of individual nutrients or foods with the levels of human milk compounds [7]. Dietary pattern analysis – considering diet as an overall exposure and reducing the complexity of nutritional intake to a smaller number of dietary patterns – has only been used in a few studies to identify either patterns in maternal nutrition [6,8] or patterns in human milk composition [9-12].

Objectives

The present analysis aims to evaluate the association between maternal dietary patterns and human milk energy density, macronutrients and fatty acid (FA) composition.

Methods

The MEDIDIET study is an Italian observational study including 300 healthy breastfeeding mothers [13]. Participants were 25-41 years old women who gave birth to healthy term infants and exclusively breastfed from birth to the day of milk collection. To be enrolled in the study, mothers had to be healthy, non-smokers, non-abusers of drugs or alcohol, non-severely obese, and not on a restricted diet.

Human milk was collected at 6 ± 1 weeks postpartum, and analysed in terms of macronutrient composition (i.e., protein, lactose, fat), energy density, and FA profile.

Maternal diet from partum to the day of milk collection was assessed by trained interviewers using a valid and reproducible food frequency questionnaire (FFQ) [14,15], within the same visit in which human milk was collected. The FFQ included information on weekly intake of 78 foods, recipes and non-alcoholic beverages. Maternal macro- and micronutrient intakes, as well as total energy, were estimated through an Italian food composition database [16,17].

Maternal dietary patterns were identified using an exploratory principal component factor analysis (PCFA) based on 31 nutrients. The number of dietary patterns was selected considering the scree plot, factor eigenvalues >1, and interpretability. Dietary patterns were orthogonally rotated (Varimax option) to achieve a simpler factor loading structure with better interpretability. We labelled the patterns considering for each dietary pattern those nutrients with a factor loading ≥0.63 in absolute value.

We assessed the relationship between maternal dietary patterns and foremilk macro-nutrient and FA components using Pearson's correlation coefficient.

Results

PCFA allowed to identify 5 maternal dietary patterns that explained over 80% of the variance of the maternal nutrient intakes. The first dietary pattern, labelled "Vitamins, minerals, and fibre", was characterized by high loadings on fibre, folate, potassium, vitamin C, beta-carotene equivalents, iron, and vitamin E (22% explained variance). The "Proteins and fatty acids with legs" dietary pattern had as dominant nutrients animal protein, saturated fatty acids (SFA), cholesterol, calcium, phosphorus, zinc, and riboflavin (21% explained variance). The "Fatty acids with fins" dietary pattern had the greatest loadings on eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), vitamin D, and docosapentaenoic acid (DPA) (15% explained variance). The "Fatty acids with leaves" dietary pattern had as dominant nutrients monounsaturated fatty acids (MUFA), linoleic acid (LA), lycopene, vitamin E, and α-linolenic acid (ALA) (12% explained variance). The last dietary pattern identified was "Starch and vegetable proteins", characterized by greatest loadings on starch, vegetable protein, and sodium (10% explained variance).

Table 1 shows the correlation coefficients between human milk components and continuous factor scores of the maternal dietary patterns identified in the MEDIDIET study.

Table 1 – Pearson's correlation coefficients between human milk components and continuous factor scores of the five maternal dietary patterns identified in the MEDIDIET study, using principal component factor analysis (PCFA).

	Vitamins, minerals and fibres	Proteins and fatty acids with legs	Fatty acids with fins	Fatty acids with leaves	Starch and vegetable proteins
Energy (kcal/100ml)[1]	-0.09	-0.02	-0.03	0.05	-0.10
Lactose (g/100ml)[1]	0.00	-0.01	-0.03	0.03	0.12
Protein (g/100ml)[1]	0.01	0.05	-0.02	0.06	0.09
Fat (g/100ml)[1]	-0.09	-0.02	-0.03	0.05	-0.10
SFA (% of FA)[2]	0.00	0.12	-0.06	-0.20	0.01
MUFA (% of FA)[2]	-0.02	-0.19	0.06	0.17	0.04
PUFA (% of FA)[2]	0.03	0.11	0.01	0.07	-0.09
ω-6 (% of FA)[2]	-0.02	0.12	-0.03	0.06	-0.07
LA (% of FA)[2]	-0.02	0.11	-0.03	0.06	-0.08
AA (% of FA)[2]	-0.04	0.11	0.06	-0.11	0.02
ω-3 (% FA)[2]	0.28	-0.05	0.23	0.08	-0.10
ALA (% of FA)[2]	0.25	-0.01	0.13	0.13	-0.07
EPA (% of FA)[2]	0.23	-0.06	0.25	0.01	-0.08
DHA (% of FA)[2]	0.20	-0.10	0.25	0.01	-0.10
DPA (% of FA)[2]	0.21	-0.01	0.19	0.08	-0.07
ω-6/ω-3 ratio[2]	-0.23	0.10	-0.21	-0.04	0.05
LA/ALA ratio[2]	-0.19	0.07	-0.13	-0.08	0.00
AA/EPA ratio[2]	-0.27	0.04	-0.26	-0.05	0.10
EPA/DHA ratio[2]	0.11	0.09	0.05	0.05	-0.03
AA/DHA ratio[2]	-0.21	0.13	-0.27	-0.01	0.10
LA/DHA ratio[2]	-0.19	0.12	-0.27	0.06	0.03

[1] This component was missing in 1 subject. [2] This component was missing in 18 subjects.

AA: arachidonic acid; ALA: α-linolenic acid; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; EPA: eicosapentaenoic acid; FA: fatty acids; LA: linoleic acid; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids; SD: standard deviation; SFA: saturated fatty acids.

No correlations were observed between energy and macronutrients in human milk and the identified dietary patterns, with the exception of a weak positive association between lactose and the "Starch and vegetable proteins" dietary pattern. The "Vitamins, minerals and fibres" and the "Fatty acids with fins" patterns were positively correlated with human milk concentrations of ω-3, and its subcomponents (ALA, EPA, DPA, and DHA), while the correlation was negative for ω-6/ω-3, LA/ALA, AA/EPA, AA/DHA, and LA/DHA ratios. The "Proteins and fatty acids with legs" dietary pattern was weakly positively correlated with human milk content of SFA and ω-6, and with AA/DHA and LA/DHA ratios, while a negative correlation emerged with MUFA. There were positive correlations between the "Fatty acids with leaves" dietary pattern and MUFA, and ALA, and a negative correlation with SFA. Lastly, the "Starch and vegetable proteins" dietary pattern showed a weak positive correlation with lactose.

Conclusions

In the present study, 5 major dietary patterns were identified among Italian breastfeeding mothers and their relationships with human milk macronutrients and FA profile were evaluated. Some human milk compounds – including FA, and in particular ω-3 and its subcomponents – are likely influenced by maternal dietary habits during breastfeeding. Our results suggest that an adequate maternal nutrition during lactation may be important provide the infant with a milk with adequate amounts and quality of nutrients for an appropriate nutrition.

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MODELING FOR THE STRINGENCY OF LOCK-DOWN POLICIES: EFFECTS OF MACROECONOMIC AND HEALTHCARE VARIABLES IN RESPONSE TO COVID-19 PANDEMIC

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Introduction

The SARS-CoV-2 pandemic has recalled the constant threat that viruses represent to global health. If we compare the numbers of the affected people by SARS-CoV-2 with those of the previous epidemics of the past two decades, what stands out is a sharp difference in terms of the spread of the disease [1].

The scientific community has found evidence of a strong correlation between the health status of a population and some macroeconomic measures. However, in the case of infectious diseases prior to Covid-19, researchers focused more on the economic translation of human loss due to fatalities [2]. Conversely, for Covid-19 disease public health planners need to investigate the correlation existing between economic and sanitary characteristics of the sample countries and the extent of the lock-down policies implemented by policymakers.

Aim

The scope of this study is to identify the factors that can significantly influence the restriction measures adopted by the governments in response to the Covid-19 pandemic. We assume the stringency of lock-down policies could not only be influenced by the epidemical data, but also by previous features of the selected countries.

Materials and methods

A total of 39 countries have been selected, which accounted for more than 70% of global confirmed infections by SARS-Cov-2, as of June 1st, 2020. We adopted the database of Worldometers as a reference for Covid-19 epidemiologic data [3]. The reliability of this database is certified by John Hopkins CSSE and American Library Association (ALA) [4]. To assess the extent and the level of lock-down reached by the countries, we have referred to the Government Response Stringency Index at the first day of lock-down, calculated by Oxford University and presented by Our World in Data [5]. We analyzed the pre-pandemic characteristics of the countries of interest. We adopted 2018 as a reference for macroeconomic and healthcare data, to prevent any chronological bias as the date of the most recent update made for all the 39 countries included in this study.

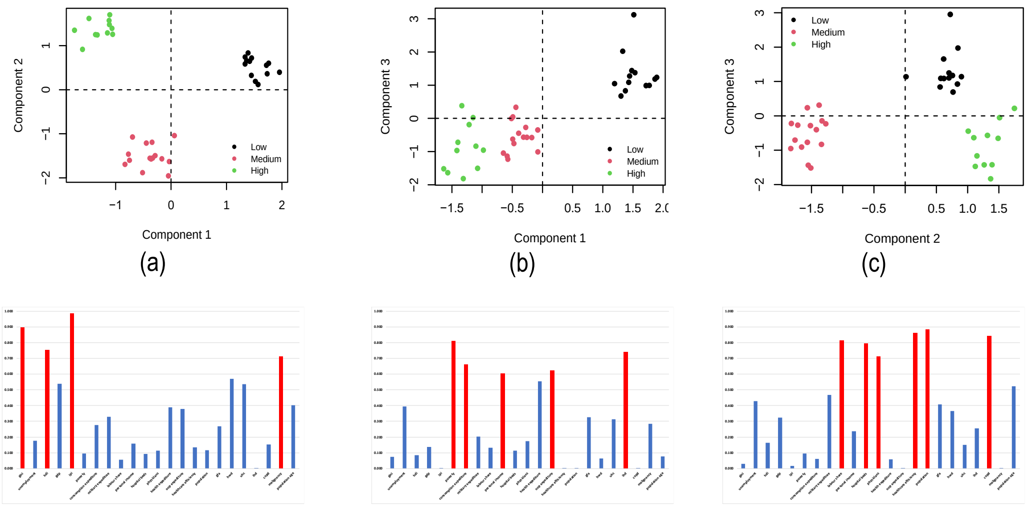
The Government Response Stringency Index was categorized in 3 stringency groups defined by tertiles of the stringency index distribution. On the obtained classes, a discriminant analysis performed via partial least squares procedure was applied (i.e., a PLS-DA model) [6, 7]. In order to define which variables have the biggest contribution on the class prediction, a minimum cut-off of 0.6 on the relative contribution was used.

Results

The median value of the stringency index measured on all 39 selected country was equal to 81.02 (IQR: 67.36-84.26). The 33rd and the 67th percentile of stringency index distribution were equal to 69.31 and 82.41 respectively. A low stringency (from 0 to 69) was adopted by 13 countries, a medium stringency (from 69 to 82) was adopted by 15 countries, and a high stringency (from 82 to 100) was adopted by 11 countries.

The distribution of the three groups of country (low, medium, high) obtained by the selected PLS-components are shown in figure 1 (panel a, b, c): Components 1 and 3 have a positive effect toward the low

degree of stringency, while Component 2 has a positive effect toward the high degree of stringency index; finally, both Components 1 and 3 have a negative effect toward the medium degree of stringency. The relative contribution of the variables for each component are reported in figure 1 (panel d, e, f)
In the first Component, the variables with a relative contribution bigger than 0.6 are Gini coefficient (gini), Human Development Index (HDI); Legatum Prosperity Index (LPI); and Malignant Neoplasms (malignancy); in the second Components there are the percentage of people living with less than 1.90% per day (poverty), the Final Consumption Expenditure (consumption expenditure), the Average Personal Income (personal income), Out-Of-Pocket Expenditure (oop expenditure), and Ischemic Heart Disease (IHD); in the third Components there are the Labor share (labor share), Hospital Beds (hospital beds), Physicians (physicians), the overall performance of the Healthcare System (healthcare efficiency), the number of the population (population), and the incidence of Chronic Obstructive Pulmonary Disease (COPD).



(a) (b) (c)

(d) (e) (f)

Figure 1. (a) Distribution of country by stringency group on the first and the second components; (b) Distribution of country by stringency group on the first and the third components; (c) Distribution of country by stringency group on the second and the third components; (d) Relative contributions of the variables with respect to the Component 1 (in red if <0.6); (e) Relative contributions of the variables with respect to the Component 2 (in red if <0.6); (f) Relative contributions of the variables with respect to the Component 3 (in red if <0.6).

In the Component 1, gini is negatively correlated, while the remaining three (HDI; LPI; and malignancy) are positively correlated. In the Component 2, poverty, consumption expenditure, and personal income are positively correlated, oop expenditure and IHD are negatively correlated. The Component 3 is negatively affected by labor share, hospital beds, physicians, and healthcare efficiency; positively impacted by population and COPD.

Conclusions

The following conclusions can be drawn: *(i)* macroeconomic features can directly affect the extent of the implemented lock-down policies, in terms of inequality and development; *(ii)* the study on the healthcare and fiscal variables also revealed a correlation with the stringency of lock-down policies. This result could be interpreted as an effect of the different fiscal regimes, and of the different extent of investments in social and health care in the sample countries. Both these findings could be drivers of a vicious cycle, condemning unequal economies to suffer the most from the economic impact of stringent lock-down policies.

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THE AUTOMATION OF SYSTEMATIC REVIEWS: A CASE STUDY ON ECMO SUPPORT

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INTRODUCTION

Automation in Systematic Reviews (SRs) is a necessity dictated by the need to produce transparent, verifiable and reproducible results more quickly, in the face of the impressive expansion of published scientific literature. In the last few years, scientific literature, especially in the health field, has grown exponentially (e.g. PubMed database alone has more than 32 million citations). In this scenario, SRs cover the highest level of evidence, as they summarize several hundred (or thousands) articles together.

SRs are time and resource consuming, requiring approximately 1 year from protocol registration to submission for publication [1]. It is therefore essential to identify tools that can accelerate specific steps of SR production.

Four main tasks are susceptible to automation: recovering relevant evidence, evaluating studies, synthesizing evidence, and publishing the review. For each, automation technology can improve the time required and the efficiency. The International Collaboration for the Automation of Systematic Reviews (ICASR) has identified several automation tools whose development could further accelerate the SR processes [2]. Some of these instruments involve greater integration between existing instruments, while others are new and autonomous.

A small and experienced SR team from the Institute for Evidence-Based Healthcare (IEBH), completed a moderately sized SR in 2 weeks using multiple SR automation tools [3]. However, because the results were based on a single SR project with a clearly defined focus with a narrow question, further work is needed before stating that they are generalisable to other SR projects or other teams conducting SRs. Should the process be adaptable to other SRs, it would realise considerable time and efficiency savings.

OBJECTIVES

We aim to exploit different automation tools to conduct a SR of predictive models of mortality in patients undergoing Extra-Corporeal Membrane Oxygenation (ECMO) therapy, with specific regards to their discriminatory and calibration power as well as to their feasibility in the emergency setting [4].

METHODS

The study protocol of the SR is registered on the Open Science Framework (OSF) platform (https://osf.io/fevw5).

We automated three steps of the SR:

1. String Translation. Different Databases need different Strings, so we used the tool Search Refiner, developed by Harry Scelles and Hang Li from the University of Queensland [5];

2. Offline Deduplicator. To deduplicate the reference, we used the offline Deduplicator available on Systematic Review Accelerator. This tool has been developed by the Institute for Evidence-Based Healthcare (IEBH) of Bond University [6];
3. Citation Management. To manage references and to decide which are relevant and which are not, we used the Rayyan tool, a web-based tool that can expedite the titles and abstracts screening [7].

RESULTS

The starting string was built on PubMed as ("extracorporeal membrane oxygenation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "membrane"[All Fields] AND "oxygenation"[All Fields]) OR "extracorporeal membrane oxygenation"[All Fields] OR "ecmo"[All Fields]).

With Search Refiner, we translated this PubMed strings instantly to be used on all the other queried databases: CINAHL, Embased, Medline, and Scopus. The search identified 85568 references.

With the IEBH Offline Deduplicator, we used 3 PC working days to deduplicate the references (to make sure the program identified all duplicates, we ran 2 deduplication cycles). The references were reduced from 85568 to 43161.

With the Rayyan tool, we screened 43161 references (title and abstract) in 42 days (not full time). In particular, two reviewers (G.L. and F.A.) needed 1811 minutes to complete this activity (1026 + 785 minutes).

CONCLUSIONS

A systematic review is a process that encompasses many phases and follows a pre-specified protocol to identify, select, evaluate and synthesize evidence to answer a detailed research question. SRs are considered the highest level of evidence to underpin clinical and policy decisions.

SRs synthesize evidence to answer a specific question, using methods that are transparent and reproducible. Technologies to automate SRs have simmered in the background for more than a decade [1]. Indeed, even today, they are time and resource consuming, requiring approximately 1 year from protocol registration to submission for publication [3].

In this SR we introduced automation in three tasks (i.e., string translation, deduplication, and title and abstract screening) with a gain in terms of reproducibility and time (45 working days). Other tools need to be identified and validated to accelerate the further steps of a SR.

Researchers have developed methods that aim to automate different steps of the evidence synthesis pipeline via machine learning. This remains an important research direction and has the potential to dramatically reduce the time required to produce standard evidence synthesis products [8], allowing researchers to be more efficient and effective in producing and disseminating SRs.

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RIACUTIZZAZIONE E MORTALITÀ DELLA FIBROSI POLMONARE IDIOPATICA NELLA REGIONE MARCHE ATTRAVERSO L'USO DELLE FONTI SECONDARIE

Risultati del progetto Motive (PRIN 2019-2021, Cod. 2017728JPK)

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Introduzione

La fibrosi polmonare idiopatica (FPI) è la più frequente e severa tra le pneumopatie infiltrative diffuse. Il decorso della malattia è eterogeneo: lenta progressione con periodi di relativa stabilità, rapido declino o peggioramenti acuti [1].

Obiettivi

Valutare i fattori demografici e clinici associati al rischio di morte e di riacutizzazione nei pazienti con nuova diagnosi di FPI residenti nella Regione Marche nel periodo 2014-2019.

Metodi

Studio osservazionale prospettico, relativo agli assistiti residenti nella Regione Marche con età ≥18 anni.

La coorte incidente e gli esiti della malattia sono stati individuati attraverso il collegamento dei database sanitari amministrativi regionali: Anagrafe Assistiti, Schede di Dimissione Ospedaliera (SDO), Distribuzione diretta dei farmaci.

Sono stati inclusi i soggetti dimessi con diagnosi primaria o secondaria di FPI (ICD-9 CM 516.3) o con una prescrizione di antifibrotico (ATC L04AX05, L01XE31, L01EX09) entro il 1° dicembre 2019. La data minore tra dimissione ospedaliera e prescrizione farmaceutica è stata considerata come proxy di insorgenza della malattia (data indice). Sono stati esclusi i soggetti residenti da meno di tre anni dalla data indice, che avevano una SDO per FPI o una prescrizione di antifibrotico nel triennio 2011-2013.

L'inizio dell'osservazione coincideva con la data indice e terminava per riacutizzazione, decesso per qualsiasi causa, censura per fine assistenza sanitaria o al 31 dicembre 2019. Tutti i pazienti sono stati seguiti per almeno 30 giorni.

La riacutizzazione veniva definita come dimissione con diagnosi primaria o secondaria di FPI successiva alla data indice; la data di decesso nell'anagrafe assistiti, eventualmente integrata con quella nelle SDO, definiva lo stato in vita del paziente.

Il rischio di riacutizzazione è stato stimato attraverso l'analisi della sopravvivenza, considerando il decesso per tutte le cause come evento competitivo. L'analisi è stata condotta stratificando la popolazione per sesso, classi di età (<75, ≥75 anni), trattamento con antifibrotici (Sì, No), e condizioni di salute all'insorgenza della malattia. Un soggetto era considerato in trattamento se aveva avuto almeno una prescrizione di antifibrotico; lo stato di salute è stato misurato attraverso il Multisource Comorbidity Score (MCS) valutato nel biennio precedente alla data indice e considerato in classi (0-4, 5-14, ≥15, punteggi elevati indicano una peggiore condizione di salute). Il test di Grey è stato utilizzato per il confronto fra le curve di rischio cumulativo.

La regressione multipla di Cox per rischi competitivi è stata applicata per stimare il rischio composito di riacutizzazione per FPI e di morte in funzione delle variabili risultate significative all'analisi univariata. La proporzionalità fra i rischi è stata verificata utilizzando i residui di Schoenfeld. Le variabili che violavano l'assunto di proporzionalità sono state inserite nel modello come variabili di stratificazione del rischio di base.

Le analisi sono state effettuate con il software R e i risultati sono stati presentati come stime per intervallo al 95% (IC 95%).

Risultati

Sono stati individuati 766 nuovi casi di FPI, di cui 578 (75,5%) attraverso le SDO. L'età mediana era di 75 anni (1°-3° quartile 69-81 anni) e il 67,6% di sesso maschile; il 43,7% aveva un punteggio MCS compreso tra 5-14 e il 15,1% ≥ 15. Durante il periodo di follow-up, 317 pazienti (41,4%) avevano ricevuto almeno una prescrizione di antifibrotico.

Si sono verificate: 145 riacutizzazioni (67,5% maschi) e 310 decessi, di cui 220 senza riacutizzazione (71,4% maschi).

I tempi mediani alla riacutizzazione e al decesso sono risultati rispettivamente pari a 8,1 (1°-3° quartile 1,9 – 18,1 mesi) e di 5,8 mesi (1°-3° quartile 0,5 – 17,4 mesi); il tempo mediano di follow-up per i soggetti che non hanno sperimentato gli eventi di interesse era di 22,4 mesi (1°-3° quartile 11,4 – 41,7 mesi).

Il rischio cumulativo di riacutizzazione e di morte a 5 anni erano rispettivamente del 26,6% (IC 95%: 22,3 – 31,1) e del 41,1% (IC 95%: 35,6 – 46,5).

La figura illustra le curve di rischio in funzione del sesso, classi di età, trattamento antifibrotico e classi di MCS. Il rischio di riacutizzazione era significativamente maggiore nei pazienti con <75 anni all'insorgenza (p=0,014); il rischio di morte era significativamente maggiore nei soggetti con una età all'esordio ≥ 75 anni (p<0,001), nei soggetti non trattati (p<0,001), e nei pazienti con un MCS ≥ 15 (p<0,001) o compreso tra 5-14 (p<0,001) rispetto ai pazienti con un MCS tra 0 e 4.

La variabile trattamento violava l'assunto di rischi proporzionali, pertanto è stata inclusa nel modello come variabile di stratificazione del rischio di base. I soggetti con MCS compreso tra 5-14 avevano un rischio di riacutizzazione maggiore (HR=1,44; CI 95%: 1,01-2,08) dei pazienti con un MCS 0-4.

Il rischio di decesso era significantemente maggiore nei pazienti con età all'insorgenza ≥75 anni (HR=2,08; CI 95%: 1,51-2,85), e con un MCS compreso fra 5-14 (HR=2,11; CI 95%: 1,47-3,03) o ≥15 (HR=3,70; CI 95%: 2,41-5,67) rispetto ai pazienti con un MCS 0-4.

Conclusioni

L'utilizzo dei database amministrativi ha permesso di valutare la FPI nell'intera popolazione adulta marchigiana, individuando una elevata mortalità e un elevato rischio di riacutizzazione, già entro il primo anno dalla diagnosi.

In presenza del trattamento il rischio di morte si riduce considerevolmente, tuttavia l'entrata in trattamento è condizionata ad una minore gravità della malattia. Il trattamento non risulta avere un effetto sulla riacutizzazione. L'età avanzata all'insorgenza è significativamente associata ad una minore sopravvivenza; le condizioni cliniche generali alla presentazione della malattia contribuiscono ad incrementare il rischio di riacutizzazione e di morte.

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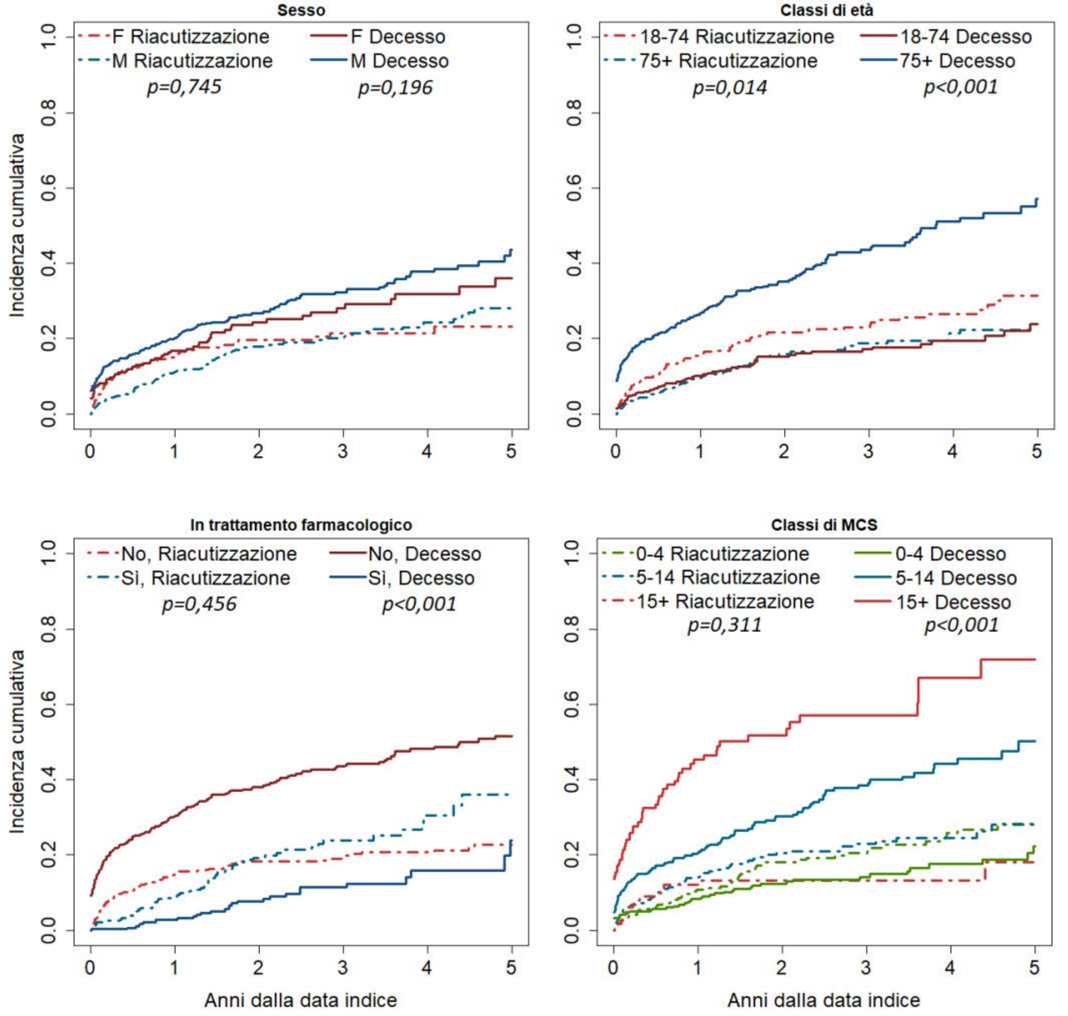
Funzione d'incidenza cumulativa del rischio di riacutizzazione e di morte stratificata per sesso, classi di età, trattamento farmacologico e classi di MCS dei pazienti con fibrosi polmonare idiopatia nella Regione Marche (il valore di p si riferisce test di Grey).



NON-ENZYMATIC ANTIOXIDANT CAPACITY AND MORTALITY: RESULTS FROM A SWEDISH COHORT STUDY

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Introduction: Antioxidants can prevent oxidative stress, which is considered a principal risk factor for chronic diseases like cardiovascular diseases (CVD) and cancer [1]. These chronic conditions have been the leading cause of death in the last ten years [2]. The effect of dietary antioxidants in the human diet can be measured by the Non-Enzymatic Antioxidant Capacity (NEAC) [3]. Few studies have investigated the relationship between NEAC in the overall diet and all-cause or cause-specific mortality, and they have found inconsistent results [4,5,6,7].

Objectives: This study aimed to assess the association between dietary NEAC and the risk of overall and cause-specific mortality in a large Swedish prospective cohort. The specific outcomes of interest were all-cause mortality, CVD mortality, cancer mortality, and other-cause mortality.

Methods: NEAC was determined by a validated food-frequency questionnaire at the beginning of the follow-up. We used the FRAP assay for the main analyses. We categorized the distribution of NEAC in sex-specific quartiles, and we fitted Cox proportional hazards regression models to estimate hazard ratios (HRs) with 95% confidence intervals (95% CI). To assess possible nonlinear associations, we fitted restricted cubic splines for each outcome of interest [8]. Moreover, we investigated a linear trend across the NEAC quartiles, including in the Cox model the estimated median value of each quartile.

Results: In the Swedish National March Cohort, 34,891 men and women free from cancer and CVD were followed through record linkages from 1997 until 2016. During 632,937.72 person-years of follow-up, there were 5,752 deaths, including 1,649 from CVD, 1,812 from cancer, and 2,291 from other causes. After adjusting for potential confounders, we found an inverse association, using the FRAP assay, between high values of dietary NEAC and all-cause mortality (HR (95% CI): 0.86 (079-0.94)) when comparing subjects in the highest quartile with the lowest. The multivariable-adjusted HRs (95% CI) for CVD, cancer, and other-cause mortality comparing the highest quartile with the lowest were 0.86 (0.72-1.03), 0.86 (0.74-1.00) and 0.85 (0.73-0.98), respectively. All p-values for trend were significant for the different outcomes. The regression splines for all-cause and cause-specific mortality revealed no evidence of departure from linearity, and they showed decreasing trends of the HRs.

Conclusions: Our findings suggest that higher dietary NEAC intake is associated with a lower risk of overall mortality and cause-specific mortality. This work was supported by the Swedish Cancer Society, ICA AB, and Telefonaktiebolaget LM Ericsson.

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Table 1: Hazard ratios (HRs) with 95% confidence intervals (95% CIs) for NEAC (FRAP) in relation to different types of deaths, the Swedish National March Cohort, 1997

	No. of deaths	Person-Years	Incidence rate[a] (per 100'000 person-years	Age-and sex adjusted HR (95% CI)	Multivariable HR (95% CI)[b]
All-cause					
Q1	1345	158834.07	2461.4	1.00 (reference)	1.00 (reference)
Q2	1425	158302.66	2185.8	0.93 (0.86-1.00)	0.93 (0.85-1.01)
Q3	1426	158363.46	2284.6	0.88 (0.82-0.95)	0.90 (0.82-0.98)
Q4	1556	157437.54	2192.5	0.86 (0.80-0.92)	0.86 (0.79-0.94)
p for trend				< 0.05	< 0.05
CVD cause[c]					
Q1	381	158834.07	1056.4	1.00 (reference)	1.00 (reference)
Q2	438	158302.66	894.6	0.99 (0.86-1.14)	1.07 (0.90-1.27)
Q3	408	158363.46	995.5	0.87 (0.76-1.00)	0.94 (0.79-1.12)
Q4	422	157437.54	816.8	0.78 (0.68-0.90)	0.86 (0.72-1.03)
p for trend				< 0.05	0.02
Cancer cause[d]					
Q1	434	158834.07	518.7	1.00 (reference)	1.00 (reference)
Q2	449	158302.66	496.5	0.93 (0.82-1.06)	0.91 (0.79-1.06)
Q3	452	158363.46	488.3	0.89 (0.78-1.01)	0.92 (0.79-1.06)
Q4	477	157437.54	489.5	0.87 (0.76-0.99)	0.86 (0.74-1.00)
p for trend				0.03	0.06
Other causes[e]					
Q1	530	158834.07	886.3	1.00 (reference)	1.00 (reference)
Q2	538	158302.66	794.8	0.88 (0.78-1.00)	0.88 (0.76-1.02)
Q3	566	158363.46	800.8	0.88 (0.78-0.99)	0.87 (0.75-1.00)
Q4	657	157437.54	886.3	0.90 (0.80-1.01)	0.85 (0.73-0.98)
p for trend				0.17	0.04

[a] Age-adjusted incidence rates, based on 5-year age categories distribution of follow-up person-years of the entire population.

[b] Adjusted for age, sex, BMI (kg/m2: underweight (<18.5), normal weight (18.5-24.9), overweight (25-29.9), obesity (>=30)), educational level (<13 years, >13 years), hypertension (yes/no), smoking status (never, former, current <30 packs/years, current >=30 packs/years), total physical activity (METh/day), alcohol (g/month), vitamins supplements intake (yes/no), diabetes (yes/no), occupational status (employed, unemployed, retired, on sick leave, other).

[c] Stratified for sex and hypertension.

[d] Adjusted for age, sex, BMI (kg/m2: underweight (<18.5), normal weight (18.5-24.9), overweight (25-29.9), obesity (>=30)), educational level (<13 years, >13 years), smoking status (never, former, current <30 packs/years, current >=30 packs/years), total physical activity (METh/day), alcohol (g/month), vitamins supplements intake (yes/no), occupational status (employed, unemployed, retired, sick, other); stratified for sex.

[e] Stratified for sex, occupational status smoking and BMI.

NORMATIVE VALUE DERIVATION OF THE BAIN-FINDLEY CLINICAL TREMOR RATING SCALE FROM DIGITAL SPIRAL DRAWINGS AMONG ADULTS OF A GENERAL POPULATION STUDY.

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Introduction

Every human being has a slight action tremor of the hands.[1] This physiological tremor increases with age, undergoes daily fluctuations and is influenced by excitement, nutrients and drugs. Tremor is also a symptom of many diseases, particularly in essential tremor (ET) and Parkinson's disease (PD) patients.[2] Tremor has both static and kinetic features, broadly described by involuntary oscillations around a joint. Symmetric postural hand and arm tremor is typical of ET.[3] Spiral drawing on paper is generally rated clinically to assess task-directed hand tremor severity.[4] Digital spiral drawing represents a technological advanced alternative suitable for use at large scale. To date, evidence is limited on the boundaries within which tremor may be considered ordinary in the general population.

Aims

We aimed to derive the normative range and frequency distribution of the Bain-Findley clinical tremor rating scale (TRS),[4] to assess tremor from drawn spirals, among an adult population sample from the Cooperative Health Research In South Tyrol (CHRIS) study, according to age, sex and dominance of the drawing hand.

Methods

Digital spiral drawing was assessed in 10,994 participants recruited between February 2013 and December 2018 in the ongoing CHRIS study,[5] using a Wacom Intuos 5L Digitizer tablet connected to a PC with 200Hz sampling frequency, 5080lpi resolution, 2048 pressure levels and ±0.25mm accuracy. Participants were instructed to draw 2 or 6 spirals with a digital pen within margins of a clockwise Archimedean spiral template printed on paper and attached onto the surface of the tablet, starting from the center, with each hand, in alternate sequence. Participants were blind to the digital trace on screen. Drawing sessions were digitally recorded using a semi-automated in-house developed software. The hand dominance was self-reported by each participant at the start of the drawing session. Participants were free to start the session with their hand of preference.
We sampled 3000 spirals of paired hands from 1500 selected participants among the first two available spirals drawn by each participant. For the selection, we developed an ad-hoc iterative algorithm based on 15 digital spiral analysis (DSA) automated metrics derived from each digitized trace, and the age and sex of participants. The metrics captured various aspects of the tracing including tremor amplitude, acceleration, speed, and pressure. The selection algorithm maximized the variability across metrics and the coverage of participant demographics.
Spirals were then extracted and digitally printed on a bitmap at 300 dpi when displayed at actual size, with trace mark and pattern width reflecting the applied pressure on the pen. All 3000 spirals were then randomly uploaded on an online assessment form to return their TRS score between 0 and 10, by an expert neurologist.[4]

Finally, we derived the frequency of clinical tremor rating boundaries and normative distribution percentiles according to sex, age, and drawing hand dominance. Frequencies and percentiles were calibrated to the age and sex distribution of the target population by post-stratification weights and accounted for the clustering of spirals within participant.

Results

The median age of the present study participants was 51 (interquartile range:34-66). Sexes were balanced within the extracted sample (50.8% females). By exclusion criteria, there were 2874 spirals available for analysis. All metric distributions were slightly flattened and had higher variability, compared to their original distribution in the overall CHRIS sample. Sampled participants’ age reflected greater proportion of the elderly population compared to the CHRIS participants, consistently with extreme DSA metric values within this group.

TRS scores on the selected spirals ranged between 0 and 9 (median=2; interquartile range:2-3). Men (M) returned higher scores than women (W), while spirals drawn with the dominant hand (D) had lower scores than those drawn with the non-dominant hand (ND). Accounting for the survey design, mean TRS scores were 2.43 (95%CI: 2.38-2.49), 2.11 (2.05-2.16), 2.23 (2.17-2.28) and 1.78 (1.73-1.84) in the 4 groupings M-ND, M-D, W-ND, W-D, respectively.

The proportion of participants with TRS scores of 0 (no evidence of tremor) was particularly high among the W-D (2.38%), while the proportion of scores >4, corresponding to a clinically relevant magnitude of tremor amplitude,[6] within the same grouping was lowest at 0.82%. The M-ND had the highest proportion of TRS scores>4 (1.64%). All spirals within the 5-th percentile and 95-th percentile considered as normative range were rated between 1 and 4, except in the W-D grouping, whose 95-th percentile was equal 3. TRS scores increased on a quadratic function with age across all 4 subgroups (adjusted Wald test for age^2 $p<0.001$).

Conclusions

To our knowledge, this is the first study to investigate normative ranges of TRS scores from digital spiral drawings on a large population set of predominantly healthy adult individuals, representative of their target population. Normative scores and proportions of meaningful boundaries varied between men and women and according to both age and the drawing hand dominance, with relatively more favorable values among women, younger participants and for the dominant hand. The methods are easily exportable to other population settings using a similar template to the present digital spiral analysis, even on a larger scale. Results deserve external independent validation in available population-based studies that used comparable designs and outcome.

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THE UNEVEN GLOBAL IMPACT OF THE COVID-19 PANDEMIC: A 100-FOLD MORTALITY DIFFERENCE BETWEEN THE WEST AND THE EAST

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Background

The current coronavirus disease 2019 (COVID-19) has rapidly spread around the globe and affected countries unevenly [1,2]. In particular, already in the Spring 2020 differences were perceivable between two regions: the West and the East.

Aims

To identify possible multidimensional global health determinants responsible for different impact of the COVID-19 pandemic in term of mortality by conducting an ecological study. A special focus was on the comparison between two regions (the West and the East).

Methods

We conducted an ecological analysis describing country-specific parameters of the global epidemiology of COVID-19 during 2020 [2]. Overall, 156 countries with a population size ≥1 million people, accounting for 79% of the 197 countries worldwide, were included. The association of log-transformed COVID-19 deaths per million with explanatory variables was investigated using ordinary least squares (OLS) regression models. All continuous exploratory variables were standardized before their inclusion in the multivariate analyses.

We developed and tested three ordinary-least squares sub-models based on different dimensions: (i) demographics and health factors (eg, gross domestic product per capita, % urban population, prevalence of tobacco smoking), (ii) health system preparedness (eg, preparedness scores, density of medical doctors and hospital beds), and (iii) structural determinants (eg, Gini coefficient, current health expenditure, island countries) The resultant sub-modelling significant predictors of COVID-19 deaths (at $p<0.1$ level) were merged into a final regression model, adjusting also for possible confounders (ie, stringency index and timeliness of stay-at-home requirements). To check for geographical autocorrelation, cluster-robust standard errors (using a clustered sandwich estimator) were calculated. The West (n=28) was defined as countries of the European Union, United States, and Canada. The East (n=17) was defined as countries of South East Asia and the Western Pacific Region by the World Health Organization. Key variables in the West were contrasted with those in the East, and speed of response was examined. Furthermore, data of relative search volume (RSV) of "face masks" from Google Trends was used to observe if identification of a temporal pattern was possible. Statistical analysis was performed using STATA version 16.1.

Results

Globally, 2.24 million COVID-19 deaths were documented in 2020, with Western countries experiencing a median mortality 114 times higher that of the East. Significant variables at the final OLS model (Figure 1) associated to increased COVID-19 mortality were median age of the population (adj β=0.370, 95%CI: 0.238

to 0.501), prevalence of obesity (adj β=0.358, 95%CI: 0.260 to 0.455), and democracy index (adj β=0.353, 95%C: 0.232 to 0.475). Political stability (adj β=-0.297, 95%CI: -0.428 to -0.166) and previous experience with SARS in 2002-2003 (adj β=-0.311, 95CI: -0.552 to -0.069) were protective. None of the indexes and scores used for measuring preparedness (ie, the International Health Regulations average score and the Global Health Security score) were retained in the final OLS model from the stepwise selection.

In the 2020, COVID-19 cumulative mortality in the West increased nearly 8,000-fold from March to May, but only 4.5 times in the East; the relative increases were 2.9 and 6.0, respectively, from June to December.

In the East, internet users increased searches for masks at the end of January 2020, while in the West such web-searches were delayed until March-April and the temporal delay persisted after adjusting for the date of each country's first confirmed case.

Differences between the West and the East for some determinants were identified, including the prevalence of obesity in adults (ie, 23% and 6% in the West and in the East, respectively).

Results were robust enough to pass robustness checks, adjustments for measures implemented by governments throughout the 2020, and geographical autocorrelation.

Conclusions

Our ecological study identified some global multidimensional determinants associated with increased COVID-19 deaths. Besides, rapid response from governments, higher testing coverage per case and early mask wearing in most of Asia may have contributed to the East's ability to contain the epidemic. However, in the current pandemic, lower mortality in the East can reflect a lower SARS-CoV-2 circulation in the region; thus, large part of the population remains vulnerable to suffer from COVID-19 until enough people are vaccinated .

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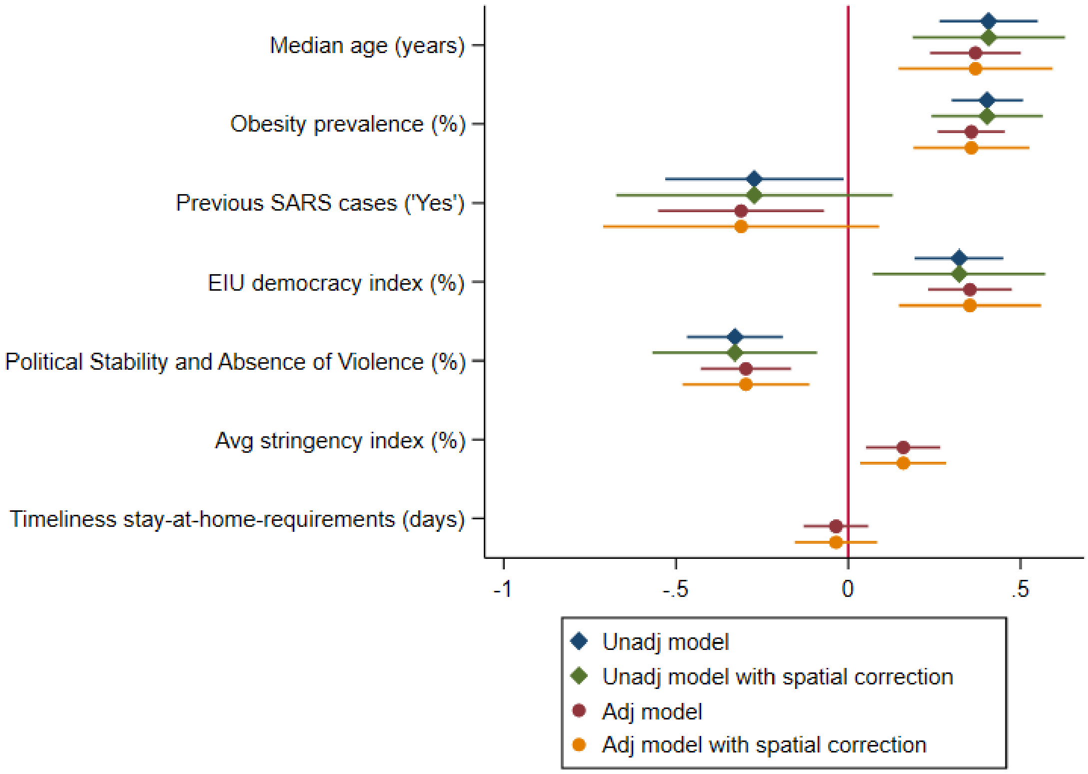

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Figure 1. Forest plot of the final multivariate OLS regression model of COVID-19 mortality in 2020 adjusted for response measures, with spatial autocorrelation correction (n=130). Note: three countries (ie, Mongolia, Thailand, Papua New Guinea) were removed because outliers.

L'EFFETTO INDIRETTO DELL'EPIDEMIA DA COVID-19 SUL TRATTAMENTO DEI PAZIENTI CON DISTURBO MENTALE GRAVE. IL PROGETTO MOVID

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INTRODUZIONE

L'impatto dell'epidemia da CoViD-19 sui pazienti affetti da patologie croniche è stato dirompente, per una serie di molteplici motivi. Prima di tutto, numerosi studi hanno dimostrato come i pazienti caratterizzati da un profilo clinico più compromesso siano esposti a un maggior rischio di contrarre l'infezione da CoViD-19, oltre che di sviluppare forme severe di tale patologia. Inoltre, le misure restrittive di contenimento della pandemia adottate dalle autorità hanno aumentato il rischio di sperimentare l'insorgenza o il peggioramento di patologie croniche. Per quanto riguarda l'ambito della salute mentale, l'emergenza pandemica ha avuto un forte impatto sull'insorgenza di disturbi mentali e delle manifestazioni cliniche ad essi associati; impatto, a breve o lungo termine, oggetto di valutazione in numerosi progetti internazionali. Inoltre, nel dibattito scientifico ha acquisito un notevole interesse la valutazione dell'impatto a lungo termine della pandemia, e delle associate misure di contenimento, sulla salute e sul ricorso a servizi di assistenza nell'ambito di salute mentale. Infatti, tali misure restrittive, oltre ad aumentare il rischio di insorgenza di patologie croniche, hanno anche causato una riduzione della capacità dei sistemi sanitari di diagnosticare precocemente, monitorare e trattare i pazienti affetti da malattie e condizioni croniche, tra cui i disturbi mentali gravi.

OBIETTIVI

Il progetto MoViD (Monitoraggio e Valutazione dei Livelli Essenziali di Assistenza nel corso dell'epidemia da CoViD-19) per la saluta mentale ha l'obiettivo di valutare come si è modificato durante l'emergenza pandemica l'accesso ai livelli essenziali di assistenza e la qualità della cura erogata ai pazienti affetti da disturbo mentale grave.

METODI

Per la realizzazione di questo studio sono stati utilizzati gli archivi sanitari amministrativi della regione Lombardia. Tramite questi archivi amministrativi è stato possibile identificare la coorte di pazienti, residenti ed assistiti dal SSR al 01/01/2020, in contatto con le strutture territoriale dei Dipartimenti di Salute mentale (DSM) ed affetti da disturbo mentale grave prevalente (i.e., disturbo schizofrenico, depressivo, bipolare, di personalità). Ognuno di questi pazienti prevalenti è stato osservato dal 01/01/2020 fino alla prima data tra il 30/09/2020 (data di fine disponibilità dei dati), la data di decesso o la data di trasferimento in altra regione.

I mesi del 2020 sono stati classificati in tre periodi, ciascuno corrispondente a un diverso livello di esposizione (dipendente dall'intensità delle restrizioni adottate dalle autorità in ciascuno dei 3 periodi individuati): "No Covid" (gennaio/febbraio), "Covid lockdown" (marzo/maggio) e "Covid no lockdown" (giugno/settembre).

Nel periodo di osservazione, per ognuno dei pazienti identificati è stata valutata la continuità della cura con una serie di trattamenti la cui erogazione continuativa è raccomandata per i pazienti affetti da disturbo mentale grave: trattamento farmacologico, qualsiasi intervento territoriale con le strutture dei DSM, interventi psicosociali, interventi di psicoterapia, visite psichiatriche. Per quantificare la diversa propensione all'erogazione continuativa di ognuno di questi differenti trattamenti in questi tre periodi (ossia l'esposizione di interesse), è stato adottato, sicché il follow-up è lungo ed il paziente attraversa tutti i periodi dell'anno (e dunque tutte le categorie di esposizione previste), un approccio basato su un disegno Self-Controlled Case Series. Una coorte di riferimento è stata identificata, applicando gli stessi criteri di inclusione/esclusione ma anticipando di un anno il reclutamento (anno di valutazione: 2019), al fine di aggiustare le stime ottenute per il trend temporale nello svolgimento dei trattamenti in esame.

RISULTATI

La coorte di pazienti in contatto con le strutture dei DSM regionali e affetta da un disturbo mentale grave prevalente al 01/01/2020 risultava essere composta da 90'573 pazienti (30'584 affetti da disturbo schizofrenico, 33'005 depressivo, 11'588 bipolare, 15'396 della personalità).

Confrontati con i periodi non epidemici, si sono osservate riduzioni significative nell'erogazione delle prestazioni sanitarie raccomandate (tranne che per le visite psichiatriche) durante i periodi caratterizzati da misure restrittive per tutti i 4 disturbi mentali gravi (Tabella 1). In particolare, le riduzioni più marcate sono state osservate nell'erogazione, e continuità, degli interventi psicosociali (riduzione del 62%, con 95% IC: 61%-63%) e territoriali nel loro complesso (riduzione del 34%, con 95% IC: 33%-35%) ai pazienti schizofrenici, e nelle visite psichiatriche (riduzione del 23%, con 95% IC: 21%-25%) per i pazienti affetti da disturbo depressivo. Tali rapporti tra i tassi di svolgimento tra i due periodi caratterizzati da restrizioni rispetto a quello "No Covid" suggeriscono un importante calo dell'erogazione di tali prestazioni: durante il lockdown, mentre tali riduzioni risultano meno marcate per il periodo con restrizioni limitate, suggerendo un graduale ritorno ai livelli pre-Covid. Tale andamento non risulta invece per il trattamento farmacologico.

CONCLUSIONI

Il nostro studio ha permesso di valutare il calo dell'accesso ai livelli essenziali di assistenza, e della relativa qualità della cura erogata, per i pazienti affetti da disturbo mentale grave. Tali risultati, possono contribuire a programmare gli interventi atti a recuperare l'assistenza ritardata e allocare risorse al fine di recuperare questi ritardi e mancanze.

Tabella 1. Effetto delle misure restrittive (esposizione) sull'aderenza agli interventi clinici raccomandati (outcomes) sulla coorte di pazienti affetti da disturbo mentale grave prevalente al 01/01/2020. In tabella sono riportate le stime dei rapporti tra i tassi di svolgimento degli interventi raccomandati (IRR and relativi 95% IC), ottenute tramite il disegno SCCS. Lombardy, Italy, 2019-2020.

	Schizofrenia	**Depressione**	**Disturbo Bipolare**	**Disturbo Personalità**
Interventi Territoriali				
No CoViD	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
CoViD lockdown	0.66 (0.65 – 0.67)	0.71 (0.70 – 0.72)	0.72 (0.71 – 0.74)	0.73 (0.72 – 0.75)
CoViD no-lockdown	0.79 (0.78 – 0.80)	0.87 (0.86 – 0.89)	0.87 (0.86 – 0.89)	0.84 (0.83 – 0.85)
Interventi Psicosociali				
No CoViD	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
CoViD lockdown	0.38 (0.37 – 0.39)	0.50 (0.49 – 0.51)	0.43 (0.42 – 0.44)	0.47 (0.46 – 0.48)
CoViD no-lockdown	0.65 (0.63 – 0.67)	0.74 (0.72 – 0.76)	0.71 (0.69 – 0.73)	0.70 (0.68 – 0.71)
Psicoterapia				
No CoViD	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
CoViD lockdown	0.99 (0.93 – 1.05)	0.84 (0.80 – 0.88)	0.97 (0.89 – 1.05)	0.97 (0.92 – 1.03)
CoViD no-lockdown	0.95 (0.90 – 1.00)	0.85 (0.81 – 0.89)	0.88 (0.81 – 0.95)	0.90 (0.85 – 0.95)
Visite psichiatriche				
No CoViD	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
CoViD lockdown	0.87 (0.85 – 0.89)	0.77 (0.75 – 0.79)	0.85 (0.82 – 0.88)	0.96 (0.93 – 0.99)
CoViD no-lockdown	0.91 (0.89 – 0.93)	0.88 (0.86 – 0.90)	0.89 (0.86 – 0.93)	0.96 (0.93 – 0.99)
Trattamento farmacologico				
No CoViD	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
CoViD lockdown	0.96 (0.94 – 0.97)	0.93 (0.91 – 0.94)	0.94 (0.92 – 0.96)	0.95 (0.93 – 0.98)
CoViD no-lockdown	0.76 (0.75 – 0.77)	0.76 (0.75 – 0.78)	0.76 (0.75 – 0.78)	0.77 (0.75 – 0.79)

LIFESTYLE FACTORS AND RISK OF MORBIDITY AND MULTIMORBIDITY IN THE SWEDISH NATIONAL MARCH COHORT: PRELIMINARY RESULTS

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Introduction

Life expectancy has increased worldwide going from 45.7 years in 1950 to 72.6 years in 2019. [1] Chronic diseases, defined as health problems requiring ongoing management over a period of years or decades, [2] today represent the predominant burden of healthcare and, when combined, create additional challenges to patient care, since most guidelines do not provide recommendations for patients presenting with multiple diseases. [3] The prevalence of multiple chronic conditions is heterogeneous among published studies, depending on the definition of multimorbidity. [4,5,6,7] In a cross-sectional study based on more than 1 750 000 individuals based in Scotland, 23.2% of the included subjects, with no restriction of age, were found to have at least two chronic disorders from a pool of 40. [8] Nevertheless, epidemiological data are often analyzed in a disease-specific manner, disregarding the complexity of multimorbid patients.

Aim In our study we wanted to investigate the role of lifestyle risk factors on incident morbidity and multimorbidity of four selected groups of diseases, i.e., major adverse cardiac events (MACE), malignant cancer at any site excluding non-melanoma skin cancer, mental and psychiatric disorders (MD) and neurodegenerative disorders (NDD) combined, and diabetes.

Methods Our study population is a Swedish cohort established in 1997 and counting more than 40 000 participants, the Swedish National March Cohort (SNMC). [9] Risk factors were assessed based on self-reported information from the questionnaire given to the SNMC participants at cohort inception, while outcome assessment was possible thanks to the complete and reliable Swedish national registers. [10,11,12,13,14]
Smoking, alcohol consumption, body mass index (BMI), physical activity, and diet were standardized to a healthy lifestyle score from 0 to 4, where 0 represents the worst habit and 4 the best for each of the five lifestyle factors. Subjects with a history of any of the selected diseases, aged less than 20, or with missing information on any lifestyle factor were excluded from the study population. Included subjects were followed until 31st December 2016 or death. Outcomes of interest were organized in a multi-state framework, with states given by the first incident disease from one of the four selected groups, and multimorbidity. Multivariable hazard ratios and 95% confidence intervals (CI) from Cox models were reported for each of the four selected groups of incident diseases and for multimorbidity. [15] All models included the five healthy lifestyle scores modeled as continuous, and were adjusted for age, sex, education, and calorie consumption; the model for multimorbidity, additionally, was adjusted for first incident disease. Heterogeneity between males and females was studied by adding an interaction term, and all models were also repeated stratifying by sex regardless of heterogeneity. All analyses were performed using SAS 9.4 and R version 4.0.2.

Results Our final study population consisted of 26 352 subjects, of which 67% were females, and were followed for a median time of 19.2 years. Median age at the beginning of follow-up was 51 years with interquartile range

(IQR) 40-62 years. The first incident disease was MACE for 2399 (9.1%) participants, cancer for 3483 (13.2%), MD or NDD for 2360 (9.0%), and diabetes for 1284 (4.9%). Of the 9527 subjects with a first disease (median age at diagnosis 70 years, IQR: 60-78), 2281 (23.9%) transitioned to multimorbidity after a median time of 6.8 years (IQR: 3.0-11.3). Results on the association between the lifestyle factors and the outcomes are presented in Table 1. Hazard ratios refer to one unit increase in each score, i.e., from a worse to a better habit. Smoking was consistently associated with all the outcomes, with the highest impact on MD+NDD (HR: 0.84, 95%CI 0.80-0.87), the impact being higher among females (HR: 0.76, 95%CI 0.71-0.82) (p for heterogeneity: <0.01). A decreased consumption of alcohol was associated with higher risk of MACE (HR: 1.07, 95%CI 1.04-1.10), but with lower risk of malignant cancer (HR: 0.97, 95%CI 0.95-1.00). A lower BMI was a risk factor for MD+NDD (HR: 1.05, 95%CI 1.02-1.08), and protective against all the other outcomes, reducing by half the risk of diabetes (HR: 0.51, 95%CI 0.49-0.54). Physical activity was found to be protective for diabetes among men (HR: 0.89, 95%CI 0.83-0.94) (p for heterogeneity: 0.01), for MACE (HR: 0.95, 95%CI 0.92-0.98) and MD+NDD (HR: 0.97, 95%CI 0.94-1.00). The diet score was found to be associated only with MD+NDD (HR: 0.96, 95%CI 0.93-0.99), even though one unit increase reduced the risk of death of about 5% (data not shown). Only smoking and BMI at baseline were found to be associated with the risk of multimorbidity.

Conclusions

We reported preliminary results on the association between lifestyle risk factors and the occurrence of important incident diseases and of multimorbidity, showing a clear role of smoking, BMI, alcohol, and physical activity. Our initial goal to build an overall healthy lifestyle index score, as proposed before [16,17] has been partially reconsidered and we have modeled the effect of each of the components on the different outcomes. In addition, we intend to take into account the effect of other relevant variables such as patterns and quality of sleep [18]. We will also investigate: i) other healthy lifestyle score alternatives for diet [19], possibly adapted to the Swedish food pattern; ii) the effect of possible inverse causation by dropping the first years of follow-up; iii) the impact of missingness by implementing multiple imputation; iv) the shape of the dose-response relationship between exposures and outcomes, particularly for alcohol consumption [20] and BMI [21,22]). Multistate models will be considered for the described framework, also accounting for death as absorbing state.

Table 1. Multivariable Cox models for MACE, MD and NDD, Diabetes, Cancer, and multimorbidity, overall and stratified by sex.

		Overall		By sex		
				Males	Females	
Outcome	Variable	HR (95%CI)	*p*	HR (95%CI)	HR (95%CI)	*p*
MACE	N (events)	26352 (2399)		8698 (1273)	17654 (1126)	
	Smoking	0.88 (0.84-0.92)	*<0.01*	0.89 (0.83-0.95)	0.86 (0.81-0.92)	*0.70*
	Alcohol	1.07 (1.04-1.10)	*<0.01*	1.07 (1.03-1.12)	1.08 (1.03-1.13)	*0.33*
	BMI	0.92 (0.89-0.95)	*<0.01*	0.92 (0.88-0.96)	0.92 (0.88-0.96)	*0.97*
	Physical activity	0.95 (0.92-0.98)	*<0.01*	0.94 (0.90-0.98)	0.97 (0.93-1.02)	*0.12*
	Diet	1.00 (0.97-1.04)	*0.86*	1.04 (0.99-1.08)	0.97 (0.92-1.01)	*0.09*
MD+NDD	N (events)	26352 (2360)		8698 (715)	17654 (1645)	
	Smoking	0.84 (0.80-0.87)	*<0.01*	0.76 (0.71-0.82)	0.87 (0.83-0.91)	*<0.01*
	Alcohol	1.03 (1.00-1.06)	*0.05*	1.03 (0.98-1.09)	1.03 (0.99-1.07)	*0.78*
	BMI	1.05 (1.02-1.08)	*<0.01*	1.06 (1.00-1.12)	1.04 (1.01-1.08)	*0.92*
	Physical activity	0.97 (0.94-1.00)	*0.04*	1.01 (0.96-1.06)	0.95 (0.92-0.99)	*0.06*
	Diet	0.96 (0.93-0.99)	*0.01*	0.97 (0.91-1.02)	0.96 (0.92-0.99)	*0.33*
Diabetes	N (events)	26352 (1284)		8698 (543)	17654 (741)	
	Smoking	0.88 (0.83-0.93)	*<0.01*	0.87 (0.79-0.95)	0.89 (0.82-0.95)	*0.86*
	Alcohol	1.03 (0.99-1.08)	*0.13*	1.03 (0.96-1.09)	1.04 (0.98-1.10)	*0.57*
	BMI	0.51 (0.49-0.54)	*<0.01*	0.52 (0.47-0.56)	0.51 (0.48-0.55)	*0.87*
	Physical activity	0.94 (0.90-0.98)	*<0.01*	0.89 (0.83-0.94)	0.98 (0.93-1.04)	*0.01*
	Diet	0.98 (0.94-1.02)	*0.38*	0.96 (0.89-1.02)	1.00 (0.94-1.05)	*0.33*
Cancer	N (events)	26352 (3484)		8698 (1414)	17654 (2070)	
	Smoking	0.89 (0.86-0.92)	*<0.01*	0.88 (0.83-0.93)	0.90 (0.87-0.95)	*0.60*
	Alcohol	0.97 (0.95-1.00)	*0.04*	0.97 (0.93-1.00)	0.98 (0.95-1.01)	*0.89*
	BMI	0.94 (0.92-0.96)	*<0.01*	0.93 (0.89-0.97)	0.94 (0.91-0.97)	*0.63*
	Physical activity	1.01 (0.98-1.03)	*0.63*	0.99 (0.95-1.03)	1.01 (0.98-1.05)	*0.57*
	Diet	0.99 (0.97-1.02)	*0.64*	1.01 (0.97-1.05)	0.98 (0.95-1.01)	*0.03*
Multimorbidity	N (events)	9527 (2281)		3945 (1156)	5582 (1125)	
	Smoking	0.91 (0.87-0.95)	*<0.01*	0.88 (0.83-0.93)	0.93 (0.87-0.99)	*0.14*
	Alcohol	1.03 (1.00-1.06)	*0.07*	1.02 (0.98-1.07)	1.03 (0.99-1.08)	*0.84*
	BMI	0.91 (0.88-0.94)	*<0.01*	0.92 (0.87-0.96)	0.91 (0.87-0.96)	*0.69*
	Physical activity	0.99 (0.96-1.02)	*0.57*	1.02 (0.98-1.06)	0.97 (0.93-1.01)	*0.12*
	Diet	1.02 (0.99-1.05)	*0.24*	1.02 (0.97-1.07)	1.02 (0.97-1.07)	*0.83*

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AGREEMENT BETWEEN CLINICAL AND ADMINISTRATIVE DATA OF MAJOR COMORBIDITIES IN PEOPLE WITH MULTIPLE SCLEROSIS

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Background

Increasing evidence suggests that comorbidities commonly affect individuals living with multiple sclerosis (MS) and adversely affect clinical outcomes [1]. Comorbid conditions are common in people with MS, and can lead to poorer outcomes, negatively impacting on MS course, delay of diagnosis, progression of disability and treatment management and adherence [2]. In addition, physical and mental comorbidities strongly impact on quality of life [3]. Potential comorbidity data sources include self-report, medical records, and administrative databases. The validity of self-reported comorbidity data in persons with MS varies by condition [4]. Traditionally, the gold standard for capturing information about pre-existing comorbidities is clinical interviews, but in large epidemiological studies, this is not feasible. Administrative data are accessible and, cost-effective and cover large populations, potentially supporting research questions which cannot be addressed using interviews or records review. Previous studies have shown that coding of comorbidities within administrative datasets has varying levels of agreement with medical records [5]. Although comorbidity is important in MS, few validated methods for its assessment exist.

Aims

The aim of the study was to quantify, in a sample of pwMS, the agreement between documentation of major comorbidities within patients' medical records, and comorbidities identified through the local health authorities administrative system.

Methods

Retrospective medical record review was conducted to collect data about major comorbidities using a sample of pwMS enrolled from two Multiple Sclerosis centers (clinical and rehabilitation) of North Italy. Diagnoses codes of the comorbidities (depression, anxiety, diabetes, hypertension, cancer, autoimmune diseases, heart disease, vascular diseases, cerebrovascular diseases, stroke, broncopathy, hyperlipidaemia, diseases of the connective tissue, liver disease, dementias, chronic renal failure) were searched in the same pwMS sample by the local health authorities, presence of comorbidity was defined by a specific algorithm currently used for monitoring prevalence of chronic diseases.

Comorbidities prevalence and 95% confidence intervals were calculated by data source. To evaluate the degree of agreement between the clinical and the administrative data sources, with regards to presence of comorbidities, we used Cohen's Kappa, Bias Index (BI), Prevalence Index (PI), prevalence-adjusted bias-adjusted kappa (PABAK), and positive and negative percentage agreement.

Results

We included in this analysis 635 pwMS that have the comorbidity information both by administrative and clinical data. Based on clinical data, 52.9% of pwMS had at least one co-morbidity, compared to 59.7% of patients having a condition coded in administrative data. There was a substantial difference in prevalence between the two data sources for depression (40.6% to 16.1%) and anxiety (2.8% to 12.3%), less evident for cancer (9.3% to 4.6%), hypertension (16.9% to 20.3%) and autoimmune diseases (6.0% to 9.3%). We found that the prevalence of depression, cancer, heart disease, broncopaty and cerebrovascular diseases from administrative data were higher than that from clinical data, while hypertension, autoimmune diseases, hyperlipidaemia, anxiety, vascular diseases and diseases of the connective tissue were lower than that from clinical data. The diabetes prevalence resulted same in both sources.

Kappa ranged from <0.001 (poor agreement) for dementias and stoke to 0.94 (excellent agreement) for diabetes, whereas for PABAK, it was from 0.32 (depression) to 0.99 (dementia and chronic renal failure), with the PABAK value greater than kappa for all conditions evaluated.

Overall, we observed a small bias effect (BI ranged from -0.09 to 0.25) but a very large prevalence effect (PI ranged from -1.00 to -0.43). The Kappa and PABAK differed considerably for a number of specific comorbidities, indicating the k statistic was vulnerable to change due to sparse data for these categories.

Overall, there was poor agreement (<0.20) between clinical records and administrative data for hyperlipidaemia, cerebrovascular diseases, vascular diseases, anxiety, dementias and stroke but substantial or excellent agreement when adjusting for prevalence-adjusted bias-adjusted kappa (PABAK). Similarly, cancer, autoimmune diseases, heart disease, broncopathy, diseases of the connective tissue, liver disease and chronic renal failure from fair (kappa 0.20- 0.40) to excellent agreement (PABAK > 0.80). There was excellent/substantial agreement between sources for diabetes and hypertension to both kappa and PABAK. There was fair agreement between sources for depression to both kappa and PABAK. Most of comorbidities had a very good negative agreement indicating excellent agreement when there was no comorbidity diagnosis from either source. Diabetes and hypertension were the only two comorbidities that had very good and good positive agreement (88.0% and 75.4%, respectively). The other positive agreements ranged from 0% for dementias and stroke to 40% for depression.

Conclusion

Overall, the bias effects were relatively small, but the prevalence effect was very large. For this reason, as suggested by Byrt [6], in our study we reported the positive and negative agreement in order to improve the interpretation of Kappa. The results showed the administrative and clinical data agreed well when the patient did not have the comorbidity in either source of data. In contrast, the concordance was relatively poor for most comorbidities, except for diabetes and hypertension where we observed a good positive agreement.

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REGRESSION DISCONTINUITY DESIGN IN LIFECOURSE EPIDEMIOLOGY

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Introduction In life course epidemiology the goal of many studies is to determine the causal effect of an exposure on health outcomes. A major challenge in observational studies is the possibility of unmeasured confounding and several analytical and design approaches have been developed and extensively used in the past decades to obtain a potentially unbiased estimate of an exposure effect. The regression discontinuity design (RDD) is a quasi-experimental approach applied in circumstances where a continuously measured variable (assignment variable) presents a clearly defined cut-off point above or below which the population is at least partially assigned to treatment or exposure. Assignment variable creates a discontinuity in the probability of treatment or exposure at threshold, where the direction and magnitude of the jump is a direct measure of the causal effect of a treatment/exposure on an outcome for subjects near the cut-point. When the assignment rule perfectly determines exposure regression discontinuity takes a sharp design (e.g. imposed policy measures); if the assignment rule affects the probability of exposure creating a discontinuous change at the threshold, but without an extreme 0-to-1 jump, regression discontinuity takes a fuzzy design (e.g. optional participation in programs).

Objectives We aimed to apply the fuzzy RDD in the context of life course epidemiology, focusing in particular on perinatal epidemiology and the birth cohort research. The estimated RDD effects were compared with the estimates of standard multivariable regression analysis.

Methods We analysed the data of two Italian birth cohorts with approximately 4500 children delivered spontaneously, after the 32nd week of gestation and with less than 4000 grams. The fuzzy RDD was used to identify the causal effect of breastfeeding, relying on the fact that rooming-in, which favours the initiation of breastfeeding, is less common in newborns below 2500 grams (i.e. low birth weight [LBW]), and that artificial formula-feeding to promote growth, mostly recommended for LBW newborns threats the initiation and establishment of successful breastfeeding. We dealt with partial compliance by using the assignment rule (2500 grams) as an instrumental variable for breastfeeding. We analysed multiple offspring outcomes, but focused in particular on infant weight at 18 months of age. Within a fuzzy RDD, the local average treatment effect (LATE) of breastfeeding around the cut-off point was obtained using the two-stage least squares (2SLS) regression analysis. The robustness of the results was tested with several birth weight bandwidths and with multiple other validity checks.

Results Within the 500g around the birth weight threshold there were 1118 spontaneously delivered newborns, with gestational age of at least 32 weeks. The prevalence of non-breastfed infants was 6.6%, while the prevalence of LBW newborns was 13.1%. The first-stage regression results, using breastfeeding (yes vs. no) as a dependent variable and LBW as the instrument (a binary indicator for infant birth weight crossing 2500 grams), reveal that below 2500 grams, the prevalence of non-breastfeeding increases by

8.8 percentage points (95% confidence intervals [CI]: 0.7-16.9), indicating a discontinuous jump in the probability of breastfeeding at 2500g of birth weight (Figure 1).

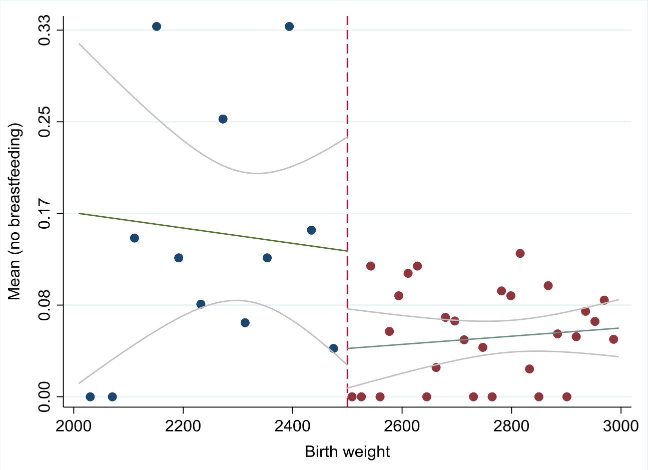

Figure 1. First-stage effects: discontinuity in breastfeeding

The fuzzy RDD estimate reveals that within the 500g around the threshold non-breastfed infants weight on average 275g more at 18 months of age compared with infants who were breastfed for at least one month. Due to a relatively limited sample size the confidence intervals of the LATE were quite wide. Using a conventional multivariable regression analysis (adjusted for maternal age, maternal educational level [high vs. medium/low], maternal country of birth [Italy vs. Other], maternal parity [nulliparous vs. multiparous], maternal pre-pregnancy BMI, birth weight and cohort identifier) it emerges that non-breastfed infants weight on average 292 grams more (95% confidence intervals: 16-568 grams) than breastfed infants.

Conclusions Despite the small sample, using the fuzzy RDD, we found that non-breastfed infants weight on average more already at 18 months of age compared with infants who were breastfed. In this setting, the RDD findings were similar to those obtained using multivariable regression analysis, indicating that the latter are likely free of residual confounding. If confirmed in a larger cohort and different settings, discontinuity in breastfeeding at 2500g of birth weight observed in our analyses could serve as a stepping stone for future studies assessing the effects of breastfeeding on later childhood outcomes.

SVILUPPO E VALIDAZIONE DI UN INDICE PROGNOSTICO PER IDENTIFICARE GLI INDIVIDUI PIÙ VULENERABILI ALLE FORME SEVERE DEL COVID-19

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INTRODUZIONE

Numerosi studi hanno evidenziato come gli individui affetti da alcune malattie croniche, come l'ipertensione ed il diabete, hanno un aumentato rischio di contrarre l'infezione da SARS-CoV-2 e di sviluppare forme severe di Covid-19. Oltre alle singole condizioni, un profilo clinico più compromesso, ossia la presenza di molteplici patologie e/o l'assunzione di differenti terapie farmacologiche, rende più vulnerabili gli individui a sperimentare forme severe della malattia.

Riuscire a stratificare la popolazione generale in funzione del rischio di sviluppare forme cliniche severe o fatali della malattia permetterebbe di mettere in sicurezza questi individui con opportune misure di prevenzione (ad esempio, il vaccino) e di trattamento.

OBIETTIVI

Questo progetto si prefigge i seguenti obiettivi: (i) identificare i singoli predittori del rischio di sviluppare una forma severa/fatale del Covid-19; (ii) sviluppare un indice prognostico partendo da queste condizioni.

METODI

La lista delle condizioni candidate alla predizione del rischio è stata ricavata dall'insieme delle condizioni considerate in alcuni indici di complessità clinica, sia internazionali (come gli indici di Charlson, Chronic Disease Score, Elixhauser) che italiani (Multisource Comorbidity Score e Chronic Related Score), e dalla letteratura corrente sui fattori di rischio clinico. Per ogni predittore sono stati identificati i codici ICD-9-CM e ATC che ne tracciano la presenza dai flussi amministrativi.

L'identificazione dei singoli predittori e l'assegnazione dei pesi è stata condotta mediante l'analisi dei dati della Regione Lombardia durante la prima ondata (febbraio-giugno 2020). A tal fine, tutti i beneficiari del Servizio Sanitario della Regione Lombardia da almeno due anni, che avevano età compresa tra 18 e 79 anni e che non erano ospiti di una struttura residenziale sono stati identificati. Per ogni individuo, è stata valutata la presenza delle condizioni candidate nel periodo gennaio 2018-febbraio 2020. Inoltre, sono stati identificati gli individui che hanno sviluppato l'esito di interesse, ossia una forma severa del Covid-19 (accesso in terapia intensiva o decesso) fino a giugno 2020. Per identificare i predittori, un modello di regressione logistica è stato interpolato in modo da ottenere una stima degli odds ratio (e dei corrispondenti intervalli di confidenza al 90%) relativi all'associazione tra genere, età (nelle categorie 18-45, 46-59, 60-69 e 70-79 anni) e l'esposizione ai singoli predittori candidati, e l'odds dell'esito in studio. Il metodo LASSO è stato impiegato per selezionare le variabili indipendentemente associate all'esito. Per costruire l'indice, i coefficienti del modello sono stati moltiplicati per 10, arrotondati all'intero più vicino e sommati. Il punteggio complessivo è stato denotato Covid-19 Vulnerability Score (CVS).

Per validare il CVS, l'indice è stato applicato a più set di validazione costituiti da altre popolazioni sezionate con gli stessi criteri di quelli applicati alla popolazione lombarda usata per costruire il punteggio. Innanzitutto, sono stati identificati i beneficiari del Servizio Sanitario della Regione Lombardia che al 1° luglio 2020 non avevano ancora sperimentato infezione accertata di SARS-CoV-2. Per questi, è stato valutato l'esito nel periodo luglio-dicembre 2020. Inoltre, sono stati identificati i beneficiari dei Servizi Sanitari delle Regioni Valle d'Aosta, Marche, Puglia e Sicilia al 1° marzo, ed è stato valutato l'esito in tutto il 2020. La capacità predittiva del CVS è stata valutata mediante discriminazione e calibrazione, e i corrispondenti risultati sono stati confrontati con quelli degli indici di Charlson e del Multisource Comorbidity Score.

RISULTATI

Sono stati identificati 7.655.502 beneficiari del Servizio Sanitario della Regione Lombardia da almeno due anni, che avevano età compresa tra 18 e 79 anni e non erano ospiti di una struttura residenziale. Durante la prima ondata epidemica (febbraio-giugno), questa coorte ha sperimentato 9.160 eventi critici (ricoverati in terapia intensiva) e/o fatali.

Il modello ha selezionato 31 condizioni cliniche e demografiche che predicono il rischio dell'esito. Oltre all'età avanzata ed al genere maschile, le condizioni cliniche che maggiormente predicono l'esito sono il diabete (soprattutto se in trattamento con insulina), psicosi, e malattie vascolari periferiche e coronariche.

La coorte di validazione consta invece di 15.441.033 beneficiari dei Servizi Sanitari delle 5 regioni partecipanti, e che hanno generato 7.031 esiti. In termini di discriminazione, l'area sotto la curva ROC (AUC) relativa al CVS era di 0,89, comparata a 0,60 e 0,77 per l'indice di Charlson e del Multisource Comorbidity Score. La capacità discriminatoria è risultata essere del tutto sovrapponibile nelle diverse regioni, infatti l'AUC era 0,86, 0,86, 0,85 e 0,86 nelle regioni Valle d'Aosta, Marche, Puglia e Sicilia. Infine, si è osservato un buon accordo tra le probabilità predette con il CVS e quelle osservate (intercetta di calibrazione prossima a 0 e coefficiente angolare di ricalibrazione pari a 0,93).

CONCLUSIONI

Il progetto ha permesso di identificare i singoli predittori e di costruire un indice per predire lo sviluppo di forme severe del Covid-19. Dal momento che il CVS ha mostrato ottime capacità discriminatorie e superiori rispetto ad indici generici di complessità clinica, e che queste capacità sono risultate sovrapponibili nello spazio e nel tempo, l'indice può essere usato per identificare gli individui più vulnerabili a cui indirizzare interventi prioritari.

SATISFACTION WITH ONLINE TEACHING OF MEDICAL STATISTICS DURING THE COVID-19 PANDEMIC: A SURVEY BY THE EDUCATION COMMITTEE OF THE ITALIAN SOCIETY OF MEDICAL STATISTICS AND CLINICAL EPIDEMIOLOGY (SISMEC)

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Introduction

The Covid-19 pandemic, which leaded to the suspension of face-to-face lectures in February 2020, forced teachers to move all didactic activities online in a couple of days. Clear indications about the modalities to deliver distance learning were missing at the time of the outbreak, or if any, varied a lot between academic institutions. Moreover, none of the Italian public universities traditionally used distance learning and was prepared to approach it. Therefore, in May 2020 the Italian Society for Medical Statistics and Clinical Epidemiology (SISMEC) wondered at a national level about the comparison of methods for delivering online courses of medical statistics and epidemiology, as well as possible tools for evaluating the students’ acquired knowledge.

Aims

The Committee conceived an online survey to be administered to the Italian academics of medical statistics (MED/01) with a twofold aim: on the one hand, to highlight some opportunities that the situation had generated, including the degree of teachers’ satisfaction, and on the other hand, to highlight the limitations of online teaching.

Methods

The survey was structured into four sections: the first one collected information about the academic role, age and gender of the respondent; the second one focused on characteristics of online teaching and perceived teacher’s satisfaction; the third one focused on online exams, and the final section focused on future perspectives of online teaching of medical statistics and epidemiology.

A list of Italian academics of medical statistics (MED/01) was retrieved on April 30 2020th from the online freely available official database of the Italian Ministry of Education, University and Research (MIUR), and then their institutional e-mail addresses collected. Subsequently, an e-mail providing with information about the aims of the survey, and the URL link to access it, was sent out to the 122 identified Italian academics. No incentives were provided to complete the online questionnaire, which took approximately 10 minutes. The survey was also publicized on the SISMEC website and through the society’s newsletter in order to reach adjunct (contract) professors.

Categorical variables were described in terms of frequencies while continuous variables in terms of median and range. Bar plots were used to graphically represent results from selected questions.

Satisfaction was defined with a score greater than or equal to 7/10 at the survey questions “From 1 to 10, how much did you enjoy delivering online teaching?” and “From 1 to 10, how much did you enjoy delivering online exams?”, respectively.

Results

A total of 94 questionnaires were completed. Among all the respondents, 23 (24%) were full professors, 39 (41%) associate professors, 27 (29%) assistant professors and 5 (5%) adjunct professors.

The online teaching experience during the first months of the COVID-19 pandemic was different with regards to the number of teaching hours, the number of courses and the number of students. Educational provision varied across our sample: 21 (24%) chose to provide their lessons only asynchronously, 31 (35%) only synchronously, 18 (20%) synchronously but also provided asynchronous material, and 18 (20%) alternating the two modalities. Although technical difficulties during online teaching were experienced by 19 (22%) academics, a satisfaction score of 7 or more out of 10 was reached by 66 of them (75%). Nevertheless, 42% still found online teaching less effective than traditional modalities.
Among 69 academics who had delivered online exams at the time of the survey (73%), 20 (22%) choose an oral, 26 (29%) a written and 37 (41%) a mixed (oral and written) modality. A satisfaction score of 7 or more out of 10 for online exams was declared by 40 (62%). The experience with online exams was judged more difficult compared to the experience with online teaching, and relatively more negative evaluations were expressed (12% scores of 1 or 2 out of 10).
For what concerns future perspectives, 65% of the academics gave to their perceived effectiveness of online teaching of medical statistics and epidemiology a score of at least 7 out of 10 (Figure 1).

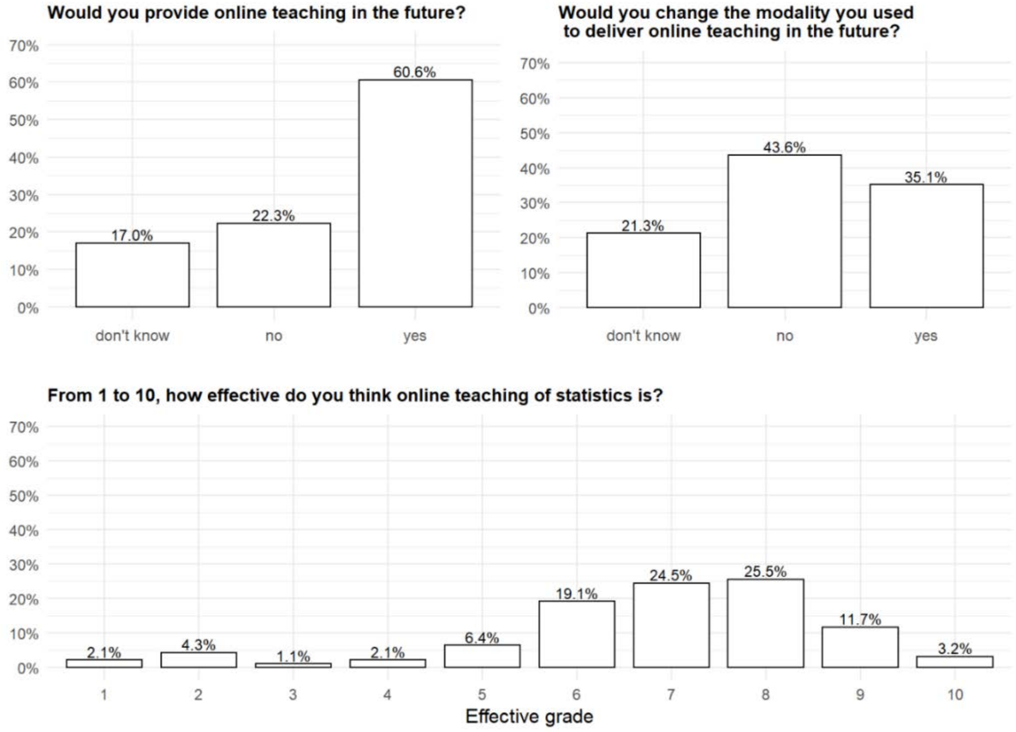

Figure 1. Perspectives of online teaching of medical statistics and epidemiology in a sample of 94 Italian academics of medical statistics.

Conclusions

Online teaching could have been initially considered only as a rescue modality to deliver educational activities during the COVID-19 pandemic. As written by Gallo et al. [1] in a recent report of the Education Committee of the SISMEC, a change of education routines might be perceived as some loss of teacher identity. Despite that, the survey findings showed that 61% of Italian academics of medical statistics declared to be favourable to provide online teaching of medical statistics and epidemiology in the future. However, this positive view should be interpreted with caution since distance education cannot substitute the unique value of teaching and knowledge exchange that could only be transmitted through a personal interaction between students and teachers (2, 3). These indications may be useful to improve the quality of the teaching process in the future.

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ATTI DEL
XI CONGRESSO NAZIONALE
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ed Epidemiologia Clinica

Giovedì 16 settembre 2021

AULA PARALLELA

METODI BIOSTATISTICI

COMPARISON OF PROPENSITY SCORE BASED METHODS FOR ESTIMATING MARGINAL HAZARD RATIOS WITH COMPOSITE UNWEIGHTED AND WEIGHTED ENDPOINTS: SIMULATION STUDY AND APPLICATION TO HEPATOCELLULAR CARCINOMA

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Introduction. Propensity score (PS) methods are increasingly being used in observational studies to delete or minimize bias due to confounding in estimating the treatment effect. Some PS methods allow to estimate marginal effects rather than conditional effects as usually produced by standard regression models. The advantage of a marginal effect relies on its causal interpretation. For instance, the Average Treatment Effect (ATE) describes the impact of treatment that could be observed in the counterfactual situation where the whole population is moved from untreated to treated.

A common approach to quantify the treatment effect in survival analyses is the ratio of the hazards between the treated and the untreated, often estimated using the Cox model. Simulation studies showed that, under common assumptions such as exchangeability and positivity, PS matching and Inverse Probability Weighting (IPW) are reliable methods to estimate marginal hazard ratios for single end-points [1]. When the endpoint of interest is composite, it can be of interest to assign a different weight to the single events depending on their clinical relevance. To this purpose, Ozga and Rauch recently proposed a weighted effect measure together with the corresponding non-parametric estimator called the "weighted all-cause hazard ratio" (WACHR) [2].

Aims. We used the estimator of Ozga and Rauch, in combination with PS-matching and IPW, to estimate the marginal hazard ratio for a weighted composite endpoint. The motivating example is taken form the HERCOLES study on hepatocellular carcinoma were the aim was to compare the impact of two surgical techniques (anatomic resection vs wedge resection) on the disease free survival, defined as time from surgery to the first of the following events: local hepatic recurrence (i.e. recurrence on the surgical cut of the liver), non-local hepatic recurrence and death without recurrence. It was of interest to assign a different relevance to each specific event (death being the worst event but also considering local recurrence more severe than non-local one). Moreover, we run simulation studies to evaluate the performance of PS matching and IPW in estimating the marginal hazard ratio with a composite weighted end-point.

Methods. Rauch et al. [3] introduced the idea of the weighted all-cause hazard as a weighted sum of the cause-specific hazards using fixed non-negative weights. The WACHR is then simply the ratio of the weighted all-cause hazards under the two treatments. Ozga et al. [2] propose to replace the cause-specific hazards by the cumulative cause-specific hazards, which can be estimated using the non-parametric Nelson-Aalen method. Of note, since the quantity of interest is the instantaneous cause-specific hazard, to ensure that the ratio between cumulative hazards and instantaneous hazards is the same, one must rely on the assumption of proportionality of the cause-specific hazards. Standard errors, and thus confidence intervals, for the WACHR have to be calculated based on resampling methods (e.g. bootstrap).

In our application, we first selected the possible confounders among the prognostic characteristics of the patient and the tumor that had a different distribution between the two treatment groups. Subsequently, using a logistic regression model, we calculated the PS (i.e. probability of being treated with anatomic resection) and then we obtained: i) a PS matched sample (by applying a nearest-neighbor matching algorithm based on PS); 2) an inverse probability weighted population (by building weights as inverse of PS). Finally, we applied the WACHR estimator of Ozga and Rauch on the PS matched and IPW weighted population to estimate the marginal treatment effect on the composite weighted end-point. The weights of each specific event were chosen, in accordance with the study clinicians, as follows: 1 for death, 0.8 for local recurrence and 0.5 for non-local one.

Results. A total of 1089 patients were enrolled, 34% (n=367) underwent wedge surgery and the remaining 66% (n=722) anatomic surgery. The patients alive and without any type of recurrence at the end of the follow-up (median 55 months) were 524 (48%); 91 (8%) developed a local recurrence; 408 (38%) had other types of recurrence and the remaining 66 (6%) died. Twelve confounders were selected: age, gender, presence of cirrhosis, Child-Pugh grade, HCV, histological grading, number of nodules, largest nodule size, INR, platelets, adjuvant therapy and ASA score. Three-hundred-thirty pairs were formed after PS matching. A good level of balance on the distribution of confounders was found both in PS matched sample and in the IP weighted sample (absolute standardized mean differences < 0.1). Observing the estimated marginal WACHR and its bootstrap confidence interval (figure 1), both using PS matching and IPW, there is no clear evidence that the type of surgical resection affects the weighted composite endpoint, although there is a trend indicating that wedge resection could increase the risk of unfavorable outcome.

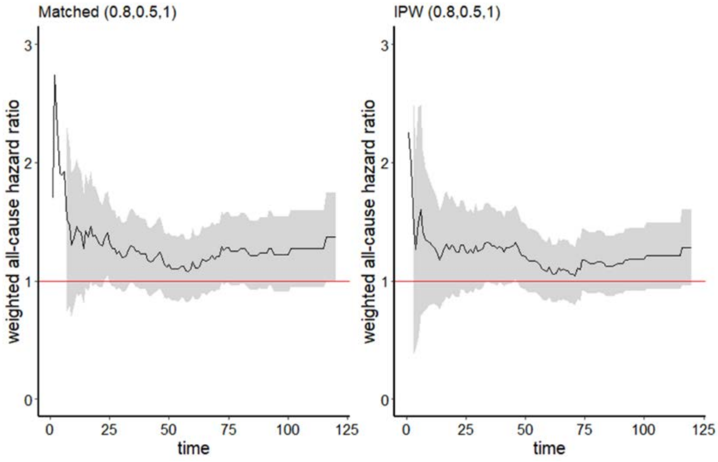

Figure 1. Non-parametric estimates over time of the marginal weighted all-cause hazard ratio (WACHR) after applying PS matching and IPW.

Conclusions. PS matching and IPW can be applied to estimate the marginal effect of treatment in terms of hazard ratio even when the endpoint of interest is composite and a different relevance is assigned to each specific event. Besides standard assumptions (i.e positivity, conditional exchangeability) the assumption of proportionality of each cause-specific hazard is needed. The choice of the weights to be assigned is a critical decision that should be taken in accordance with study clinicians.

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Modello SIRD tempo variante ed età dipendente per la simulazione di strategie vaccinali dinamiche

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Introduzione

Da dicembre 2019, un virus chiamato coronavirus 2 da sindrome respiratoria acuta grave, SARS-CoV-2, ha rapidamente colpito Wuhan, Cina, e nel marzo 2020 si era già diffuso in quasi 200 paesi [1]. L'OMS ha dichiarato lo stato di pandemia globale l'11 marzo 2020, in questo modo, il CoViD-19 è diventato rapidamente uno dei principali casi di studio non solo dal punto di vista clinico ma anche modellistico [2]. Da Marzo/Aprile 2020, la maggior parte degli stati del mondo si sono ritrovati in un gravoso stato di emergenza e sono state messe in rilievo tutte le problematiche di ciascun sistema sanitario. In questo contesto è scaturita la necessità di avere informazioni e strumenti di supporto alle decisioni che dessero delle risposte nel più breve tempo possibile.

Dal punto di vista matematico-statistico possiamo identificare due filoni principali di studio. Il primo è quello relativo allo sviluppo di modelli matematici per la previsione del trend della pandemia e per l'individuazione da modello degli asintomatici, il secondo invece si focalizza sull'utilizzo del modello in simulazione per comprendere meglio l'impatto dei lockdown e altre strategie di contenimento e successivamente dei piani vaccinali. I principali modelli sviluppati sono i modelli a compartimenti. In base al tipo di informazioni a disposizione sono stati implementati modelli dal più semplice SIR al più complesso SIDARTHE [3-8].

In questo periodo, inoltre, non sono state solamente messe in evidenza le difficoltà dal punto di vista sanitario, ma anche quelle organizzative e di raccolta e divulgazione delle informazioni. Per quanto riguarda la situazione italiana sono state rilevate delle forti discrepanze tra le due principali banche dati pubbliche, quella della Protezione Civile (PC) e quella dell'Istituto Superiore di Sanità Pubblica (ISS) [9,10]. In una ci sono informazioni giornaliere riguardanti morti, infetti e ricoverati nell'altra ci sono informazioni altrettanto utili, segmentate per esempio per fasce di età o sesso ma sono quasi settimanali. Oltre a questo, non sono da trascurare quei problemi riscontrati in quasi tutti i Paesi riguardanti la difficoltà di classificare i guariti, i ritardi nella comunicazione delle morti o dei risultati dei tamponi, errori nei sistemi diagnostici, ecc. [11]

Obiettivi

L'obiettivo è quello di creare delle simulazioni dinamiche per l'allocazione ottima dei vaccini a disposizione. Questa necessità si crea perché le simulazioni da modello sono fortemente dipendenti dalle condizioni iniziali e dalle dosi di vaccino disponibili.

Metodi

Sono stati utilizzati i dati giornalieri della PC dal 27 Dicembre 2020 al 26 Aprile 2021. Successivamente sono stati riproporzionati secondo le distribuzioni per età ottenute dai bollettini quasi settimanali dell'ISS [9,10]. Dall'ISS sono stati ottenuti anche i contratti dei vaccini stipulati con le case farmaceutiche e spettanti all'Italia [12]. I dati delle vaccinazioni, invece, sono stati resi pubblici dal Commissario straordinario per l'emergenza Covid-19 [13].

Con i dati a disposizione è stato stimato un modello SIRD (susceptible, infected, recovered, dead) suddiviso in 10 fasce di età ciascuna di 10 anni. I parametri sono tempo-varianti e aggiornati mediante tecniche di tracking [14].

Le ottimizzazioni utilizzate nelle simulazioni sono la minimizzazione dei morti e quella degli infetti. Le simulazioni sono state eseguite ogni 15 giorni a partire dal 27 Dicembre e hanno una durata di 60 giorni. Le dosi di vaccino giornaliere da somministrare sono state ottenute dai dati reali fino a quando la simulazione non eccede il 27 aprile, dai contratti stipulati con le aziende farmaceutiche altrimenti. Le simulazioni tengono conto dei quattro diversi vaccini a disposizione, delle dosi da somministrare per ciascun vaccino, dei giorni tra le dosi e dei cambi di efficacia.

Risultati

Dalla Figura 1 possiamo osservare la percentuale di soggetti già vaccinati per ciascuna classe di età all'inizio della simulazione (rettangolo nero). In rosa viene identificata l'allocazione dei vaccini secondo la funzione costo dei morti. Possiamo notare che indipendentemente dal valore di *Rt* questa funzione costo alloca i vaccini disponibili nelle classi di età più avanzate portandole a saturazione per poi gradualmente scendere. L'unica simulazione che dà un risultato differente è quella del 25 Febbraio. In questo caso non viene portata a saturazione la classe degli over 90 e viene allocata una percentuale maggiore di vaccini nelle due classi di età sottostanti (90% vs 60%). Questo è dovuto al fatto che in quella fase i nuovi morti negli over 90 erano nettamente in calo, mentre, le classi 70-79 e 80-89 erano costanti o in aumento.
La strategia degli infetti invece risulta essere un po' più instabile, in particolare, ad inizio piano vaccinale, quando le dosi erano in numero contenuto e l'*Rt* era maggiore di 1 (11 e 26 gennaio). In questo caso il modello dà la priorità agli over 90 e agli under 30. Successivamente con le simulazioni con *Rt*<1 il modello copre circa il 15% della classe over 90 e alloca le dosi a disposizione nelle classi dai 20 ai 60 anni.

Conclusioni

I modelli a compartimenti sono dei modelli non particolarmente complessi ma con una buona applicabilità. Attualmente sono molto utilizzati in simulazione per ottenere strategie ottime per i piani di vaccinazione. Il modello tempo-dipendente stratificato per età e utilizzato con simulazioni dinamiche dà una buona comprensione del fenomeno permettendo di tenere in considerazione i repentini cambiamenti della pandemia e delle quote vaccinali. Le due strategie portano ad esaurire la pandemia in tempi piuttosto simili, perciò una buona strategia vaccinale sarebbe potuta essere una strategia mista. Superato il mese di gennaio in cui i morti giornalieri erano in aumento avremmo potuto iniziare a vaccinare i giovani.

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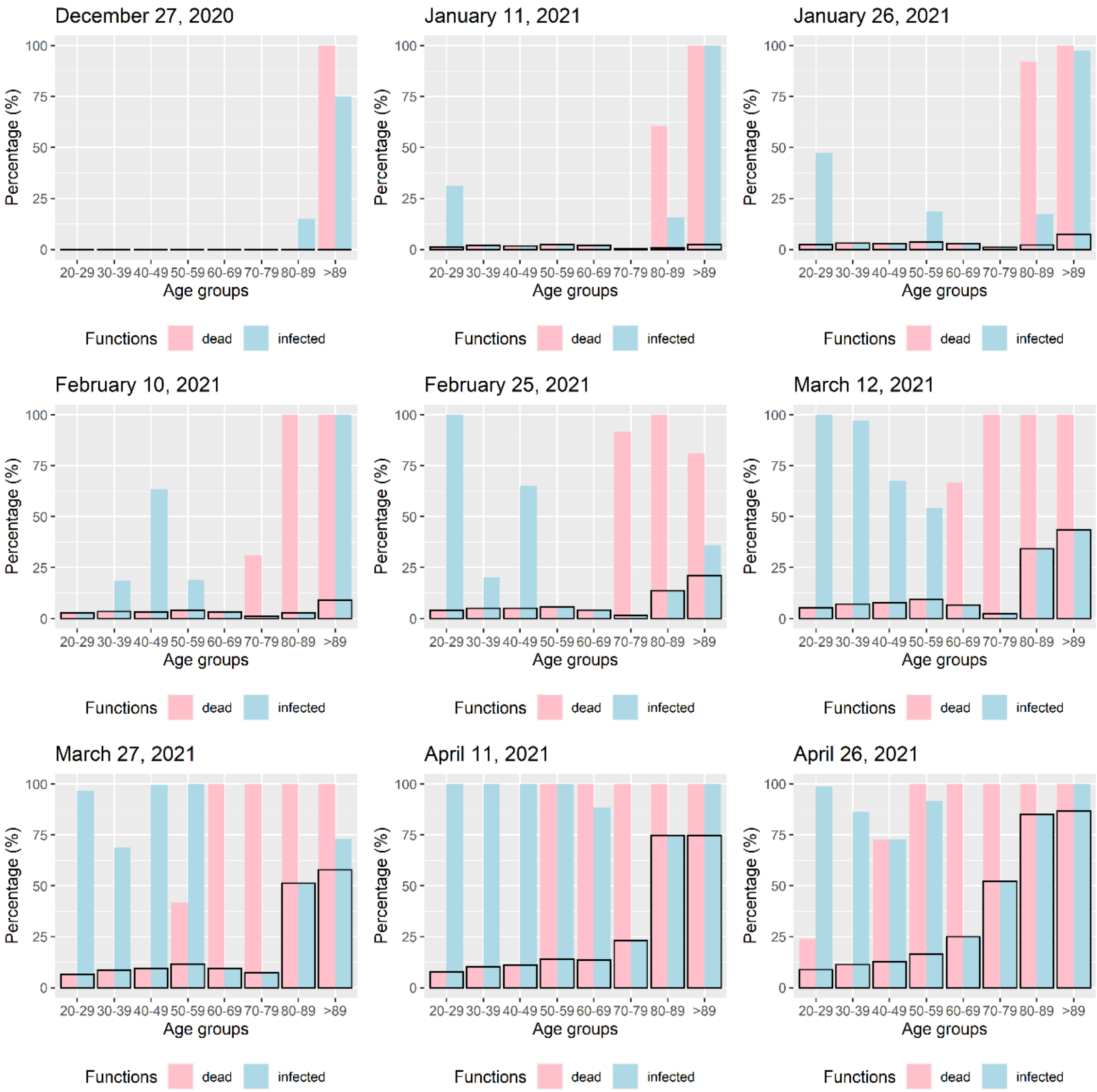

Figura 1. Percentuali dei soggetti da vaccinare secondo le funzioni costo dei morti e degli infetti.

Predicting hemodynamic failure development in PICU using Machine Learning Techniques

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Introduction: Primary or secondary hemodynamic failure (HF) diagnosis in children could be often associated with congenital or vascular malformations or cardiomyopathies, in lower prevalence with infective endocarditis, myocarditis, rheumatic fever, pneumonia, anthracycline toxicity, and renal disorders [1]. In the last year, an increased rate of HF and myocardial dysfunction requiring Pediatric Intensive Care Unit (PICU) admission seemed to be largely spared the SARS-CoV-2 inflammatory multisystem syndrome [2]. In rare cases, pediatric HF could arise during hospitalization, especially in critically ill patients with severe baseline conditions, leading to a further worsening of the patients' clinical status. Due to the rarity of the phenomenon, it is necessary to apply to large registries - that collect a vast amount of clinical information - statistical methods that can both manage a high number of variables considered and account for the significant imbalance between the groups as advanced machine learning techniques (MLTs).

In the adult population with HF, machine learning algorithms create risk scores estimating the likelihood of a heart failure diagnosis and the probability of outcomes such as all-cause mortality, cardiac death, and hospitalization [3–6]. MLTs are also increasingly used for hard outcome prediction in the clinical setting (e.g., in-hospital cardiac arrest) since they present several advantages over traditional methods and show promising performance and better power than the existing prediction systems [7,8]. However, to our best knowledge, no studies explore the issue of HF development in pediatric patients during the ICU length of stay.

Aims: To identify predictors of new-onset HF during PICU stay testing a set of MLTs, comparing their ability to predict the outcome of interest by considering the main imbalance management techniques.

Methods: PICU admission data were extracted from the Italian Network of Pediatric Intensive Care Units (TIPNet) Registry. We included patients admitted to 25 Italian PICUs in the period included between 01/01/2010 and 31/12/2020. Only patients aged less than 18 years and for whom congenital heart disease or cardiovascular insufficiency was not the reason for PICU admission were considered. The outcome was represented by the development of hemodynamic failure (HF) during the PICU stay. Predictive models for HF during the PICU stay have been developed using Generalized Linear Model (GLM), Recursive Partition Tree (RPART), Random Forest (RF), Neural Networks models, and Extreme Gradient Boosting (XGB). Since the outcome of interest is an infrequent event, a crucial numerical imbalance between the two groups was expected to be observed. Therefore, downsampling and upsampling techniques for imbalance control have been applied [9,10]. The missing values imputation has been performed by using a Multivariate Imputation by Chained Equations method (MICE). The models have been tuned within 100 bootstrap resampling iterations. A random search procedure has been considered to identify the tuning parameters. The model performances (ROC, Accuracy, F statistics, sensitivity, and specificity) have been computed within resamples and adjusted for over-optimism to internally validate the performance adjusting for overfitting [11].

Results: Among an overall sample of 29,494 subjects, only 399 developed HF during the PICU stay. The median age was about two years, and the male gender was the most prevalent. Comparing to the other sampling method, downsampling shows a better performance. After missing data imputation, Random Forest and XGB algorithms outperformed the other MLTs in predicting the development of HF during PICU stay (Figure 1). In particular, XGB presented a better ROC measure (median 0.780, IQR 0.770 - 0.793), and, looking at the values of sensitivity and specificity, it provided a better balance than the other techniques between these two measures. PIM 3 score and age, together with base excess, were found to be the strongest predictors of in-PICU HF development. Conversely, organ failure at admission, comorbidities and previous medical aids use, admission type, and the presence of very high-risk or high-risk diagnosis were found to provide only a small contribution in predicting the outcome.

Conclusions: Present findings suggest that MLTs may be a promising opportunity to predict HF development in pediatric patients during ICU stay by exploiting baseline information collected by a multicenter registry. However, further research is needed to improve their accuracy level and to better evaluate their usefulness in clinical practice.

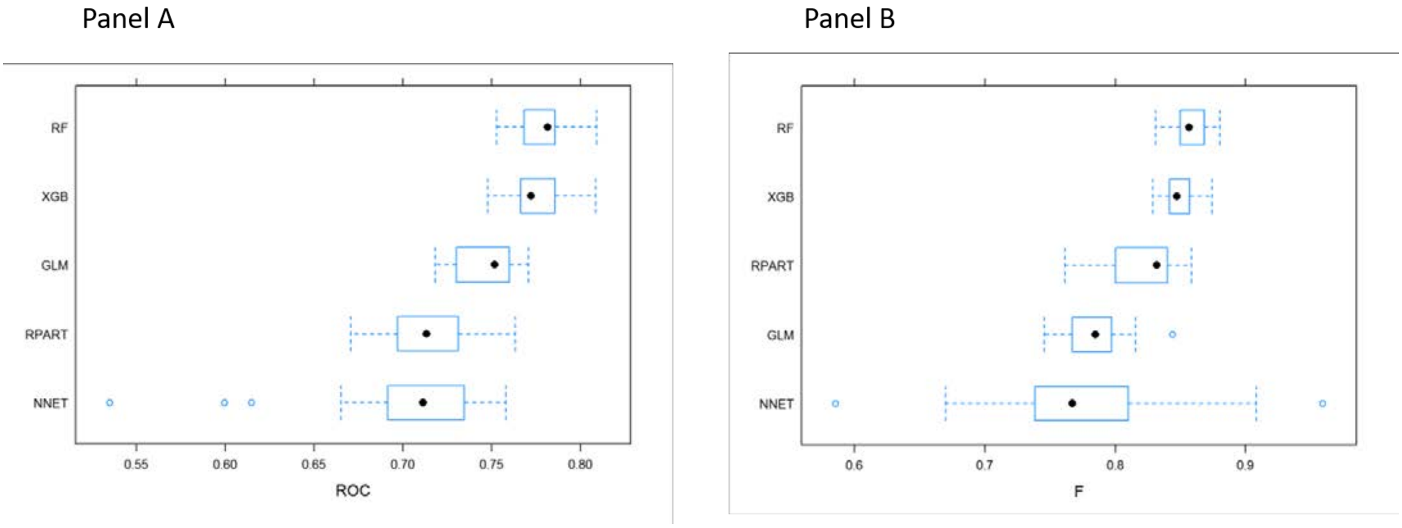

Figure 1. Comparison of the performance of the MLT algorithms: ROC (Panel A) and F-score measure (Panel B)

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LE TRAIETTORIE DI EDSS IN PAZIENTI CON DIFFERENTE ESORDIO DI SCLEROSI MULTIPLA

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Introduzione

I casi di sclerosi multipla (SM) ad esordio tardivo con comparsa della prima manifestazione clinica dopo i 50 anni (late onset multiple sclerosis LOMS), sono meno del 10%[1] e sono caratterizzati da un decorso più aggressivo e una severa disabilità, rispetto ai casi di SM ad esordio giovanile (esordio sotto i 40 anni young onset multiple sclerosis YOMS).Invece poco si conosce sul tipo di esordio (caratterizzato dal tipo di primo sintomo) e la prognosi [2] dei LOMS.

Obiettivi

L'obiettivo primario di questo progetto è quello di descrivere le traiettorie di disabilità dei pazienti con SM. L'obiettivo secondario è quello di valutare le caratteristiche associate ai gruppi con differente andamento di disabilità nel tempo.

Metodi

I dati utilizzati per le traiettorie provengono dal registro italiano di SM. La scala EDSS, che misura la disabilità delle persone con sclerosi multipla, è stata utilizzata per descrivere l'andamento delle traiettorie dei pazienti in venti visite. Sono stati esclusi i soggetti che nel registro avevano una sola visita e si è scelto per ciascun anno di utilizzare l'ultimo EDSS raccolto.

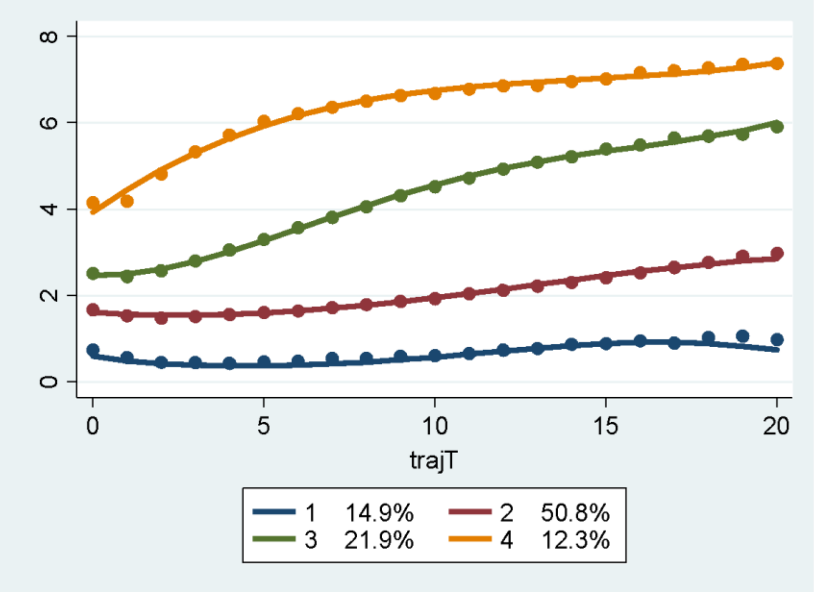
Le traiettorie sono state implementate utilizzando i modelli Group Based Trajectory Modeling (GBTM) [3, 4] che permettono di identificare dai dati gruppi latenti di soggetti che hanno un andamento simile dell'outcome nel corso del tempo utilizzando le relative probabilità di appartenenza. Successivamente i profili di ciascun gruppo sono stati descritti utilizzando un modello multinomiale attraverso i relativi RRR e intervalli di confidenza al 95%. Il livello di significatività statistica è stato posto al 5% e le analisi sono state effettuate con Stata ® 16.

Risultati

Dei 20826 pazienti presenti nel registro 16159 rispettavano i criteri d'inclusione ed esclusione.

Il miglior modello ha identificato 4 gruppi con differenti traiettorie di disabilità (Figura 1). Il gruppo con andamento di EDSS più severo, rappresentati dalla traiettoria in giallo, è composto dal 12.3% di soggetti con sclerosi che riportano un punteggio medio di EDSS superiore a 4 punti e che s'incrementa nel corso del tempo superando i 6 punti. La traiettoria in verde rappresenta il 21.9% del campione e mostra nel tempo un delta nel punteggio di EDSS di oltre 3 punti. Invece in rosso vi è la traiettoria del gruppo più corposo (50.9%) che riporta un andamento di EDSS costante fino a 10 visite ma che tende ad incrementarsi nell'ultimo periodo. Infine il gruppo con traiettoria blu è formato dal 14.9% dei pazienti che hanno un punteggio di EDSS costante nel tempo e meno severo che s'attesta, in media, intorno ad un punto.

Figura 1 Le traiettorie dei pazienti con sclerosi multipla: in blu il gruppo 1 con andamento di EDSS più basso, in rosso il gruppo 2 con andamento medio-basso, in verde e in giallo rispettivamente il gruppo 3 e 4 con andamento della disabilità più alti.



Per quel che concerne i fattori associati ai 4 gruppi con differenti traiettorie, il modello multinomiale mostra che la probabilità di appartenere a gruppi con severità più alta (in rosso o verde o giallo traiettoria che "peggiora") è superiore per i LOMS rispettivamente di 1.7, 4.1 e quasi 7.0 volte (p<0.001). Per quanto concerne il genere, la probabilità di appartenere a gruppi con severità più alta (traiettorie verde e gialla) si riduce se si è una paziente di sclerosi rispettivamente del 16% e del 19% (entrambi p=0.002). Mentre per il primo sintomo all'esordio della malattia si nota che: per i pazienti con sintomi al tronco encefalico la probabilità di appartenere a gruppi con traiettoria più severa di EDSS aumenta rispettivamente di 1.24, 1.45 e 1.86 volte (rispettivamente p=0.006, p<0.001, p<0.001). Nei pazienti con sintomi spinali, la probabilità di appartenere a gruppi con traiettoria più severa di EDSS aumenta rispettivamente di 1.19, 1.25 e 2 volte (rispettivamente p=0.038, p=0.011, p<0.001). I pazienti con sintomi sopratentoriali la probabilità di appartenere a gruppi con traiettoria più severa di EDSS aumenta di 1.3, 2.03 e quasi 2.5 volte (rispettivamente p=0.001, p<0.001, p<0.001), mentre per i pazienti con sintomi ottici non vi è differenza, in termini di probabilità, di appartenere a traiettorie con andamento di EDSS più severo (p>0.05).

Conclusioni

4 gruppi con differenti traiettorie di disabilità accumulate sono stati identificati nel registro di pazienti con sclerosi multipla. Due gruppi hanno un andamento costante nel tempo e con punteggi medi massimi di EDSS intorno a 2 mentre gli altri due gruppi hanno andamenti che partono dai due o quattro punti e che raggiungono i 5 e 7 punti di EDSS nel corso del tempo. Per quel che concerne

i sintomi d'esordio dei differenti pazienti si nota un'eterogeneità escludendo il sintomo ottico trasversale ai quattro gruppi.

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A MIXED-WAVELET DYNAMIC SURVIVAL MODEL TO CHARACTERIZE DYSKALEMIA IN CHRONIC HEART FAILURE

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Introduction

Heart failure is a consequence of many cardiovascular diseases and, despite improvements in treatments, mortality and hospitalization rates remain high. Potassium has been found to be an important biomarker to monitor since Heart Failure itself together with the pharmacological treatment and comorbidities are likely to cause potassium alterations. Dyskalemia is defined as disorders of potassium but it remains poorly characterized in heart failure patients. In general, both low levels (hypokalemia) and high levels (hyperkalemia) of potassium can lead to life-threatening conditions. Clinical guidelines set the normal range of serum potassium between 3.5–5.0 mmol/L in the general population. However, recent studies have raised serious concerns about its validity in heart failure[1], [2]. In addition, dyskalemia in clinical practice is defined without taking into account that potassium measurements are subject to measurement errors. It also does not exploit the dynamic nature of the biomarker and a patient can be considered dyskalemic on the basis of only one measurement. Clinical implications of correctly identifying dyskalemia have important consequences for patients since it often leads the medical doctor to decide to suspend life-saving therapy.

Aims

The aim of this work is to provide a method to obtain an alternative characterization of dyskalemia specific for the heart failure population. This characterization is obtained through a dynamic survival model based on a time-dependent representation of potassium.

Methods

Data comes from a cohort observational, non-interventional study on subjects living in Trieste area who had a cardiological evaluation from November 1, 2009 until December 31, 2017 included in the E-Chart in the Cardiovascular Observatory of Trieste[4]. The cohort was followed from the index date, defined as date of first ambulatory visit with a potassium measure available, until the time of death or the end of the follow-up (administrative study closure date, fixed at 31 December 2018).

We propose a novel a 2-stage approach that enables to study the association between potassium and survival. The representation of the individual potassium trajectories considered accommodates (1) a long term trend, (2) short-term oscillations and (3) measurement error. The long-term trend was modelled with Linear Mixed Effects Model. Short-term oscillations were estimated using a band-pass filter based on Morlet wavelet transform[5], [6]. This was applied to the "residual" individual trajectory obtained after removing the estimated long- term trend from the observed one. This approach allows us to separate the error term, representing measurement errors, from changes in the trajectory happening at each time *t* and started from 2 to 365 days before. Moreover, since wavelets filters have an additive structure with respect to the period, we can separate oscillation of potassium happening very suddenly (e.g. few days) from the ones happening over periods of weeks or even months. To study the association between potassium and the risk of death a dynamic proportional hazard model was specified. It contained fixed covariates regarding clinical characteristics of the subject and the following time-dependent covariates regarding potassium:

a. A continuous covariate representing the individual trajectory estimated daily which combines the long term and short term oscillations
b. Categorical variables indicating the presence of short-term oscillations with different durations

Results

3777 patients with a diagnosis of Heart Failure and a cardiovascular visit in the period 01/01/2009 – 31/12/2017 were considered in the study. The median age in the cohort is 77 (IQR: 70-82) and 58% of them are males. 46% of subjects has a reduced left-ventricular ejection fraction and 47% present ischemic heart disease. Furthermore, 48% of the subjects suffers from more than 3 non-cardiac comorbidities. At the index measurement the median potassium value is 4.34 (IQR: 4.02-4.7) mmol/L and the proportion of patients outside the normality cut-off are 10.5% and 4% for the upper and lower limit respectively. During the follow-up, 56% of patients go beyond the limit of 5 mmol/L whereas 50% go below 3.5 mmol/L at least once. If we consider two consequent measurements at a minimum distance of 6 days and a maximum of 2 months, we find 645 (17%) patients that have persistently potassium greater than 5 mmol/L whereas 216 (5.7%) have persistently potassium smaller than 3.5 mmol/L. The number of deaths observed in the cohort is 1696 (45%) and the median survival time is 6 years. The adjusted hazard ratio with respect to an estimated potassium value of 4.15 mmoL is reported in Figure 1.

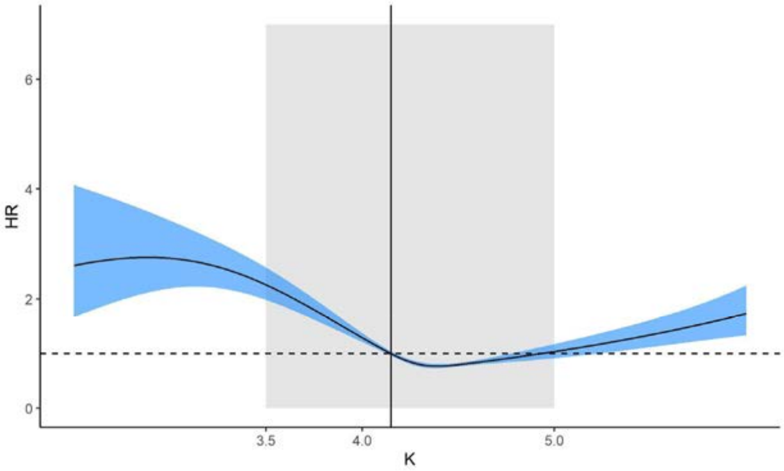

Figure 1 Adjusted Hazard Ratio of mortality for the dynamic estimated potassium level. The vertical line corresponds to the reference value of 4.15 mmoL. The grey area represents the normal range currently employed in the clinical practice. 95%CI is reported in blue.

It can be observed how potassium has a non-linear effect on the hazard of death and that lower values of potassium rapidly increase the risk. The HR is significantly above 1 also for values greater than 6 mmoL. Therefore, these results are not in favor of the current cut-offs used in the literature. Moreover, from the model it emerged an independent negative prognostic role of very sudden oscillations in potassium values happening within 2-14 days (HR Upward: 1.48 ,95%CI: 1.13-1.49; HR Downward: 1.53, 95%CI: 1.27- 1.85). Furthermore, the model improves the AIC with respect to the model which includes the long-term trend only.

Conclusion

In chronic disease such as heart failure, patients are followed for long period of times. In these settings standard methods to study the association between biomarkers and survival capture the long-term trend while discarding as errors changes happening over few months or days. Since potassium can have very sudden changes, in order to better characterize dyskalemia and to exploit the dynamic nature of potassium, we developed a 2-stage approach that enables to study the association between potassium and survival.

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DOES OUTGOING JOB MOBILITY INFLUENCE WORKERS MENTAL HEALTH? A PROPENSITY SCORE APPROACH

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Introduction

People suffering from depression or anxiety amount to about 264 million worldwide, and the cost of loss in productivity to the world health system is equal to US$ 1 trillion each year [1]. Mental health is strictly connected with work as well as work mobility. The impact on health of work mobility, meant as outgoing job mobility (change of employer), is controversial. In fact, it is well known that changing jobs is the main method to get career advancement and a salary increase [2], and that it is mostly associated with an increase in job satisfaction and reduction of strain after job change [3, 4]. However, there is some evidence that a series of changes among unrelated jobs is associated to high mortality risk [5], that change in employment is a significant risk factor for cardiovascular diseases [6] and that frequent job mobility is associated with mental health and psychiatric problems [7, 8]. This study aimed to assess whether job mobility has an impact on mental health, measured as the intake of neuropsychological drugs. To this aim, a cohort of Belgian employees built-up from the medical registers of the IDEWE data warehouse was followed-up for twenty-seven years. In order to accurately estimate the effect of job mobility on the onset of neuropsychological diseases, a propensity score matching with time-dependent covariates was applied. Specifically, the propensity score approach was used to eliminate systematic differences in subjects' characteristics and avoid bias, and balance the distribution of the covariates at every time point.

Methods

We performed a retrospective longitudinal cohort study on Belgian workers. The data were drawn from the largest central repository of data on Belgian employees, the IDEWE data warehouse. IDEWE is a Belgian External Service for Prevention and Protection at Work. It contains data from the annual health check of Belgian workers executed by occupational nurses and physicians that recorded and encoded these data in an electronic format using international or national classification standard [9]. The analysed dataset includes data on 11,246 employees with measurements collected between 1993 and 2019 and 12 variables related to demographic (age, sex), physical and behavioural (obesity, smoking habits, sport), occupational (job mobility) and work-related risks. The neuropsychological treatment (response variable) was a binary variable with the "No" category indicating that a subject in a particular year did not take any medication for neuropsychological diseases, "Yes" otherwise. Job mobility was a binary variable coded equally to "No" if the employee was still at the original employment or "Yes" if she/he left the organisation. Among the work-related risks, there were considered the following binary variables: shift-work, noise, manual tasks, stress, physical load. Categorical variables were summarised through counts and percentages, while quantitative variables were dichotomised, assuming the median as a cut-off value.

In order to reduce selection bias and confounding effects, a Propensity Score approach was used to match each subject with experience of outgoing job mobility with at least one other subject with similar characteristics at that time point, without this experience. The Cox proportional hazard model with time-varying covariates was used to estimate the PS, with job mobility (treatment) as response and all the explanatory variables described above included as covariates. Optimal bipartite matching was used to match patients sequentially, and cases were matched with controls with the ratio of 1:3 using the hazard of being treated at a certain time point for each subject [10]. Covariates were considered balanced if the absolute Standardised Mean Differences (SMD) was ≤ 0.1 [11]. After that, Cox proportional hazard model with time-varying covariates was used to estimate the effect of job mobility on neuropsychological treatment. Hazard ratios (HR) were computed together with 95% confidence intervals. Data were analysed using the R software (version 4.0.2), and a p-value < 0.05 was chosen as the statistical significance cut-off.

Results

The unmatched sample included 11246 subjects, where 922 (8.2%) workers experienced outgoing job mobility during the follow-up, while at the baseline they were 368 (3.3%) (Table 1). In the matched sample, we reached a balance with SMD<0.01 for all the covariates. Table 1 showed the distribution of the covariates in the unmatched and matched sample. Subjects in the matched sample were mainly male, were less than 38 years old, did not smoke, were physically active, and normal weighted. Furthermore, these workers were not exposed to shift-work, noise, manual tasks, stress, and physical load.

		Unmatched No Job change n=10878	Unmatched Job change n=368	Matched No Job change n=2319	Matched Job change n=773	Unmatched SMD	Matched SMD
Age (%)	0	5084 (46.7)	279 (75.8)	1628 (70.2)	544 (70.4)	0.625	0.004
	1	5794 (53.3)	89 (24.2)	691 (29.8)	229 (29.6)		
Sex (%)	Female	4664 (42.9)	167 (45.4)	915 (39.5)	307 (39.7)	0.050	0.005
	Male	6214 (57.1)	201 (54.6)	1404 (60.5)	466 (60.3)		
Smoker (%)	No smoker	7862 (72.3)	269 (73.1)	1726 (74.4)	564 (73.0)	0.018	0.033
	smoker	3016 (27.7)	99 (26.9)	593 (25.6)	209 (27.0)		
Obesity (%)	0	9012 (82.8)	320 (87.0)	1903 (82.1)	630 (81.5)	0.115	0.015
	1	1866 (17.2)	48 (13.0)	416 (17.9)	143 (18.5)		
Sporter (%)	No sporter	3497 (32.1)	119 (32.3)	692 (29.8)	253 (32.7)	0.004	0.062
	sporter	7381 (67.9)	249 (67.7)	1627 (70.2)	520 (67.3)		
Shift-work (%)	0	9062 (83.3)	309 (84.0)	1856 (80.0)	646 (83.6)	0.018	0.092
	1	1816 (16.7)	59 (16.0)	463 (20.0)	127 (16.4)		
Noise (%)	0	6922 (63.6)	250 (67.9)	1361 (58.7)	491 (63.5)	0.091	0.099
	1	3956 (36.4)	118 (32.1)	958 (41.3)	282 (36.5)		
Manual tasks (%)	0	2910 (26.8)	75 (20.4)	538 (23.2)	189 (24.5)	0.151	0.029
	1	7968 (73.2)	293 (79.6)	1781 (76.8)	584 (75.5)		
Stress (%)	0	10857 (99.8)	368 (100.0)	2267 (97.8)	763 (98.7)	0.062	0.072
	1	21 (0.2)	0 (0.0)	52 (2.2)	10 (1.3)		
Physical load (%)	0	10254 (94.3)	342 (92.9)	2030 (87.5)	680 (88.0)	0.054	0.013
	1	624 (5.7)	26 (7.1)	289 (12.5)	93 (12.0)		

Table 1 – Covariates comparison between unmatched and matched sample, stratified by job mobility

Before the propensity score matching, outgoing job mobility was an important risk factor for neuropsychological medication (HR= 1.330, 95%CI=(1.135 - 1.559), P-value<0.001). Also after propensity score matching, the Cox proportional hazard model showed a similar result for job mobility with a slightly higher hazard ratio (HR= 2.065, 95%CI=(1.397, 3.052), P-value <0.001).

Conclusions

Our study found that workers with experience of outgoing job mobility have a statistically significant higher risk of neuropsychological treatment. The estimated risk from the unmatched sample was confirmed and strengthened after the covariates' adjustment based on the PS.

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DEVELOPING AN ALGORITHM FOR THE EARLY DETECTION OF COVID-19 OUTBREAKS USING DATA FROM ADMINISTRATIVE HEALTHCARE DATABASES: THE ALERT COV PROJECT

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Introduction. During the global emergency caused by the SARS-CoV-2 pandemic, health authorities have repeatedly stressed the need for an effective outbreak tracking system. Large-scale testing programs are indispensable for monitoring the spread of the infection. However, it is difficult to monitor the entire population extensively and quickly relying only on conventional tools, such as swabs, due to logistical and organizational reasons. This can lead to a delay in the identification of COVID-19 outbreaks.

Objectives. This abstract presents the methodology underlying Alert CoV, an ongoing project supported by the Italian National Institute of Statistics (ISTAT) and the Italian National Institute of Health (ISS) and involving universities and both administrative and scientific institutions. The project intends to evaluate the possibility of early detecting COVID-19 outbreaks with high territorial detail monitoring the temporal trend in the use of particular services provided by the National Health System (NHS). This type of information is automatically collected in administrative healthcare databases, which could therefore be used to monitor the entire population almost in real time.

Methods. The inhabitants of five Italian regions (Marche, Abruzzo, Campania, Apulia and Sicily) and two Local Health Units of the Lombardy region (Bergamo and Val Padana) were identified and geo-referenced based on their residential address. In this way, it was possible to classify the citizens into groups representing the census units to which they belong. We have identified a set of services provided by the NHS that, based on clinical hypotheses, could be useful in monitoring pathogens that may spread via airborne transmission (including the SARS-CoV-2). In the preliminary phase of the project, we considered (i) prescriptions of paracetamol, (ii) antibacterials for systemic use, (iii) anti-inflammatory and antirheumatic products, (iv) corticosteroids for systemic use, (v) chest X-rays performed on an outpatient basis and (vi) access to the emergency room (for any cause). Using information retrieved from the administrative databases, we calculated the number of times these six services were used within each census unit on a weekly basis from 2014 to 2020. Therefore, six count time series have been identified for each census unit. The aim is to monitor the trend in the use of the selected services during 2020, and generate a warning signal whenever an unusual peak is identified in a certain territorial unit, considering previous years as a period of historical comparison. During the preliminary phase of the project, this procedure is carried out considering each of the six predictors separately. To generate the warning signals, we are using in parallel three epidemiological surveillance algorithms that allow taking into account the temporal trend and the annual seasonality of the time series. Two model consist in different versions of the algorithm originally proposed by Farrington et al. [1, 2], while the third model is the GLR based monitoring scheme described by Höhle and Paul [3]. Farrington's algorithms are very well suited to identify sharp peaks of the counting variable along the time series, while the latter also allows the detection of slight but sustained increases

over time. For each week of 2020 and for each census unit, we also collected data on the number of people who tested positive for SARS-CoV-2 infection following the swab. In this way, it is possible to validate the signals generated by the algorithms, comparing the presence of the latter with the number of positive cases officially detected during the following weeks in the census unit under examination.

Results. The project is still ongoing and only preliminary, but encouraging, results have been obtained. The models have interesting predictive performances with respect to some of the predictors considered, especially with regard to the period of the first epidemic wave.

Conclusion. Administrative health databases could be a valuable support tool for the timely monitoring of the COVID-19 pandemic. Furthermore, outbreak detection algorithms using non-specific predictors should be considered in the future in the event of the spread of new infectious diseases.

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STATISTICAL GENOMIC APPROACHES TO EVALUATE SEX-BASED DIMORPHISM OF ANTICANCER IMMUNE RESPONSE AND MOLECULAR MECHANISMS OF IMMUNE EVASION

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Introduction

Sex is an important factor in the pathogenesis and prognosis of many diseases and can modulate pharmacokinetics, pharmacodynamics, and toxicities of drugs. It also affects immune response as a reflection of interactions between genes, hormones, the environment, and microbiome composition. [1–3]
Despite this, gender-specific medicine appears as a neglected dimension: in clinical studies women are under-represented and sex-based differences in the presentation, treatment, progression, and adverse events of diseases are rarely analyzed and reported [4].
In 2018, we found that, considering patients affected by several types of advanced cancers and treated with immune checkpoint inhibitors as monotherapy, males derive larger effect on overall survival (OS) then females do [5]. In 2019, we reported that women with advanced lung cancer derive larger benefit than men from the combination of chemotherapy (CT) to an anti-PD-1/PD-L1. We found an interaction between patients' sex and the efficacy in OS of two therapeutic strategies (anti-PD-1/PD-L1 alone or in combination with CT compared to standard CT) with opposite direction of the effect in men and women: men derive larger benefit than women with an anti-PD-1 treatment alone, while women have better survival with anti-PD-1/PD-L1 plus CT [6].
We explored differences in molecular mechanisms that drive anticancer immune response as well as in immune evasion mechanisms exploited by non-small cell lung cancers (NSCLCs) arising in men and women [7] using gene-expression data of 2,575 early-stage NSCLCs from 7 public datasets.

Aims

The aim of the present study was to present the statistical genomic approach used to analyze the sex-based dimorphism of the response to lung cancer immunotherapy, under the hypothesis that the heterogeneity of response to different immunotherapeutic strategies might be due to differences in the molecular mechanisms that drive anticancer immune response in men and women.

Methods

We focused on the 7 largest datasets on adenocarcinoma and squamous cell carcinoma publicly available in the Lung Cancer Explorer (LCE) project.
Gene-expression data were analyzed using different tools:

1. the validated xCell algorithm [8] was applied to estimate the abundance of 64 cell types in the tumor microenvironment (TME); for each single dataset, mean values of enrichment score (ES) for each cell were calculated in tumors of men and women and then compared.
2. a curated list of 78 genes with a key role in anticancer immune response was derived from Thorsson et al. [9], and the expression levels of each gene were compared between tumors of male and female.
3. the validated Tumor Immune Dysfunction and Exclusion (TIDE) tool [10] was applied to quantify the activation status of two major mechanisms of immune-evasion exploited by tumors: the T-cell dysfunction and the T-cell exclusion mechanisms; both scores were compared between tumors of male and female.

All comparisons were performed using linear regression models adjusted for patient age, stage at diagnosis, tumor-histotype and smoking status. Meta-analyses of the adjusted sex-related differences obtained in each single dataset were performed using random-effects models and the false discovery rate (FDR) was used to correct for multiple comparisons.

Moreover, the Gene Set Enrichment Analysis (GSEA) was applied to gene-expression data. The GSEA evaluates gene-expression data at the level of gene set and determines whether the gene set(s) analyzed is(are) correlated with the phenotypic class of interest (e.g., normal samples vs tumor samples, females vs males, etc.) [11].

We modified the original methodology calculating first sex-related differences for each individual gene in each dataset and then applying a random-effects model to estimate the overall strength of the association between each gene and sex. The GSEA method using the C5 collection of the MsigDB was then applied on the meta-analytic T-test statistics. Gene labels were permuted to estimate the FDR-corrected statistical significance of the normalized ES. [7]

All the analyses (including the meta-analytical extension of the GSEA) were implemented and performed using the SAS software v. 9.4 (SAS Institute, Cary, NC).

Results

We analyzed 1528 (59.3%) tumor samples from men and 1047 (40.7%) from women. The TME of females was characterized by significantly greater T-cell dysfunction status, higher expression of inhibitory immune-checkpoint molecules and higher abundance of immune-suppressive cells, including dendritic cells, macrophages, NKT, CD4+, B-cells, CAF and Tregs. By contrast, the TME of males was significantly enriched for a T-cells excluded phenotype. 5917 gene sets were analyzed with the GSEA, 251 of which were related to anticancer immune response. Among the top 1% gene sets significantly enriched in the TME of women there were 39 directly related to anticancer immune response, while none of the top 1% gene sets significantly enriched in tumors arising in men as compared with women were directly related to anticancer immune responses. [7]

Conclusions

We showed that, on average, women mount stronger and more structured immune-response against NSCLC compared to men, proved also by the results of the GSEA which highlighted that most of the molecular pathways and biological processes significantly enriched in the TME of women are directly related to the anticancer immune response.

Our data provided a proof of the importance of the features of the host immune system in shaping the immune response against cancer and support the need to test different therapeutic strategies in male and female populations to further improve the use of immunotherapy. For example, accrual and design of trials of immunotherapy might best be performed separately for men and women, with proper sample size planning for both.

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STATISTICAL METHODS FOR ESTIMATION OF THE ASSOCIATION BETWEEN MULTIPLE ENVIRONMENTAL EXPOSURES AND LUNG FUNCTION IN THE ROCAV STUDY

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Introduction

Attention to the impact of long-term exposure to airborne pollutants on respiratory function is increasing worldwide. Most of the evidence in literature on this association so far come from single-pollutant linear regression models [1], also due to the elevated degree of correlation between pollutants. However, these do not properly take into account mixture exposure, and neither allow investigating non-linear relationships nor possible interaction effects between pollutants. The Bayesian kernel Machine regression (BKMR) [2] is a novel statistical method that models the outcome as a flexible kernel function of the exposures variables, which allows to study the joint effect of multiple pollutants identifying interactions and non-linear effects in a high correlated scenario. In this study we applied linear regression and BKMR to evaluate the effect of a pollutant mixture on lung function.

Aim

The objective of this study was to assess the relationship between long-term ambient air pollution and lung function in a healthy adult population in the city of Varese, using two statistical approaches: linear regression model and BKMR.

Materials and methods

Study population. We used data from the ROCAV (Risk of Cardiovascular diseases and abdominal aortic Aneurysm in Varese) cohort study. In the ROCAV study, 3777 participants aged between 50 and 75, residents in the city of Varese, were recruited between June 2013 and May 2016. Each participant completed a questionnaire survey with socio-demographic and lifestyle information, and anthropometric parameters at time of enrollment were collected. The full study protocol and collected data have been described previously [3]. In the present study we considered never-smoker participants without respiratory condition (asthma, chronic bronchitis, COPD) at recruitment who completed a valid and reliable spirometry test (N=1499, 56% male, mean±sd age: 66±7 years).

Lung function. Spirometry was used to assess the lung function in ROCAV participants. For the analysis the highest value of forced vital capacity (FVC) and forced expiratory volume 1s (FEV_1) were used. Predicted values based on age, sex, height and ethnicity were computed for FVC and FEV_1 according to the Global Lung Function Initiative (GLI) 2012 using the R spiro macro [4]. The difference between the observed and predicted value of FVC (ΔFVC) and FEV_1 (ΔFEV_1) was used as dependent variable in the analyses. A negative value indicates an accelerated lung function decline as compared to the physiological trend due to age.

Environmental exposure. The annual average exposures to airborne pollutants concentrations over a domain 40 km wide at a spatial resolution of 1 km was modelled using FARM (Flexible Air quality Regional Model) [5]. The input data, including the regional emission inventory, 3D hourly meteorological and chemical boundary conditions, were referred to 2018. The considered exposures (particulate matter (PM_{10}, from 0.1 to 10 µm and $PM_{2.5}$ from 0.1 to 2.5 µm), Nitrogen dioxide (NO_2), Sulfur Dioxide (SO_2), Benzene (C_6H_6) and Ozone (O_3)) were linked to geocoded residential addresses of ROCAV participants.

Statistical analysis.

The association between a single environmental exposure and ΔFEV_1 and ΔFVC was studied by multiple linear regression. Furthermore, we applied the BKMR to model the effect of the pollutant mixture analyzing potentially non-linear and interaction effects in presence of high correlation between exposures. Single $PM_{2.5}$, PM_{10} and NO_2 jointly with SO_2, C_6H_6 and O_3 were considered as mixtures. The average posterior inclusion probabilities (PIPs), which provide measures of variable importance for each exposure, were provided for BKMR together with graphic summaries of the contribution of the individual exposures to the outcome and their interaction. Age, sex, height and educational level were considered as confounding factors in all analysis.

Results

Analyzing the individual pollutants using single-pollutant linear regression models, a 10µg/m^3 increase in $PM_{2.5}$, PM_{10} and NO_2 exposure showed a negative association with ΔFEV_1 (from -12.2mL to -21.8mL, [95% confidence interval (CI) from -172.3; 131.7]) and ΔFVC (from -30.7mL and -65.9mL, [CI: from -253.4; 121.7]). Average pollutants' levels (PM10: 14µg/m^3; PM2.5: 12.5µg/m^3; NO2: 20µg/m^3) were below the law limits; in addition, high correlation was observed between all pollutants ($r>0.9$). When considering the joint effect of the mixture, BKMR identified possible nonlinear relationship between PM_{10} and ΔFEV_1 and between NO_2 and ΔFVC, with higher difference at moderate to high PM_{10} and NO_2 levels. All pollutants' PIPs were in the range 40-65%. No evidence of interactions between pollutants were evident in all the models.

Discussion

Although the results are not significant, the estimates of the linear model align with those reported in the literature, highlighting a possible negative association between pollutants and lung functions. Furthermore, BKMR allowed to identify nonlinear relationships between exposure and outcome and to study possible interactions between pollutants. Results showed that no pollutant overcome the others in terms of effect, but rather all contribute to the relationship with the outcome. Limitations behind these results include: 1) the exposure measured on a too high-granularity grid and 2) data available only for the city of Varese, lead to a distribution of pollutants too homogeneous among participants; moreover, 3) the high correlation among pollutants could limit the performances of all models. Future work must extend the geographical area of analysis and estimate the exposures on a more detailed grid, also considering analysis strategies including different statistical approaches, in order to get a more detailed picture and understanding of the studied problem.

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CLASSIFICAZIONE DEI SEGNALI ECG ATTRAVERSO LA FUZZY CLUSTERING FUNZIONALE

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Introduzione

Negli ultimi anni, l'analisi dei dati funzionali (Functional Data Analysis - FDA) ha attirato l'attenzione di molti ricercatori sia in ambito metodologico che applicativo [1,2,3,4,5]. L'idea di base dell'FDA è di trattare il dato funzionale come un'unica entità. Questa tecnica statistica è particolarmente utile quando il dato disponibile è una serie storica ad alta dimensionalità. In ogni caso, l'FDA può essere estesa anche a dati che non presentano quest'ultima caratteristica; infatti può essere utilizzata con un obiettivo diverso dalla semplice riduzione dimensionale, ad esempio per sfruttare le informazioni aggiuntive rese disponibili da alcuni strumenti funzionali come le derivate, l'area sotto la curva, la curvatura e diversi tipi di distanza tra le unità statistiche basate sulle metriche e semi-metriche che sono state proposte in letteratura per valutare la dissimilarità nel contesto funzionale. Sebbene il dominio delle funzioni generalmente sia il tempo, l'FDA si può applicare anche se il parametro di riferimento è diverso dal tempo.

Obiettivi

In campo medico, vi sono numerosi casi in cui i dati disponibili sono, per natura, funzione del tempo, come ad esempio l'elettrocardiogramma (ECG). Questo tipo di segnale che registra l'attività del cuore per il monitoraggio di svariate patologie legate al malfunzionamento dello stesso, ben si presta ad essere analizzato utilizzando l'FDA.

Un metodo statistico molto utilizzato per analizzare l'ECG è quello della classificazione, sia supervisionata che non supervisionata. In questa ricerca ci concentriamo sulla classificazione non supervisionata ovvero il clustering con l'obiettivo di identificare gruppi di pazienti con caratteristiche omogenee.

Metodi

In questa ricerca proponiamo un approccio originale alla classificazione dei pazienti introducendo il concetto di fuzzy clustering funzionale. L'idea di base è quella di proporre una classificazione dei segnali seguendo l'approccio FDA ma in modo tale che il risultato finale della classificazione sia "sfumato". In particolare, proponiamo l'uso congiunto del functional k-means e del fuzzy clustering classico basandoci sulla semi-metrica delle componenti principali funzionali come misura di similarità tra le unità statistiche nonché come metodo di riduzione dimensionale.

Il functional fuzzy k-means (FFKM) può essere riassunto come segue:

1. *Dato* $Y_{N\times T} = \left[y_{ij}\right]$ *: un dataset le cui righe rappresentano le unità statistiche* $(i = 1,2,\dots,N)$ *e le colonne il dominio del tempo* $(j = 1,2,\dots,T)$*, Seguendo il classico approccio FDA, convertire i valori osservati* $y_{i1}, y_{i2}, \dots, y_{iT}$ *per ogni unità ad una forma funzionale adatta [1].*

2. *Eseguire l'analisi funzionale in componenti principali (FPCA) e selezionare un certo numero K di componenti principali funzionali che spieghino una parte soddisfacente della variabilità delle funzioni originali, cioè all'incirca il 70-80% [2,3,4].*
3. *Una volta ottenuta la matrice* $V_{N\times K} = [v_{ik}]$*, dove* v_{ik} *è lo score della generica componente principale funzionale per la funzione generica* $x_i(t)(i = 1,2,\dots,N)$*, scegliere il numero di cluster* $1 < G < N$*, l'esponente della fuzziness* $m > 1$*, e un grado di tolleranza* $\epsilon > 0$*.*

4. *Inizializzare la matrice di partizioni fuzzy* $U^0 = \left[u_{ig}^0\right]$*.*

5. *Calcolare i centroidi del cluster* $v_g \in \mathbb{R}^p$ *:*

$$v_g^{(l)} = \frac{\sum_{i=1}^{N}\left(u_{ig}^{(l-1)}\right)^m v_i}{\sum_{i=1}^{N}\left(u_{ig}^{(l-1)}\right)^m},\ 1 \le g \le G$$

   dove l *rappresenta gli steps dell'algoritmo.*

6. *Calcolare le distanze tra i centroidi e le unità statistiche aggiornando poi la matrice di partizioni [5], e calcolare la funzione obiettivo* $J_m(U,v) = \sum_{g=1}^{G}\sum_{i=1}^{n} u_{ig}^m d_{ig}^2$

7. *Verificare se la funzione obiettivo converge o stabilire una regola di arresto sulla base del grado di tolleranza* ϵ*.*

8. *Infine, l'algoritmo FFKM risulta una matrice di partizione sfocata. Quindi, le curve originali appartengono a ciascun gruppo con diversi "gradi di appartenenza".*

Si propone una possibile applicazione utilizzando i dati dell'ECG raccolti da R. Olszewski come parte della sua tesi "Generalized feature extraction for structural pattern recognition in time-series un battito cardiaco [6].

Risultati

Il risultato più interessante di questo approccio applicato ai segnali ECG consiste nel fatto che i gruppi ottenuti sono "fuzzy", ovvero tutti i pazienti appartengono a tutti i gruppi con un diverso grado di verità. In figura 1 si osserva che il gruppo di funzioni con un colore che tende al rosso è caratterizzato da segnali ECG di pazienti sani. Al contrario, più le curve tendono al verde, più trattasi di pazienti malati, di particolare interesse sono le curve con un colore intermedio, in quando appartengono a pazienti che si trovano in una *condizione intermedia che merita maggiore attenzione e quindi ulteriori esami strumentali per meglio comprendere se trattasi di sani o malati.*

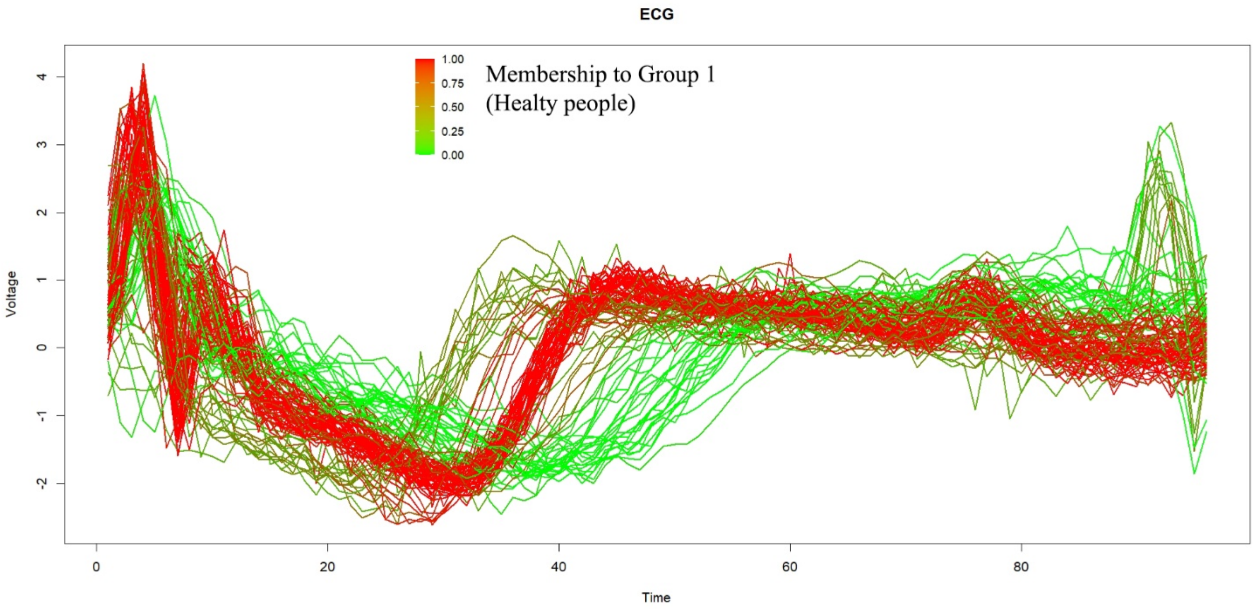

Figura 1.Classificazione fuzzy di ECG

Conclusioni

Il grado di appartenenza a diversi gruppi è di particolare interesse in campo medico perché può essere sfruttato come strumento di informazioni addizionali. Infatti, una volta identificati dei pattern medi di ECG che possono essere legati in diversa misura ad un gruppo di pazienti sani ed un gruppo di pazienti malati, la diversa misura di appartenenza dei pazienti a tali gruppi può essere di interesse per identificare pazienti che necessitano di ulteriori analisi nel caso in cui presentino un grado di appartenenza "sospetto" anche al gruppo dei malati, e viceversa.

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APPLICATION OF WEIGHTED QUANTILE SUM (WQS) REGRESSION TO GENETIC DATA

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Introduction

Since the advent of DNA hybridization microarrays, a persistent challenge in this field is to analyze and interpret genes or pattern of expression affecting a particular phenotype. Different methods like single sample Gene Set Enrichment Analysis (ssGSEA) [1] have been developed to score individual samples against gene sets. This method summarizes the gene expression in a single enrichment score for each pairing of sample and gene set independently by the condition. The effect of the score on the considered dependent variable can be tested in a standard regression model allowing to overcome the problem of the high dimensionality of the data. However, a limit of this approach is the unsupervised estimate of the score.

Objectives

Weighted Quantile Sum (WQS) [2] regression is a novel statistical method that can deal with high dimensional data especially through its random subset extension [3], and it is able to estimate a score in the presence of the outcome better identifying the true genes which expression affects the dependent variable. Through this work we propose the application of WQS regression within the context of the biological pathways testing its performance compared to the ssGSEA and applying it in a real case study.

Methods

In order to apply the WQS regression in the context of a pathway analysis we propose to apply the WQS with double index as per the following equation:

$$g(\mu) = \beta_0 + \beta_{1p}\left(\sum_{i=1}^{c} w_{ip}\, q_i\right) + \beta_{1n}\left(\sum_{i=1}^{c} w_{in}\, q_i\right) + \boldsymbol{z}'\boldsymbol{\varphi}$$

where c is the number of genes, w_{ip} and w_{in} are the weights associated to each component for the positive and negative direction respectively, q_i are the values of the components scored into quantiles (quartiles, deciles, ...), β_{1p} and β_{1n} are the two parameters that measure the positive and negative effect of the mixture on the outcome and $\boldsymbol{z}'\boldsymbol{\varphi}$ are the vector of covariates and its parameters respectively. Both sets of weights have to sum to one ($\sum_{i=1}^{c} w_i = 1$), and have to be between 0 and 1 ($0 \le w_i \le 1$), while β_1 parameters have the following constraints: $\beta_{1p} \ge 0$ and $\beta_{1n} \le 0$. The weight estimation step is usually performed on B bootstrap sample of a training set, however in this work we applied a random subset implementation of WQS selecting a subset of $k = \sqrt{c}$ elements in the mixture at each iteration. Once the weights are estimated for each bootstrap sample, the average of the weights is estimated and the final model is fitted on a validation set.

In this study the two indices are necessary to identify an effect of the up- or down-regulation of the genes on the considered outcome. A single score may be necessary to represent the pathway hypothesized to affect the condition of interest. In this case a second model has to be fitted. If only one of the two scores is statistically significant then a WQS regression with single index has to be performed choosing the same direction of the significant association:

$$g(\mu) = \beta_0 + \beta_1\left(\sum_{i=1}^{c} w_i\, q_i\right) + \boldsymbol{z}'\boldsymbol{\varphi}$$

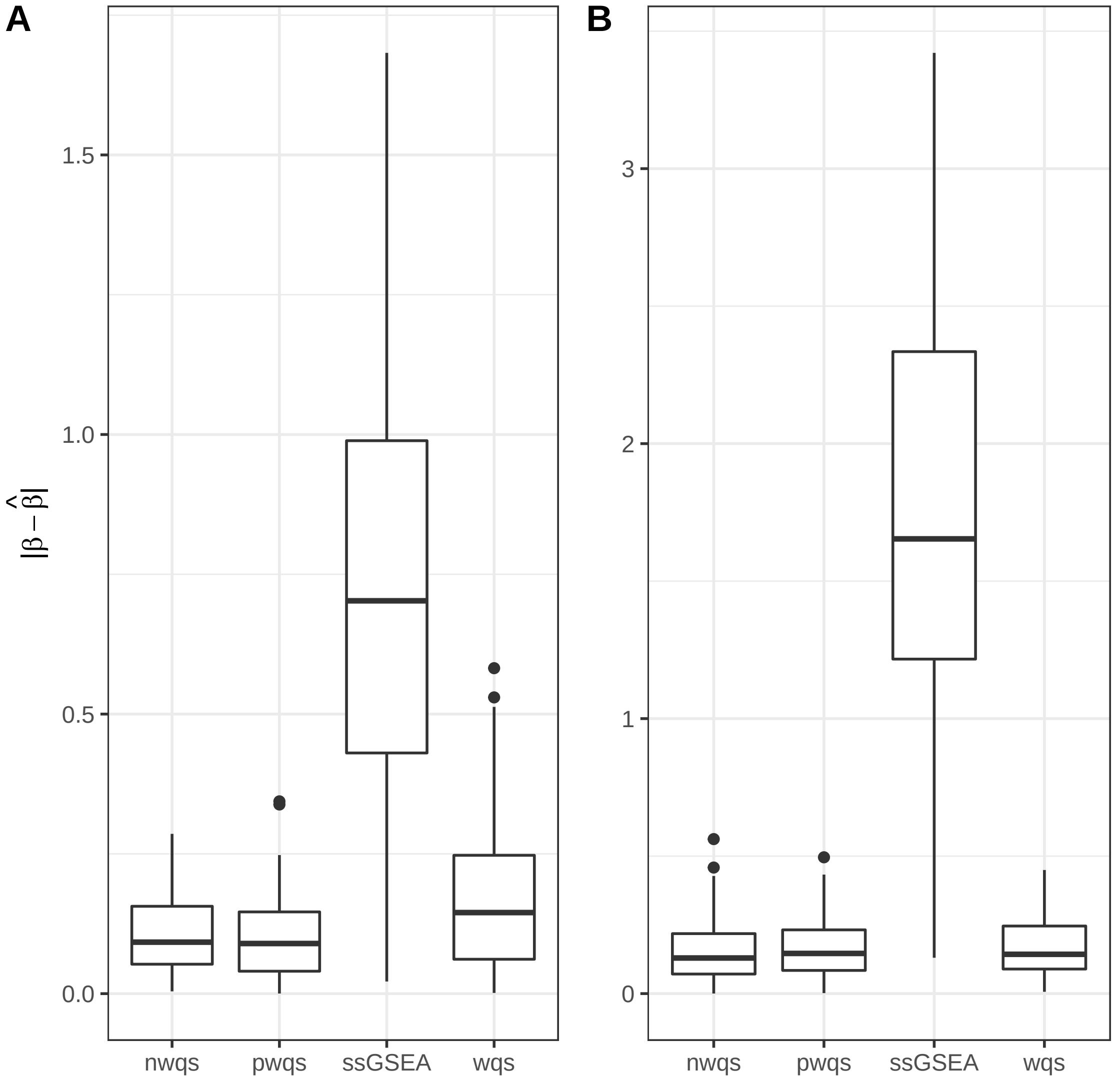
If there is an effect of both indices, the genes with the highest weights (selected as those above the prespecified cutoff $\tau = \frac{1}{c}$) associated to the index representing the opposite direction to the one identified by the pathway are multiplied by -1 to reverse their effect. A WQS regression with single index can now be fitted to estimate the association between the gene set and the outcome.

To test the performance of the WQS in estimating the effect of a chosen gene set on an outcome we considered data from the curatedOvarianData [4] from The Cancer Genome Atlas (TCGA) program. This dataset included patients with ovarian cancer providing uniformly prepared microarray data for 2970 patients from 23 studies with documented clinical information. A total of 578 subjects being part of the TCGA study were considered in our analysis. In the simulation study two outcomes were generated from a normal distribution where the first was built under the assumption of a double directionality of the association while the second was identified considering only a positive effect of the gene set.

Results

*In the first simulation scenario the WQS with double index showed more accurate estimates of the regression parameters compared to ssGSEA showing a bias reduction of the 85.4% (figure 1A). Once we reversed the variables associated to the down-regulated genes with a weight greater than the prespecified cutoff we can still see a better performance of the WQS with single index reducing the bias of the 77.3%. In the second scenario WQS with double index did not detect a negative effect of the score on the dependent variable; we then applied the WQS with single index setting a positive direction and we could still see a better performance compared to ssGSEA reducing the mean error of the 90.2% (figure 1B). When we applied the ssGSEA to estimate the genetic score and test its effect on the outcome through a logistic regression we find a negative but not statistically significant effect (*β *-1.017; 95%CI -2.356, 0.300). The WQS regression with double index showed a significant association in the negative but not in the positive direction (*β *-0.230; 95% CI -0.399, -0.055 and* β *0.157; 95% CI -0.111, 0.416 respectively). When we applied the WQS regression with single index after reversing the distribution of the down-regulated genes we observed an increased risk of death corresponding to higher score values (*β *0.923; 95% CI 0.499, 1.397).*

Figure 1. Boxplots of the absolute difference between the true and estimated value of the regression parameter associated to the score for each method (WQS with double index (positive WQS (pWQS) and negative WQS (nWQS)), ssGSEA and WQS with single index) applied to test the effect on the two outcomes.



Conclusions

WQS regression has the great advantage to be a supervised method able to build an index that attributes higher weights to those genes whose down- or up-regulation shows a higher effect on the outcome. Through this study we compared the performance of WQS and ssGSEA, the most used approach in this context, and we observed how WQS gives more accurate estimates of the effect of the genetic score on the dependent variable. The application of WQS and ssGSEA to the case study confirmed the ability of WQS in determining the biological pathway: in our case we were able to find a significant role of the genes involved in cell-cycle in the risk of death for ovarian cancer which was not observed applying ssGSEA.

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AN INDIVIDUAL PATIENT DATA META-ANALYTIC APPROACH TO ANALYZE CONTINUOUS PATIENT-REPORTED OUTCOMES

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Introduction

Patient-reported outcomes (PROs) are used to evaluate medical treatments or health interventions. PROs, especially health-related quality of life (HRQoL), are particularly relevant in cancer randomized clinical trials (RCTs). PROs can be assessed through both generic and disease-specific validated scales, having different score ranges. There is no standard way of analyzing PROs in RCTs and subsequently a wide range of methods is used, from mean change comparison at a given time point to longitudinal analysis. The various ways data are analyzed and presented make it challenging to perform a systematic review and summarize the evidence in favor of a treatment in terms of improvement in QoL with a meta-analytic approach. [1] Therefore, in the literature a standard methodology to meta-analyze PRO scores is still lacking.

Aims

The aim of the present study is to propose a methodology to compare continuous PROs between treatment groups, using a meta-analytic approach.

As a motivating example, we applied our proposed methodology to PROs assessed in RCTs testing immune checkpoint inhibitors (ICIs) treatments versus anticancer treatments other than ICIs in patients with advanced solid tumors.

Methods

Meta-analyses of individual patient data (IPD) are considered the gold standard of meta-analysis, having many advantages over meta-analyses based on aggregate data (AD). When IPD of continuous outcomes are available both at baseline and at follow-up visits, either a one-stage or a two-stage approach can be used. Briefly, the one-stage approach estimates an overall effect using a single statistical model (e.g. linear mixed-effects model) that accounts for the clustering among patients within studies. In the two-stage approach, study-specific estimates are firstly obtained from the IPD from each study and then combined by a traditional meta-analytical model. [2] To overcome the impractical task of obtaining IPD directly from trials investigators, we suggest using the algorithm proposed by Papadimitropoulou et al [3] that allows to reconstruct pseudo IPD from reported AD for a continuous outcome available at baseline and at a follow-up timepoint. This method generates pseudo IPD that can be analyzed in the same way as the original IPD, yielding identical results in terms of parameters estimates from regression linear models. On the other hand, the required input data (i.e., for the normal outcome case, sufficient statistics such as group means (μ), standard deviations (SD), and sample sizes (N) within each study) are not always available in the original papers and must be either imputed or derived.

In our motivating example, we considered the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 global health status (GHS)/QoL and the EQ-5D-3 L visual analog scale (VAS) questionnaires measured at 12th and 24th week after treatment initiation as PROs of interest. The GHS scale includes two items which explore the patients' overall health and QoL, while the EQ-5D evaluates the patient's self-rated health state on a vertical VAS. In both cases, scores range from 0 to 100, and higher scores represent a better health state. A clinically meaningful change is typically ≥10 points for the EORTC QLQ-C30 and ≥ 7 points for the EQ-5D VAS. [4,5]

We therefore constructed, for each arm of the included study, the pseudo IPD using N, μ, and SD of PRO scores reported or derived at baseline and at the considered timepoints, according to the algorithm. For studies in which mean PROs information were presented only for weeks different than the 12th or the 24th, we estimated them via linear interpolation of the data available at the previous and subsequent timepoints. Then, we used a two-stage meta-analytic approach based on pseudo IPD to obtain the pooled estimate of the mean change in PRO scores between baseline and the FUP weeks of interest. In addition, we also applied the one-stage approach, in order to explore the interaction between FUP timepoints and treatment effects, while adjusting for baseline score, in a linear mixed-effect model. All analyses were conducted using SAS 9.4 and R 3.6.0.

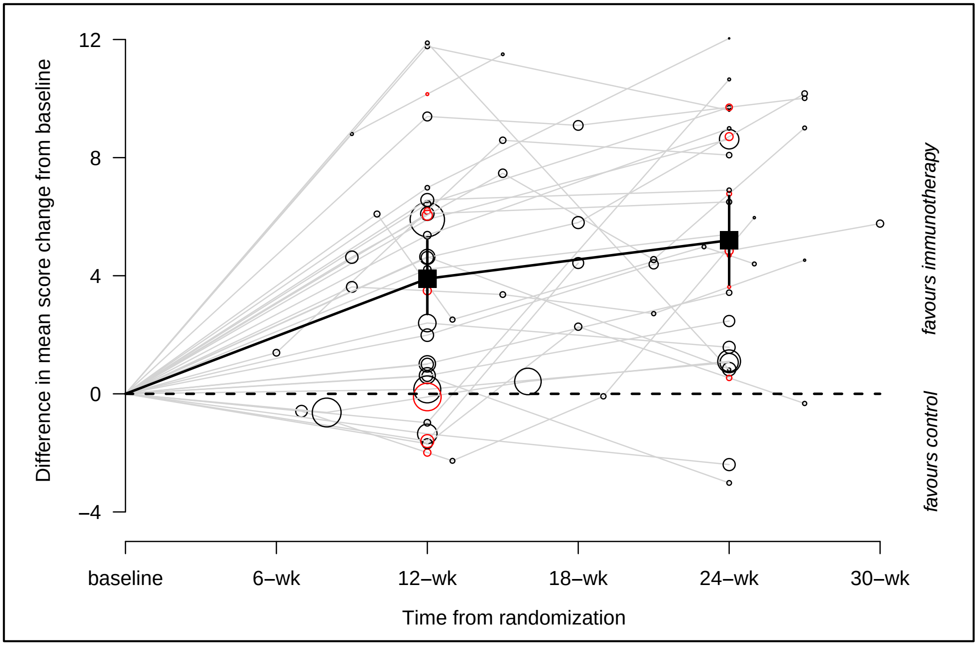
Results

Twenty-eight RCTs were included in the meta-analysis, for a total number of 15321 individual PROs assessment recorded at baseline and at 12 weeks of FUP (28 RCTs, 30 pairwise comparisons between arms) and 14049 at 24 weeks (25 RCTs, 27 pairwise comparisons between arms).

The adjusted pooled effects obtained from the two-stage meta-analysis based on pseudo IPD were 3.9 (95% CI, 2.7–5.2) at week 12 and 5.2 (95% CI, 3.7–6.7) at week 24, favoring immunotherapy-containing arms. The figure below shows the difference in PROs mean change from baseline to 12 weeks and to 24 weeks for each treatment comparison and the pooled estimates with corresponding 95%CI obtained from the two-stage meta-analysis (Figure).

The results of the mixed model, adjusted for baseline score, were consistent with those observed in the two-stage approach. Notably, there was a significant interaction between the treatment group and week of PROs assessment (p=0.02), indicating a significant progressive improvement of the PROs mean change during FUP in favor of immunotherapy.

Figure. Difference in mean change from baseline reported for each treatment comparison (black circles) and pooled estimates (with 95% CI) at 12 and 24 weeks (black squares). Values not reported or derivable at 12 or 24 weeks were estimated using the information at the previous and subsequent available time and represented by red circles. The size of each circle reflects the precision of each effect.



Conclusions

The use of pseudo IPD has already been proposed in meta-analysis of survival outcomes by some authors, Guyot et al [6] and Liu et al [7] among others. As far as we are aware, however, this is the first time that a methodology based on reconstructed IPD is suggested to meta-analyze PRO data from RCTs. Since the efficacy of ICIs on survival has been deeply investigated in the last years, while their impact on the patients' quality of life has been less explored, as compared with that of other available anticancer treatments, we decided to use this setting as an example for applying our methodology. In 2018, Nishijima et al. [8] published a meta-analysis where PROs between ICIs and standard-of-care therapy in patients with advanced cancer were compared. Considering only 9 trials reporting the EORTC QLQ-C30 global health status/QoL, a pooled mean change difference between treatment groups of 5.1 (95% CI, 3.3–6.9) was found, suggesting a benefit of ICIs. However, using AD, the authors could not perform adjustments for potential baseline imbalances nor evaluations of treatment-time interactions. Moreover, they never clearly defined the follow-up times at which the change in PROs were assessed.

In our application, we meta-analyzed PROs from more than 15000 patients and 28 RCTs to explore the impact of ICI treatments on the HRQoL of patients with metastatic solid tumors. Our results demonstrate a favorable impact of immunotherapies on patients' quality of life as compared with control arms non-containing immunotherapy, across a large spectrum of solid tumors. We showed the usefulness and practicality of performing a meta-analysis by using pseudo IPD reconstructed from available aggregate PROs. The use of pseudo IPD instead of AD reduces the risk of bias in the results and provides greater flexibility to analyze data using a one- or a two-stage approach.

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A DEEP LEARNING APPROACH FOR A SPATIO-TEMPORAL FORECASTING OF COVID-19 IN THE REGGIO EMILIA AREA, NORTHERN ITALY

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Introduction

The first case of COVID-19 in Italy was diagnosed in Lombardy region on February 20, 2020. Soon, the epidemic spread throughout Northern Italy, primarily in Lombardy, Veneto and Emilia Romagna. Then, on March 9, 2020, a lockdown was imposed and it has been shown that mobility was directly associated with daily cases. At the end of summer 2020, the second epidemic wave arrived again mainly in the Northern regions.

One potential explanation for this geographical differential diffusion of the epidemic across the country is that this area is the most polluted in Italy. In fact, in such areas, people are more affected by chronic-degenerative diseases, and therefore more skeptical of the serious consequences of COVID-19. Some studies showed a positive association of particulate matter (PM10, PM2.5) and nitrogen dioxide (NO_2) to incidence of COVID-19, but the direct effect is still unclear [1]. Moreover, other studies showed that low temperature and humidity are favorable factors for the spread of respiratory virus diseases.

Forecasting of occurrence of new COVID-19 cases and hospitalizations as well is paramount to optimize the resources and adopt measures to contain the spread of the disease.

To model the impact of meteorological, pollution and mobility data on COVID-19 spread, Machine Learning techniques such as Long-Short Term Memory (LSTM) have been applied since the 2003 SARS epidemic to forecast respiratory virus diffusion [2].

Recently, Deep Learning (DL) models have been developed for COVID-19 epidemic and showed promising potential. Paul et al [3] applied a Convolutional LSTM (ConvLSTM) model to forecast daily new cases in the initial phase of pandemic in US and Italy, formulating COVID-19 forecasting dealing with spatial and temporal correlations in data. In fact, it is reasonable to assume that the forecast in an area depends on its own historical data, but also by other neighborhood's information, i.e. people movements or similar environmental conditions.

Aim

The aim of this study is to develop a prediction model to forecast at local level the real-time transmission of SARS-COV-2 virus, in terms of new cases and new hospitalizations, keeping into account spatio-temporal correlations in Reggio Emilia province.

Our DL model could be used to help policy makers and healthcare providers to manage the COVID-19 epidemic and to better allocate healthcare resources in real-time.

Methods

This study focuses on Reggio Emilia province, severely hit by the first wave of COVID-19 epidemic. The outcomes included new infections (i.e. cases with RT-PCR positive SARS-CoV-2 test) and hospitalization due to COVID-19, i.e. a hospitalization occurring in a confirmed case (from -2 days before diagnosis up to 21 after).

We computed pollution data (PM10, PM2.5, NO_2*) air concentration with the UTAQ model [4] and meteorological data (air temperature, relative humidity, wind speed and solar radiation) with the COSMO-5M model [5], meanwhile to obtain mobility data we used Very-High Resolution satellite images.*

The computing domain on Reggio Emilia province is a grid of 40 cells, each with a size of $(12\ km)^2$*; the forecasts are performed on the single cells, and at the province level by summing up the cells' predictions.*

We constructed a ConvLSTM model, which can learn the dynamics of epidemic spread with high spatial resolution and degree of accuracy due to its capability of nonlinear representation.

The ConvLSTM model had 2 convLSTM layers and a dense layer. The activation function in the dense layer was linear. We applied a Mean Standardized Error loss function, with the optimizer stochastic gradient descending algorithm.

Case and hospitalization models use a data window of 7 days for each input variable (e.g. from t-7 to t-1) in order to forecast the 7th day after (e.g. t+6). All input and output data are considered as 7 days average to smooth the daily variation due to daily variance of case detections and hospitalization.

We used data from August 1, 2020 to January 31, 2021 as the training set, and data from February 1 until March 31, 2021 as the validation set.

We evaluated the performances of the models in terms of Mean Absolute Error (MAE) and Mean Absolute Percentage Error (MAPE).

We built ConvLSTM models in R using Keras [6].

Results

33,962 new COVID-19 cases and 2,505 hospitalizations were registered in the province from August 1, 2020 to March 31, 2021.

We tried different input variables combinations, and the best performances were obtained when daily new cases and mobility were used to forecast new COVID-19 hospitalizations, and when daily cases, mobility, solar radiation and PM2.5 were used to forecast new SARS-CoV-2 infections, with appropriate time lags.

When new cases were forecasted in the entire Reggio Emilia province, the mean observed value (MOV) was 220.68, the MAE 6.4, and the MAPE 3%; meanwhile in the cell mostly occupied by Reggio Emilia city the MOV was 51.6, the MAE 8.4, and the MAPE 15%.

When new hospitalizations were forecasted, we obtained a MOV of 16.97, a MAE of 1.61, and a MAPE of 9.6% in the entire province of Reggio Emilia. If we look only at the cell of Reggio Emilia, the MOV was 3.99, the MAE 0.54, and the MAPE 13%.

In Figure 1, predicted and observed distributions in the validation set are shown, at the province level.

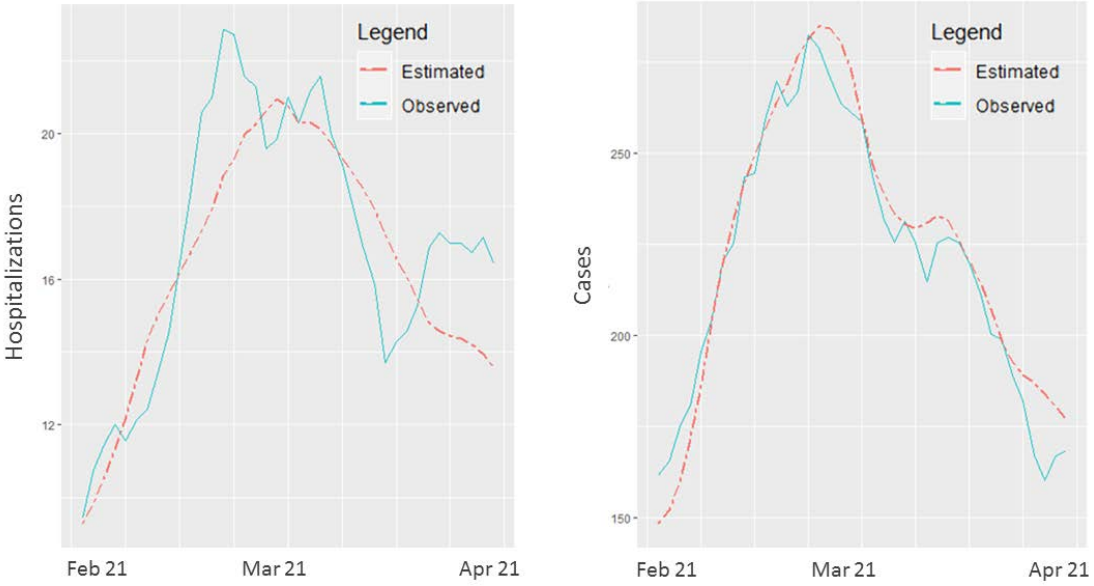

Figure 1: Observed vs estimated distributions of new COVID-19 hospitalizations (left side) and new COVID-19 cases (right side) in the validation set at the province level.

Conclusion

In this study, we showed that ConvLSTM could achieve good performances in forecasting new cases and new hospitalizations due to COVID-19, taking advantage of a spatio-temporal DL representation. Furthermore, this approach allows accurate predictions at a local level, a fact that could be of fundamental importance to help in optimizing the real-time allocation of health resources during an epidemic emergency.

Acknowledgements

This study is funded by European Spatial Agency ESA (ESA Contract No. 4000131356/20/NL/AF) in the project EPICO19 (EPIdemiological COvid-19 model - https://www.epico19.eu/en/).

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FUNCTIONAL MODELLING OF RECURRENT DRUG PURCHASES AND RE-HOSPITALIZATIONS ON SURVIVAL IN HEART FAILURE PATIENTS: A REAL-WORLD CASE STUDY

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Introduction

In the past few decades, large amounts of Real-World Data (RWD) related to utilization of healthcare services or to financial and clinical information were routinely and continuously collected in large administrative databases [1]. The use of administrative RWD allowed for a real-time monitoring of population-based records that implied a strong external validity, leading to significant improvements in healthcare area and becoming an accepted practice in clinical biostatistics [2].

One of the main strengths of administrative RWD is that they can be used to investigate many different areas [3], such as safety concerns or profile of drug uses. Patients' clinical history of hospitalizations or drugs consumption could be reconstructed using administrative registries data related to (i) admission to hospital (Hospital Discharge Charts) and (ii) pharmaceutical purchases. This information is fundamental in chronic diseases, such as Heart Failure (HF) which will be the context considered for the present work. Indeed, two key characteristics in HF treatment are re-hospitalisation events [4-5], which usually herald a substantial worsening of patient's survival prognosis, and the simultaneous and repeated consumption of multiple drugs, which could improve their clinical status, functional capacity and quality of life [6]. Therefore, it is extremely important to develop methodologies able to extract from RWD additional information related to these events in a novel and tailored way, properly taking into account their possibly time-varying nature. These customized features may reflect patient's health status and can be used to model an outcome of interest.

Aims

In order to provide a joint description of the HF related long-term survival and of the time-varying processes that may affect it, the purposes of our study are (i) to enrich the information available for modelling survival with relevant dynamic functional features related to the repeated events of drugs purchases and HF re-hospitalizations, as well as (ii) to provide a new setting for quantifying the association between time-varying processes and time-to-death.

Methods

We developed a *Marked Point Process formulation for Recurrent Events (MPPRE)* [7] to model the realized trajectories of the *compensators* underlying the processes of re-hospitalizations and drug purchases during the 1-year observation period for all the patients. The compensators represent our functional data that we used to enrich the information available for modelling time-to-death. In order to quantify the association between multiple functional compensators and patients' overall survival, we performed Functional Principal Component Analysis (FPCA) [8] to include the resulting scores into a predictive survival model.

We analysed the *HFData* administrative databases provided by *Regione Lombardia - Healthcare Division* related to patients with a primary diagnosis of HF [9]. We considered a representative sample of 4,541 new incident patients with the first HF discharge between 2006-2012. Among the evidence-based drugs for HF treatment [6,10-11] we focused on Angiotensin-Converting Enzyme (ACE) inhibitors, Beta-Blocking (BB) agents, and Anti-Aldosterone (AA) agents. Since data on drugs prescriptions were neither publicly available nor accessible, the approximation of drug consumption with drug purchase was the only viable option [12].

Results

Applying MPPRE [7], we reconstructed the monotonically non-decreasing trajectories of the compensators (see Figure 1) of the four considered stochastic processes of interest (i.e., ACE purchases, BB purchases, AA purchases and HF re-hospitalizations) during the observation period for all the patients. For each patient, the compensator curve constitutes our functional datum and represents the expected number of events by time t given the covariates, i.e., the dynamic evolution of the events risk. This means that for a patient with a higher curve the cumulative risk of a new event is higher over time compared to a patient with a less steep curve. The large variability of the compensators across different patients reflects the variability of the realizations of their recurrent events.

The scores obtained from FPCA allowed to distinguish patients with different events risks and different events timing. These characteristics were finally included into a predictive functional Cox model for overall survival. Results showed that a proper ACE/BB drug intake is correlated to longer life expectancy [HR<1]. On the contrary, patients experiencing many hospitalizations in the past presented a higher risk of dying [HR>1]. Interestingly, even if the second PC of compensators related to HF re-hospitalization process concerned only the 2% of the total explained variance of the original functional data, it was strongly significant with HR=0.77<1 (95% CI=[0.72;0.83]). This means that patients with many hospitalizations at the beginning of the observation period and few hospitalizations in the end have higher survival probability, since they probably correspond to the ones who had already experienced a critical phase of the disease and survived from it.

Conclusions

In the end, our approach constitutes a novel and flexible methodology that can be used to quantify the effect of personal behaviours and therapeutic patterns on survival, providing new insights in the direction of personalized treatment. Its possible generalization to many different settings, added to a cooperation with medical staff, could lead to improvements in the definition of a useful tool for health care assessment and treatment planning.

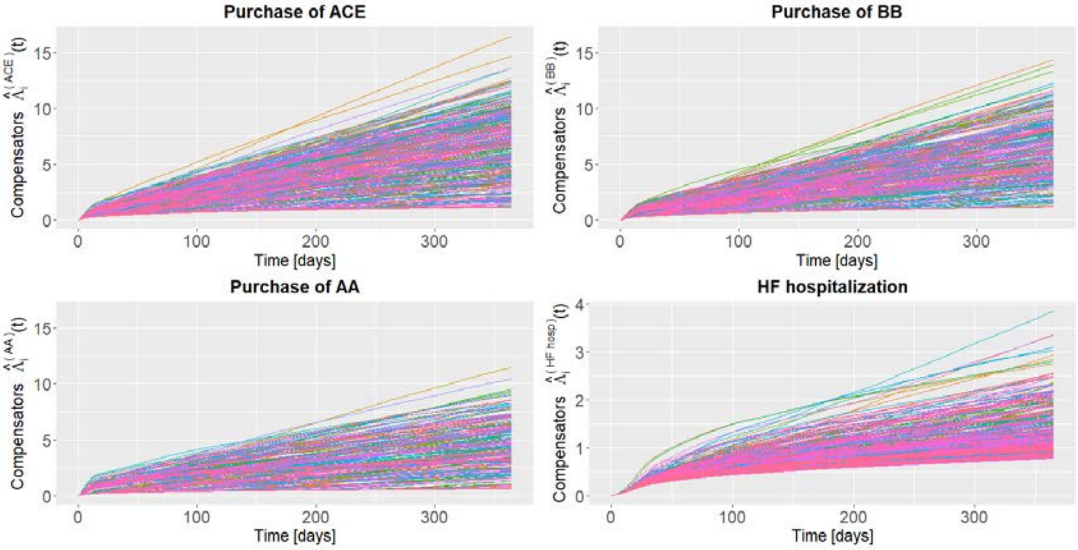

Figure 1. Compensators of the marked point processes of purchases of ACE inhibitors (top-left panel), BB agents (top-right panel), AA (bottom-left panel) and of HF hospitalizations (bottom-right panel) for a sample of 500 HF patients belonging to the *HFData* administrative database. Each line is related to a different patient.

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MINDFULNESS-BASED INTERVENTIONS VIA MOBILE APP: THE EFFECT OF PRACTICES AND THE PREDISPOSITION OF CANCER PATIENTS

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Introduction

Depressive disorders in cancer patients are significantly higher than in the general population [1], with consequences on their quality of life and response to treatment and prognosis. Several e-health systems have been developed in the last years to treat and prevent depression, even if only very few showed evidence of effectiveness. Nevermind is a device support system that deliver personalized lifestyle and mindfulness interventions to help oncological patients to reduce depressive symptoms. Mindfulness-based interventions are psychological treatments, aimed at influence emotion regulation, which have been shown to be beneficial in reducing depression and anxiety [2].

Objectives

The aim of this study was to analyze the effect of mindfulness-based treatment administered to cancer patients in relationship with the number of practices and to draw a profile of patients predisposed to mindfulness meditation practice.

Methods

Participants diagnosed with breast (n = 80) and prostate cancer (n=49) were enrolled at St Luigi University Hospital (Orbassano, Italy) and Città della Salute e della Scienza University Hospital (Turin, Italy). Clinical data were collected at the baseline and post-treatment time. Depression was measured with Beck's Depression Inventory (BDI-II) [3], a 21-item scale. Subscales of Depression Anxiety Stress Scale (DASS-21) [4] were used to assess the severity of anxiety and stress. Nevermind mobile application was used to record the number of mindfulness-based practices during the 12 weeks intervention period.

We categorized the number of practices carried out in 3 group using 0.33 and 0.66 quantiles then we used them to predict the outcome variables of depression, anxiety, and stress. Linear mixed models were performed to assess the mean difference for each outcome measure between dose, time, and their interaction term. Then a latent class analysis was carried out to identify the characteristics of patients who have a disposition to mindfulness.

All the statistical analyses were performed with the R version 4.0.2 [5]. We used the lmerTest package for the mixed effects model and the poLCA [6] package for the latent class analysis.

Results

Patients complete a median number of 15 mindfulness practices (IQR: 4-46). To explore dose-response effects, patients were grouped according to the number of mindfulness practices they carried out. We *considered 3 groups based on tertiles and defined them as low (less than 8 practices), medium (between 8 and 34 practices) and high (more than 34 practices).*

Linear mixed models were performed considering time, dose (i.e., the number of mindfulness practices carried out) and time-dose interaction terms. Patients who completed a medium number of practices showed a significant mean reduction of anxiety (-1.47; 95%CI: -2.84; -0.11), and stress (-2.40, 95%CI: -4.26; -0.55). Patients in the high group had a mean reduction of -4.96 (95%CI: -8.66; -1.27) in depression, -2.02 (95%CI: -3.39; -0.65) in anxiety, -3.35 (95%CI: -5.22; -1.48) in stress. In Table1 marginal effects of the groups of practices for each model are reported.

Table1: Marginal effect of specific group of practices in time

	T0		*T1*		*Difference*	
Practice	*Predicted effect*	*CI*	*Predicted effect*	*CI*	*Mean Difference*	*CI*
BDI-II						
Low	*11.67*	*[8.55- 14.78]*	*9.53*	*[6.42- 12.65]*	*-2.14*	*[-2.94- -1.34]*
Medium	*11.60*	*[9.00- 14.21]*	*9.02*	*[6.42- 11.62]*	*-2.58*	*[-3.14- -2.02]*
High	*13.41*	*[10.75- 16.08]*	*6.32*	*[3.65- 8.98]*	*-7.09*	*[-7.67- -6.51]*
DASS-A						
Low	*3.50*	*[2.30- 4.70]*	*4.30*	*[3.10- 5.50]*	*0.80*	*[0.49- 1.11]*
Medium	*3.00*	*[2.00- 4.00]*	*2.33*	*[1.32- 3.33]*	*-0.67*	*[-0.89- -0.45]*
High	*3.20*	*[2.17- 4.22]*	*1.98*	*[0.95- 3.00]*	*-1.22*	*[-1.45- -0.99]*
DASS-S						
Low	*6.10*	*[4.40- 7.80]*	*7.67*	*[5.97- 9.36]*	*1.57*	*[1.13- 2.01]*
Medium	*6.79*	*[5.37- 8.21]*	*5.95*	*[4.54- 7.37]*	*-0.84*	*[-1.14- -0.54]*
High	*6.49*	*[5.04- 7.94]*	*4.71*	*[3.26- 6.16]*	*-1.78*	*[-2.10- -1.46]*

Latent class regression was performed to obtain profile patients with disposition to mindfulness mediation practice delivered via mobile app. We considered age, gender, educational level, type of employment, marital status, cohabiting people, and the baseline level of depression, anxiety and stress, as manifest variables. We performed a model with 3 latent classes of practice. The posterior probabilities of belonging to each class were 0.47 for the first, 0.22 for the second, 0.31 for the third. Patients in the first class were 72% men, 57% >60 years old, 57% with diploma, 60% retired, 74% married, 56% living with their spouse/partner, 66% with no depression, 58% with no anxiety, 72% with no stress. Patients in the second class were 78% women, 56% 50-60 years old, 59% with diploma, 73% with a full-time job, 100% married, 76% living with spouse/partner and children, 43% with normal level of depression, 41% with normal level of anxiety, 50% stressed. Patients in the third class were 100% women, 30% 50-60 years old, 58% with diploma, 37% retired, 49% single or separated/divorced, 45% living alone or alone with children, 64% depressed, 49% anxious, 49% stressed.

Conclusions

Our results showed that the higher the number of mindfulness-based practices the greater is the reduction of depression, anxiety, and stress symptoms. Latent class analysis identified 2 clusters of patients, based on the number of mindfulness practices: patients who carried out many practices and patients who carried out only few practices. In the latter cluster of patients, two different profiles were detected: men about 60 years old, retired, married, and living with their partner, without any of depression, anxiety, stress symptoms; women between 50 and 60 years old, retired, single or divorced living alone with depression, anxiety, stress. Patients who practice most were women married and living with their family, with a fulltime job, stressed but not depressed or anxious.

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ATTI DEL

XI CONGRESSO NAZIONALE

sismec 2021

Società Italiana di Statistica Medica
ed Epidemiologia Clinica

Venerdì 17 settembre 2021

AULA PLENARIA

METODI BIOSTATISTICI

MODELLI COMPORTAMENTALI FLESSIBILI PER ESPERIMENTI CATTURA-RICATTURA IN TEMPO CONTINUO

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Introduzione

Il campionamento cattura-ricattura viene utilizzato per ottenere una stima della numerosità incognita N di una popolazione in contesti in cui non è possibile determinare l'ampiezza della popolazione mediante censimento. L'idea di base di tale modellistica è quella di campionare la popolazione oggetto di studio più volte ed utilizzare l'informazione fornita dalle ricatture per fare inferenza su N.

Nel caso più generale si può pensare che siano presenti 4 componenti di variabilità che incidono sulla probabilità/tasso di cattura di un individuo: (i) eterogeneità osservata in cui la propensione alla cattura dipende da covariate osservabili durante l'esperimento (classe di modelli M_o), (ii) eterogeneità non osservata in cui vengono introdotti effetti casuali per catturare tale effetto (classe di modelli M_h), (iii) effetti temporali indipendenti dal soggetto in cui il tasso di cattura varia ad ogni istante in modo uniforme per tutti i soggetti della popolazione (classe di modelli M_t) e (iv) risposta comportamentale alla cattura (classe di modelli M_b), in cui il verificarsi dell'evento 'cattura' può modificare temporaneamente o permanentemente il rischio di cattura nel resto dell'esperimento. Ovviamente è possibile una combinazione delle fonti di variabilità di cui sopra e il modello più generale è indicato come M_{hotb}.

Obiettivi

Questo lavoro è incentrato sulla problematica degli esperimenti cattura-ricattura in tempo continuo in cui le osservazioni possono innescare una risposta comportamentale complessa che potrebbe influenzare il tasso di cattura negli istanti successivi [1]. In particolare, sarà considerato l'utilizzo di un processo di punto con interazione temporale in cui il verificarsi di un evento può modificare il rischio di eventi futuri. A tale scopo saranno utilizzati processi di punto denominati self-exciting [2], [3] e self-correcting [4]. In un processo auto-eccitante, il verificarsi di un evento fa sì che la funzione di intensità condizionata aumenti negli istanti successivi (effetto 'trap-happiness'). Al contrario in un processo auto-correggente il verificarsi di un evento produce una diminuzione nella funzione di intensità condizionata (effetto 'trap-shyness').

Metodi

Il contributo metodologico in questo lavoro è stato duplice. Innanzitutto, è stato dato un contributo alla letteratura sui processi di punto temporali definendo una combinazione di processi di punto auto-eccitanti/auto-correggenti, e quindi consentendo a ciascun evento di poter far aumentare e/o diminuire il tasso di accadimento di eventi futuri. In secondo luogo, viene mostrato come i fenomeni auto-eccitanti e auto-correggenti possono essere utilizzati per specificare risposte comportamentali complesse e flessibili in modelli di cattura-ricattura a tempo continuo

Risultati

Il dataset oggetto di studio, che è stato da spunto motivazionale per il nostro modello comportamentale, si riferisce ai dati originali sugli spacciatori sanzionati in Italia ai sensi della Legge 309/90 (legge Bossi-Fini) da parte delle forze dell'ordine italiane tra il 2005 e il 2006. Il numero di soggetti osservati identificati almeno una volta è n = 4271; 3831 di questi erano maschi, mentre solo 440 femmine. L'età mediana era di 32 anni (media 33 anni), con primo quartile pari a 26 e il terzo a 39 anni. La grande maggioranza dei soggetti, ovvero 4170, è stata catturata una sola volta, 99 soggetti sono stati catturati due volte e solo 2 sono stati arrestati tre volte. Questa distribuzione fortemente asimmetrica può essere conseguenza di una combinazione di diversi fattori: innanzitutto, la probabilità di catturare lo stesso spacciatore entro due anni è molto bassa, soprattutto nelle grandi città; inoltre si ha che le sanzioni e le conseguenze legali diventano più severe dopo la prima cattura e quindi per tale motivo è ipotizzabile un effetto di tipo trap-shyness.

In Tabella 1 sono riportate le stime ottenute tramite il nostro approccio e come competitor sono stati considerati i principali stimatori per dati in tempo continuo: gli stimatori di Chao [5], di Chao generalizzato (GC) [6] [7], i modelli Mt e Mth disponibili nel pacchetto R "stime" [8]. In Tabella 1 sono riportate le stime della numerosità della popolazione N, il corrispondente intervallo di confidenza al 95% e l'AIC. Sono riportate solamente una selezione dei modelli da noi stimati, tralasciando i modelli che avevano prestazioni nettamente peggiori in termini di AIC.

Il miglior modello in termini di AIC è risultato essero il modello M_{h2tb} che oltre all'effetto comportamentale include anche l'eterogeneità non osservata basata su C = 2 classi latenti e la componente temporale il quale ha prodotto una stima di N pari a 91387 (con 95% IC: 75149 - 107625). Inoltre, è stato stimato che circa il 60% degli spacciatori ha subito una risposta comportamentale di tipo self-correcting secondo la quale, a parità di tutte le altre condizioni, la probabilità di essere arrestati dalla polizia diminuiva in seguito ad una cattura.

Tabella 1

	$\hat{N}$	95% CI	AIC
M_{h2tb}	91387	(75149; 107625)	604.00
M_{h2t}	91387	(74929; 107845)	606.00
M_{h2ot} (sex, age)	93063	(72882; 113245)	608.24
M_{h2tb}	91332	(73137; 109528)	614.00
M_{h2otb} (sex, age)	93100	(75537; 110662)	616.25
M_{h3otb} (sex, age)	93123	(75060; 111186)	624.25
M_{1bt}	91397	(75027; 107768)	719.45
M_{1otb} (sex, age)	93124	(73224; 113024)	721.69
M_{h2b}	91373	(75136; 107609)	727.45
M_{h2ob} (sex, age)	93093	(73852; 112334)	729.70
Chao	92093	(73981; 110205)	717.35
M_t	91168	(74641; 107694)	732.92
M_{th}	110963	(68315; 153611)	760.55
GC (sex,age)	93986	(91190; 96781)	737.21

Conclusioni

Nella letteratura recente sono presenti numerose proposte relative a modelli comportamentali per esperimenti cattura-ricattura in tempo discreto [9], [10], [11]. L'estensione al tempo continuo, tuttavia, era ancora relativamente inesplorata. In questo lavoro è stato proposto un approccio comportamentale flessibile in un inquadramento del tutto generale per la stima della numerosità della popolazione in popolazioni chiuse per esperimenti cattura-ricattura in tempo continuo.

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LONGITUDINAL PROFILE OF A SET OF BIOMARKES IN PREDICTING COVID-19 MORTALITY USING JOINT MODELS

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Introduction

In survival analysis, time-varying covariates are endogenous when their measurements are directly related to the event status and incomplete information occur at random points during the follow-up [1]. Consequently, the classical time-dependent Cox model [2] leads to biased estimates. Joint models (JM) allow to correctly estimate these associations combining a survival sub-model (used to predict hazards for a set of time-invariant covariates) and longitudinal sub-model (used to predict time-varying covariates) by means of a shared parameter (random effects of the longitudinal sub-model are inserted in the survival one) [1].

During the first wave of COVID-19 pandemic, physicians at Istituto Clinico di Città Studi in Milan collected a set of inflammatory biomarkers in order to understand what might be used as prognostic factors in mortality of COVID-19 disease. Biomarkers were collected repeatedly over the follow-up. Furthermore, particularly in the first epidemic outbreak, physicians did not have standard protocols for management of COVID-19 disease and for this reason, measurements of biomarkers were highly incomplete especially at the baseline.

Aim

The aim of the present study is twice. Using data on COVID-19 patients, we firstly evaluate the effect of a single biomarker on COVID-19 mortality using JM and time-dependent Cox model in order to compare estimates. Second, we present JM estimates for the whole set of biomarkers to evaluate their association on mortality risk.

Methods

Between February and March 2020, a total of 403 COVID-19 patients were admitted. Baseline characteristics included sex and age, whereas biomarkers measurements, during hospital stay, included log-ferritin, log-lymphocytes, log-neutrophil granulocytes, log-C-reactive protein, glucose and LDH. Logarithmic transformation was used to account for the skewedness of the measurements. A Bayesian approach using Markov chain Monte Carlo algorithm were used for fitting JM. Independent and non-informative priors for the fixed effects (age and sex) and for shared parameters (subject-specific predicted biomarkers levels) were used. Furthermore, a natural cubic spline with 2 knots was used to model the subject-specific biomarkers levels through time considering possible mild non-linear effects. Age was also modelled using a natural spline with 2 knots. Analyses were performed with the JMbayes [3] package in R Statistical Software [4].

Results

During the follow-up, 140 patients died, 99 were discharged and 164 were moved in other structure. The median of follow-up was 14 days (range: 0-78 days).

Hazard ratios (HR) from a (biased) time-dependent Cox and joint models for log-ferritin levels were 2.10 (1.67-2.64) and 1.73 (1.38-2.20), respectively.

The estimates obtained from univariable JM showed decreased level through time for expected levels of log-ferritin, log-neutrophil granulocytes (count), log-D-dimer, glucose and LDH according to the negative coefficients for the splines of time at measurements (table 1). Expected levels of these biomarkers increased with age and men showed higher levels than women. The expected log-lymphocytes count increased through time, whereas it decreased with age and no association emerged with sex. For log-C-reactive, expected levels showed a mixed trend through time: levels initially decreased according to the negative coefficient for the first part of follow-up and increased thereafter. Expected log-C-reactive levels increased with age and men showed higher levels.

In univariable JM, all biomarkers were significantly associated with Covid-19 mortality. For all biomarkers, an increase in levels was associated with increasing mortality risk, except for lymphocytes. In particular, doubling of levels for log-lymphocytes count was associated with nearly halving mortality risk (HR=0.58; 95% CI: 0.46-0.73). The strongest associations were observed for log-neutrophil granulocytes (doubling of levels resulting in a HR=2.87; 95% CI: 2.30-3.51), for log-C-reactive protein (doubling of levels resulting in HR=2.44; 95% CI: 2.01-2.97) and glucose (an increase of 100 mg/dl resulting in a HR=2.89; 95% CI: 1.92-4.26).

The multivariable JM was estimated using data on 320 patients with 96 (30%) events (after exclusion D-dimer due to the high number of patients with missing values). For ferritin and lymphocytes there were no more evidence of association with mortality. The strength of the association was attenuated for log-neutrophil granulocytes (doubling of levels resulting in a HR=1.78; 95% CI: 1.16-2.69), log-C-reactive protein (doubling of levels resulting in a HR=1.44; 95% CI: 1.13-1.83), LDH (doubling of levels resulting in a HR=1.28; 95% CI: 1.09-1.49), and glucose (an increase of 100 mg/dl resulting in a HR=2.44; 95% CI: 1.28-4.26).

However, the strongest effect in both univariable and multivariable JM was observed for age with a HR starting to rapidly increase approximately at 60 years.

Conclusions

The JM is the candidate tool to analyse these complex data involving the evaluation of some biomarkers as prognostic factors for the new COVID-19 disease. Incomplete information of biomarkers measurements (frequently at the baseline) makes the classical time-dependent Cox model not optimal for estimating these associations. Possible alternative is the use of landmarking [5], an exploration that we are evaluating for this comparative project.

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Table 3. Model estimates from univariable and multivariable joint models.

Variables	Univariable Model		Multivariable Model	
	Effect (95% CI)	p-value	Effect (95% CI)	p-value
Longitudinal process – log-ferritin level (ng/ml)				
Intercept	5.18 (4.67, 5.67)	p<0.01	4.88 (4.35, 5.43)	p<0.01
ns(time at measurements in days, 2)1[a]	-1.05 (-1.32, -0.77)	p<0.01	-1.02 (-1.70, -0.40)	p<0.01
ns(time at measurements in days, 2)2[b]	-1.69 (-2.23, -1.08)	p<0.01	-1.93 (-3.55, -0.54)	p=0.01
Sex (male vs female)	0.53 (0.34, 0.70)	p<0.01	0.66 (0.47, 0.85)	p<0.01
ns(age in years, 2)1[c]	2.13 (1.15, 3.06)	p<0.01	1.70 (0.70, 2.72)	p<0.01
ns(age in years, 2)2[d]	0.20 (-0.18, 0.59)	p=0.31	0.02 (-0.39, 0.44)	p=0.95
Longitudinal process – log-lymphocytes count				
Intercept	0.68 (0.29, 1.05)	p<0.01	0.69 (0.42, 0.95)	p<0.01
ns(time at measurements in days, 2)1[a]	1.11 (0.95, 1.27)	p<0.01	1.21 (0.88, 1.56)	p<0.01
ns(time at measurements in days, 2)2[b]	0.52 (0.40, 0.65)	p=0.01	0.87 (0.35, 1.42)	p<0.01
Sex (male vs female)	-0.11 (-0.25, 0.03)	p=0.11	-0.15 (-0.25, -0.06)	p<0.01
ns(age in years, 2)1[c]	-1.47 (-2.20, -0.72)	p<0.01	-1.25 (-1.74, -0.76)	p<0.01
ns(age in years, 2)2[d]	-0.69 (-0.97, -0.39)	p<0.01	-0.51 (-0.72, -0.28)	p<0.01
Longitudinal process – log-neutrophil granulocytes count				
Intercept	0.90 (0.59, 1.22)	p<0.01	0.86 (0.56, 1.15)	p<0.01
ns(time at measurements in days, 2)1[a]	-1.10 (-1.41, -0.80)	p<0.01	-0.55 (-1.08, 0.05)	p=0.07
ns(time at measurements in days, 2)2[b]	-2.88 (-3.50, -2.25)	p<0.01	-1.28 (-2.31, -0.01)	p=0.05
Sex (male vs female)	0.25 (0.14, 0.38)	p<0.01	0.29 (0.18, 0.40)	p<0.01
ns(age in years, 2)1[c]	1.25 (0.63, 1.86)	p<0.01	0.84 (0.30, 1.39)	p<0.01
ns(age in years, 2)2[d]	0.90 (0.64, 1.14)	p<0.01	0.55 (0.33, 0.78)	p<0.01
Longitudinal process – log-D dimer (ng/ml)				
Intercept	4.34 (3.62, 5.01)	p<0.01	-	-
ns(time at measurements in days, 2)1[a]	-1.72 (-2.02, -1.39)	p<0.01	-	-
ns(time at measurements in days, 2)2[b]	-2.99 (-3.47, -2.57)	p<0.01	-	-
Sex (male vs female)	0.35 (0.10, 0.61)	p=0.01	-	-
ns(age in years, 2)1[c]	4.18 (2.93, 5.52)	p<0.01	-	-
ns(age in years, 2)2[d]	1.57 (1.01, 2.09)	p<0.01	-	-
Longitudinal process – log-C-reactive protein (ml/l)				
Intercept	-0.18 (-0.70, 0.34)	p=0.50	-0.12 (-0.70, 0.43)	p=0.69
ns(time at measurements in days, 2)1[a]	-4.43 (-5.30, -3.56)	p<0.01	-4.10 (-5.59, -2.52)	p<0.01
ns(time at measurements in days, 2)2[b]	0.54 (-1.48, 2.58)	p=0.59	2.33 (-1.04, 6.10)	p=0.18
Sex (male vs female)	0.49 (0.31, 0.69)	p<0.01	0.49 (0.28, 0.70)	p<0.01
ns(age in years, 2)1[c]	4.27 (3.23, 5.29)	p<0.01	3.45 (2.42, 4.52)	p<0.01
ns(age in years, 2)2[d]	1.01 (0.60, 1.41)	p<0.01	0.52 (0.02, 1.00)	p=0.04
Longitudinal process – glucose (mg/dl)/100				
Intercept	86.58 (83.00, 90.12)	p<0.01	77.27 (65.91, 88.76)	p<0.01
ns(time at measurements in days, 2)1[a]	-19.15 (-27.92, -10.52)	p<0.01	-0.80 (-16.66, 14.61)	p=0.92
ns(time at measurements in days, 2)2[b]	-10.09 (-20.68, 0.29)	p=0.06	-1.54 (-20.02, -17.47)	p=0.86
Sex (male vs female)	1.01 (0.95, 1.08)	p<0.01	12.33 (4.57, 19.78)	p<0.01
ns(age in years, 2)1[c]	58.28 (57.94, 58.65)	p<0.01	36.10 (19.21, 53.01)	p<0.01
ns(age in years, 2)2[d]	12.27 (12.13, 12.41)	p<0.01	2.82 (-10.77, 15.95)	p=0.67
Longitudinal process – LDH/100				
Intercept	106.22 (1.40, 2.77)	p<0.01	97.42 (77.40, 116.33)	p<0.01
ns(time at measurements in days, 2)1[a]	-26.77 (-43.74, -9.79)	p<0.01	8.24 (-10.46, 26.40)	p=0.36
ns(time at measurements in days, 2)2[b]	-3.40 (-22.74, 16.14)	p=0.72	-7.02 (-27.95, 13.12)	p=0.49
Sex (male vs female)	23.52 (23.29, 23.73)	p<0.01	58.08 (40.70, 75.22)	p<0.01
ns(age in years, 2)1[c]	243.14 (241.65, 243.90)	p<0.01	48.13 (27.32, 70.79)	p<0.01
ns(age in years, 2)2[d]	81.11 (80.73, 81.49)	p<0.01	0.59 (-19.33, 19.95)	p=0.96

Variables	log-hazard (95% CI)	p-value	log-hazard (95% CI)	p-value
Time-to-event process				
Sex (male vs female)	-		0.74 (0.26, 1.20)	p<0.01
ns(age in years, 2)1[c]	-		9.31 (3.35, 15.75)	p<0.01
ns(age in years, 2)2[b]	-		3.82 (2.57, 5.26)	p<0.01
log-ferritin (ng/ml)	0.55 (0.33, 0.79)	p<0.01	-0.13 (-0.47, 0.22)	p=0.48
log-lymphocytes	-0.78 (-1.11, -0.44)	p<0.01	0.04 (-0.43, 0.53)	p=0.89
log-neutrophil granulocytes	1.52 (1.20, 1.81)	p<0.01	0.83 (0.21, 1.43)	p=0.01
log-C-reactive protein (ml/l)	1.29 (1.01, 1.57)	p<0.01	0.53 (0.18, 0.87)	p<0.01
LDH/100 (UI/l/100)	0.55 (0.46, 0.64)	p<0.01	0.25 (0.09, 0.40)	p<0.01
glucose (mg/dl/100)	1.06 (0.65, 1.45)	p<0.01	0.89 (0.25, 1.45)	p=0.01

Both models were adjusted by age (modelled by a natural spline with 2 knots) and sex. In the longitudinal model also time was modelled by a natural spline with 2 knots. The association parameter between the time to event and longitudinal processes are reported in the *time-to-event* section. Parameter estimates for age and sex in the univariable Cox models are not reported. [a]First coefficient for time at measurements according to natural spline (ns); [b]Second coefficient for time at measurements according to natural spline(ns); [c]First coefficient for age according to natural spline (ns); [d]Second coefficient for age according to natural spline(ns).

TRANSITION DETECTION IN COVID-19 DYNAMICS: A NOVEL STATISTICAL APPROACH

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1. Introduction

The epidemic dynamics, can be equated to a Spatially Extended Non-Linear Dynamic Random System, governed by parameters that vary in time and space following, on average, deterministic trajectories. These trajectories are described by deterministic models (mean field), SIR, SEIR, SIS etc. If the spatial (geographical) aspect is included in the SIR model, and if we consider the autoregressive component, we step into temporal and/or space-time SIRARS or SIRAR models [2]. For a stochastic component is included in the dynamics, we deal with multivariate birth/death random processes typical of population dynamics. The above models require a lot of data for reaching stability of the parameter estimates and, therefore, are not suitable in the early stages of the epidemic. In the case of SARS-CoV-2, diffusion control interventions arrived late since the emergence of the first cases I(t0). The first data on the number of infected date back to 24/02/2020 and, after about ten days, the first lock-down was put in place. From that date, the evolution of the epidemics can be considered as a response of a dynamic system to an initial impulse. The dynamics of the first days, however, contain the necessary information on the evolution of the epidemic without any external intervention. To analyze the dynamics of the epidemic, starting from the beginning of the virus spreading - when data are insufficient to make an estimate by adopting a SIR model - a "sigmoid family" model was introduced. That approach allowed the estimation of the epidemic peak using the few data gathered before mid-March. Based on this analysis, the peak had been expected to occur by the end of April. Later on, the real data of the epidemic evolution confirmed the prediction. Using an exponential model, a backward prediction was pursued generating an estimate of twenty infected persons in the middle of October 2019. A predictive index to evaluate and forecast the time evolution of epidemics has been built (RI) [2]. This index allows to predict the regime change in epidemics trajectories because, at odds with R(t) that only pertains to the infected number, stems from both the input (infected) and output (removed) compartments of epidemic system.

2. Aim

We provide tools for both the rapid forecast of the epidemic peak and the detection of dynamics regime changes. A further refinement, reported in the present work, led to the generation of reliable early warning signals anticipating the transition behavior of epidemic system.

3. Methods

To specify the sigmoid we solve the Bernoulli differential equation with initial condition $N(0)=224$ and $N(l)=8514$, (where l is the time delay-20 days) was determined applying the back-propagation method [5]. The time window went from the end of February to March 16. Accordingly, the average value of the RI (dH/dI) index was calculated from the healed (H) and infected (I) curves within each field (regime). The fields correspond to T_0 = starting point, with a very low number of infected and practically no healed patients. T_1 = initial exponential increase in the epidemic phase, featuring a marginal number of infected compared to healed patients. T_2 = inflection of the curve of infected, corresponding to the beginning of the exponential increase of fatal cases. T_3 = plateau, the phase of the curve of infected, showing a trend toward reduction with simultaneous exponential increase in the number of healed. T_4 = drastically drop of infected patients and exponential increase of the healed, (*fig.1*). The robustness to the uncertainty of the infected number of the proposed index derives from both the use of daily differential (instead of the total number of infected), and the long delay between the infection and the declaration of "complete recovery" assigning a patient to the H compartment

4.Results

The model relies upon the following estimated equation*:*

$$N\ (t)\ =\ (8514 * a)/\left(exp\ (-a * t)\ +\ b * 224\right)$$

Being *N (t)* = number of actually infected at time *t,* 224= number of infected at February 24, and 8514 the infected at March10. The model shows a delay effect (autocorrelation) of 18-22 days in the epidemic. Model fitting was based on the data relative to the interval February 24 –March 16, and the coefficients (95% confidence limits) were:

a = 0.1466 (0.1401, 0.1531)

b = 5.173e-05 (4.605e-05, 5.741e-05)

Goodness of fit: Square R: 0.9307; Adjusted square R: 0.9294 ; RMSE: 1.057e + 04

The model was built on the data until March 16 and correctly predicted the onset of the end of April peak.

Backward prediction model

The daily infected at time *t-j* is given as:

$$N(t-j) = N(t)/(1+\alpha)^j$$

Where: *N (t)* = leveled number of infected at day *t*, alpha = geometric mean of the first 10 days and *j*=numbers of days before *t*.

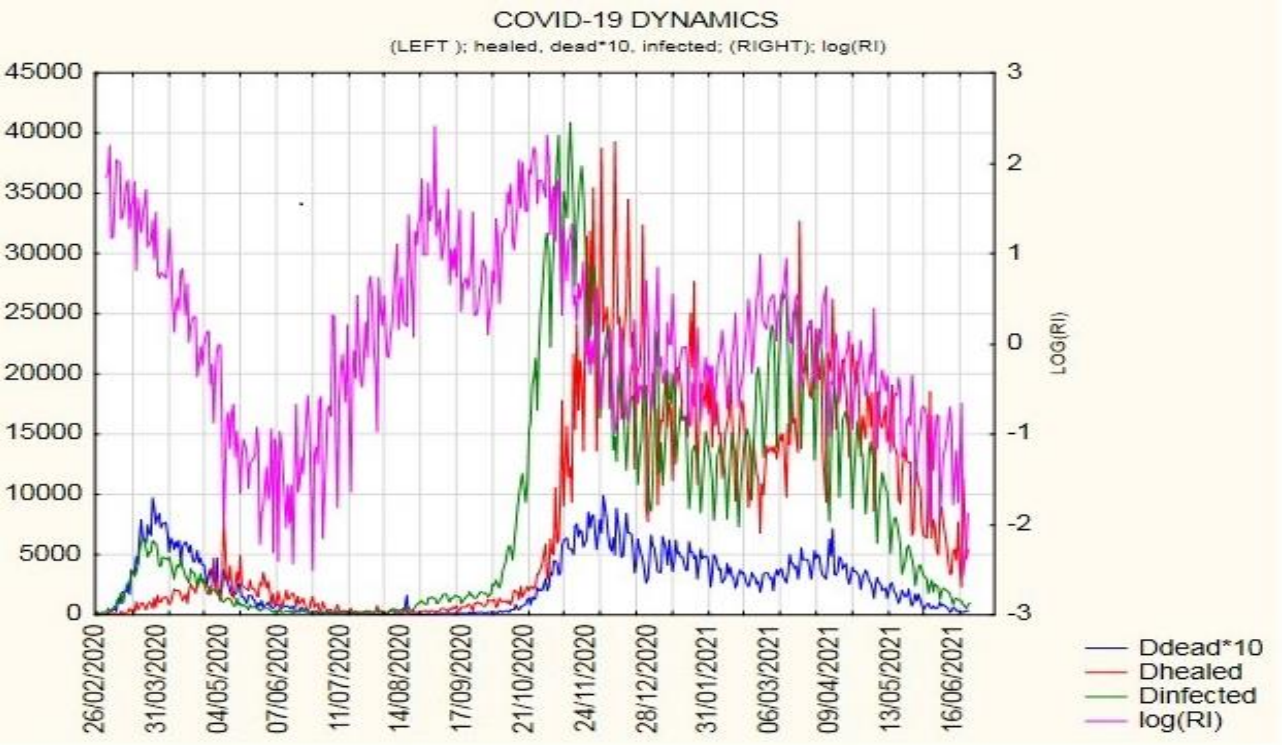
$$N(t-j) = 202/(1+0.02353808)^j$$

For *j* = 130, we get *N (t-j)* = 10; from February 24, subtracting 130 days we arrive in mid-October.

Conclusions

The proposed index allows detecting tipping points, which anticipate regime changes in a very reliable way. Moreover, this approach allows tracing back the beginning of the epidemic to October 2019 consistently with recent emerging evidences. The model-free character of the proposed index and the possibility to use very initial (and uncertain) data for the proposed logistic approach can be of paramount importance in controlling epidemics spread. It is worth of interest that, when the number of accesses is plotted against the number of Covid-19-related casualties, we found a near to unity correlation between these two parameters largely invariant in time and space (i.e., Italian regions display the same trend without appreciable differences). This strong and invariant relation makes trends of care unit’s occupancy predictive of epidemic extinction, with accuracy higher than that offered by rate of infected or recovering patients, which are biased by uncertainty of collected data and regional-related fluctuations. The model without any modification allows in forecasting 2021 tipping points of epidemic outbreaks.

Fig.1.



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A posteriori dietary patterns by Hispanic/Latino background and site: the use of Bayesian multi-study factor analysis in the Hispanic Community Health Study/Study of Latinos

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Introduction

The Hispanic/Latino population is the fasting growing segment of the US population. Compared to non-Hispanic Whites and Blacks, Hispanics/Latinos have a higher prevalence of cardiometabolic disease risk, but a lower all-cause mortality rate. Dietary behaviors are an important contributor to cardiometabolic disease and vary greatly by ethnic background and regionality. Given the diversity of the Hispanic/Latino ethnicities living in the US, further investigation is warranted to understand how these nuances interplaying with US regionality can influence certain dietary habits/behaviors. Dietary patterns (DPs) are combinations of various dietary components intended to summarize total diet or key aspects of diet, while taking advantage of well-known synergistic effects between individual dietary components that can influence human health. A *posteriori* DPs are defined from the application of multivariate statistics, including (but not limited to) principal component and factor analyses. New statistical methods like multi-study factor analysis have been recently used to distinguish subpopulation-specific DPs (i.e., study-specific or country-specific features within an international consortium or group-specific features within a single study), as well as those shared among all groups in a population [1].

The Hispanic Community Health Study/Study of Latinos (HCHS/SOL), the most extensive and ongoing community-based cohort of Hispanic/Latino adults in the US to date, provides a unique opportunity to identify shared and group-specific *a posteriori* DPs for this vastly diverse population as it recruited in 4 distinct urban centers. We aimed to identify shared and subpopulation-specific DPs based on the cross-section of ethnic background and center of recruitment, to provide evidence for culturally tailored interventions in the future. We opted for nutrient-based DPs to better capture the biological mechanisms behind original and acquired culinary traditions.

Aims

The present work aims to: 1. identify shared and subpopulation-specific (nutrient-based) DPs within the HCHS/SOL study; 2. validate the identified nutrient-based DPs in terms of food-group consumption.

Methods

The Hispanic Community Health Study/Study of Latinos

The HCHS/SOL is a population-based cohort study designed to identify disease prevalence rates and risk factors of Hispanic/Latino populations residing within 4 urban US communities (Bronx NY, Chicago IL, Miami FL, and San Diego CA) and representing individuals with seven ethnicity backgrounds (Cuban, Dominican, Mexican, Puerto Rican, Central and South American, and mixed). Participants were selected using a probability sampling design, as previously described in detail [2].

From March 2008 to June 2011, 16,415 US Hispanics and Latinos were enrolled. Baseline data included medical history, physical examination, assessments of acculturation to the US culture, health behaviors, and health care access [3]. Dietary habits at baseline were assessed using two 24-hr recalls, the first conducted in person and the second via telephone <=30 days after the baseline interview. Interviews were conducted with the Nutrition Data System for Research (NDS-R) software, which also allowed for estimation of intakes for nutrients and other compounds (indicated as nutrients hereafter). Nearly all (99%) participants provided at least one recall.

Selection of subjects

We excluded Hispanics and Latinos from other or mixed backgrounds, with dietary recalls considered unreliable, or provinding extreme energy intake at either the nutrient or food level. We also excluded subpopulations left with less than 200 participants after previous exclusions (i.e., Bronx-South American). All these exclusions resulted in a final sample size of 15,021 participants for the analysis.

Selection and preprocessing of nutrient intakes

From the NDS-R list, we selected 42 nutrients that well represent the overall diet for Hispanics/Latinos. For each participant, nutrient intakes were derived from either one available reliable recall or the mean of the two available reliable recalls. Nutrient intake data were log-transformed to improve adherence to the normality assumption of the shared and subpopulation-specific factors, as required by the Bayesian multi-study factor analysis (BMSFA).

Statistical analysis

BMSFA was carried out on the correlation matrices of the log-transformed nutrient intakes. The total number of factors to retain was selected using the spectral decomposition of both the shared and subpopulation-specific DPs. After the singular value decomposition method used in the BMSFA for identifiability, the varimax rotation was applied to the shared factor-loading matrix to achieve a better-defined loading structure [4]. Nutrient-based factor scores were finally validated against selected food groups from the 24-hr recalls [1]. Calculations were carried out using the open-source R program [5].

Results

The selected model included four shared (62.5% of total variance explained) and twelve subpopulation-specific DPs (variance range: 8.17-9.21%), one for each of the 12 combinations of background and site (Figure 1). The first common factor loaded highly on vegetable protein, several minerals, vitamin B1, niacin, natural folate, and soluble and insoluble fiber. We defined this DP as *Plant-based foods*. The second common factor loaded highly on short- and medium-chain saturated fatty acids and calcium, vitamins B2, B12, D, and retinol. We defined this DP as *Dairy products*. The third common factor loaded highly on Eicosapentaenoic Acid (EPA), Docosapentaenoic acid (DPA), and Docosahexaenoic Acid (DHA). We defined this DP as *Seafood.* Lastly, the fourth common factor loaded highly on several fats, including long-chain saturated and monounsaturated fatty acids, linoleic and linolenic acids, total *trans* fatty acids, and natural alpha-tocopherol. We defined this DP as *Processed foods*. At the subpopulation level, San Diego-Mexican and Chicago-Puerto Rican DPs differed from the rest of the subpopulations in terms of their DPs, which mostly loaded on animal protein, arachidonic acid, and niacin. These three nutrients were the only dominant ones in four subpopulations. Due to the impossibility of carrying out a rotation on the subpopulation-specific DP, the previous nutrients were also present but were opposed to small and medium-chain fatty acids in three subpopulations (Bronx-Central American, Miami-Central American, and Bronx-Mexican) or opposed to soluble and insoluble fibers and folate in another three subpopulations (Bronx-Dominican, Chicago-Mexican, Chicago-South American). When interpreted in terms of food groups, the identified DPs confirmed the names attributed to them as based on the factor-loading matrices.

Conclusions

In its first application in nutritional epidemiology, BMSFA succeeded in simultaneously estimating well-interpretable shared and subpopulation-specific DPs within 12 combinations of background and site. In its Bayesian version, multi-study factor analysis revealed nuances in subpopulation-specific DPs that suggested it was worth to disentangle dietary habits at the intersection of background and site, with potential additional implications on the association between DPs and health outcomes.

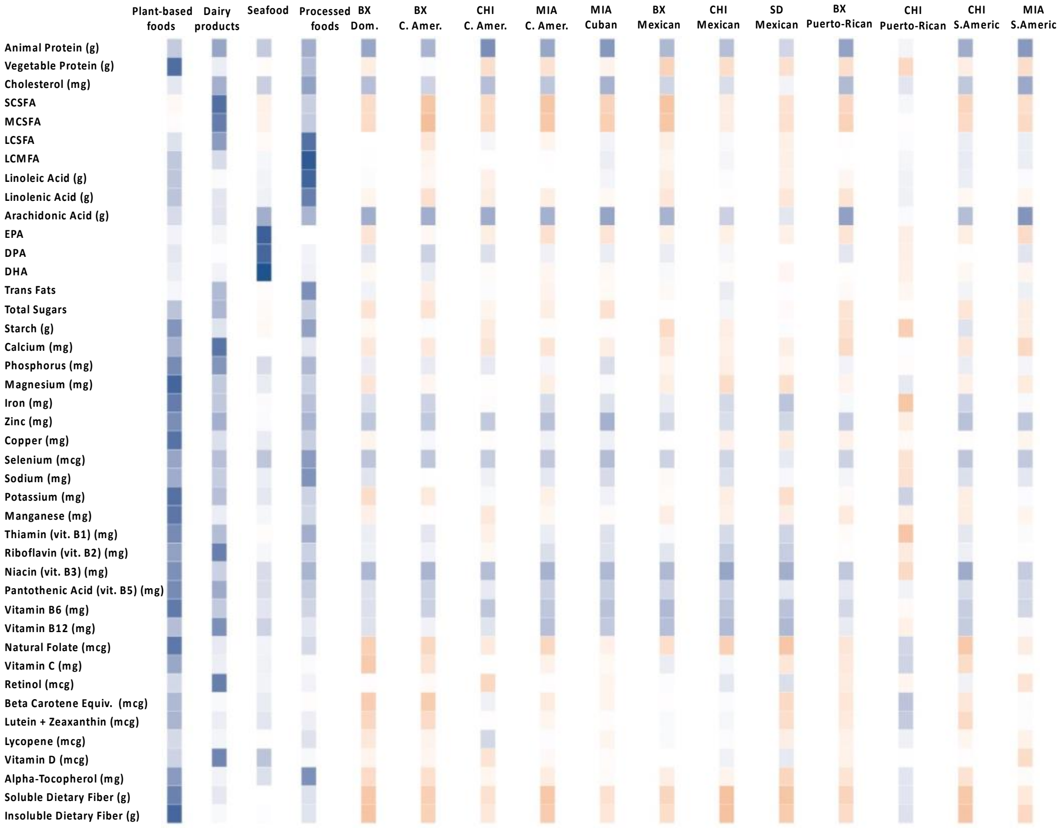

Figure 1 – Heatmap of the estimated factor loadings for the shared (left) and background/site-specific (right) dietary patterns. Hispanic Community Health Study/Study of Latinos – baseline examination (2008-2011).

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MACHINE LEARNING METHODS FOR PREDICTING MORTALITY RISK IN COVID-19 PATIENTS ADMITTED TO SEVERAL CARDIOLOGY UNITS

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Introduction

From the beginning of 2020, the Coronavirus disease (COVID-19) pandemic has dramatically affected the health systems worldwide and a common goal is to control and manage the virus. One interesting line of research is the use of Machine Learning (ML) algorithms for understanding and fighting COVID-19[1]. Several studies applied these methods for predicting the risk mortality[2],[3],[4] since an early recognition of critical patients can help to mitigate the burden on health systems.

ML have some noticeable advantages over traditional models. First, they can capture nonlinear relationships among outcome and clinical features[5], and second, they can handle problems such as multicollinearity and missing values.

In this study ML algorithms were applied on a cohorts of patients hospitalized in several Italian cardiology units in order to quickly identify which of them has a high risk of in-hospital death.

Aim

The aim of this analysis is to obtain a simple risk score for in-hospital mortality in patients with COVID-19, based on a limited number of features collected at hospital admission in cardiology unit.

Methods

The study has involved a cohort of consecutive patients with laboratory-confirmed COVID-19 who were hospitalized in several Italian cardiology units during Spring 2020. The database included data on patients' demographics, medical history, in-hospital clinical course including laboratory findings collected at admission, treatments and mortality (outcome). Variables with more than 20% of missing values were excluded. For the others, missing values were imputed with an appropriate ML procedure for continuous or categorical data which considers complex interactions and nonlinear relationships.

The Lasso procedure (a variable selection method) was used with a $\lambda=0.07$ for reducing the covariates number.

To overcome potential multicollinearity problems and modeling nonlinear relationships, in-hospital mortality was estimated by means of a Random Forest (RF), an ensemble learning method belonging to ML approach.

The dataset is randomly divided in two subsamples with the same percentage of death/alive people of the entire sample: training set contains 80% of the data and test set the remaining 20%.

The training set is used in the calibration procedure where a RF models in-hospital mortality with the covariates selected by Lasso. Its accuracy was measured by means of the ROC curve, obtaining AUC, sensitivity, specificity and related 95% CI computed with 10,000 stratified bootstrap replicates.

From the RF the relative Variable Importance Measure (relVIM) was extracted in order to understand which of the selected variables had the greatest impact on outcome. This measure provides a ranking from the most (relVIM=100) to the less important variable. Moreover, a 2D plot called Partial Dependence Plot (PDP) was obtained with the aim of describing the functional relationship between each covariate and the predictions obtained. It reports in x-axis one covariate per time and in y-axis the predictions.

The model obtained is compared with another ML method, the Gradient Boosting Machine (GBM) and with the logistic regression, where the predictions were cross validated.

Finally, to understand if each model has the same performance in sample (training) and out of sample (test), the two AUCs were compared by means of the DeLong's test.

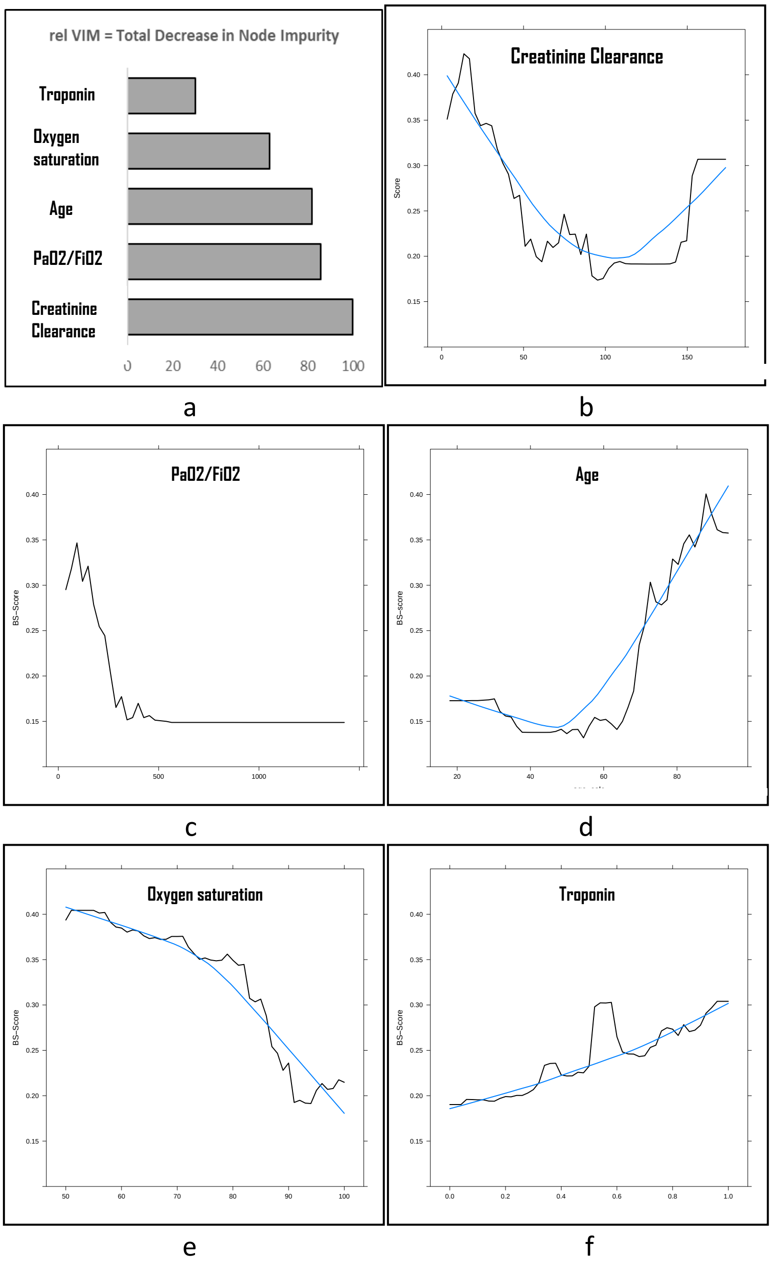
Results

Starting from the dataset with 701 patients for 40 variables, the Lasso procedure selected the following 5 variables: Age, Oxygen saturation (SpO2), PaO2/FiO2, Creatinine Clearance (CrCl) and dichotomized Troponin (normal vs elevated).
The RF model was estimated on the training set which contains 561 patients and then tested out of sample on the test set (140 patients). The predictions obtained from this model can be interpreted as the probability of in-hospital death of each patient.
The best performance out of sample, in terms of AUC and sensitivity, is provided by the RF that shows an AUC of 0.78 (95% CI: 0.68-0.88) and sensitivity equals to 0.88 (95% CI: 0.58-1.00). In fact, for GBM the AUC is 0.75 (0.65-0.84) and sensitivity 0.73 (95% CI 0.55-0.94) while for logistic regression the AUC is 0.55 (95% CI 0.43-0.67) and sensitivity 0.77 (95% CI 0.17-0.97). Moreover, RF is the unique methodology that provided the same performance in sample and out of sample (DeLong's test p-value=0.782).
Extracting the relVIM from RF, a ranking from the most (CrCl) to the less (dichotomized Troponin) important feature in predicting the outcome is visualized in Figure 1.a. Finally, PDPs (Figure 1.b-1.f) show the relationships between one variable per time (in *x*-axis) and the score obtained from RF (in *y*-axis).

Conclusions

In this study, a risk score of in-hospital mortality for patients with COVID-19 is proposed. This score involves only 5 features, but its performances are good in terms of sensitivity. An important aspect offered by the score is that it is based on biomarkers that may be obtained by the emergency laboratory in less than an hour. This score could be a good support to clinicians to identify patients with a higher risk of developing complications and that need a more aggressive treatment.

Figure 1: Relative Variable Importance extracted from the Random Forest (panel a) and Partial Dependence Plots (panel b-f) of each features respect the risk score of death for patients with COVID-19



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MORTALITÀ PER COVID-19 IN PROVINCIA DI BOLZANO: REVISIONE DELLE CAUSE INIZIALI DI MORTE MEDIANTE APPLICAZIONE DI TECNICHE DI MACHINE LEARNING

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Introduzione

Le elaborazioni effettuate sulle schede di morte ISTAT relative ai soggetti residenti in Provincia di Bolzano hanno evidenziato, nel bimestre marzo-aprile 2020 (prima ondata), una minore frequenza assoluta di decessi dovuti a Covid-19, rispetto a quanto emerso in novembre-dicembre 2020 e gennaio-febbraio 2021 (seconda ondata). L'eccesso della mortalità in confronto al quinquennio precedente, presenta invece un andamento contrario, con valori superiori in marzo-aprile 2020 rispetto a novembre 2020-febbraio 2021. Mentre nella seconda ondata tale eccesso viene spiegato completamente dalle morti per Covid-19, ciò non si rileva nella prima ondata epidemica. Si ipotizza, quindi, vi sia un certo numero di decessi nel bimestre marzo-aprile 2020, erroneamente non assegnati all'infezione da Covid-19, quale causa iniziale di morte. Il ritardo di pubblicazione dei documenti emanati dalla WHO [2,3,4] e dall'ISTAT [5], con le indicazioni per la compilazione della scheda di morte in presenza di Covid-19, ha probabilmente influito sulla completezza della segnalazione dell'infezione da Covid-19 nelle schede, nei mesi iniziali dell'epidemia. È possibile, infatti, che nella prima ondata epidemica, in mancanza di informazioni precise, alcuni medici necroscopi non abbiano riportato le infezioni da Covid-19 ritenute probabili o solamente sospette, che invece hanno correttamente segnalato nella seconda ondata.

Obiettivi

Obiettivo del presente lavoro è quello di definire un modello di classificazione, che sia in grado di (a) analizzare la relazione tra le diagnosi di morte riportate nella scheda ISTAT e la causa iniziale di morte (infezione da Covid-19/altre cause di morte), (b) "imparare" la struttura tra le diagnosi di morte e la causa iniziale di morte e (c) analizzare nuove schede di morte e predire la causa iniziale di morte. Il modello di classificazione predisposto potrebbe essere impiegato operativamente per l'individuazione delle schede di morte relative al bimestre marzo-aprile 2020, collegate ad una probabile mancata segnalazione dell'infezione da Covid-19.

Metodi

Il data-set utilizzato, è stato estratto dall'archivio del Registro delle Cause di Morte (RCM) della Provincia di Bolzano, relative a soggetti residenti e deceduti in Provincia di Bolzano nei mesi di marzo, aprile, novembre, dicembre 2020 e gennaio, febbraio 2021. Il data-set risulta composto complessivamente da 3.319 record, di cui: 1.192 relativi a deceduti in marzo-aprile 2020, 2.127 nel periodo novembre 2020-febbraio 2021, 957 con causa iniziale di morte "infezione da Covid-19" e 2.362 con altre cause di morte.

Alcuni autori [6,7,8,9], verificando la somiglianza tra le sequenze di codici diagnostici contenute negli archivi sanitari correnti ed il linguaggio naturale, suggeriscono la possibilità di trasferire le tecniche normalmente utilizzate nel Natural Language Processing (NLP), per l'addestramento di rappresentazioni complesse di record tratti da flussi sanitari correnti. Nell'elaborazione dei dati, i singoli codici diagnostici ICD-10 sono stati considerati come se fossero parole; di conseguenza, i profili diagnostici costituiti dall'insieme dei codici riportati nelle quattro cause di morte, sono stati considerati come frasi e l'intero record di un soggetto come documento. Ciò ha consentito di estrarre conoscenza dalle stringhe di testo contenute nel data-set sopra descritto, attraverso l'applicazione sia del text mining processing classico, sia del modello BERT [10,11].

L'addestramento del modello di classificazione è stato realizzato mediante gli algoritmi di Machine Learning Support Vector Machines [12] e Random Forest [13] ed è stato effettuato nel sub-set di dati contenente l'80% delle stringhe di testo con le diagnosi delle schede di morte appartenenti alla seconda ondata epidemica; il restante 20% è stato impiegato come test set. Il modello così addestrato e testato è stato successivamente applicato al set di dati relativi alla prima ondata dell'epidemia, in modo da individuare i casi falsi positivi che risultano dal modello di classificazione, che identificano le schede con causa iniziale di morte non attribuita all'infezione da Covid-19 secondo le consuete regole di assegnazione, ma classificate dal modello addestrato invece come mortalità per Covid-19.

Risultati

Impiegando l'algoritmo BERT nell'estrazione della conoscenza dalle stringhe di codici diagnostici, si osserva un netto miglioramento delle performance, espresse dalla Balanced Accuracy.
L'algoritmo di classificazione più adatto sembra essere l'SVM Radial, con performance leggermente più elevate sul test set. Il modello addestrato con questo algoritmo individua 98 casi falsi positivi (8,22%), di cui 68 in marzo e 16 nella prima settimana di aprile 2020. La mediana dei valori "prob" (livello di confidenza associato a ciascuna predizione) dei 98 falsi positivi identificati è pari a 0,799.

	Balanced Accuracy sul test set	Numero falsi positivi sul test set	Balanced Accuracy sul data-set marzo-aprile 2020	Numero falsi positivi sul data-set marzo-aprile 2020	Mediana dei valori "prob" dei casi falsi positivi
Text mining classico					
SVM Linear	0,7936	2/425 (0,47%)	0,7380	38/1192 (3,19%)	0,910
SVM Radial	0,7791	2/425 (0,47%)	0,7267	38/1192 (3,19%)	0,964
Random Forest	0,7936	2/425 (0,47%)	0,7383	48/1192 (4,03%)	0,925
BERT					
SVM Linear	0,8620	21/425 (4,9%)	0,8280	81/1192 (6,80%)	0,648
SVM Radial	0,8724	15/425 (3,53%)	0,8170	98/1192 (8,22%)	0,799
Random Forest	0,8688	15/425 (3,53%)	0,7938	99/1192 (8,31%)	0,700

Conclusioni

I modelli di classificazione di stringhe di codici diagnostici ICD-10 sperimentati, hanno evidenziato buone performance, e sono stati impiegati per l'individuazione delle schede di morte ISTAT, relative alla prima ondata epidemica (marzo-aprile 2020), collegate ad una probabile mancata segnalazione dell'infezione da Covid-19. Operativamente, i risultati delle analisi eseguite possono essere utilizzati per prioritarizzare la scelta dei soggetti deceduti/schede di morte da sottoporre a eventuale revisione della documentazione clinica, migliorando così la qualità dei dati relativi alla mortalità per Covid-19. Un miglioramento nei risultati dello studio è stato osservato con l'applicazione del modello per l'elaborazione del linguaggio naturale BERT, in grado di considerare il contesto di ciascuna frase sia dal lato destro, sia dal lato sinistro di ogni parola. Questa capacità di modellare contesti bidirezionali è indubbiamente importante proprio per l'analisi di stringhe di testo contenenti codici relativi a diagnosi o prestazioni sanitarie.

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ATTI DEL
XI CONGRESSO NAZIONALE
sismec 2021

Società Italiana di Statistica Medica
ed Epidemiologia Clinica

Venerdì 17 settembre 2021

AULA PARALLELA

EPIDEMIOLOGIA (GENERALE E CLINICA)

IMPACT OF FRAILTY ON OUTCOME AFTER TRAUMATIC BRAIN INJURY: DATA FROM CENTER-TBI VALIDATED IN TRACK-TBI

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Introduction. Frailty is a consequence of cumulative deterioration in several physiological domains, and is envisioned as a state of vulnerability after a stressor event. Rockwood developed a Frailty Index (FI) that incorporates the accumulation of deficits across different domains measuring frailty from a multidimensional perspective [1-2]. The proposed FI is reproducible and has proved to be applicable to many diseases and conditions, as items from the FI may be incorporated or omitted according to the clinical context.
Substantial evidence shows that frailty is associated with poorer outcomes in individuals admitted to hospital for heterogeneous medical and surgical conditions requiring intensive care, including recently, COVID. Little has been reported regarding the association of frailty and outcomes for patients with traumatic brain injury (TBI) across the range of injury severity. In these few studies, frailty was frequently assessed with tools that do not fully capture the multidimensional biological and physiological dimensions of frailty and limited their exploration to older adults. Chronological age, TBI severity, clinical, and tomographic data are customarily utilized as early descriptors and predictors of outcome post injury. However, the widely used TBI prognostic models (i.e., Extended-IMPACT [3]), which incorporate age along with other indicators of trauma severity, result in not optimal prognostic performances among TBI patient. Assessing pre-traumatic patient status through the evaluation of frailty may better inform prognosis.

Aims. There is scant evidence on the impact of frailty in patients with traumatic brain injury (TBI). The present study aims to assess and externally validate whether frailty - captured with an accumulation of deficits approach - is associated with 6-month outcome in a large cohort of TBI patients

Methods. The Collaborative European NeuroTrauma Effectiveness Research in TBI "CENTER-TBI" study is a longitudinal, prospective study enrolling patients with TBI presenting to 65 centers in Europe. The current sub-study was preregistered on the CENTER-TBI proposal platform and included TBI subjects in the strata admitted to hospital for whom outcome evaluation at 6 months was available. A cumulative deficit approach was used to create a novel frailty index (CENTER-TBI FI) based on 34 items derived from data available in the CENTER-TBI database. From the individual cumulative CENTER-TBI FI (range 0-34), we obtained a standardized value (range 0-1), with high scores indicating higher levels of frailty. The role of the CENTER-TBI FI on the 6-month GOSE was assessed through a proportional odds logistic model adjusted for predictors of the Core IMPACT model (i.e., age, motor GCS at arrival, and pupillary reactivity). GOSE was evaluated as an ordinal outcome with 4 categories: dead (GOSE 1), vegetative state and severe disability (including lower and upper-severe disability, GOSE 2-3-4), moderate disability (including lower and upper-moderate disability, GOSE 5-6), and good recoveries (including lower and upper good recovery, GOSE 7-8). The proportionality assumption was checked for all variables, while the linearity assumption was assessed for continuous variables. In addition, to evaluate the potential differential value of the CENTER-TBI FI on older adults (defined as aged ≥65 years according to the WHO), an interaction term was assessed with a likelihood ratio test. External validation was performed on data from Transforming Research and Clinical Knowledge in TBI (TRACK-TBI), a prospective, observational study co-designed with CENTER-TBI, that enrolled patients with TBI at 18 U.S. Level I trauma centers.

Results. A total of 2993 from CENTER-TBI participants were included in this analysis. The overall median CENTER-TBI FI score was 0·09 (I-III quartiles=0·03-0·15), with median score of 0·16 (I-III quartiles=0·09-0·25) in older adults (age ≥ 65 years). Increase in frailty was significantly associated with the probability of death or severe disability (cumulative odds ratio=1·03, 95%CI 1·02 to 1·04, p<0·0001), and was stronger for participants admitted to hospital wards (OR=1.05, 95%CI 1·03 to 1·06, p<0·0001) compared with those admitted to the ICU (OR=1.02, CI95% 1·01 to 1·03 p=0·0008). Data from the TRACK-TBI (n=1667) external validation cohort supported the robustness and reliability of these findings.

Conclusions. With the ageing of the TBI population, and frail patients more prone to experiencing a traumatic event, accurately assessing frailty has taken on increasing relevance. We developed and externally validated a TBI-specific FI. Our results indicate a significantly increased risk of unfavourable outcome in participants with a high FI score, regardless of age, and a greater impact for the subset of patients with less severe trauma. Systematic screening of frailty in primary care may help to identify patients at risk of poorer outcome after mild to moderate TBI.

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FORECASTING DRINKING BEHAVIOR AMONG ADOLESCENTS IN HBSC COUNTRIES: A BAYESIAN FRAMEWORK FOR MAKING PREDICTIONS

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Introduction

Alcohol use and abuse in adolescence may have a variety of adverse social, physical and psychological consequences for young people including missing school, school failure, having unprotected sex (with unintended pregnancy and sexually transmitted diseases as consequences), destructive behavior, increase in injury likelihood, violence and even deaths [1-5].

The behavioral pattern of adolescents who consume alcohol can become even more complex: findings from many studies confirm the co-occurrence of health risk behaviors, the idea that young adolescents exhibit multiple health risk behaviors that tend to cluster together [6-9] and also the evidence of strong similarities between countries in the clustering of adolescent risk behaviors [10].

Despite a trend of declining in alcohol consumption simultaneously to its abstinence increase among adolescents highlighted by different authors [11,12] and confirmed by data from the two most recent waves of HBSC surveillance (2014 and 2018), alcohol remains the most commonly substance used by 15-year-olds: overall almost three in five have drunk alcohol in their lifetime, compared with one in four for smoking and around one in seven that use cannabis [13,14]. For decades two main models of alcohol consumption among adolescents have been described in Europe: the "dry culture" model in Northern Europe, characterized by sporadic consumption, mainly concentrated in the weekend, outside of mealtimes with the primary aim to get drunk; the "wet culture", specific to the Mediterranean countries, characterized by more regular alcohol consumption, with greater overall quantities, but associated with meals and rituals. In this framework, Italy had a long-standing "wet culture" that has always been associated with high levels of alcohol consumption, especially wine [15,16]. However, recent reports indicate also for Italy and other Mediterranean countries an increase of the phenomenon of drinking ''out of meal'' and the growing tendency to approximate a Northern European style in the use of alcohol, that is, binge drinking [17,18].

Aims

Aim of our study is to work on alcohol trends in the last 30 years of HBSC surveillance to implement a Bayesian framework for clustering longitudinal observations and make projections for the next survey (2022). Inclusion criteria for countries are: availability of data from the last survey (2018) and of at least 3 out of 9 waves since 1986.

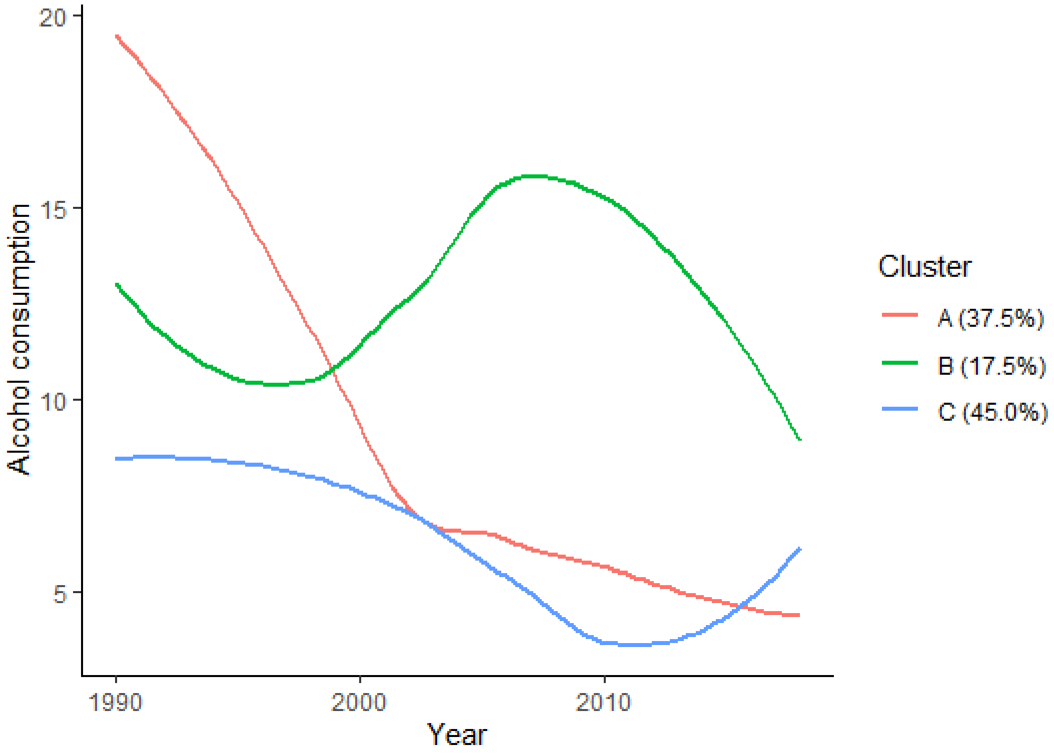
Methods

Measures. Adolescents were asked how often they consumed alcoholic beverages, included beer, wine, spirits, alcopops, aperitifs, cider, cocktail and other. Answer categories were: 'never', 'rarely', 'monthly', 'weekly' and 'daily' alcohol consumption. Responses were coded as less than weekly and weekly or more frequently.

Statistical analysis. A Bayesian clustering model was run on the time series of weekly alcohol consumption in HBSC countries. The Bayesian clustering model was based on Dirichlet Multinomial Clustering on the weekly alcohol consumption. The probabilistic model for the latent cluster membership was defined using a multinomial logit model. Finally, a semi-parametric Bayesian analysis based on a non-parametric Dirichlet process prior was carried out to better explain the heterogeneity between clusters. A Gibbs sampler approach was used to obtain samples from the posterior distribution with 50,000 iterations and 10,000 burn-in iterations.

Results

In preliminary results, three clusters were identified according to the marginal posterior, which was considered the natural measure of the appropriateness of grouping, i.e., the clustering that maximized the marginal posterior was taken to be optimal. The size of the clusters was 18 (45%), 7 (17.5%) and 15 (37.5%) out of 40 countries. The trajectories over time of alcohol weekly consumption are shown in figure 1.



Conclusions

Data from the last international survey confirm alcohol as the most commonly used substance by 15-year-olds, despite the decline of lifetime use in recent years, and a general trend in reduction of more frequent consumption (weekly or more) in the last decades.

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SEX-RELATED DIFFERENCES IN ACUTE CORONARY SYNDROME HEALTHCARE: EVIDENCE FROM AN ITALIAN REAL-WORLD INVESTIGATION

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Background: Cardiovascular diseases are the leading cause of death globally, accounting for 17.9 million deaths each year. Acute coronary syndrome (ACS), which causes most of the deaths related to ischaemic heart disease, includes different manifestations of myocardial ischemia. Considerable evidence has been provided in the last years showing sex differences in epidemiology, treatment, and outcomes in ACS patients. Several studies demonstrated that women are older and have more comorbidities at the first ACS episode, explaining the observed differences in in-hospital mortality and in the brief-term prognosis. In addition, evidence exists that women were less treated in hospital. However, few studies investigated sex differences in the out-of-hospital management of ACS, especially for no pharmacologic treatments, observing conflicting findings. With these premises, a large real-world study investigating the cohort of patients admitted to the hospital for their first episode of ACS was carried out.

Aim: This study investigates in a cohort of patients discharged for ACS whether there are sex differences in: (i) the risk of experiencing relevant clinical events (second ACS episode, cardiovascular hospitalization, all-cause death), (ii) treatments and assistance, and (iii) the effect of treatments on preventing clinical outcomes.

Methods: The cohort of 90,779 patients resident in Lombardy Region (Italy), aged 40-90 years, who were hospitalized for ACS during 2011-2015 was identified through administrative databases and followed until 2018.

A logistic regression model was used to compare the intra-hospital mortality among women and men providing odds ratio estimate (OR) and its 95% confidence interval (CI). The probability of experiencing a specific outcome (ACS, any other cardiovascular event or death) from the day after the hospital discharge until the end of follow-up was estimated through the cause-specific cumulative incidence function.

Exposure to post-hospital recommendations, including the use of selected drugs (beta-blockers, statins, renin–angiotensin system blockade agents, and dual antiplatelet treatment), diagnostic procedures (echocardiogram, electrocardiogram, and cardiologic visit), laboratory tests (lipid profile test) and cardiac rehabilitation, was recorded during the year after the index hospitalization. Standardized Differences and McNemar tests were performed to compare adherence to healthcare services between men and women.

The probability of experiencing a specific outcome (ACS, CV event or death) from the day after the index discharge until the end of follow-up was estimated through the cause-specific cumulative incidence function.

To investigate whether sex modifies the relationship between adherence to recommendations and the risk of the composite outcome (cardiovascular hospitalization or death), a proportional hazard regression model was fitted to estimate the hazard ratio (HR) and its 95% confidence interval (CI).

Results: Among 90,779 patient at first ACS episode there were 31,671 women (34.9%) and 59,108 men (65.1%). Women were older, with a mean age of 75.05 years (standard deviation SD 11.19) vs. a mean age of 67.63 years in men (SD 11.99), and had a worst clinical profile.
Women showed a higher unadjusted risk of in-hospital death compared to men (OR: 1.69, 95%CI: 1.60 – 1.79). There was no evidence of between-sex differences in in-hospital mortality after adjusting for baseline characteristics (OR: 1.02, 95%CI: 0.96 – 1.08). At 5 years from the index discharge, among those who survived the index hospitalization, 54% vs. 45% of women and men respectively experienced at least a health-related outcome (p<0.001). After taking into account for personnel characteristics (such as age, MCS score, comorbidities), these figures were 50% and 54% (p<0.001), respectively.
Among the 63,422 subjects that accumulated more than one year of follow-up, men were more exposed to healthcare recommendations. Men were prescribed more drug therapies, especially statins (90% vs. 78%, p-value<0.001) and beta-blockers (83% vs. 80%, p-value<0.001) drugs. Overall, 41% of men and 29% of women received at least three out of four drugs (p<0.001). Among drug users, more men were adherent to the treatment (77% vs. 65% for statins users, 59% vs. 55% for beta-blockers users). In addition, men underwent more outpatient services, both in terms of controls (83% vs. 79% men vs. women underwent at least two out of three controls respectively, p-value<0.001) and cardiac rehabilitation (5% vs. 2%, p-value<0.001).
An adjusted Cox regression model showed that men risk to have relevant clinical outcomes after ACS discharge about 14% times more than women (95% CI: 8% - 19%), and confirmed that greater adherence to recommendations is associated with a lower probability of experience clinical outcomes, especially adherence to cardiac rehabilitation program. According to the p-value of the interaction terms, there was no evidence that sex modified the relationship between recommendations and the clinical composite outcome.

Conclusions: Because advantages for both women and men are expected from improving adherence with guidelines-driven recommendations, a tight out-of-hospital healthcare control of ACS patients must be considered the cornerstones for obtaining clinical benefits.

HOW TO INVESTIGATE HUMAN HEALTH EFFECTS RELATED TO EXPOSURE TO MIXTURES OF PFAS: A SYSTEMATIC REVIEW

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Introduction

Humans are daily exposed to several per- and polyfluoroalkyl substances (commonly known as PFAS) [1], a group of man-made chemicals that are resistant to degradation in the environment and tend to bioaccumulate in the human body [2]. Epidemiological research has associated exposure to PFAS to a wide range of adverse health effects, involving cardio-metabolic, immune, endocrine and reproductive systems [3].

Most studies considered each PFAS individually, while the health effect of their simultaneous exposure have only recently become a pressing issue [4] [5]. Although several statistical methods can model the exposure as a function of the mixture of exposure, none of them outperforms the other. The decision must be made based on strengths and limitations of each approach, as well as their relevance to the primary research question [6].

Objectives

We aim to perform a comprehensive overview of the existing studies which evaluated the association between exposure to mixtures of PFAS and any adverse human health effect, reviewing the statistical methods used in these studies.

Methods

The search was conducted according to the general methodology of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [7]. We considered PubMed, Embase and Scopus databases, selecting a series of keywords referred to "PFAS and synonyms" and "mixture"; considering that available information about health effects related to PFAS exposure is very broad, we did not include keywords related to this topic. The search was limited to papers published in the last ten years (between 1st January 2011 and 8th April 2021), since the most recent and accurate statistical methods used to evaluate the effects of mixtures were developed after 2014 [8] [9].

Covidence software was used to screen and select relevant papers. The screening was conducted by two reviewers working independently. Complete information on inclusion criteria, based on PECO (population, exposure, comparator and outcome) format, can be found in Table 1. Review articles and conference abstracts were not included. A supplementary search was conducted screening the references contained in the selected papers, for identifying additional literature.

Table 1. Population, Exposure, Comparator, and Outcome (PECO) criteria

PECO element	Evidence
Population	Human: any population without restrictions
Exposure	Measured occurrence of exposure to a mixture of at least two different PFAS, or to various mixtures including PFAS among their components; the entity of exposure needs to be measured by determining concentrations of PFAS in biological fluids
Comparator	-
Outcome	Any type of effect on human health

Results

A total of 3,640 studies were retrieved using the search strings mentioned above; 1,520 duplicates were removed, and 2,120 remaining papers were eligible for the selection process. After title/abstract screening, 94 papers were selected for a full-text review; 53 studies were further excluded, leaving 41 papers considered for the present review. The references' screening returned a total of 4 additional papers to be included.

Most of the studies were conducted in Asia (n=22) and North America (n=17), followed by Europe (n=6). The totality of the studies covers a period of data collection that ranges from 1991 to 2018.

Almost all the studies (n=37) were published in the years 2019-2021, suggesting that the interest on the mixture's topic has highly increased in the last few years.

The population of interest in most of the included studies are pregnant women or mother-child pairs (n=28); the remaining studies include adult populations or children. The interest in evaluating adverse effects of PFAS exposure in utero is due to the underlying biological mechanism of these compounds [10]. PFAS typically bioaccumulate with higher prevalence during pregnancies, passing through the placental barrier, which may disrupt fetal development [11].

Most of the study designs are cohort studies (n=27), followed by cross-sectional studies (n=14). The median sample size is 499, with minimum of 56 and maximum of 8778 participants included. Concentrations of PFAS were measured in serum or plasma samples, and mixture effects were assessed considering an average of 6 different PFAS.

Several statistical methods are used to assess the mixture effect; most commonly Weighted Quantile Sum (WQS) regression (n=17) and Bayesian Kernel Machine Regression (BKMR, n=18) are used, followed by Principal Components Analysis (PCA, n=9), Structural Equation Modeling (SEM, n=4) and Machine learning g-computation (n=4).

The included studies investigated a wide range of health outcomes: immunity (n=8), fetal development (n=5), neurodevelopment (n=4), reproductive hormones (n=6), thyroid homeostasis (n=7) and outcomes related to metabolic pathways (n=15).

Conclusions

This works highlighted the importance of evaluating the effect of exposure to multiple chemical compounds, which occur in the environment simultaneously. The necessity to assess the toxicity as a joint effect, taking into account possible interactions, is now well recognized in epidemiological studies [12].

The results of the review show that the most used methods are WQS and BKMR, even if there is still difficulty in finding an adequate statistical method that can fully assess the role of mixtures, to the point that some authors believe that existing methods can be used as complementary, rather than equal in utilization [13].

Further investigation is needed to understand which of the existing methods performs better in multi-pollutant analysis, once the research objective has been defined. Given the fact that this problem is relatively recent, implementation of novel approaches to explore the association between mixtures and health outcomes is still ongoing [14].

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PROGNOSTIC ROLE OF TUMOR/STROMAL CXCR4-CXCL12-CXCR7 EXPRESSION IN MITO16A ADVANCED OVARIAN CANCER PATIENTS

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Introduction

Epithelial ovarian cancer (EOC) accounts for approximately 90% of ovarian cancers [1]. Poor prognosis depends on late diagnosis, acquired resistance to platinum-based regimen [2,3] and recurrence [4]. The anti VEGF antibody, bevacizumab, prolongs progression-free survival in newly diagnosed and relapsed EOCs [5]. It is crucial to identify biological features allowing patient characterization and optimal therapeutic approach [6]. Accumulating evidence suggests that the CXCL12/CXCR4/CXCR7 axis plays a pivotal role in tumor development, survival, angiogenesis, metastasis, and tumor microenvironment.

Aim

We evaluate the prognostic role of CXCR4/CXCL12/CXCR7 expression, neoplastic epithelial and stromal cells in advanced ovarian cancer patients participating to MITO16A (EudraCT number: 2012-003043-29).

Methods

The MITO16A is a single arm, multicenter, open-label, non-comparative, phase IV trial. 398 patients were included from 47 participant centers. Primary endpoint included investigation of possible prognostic biomarkers for using bevacizumab in OEC first line chemotherapy. Immunostaining was performed for CXCR4, CXCR7 or CXCL12 using Tissue Microarrays (TMA) from paraffined samples. Staining intensity was scored as 0 (negative), 1 (weak), 2 (moderate), or 3 (strong). The percentage of tumor cells stained were counted and H-Score was calculated. Marker's expression was separately evaluated on epithelial ovarian cancer cells and stromal cells within each TMA core.

Data were described using mean and standard deviation or median and interquartile range for quantitative variables, – according to their distribution, and absolute and relative frequency for qualitative variables. Each single biomarker was graphically described by histogram evaluating its distribution and highlighting the presence of high frequencies of 0 values. The correlation between biomarkers was investigated by a modified version of Kendall test for zero inflated values [7]. The association of each biomarker with the clinical prognostic factors was assessed using the Wilcoxon rank test for zero-inflated data for dichotomous variables and the Kruskal-Wallis zero inflated for categorical variables, both test with the use of permutation. Prognostic effect of clinical characteristics and biomarkers was tested considering Progression Free Survival (PFS) and Overall survival (OS) as endpoints. PFS was defined as the time from the inclusion into the study to the first occurrence of either death for any cause or disease progression. OS was defined as the time from the inclusion into the study and death for any cause. For each pair of biomarkers (epithelial and stromal expression) the prognostic value of biomarker pair was tested: 1) estimating a model with the biomarkers as continuous variable after testing the linearity assumption using fractional polynomial and a dummy variable to estimate effect of 0 value, and testing interaction between tumor and stromal biomarker expression; 2) searching for the best cut-off value defined as the biomarker value that minimize the p-value of HR in a model adjusted for the other component (epithelial or stromal). The best cut-off search was calculated on PFS and then applied to the OS. To adjust for overfitting HRs estimates of best cut-off categories were calculated using a shrinkage procedure with 95% CI calculated with bootstrap-percentile method [8]. All analyses was then adjusted for clinical characteristics: age, ECOG performance status (PS), Residual disease, FIGO stage and Tumor histology. Data were analyzed using R software version 3.6.0.

Results

308 EOC patients enrolled in the study Mito 16A were evaluated for tumor epithelial and stromal expression through immunohistochemistry. In the defined population, the median age was 58.8 years (range 49.8-65.9), with 28.6% of patients ≥65 years old. At diagnosis, most patients had a good PS ECOG 0 (80.2%) and FIGO stage IIIC (71.1%). High grade serous carcinoma was the most common histological type (85.7%). Correlations among markers were weak suggesting that CXCR4, CXCL12 and CXCR7 expression is independent in EOC. Stromal CXCR7 and CXCL12 significantly associated with FIGO stage (p=0.007 and 0.033, respectively). Stromal CXCR7 and CXCL12 were significantly reduced in FIGO stage IV coherent with a tumor microenvironment migration favoring.

Out of 308 patients analyzed 221 progressed and 102 died. In the univariate survival analysis considering continuous biomarkers no significant associations were detected for PFS and OS. In univariate analysis considering biomarkers cut-off, epithelial high CXCL12 appeared negatively associated with PFS (HR 1.39, 95%CI 1.06-1.81, p=0.016) and OS (HR 1.64, 95%CI 1.11-2.42, p= 0.014); no associations were found for CXCR7 and CXCR4 with PFS or OS. However, using the shrinkage procedure with confidence interval bootstrapCXCL12 lost significant p value (Table1). Similar results were found in multivariate analysis.

Conclusions

This study represents the first prospective study in which the whole axis was systematically evaluated in a homogeneous EOC population. Our findings shed light into the key role of CXCL12, CXCR7 and CXCR4 through objective and rigorous statistical methods well-controlled in ovarian cancer clinical data.

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Table 1. Univariate analysis of biomarkers best cut-off for PFS and OS, original and shrunken coefficients.

	Original coefficients			**Shrunken coefficients**		
	HR	**IC(95%)**	**p**	**HR**	**IC(95%)**	**p**
			Progression Free Survival			
CXCR7 epithelial (> 36.7 vs ≤ 36.7)	0.79	(0.6-1.04)	0.093	0.86	(0.4-1.85)	0.695
CXCR7 Stromal (> 20.0 vs ≤20.0)	1.16	(0.88-1.54)	0.297	1.01	(0.49-2.09)	0.974
CXCL12 epithelial (> 21.7 vs ≤21.7)	1.39	(1.06-1.81)	**0.016**	1.31	(0.67-2.58)	0.430
CXCL12 Stromal (> 6.7 vs ≤6.7)	0.67	(0.4-1.11)	0.117	0.79	(0.4-1.56)	0.490
CXCR4 epithelial (> 130.0 vs ≤ 130.0)	0.69	(0.43-1.08)	0.106	0.79	(0.34-1.83)	0.585
CXCR4 Stromal (> 65.0 vs ≤ 65.0)	0.77	(0.51-1.16)	0.209	0.91	(0.42-1.96)	0.807
			Overall Survival			
CXCR7 epithelial (> 36.7 vs ≤ 36.7)	0.84	(0.56-1.28)	0.423	1.10	(0.19-6.21)	0.916
CXCR7 Stromal (> 20.0 vs ≤20.0)	1.23	(0.81-1.86)	0.335	0.98	(0.2-4.9)	0.985
CXCL12 epithelial (> 21.7 vs ≤21.7)	1.64	(1.11-2.42)	**0.014**	1.51	(0.66-3.48)	0.334
CXCL12 Stromal (> 6.7 vs ≤6.7)	0.54	(0.24-1.24)	0.149	0.73	(0.12-4.47)	0.732
CXCR4 epithelial (> 130.0 vs ≤ 130.0)	0.56	(0.27-1.18)	0.130	0.72	(0.13-4.02)	0.710
CXCR4 Stromal (> 65.0 vs ≤ 65.0)	0.68	(0.37-1.24)	0.210	0.87	(0.21-3.68)	0.849

COSTS AND EFFECTIVNESS OF THE EARLY-ARTHRITIS CLINIC IN THE MANAGEMENT OF PATIENTS WITH RHEUMATOID ARTHRITIS. RESULTS FROM THE RECORD LINKAGE OF RHEUMATIC DISEASE STUDY AND THE ELECTRA STUDY OF THE ITALIAN SOCIETY FOR RHEUMATOLOGY.

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Background

The diagnosis and treatment of inflammatory rheumatic diseases - and of rheumatoid arthritis (RA) in particular - can be delayed implying a long waiting period for an appointment with a rheumatologist [1]. Early access to an accurate diagnosis, prognostic stratification and early treatment with strict monitoring of clinical response are the fundamental steps for a correct management of patients with early-onset RA. Although the possibilities and the potential of the health model of an early arthritis clinic (EAC) to deliver the aforementioned aims have been known since 1980s [2], such clinics are not widespread in Italy. A reason can be that despite there is supported evidence that dedicated EACs improve referral lag time and reduce delay in establishing disease-modifying therapy, it remains questionable whether EACs improve relevant disease outcomes and are economically sustainable [3].

Objective

Aim of this analysis is to evaluate whether treating patients in an EAC or in non-specialized facilities (non-EAC) implies a difference in terms of number and length of hospitalizations, of adherence to international quality of care guidelines and of costs in euros.

Methods

The design of the study involves two cohorts: i) patients with incident RA treated in the EAC of IRCCS San Matteo of Pavia (Lombardy), ii) patients with incident RA treated in non-specialized facilities (non-EAC) of Lombardy, recruited from RECORD database based on administrative healthcare database (AHD). For both cohorts the enrolment period was from 2006 to 2011.

For each patient of EAC cohort, clinical information and information from AHD were available (the ELECTRA database).

From RECORD database, we excluded patients already present in ELECTRA and we randomly selected the cohort of non-EAC patients, with a ratio of 1:4 respect to subject of EAC cohort.

Each member of both cohorts was followed from diagnosis for two years to identify the costs of care (in terms of hospitalization, drugs and outpatient services), the number and length of hospitalizations, and the adherence to quality of care guidelines (dichotomized in high/medium vs low adherence) [4].

To model the costs, a quantile regression model (to estimate the difference in the median costs of EAC and non-EAC group) was applied whereas the number of hospitalizations and the days of hospitalization was modelled by a zero-inflated negative binomial regression model. Finally, a penalized logistic regression model (with lasso penalty) was considered when the outcome was the adherence to quality of care guidelines to shrink model coefficients. The tuning parameter for penalization was obtained through *likelihood cross-validation. The 95% confidence intervals (CI) of penalized logistic regression coefficients were obtained through 1000 bootstrap re-sampling. All estimates were adjusted for sex, age, year of RA diagnosis, Charlson Comorbidity Index (CCI), a polypharmacy indicator and the number of hospitalizations before diagnosis.*

To compare EAC versus non-EAC in terms of costs we considered the incremental cost-effectiveness ratio (ICER). Due to skewness of costs distribution, we calculated two ICER derived from the ratio between the mean (or median) of days free from hospitalization, as effectiveness measure, and the mean (or median) of daily costs, as numerator. Estimates of ICER and corresponding 95% CI were obtained via 1000 bootstrap re-samplings.

Results

The EAC cohort consisted of 430 patients and non-EAC of 1720. Both cohorts consisted predominantly of female patients. In EAC cohort patients were significantly younger (53.5 vs 55.9), with higher CCI (0.33 vs 0.25) and polypharmacy index (5.3 vs 4.7).

The difference in median costs between EAC and non-EAC, adjusted for the covariates mentioned above, was 420.8 euros. In other terms, the National Health Systems (NHS) should spend an additional 420.8 euros to treat for two years a patient with RA in EAC.

The expected number of hospitalizations and the length of stay were statistically higher in non-EAC versus EAC (1.51 [1.24, 1.85] and 2.29 [1.64,3.20] respectively). The risk for a patient to fall into the "low adherence quality of care" group was significantly higher than for a patient managed in EAC.

The estimated mean-based ICER was -147.5 euros [-841, 527]. The estimated median-based ICER was 268.59 [90.4, 597.3]. Considering the ICER calculated with the mean values, an earned day free from hospitalization for an EAC patient corresponds also to a cost saving of 147.5 euros. Instead, considering the ICER with median values, the additional cost will be equal to 268.6 euros.

The two plots below show the distribution of mean-based and median-based ICER obtained through bootstrap re-sampling (Figure1).

Conclusion

In conclusion, patients treated in an EAC show a significant increase in all the efficacy outcomes analyzed, in particular they show greater adherence to guidelines and a reduction in the length of hospitalization.

Policy makers should evaluate the sustainability of costs for treatment of RA patients in an EAC.

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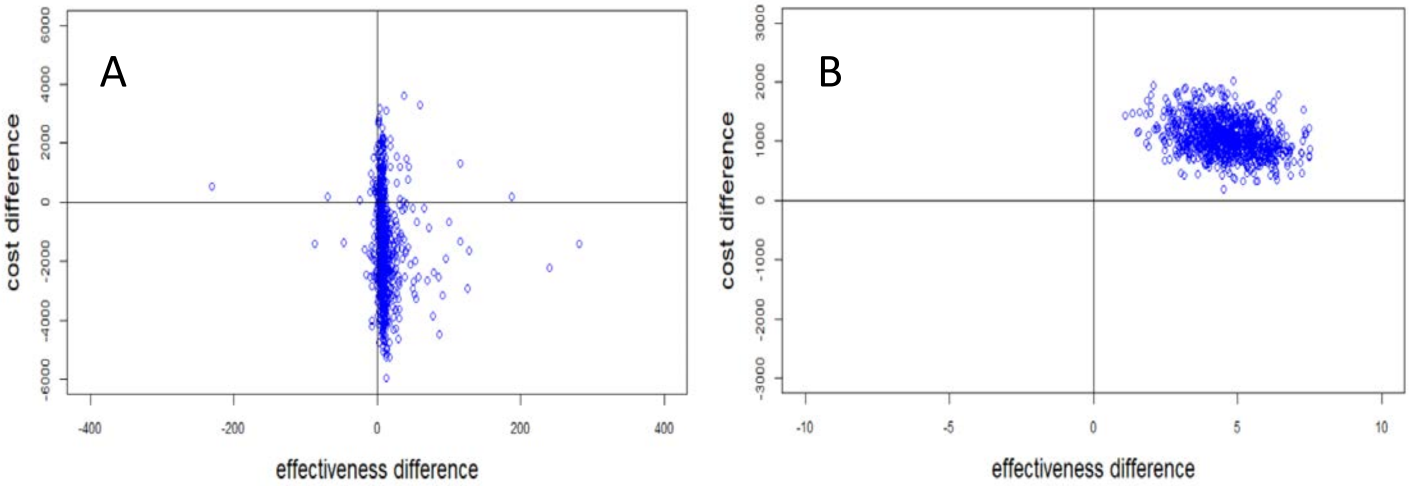
Figure

Figure1. Mean-based ICER (panel A) and median-based ICER (panel B) obtained through bootstrap re-sampling. The points represented in the figure show the ICER calculated in each bootstrap replication. On the horizontal axis the mean or median difference in costs between EAC and non-EAC is shown, while on the vertical axis the mean or median difference in days free from hospitalization is shown.



ATTI DEL

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POSTER

EPIDEMIOLOGIA (GENERALE E CLINICA)

Risk Factors Associated with Nursing Home Covid-19 Outbreaks: A Retrospective Cohort Study

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ABSTRACT

Introduction

Long-term care facilities for the elderly encompass a broad range of institution types, with or without the delivery of skilled nursing care [1] and bear a disproportionate amount of the disease burden and mortality [2]. It has proved to be one of the most at-risk environments for COVID-19 infections globally due to various contributing factors [3]. The COVID-19 pandemic has affected the vulnerable people hosted in residential facilities more than any other category, with this group making up between 19% and 72% of all SARS-CoV-2-related deaths [1]. This is, therefore, important to understand the trends and risk factors associated with the spread of COVID-19 in long-term care facilities.

Objectives

This study examined the relationship between the extent of COVID-19 outbreaks and nursing home's characteristicsamong nursing homes located in the Autonomous Province of Trento (Italy) during the "first wave" (March-May 2021) of the COVID-19 pandemic.

Methods

A retrospective cohort study was conducted by enrolling all the 57 nursing homes with a total of 5,145 licensed beds in the Autonomous Province of Trento, Northeastern Italy. Data on cases of SARS-CoV-2 infection was obtained from the Healthcare Trust of the Autonomous Province of Trento, the provincial entity in charge of collecting and reporting all official data since the onset of the pandemic. All diagnoses were confirmed with molecular diagnostics for SARS-CoV-2 (Reverse Transcription Polymerase Chain Reaction, RT-PCR) performed in the provincial reference laboratory. Organizational and structural specific information and data related to IPC measures were retrieved from another study carried out in May 2019 as part of a broad regional project initiated to improve infection prevention and control programs and tackle antibiotic resistance in nursing homes. This data was collected using a standardized questionnaire that was piloted and administered to all nursing homes in the province. The association between the median cumulative incidence of COVID-19 cases (confirmed with an RT-PCR molecular test) among residents and the characteristics of the nursing homes was assessed by Mann–Whitney U test, Kruskal–Wallis test or Spearman rho, when appropriate. To evaluate the potential confounding of geographical area (North, South, East, West) on the infection prevention and control measures, a two-level random intercept logistic model was fitted to the data, with level 1 units (patients in nursing homes) nested into level 2 units (nursing homes). The dependent variable was being a case of COVID-19 (dichotomous variable), and we included, as independent variables, the geographical area and the infection prevention and control measures separately in the model.

Results

Overall, 37 (64.9%) of the 57 facilities had reported at least 1 resident COVID-19 case, with a median cumulative incidence of 4.8% (Interquartile Range (IQR): 0-40%). The median cumulative incidence of outbreaks of COVID-19 in nursing homes participating in the survey was 2.9%, and 17% among homes not participating, but this difference was not statistically significant. The cumulative incidence of COVID-19 in nursing homes was moderately correlated with the cumulative incidence of COVID-19 in the municipalities where the nursing homes were located. The median cumulative incidence for the nursing homes was

significantly associated with the geographical region (p=0.002). Nursing home cases clustered in the Western part of the province showed the highest median cumulative incidence (45%) compared to others: this part of the province borders to Lombardy region that was the most affected by the COVID-19 pandemic. The implementation of outbreak management procedures seemed to be associated with a lower median incidence of COVID-19, without reaching statistical significance. All the other variables considered in our analysis were not significantly associated with the extent of COVID-19 outbreaks in nursing homes. The multivariate models confirmed that none of the considered infection prevention and control measures was significantly associated to the likelihood of being a case of COVID-19. In each model, the likelihood of being a case was significantly larger in the Western region with respect to the remaining areas of the province.

Conclusions

The COVID-19 outbreak in this region confirmed the vulnerability of nursing homes in the face of the COVID-19 pandemic. In this national cohort study of long-stay nursing home residents, the risk of SARS-CoV-2 was associated with the geographic area. However, in our study, there were no other factors associated with COVID-19 infections.

We could explain our findings in the context of the extraordinary impact of the COVID-19 pandemic in Italy, with a sustained viral circulation across all of Northern Italy, including the Autonomous Province of Trento, as well as a very rapid spread of cases and deaths in the first phase (February-May 2020) in nursing homes [ISS]. In view of this pandemic, it could be hypothesized that no structural, staffing or other identifiable factors related to ongoing prevention and control programs could have been crucial in effectively contrasting the spread of COVID-19 in nursing homes in Italy in the early stages of the pandemic.

The lack of an association between IPC measures and the reporting of COVID-19 cases could also be explained by the exceptionality of the infection control measures needed. In order to deal effectively with comparable scenarios in the future, it is necessary to design and plan tailored measures that can be implemented as quickly as possible, if necessary, which should regularly be updated in cooperation with local public health authorities.

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BLOOD BACTERIAL DNA IN RELATION TO ADENOMA AND COLORECTAL CANCER RISK.

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Introduction

Colorectal cancer (CRC) is the 3rd more common cancer worldwide [1]. In Europe, predicted deaths were 174 600 in 2020 corresponding to a (world standardized) rate of 15.4/100 000 in men and 8.6/100 000 in women [2-4].

CRC screening programs can suffer of low adherence with CRC screening recommendations - mainly due to the refusal of fecal test. Innovative, non-invasive diagnostic tests would be of support for CRC control [5, 6].

Dietary habits, such as high red-meat consumption, low intakes of plant foods, fiber, calcium, and other dietary aspects, sedentary lifestyles, high body mass index, alcohol drinking, tobacco smoking, and diabetes are recognized risk factor for intestinal adenoma (IA) and CRC [7-9]. Diet has been proposed to exert a role in shaping compositional features of the gut microbial ecosystem.

The microbiota may influence CRC through various mechanisms including microbial-derived metabolism, bacteria-derived genotoxin production, modulation of host defenses and inflammation pathways. Microbe-associated molecular patterns exacerbate inflammation in colorectal carcinogenesis, mediating the loss of barrier function that in turn can lead to an increase of bacterial translocation into the lamina propria, [10-12]. Bacteria or bacterial products can promote pro-inflammatory responses and consequently increase tumorigenesis. In this context, a disruption of the epithelial barrier in CRC results in a leaky gut that allows the translocation of intestinal microbes or their components into bloodstream.

Objective

We conducted a study to investigate whether bacterial translocation from gastrointestinal tract to bloodstream is associated to IA and/or CRC risk. In particular, an epidemiological and metagenomic approach was used to evaluate the relation of the bacterial DNA load and the bacterial taxonomic groups - assessed by 16S rRNA profiling - in blood with the risks of IA and CRC. These findings can serve as a basis to evaluate new non-invasive techniques for an early CRC diagnosis through the analyses of bacterial DNA circulating in peripheral blood.

Methods

The study included 100 CRC cases (histologically confirmed), 100 matched IAs and 100 matched healthy controls to cases by study centre, gender and age (+/- 5 years), recruited in two hospitals of Milan. Subjects were selected among patients aged 20-85 with a scheduled colonoscopy in one of the participant hospitals. Colonoscopy reports were revised to determine CRC, IA and non-cancer/IA hereinafter (healthy) controls.

Participants were face-to-face interviewed by trained operators through a questionnaire that includes information on socio-demographic information, smoking habits, physical activity, occupational exposures, medical history, oral diseases, drug use (e.g. antibiotics), sleeping habits and cancer family history. A reproducible and valid food frequency questionnaire (FFQ) was developed to assess patients' usual diet. Blood samples were also collected before colonoscopy and immediately stored at -80 ºC.

DNA extraction, qPCR quantification and taxonomic profiling by Illumina MiSeq sequencing of the 16S rRNA gene copies were performed from all samples in the same experiment.

The relation between total bacterial load and CRC risk was estimated through multiple conditional logistic regression. Polytomous logistic regression was used to estimate separate odds ratios (OR) for colon and rectal cancer. The differences in terms of relative abundance of bacteria at various taxonomic levels were estimated trough Welch test after DESeq2 normalization of data, based on negative binomial distribution (R package "DESeq2" v1.26.0). Technique of factor analysis was applied to reduce the redundancy of variability of microbiome data. Random Forest was used to infer whether there was a set of variables able to discriminate which group the samples belong to.

Results

There was an overrepresentation of blood 16S rRNA gene copies in colon cancer, especially in right colon, as compared to tumor-free controls, including IA and healthy subjects. The OR of colon cancer for the highest versus the lowest three quintiles of gene copies (≥ 9707 versus <7618 copies) was 2.62. (95% confidence interval=1.22-5.65). The risk significantly increased (p for trend=0.013) and continues to increase for higher levels than the highest upper cut-off quintile. No difference was found for rectal cancer and for IA. For high 16S rRNA gene copies, colon cancers had increased community diversity than controls but did not differ in terms of community evenness. CRC patients had an increased abundance of Peptostreptococcaceae and Acetobacteriaceae than controls/IA and a reduced abundance of Bacteroidaceae, Lachnospiraceae, and Ruminococcaceae. We identified a set of variables that discriminate between CRC and controls/IA with an accuracy of 0.70 through the Random Forest supervised method.

Conclusion

Our data corroborate the hypothesis of a greater bacterial translocation from the gastrointestinal tract to bloodstream in colon cancer patients. These data also gave information regarding the overall entity of bacterial translocation in healthy adults. Moreover, this project can serve as a pilot study to offer a validated framework of standardised procedures in order to elaborate microbiological data and to design future epidemiological studies involving microbial ecosystem analysis of potential interest for early CRC diagnosis.

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COVID-19 E PARTI PRETERMINE: PRIMI RISULTATI DI UNO STUDIO PILOTA SU UNA CASISTICA DI MADRI TORINESI

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Obiettivi

Dato il crescente interesse verso lo studio di eventi sanitari post-Covid, il presente studio desidera valutare un eventuale aumento di rischio di parto pre-termine in madri positive a SARS-COV-2 che hanno partorito durante la pandemia 2020.

Materiali e Metodi

Il presente studio desidera essere per ora uno studio pilota condotto per ora sulla casistica ristretta a 229 parti avvenuti presso l'ospedale S. Anna di Torino nel periodo settembre 2020 - gennaio 2021 da madri appartenenti a categorie non a rischio.
La casistica in studio è stata classificata in 'parti pretermine' (Casi) e 'parti a termine' (Controlli). Tutte le madri coinvolte nello studio hanno fatto un tampone per SARS-CoV-2 al momento del ricovero ospedaliero.
I dati demografici, i sintomi correlati al COVID-19, le comorbilità materne e i dati sull'esposizione a possibili fattori di rischio per la nascita pretermine sono stati raccolti mediante intervista.
Assumendo una prevalenza di infezione del 15% nel gruppo di controllo basato sul modello gerarchico bayesiano [1] e data una significatività di 0.05 si è potuto stimare che la dimensione campionaria disponibile permette di raggiungere una potenza dell'80%.
Il test di Mann-Whitney e il test chi quadrato o il test esatto di Fisher sono stati utilizzati per confrontare rispettivamente misure quantitative e qualitative tra Casi e Controlli.
Al fine di valutare eventuali associazioni tra Covid-19 e parti pretermine, sono stati stimati modelli di regressione logistica. I risultati sono presentati in termini di Odds Ratio (OR) con il relativo intervallo di confidenza al 95% (95%CI).
Le analisi statistiche sono state eseguite utilizzando il software SAS ver. 9.4 per Windows (SAS Institute, Carey, NC, USA).
.

Risultati

Nello studio sono state incluse un totale di 229 donne, 102 nel gruppo dei casi e 127 nel gruppo di controllo. 53 sono risultate positive al SARS-CoV-2, 21 tra i Casi e 32 tra i Controlli.
L'incidenza di COVID-19 non sembra evidenziare particolari differenze tra Casi e Controlli (3.48% casi e 4.83% controlli, p=0.2308) e non sono state evidenziate differenze statisticamente significative nei fattori di rischio tra i due gruppi.
Sulla base dei risultati ottenuti dai modelli di regressione logistica, sembrerebbe che nessuna associazione statisticamente significativa emerge dalla stima dei rischi, suggerendo quindi che l'infezione da COVID-19 non sembra essere un fattore di rischio per parto pretermine (OR = 0.77, 95%CI 0.412-1.438).

Conclusioni

I risultati presentati sono per ora da leggere a titolo descrittivo, ma lo studio sembra evidenziare che le madri con diagnosi di COVID-19 lieve o asintomatiche non sembrano essere più a rischio di parto pretermine rispetto alle madri sane. L'infezione virale materna lieve non sembra quindi svolgere un ruolo nella nascita pretermine, ma all'interno della comunità scientifica resta alto l'interesse a chiarire se l'infezione a COVID-19 possa aver influito sulla gravidanza e sull'ossigenazione placentale e fetale. A tal fine il nostro studio sta attualmente ampliando la casistica con la partecipazione anche di altri centri piemontesi che permetteranno ulteriori approfondimenti sull'argomento.

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DIETA IPOCALORICA E RISPOSTA ALLA CHEMIOTERAPIA NEOADIUVANTE NELLA CURA DEL TUMORE AL SENO

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Introduzione

Diversi studi hanno dimostrato che la restrizione calorica (CR) migliora i fattori metabolici e ormonali implicati nella patogenesi del diabete di tipo 2, delle malattie cardiovascolari e del cancro[1]–[4]. Le cellule cancerose sfruttano la glicolisi aerobica per mantenere il loro alto tasso di proliferazione (effetto Warburg). La restrizione calorica (CR) potrebbe aumentare lo stress ossidativo nelle cellule tumorali, favorendo l'apoptosi, riducendo la proliferazione e l'angiogenesi attraverso bersagli molecolari come IGF-1/Akt mTOR e AMP-K. Il presente lavoro desidera presentare i primi risultati dell’effetto della CR combinata con la chemioterapia neoadiuvante (neo-CT) rispetto a una dieta standard combinata con la neo-CT nelle donne con diagnosi tumore al seno (BC).

Materiali e Metodi

Lo studio è un open trial, non farmacologico, randomizzato approvato dal Comitato Etico della Città della Salute e della Scienza di Torino. Nel periodo 2012-2020 sono state reclutate 85 pazienti con diagnosi di carcinoma mammario e indicazione al trattamento chemioterapico neoadiuvante, delle quali 25 donne hanno seguito un regime di restrizione calorica durante il trattamento neoadiuvante (gruppo di intervento) controllato da un nutrizionista e da un dietista registrato, mentre 60 hanno seguito una dieta libera durante il trattamento neoadiuvante (gruppo di controllo).

I criteri di ammissibilità erano (i) diagnosi di carcinoma mammario invasivo (BC), senza lesioni secondarie e senza alcun trattamento precedente (chemioterapia, terapia ormonale, radioterapia); (ii) diagnosi di carcinoma mammario invasivo duttale o lobulare con o senza DCIS (può essere reclutato anche il carcinoma mammario infiammatorio); (iii) età compresa tra i 18 ei 70 anni; (iv) Performance status ECOG <2; (v) neuropatia periferica di grado < 1; (vi) parametri ematologici (valori minimi): neutrofili (numero assoluto) >1500/mm3, emoglobina > 8,0 g/dl; conta piastrinica >100.000/mm3; (vii) bilirubina totale entro i limiti normali; (viii) valori di AST e ALT inferiori o uguali a x1,5 il limite superiore normalmente; (ix) BMI compreso tra 20 kg/m2 e 35 kg/m2, senza diminuzione ponderale >5% negli ultimi 3 mesi. Il consenso informato scritto è stato ottenuto da tutti i partecipanti allo studio.

La dimensione del campione disponibile permette allo studio di raggiungere una Potenza dell’80%.

Al fine di evidenziare gli effetti della dieta sull'evoluzione della malattia sono stati eseguiti modelli di Regressione logistica aggiustati per fattori di rischio. I risultati sono presentati in termini di OR grezzi e aggiustati e relativi Intervalli di confidenza al 95%.

Risultati

Le analisi preliminari dello studio mostrano che una risposta completa al trattamento è stata raggiunta dal 72.2% nel gruppo CR e solo dal 28.8% nel gruppo di controllo. I risultati sembrano evidenziare un effetto positivo della dieta sulla risposta alla terapia (OR=4.12 95%CI da 1.29 a 13.11); associazione che rimane consistente e statisticamente significativa anche dopo l'aggiustamento per i principali fattori di confondimento.

Conclusioni

I risultati sono per ora preliminari e devono quindi essere letti con tutte le cautele del caso, ma sembrano evidenziare che il regime dietetico ipocalorico, sotto lo scrupoloso monitoraggio di un nutrizionista e di un dietologo esperto, potrebbe rappresentare un metodo efficace ed economico nel potenziare la citotossicità della neo-TC standard portando un evidente beneficio nelle pazienti con tumore al seno.

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LACK OF EFFECT ON IN-HOSPITAL MORTALITY OF DRUGS USED DURING COVID-19 PANDEMIC: FINDINGS OF THE RETROSPECTIVE MULTICENTER COVOCA STUDY.

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Introduction

During COVID-19 pandemic, the use of several drugs has represented the worldwide clinical practice. However, though the current increase of knowledge about the disease, there is still no effective treatment and information about a proper timeline for the usage of drugs [1].

Aims

On these bases, we aimed to retrospectively assess the frequency of use of drugs, both as a single class and in association with each other, and the effects of therapeutic regimens started in hospitalized patients on in-hospital mortality. We also evaluated whether an early or delayed use of these drugs could determine different outcomes.

Methods

COVOCA (COVID-19 population hOspitalized in CAmpania Region) is a retrospective observational cohort study, which involved 18 COVID centres throughout Hospitals of Campania Region [2]. All adult patients diagnosed by nasopharyngeal swab with completed admission (discharge/death) between March and June 2020 were included. Demographic, anthropometric, and clinical data, such as pre-existing chronic diseases, and the need for respiratory support were collected at admission.

Data on drug therapies introduced during hospitalization, were widely collected. Particularly for most reported treatment and of interest in COVID-19 literature, in parallel to the description of whether they were used, a time-lag variable was created to identify patients undergoing either to an early or late treatment. This was done to avoid survivorship bias, considering that patients who live longer are more likely to receive a certain treatment/combination [3]. Specifically, the time-lags variable (early/late) was categorized using a cut-off time (day-2). Day-2 represents treatments performed within the first two days since admission, considering day-0 as the time of hospitalization. Under this pattern, treatments were classified as: No treatment, early treatment (until day 2) and late treatment (from day 3 onwards). Kendall's Tau-b coefficient was used to measure the ordinal association between specific COVID-19 treatments (No Treatment - Early Treatment - Late Treatment) [4]. Tau-b coefficient has been interpreted according to the following criteria: very weak if lower than ± 0.10, weak if from ± 0.10 to ± 0.19, moderate if from ± 0.20 to ± 0.29, strong if higher than ± 0.30. Multivariable logistic regression models were performed to evaluate association between in-hospital mortality and specific COVID-19 treatments. Drug treatments were evaluated in the model individually using the time-lag cut-off and adjusted according to previous findings [2], including as covariates age, sex, Glasgow Coma Scales (GCS/15), Respiratory Severity Scale (RSS), Chronic Liver Disease, and Malignancies. Moreover, each model was fitted both on the whole population and on a subpopulation excluding patients under invasive ventilation/OTI on admission, to test the effect of drugs in a less compromised population. Odds ratios and 95% confidence intervals (OR—95% CI) have been calculated for all models. A p-value <0.05 was considered as statistically significant. All analyses were performed using statistical software STATA 16.

Results

618 patients were included in the study, mainly males (61.3%), with a mean age of 65 years (Standard Deviation 15.2) and a median duration of hospitalization of 20 days [Interquartile Range 13-29 days]. At the time of hospitalization, 63.6% of patients did not show any symptom of ARDS, while moderate and severe symptoms were observed, respectively, in about the 13.1% and 7.4%.

In addition, as for the RSS, 330 patients (53.4%) received respiratory support, at the time of hospitalization, either with Venturi mask or nasal cannula. Only the 13% needed either noninvasive ventilation (NIV) or Orotracheal intubation (OTI). 46 patients (7.4%) showed moderate to severe impaired consciousness according to GCS/15.

Patients were differentiated based on either an early (within the first two days since admission) and late administration (from day 3 in after). As reported in Table, 72% of patients underwent to an early treatment with antivirals. Antibiotics were administered at beginning of hospitalization in the 65% of patients, whilst hydroxychloroquine and anticoagulants in almost half of the study cohort. Corticosteroid therapy administration was almost similar both early and late during hospitalization (20.9% and 15.8%, respectively), whilst monoclonal antibodies, especially Tocilizumab, were larger prescribed late during hospitalization.

We further assessed whether there was a drug-drug correlation related to the administration timeline by the Tau-b coefficient. Particularly, the 48.2% (n=298) were administered both antibiotics and hydroxychloroquine on the day of admission, with a $\tau = 0.43$. Strong positive correlations, though slightly lower, were observed also for what concerned early administration of both anticoagulants/antivirals and hydroxychloroquine ($\tau = 0.38$ and $\tau = 0.32$, respectively), as well as for the early combination of antibiotics and anticoagulants ($\tau = 0.36$).

During the observation period, 143 in-hospital mortality events were recorded, with a cumulative incidence of 23.1%. We fitted different multivariable models to test for the association between in-hospital mortality and each COVID-19 specific therapy, according to the time of administration and, furthermore, stratified on the whole population as well as on a subpopulation excluding patients who were already under OTI on admission. All models did not disclose any significant association.

Conclusions

This retrospective observational study is the first to report both management and in-hospital mortality in Campania region. According to our findings, no drug class used during the pandemic, significantly changed mortality risk, regardless of therapy beginning.

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Table. COVID-19 therapies administered during hospitalization (n=618).

Parameter	
Hydroxychloroquine, n (%)	
No	189 (30.6%)
early treatment	349 (56.5%)
late treatment	80 (12.9%)
Anticoagulants, n (%)	
No	202 (32.7%)
early treatment	325 (52.6%)
late treatment	91 (14.7%)
Antibiotics, n (%)	
No	153 (24.8%)
early treatment	402 (65.0%)
late treatment	63 (10.2%)
Monoclonal Antibodies, n (%)	
No	514 (83.2%)
early treatment	41 (6.6%)
late treatment	63 (10.2%)
Antivirals, n (%)	
No	107 (17.3%)
early treatment	445 (72.0%)
late treatment	66 (10.7%)
Corticosteroids, n (%)	
No	391 (63.3%)
early treatment	129 (20.9%)
late treatment	98 (15.8%)
Immunosuppressive, n (%)	5 (0.8%)
Antiplatelets, n (%)	
No	567 (91.7%)
Aspirin	38 (6.1%)
Double Antiplatelet	5 (0.8%)
Other	8 (1.3%)
Paracetamol, n (%)	176 (28.5%)
NSAIDs, n (%)	14 (2.3%)
Plasma recovered, n (%)	10 (1.6%)
Immunoglobulins, n (%)	9 (1.5%)
Antiarrhythmics, n (%)	13 (2.1%)
Vasoactive, n (%)	14 (2.3%)
Inotropes, n (%)	10 (1.6%)
Crystalloids, n (%)	99 (16.0%)
Electrolytes, n (%)	38 (6.1%)
Albumin, n (%)	33 (5.3%)
Other COVID19 drugs, n (%)	72 (11.7%)

Abbreviations: NSAIDs: Nonsteroidal anti-inflammatory drugs

** the time-lags variable (early/late) was categorized using a cut-off time (day-2). In depth, treatments were classified as: No treatment, early treatment (if occurred until day 2) and late treatment (from day 3 onwards). From immunosuppressive drugs onwards, only utilization rates were presented.

Dati socio-demografici dell'ASL Taranto, aggiornati al 2021

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Introduzione

L'ASL Taranto opera su un territorio che si estende su una superficie di 2.436,67 Kmq ed è caratterizzato dalla presenza di un territorio pianeggiante per poco più della metà del totale (1.342,39 Kmq^2), con una significativa estensione costiera, mentre per la restante parte il terreno è collinare (1094,28 Km^2). Secondo i dati ISTAT, la popolazione residente della provincia di Taranto al 1° gennaio 2020 ammonta a 560048 abitanti, di cui 288365 uomini e 288365 donne.La popolazione della provincia di Taranto è distribuita amministrativamente in 29 comuni, organizzati in 6 distretti socio-sanitari. Il comune più popoloso è la città di Taranto, dove risiede circa il 34% della popolazione (189366 abitanti). Martina Franca è il secondo comune più popoloso (47413 abitanti). Seguono Massafra, Grottaglie, Manduria e Ginosa, tutte con una popolazione di oltre 20.000 abitanti. I comuni più piccoli (meno di 5.000 abitanti) sono in tutto cinque e in essi vive meno del 3% della popolazione della provincia.

Obiettivi

L'obiettivo primario delle nostre valutazioni demografiche è quello di fornire indicazioni utili al processo di ottimizzazione nella distribuzione delle risorse finanziarie in sanità pubblica. Inoltre l'attenta analisi degli indici di mortalità e il confronto con altre province della nostra Regione sarà svolta al fine di valutare la presenza di eventuali fattori di rischio ambientali.

Dati e Metodi

Tutti i dati relativamente alla provincia di Taranto che sussistono negli ultimi 12 anni sono stati estratti dalle banche dati ISTAT[1]. Nello studio sono stati valutati i seguenti indicatori demografici:

1. Quoziente di natalità
2. Quoziente di mortalità
3. Quoziente di nuzialità
4. Saldo migratorio interno
5. Saldo migratorio con l'estero
6. Saldo migratorio per altro motivo
7. Saldo migratorio totale
8. Crescita naturale

9. Tasso di crescita totale(calcolato come PGR= P(t2)-P(t1)/P(t1)/(t2-t1))
10. Tasso di fecondità totale (o numero medio di figli per donna)
11. Età media al parto
12. Speranza di vita (a 0 e a 65 anni distinta per sesso e per entrambi i sessi)
13. Struttura della popolazione (percentuale di popolazione per le seguenti classi di età: 0-14, 15-64, 65 e più)
14. Indicatori di struttura (indice di dipendenza strutturale, indice di dipendenza anziani, indice di vecchiaia, età media della popolazione).
15. Indice di invecchiamento calcolato come $IV=P\geq 65anni/P<14anni*100$.

Risultati

Ad oggi la provincia di Taranto presenta un indice di invecchiamento attivo di 181,2 che è risultato in costante aumento negli ultimi 12 anni. Di conseguenza, l'area ha mostrato una speranza di vita alla nascita pari 82,6 anni con una differenza significativa tra i sessi (maschi vs femmine, rispettivamente 80,5aa e 84,7aa). Nello stesso arco temporale si è osservato aumento anche per l'età media che è risultata pari 45,4 anni. Il tasso di crescita della popolazione calcolato nello stesso periodo è risultato pari a -7,1 coerentemente con l'andamento degli ultimi dodici anni. L'analisi della distribuzione delle classi di età ha mostrato una diminuzione continua della classe 0-14 anni (13%) una classe costante 15-65 anni (23%) e una classe anziani > 65 anni in aumento (65%).

Conclusioni

Le caratteristiche demografiche illustrate sono costantemente monitorate e utilizzate dalla Struttura di Epidemiologia e Statistica ASL TA come substrato di analisi socio-sanitarie utili a 1) prevedere una corretta distribuzione dei servizi sanitari del territorio per garantirne la fruibilità ai cittadini delle aree rurali meno densamente abitate (Regione Lombardia PSR 07.04.2021 interventi in materia sanitaria, sociale e culturale perla popolazione nelle aree rurali, Regione Puglia Bando PSR in Progress) 2) studiare la presenza di possibili fattori di rischio per la salute nelle aree maggiormente urbanizzate (cfr. Rapporto Osserva Salute Università Cattolica, Rischi per la salute in aree densamente abitate).

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GUT MICROBIOTA COMPOSITION CHANGES AFTER NINE WEEKS OF HIGH-INTENSITY CYCLING TRAINING IN HEALTHY COLLEGE STUDENTS

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Introduction: The gut microbiota composition is associated with environmental and behavioural factors, such as age, diet, and physical exercise; its association with human health has been increasingly studied in the last decades. In particular, physical exercise seems to be related with positive changes in the gut microbiota diversity and community, both in animal and human studies. Higher microbial diversity, different taxonomic and functional composition, and a strong association with athletes performance in elite athletes respect to non-elite was recently reported [1]. However, intervention studies which investigated the effects of a training program on microbiota composition are just a few. Rettedal et al. [2] investigated the effect of a short-term high-intensity interval training period on the gut bacterial composition of lean and overweight men, failing to find changes neither in diversity nor composition of the microbiota.

Objective: This study aimed to investigate changes in gut microbiota profiles following nine weeks of high-intensity cycling training in healthy young adults, and draw associations among microbial modifications, diet, and sports performance.

Methods: 17 healthy male college students performed 36 high-intensity training sessions during nine weeks. Before and after the training period, each participant performed a maximal graded exercise test to assess VO_{2max}, W_{peak} and power at lactate thresholds. Diet was daily monitored from two weeks before the beginning of the training period until the end of the study. Faeces samples were collected at baseline and after the nine weeks of training. For 16SrDNA sequencing, the total microbial DNA of the samples was extracted. After assessing DNA concentration and purity, samples were stored at -80° until processing. Alpha diversity indexes (Chao1, Shannon H and Simpson) were calculated, and a Permutational Analysis of Variance for repeated measures was used to test pre-post differences in the relative abundance of all taxonomic levels (phyla, classes, orders, families, genera and species), with subjects' ID as strata for pairing. A correlation matrix was calculated on the post-pre differences of the relative abundance of the 29 remaining genera, and to draw associations among variations in microbial composition, physical and dietary features.

Results: Physical exercise induced changes in microbiota composition, at all taxonomic levels analysed ($p<0.05$ for all). *Firmicutes*/*Bacteroidetes* ratio increased in post-training (median: 1.50) respect to pre-training (median: 0.89) ($p=0.039$). Changes in post-pre training in physical composition, performance indexes and several macro and micronutrient intake were associated with alterations of specific gut microbiota genera (Figure 1).

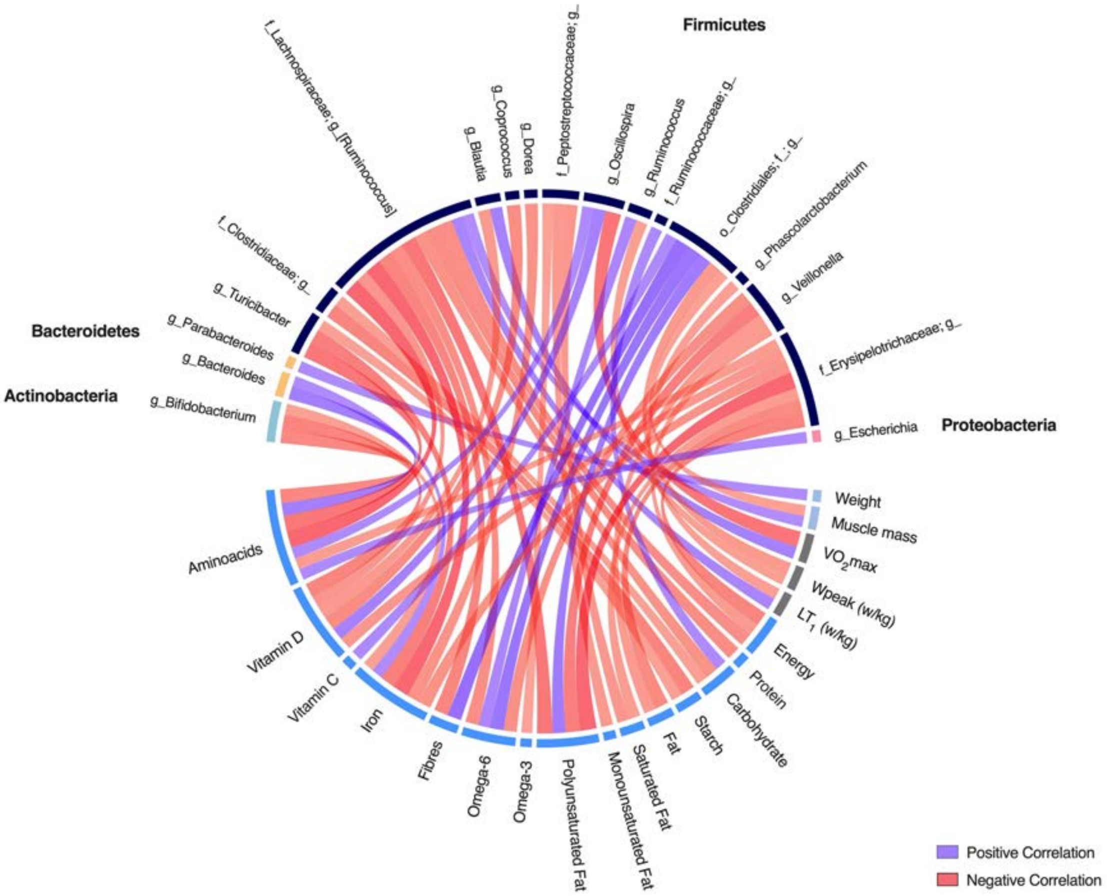

Figure 1. Spearman correlations between post-pre training delta of environmental factors and microbiota (genus level, cut-off relative abundance >1%). Only significant correlations ($r \geq 0.485$) are reported.

Conclusions: Physical activity modifies the gut microbiota, exerting health benefits on the host. This work showed that nine weeks of high-intensity training induced modifications in gut microbiota composition, but not in its diversity or richness. Some relevant bacterial taxa were modified after the training period shifting the gut microbial population towards a healthier microbiome.

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A RANDOM POPULATION SAMPLE AND 10 FOLLOW-UPS: ONE YEAR OF COVID-19 PANDEMIC SEEN THROUGH THE CHRIS COVID-19 STUDY.

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Introduction

Starting in the late 2019, the COVID-19 pandemic has now affected the entire world. Many countries have experienced more than one pandemic wave, each characterized by different magnitude and duration. However, marked geographical differences are being observed even within small regions. The example of South Tyrol might be instructing: during the first pandemic phase, areas with a very high incidence were observed [1] amidst areas with a very low incidence [2]. However, between late 2020 and early 2021, areas with low baseline incidence became more informative for studying the epidemiological dynamics of the pandemic.

In July 2020, we initiated the Cooperative Health Research In South Tyrol (CHRIS) COVID-19 study, a longitudinal project to monitor SARS-CoV-2 infections in Val Venosta (South Tyrol, Italy). The newly launched project was based on the CHRIS study [3], an ongoing, longitudinal, general population study with 13,393 adults recruited at baseline, in 2018. We randomly drawn a population-representative sample of 1450 CHRIS participants, reflecting the age group-sex distribution of the adult population of the study area to estimate the cumulative incidence of SARS-CoV-2 infection during the first pandemic wave. Regular online questionnaires and laboratory test follow-ups were implemented to monitor the progress of the pandemic to date.

Aims

This first analysis of the CHRIS COVID-19 study aimed to characterize the spread and course of the COVID-19 pandemic in middle and upper Val Venosta (South Tyrol, Italy) between February 2020 and May 2021.

Methods

Participants were 845, who responded to an online screening questionnaire including questions on COVID-19 related anamnesis, symptoms and lifestyle. Contextually, they were invited to undergo a nasopharyngeal swab for PCR test and a serum antibody test. Follow-up of all participants who tested negative to this baseline assessment was conducted by administering a shorter online questionnaire every 4 weeks for updating the anamnesis or symptomatology.

Incidence was estimated with the Clopper-Pearson method for extreme proportions [4]. Association between baseline incidence and anamnesis and symptoms was assessed using Fisher’s exact test (significance level: 0.001). The temporal trend of the total number of reported symptoms for each individual was assessed by fitting zero-inflated negative binomial linear models with random intercept, using the month on which symptoms were reported as a predictor. We used longitudinal cluster analysis based on the k-means method to model the symptoms’ dynamic over time [5], with the optimal number of clusters defined according to the Calinski & Harabatz criterion [6].

Results

Until August 2020, the estimated cumulative incidence of SARS-CoV-2 infection in the study area was 0.95% (95% confidence interval, CI, 0.41-1.86%), calibrated to the age and sex distribution of the population. Positivity was associated with having undergone a nasopharyngeal swab, having had a previous positive serological test, or having been isolated because of suspected or confirmed SARS-CoV-2 infection. The risk of infection was associated with the number of reported symptoms, loss of taste, loss of smell, and dry cough.

Between September 2020 and May 2021, of the 836 participants testing negative at the baseline, 699 completed at least one and up to 10 follow-up questionnaires. Of them, 60.5% (95%CI 57.1-63.8%) underwent 1+ nasopharyngeal swabs and 20.5% (95%CI 17.1-24.3%) reported to have tested positive at least once.

The temporal trend of the cumulative number of reported symptoms for each participant showed that infections peaked in October 2020 (2nd pandemic wave) and in February 2021 (3rd pandemic wave), closely resembling the shifted trends of hospitalizations and intensive care admissions reported by the local healthcare system in the same period. The zero-inflated mixed-model, showing the pattern of the pandemic waves both by the presence of symptoms and by the cumulative number of reported symptoms, confirmed these findings. Similar patterns emerged from the dynamic of single symptoms, where cluster analysis showed that the main peaks were associated with clusters containing the most common COVID-19-related symptoms [7]. Lower intensity clusters reflected flat patterns mainly comprising generic symptoms. Predictive analyses based on individual symptoms confirmed the symptomatic profile associated with COVID-19 reported previously [8].

Conclusions

During the first pandemic phase, the middle and upper Val Venosta had lower incidence of SARS-CoV-2 infections than nearby regions. Subsequently, the trend became more similar to that observed in South Tyrol, with a heavy second wave in autumn 2020 and a further third wave in early 2021. The observed proportion of PCR-positive persons suggests that no herd immunity could have been achieved spontaneously.

This monitoring presented major methodological challenges from an epidemiological perspective. Data collection was conditioned by public health interventions aimed at countering the pandemic itself, which may have also altered individual behavior. These circumstances may translate into selection bias. Furthermore, testing capacity and screening guidelines have been following different patterns through the period, altering the probability of having undergone a PCR test. For example, by late November 2020, a mass screening through a rapid antigen test via nasopharyngeal swab involved ~70% of the population, resulting in a peak of tests and positive cases observed within a narrow time window. Analyzing the reported symptoms in addition to measures of disease occurrence can add value to monitoring the temporal trend of infections, since not all individuals have equivalent propensity to receive a test.

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HEALTH COMPLAINTS AND WELLBEING: TEMPORAL TREND AMONG ITALIAN ADOLESCENTS

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Introduction

In the 20th century, the concept of health has evolved to include the notion of well-being: according to the WHO, health is a state of complete physical, psychological and social well-being, and not just the absence of disease and infirmity [1]. In approaching the concepts of health and well-being, mental health is central for its impact on public health: WHO projections indicate in fact in 2020 depression as the second cause of illness, emphasizing adolescence as a fundamental period in forming the features of adult mental health [2].

Aims

The aim of our study was to explore trends of health complaints and wellbeing from 2010 to 2018 and to evaluate the role of socioeconomic and contextual factors of change over time.

Methods

Data from the Italian Health Behaviour in School-aged Children (HBSC) 2010, 2014 and 2018 surveys were analysed [3,4,5]. Representative samples of students aged 11, 13, and 15 years were recruited from school classes located throughout all Italian regions, using standardized and self-administered questionnaires to collect information about a wide range of topics [4,5]. A cognitive scale (LS) was used for well-being (“Which number best describes your situation from 0 (The worst possible life) to 10 (The best possible life)? ”) and the range of possible values (0-10) was dichotomized (0-8 vs. 9-10). The students were also asked how frequently they suffered from certain symptoms (headache, stomach pain, back pain, feeling down, being in a bad mood, nervous, difficulties in getting to sleep, and feeling dizzy). Responses were given on a 5-point scale: a summary scale was created with a range of 0-32 points; higher scores indicating a greater intensity of health complaints (HC), treated both as a continuous scale and as a dichotomized variable (≥2 health complaints more than once a week). Confirmatory factor analysis (CFA) was performed: a single factor model (i.e., all items of the HBSC-SCL were supposed to be represented by the same factor) was compared to a model comprising two correlated factors (psychological and somatic), both for continuous and dichotomized variable. The two-factors model for dichotomized variable fitted the data best, so it was adopted as outcome variable in trend estimation. Multivariate linear and logistic regression models were performed to fit the trends over time of HC and LS (dependent variables), using survey year, SES and geographic area (North, Centre, South) as socioeconomic independent variables, and social support (family, school and peers) as contextual factors. Due to interaction, analyses were stratified by gender and age. All the analyses were performed considering survey design effects (including stratification, clustering, and weighting).

Results

Results were based over 165000 students, of which 35.6%, 28.8% and 35.6% respectively in 2010, 2014 and 2018, with similar gender and age distribution among the three waves. Cognitive scale of wellbeing

(LS) was steady between 2010 and 2018, showing a significant decreasing trend among age in both boys and girls. Psychosomatic health complaints increased, mainly for psychological symptoms, in all age and gender groups: in boys, from 26.7% to 31.5% among younger (OR: 1.02, CI95%: 1.00-1.03), from 25.6% to 32.1% in the 13 year olds (OR: 1.03, CI95%: 1.02-1.05) and from 29.6% to 35.9% in the 15 year olds (OR: 1.04, CI95%: 1.02-1.05); in girls, from 28.6% to 37.6% among younger (OR: 1.03, CI95%: 1.01-1.05), from 40.8% to 50.1% in the 13 year olds (OR: 1.05, CI95%: 1.04-1.07) and from 40.8% to 54.1% in the 15 year olds (OR: 1.06, CI95%: 1.05-1.07). Family and peer support resulted significantly associated with health complaints, playing a protective role.

Conclusions

Our findings in a representative sample of Italian adolescents suggest that overall prevalence rates of health complaints, mainly psychological symptoms, were increased from 2010 and 2018. It will be interesting to assess whether this trend will be confirmed following the covid pandemic in the next survey in 2022.

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ASSOCIAZIONE TRA ESITI CARDIOVASCOLARI/MORTALITÀ E INTERRUZIONE DEL TRATTAMENTO CON STATINE NEI PAZIENTI ANZIANI IN POLITERAPIA

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Introduzione

L'invecchiamento della popolazione è caratterizzato da un aumento delle comorbidità e della politerapia. Tuttavia, l'esposizione alle malattie croniche ed ai diversi trattamenti può determinare l'insorgenza di eventi avversi. Il presente studio valuta il processo di deprescrizione, ovvero la riduzione o l'interruzione graduale dei farmaci, al fine di ridurre eventi avversi e migliorare la salute dei pazienti.

Obiettivi

Il presente studio osservazionale di coorte retrospettivo è finalizzato alla valutazione delle implicazioni cliniche causate dall'interruzione del trattamento con le statine in un'ampia coorte di pazienti anziani in politerapia.

Metodi

È stato condotto uno studio di popolazione basato sull'utilizzo dei database sanitari della Regione Lombardia. Lo studio è stato progettato secondo una procedura in due fasi.

Il primo step ha avuto l'obiettivo di identificare i pazienti in politerapia e, tra questi, quelli che hanno interrotto la terapia con statine. A tal fine, i quasi 2,3 milioni di beneficiari del Servizio Sanitario della Regione Lombardia che durante il cosiddetto periodo di pre-follow-up (ovvero dal 1 ottobre 2013 al 31 gennaio 2015) avevano (i) almeno 65 anni, (ii) erano residenti in Lombardia da almeno 3 anni, ed (iii) erano in trattamento con statine, antipertensivi, antidiabetici e antiaggreganti sono stati identificati. Questi pazienti sono stati seguiti dal 1 febbraio 2015 fino alla data di discontinuità con statine o al termine dello studio (2018).

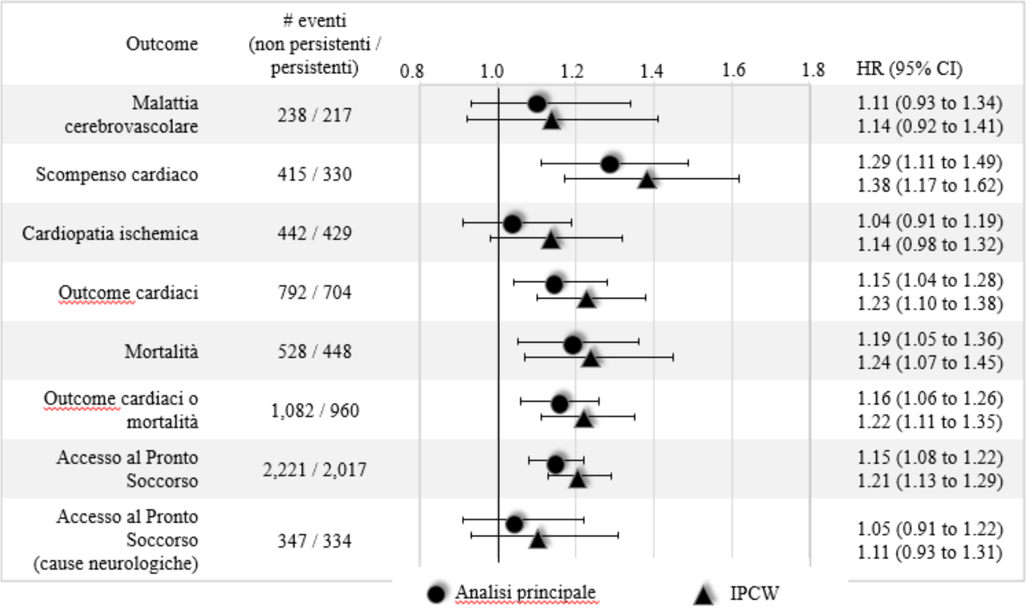
La seconda fase mirava a confrontare l'insorgenza di diversi esiti clinici tra i pazienti che avevano oppure che non avevano interrotto le statine, ma in trattamento continuo con le restanti terapie farmacologiche. Pertanto, è stato realizzato un propensity score matching [1] tra i soggetti in trattamento continuo con statine e coloro che presentavano almeno un episodio di discontinuità. Le coppie di pazienti persistente-discontinuante, che non dovevano aver interrotto i tre co-trattamenti nei 6 mesi successivi alla data di appaiamento (giorno in cui il paziente discontinuante ha interrotto il trattamento con statine), sono state seguite fino al verificarsi di uno degli esiti clinici di interesse, ossia ricovero per patologia cardiovascolare, accesso in pronto soccorso, decesso. Un modello di Cox è stato interpolato per stimare l'hazard ratio (HR), e l'intervallo di confidenza (IC) al 95%, degli esiti clinici associati all'interruzione delle statine.

Come analisi della robustezza, il follow-up dei pazienti è stato censurato alla data di discontinuità di uno dei tre co-trattamenti. Dal momento che la censura potrebbe essere informativa, è stato applicato il metodo dell'inverse probability censoring weighting (IPCW) [2]. Il metodo IPCW consiste nell'assegnare a ciascun individuo un peso inversamente proporzionale alla probabilità di censura, condizionato alle covariate misurate fino alla censura, e generato da un modello di regressione di Cox tempo dipendente.

Risultati

I 29.047 pazienti esposti alla politerapia avevano età media di 76,5 anni, il 63% erano uomini, 1/5 mostrava cardiopatia ischemica, ed 1/12 soffriva di malattie cerebrovascolari, scompenso cardiaco e/o malattie respiratorie. Nel complesso, 2/3 dei pazienti inclusi presentavano comorbidità.

Rispetto ai pazienti persistenti, coloro che avevano interrotto le statine mostravano un aumentato rischio di ricoveri ospedalieri per scompenso cardiaco e qualsiasi esito cardiovascolare, decesso e accesso al pronto soccorso per qualsiasi causa (**Figura**).



Outcome	# eventi (non persistenti / persistenti)	HR (95% CI)
Malattia cerebrovascolare	238 / 217	1.11 (0.93 to 1.34) 1.14 (0.92 to 1.41)
Scompenso cardiaco	415 / 330	1.29 (1.11 to 1.49) 1.38 (1.17 to 1.62)
Cardiopatia ischemica	442 / 429	1.04 (0.91 to 1.19) 1.14 (0.98 to 1.32)
Outcome cardiaci	792 / 704	1.15 (1.04 to 1.28) 1.23 (1.10 to 1.38)
Mortalità	528 / 448	1.19 (1.05 to 1.36) 1.24 (1.07 to 1.45)
Outcome cardiaci o mortalità	1,082 / 960	1.16 (1.06 to 1.26) 1.22 (1.11 to 1.35)
Accesso al Pronto Soccorso	2,221 / 2,017	1.15 (1.08 to 1.22) 1.21 (1.13 to 1.29)
Accesso al Pronto Soccorso (cause neurologiche)	347 / 334	1.05 (0.91 to 1.22) 1.11 (0.93 to 1.31)

Conclusioni

Tra i pazienti di età pari o superiore a 65 anni esposti a politerapia con almeno un episodio di discontinuità alle statine (ed in trattamento continuo con antiipertensivi, antidiabetici e antiaggreganti) è stato rilevato un aumento del rischio degli esiti cardiovascolari e del decesso per qualsiasi causa. Considerando l'efficacia delle statine nella prevenzione cardiovascolare primaria e secondaria e la ridotta insorgenza di effetti avversi indotti dalle statine, i professionisti sanitari dovrebbero valutare attentamente l'interruzione di questi farmaci nei pazienti anziani.

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EPIDEMIOLOGIA DELL'INFEZIONE DA SARS-COV-2 NEL PIEMONTE ORIENTALE: VALUTAZIONE RETROSPETTIVA NELLA PROVINCIA DI VERCELLI.

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Introduzione. La malattia COVID-19 è una patologia virale respiratoria acuta grave causata dal coronavirus SARS-CoV-2, un nuovo *betacoronavirus* originariamente identificato in pazienti con sintomi respiratori acuti a Wuhan (Cina) nel mese di Dicembre 2019 [1].

A seguito della rapida diffusione dell'infezione, della gravità della malattia, dell'aumento dei casi al di fuori della Cina e del numero di paesi colpiti, l'OMS ha dichiarato l'infezione da SARS-CoV-2 una pandemia globale nel marzo 2020 [2]. Infatti, a partire da gennaio 2020, circa altri 20 Paesi hanno segnalato casi di COVID-19 a livello internazionale, compresa l'Italia che è stata il primo dei Paesi occidentali ad essere stato gravemente colpito da un numero relativamente elevato di decessi [3, 4]. Nonostante la scarsa conoscenza dell'epidemiologia del SARS-CoV-2 circolante in Italia, la sua diffusione nel nostro Paese è probabilmente iniziata da diverse introduzioni multiple dalla Cina e dalla Germania seguite dalla rapida trasmissione autoctona in Italia [5]. Molteplici fattori hanno contribuito alla sua diffusione nel nostro paese e, alla luce di ciò, studi epidemiologici approfonditi e integrati nelle strategie di sanità pubblica si rendono necessari al fine di ottenere conoscenze utili per il controllo di un improvviso evento infettivo pandemico.

Obiettivi. Lo scopo di questo studio è stato il rilevamento dei casi positivi di infezione da SARS-CoV-2 nella provincia di Vercelli durante il periodo Febbraio 2020 – Novembre 2020, al fine di valutare l'epidemiologia sul territorio dal punto di vista spaziale e temporale.

Metodi. Tutti i dati epidemiologici sono stati estratti dalla piattaforma CSI Piemonte in forma anonima e riguardano i tamponi eseguiti nella provincia di Vercelli nel periodo Febbraio 2020 - Novembre 2020. Per ogni paziente sono stati considerati l'età, il genere, il comune di residenza, il risultato e la data di esecuzione del tampone. Ai fini del presente studio, sono stati considerati solamente i risultati dei tamponi eseguiti con metodica molecolare. Sul database in esame, è stato eseguito il calcolo dei tassi standardizzati di incidenza (SIR) per località, età e sesso così da evidenziare eventuali scostamenti in determinate aree geografiche o in categorie di popolazioni rispetto alla media provinciale. In questo modo è possibile la standardizzazione dei valori epidemiologici ottenuti e la corretta valutazione delle differenze locali in relazione alle variazioni della struttura demografica territoriale.

Risultati. Nel periodo in studio è stato eseguito un totale di 49388 tamponi, di cui 6715 positivi nella provincia di Vercelli. i Comuni dove sono stati eseguiti il maggior numero sono il capoluogo con 15611 tamponi di cui 2283 positivi e Borgosesia con 3111 tamponi di cui 495 positivi. I maggiori tassi di positività sono stati osservati tra le donne nelle fasce di età 20-24 (14,3%) e 90-94 (14,1%), mentre tra gli uomini le fasce più interessate erano 20-24 (19,7%) e 55-59 (18,7%). L'analisi complessiva negli altri gruppi di età indicava una distribuzione dell'infezione virale omogenea all'interno della popolazione (12,9%). Tuttavia, i risultati ottenuti hanno evidenziato degli incrementi statisticamente significativi in alcuni comuni della Provincia in relazione al sesso. Il genere femminile mostra un aumento significativo nei Comuni di Borgo Vercelli (SIR: 2,23) Caresanablot (SIR: 2,62) e San Germano V (SIR: 2,42). Per i maschi, i maggiori aumenti sono stati osservati a Costanzana (SIR: 2,81) e Caresana (SIR: 2,01). Nel complesso gli aumenti sono elevati e statisticamente significativi per entrambi i sessi nelle realtà di Borgo Vercelli (SIR: 1,80), Caresanablot (SIR: 2,29), Costanzana (SIR: 2,08) e San Germano V (SIR: 2,07).

Conclusioni. L'analisi epidemiologica condotta sull'area della provincia di Vercelli ha permesso di osservare degli incrementi significativi dell'infezione virale in alcuni comuni specifici. Le ipotesi ad oggi più plausibili per spiegare le differenze in tali contesti sono probabilmente basate su due aspetti. Il primo legato alla maggiore presenza di strutture per anziani in tali comuni, unitamente ad un maggior numero di tamponi ivi eseguiti per rilevare tempestivamente potenziali cluster di infezione. Il secondo aspetto, a carattere ambientale, risiede nell'ubicazione dei comuni con valori di SIR elevati i quali, ad esclusione di Borgosesia, sono dislocati nel basso vercellese, area a forte antropizzazione agricola e industriale. In virtù del nesso tra livelli di inquinamento e diffusione del virus riportati da alcuni studi, è plausibile ipotizzare un ruolo delle polveri sottili come veicolo della diffusione del virus. In conclusione, grazie ai dati derivati da questa analisi epidemiologica è stato possibile identificare aree geografiche della provincia di Vercelli con una maggiore incidenza dell'infezione virale e sulle quali si rende necessario eseguire ulteriori studi volti a indagare i motivi di tali aumenti. Ciò sarà particolarmente utile nella comprensione degli elementi ambientali favorenti la diffusione dell'infezione da SARS-CoV-2.

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INDAGINE SULLE CARATTERSTICHE DELLA POPOLAZIONE DEI LAVORATORI DELLA FONDAZIONE IRCCS POLICLINICO SAN MATTEO DURANTE LA SECONDA ONDATA DELL'EPIDEMIA DA SARS-COV-2

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Introduzione

Il nuovo coronavirus SARS-CoV-2, identificato in Cina alla fine del mese di dicembre 2019, è la causa della sindrome respiratoria COVID-19 e si è diffuso rapidamente in tutto il mondo. L'Ospedale San Matteo dal 22 febbraio 2020 è stato individuato come centro di riferimento COVID-19 ed il primo caso italiano è stato ricoverato nel reparto di Terapia Intensiva in data 21 febbraio 2020. Tra i mesi di giugno e luglio 2020, si è effettuata un'analisi sui lavoratori della Fondazione sottoposti a tampone durante la prima ondata (fine febbraio - inizio maggio), utilizzando esclusivamente i dati del Medico Competente e delle cartelle cliniche[1]. Lo strumento del questionario ha permesso di indagare più aspetti e raccogliere dati utili per maggiori approfondimenti e studi.

Obiettivi

L'obiettivo generale dello studio è stato quello di condurre un'indagine esplorativa sulle caratteristiche relative ad un campione della popolazione dei lavoratori all'interno dell'IRCCS Policlinico San Matteo. Nello specifico è stato descritto il profilo dei lavoratori (caratteristiche socio-demografiche e cliniche, gli stili di vita e le caratteristiche legate all'ambiente di lavoro) e si è voluto indagare l'eventuale associazione con l'infezione. Si è inoltre stimata la prevalenza di pregressa infezione da SARS-CoV-2 (accertata da positività a test molecolare o sierologico) in tale campione di lavoratori.

Metodi

È stato distribuito un questionario ai dipendenti del Policlinico nel momento in cui si presentavano in ambulatorio per la somministrazione del vaccino antinfluenzale. I dati son stati raccolti tra il 16 novembre 2020 e il 20 dicembre 2020. Il questionario conteneva domande inerenti la mansione svolta all'interno dell'ospedale, la classificazione del reparto di lavoro (destinato a pazienti Covid o meno), le abitudini degli intervistati, l'eventuale positività a tampone molecolare o sierologico, la percezione del rischio legato all'infezione da SARS-CoV-2, l'educazione all'uso dei DPI. Sono state condotte analisi univariate sia per le variabili qualitative (Chi-square test) che quantitative (Mann-Whitney), in relazione alla pregressa infezione. Nel modello logistico son state inserite le variabili significative all'analisi esplorativa (*p-value* <0.1), con l'eccezione di sesso ed età, inclusi nel modello in quanto di interesse clinico relativamente all'outcome di studio. I dati son stati analizzati con software STATA 16.1 (2019).

Risultati

Son stati raccolti i dati relativi a 1093 questionari. Si son esclusi 28 questionari in quanto incompleti, o riferiti a studenti tirocinanti, per un totale di 1065 questionari analizzati. Il campione era composto da 32.5%

soggetti di sesso maschile e 67.5% soggetti di sesso femminile. La prevalenza di soggetti risultati postivi ad almeno un tampone molecolare e/o sierologico è stata del 17.1% ($IC_{95\%}$: 14.9-19.5%). L'età mediana era pari a 42.0 anni (IQR 31.0-52.0), il BMI mediano era di 22.8 (IQR 20.5-25.6); per tali dati non si è riscontrata differenza significativa tra i soggetti positivi all'infezione e quelli non infettati (p=0.8119 e p=0.767 rispettivamente). Il 70.7% dei soggetti ha dichiarato di non fumare, il 20.8% di esser un fumatore e l'8.5% di esserlo stato: anche in questo caso non è emersa alcuna associazione statistica tra la pregressa infezione e l'abitudine al fumo (p=0.549). Il 13.7% dei soggetti con pregressa infezione ha dichiarato di esser iperteso, mentre il 24.2% di aver almeno una comorbidità (malattie respiratorie, gastrontestinali, endocrino-metaboliche, neoplastiche). Il 33.3% dei soggetti risultati positivi ha dichiarato di esser genitore di bambini in età scolare, mentre il 6.1% di adoperare abitualmente mezzi pubblici. Per tutte queste variabili non si è rilevata alcuna differenza significativa nella distribuzione delle risposte tra i soggetti con pregressa infezione e quelli non contagiati (p>0.05). Il modello di regressione logistica univariata ha indicato come l'abitudine al consumo di alcool sembrerebbe esser un fattore protettivo (OR= 0.68; $IC_{95\%}$=0.48-0.97), mentre l'aver lavorato in un reparto con pazienti Covid un fattore di rischio per l'infezione (OR=1.55; $IC_{95\%}$= 1.07-2.23). Per quanto riguarda la mansione e il livello di percezione del rischio di infezione, nonostante le differenze osservate nella distribuzione tra infettati e non all'analisi univariata, non si sono ritrovati aumenti di rischio significativamente rilevanti all'interno del successivo modello logistico tali da classificarli come potenziali fattori predisponenti (p>0.05).

Conclusioni

Nel corso della seconda ondata la prevalenza di positività all'infezione di SARS-CoV-2 è aumentata (a maggio 2020 era dell'11.3%; $IC_{95\%}$: 9.7-13.2%). Nella prima ondata, a parità di accessibilità e di uso corretto dei DPI di tutti gli operatori sanitari del ospedale, il maggiore e più prolungato contatto con i pazienti affetti da COVID-19 è stato uno dei fattori di rischio cruciali per l'infezione da SARS-CoV-2. Anche in base a quanto osservato tramite questa survey, si può notare come l'aver lavorato all'interno di un reparto in cui eran ricoverati pazienti Covid+ abbia aumentato il rischio di infezione. Il dato relativo all'alcool necessita di esser approfondito in successive indagini. Nel precedente studio, l'incremento di BMI e l'abitudine al fumo son sembrati esser fattori di rischio per l'infezione. Dalla presente indagine invece si è visto come non sembrerebbero esserci dei fattori statisticamente associati con la possibilità di contrarre SARS-CoV-2, ad eccezione del maggior rischio derivante dal contatto con pazienti positivi al Covid, nonostante il corretto uso dei DPI. Questa indagine rimane ad uso esclusivamente esplorativo, al fine di indagare eventuali fattori predisponenti l'infezione da SARS-CoV-2 per una migliore prevenzione nel limitare il rischio di contagio.

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Tabella 1

		Covid +	***Covid -***	***OR ($IC_{95\%}$)***	***p-value***
Sesso (n 1065)	M	28.6%	33.3%	0.78 (0.53-1.12)	0.178
	F	71.4%	66.7%	1.00	
Età (anni) (n 1058)		42.0 IQR (32.0-52.0)	42.0 IQR (31.0-52.0)	1.00 (0.99-1.02)	0.786
Alcool (n 1052)	Sì	36.5%	43.9%	0.69 (0.48-0.97)	0.035
	No	63.5%	56.1%	1.00	
Reparto Covid (n 1056)	Sì	54.2%	43.6%	1.55 (1.08-2.23)	0.018
	No	45.8%	56.4%	1.00	
Ruolo* (n 1065)	0	17.0%	22.8%	1.00	0.324
	1	83.0%	77.2%	1.27 (0.79-2.05)	
Percezione Rischio (n 1035)	0	2.9%	2.0%	1.05 (0.91-1.21)	0.543
	1	6.3%	5.2%		
	2	17.1%	17.2%		
	3	29.1%	39.3%		
	4	24.6%	22.9%		
	5	20.0%	13.4%		

* 0: potenzialmente non esposti (Tecnici, Amministrativi e Ricercatori non medici)
1: potenzialmente esposti (Medici, Infermieri, Ostetriche, OSS)

Determinants of the severity of rectus muscle diastasis in Italian women

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Background: Diastasis of rectus abdominis (DRA) refers to a separation of the rectus abdominis from the linea alba, which often affects multipara women [1].

Aims: The aim of this study is to investigate possible determinants of the severity of DRA, including maternal conditions (age, body mass index (BMI), smoking habits), comorbidities/treatments (diabetes, collagen diseases, hypothyroidism, use of steroids), previous pregnancies (number of term pregnancies), childbirth characteristics (Kristeller's manoeuvre, episiotomy). The association between the severity of DRA and post-partum disorders (pain/discomfort, urinary/faecal incontinence, hernias) was also investigated.

Methods: In the present observational cross-sectional study, approximately 23,000 Italian women, belonging to the Diastasi Donna® ODV association, were invited to answer an online questionnaire. The questionnaire was filled in by 4,757 (about 20.7%) aged 39±6.5 years (mean ± SD; range 22-74) with a median BMI of 23.7 $\mathrm{kg/m^2}$ (range 16.0-40.0), who had had a median of 2 pregnancies (range 0-5). The severity of DRA was defined by the distance between rectal muscles (≥ 3, 3-5, >5cm) and the extension of DRA (supra-umbilical, sub-umbilical, both). Of note, diastasis >5cm is considered as an indication for surgical treatment [2].

Significance of the association between DRA severity and potential determinants was evaluated by Fisher's exact test or chi-squared test for categorical variables and Kruskal-Wallis test for quantitative variables. In particular, faecal incontinence was assessed by Wexner score, and urinary incontinence by ICIQ-SF score. Multivariable analysis was accomplished by a multinomial logistic regression model, where muscle separation (≥ 3, 3-5, >5cm) was the response variable, BMI, number of pregnancies, Kristeller's manoeuvre and episiotomy the potential determinants, and age at interview, smoking habits, gestational diabetes, hypothyroidism, use of steroids during gestation the possible confounders.

Results: In almost two-thirds of the participants (3079/4757 = 64.6%) diastasis affected both the supra- and sub-umbilical areas. Diastasis width was medium (3-5 cm) in 55% of cases, and large (>5 cm) in 28%.The separation between rectal muscles increased with age at interview, BMI and number of pregnancies (p<0.001). In particular, separation>5cm was recorded in 18.8%, 22.8%, 33.1%, 41.9%, 44.0% of underweight, normoweight, overweight, obese, severely obese women. As regards previous term pregnancies, separation >5cm was observed in 13.0% of nulliparous women, 27.3% of women with 1-3 term pregnancies and 43.8% of women with 4 or more term pregnancies. The proportion of diabetes increased from 1.6% in women with separation <3cm to 3.0% in women with separation >5cm (p=0.008); likewise, the proportion of gestational diabetes increased from 12.6% to 16.5% (p=0.004). Among delivery characteristics, Kristeller's manoeuvre was associated with larger separation between Rectus Abdominis: the manoeuvre was reported by 19.8% of women with separation <3cm and by 25.4% of those with separation >5cm (p=0.021).

This risk profile was substantially confirmed by multivariable analysis: in the multinomial logistic regression model, when considering separation >5cm versus <3cm (reference), the relative risk ratios (RRRs) of

overweight, obese, severely obese with respect to normoweight were respectively 1.88 (95% CI 1.48-2.40), 2.57 (95% CI 1.74-3.78), 5.12 (95% CI 2.25-11.70). Rectal muscle separation increased with increasing number of pregnancies: with respect to one pregnancy, the RRRs of 2, 3, >=4 pregnancies were 3.78 (95% CI 2.95-4.84), 5.64 (95% CI 3.96-8.04), 6.18 (95% CI 3.39-11.27) respectively. Kristeller's manoeuvre, which increases intra-abdominal pressure during delivery, appeared as a risk factor for larger separation (RRR=1.51, 95% CI 1.15-1.98), while episiotomy, which facilitates delivery, seemed to be protective (RRR = 0.62, 95% CI 0.49-0.78).The prevalence of post-delivery disorders significantly increased with increasing separation of rectal muscles. The prevalence of pain/discomfort, urinary incontinence, incontinence for liquid stools was 50.6%, 64.4%, 16.3% respectively in the group with separation <3cm and rose to 80.8%, 75.4%, 20.2% in the group with separation >5cm.

Conclusion

The present study confirmed that pre-pregnancy conditions play a key role in DRA severity, in particular, the severity of rectal muscle separation increases with increasing age, BMI and number of pregnancies. Moreover, gestational diabetes and Kristeller's manoeuvre during labour also increased the severity of DRA, while episiotomy decreased it. Larger separation between rectal muscles was associated with increased risk of pain/discomfort and incontinence for liquid stools. At variance with Fei et al [1], our study found that the severity of DRA was associated with increased risk of urinary incontinence.

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Long-term effect of air pollution on re-hospitalization in children discharged from Pediatric Intensive Care Units

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Introduction: Air pollution is a known risk factor for cardiovascular, respiratory and neurological hospitalizations in the general population. Several studies assessed the effect of air pollution on subjects with specific pathologies, particularly on adult population. However, several studies have shown an association between air pollution and respiratory morbidity in children both in terms of emergency room visits and hospitalizations [1,2]. In particular, air pollution was significantly associated with higher number of hospital admissions, longer length of stay and higher economic cost of hospitalization in children with respiratory diseases, with a maximum effect observed on the day before hospitalization (sort of acute effect) [3]. Furthermore, studies on the chronic and long-term exposure to air pollution showed that children living closer to the main roads have an increased risk of developing respiratory infections [4,5]. Studies on hospital re-admission rates in children are concentrated on asthma patients. It has been found that traffic-related air pollution exposure is associated with increased odds of readmission in white children [6]. In another recent study, the single-pollutant models showed that PM2.5 concentration had a significant positive effect on risk for hospital readmissions (OR = 1.082, 95% CI = 1.008–1.162, p = 0.030). In particular, findings of this study suggest that short-term (within 4 days) exposure to air pollutants might increase the risk of preventable hospital readmissions for pediatric asthma patients [7]. In adult population, several studies tried to assess the association between air pollution levels and re-hospitalization for cardiac diseases (severe conditions), but in children there is a lack of literature on the topic of re-admissions (except for asthma patients), especially related to "frail" population.

Aims: Therefore, the main aim of this study is to evaluate the risk of re-hospitalization in children that were previously hospitalized in the Pediatric ICU (PICU), in order to evaluate the risk of readmission of a particularly fragile population.

Methods: Children hospitalized in the PICU of Padova hospital (Italy) between 2013 and 2019 were selected from hospital discharged records (index hospitalization). All subsequent hospitalizations for cardiovascular, respiratory or neurological diagnosis have been tracked until 2020. Daily data on PM10, PM2.5, NO2, temperature, atmospheric pressure and relative humidity were obtained from the monitoring stations of the Regional Agency for Environmental Prevention and Protection (ARPA).

To account for time-varying air pollution levels, a Cox model with the Andersen-Gill counting process adjusted for exposure and subject-related confounders was applied.

Results: Overall, 1204 children were admitted to the PICU and 461 of them experienced a subsequent hospitalization for cardiovascular, respiratory or neurological issues. The 73% was re-hospitalized during the first year after the PICU discharge. The relationship between re-hospitalizations and exposure to PM2.5 is non-linear, showing non-significant hazard at lower levels of PM2.5 (5 to 50 ug/m3) and an increased hazard for levels higher than 50 ug/m3. NO2 shows a similar trend with a flat slope at low levels of the pollutant and an increased hazard at concentrations over 40 ug/m3. The association with PM10 is less strong, with an increase in the re-hospitalization hazard only for exposure to very high levels of pollutant.

Conclusions: Exposure of fragile children (as those with a previous PICU admission) to high levels of air pollution could lead to severe outcome as re-hospitalization for several diseases. It is crucial to assess the association between these two events in order to adopt public health policies aimed at safeguarding this particularly fragile population.

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SURVEILLING COVID-19 EMOTIONAL CONTAGION ON TWITTER

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Introduction: Worldwide, posts related to the COVID-19 emergency have been impressively growing as a trend topic on Twitter. Everyone shared her/his subjective perspective (either positive or negative), mixed-up with legitimate and authoritative sources of information. Therefore, the fight against the pandemic seemed to encompass a rapidly evolving debate on social media, possibly resulting in emotional contagion that needs to be surveilled [1-2].

Objectives: In the current study, we aimed to examine the flow and content of tweets, considering the role of COVID-19 key events.

Methods: Benefiting from freely available data from Twitter's archives, we gathered tweets and users' data from Advanced Programming Interfaces access point and performed a focused analysis to capture the core discussions. To this purpose, both context-dependent meaning and emotion-specific features characterizing subjective perspectives were considered, distinguishing different populations of users. Following two complementary approaches, features related to the sentiment expressed in tweets were decoded and a polarity compound score with 95% Confidence Interval was computed. Sentiment analysis was performed by using both the Valence Aware Dictionary for sEntiment Reasoning (VADER) and the Covid Twitter-Bidirectional Encoder Representations from Transformers (CT-BERT) trained model specific for the COVID-19 scenario. Longitudinal trends between January 19 and March 3, 2020, were evaluated.

Results: We gathered more than 6 million tweets, of which 3,308,476 written in English. Since the first World Health Organization report (January 21, 2020), negative sentiment proportion of tweets gradually increased, with amplifications following key events. Sentiment scores were increasingly negative among most active users. Tweets' content and flow revealed an ongoing scenario in which the global emergency seems difficult to be emotionally managed with many users potentially exposed to emotionally unstable perceptions, as shown by sentiment trajectories.

Conclusions: There is the need to surveil and sustain healthy behaviors as well as community supports. Sentiment trajectories may represent the first step to better understand users' interactions and related individual- and area-level components. It appears crucial to identify, as the target of potential preventative interventions, those subjects most in need who may be engaged in emotionally unstable connections [3]. Therefore, integrating models for social media like Twitter as essential surveillance tools in the management of the pandemic and related waves might actually represent a novel preventive approach to hinder emotional contagion. Considering the existing debate on data availability, a systematic ongoing collection, collation, and analysis of data and the timely dissemination of reliable and trustworthy information are needed.

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MONITORAGGIO DEGLI ABORTI SPONTANEI E DELLE INTERRUZIONI DI GRAVIDANZA IN PUGLIA: CONFRONTO FRA L'ANNO 2019 E IL 2020.

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INTRODUZIONE

Il 30 gennaio 2020 l'OMS ha dichiarato che il focolaio internazionale da nuovo Coronavirus è un'emergenza di sanità pubblica di rilevanza internazionale [1]. L'infezione da SARS-CoV-2, identificata nella città di Wuhan, si è diffusa nel resto della Cina e in tutto il mondo, assumendo caratteristiche di pandemia. La diffusione del Covid-19 in Italia ha messo a rischio la tenuta del sistema sanitario nazionale (SSN), ed anche per questo richiesto misure restrittive urgenti. Ciò ha determinato ritardi nell'accesso alle cure, sovraccarico ospedaliero, oltre che un impatto sociale sul benessere mentale e psicologico dei pazienti, determinando, con un effetto domino, una diminuzione nella qualità della maggior parte dei servizi erogati da parte del SSN. È verosimile che anche l'area relativa alla salute materno-infantile abbia risentito degli effetti della pandemia, come diversi studi hanno dimostrato [2]. Alcuni studi, inoltre, hanno verificato nel periodo della pandemia un aumento del rischio di violenza domestica, ipotizzandone una possibile associazione con l'aumento delle gravidanze indesiderate [2,3].

OBIETTIVI

Obiettivo di questo studio è valutare l'entità di una possibile variazione nel numero di aborti spontanei (AS) e interruzioni volontarie di gravidanza (IVG), durante il periodo di lockdown. Inoltre, sarà valutata l'eventuale associazione tra tassi di contagi e tassi di abortività, a seguito delle misure restrittive adottate.

METODI

I dati utilizzati sono stati raccolti grazie al Sistema di Sorveglianza Epidemiologica che vede coinvolti il Ministero della Salute, l'Istituto Superiore di Sanità, l'Istat, le Regioni e le due Province Autonome. L'analisi ha riguardato i dati riferiti agli eventi AS e IVG registrati nella regione Puglia, presso strutture pubbliche e private, e relativi agli anni 2019 e 2020. Sono state escluse dallo studio le pazienti con età uguale o superiore a 50 anni, e l'età è stata classificata, sia per gli eventi IVG che AS, utilizzando le stesse classi presenti nella relazione per l'attuazione della legge 194/78 redatta da Ministero della salute e ISS: <15 anni, 15-19 anni, 20-24 anni, 25-29 anni, 30-34 anni, 35-39 anni, 40-44 anni, 45-49 anni [4]. I tassi di abortività grezzi mensili dell'anno 2019 e dell'anno 2020 sono stati calcolati utilizzando le rispettive popolazioni medie determinate secondo i dati ufficiali messi a disposizione dall'ISTAT [5]. I tassi sono stati successivamente standardizzati con il metodo diretto, utilizzando come popolazione standard la popolazione pugliese al 1 gennaio 2020 [5]. L'SRR (standardized rate ratio) è stato calcolato dividendo i tassi di abortività standardizzati del 2020 con quelli del 2019. Un intervallo di confidenza al 95% è stato calcolato, sotto l'assunzione della distribuzione campionaria normale del log(SRR). Un'analisi di cross-correlazione è stata implementata per confrontare la serie dei tassi di AS e IVG con la serie dei tassi di incidenza mensile dei contagi da Covid19. Sono stati considerati statisticamente significativi i risultati con p<0,05. Le analisi sono state elaborate con il software SAS/STAT Statistics, versione 9.4.

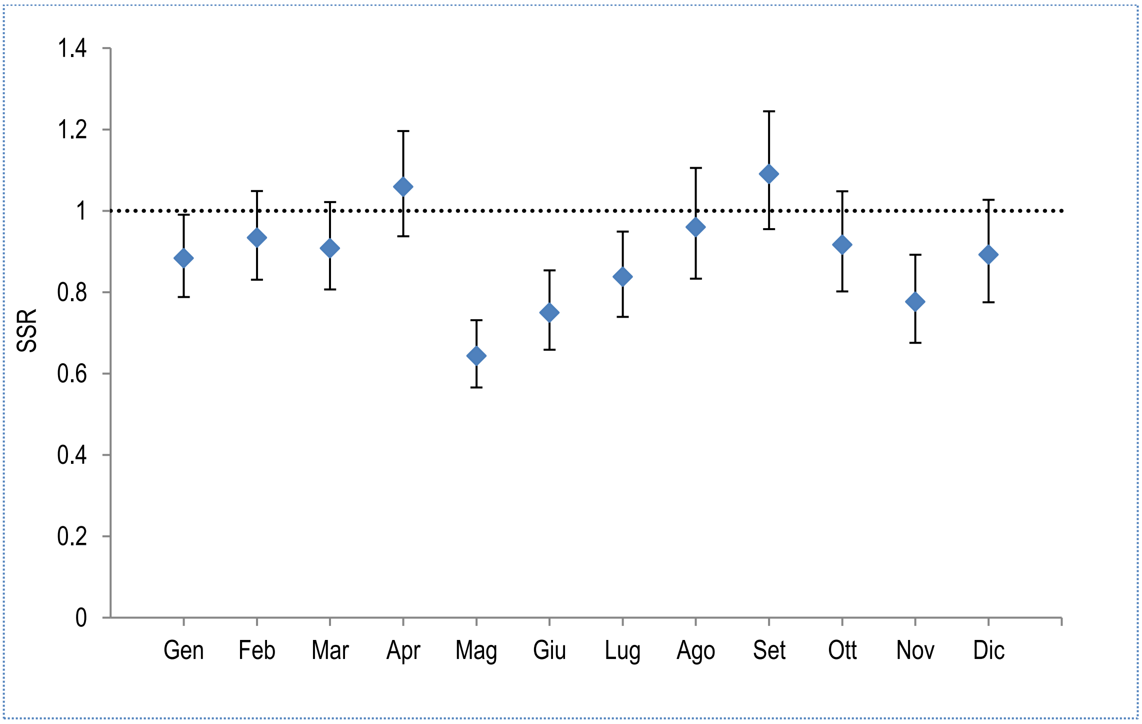
RISULTATI

Sono state incluse nello studio 11474 pazienti che hanno effettuato una IVG, di cui 6162 nel 2019 e 5312 nel 2020; 7765 pazienti che hanno subito un AS, di cui 4146 nel 2019 e 3619 nel 2020. Confrontando la distribuzione mensile degli SRR di IVG tra il 2019 e il 2020 si evidenzia una riduzione statisticamente significativa nei mesi di maggio, giugno, luglio e novembre. Come si può anche notare dal grafico in figura 1, l'SRR più basso è quello del mese di maggio (SRR: 0,643, IC95% 0,566-0,731), in cui la diminuzione delle IVG è particolarmente significativa nella classe delle pazienti tra 15 e 19 anni (SRR: 0,318, IC95% 0,182-0,558). A seguire il mese di giugno (SRR: 0,750, IC95% 0,659-0,854) e di novembre (SRR:0,776, IC95% 0,676-0,892). La diminuzione di AS dal 2019 al 2020 è risultata essere statisticamente significativa nei mesi di marzo, aprile, maggio, giugno, agosto, settembre, ottobre. L'SRR più basso è quello del mese di marzo (SRR: 0,710, IC95% 0,61-0,826), in cui la diminuzione degli AS è particolarmente significativa nelle pazienti tra 30 e 34 anni (SRR: 0.650, IC95% 0.477 -0.885) e in quelle tra 40 e 44 anni (SRR: 0,601, IC95% 0,432-0,835). Seguono i mesi di maggio (SRR: 0,736, IC95% 0,628-0,863) e di giugno (SRR: 0,783, IC95% 0,668-0,919). L'analisi di cross-correlazione non ha mostrato nessuna associazione significativa tra l'incidenza dei contagi in Puglia e i tassi di AS e IVG, neanche attribuendo a queste ultime un lag fino a 6 mesi.

CONCLUSIONI

Dall'analisi dei dati è possibile ipotizzare che le misure restrittive adottate durante il periodo di lockdown, associate alla carenza di informazioni sui servizi disponibili nello stesso periodo, abbiano impedito ad alcune donne la possibilità di accedere ai servizi per l'interruzione volontaria della gravidanza nei tempi previsti dalla legge. Inoltre, in accordo alla letteratura scientifica, l'accesso all'aborto potrebbe essere stato inibito soprattutto dalle restrizioni agli spostamenti [3]. Il nostro studio mostra una diminuzione significativa degli aborti spontanei in quasi tutti i mesi dell'anno 2020 nonché una riduzione di ricorso all'IVG nella classe tra 15 e 19 anni. In questa fascia d'età le misure restrittive potrebbero, in particolare, aver determinato una riduzione del concepimento per via della riduzione dei contatti sociali. Un'analisi dei determinanti sociali potrebbe rappresentare un successivo approfondimento per valutare la misura in cui le misure restrittive abbiano inciso su tale fenomeno.

FIGURA 1. Standard Rate Ratio (IC 95%) tra Tasso di IVG 2020 e 2019. Regione Puglia.



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STUDIO EPIDEMIOLOGICO PER CAUSE DI MORTALITA ONCOLOGICHE DAL 1980 AL 2016 NEL DISTRETTO CASALE

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INTRODUZIONE

Questo studio descrittivo è stato elaborato al fine di stimare delle eventuali condizioni anomale di mortalità dei residenti negli anni di osservazione poiché il territorio casalese, come storicamente risaputo, è stato esposto per numerosi decenni alla lavorazione dell'amianto per la produzione di svariati manufatti; tali esposizioni hanno indotto non solo un danno sanitario grave agli occupati in ambito lavorativo ma anche alla popolazione sia residente nelle aree limitrofe agli stabilimenti e sia ai famigliari degli stessi operai (esposizioni para-occupazionali).(1-3)
L'indagine qui presentata, infine, va a colmare un vuoto sanitario e conoscitivo sull'andamento epidemiologico nell'area per cause oncologiche non direttamente correlabili all'esposizione di amianto che invece sono state ampiamente studiate sia in termini descrittivi sia eziologici. (4)

Obiettivo
La finalità principale della ricerca qui presentata è di quantificare eventuali eccessi di mortalità, stratificati per età che per genere, per cause oncologiche nell'area complessiva del distretto casalese che include 48 comuni (vedi tabella successiva) . La procedura statistica presentata nel paragrafo successivo permette la standardizzazione del dato e di evitare pertanto distorsioni o errate interpretazioni dei rischi indotti ad esempio dalla differente età media. (5)

Metodi
I dati di mortalità sono stati ottenuti in forma anonima dall'Istat di Roma mentre la popolazione residente nell'area in studio è di circa 80 mila abitanti e coinvolge 48 comuni dell'area Casalese.

Per la valutazione della mortalità, riferente l'area complessiva, sono stati impiegati i seguenti indicatori epidemiologici:

- La frequenza assoluta di decessi dal 1980 al 2016 , numero di casi Osservati di patologie oncologiche e non, per sede anatomica e per fasce di età quinquennali ;
- I rapporti standardizzati indiretti di mortalità , SMR, calcolati con il metodo indiretto con il relativo intervallo di confidenza al 95%;

I casi attesi, per il successivo calcolo del SMR (Rapporto Standardizzato Indiretto di Mortalità), sono stati stimati utilizzando i tassi specifici delle diverse patologie distribuiti per classi di età quinquennali e suddivise per sesso della regione Piemonte . I tassi specifici regionali sono forniti dal servizio di Epidemiologia-Dors di Grugliasco attraverso la BDM (Banca dati di mortalità) dal 1980 al 2001 e ricavabili, per gli anni successivi, dal motore di ricerca PISTA-BDDE. Al fine della convalida statistica, inoltre, sugli SMR cosi elaborati sono stati calcolati gli intervalli di confidenza al 95% (delimitati dal Limite superiore ed inferiore) che esprimono l'ambito entro cui si colloca il vero valore dei tassi riscontrati con una probabilità pari al 95%. Per il calcolo di tali intervalli è stato utilizzato il metodo di Byar .

Risultati

La mortalità complessiva e specifica, osservata nel comune di Casale e nel distretto casalese, presentano alcune condizioni significative di attenzione e di possibile successivo approfondimento inferenziale.

Si segnalano, incrementi statisticamente significativi per le seguenti neoplasie:

- Totale tumori,
  PER IL DISTRETTO DI CASALE
  Il totale tumori evidenzia eccessi statisticamente significativi sia per il genere maschile (+10%) sia per le femmine (+9%) che totale generi (+10%). Tale ultimo incremento in termini assoluti corrisponde a circa 1300 decessi oltre l'atteso.
  PER LA CITTA DI CASALE
  La città di Casale M.to presenta valori di Smr complessivi per il totale tumori superiori a quelli stimati nel distretto casalese in entrambe i generi. Il +26% osservato equivale in termini di decessi assoluti a oltre 1500 casi oltre l'atteso
- Polmone,
  PER IL DISTRETTO DI CASALE
  Per i tumori del polmone, gli eccessi statisticamente significativi riguardano sia gli uomini (+11%), sia le donne (+8%) che il totale (+10%); quest'ultimo dato in termini di decessi assoluti equivale a oltre 260 morti oltre l'atteso.
  PER LA CITTA DI CASALE
  Anche per le neoplasie polmonari la città di Casale M.to presenta valori di Smr complessivi superiori a quelli stimati nel distretto casalese sia per femmine che uomini . Il +29% osservato equivale in termini di decessi assoluti a oltre 330 casi oltre l'atteso.
- Mesotelioma
  PER IL DISTRETTO DI CASALE
  Gli incrementi statisticamente significativi per mesotelioma riguardano tutti i sottoperiodi e indistintamente entrambe i generi. Per il totale periodo si osserva un eccesso di 8 volte per gli uomini e 10 volte nelle donne. Anche nell'analisi per fasce di età si osservano Smr significativi in tutte l'età, dove si sono osservati decessi: i valori più alti (escludendo sotto i 40 anni) si notano prevalentemente nella decade 60-69 anni e over 85 negli uomini ; più diffusa la situazione nel genere femminile con valori rilevanti in tutti i gruppi di età
  PER LA CITTA DI CASALE
  Valori complessivi di Smr praticamente doppi in Casale rispetto al distretto casalese : (uomini 7,97 vs 14,3), (donne (9,8 vs 18,4) e (totale generi 8,6 vs 15,9). I plot mostrano un graduale aumento per il genere femminile dalla fine degli anni 80 mentre sia tra gli uomini sia nel totale gli eccessi risultano pressochè costantemente e abbondantemente al di sopra del valore soglia. Non si osservano ad oggi trend di riduzione e/o incremento
- Colon-retto
  PER LA CITTA DI CASALE
  A differenza di quanto osservato per il distretto, la città di Casale evidenzia incrementi significativi in tutti e generi e totale. Il +13% come dato complessivo corrisponde a circa 75 decessi oltre l'atteso regionale.
- Leucemie
  PER IL DISTRETTO DI CASALE
  Per le neoplasie ematologiche leucemiche si registrano incrementi significativi sia negli uomini (+20%), sia nelle donne (+18%) che totale generi (+19%) ; tale ultimo incremento corrisponde in casi assoluti osservati a circa 88 morti in più dell'atteso
- Linfomi

PER IL DISTRETTO DI CASALE
Nell'analisi epidemiologica per linfomi si osserva per il totale periodo in studio un eccesso statisticamente significativo sia per gli uomini (+12%) che totale generi (+13%) che equivale a circa 48 casi oltre l'atteso regionale. I rischi per fasce di età nel genere maschile sono

- Mieloma
  PER IL DISTRETTO DI CASALE
  Anche per il mieloma multiplo come per i linfomi si registrano eccessi statisticamente significativi come dato complessivo per uomini (+35%) e sommatoria uomini e donne con +22% pari a 53 decessi oltre il dato atteso. Nei rischi per età si notano numerosi incrementi significativi nel gruppo età 50-64 anni per quanto riguarda gli uomini mentre situazione abbastanza eterogenea nelle donne
- Asbestosi
  Come per il mesotelioma anche per l'asbestosi i valori complessivi in Casale , per il periodo in studio, sono sensibilmente più elevati al distretto casalese; gli incrementi di Smr, tutti statisticamente significativi, coinvolgono tutti i sotto periodi in entrambi i generi
- Silicosi
  Il valore complessivo di Smr per Casale è superiore a quello del distretto (5,04 vs 3,34) ; da osservare nessun caso osservato sia nel genere femminile e sia a partire dal 2010 tra gli stessi uomini a suggerire un possibile trend in riduzione.

Conclusioni

L'analisi di mortalità oncologica ha confermato le criticità "storiche" per l'area Casalese con incrementi perduranti e rilevanti per quanto riguarda le patologie strettamente associate all'esposizione di amianto quali mesotelioma, tumore del polmone, asbestosi e silicosi. (6-8)

Lo studio ha anche aggiornato ed evidenziato i rischi per alcune restanti patologie tumorali ove, ad esempio, si osserva incremento per il solo comune di Casale a carico dei tumori del colon-retto : tale dato è meritevole di approfondimento in quanto fa ipotizzare a possibili fattori di rischio sussistenti tra la popolazione residente della città rispetto al resto del distretto.

Si sono evidenziate criticità per i tumori onco-ematologici dove nel caso delle forme leucemiche, il risultato di essere trasversale sia a uomini che donne, fa propendere per eventuali esposizioni di tipo ambientale piuttosto che di origine occupazionale ; quest' ultimo aspetto invece resta più probabile per i linfomi e mielomi i cui incrementi si osservano attualmente solo tra il genere maschile.

L'osservazione dei trend non fa ipotizzare, ad oggi, un'imminente e sensibile riduzione della mortalità nonostante gli indubbi risultati positivi nelle opere di bonifica che l'area di Casale e i suoi amministratori portano avanti da diversi decenni a questa parte. Ciò può far ipotizzare che all'esposizione storica dell'amianto siano sussistenti altri fattori di rischio coinvolti eventualmente nell'eziologia delle forme oncologiche non amianto correlabili. (9-10)

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INCIDENZA DELLA FIBROSI POLMONARE IDIOPATICA:
REVISIONE SISTEMATICA E META-ANALISI
Risultati del progetto Motive (PRIN 2019-2021, Cod. 2017728JPK)

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Introduzione

La fibrosi polmonare idiopatica (FPI) è una patologia rara, la cui incidenza è caratterizzata da una elevata variabilità nel mondo. Sono state effettuate due revisioni sistematiche, nel 2012 [1] e nel 2015 [2], che tuttavia non hanno prodotto alcuna stima globale.

Obiettivi

Revisione sistematica e meta-analisi per stimare l'incidenza globale della fibrosi polmonare idiopatica.

Metodi

Il protocollo dello studio è stato registrato nella rete PROSPERO (CRD42021234861).

La ricerca bibliografica per l'identificazione degli studi scritti in inglese, francese, spagnolo ed italiano è stata eseguita utilizzando MEDLINE (PubMed), Web of Science (database ISI) e Scopus, con la seguente stringa di ricerca *((idiopathic pulmonary fibrosis OR idiopathic fibrotic OR idiopathic interstitial pneumonias OR cryptogenic fibrosing alveolitis OR fibrosing alveolitis OR usual interstitial pneumonia OR Lung Diseases Interstitial OR Pulmonary Fibrosis OR lung fibrosis) AND (epidemiolog* OR incidence OR prevalence))*, applicata al titolo e/o all'abstract degli studi pubblicati prima del 6 gennaio 2021 ed eseguita indipendentemente da AF e MI. Sono stati inclusi gli studi osservazionali prospettici, che valutavano l'incidenza sia sulla popolazione totale, che in funzione del sesso e classi di età (55-74 anni, ≥75 anni), che identificavano i casi di FPI attraverso i ricoveri ospedalieri riportanti i codici ICD-9-CM 516.3/ ICD-10 J84.1.

Da ciascun articolo sono state estratte le seguenti informazioni: primo autore, anno di pubblicazione, paese di studio, periodo di studio, numero totale di casi incidenti, popolazione di riferimento, età, sesso, tassi di incidenza per 100.000 anni-persona (a.p.).

È stata eseguita una meta-analisi per stimare il tasso di incidenza globale, stratificato per età e per sesso ed età. Il modello ad effetti misti è stato considerato quando l'eterogeneità tra gli studi risultava elevata (I^2>50%). La robustezza della stima globale è stata valutata individuando l'effetto dei singoli studi sulla stima globale seguendo l'approccio *leave-one-out*, confrontando la stima di incidenza globale ottenuta escludendo uno studio alla volta. Le analisi sono state effettuate utilizzando il software R.

Risultati

Nella ricerca iniziale sono stati estratti 10.371 articoli da MI e 7.076 articoli da AF. Sono stati rimossi 5.544 (MI) e 3.747 (AF) duplicati per titolo e/o doi, dopodiché la lettura del titolo e dell'abstract ha permesso ai due autori di selezionare congiuntamente 58 articoli. Infine, dalla lettura completa degli studi, sono stati selezionati 8 studi per la stima globale sulla popolazione generale, 4 studi per la stima globale stratificata per età, 3 dei quali sono stati utilizzati per la stima stratificata per sesso ed età. Gli studi sono stati condotti in 8 distinti paesi (Canada, Danimarca, Italia, Giappone, Corea, Norvegia, Spagna, USA), dal 1984 al 2017.

Il tasso di incidenza minore è stato osservato nel 2005 in Giappone (1,22 [IC 95%: 1,12 – 1,32] per 100.000 a.p.) [3] e nel 1998-2000 in Spagna (1,40 [IC 95%:1,24 – 1,57]) [4]; quello maggiore in Canada nel periodo 2006-2013 (18 [IC 95%: 11,96 – 27,09] per 100.000 a.p.) [5], e in Corea tra il

2011-2012 (13,04 [IC 95%: 12,73 – 13.36] per 100.000 a.p.) [6]. È stata rilevata una significativa variabilità tra gli studi (I^2=100%; p<0,001), e la stima globale è risultata pari a 3,94 [IC 95%: 2,07; 7,50] per 100.000 a.p.

L'analisi di sensibilità ha evidenziato stime globali coerenti con l'analisi principale: la variabilità tra gli studi è rimasta molto alta (I^2>99,5%) con una stima di incidenza globale minima di 3,22 [IC 95%: 1,78; 5,83] per 100.000 a.p. e massima di 4,67 [IC 95%: 2,45; 8,89] per 100.000 a.p.

La meta-analisi stratificata per classi di età, ha evidenziato una incidenza globale per la classe di età 55-74 anni pari a 12,05 [IC 95%: 8,57 – 16,94] per 100.000 a.p. (I^2=95%; p<0,001), osservando una incidenza minima in Norvegia (7,50 [IC 95%: 5,80 – 9,70]) [7] e una massima negli Stati Uniti (21,46 [IC 95%: 14,91 – 30,88]) [8]. Nella classe di età ≥75 anni l'incidenza globale era di 31,53 [IC 95%: 20,49; 48,51] per 100.000 a.p. (I^2=94%; p<0,001), con il tasso più basso in Italia tra il 2005-2010 (23,13 [IC 95%: 21,86 – 24,48] per 100.000 a.p.) [9] e quello più alto negli USA tra il 1988-1990 (73,11 [IC 95%: 50,48 – 105,88] per 100.000 a.p.) [8].

La figura riporta la stima globale stratificata per sesso e classi di età. Nei maschi di 55-74 anni l'incidenza globale è risultata pari a 14,23 [IC 95%: 7,07 – 28,67] per 100.000 a.p. (I^2=93%; p<0,001), mentre per le femmine a 10,95 [IC 95%: 9,95 – 12,04] per 100.000 a.p. (I^2=39%; p=0,190).

La stima globale nei maschi con età ≥75 anni era pari a 46,93 [IC 95%: 27,52 – 50,05] per 100.000 a.p. (I^2=87%; p<0,001) mentre nelle femmine era pari a 27,13 [IC 95%: 16,71 – 44,02] per 100.000 a.p. (I^2=85%; p<0,001).

Conclusioni

A nostra conoscenza questa rappresenta la prima meta-analisi volta a stimare il tasso di incidenza globale di FPI. La stima globale dell'incidenza della fibrosi polmonare idiopatica è caratterizzata da una elevata eterogeneità, che tuttavia non ha compromesso la precisione della stima: risulta rara nella popolazione generale, ma aumenta considerevolmente nella popolazione anziana, con un'incidenza maggiore nei maschi rispetto alle femmine.

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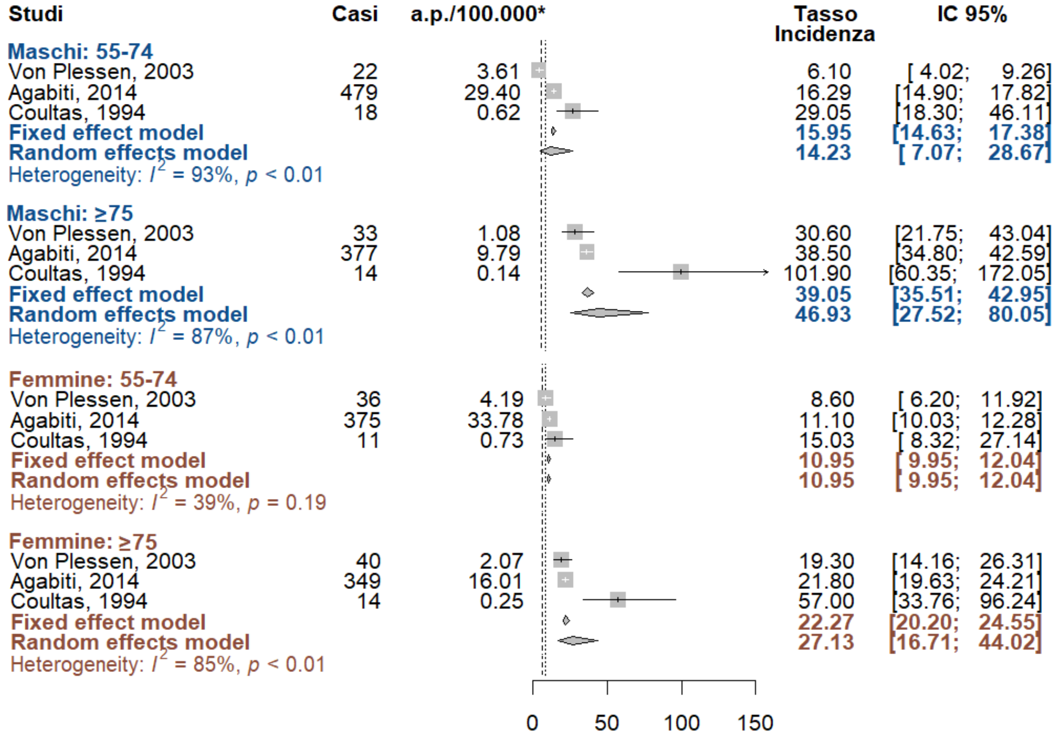
Stima dell'incidenza globale di Fibrosi Polmonare Idiopatica stratificata per sesso e classi di età.



*Anni-persona / 100.000

VALUTAZIONE DELLA QUALITÀ DELL'ARIA ALL'INTERNO DI DUE COMUNI LIMITROFI, SU CUI **INSISTE UN IMPIANTO PETROLCHIMICO**

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Introduzione

La qualità dell'aria nelle vicinanze di un impianto petrolchimico necessita di continui e attenti monitoraggi, in virtù del potenziale impatto ambientale e sulla salute dell'uomo[1,2,3,4]. Di particolare importanza sono i BTEX[5] (benzene, toluene, etilbenzene e xileni), l'acido solfidrico, il biossido d'azoto e l'anidride solforosa. I primi appartengono alla macro-categoria dei VOC (Volatile Organic Compounds) e ne costituiscono oltre il 60% nelle aree urbane[6]. L'NO (ossido di azoto) e il suo prodotto secondario (NO_2, biossido di azoto) sono gas presenti come "fondo" naturale anche in aree disabitate, tuttavia l'apporto maggiore alla loro concentrazione nell'aria è dato dal processo di combustione di carburanti fossili. L'SO_2 (biossido di zolfo o anidride solforosa) è un tracciante dell'inquinamento da impianti fissi a combustione; fra i suoi derivati più tossici vi è l'acido solforico (H_2SO_4) che costituisce la maggior componente acida dell'inquinamento atmosferico (smog pesante). Un altro composto di particolare interesse tossicologico è l'idrogeno solforato (H_2S), che può avere origini naturali o derivare da alcuni processi produttivi ed è caratterizzato da una bassa soglia olfattiva.

Obiettivi

L'obiettivo generale è stato quello di valutare la qualità dell'aria di 2 Comuni italiani limitrofi, su cui insiste un impianto petrolchimico. Nello specifico, gli obiettivi co-primari sono stati stimare le isoconcentrazioni degli inquinanti ambientali organici e non per 1) valutare le variazioni stagionali e le differenze fra i 2 Comuni, e 2) mappare la distribuzione spaziale degli inquinanti aerodispersi.

Metodi

Sono stati effettuati campionamenti dell'aria esterna in due diverse stagioni: estiva (7-11 settembre 2020) e invernale (16-20 novembre 2020), utilizzando campionatori diffusivi a simmetria radiale (Radiello®) collocati nelle medesime posizioni nelle due campagne. I punti di campionamento sono stati 11 nel Comune 1 e 21 nel Comune 2. I due Comuni si differenziano per topografia: il Comune 1 si trova sopravento rispetto all'impianto, il Comune 2 sottovento. I valori di concentrazione per ciascun inquinante sono stati descritti in termini di media e deviazione standard, o di mediana e range interquartile (se la normalità non rispettata). Sono stati usati test parametrici o analoghi non parametrici secondo il rispetto della condizione di normalità. È stato considerato significativo un *p-value* <0.05. Sono state costruite le mappe di distribuzione spaziale degli inquinanti aerodispersi mediante interpolazione con metodo Kriging. Le analisi sono state effettuate con STATA 16 e con SURFER Surface Mapping System ver. 8.06.39.

Risultati

In entrambe le stagioni, le concentrazioni medie di benzene nel Comune 1 erano significativamente inferiori rispetto al Comune 2 (Tabella 1). L'incremento occorso nel periodo invernale era statisticamente rilevante in entrambi i Comuni ($p<0.0001$). In media, nel Comune 1, la concentrazione di toluene è risultata significativamente inferiore rispetto a quella nel Comune 2, in entrambe le stagioni: i valori erano sovrapponibili tra le stagioni nel Comune 2 ($p=0.3856$), invece nel Comune 1 inferiori in estate ($p<0.0001$).

Il confronto intra-comunale tra le concentrazioni stagionali di etilbenzene non evidenziato una differenza tra i due periodi (Comune 1: $p=0.25$; Comune 2: $p > 0.90$), con una concentrazione mediana leggermente superiore nel Comune 2. Le concentrazioni mediane stagionali di orto- e metapara-xilene entro Comune non presentavano differenze significative ($p>0.05$), tuttavia, in entrambe le stagioni, nel Comune 1 si son rilevati livelli inferiori rispetto al Comune 2 ($p<0.0001$). Dei composti inorganici solo per l'NO_2 le concentrazioni estive son risultate superiori alle invernali, rispettivamente di 2.5 e 3 volte ($p<0.0001$), con un gap peraltro presente anche nel confronto comunale relativo alla prima campagna. Viceversa l'H_2S ha mostrato livelli estivi maggiori nel Comune 1, ma nuovamente il gap si è perso nella stagione successiva. Le mappe di distribuzione spaziale degli inquinanti aerodispersi descrivono chiaramente una situazione con concentrazioni di inquinanti quasi sempre inferiori ai limiti indicati per la qualità dell'aria e verosimilmente non attribuibili al sito produttivo.

Conclusioni

Per buona parte delle sostanze esaminate si riscontrano variazioni stagionali significative da un punto di vista statistico, ma trascurabili dal punto di vista quantitativo. Il confronto tra i due Comuni nelle due campagne di rilevamento, evidenzia, per quasi tutti i composti, una minor concentrazione nel Comune 1, ossia quello sopravento. Le concentrazioni rilevate sono comunque ben al di sotto dei valori limite di esposizione ambientale o di tossicità per la salute normati (EEA, 2019; ICSCs)[7,8]. L'incremento registrato nella stagione invernale è in parte riconducibile alle emissioni legate agli impianti di riscaldamento nonché al traffico veicolare (alcuni siti di rilevazione erano situati in corrispondenza di vie centrali nei 2 Comuni), nonostante l'importante riduzione del traffico concomitante al campionamento invernale (*lockdown* ministeriale come da disposizione anti-Sars-CoV-2). In due siti di monitoraggio nel Comune 1 le concentrazioni molto elevate di H_2S ($5.2\ \mu g/m^3$ e $6.1\ \mu g/m^3$) saranno oggetto di approfondimento: essendo questo sito "sopravento" rispetto all'impianto produttivo, l'eccesso non è attribuibile a quest'ultimo, bensì ad altre fonti presenti nel territorio (agricole o di depuratori). I valori anomali (specie nella campagna estiva) in una postazione di misurazione sempre nel Comune 1 per o- e mp-xilene, toluene, etilbenzene non sono verosimilmente da ricondurre all'impianto per le stesse ragioni.

Nella fase successiva si attribuirà ai residenti nei 2 Comuni, arruolati in uno studio di coorte prospettico in corso, il livello di esposizione ambientale, incrociando le coordinate di georeferenziazione di questi con le mappe di isoconcentrazione.

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Tabella 1

Campagna estiva

	Inquinante in μg/m^3	**Comune**	**n**	**range**	**media ± ds**	**mediana**	**25°-75° centile**	***Test p-value***
Composti aromatici	benzene	1	11	0.3-0.4	0.4±0.1			t = -3.07
		2	21	0.3-0.7	0.5±0.1			p = 0.0046
	toluene	1	11	1.3-2.1	1.7±0.2			t = -5.98
		2	21	1.8-5.8	3.0±1.0			p < 0.0001
	etilbenzene	1	11	0.3-0.4		0.4	0.3-0.4	M-W = -4.01
		2	21	0.3-2.4		0.5	0.5-0.5	p < 0.0001
	o-xilene	1	11	0.3-0.5		0.4	0.3-0.4	M-W = -3.93
		2	21	0.4-2.1		0.6	0.5-0.6	p < 0.0001
	mp-xilene	1	11	0.7-1.1		0.8	0.7-0.9	M-W = -4.29
		2	21	0.9-8.2		1.4	1.1.-1.5	p < 0.0001
Composti inorganici	NO_2	1	11	5.3-11	7.2±1.5			t = -3.51
		2	21	6.1-15	9.9±2.2			p = 0.0014
	SO_2	1	11	0.4-1.1		0.4	0.4-0.4	M-W = -0.50
		2	21	0.4-2.4		0.4	0.4-0.5	p = 0.7481
	H_2S	1	11	1.0-6.2		1.4	1.1-1.6	M-W = 2.84
		2	21	0.7-1.4		1.1	1.0-1.2	p = 0.0036

Campagna invernale

	Inquinante in μg/m^3	**Comune**	**n**	**range**	**media ± ds**	**mediana**	**25°-75° centile**	***Test p-value***
Composti aromatici	benzene	1	11	0.9-1.2	1.0±0.1			t = -3.90
		2	21	1.0-1.3	1.1±0.1			p = 0.0005
	toluene	1	11	1.9-2.4	2.1±0.1			t = -9.39
		2	21	2.2-3.3	2.8±0.3			p < 0.0001
	etilbenzene	1	11	0.4-0.4		0.4	0.4-0.4	M-W = -4.46
		2	21	0.4-0.7		0.5	0.5-0.6	p < 0.0001
	o-xilene	1	11	0.4-0.5		0.4	0.4-0.4	M-W = -4.62
		2	21	0.5-0.7		0.5	0.5-0.6	p < 0.0001
	mp-xilene	1	11	0.8-1.1		0.9	0.8-0.9	M-W = -4.48
		2	21	1.0-1.8		1.3	1.2.-1.4	p < 0.0001
Composti inorganici	NO_2	1	11	1.1-6.1	2.8±1.5			t = -0.72
		2	21	1.4-9.7	3.4±2.4			p = 0.4790
	SO_2	1	11	0.5-0.5		0.5	0.5-0.5	M-W = -2.12
		2	21	0.5-1.3		0.5	0.5-1.2	p = 0.0691
	H_2S	1	11	0.9-2.9		1.2	0.9-1.3	M-W = 1.21
		2	21	0.9-1.3		1.1	1.0-1.2	p = 0.2381

Comune 1 (sopravento) Comune 2 (sottovento)

LE TRAIETTORIE DI FRAGILITA' IN UNA POPOLAZIONE DI ANZIANI NON ISTITUZIONALIZZATI

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Introduzione

La fragilità ha e ha avuto nel corso del tempo un'attenzione crescente dato l'aumentare, in termini di dimensionalità, della popolazione anziana[1].
Secondo Fried [2] la fragilità è "una sindrome fisiologica" mentre per Gobbens [3] è "uno stato dinamico che colpisce un individuo che sperimenta perdite in uno o più domini (fisico,psichico,sociale). Data la complessità di tale fenomeno Rockwood [4] ha proposto un indice che riassume questi due concetti contando il numero di deficit accumulati nel tempo.

Obiettivi

L'obiettivo di questo lavoro è quello di descrivere le traiettorie di fragilità, attraverso l'indice proposto da Rockwood, in una popolazione anziana residente nel comune di Abbiategrasso.

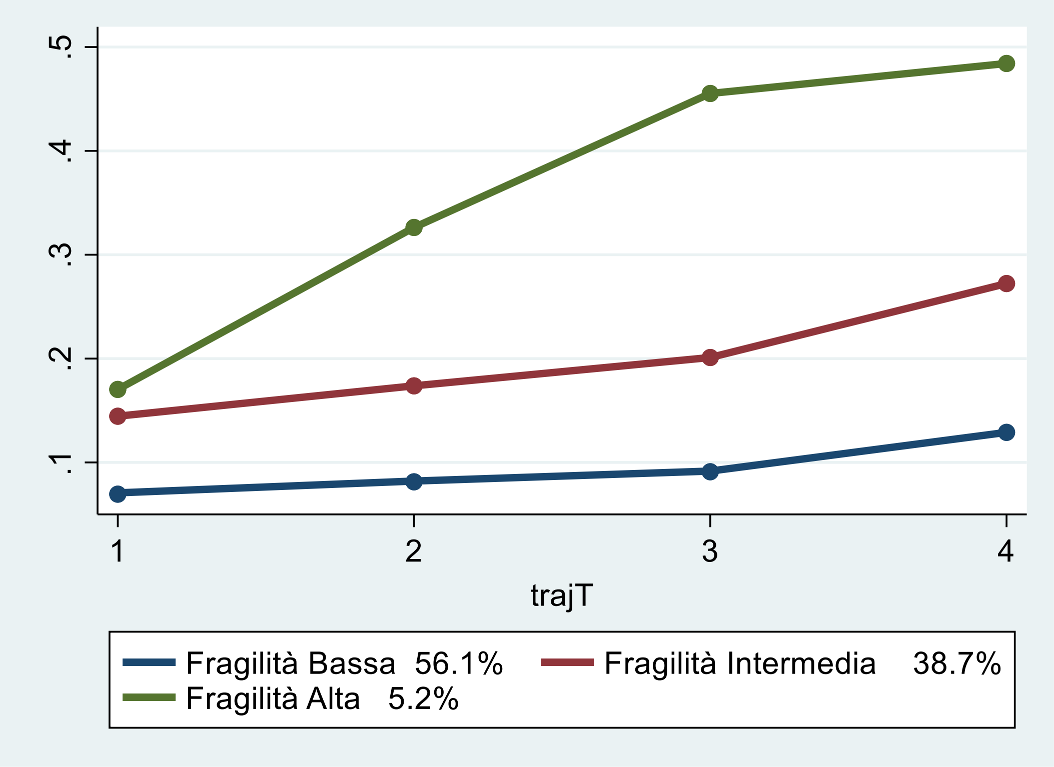
Metodi

I dati utilizzati per definire le traiettorie provengono dallo studio longitudinale di popolazione InveCeAb (Invecchiamento Cerebrale Abbiategrasso) che coinvolge soggetti nati dal 1935 al 1939 residenti in Abbiategrasso. Lo studio è iniziato nel 2010 e ha previsto 3 follow-up (2012-2014-2018). Dei 1644 pazienti eleggibili nel 2010, 1321 sono stati arruolati al baseline.
Le traiettorie sono state trovate utilizzando i modelli Group Based Trajectory Modeling (GBTM) [5, 6] che permettono di identificare, in una popolazione o in un campione, gruppi latenti di soggetti che hanno un andamento nel tempo simile dell'outcome d'interesse utilizzando le relative probabilità di appartenenza. Dopo aver identificato i gruppi con diversa fragilità si sono valutate le differenze di età al baseline, genere e scolarità utilizzando un modello multinomiale. Le traiettorie di fragilità, utilizzando almeno due rilevazioni temporali, hanno visto il coinvolgimento di 1081 anziani.

Risultati

I 1081 anziani studiati nel presente lavoro erano nel 53.7% dei casi femmine con età media pari a 72.1 anni (±1.3 anni) e un livello di scolarità media pari a 6.9 anni di studio (±3.4 anni di studio).
Il miglior modello ha identificato 3 gruppi con differenti traiettorie di fragilità (Figura 1). Il gruppo con traiettoria in verde riporta una crescente fragilità ed è composto da 57 anziani (5.27%) mentre in rosso vi sono i soggetti con una traiettoria di fragilità meno marcata ma crescente nell'ultimo periodo ed è composto da 421 anziani (39%). Il gruppo più cospicuo, il 56% del campione con traiettoria in blu, mostra un andamento sostanzialmente sovrapponibile al precedente per quel che concerne l'accumulo di deficit nel tempo, sebbene il punto di partenza sia inferiore.

Figura 1 Le traiettorie dell'andamento dell'indice di fragilità di Rockwood nei soggetti arruolati allo studio "InveCeAb" di Abbiategrasso con almeno due rilevazioni temporali.



Per quel che concerne il genere dei pazienti appartenenti alle differenti traiettorie, il modello multinomiale ha mostrato che le donne hanno una probabilità maggiore di appartenere ad una traiettoria intermedia rispetto alla traiettoria meno severa (RRR 1.40 (1.08-1.81)) p(0.010).

Mentre per il livello di scolarità la probabilità di appartenere al gruppo con un accumulo di deficit più severo si riduce del 13% rispetto a chi ha un andamento temporale di fragilità più blando per ogni anno in più di studio (RRR 0.87 (0.78-0.96)) p(0.008).

Infine per quel che concerne l'età al baseline, il modello mostra che al crescere dell'età all'arruolamento la probabilità di appartenere al gruppo più severo aumenta del 33% rispetto al gruppo con un basso accumulo di deficit (RRR 1.33 (1.07-1.66)) p(0.009).

Conclusioni

Nel campione di anziani arruolato ad Abbiategrasso sono stati identificati 3 gruppi con differenti traiettorie di fragilità. Due gruppi hanno un andamento più costante nel tempo ma con due differenti punti di partenza mentre l'ultimo gruppo ha un accumulo di deficit che aumenta nei diversi tempi di follow-up. Le caratteristiche di questi gruppi evidenziano una presenza femminile più consistente nel gruppo intermedio rispetto a quello con indice di fragilità più bassa. Per quel che concerne la scolarità e l'età al baseline si evidenzia una differenza tra il gruppo più severo e quello meno severo: più precisamente vi è una scolarità più bassa ed un età più avanzata tra coloro che appartengono alla traiettoria che cumula più deficit nel corso del tempo.

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Impatto del Covid-19 sulla terapia farmacologica territoriale nella regione Lazio

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Introduzione

La necessità di trovare tempestivamente terapie efficaci per contrastare il virus COVID-19 ha portato a formulare ipotesi sul possibile ruolo terapeutico, profilattico o di rischio di alcune terapie farmacologiche già autorizzate per altre indicazioni terapeutiche [1]. La grande attenzione mediatica ha reso molto spesso difficile discriminare tra ipotesi supportate da evidenze cliniche consolidate ed ipotesi su dati in vitro o semplicemente opinioni plausibili. In tale contesto, risulta importante valutare eventuali variazioni nei pattern di utilizzo di specifici trattamenti che, nelle diverse fasi della pandemia, sono stati candidati al trattamento e/o prevenzione del COVID-19 [2,3].

Obiettivi

Analizzare la prevalenza di prescrizioni mensile per specifiche categorie terapeutiche (es. clorochina/idrossiclorochina, azitromicina, altri antibiotici, corticosteroidi, eparinici, antitrombotici, antinfiammatori, immunosoppressori, vitamina D) nel corso della pandemia COVID-19 a livello regionale ed effettuare un confronto con i pattern di utilizzo storici; indagarne la variabilità tra le ASL e i medici di medicina generale (MMG).

Metodi

La popolazione in studio era costituita da tutti gli individui assistibili nella Regione Lazio tra il 01/01/2018 e il 31/12/2020. Per ogni anno in studio sono stati selezionati i soggetti con età ≥ di 18 anni al primo gennaio dell'anno di interesse e sono state create 12 finestre di osservazione, una per ogni mese, nelle quali era possibile verificare l'assistibilità (si/no), la ALS di assistenza e il MMG che aveva in carico il paziente. Attraverso la ricerca nel flusso delle prescrizioni territoriali di specifici codici ATC è stata ricostruita mensilmente a livello individuale l'eventuale presenza di almeno un'erogazione del farmaco/gruppo di farmaci in studio e l'uso è stato classificato incidente o prevalente sulla base delle prescrizioni nell'anno precedente. A partire da Marzo 2020 attraverso il *recod linkage* con il sistema si sorveglianza regionale COVID-19 sono stati identificati per ogni mese i soggetti che avevano contratto l'infezione e sono stati classificati come casi COVID-19 fino al primo tra questi due eventi: mese della guarigione o due mesi successivi l'incidenza. Al fine di avere un corretto denominatore, tutti i soggetti che presentavano un decesso venivano esclusi dal mese successivo la morte.

Per ogni trattamento farmacologico è stata confrontata la proporzione d'uso (numero di soggetti con almeno una prescrizione nel mese in studio per 10.000 individui) mensile 2020 con la media 2018-19 sia *overall* che separatamente per pazienti incidenti e prevalenti. Inoltre a partire da Marzo 2020 è stata identificata la proporzione d'uso relativa ai casi COVID-19. Infine, la variazione dei consumi per ASL e MMG è stata indagata calcolando media, mediana, minimo, massimo e range interquartile (IQR) della prevalenza d'uso mensile standardizzata per età e sesso nel 2020 e confrontata con i valori della distribuzione 2018-19. La variabilità per MMG è stata rappresentata utilizzando il *violin plot*.

Risultati

A titolo di esempio vengono riportati i risultati relativi all'analisi dei consumi della clorochina/idrossiclorochina (CHQ) e dell'azitromicina (AZI).

Il confronto dei consumi di CHQ (ATC: P01BA01/P01BA02) nel 2020 verso i dati storici mostra un incremento importante nella proporzione d'uso per i pazienti incidenti nei mesi di Marzo (3,1$_{\text{X10.000}}$ vs 0,8$_{\text{X10.000}}$) e Aprile (3,4 vs 0, 6$_{\text{X10.000}}$) e più contenuto nel mese di Maggio e tra Ottobre e Dicembre, solo in minima parte riconducibile ai casi COVID-19. Si è osservata una forte variabilità sia per ASL (Aprile 2020: min=1,5 $_{\text{X10.000}}$ per Latina; max=5,3 $_{\text{X10.000}}$ per Roma 1 e Rieti) che per MMG (Aprile 2020: IQR [0,0 $_{\text{X10.000}}$ - 6,0 $_{\text{X10.000}}$])

L'analisi dei consumi della AZI (ATC: J01FA10) mostra, invece, un decremento nella proporzione d'uso *overall* nel periodo tra Marzo e Settembre (media di periodo 40,6 $_{\text{X10.000}}$ vs 54,5 $_{\text{X10.000}}$) e un incremento per Ottobre (91,9 $_{\text{X10.000}}$ vs 69,0 $_{\text{X10.000}}$), Novembre (115,9 $_{\text{X10.000}}$ vs 62,9 $_{\text{X10.000}}$) e Dicembre (74,4 $_{\text{X10.000}}$ vs 69,1 $_{\text{X10.000}}$) riconducibile per lo più ai casi COVID-19. In particolare a tale incremento è associata una forte variabilità tra ASL (Novembre 2020: min=81,2 $_{\text{X10.000}}$ per Viterbo; max=124,9 $_{\text{X10.000}}$ per Roma 5) e MMG (Figura 1).

Conclusioni

L'analisi dei consumi di specifici gruppi di farmaci durante le varie fasi della pandemia COVID-19 rispetto ai pattern di utilizzo storici ha messo in luce incrementi e decrementi associati alle diverse fasi della pandemia nel Lazio. Tali fenomeni presentano un forte variabilità per MMG che richiede un attento monitoraggio e una condivisione tempestiva dei dati in modo da contrastare e prevenire la potenziale inappropriatezza prescrittiva.

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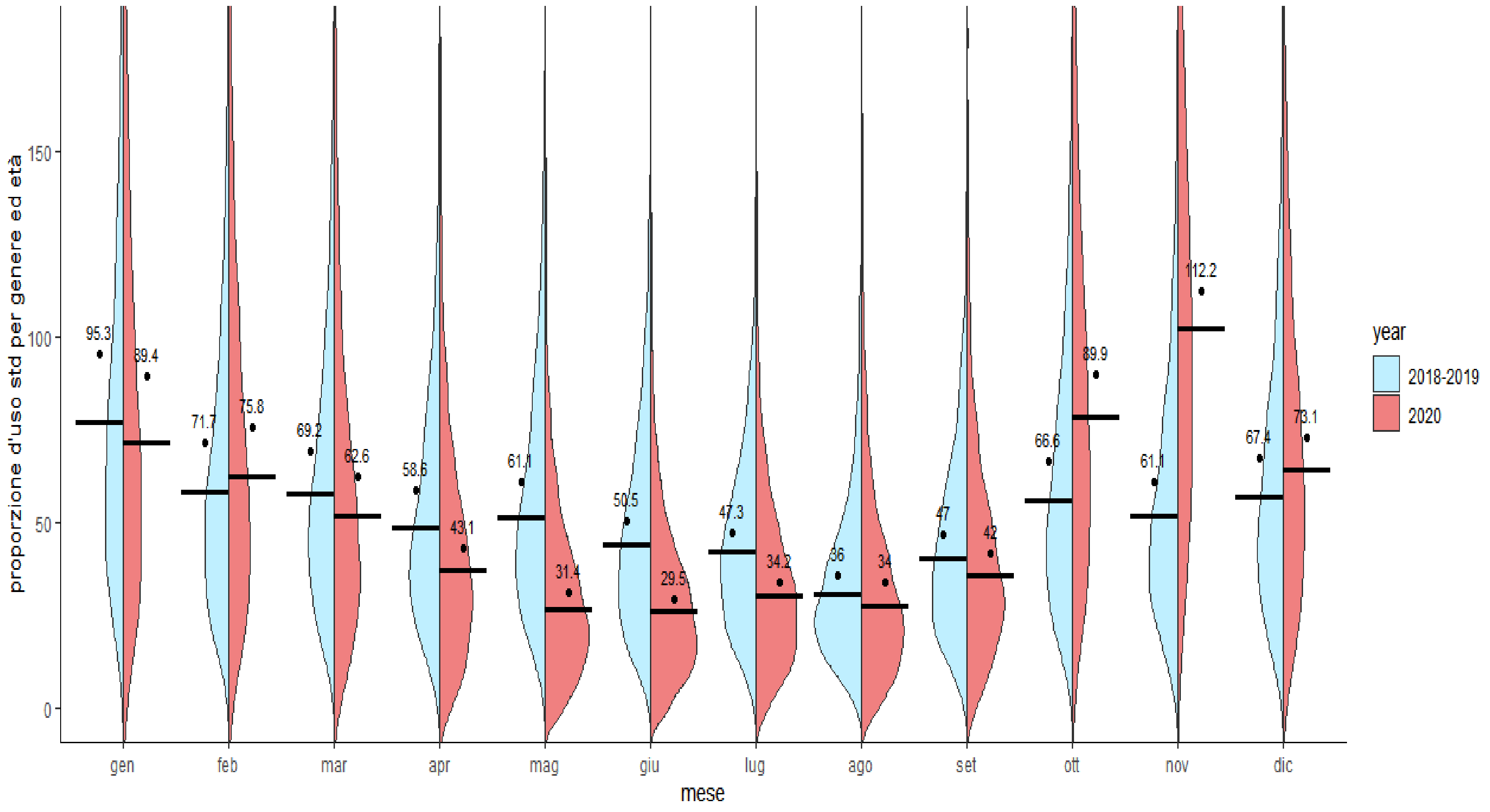
Figura 1 Violin plot della variabilità per MMG della proporzione d'uso *overall* mensile dell'azitromicina standardizzata per genere ed età 2020 verso 2018/19



Nota: il punto ed il trattino rappresentano rispettivamente la media e la mediana della proporzione d'uso

EFFETTO DELL'EPIDEMIA DA COVID-19 SUL MONITORAGGIO ED IL TRATTAMENTO FARMACOLOGICO DELLE MALATTIE CRONICHE NEI MIGRANTI IRREGOLARI

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INTRODUZIONE

In tutti i paesi del mondo, la pandemia da CoViD-19 ha colpito più duramente le persone in condizioni socio-economiche disagiate. Nei paesi occidentali, i migranti irregolari rappresentano una componente crescente di questo segmento svantaggiato della popolazione e le loro condizioni di salute sono spesso gravate da una serie di patologie croniche. Frequentemente queste persone incontrano molte difficoltà nell'accedere ai servizi sanitari pubblici e spesso l'unica assistenza medica che possono ottenere è fornita da organizzazioni non governative.

OBIETTIVI

L'obiettivo dello studio è la valutazione della misura in cui i bisogni di cura in un ampio campione di migranti irregolari afferenti ad una organizzazione non-profit di Milano sono stati soddisfatti durante i mesi intercorsi dall'inizio della pandemia alla fine del primo lockdown. In particolare, è stata valutata la continuità nell'erogazione delle visite specialistiche e dei trattamenti farmacologici a pazienti affetti da alcune malattie croniche, tra cui le malattie cardiovascolari, il diabete e i disturbi psichiatrici.

METODI

Sono stati analizzati i database elettronici di Opera San Francesco (OSF), uno dei più grandi Enti Caritativi italiani con sede a Milano, che fornisce assistenza medica gratuita a persone che vivono in condizioni di indigenza ed emarginazione sociale e che non possono fruire delle prestazioni del SSN italiano. Per gli obiettivi del presente studio è stato analizzato il numero di visite specialistiche e di dispensazioni di farmaci erogati ai pazienti che hanno avuto almeno un accesso presso OSF durante il primo periodo di lockdown per la pandemia da Sars-CoV-2 (9 marzo -18 maggio 2020). È stato, quindi, fatto un confronto con il numero di visite e di prescrizioni farmacologiche erogati nello stesso periodo del 2019 e con quelli erogati nei mesi precedenti del 2020 (7 gennaio – 8 marzo 2020). L'andamento del numero di visite è stato valutato utilizzando il metodo LOESS (Locally Scatterplot Smoothing), al fine di rimuovere la stagionalità e le fluttuazioni casuali nel tempo

RISULTATI

Il numero di individui inclusi nello studio è pari a 1914 (1814 migranti irregolari e 100 italiani). La loro età media era 42 anni, circa la metà proveniva dai paesi del Sud America, circa il 20% dall'Africa, circa il 10% dall'Asia e circa il 20% dai paesi dell'Europa orientale. Il numero di visite nei primi cinque mesi del 2020 è stato molto inferiore rispetto a quello osservato durante lo stesso periodo del 2019. Il numero di visite erogate è stato pari a 4048 durante i tre mesi del primo lockdown, 8051 nello stesso periodo del 2019 e 5681 nei primi due mesi del 2020 (Figura 1). La quantità di medicinali (sia in termini di frequenze assolute che in termini di Defined Daily Doses, DDD) dispensati da OSF ha mostrato una marcata diminuzione nel periodo in studio, e principalmente durante il periodo di lockdown. La diminuzione delle visite e della dispensazione dei farmaci è stata più evidente per i pazienti psichiatrici e quasi inesistente per i pazienti affetti da diabete. Le donne hanno mostrato una maggiore riduzione delle cure sanitarie rispetto agli uomini.

CONCLUSIONI

I migranti irregolari analizzati nel presente studio hanno mostrato differenti comportamenti riguardo le proprie abitudini nell'utilizzo delle strutture sanitarie offerte da Opera San Francesco durante il periodo del primo lockdown. I paesi occidentali necessitano di strategie finalizzate ad assistere in modo efficiente gli individui più vulnerabili dal punto di vista economico-sociale durante le epidemie.

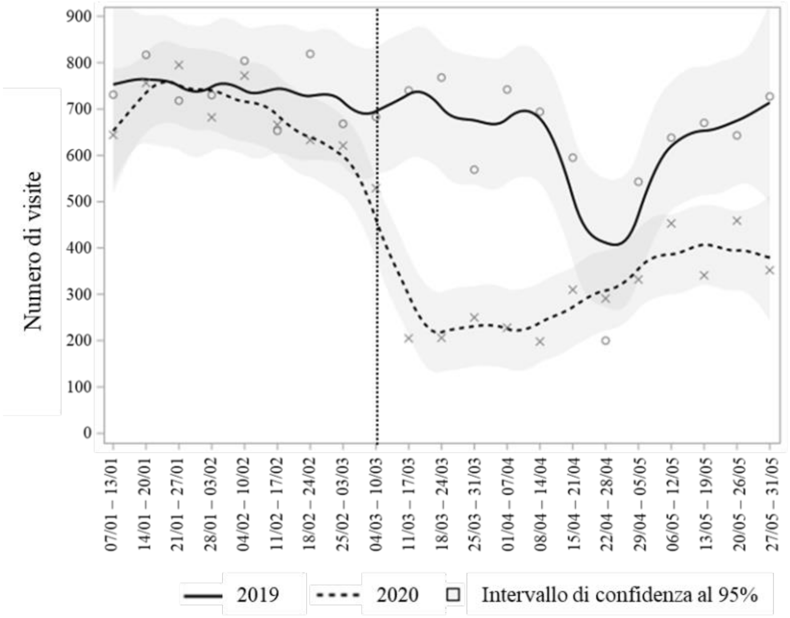

FIGURA: Andamento del numero di visite specialistiche erogate da OSF nel periodo dal 7 gennaio 2019 al 31 maggio 2019 (linea continua) e nello stesso periodo nel 2020 (linea tratteggiata). La linea verticale indica la data in cui è stato imposto il lockdown in Italia (ovvero l'8 marzo 2020). Cerchi e croci rappresentano il numero di visite osservate rispettivamente nel 2019 e nel 2020. Le aree grigie rappresentano gli intervalli di confidenza del 95%.

EFFETTO DELLA PANDEMIA SULLA MORTALITÀ INTRAOSPEDALIERA DEI PAZIENTI NON-COVID-19

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Introduzione

A seguito della diffusione dell’infezione da SARS-Cov-2 in Italia ed in Europa, venivano sollecitati i vari paesi europei ad avviare scelte di sanità pubblica che fossero in grado sia di mitigare la diffusione del coronavirus tra la popolazione che di preparare il sistema sanitario nazionale ad accogliere i pazienti affetti da questa patologia [1]. In Italia durante tutto l’anno 2020 si sono susseguite una serie di misure restrittive di sanità pubblica: quarantena per i pazienti contagiati, distanziamento sociale, utilizzo della mascherina, limitazione delle libertà individuali, chiusura delle attività commerciali, chiusura delle scuole, riduzione dei viaggi e degli spostamenti [2]. A causa delle restrizioni imposte e alla drastica riduzione dell’assistenza sanitaria, si è verificata una riduzione della qualità di vita di quei pazienti non affetti da SARS-Cov-2 ma da patologie che già prima della pandemia si potevano considerare fragili [3].

Obiettivi

Il presente studio ha lo scopo di valutare, nei pazienti non affetti da Covid-19, la possibile associazione tra il decesso in ambiente ospedaliero, le comorbidità del paziente e le scelte restrittive di sanità pubblica.

Metodi

L’analisi è stata condotta analizzando le schede di dimissione ospedaliera (SDO) della Regione Puglia relative ai ricoveri, in regime ordinario, avvenuti negli anni 2019 e 2020 presso le strutture pubbliche e private della regione. Sono state eliminate tutte le SDO del 2020 che riconducevano ai casi di pazienti affetti da Covid identificate utilizzando le “Linee Guida per la codifica della SDO per casi affetti da malattia da sars-cov-2 (covid-19)” emanate dal Ministero della Salute. Sono stati eliminati anche i ricoveri con diagnosi di patologie che potevano essere state associate al COVID e sospette di errori di codifica quali ad esempio l’insufficienza respiratoria acuta (cod.518.81) e la febbre di ndd (codice 780.6). A causa della pandemia, in Italia sono stati adottati una serie di provvedimenti di sanità pubblica di tipo restrittivo che hanno avuto un impatto anche sull’erogazione dei servizi sanitari. Pertanto, nell’arco temporale in esame sono stati individuati quattro periodi con livelli decrescenti di restrizioni: fase 1 dal 1 marzo 2020 al 30 aprile 2020, fase 2 dal 1 maggio 2020 al 15 giugno 2020 e dal 1 ottobre 2020 al 31 dicembre 2020, fase 3 dal 16 giugno 2020 al 30 settembre 2020, fase 4 (nessuna restrizione) dal 1 gennaio 2019 al 29 febbraio 2020. L’età è stata classificata in sette classi (0-4 anni, 5-14 anni, 15-24 anni, 25-44 anni, 45-64 anni, 65-75 anni, > 75 anni), mentre la comorbidità, valutata mediante l’indice di Charlson (ICH) [4,5], è stato categorizzato in quattro classi: ICH=0, 1≤ICH1≤2, ICH≥3. Tramite un modello di regressione logistica è stata valutata la possibile associazione tra il decesso del paziente durante il ricovero e la classe di età, il sesso, la classe di comorbidità ed il periodo in cui si effettuava il ricovero. È stato considerato statisticamente significativo ogni risultato con $p < 0,05$. Tutte le analisi sono state condotte con il software SAS / STAT® Statistics versione 9.4.

Risultati

Sono state incluse nello studio 782704 SDO, di cui 443722 erano dell’anno 2019 e 338982 erano dell’anno 2020. La distribuzione per sesso e per classi di età delle SDO nei due anni era pressoché sovrapponibile. Il modello di regressione logistica e le variabili esplicative del modello (classe di età, sesso, classe di indice di Charlson, fase dei provvedimenti restrittivi di sanità pubblica, interazione tra fase e classe di indice di

Charlson) risultavano statisticamente significativi. Il rischio era aumentato nei maschi (OR 1,057, IC95% 1,030 – 1,085) e nei soggetti nella classe di età 0-4 anni (rispetto alla classe di età 5-14 anni: OR 2,935, IC95% 1,698-5,075), mentre è diminuito, a partire dalla classe di età 5-14 anni, per ogni classe di età rispetto alla classe immediatamente superiore (es. età 25-44 anni vs 65-74 anni: OR 0,148, IC95% 0,134 – 0,164; età 45-64 anni vs >75 anni: OR 0,240, IC95% 0,230 – 0,249; classe di età 65-74 anni vs >75 anni: OR 0,401, IC95% 0,387 – 0,415). Gli Odds Ratio calcolati confrontando reciprocamente i singoli periodi (fasi) mettono in luce il maggior rischio di mortalità intraospedaliera nelle fasi più critiche della pandemia ed oggetto di maggiori restrizioni. Il rischio di decesso si è rivelato più elevato nella classe di severità più bassa (ICH=0), in particolare per i ricoveri avvenuti durante la fase 1 rispetto a quelli avvenuti durante la fase 4 (OR 1,761, IC95% 1,622 - 1,912) (Figura 1). Non statisticamente significativo, nelle classi di severità più estreme, solo il rischio di decesso della Fase 3 rispetto alla Fase 4: per ICH=0 (OR 1,009, IC95%, 0,948-1,075) e per ICH≥3 (OR 0,962, IC95% 0,885 – 1,045).

Conclusioni

Lo studio consente di reputare plausibile l'associazione tra il decesso in ambiente ospedaliero e le misure restrittive di sanità pubblica che sono state attuate durante la pandemia. Il rischio di decesso durante il ricovero, inoltre, è apparso crescente al rafforzarsi delle misure restrittive, indipendentemente dalle comorbidità del paziente. Dalla distribuzione dei rischi possiamo infatti supporre che nelle fasi in cui erano in vigore maggiori misure restrittive giungevano in ospedale soltanto quei pazienti che avevano in atto una patologia acuta tendenzialmente più grave che andava ad incidere sul outcome del paziente. Probabilmente, tale accesso, in accordo con la letteratura scientifica, risultava essere anche ritardato [6].

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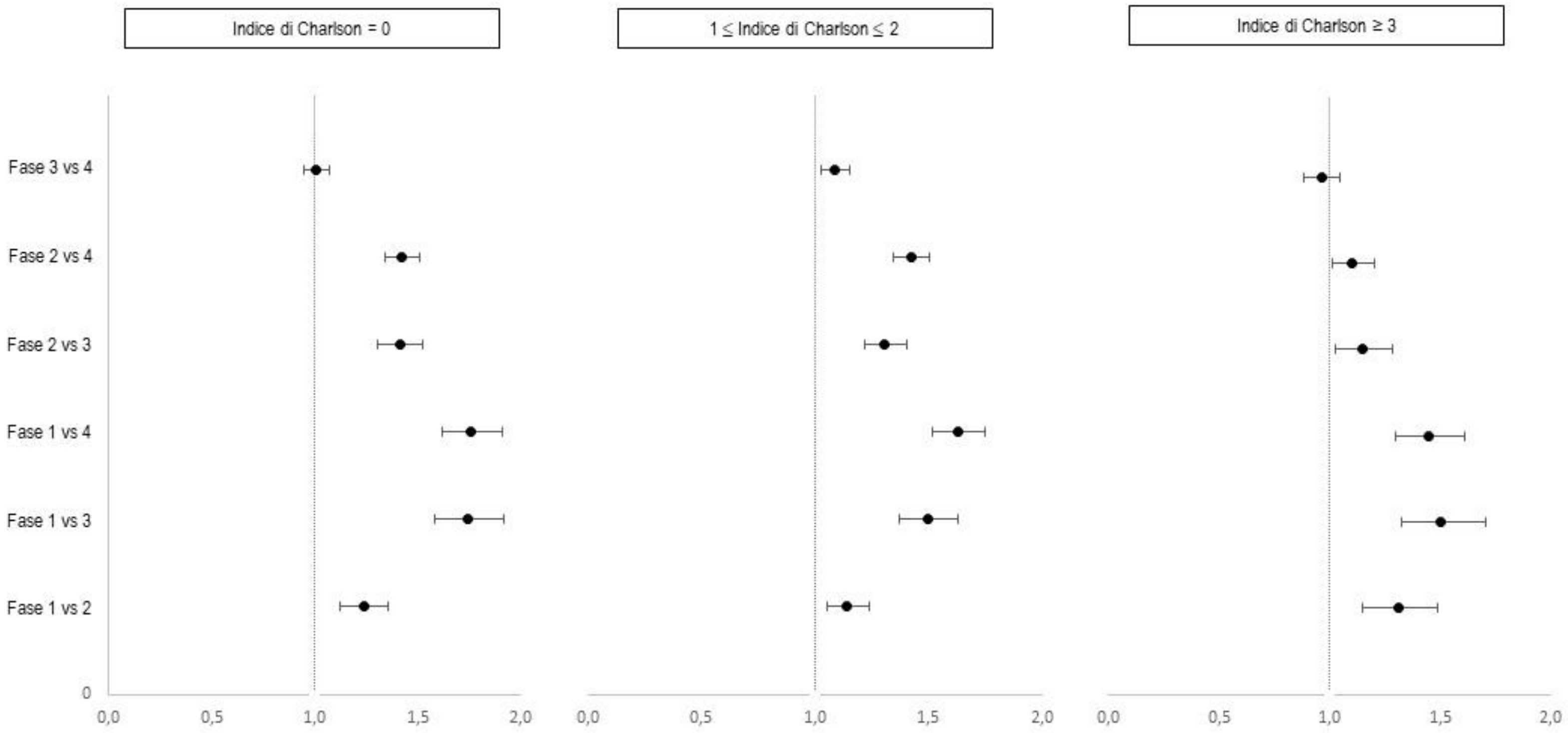

Figura 1. Forest Plot degli Odds Ratio (ed intervalli di confidenza al 95%) per la mortalità intraospedaliera. Confronto per periodo (fase) dei provvedimenti restrittivi di sanità pubblica ed Indice di Charlson.

STARTIFICATION OF CLINICAL RISK THROUGH PHENOTYPIC CLUSTERING OF COVID-19 PATIENTS TO SUPPORT THE DECISION-MAKING PROCESS AIMED AT A PERSONALIZED THERAPEUTIC APPROACH.

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Introduction

The use of clinical risk stratification methods related to patients hospitalized for COVID-19 to define a personalized therapeutic approach, are essential given the heterogeneity of clinical cases at presentation. This heterogeneity, which makes the choice of the therapeutic path difficult, can be explained by the contribution of phenotypic components that support the classification of patients and which can be identified early on admission and could have a prognostic value.

Aims

The main objective is to identify the patient's phenotype components that explain individual variability to build a risk model to be used for clinical choices in the early stages of hospitalization of COVID-19 patients.

Methods

A multicentric retrospective cohort study was set up. Study population was enrolled among consecutive patients who had tested positive on qualitative polymerase-chain-reaction assay for SARS-CoV-2 and had undergone chest computed tomography at admission (CCT). Outcome was defined as intra-hospital death. Variables with missingness above 5% were removed from the dataset and retained incomplete cases were imputed by multiple chain equation method. Multiple correspondence analysis (MCA) were performed on the dataset tuning the number of principal component to capture the 85% of variance[1]. For each patients we calculated the principal component score. We calculated the best number of cluster by Gower distance and employed a clustering methods for partitioning the number of cases that was assigned to a specific cluster[2]. To extract the main representative phenotype component for each cluster a variance test was carried out. A lasso penalized Cox regression vas employed to verify weather the cluster variable was selected and to determine the hazard ratio toward outcome for each cluster. The sample was split in a train and a test set by cluster variable with a probability of 0.7:0.3. A classification tree was trained by 10-fold cross validation employing a set of representative variables of each cluster. Predicted class for each patient were employed to build a confusion matrix to assay the performances of the classifier [3].

Results

Clustering of patients on MCA features extracted, partitioned the sample in three groups with mutual exclusive phenotype characteristics. The three groups showed a different risk of intra-hospital mortality, and each group was characterized by different phenotype characteristics. The lowest risk group was characterized by mild pneumonia, high pulmonary breathing volume, low PCR level at hospitalization and younger patients. Intermediate risk (HR=0.34) cluster patients were characterized by cardiopathy, moderate to severe pneumonia, low levels of aortic and coronary calcification. The high risk (HR=3.26) cluster patients were characterized by high levels of aortic and coronary calcification, cardiopathy, hypertension and higher age. The classification tree model obtained was characterized by an accuracy of 0.975.

Conclusion

The need for patients classification methods based on clinical risk is clear in such situation were patients heterogeneity is high. When the available knowledge is not enough to support clinical decision a unsupervised method like phenotype clustering could be effective to help patients stratification toward outcome of interest. In this study we employ phenotype clustering to obtain information about phenotype components that could be inputed to a classifier to obtain a risk stratification system. This risk stratification system could be used by clinician in the early phase of hospitalization to guide their therapeutic decisions. The main limitation of this study is represented by the lack of external validation, although methodological issues related to internal validation was taken into account.

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Smart working perception in bank and insurance companies employers during the Covid-19 pandemic: a cross sectional pilot study

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Abstract

Introduction

The Covid-19 pandemic eruption has forced companies to make agile decisions to ensure business survival and drive long-term economic recovery in a crisis that caused a historic collapse in the Worldwide.

The coronavirus outbreak has forced companies to re-assess how time of workers are leveraged, where they work, and how digital channels and sources can be used to support business continuity through the crisis and beyond [1].

A consequence of this it was been to accelerate a reflection on Smart Working (SW) to govern the necessary changes in the organization of work also in the medium term [2]: the use of SW has been a strategy to support business continuity. It is a new digitalized practice of collaborative work and was increased significantly in the companies since 2020 and in the banking sector too.

What is SW? McEwan [3] offers the following definition, 'Smart working practices are agile, dynamic and emergent. They are the outcomes of designing organizational systems that facilitate customer-focused, value-creating relationships that are good for business and good for people'.

The use of SW has been a strategy to support business continuity. It is a new digitalized practice of collaborative work and was increased significantly in the companies since 2020. In Italy, 30% of the workforce (6.7 million workers) have an occupation that can be done partially or completely from home [4,5]. Among them there are the banking and insurance sectors workers.

Aims

The aim of the present study was to describe the perception on the SW in the workers in the banking and insurance companies and finding the characteristics of subjects that consider SW an opportunity or not.

Methods

A cross-sectional study, according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was carried out [6]. The research conducted in the period from May 2020 to April 2021. The setting of the study was the bank employers and workers in the insurance companies.

A validated questionnaire on Smart Working (SWQ) was administered online[7]. SWQ was administered in anonymous way via a Google form. Potential participants of the survey are invited via email by their labour unions (CGIL, CISL, FABI, FIRST, FISAC, UILA and UILCA).

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Seventeen dichotomous items were considered as outcomes in the study. These items cover different aspects of smart working: effect on quality of life, costs, feasibility, difficulties, reduction of absences, performance, company and personal profit, career progression (table 1).

A preliminary descriptive statistics was carry out. Univariate analysis was performed in order to evaluate possible association with the outcomes and χ^2 test was applied.

The items were considered as independent variables into logistic multivariate regression models. A stepwise backward wald elimination procedure was applied. The ORs with CI95% were computed. Hosmer and Lemeshow's test (H-L) was used to estimate the goodness of fit of the models (Table1). The significant level of the analyses was set at $p<0.05$.

Results

A total of 4850 workers in banking and insurance services have been invited by email to the research survey. A sample of 1588 questionnaires was collected (response rate = 33%). 54% of the subjects was male; 71% aged from 36 to 55 years; 64% was married; 60% was with high school licensed; around 7% lived more than 50 km from their workplace.

The followed logistic regression models referred a goodness of feel with $p>0.650$.

The model that asks if the smart mode could be useful to increase the company profits reports that who agree had followed characteristics: to be not married (OR= 1.30; 95%CI: 1.04-1.61), to have higher educational level OR= 1.30; 95%CI: 1.04-1.61) and to live near to the workplace (OR= 1.92; 95%CI: 1.20-3.03). The corresponding H-L p-values was 0.998 (Table1).

Who think that work in SW mode was penalizing and complicated for the teamwork was 46 years or older (respectively OR= 1.58 with 95%CI: 1.28-1.95; OR=1.39 with 95%CI: 1.12-1.73; and), lives near to office (respectively OR= 1.98 with 95%CI: 1.26-3.10; OR=1.86 with 95%CI: 1.16-2.99). The corresponding H-L p-values were respectively 0.995 and 0.971.

The characteristics associated to who declared to have a medium-long term effect on workplace mobility costs were: male gender (OR= 1.28; 95%CI: 1.03-1.67), aged ≤45 years (OR= 1.67; 1.28-2.13) and living far away to office (OR= 4.54; 95%CI: 2.08-10.00). The corresponding H-L p- value was 0.992.

Who refers that the SW improved reconciliation between private and working life was younger (OR= 1.96; 95%CI: 1.52-2.56), with higher educational level (OR= 1.41; 95%CI: 1.12-1.85), a part time work position (OR= 1.52; 95%CI: 1.01-2.27) and lives near to the workplace (OR= 2.80; 95%CI: 1.18-3.70). The corresponding H-L p- value was 0.977.

Who consider the SW as help for career progression was younger (OR= 2.70; 95%CI: 1.67-4.34) and not married (OR= 1.67; 95%CI: 1.06-2.63). The corresponding H-L p-value was 0.808.

Who think that the adoption of this working method could be useful to improve personal performance within the company was younger (OR= 1.75; 95%CI: 1.43-2.17), not married (OR= 1.11; 95%CI: 1.02-1.56), with higher educational level (OR= 1.30; 95%CI: 1.05-1.62) and living far away to office (OR= 2.17; 95%CI: 1.43-3.33). The corresponding H-L p-value was 0.792.

Who mentions the feasible to do certain number of hours per week in smart way was female (OR= 1.36; 95%CI: 1.05-1.76), younger (OR= 1.82; 95%CI: 1.35-2.38) and lives far away to the workplace (OR= 2.13; 95%CI: 1.14-3.85). The corresponding H-L p-value was 0.689.

The workers who were more significant interested to SM way were females (OR= 1.71; 95%CI: 1.24-2.07), aged ≤45 years (OR= 1.69; 95%CI: 1.30-2.22), with higher educational level (OR= 1.37; 95%CI: 1.05-1.79) and with home-work distance ≥50 km (OR= 3.57; 95%CI: 1.79-7.14). The corresponding H-L p-value was 0.649.

Conclusion

The results underline that the digitalized work or remoted could be increase the chance for workers to balance work-life and remove the traditional activity based working to the professional and organizational identity; to the other hand it could be introduce the risk of poor solitude that doesn't increase the professional/human dimensions and the culture of subjects (social isolation) [8]. In the present study according to the literature the older workers and who lives near resulted more prudent to introduce this new digitalized practice of collaborative work. Research suggests that social isolation can impact motivation in the workplace.

Secondary the SW could introduce another phenomenon: the increase of "working hard" and reduction or the "working smart" [9]. Those who work from home could tend to report high levels of stress: when working from home it is possible to feel a lack of structure, to struggle with getting the working day going, to define when officially ending the working day and to take personal time for activities, breaks and lunch. This can throw off the work-life balance. Another aspect of home working was the possibility to have experience distractions and interruptions throughout day.

The main limit of the study is the fact that data have been collected during the COVID-19 pandemic, therefore the attitude of the respondents towards SM could have been influenced by the worries related to the unique emergency phase. The concept of agile work is broader than the one investigated in the present study. In other words, SW is not merely working from home but also using other places to carry out one's own professional activity.

Studies need to be conducted to evaluate the impact and evolution of the SW mode in the lives of workers and also in the banking and insurance sectors.

A regulation according to the McEwan's definition [3] on SW and identifying the different SW configurations could be done. Defining good practices, suggesting routine on SW could be a need in the short-term that can help to manage time and focus better on work and to prevent risks on stress and psychological effects of tomorrow's workers in bank and insurance sectors and in other too.

Table 1. Items of the SWQ considered as outcomes.

Dependent variable of the model	Hosmer and Lemeshow test of the final stepwise models
D11. I'm interested to the "smart" way of working	0.649
D12. I think that working in "smart" mode can penalize the size of teamwork	0.995
D13. I think that working away from the workplace can complicate your work properly in some way	0.971
D14. Compared to my job role, I think that it is feasible to work in "smart" mode for a certain number of hours a week	0.689
D15. I think that working in "smart" mode can be more difficult at certain times of the year	0.452
D16. I think that agile work can make it more difficult to deal with your customers/users	0.505
D18. I think that smart working can improve the reconciliation between my working life and my private life	0.977
D19. I think that smart working can improve the management of my work	0.058
D20. I think that smart working can improve the quality of my life	0.330
D21. I think that working in smart mode can have a medium-long term effect on my workplace mobility costs	0.992
D22. I think that working in "smart" working can have a medium-long term effect on the costs that the company as a whole faces	0.526
D23. I think that working in "smart" working mode can help me achieve my business goals more efficiently	0.050[a]
D24. I think that the working mode in smart working can help me take less hours of leave/to do less work absences	0.166
D25. I think that the adoption of this working method could be useful to improve my performance within the company	0.792

D26. I believe that the adoption of this working method can be useful to improve the performance of everyone within the company	0.146
D27. I think that the adoption of this working method could be useful to increase company profits	0.998
D28. I think that "smart" work can foster me career progression within my company	0.808
D29. If my company decides to adopt smart working, I consider it useful to attend an ad hoc training course	0.938[b]
D30. After the Covid-19 emergency, I think it will be appropriate to carry out smart working again	0.598

[a] the model is not a good fit.

[b] not significant variables in the last models

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Usefulness and limitations of lung flows to diagnose respiratory diseases

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Background: Pulmonologists have devoted a lot of attention to the diagnostic and prognostic significance of lung volumes (FEV1, FEV1/FVC), while lung flows (FEF25-75) are considered less useful tools to define asthma or rhinitis [1].

Aims: This study aimed to compare FEF25-75 (forced expiratory flow between 25% and 75% of FVC) in subjects without respiratory diseases (controls), with rhinitis alone, or with asthma, irrespective of rhinitis. In particular it was verified whether FEF25-75 increases the information on respiratory disorders, provided by lung volumes, such as FEV1 (forced expiratory volume in one second) FVC (forced vital capacity) and their ratio (FEV1/FVC).

Methods: The present study considered 1293 subjects, enrolled in the Gene Environment Interactions in Respiratory Diseases (GEIRD) Study, an Italian multicenter, multicase-control study [2] Subjects had been recruited in four centers: Verona (n=840) and Turin (n=281) in the Po valley, Sassari (n=148) in Sardinia and Palermo (n=24) in Sicily. FEF25-75 was assessed in 480 controls without respiratory diseases; 366 individuals with rhinitis alone, i.e. without asthma; 447 individuals with asthma, irrespective of rhinitis.
FEF25-75 was expressed as percentage of the expected value for sex, age, height (FEF25-75%). The association between FEF25-75 and respiratory diseases (controls/rhinitis alone/asthma) was evaluated by Kruskal-Wallis test in univariable analysis and by median regression in multivariable analysis, controlling for potential confounders, i.e. center, sex, age, BMI, smoking habits and exposure to passive smoking.

Results: FEF25-75% predicted was the highest in controls (median 99, p25-p75=84-119), intermediate in people with rhinitis alone (94, 75.1-112) and the lowest in people with asthma (80.3, 64-99.5) ($p<0.001$). A similar pattern was observed for FEV1% predicted and FEV1/FVC, although the differences among the three groups were less pronounced. Indeed, FEV1% predicted was 102.5% (p25-p75 = 94.4-110.9%) in controls, 100.4% (93.6-108.9%) in subjects with rhinitis, and 95.9% (87.9-105.2%) in asthmatic subjects, while FEV1/FVC was respectively 82.9 (79.3-87.1), 81.7 (77.4-85.4), 79.0 (74.2-83.0).
Inter-individual variability, as assessed by coefficient of variation, was much larger as regards FEF25-75 (CV=26.9% in controls, 28.2% in people with rhinitis only and 32.8% in people with asthma) than lung volumes (CV = 11.4%, 11.8%, 14.2% for FEV1, and CV = 7.2%, 7.7% and 9.4% for FEV1/FVC).
In multivariable analysis FEF25-75% was significantly decreased in people with rhinitis alone (median decrease = 6.9%, 95% CI 2.4 – 11.4%) or asthma (median decrease = 22.2, 95% CI 17.9-26.4%) with respect to controls. FEF25-75% was also significantly affected by sex and age: the median value was 10.0% (6.3-13.8%) higher in men with respect to women, and 17.7% (7.7-27.7%) lower in people aged 65-84 than 20-44 years.

Conclusion: FEF25-75, in spite of its high inter-individual variability, significantly decreased in people with rhinitis, and even more with asthma. Further studies are needed to verify whether FEF25-75 can increase the diagnostic and prognostic information already provided by the assessment of lung volumes.

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ENVIRONMENTAL SUSCEPTIBILITY TO MULTIPLE SCLEROSIS DISEASE: PHENOTYPE DIFFERENCES BETWEEN MIGRANT AND NATIVE PATIENTS FROM THE ***MS-MIGit*** MULTICENTRIC CASE-CONTROL STUDY

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Introduction

Multiple Sclerosis (MS) is a chronic, demyelinating disorder of the central nervous system (CNS) due to an autoimmune inflammatory process that, through multiple foci of lymphocytic infiltration and phenomena of macrophage-demyelination mediated, determines the loss of myelin sheaths at the axonal level. Statistics of the Multiple Sclerosis International Federation (MSIF), year 2012, report that global SM's prevalence is 33 cases per 100,000 inhabitants with very high variability across countries. Migration studies on MS conducted during the past six decades have explored two main issues: the relative role of environmental versus genetic exposures and the age at which individuals become susceptible to the disease [1]–[3]. There is evidence that age at migration and duration of residence in the host country modulate the disease phenotype towards that of the host country [4].

Data from the National Institute of Statistics at the 1st January 2018 report that in Italy there are more than five million migrants (8.5% of legal population), showing an increasing trend with respect to the previous years. As a consequence, a growing number of migrant SM patients will be in charge of the Italian Healthcare System in the next future. However, phenotypic characteristics of migrant patients living in Italy are little known. The *MS-MIGit* Italian multicentric study was designed with the aim to compare demographic and MS clinical characteristics between native and migrant patients.

Methods

MIGit was a multicentre, retrospective observational study. Data were collected between January 2010 and December 2020 and a total of 1299 MS patients were recruited from 8 different neurological SM Centers in Italy. Information included demographics (sex, age at immigration, duration of residence in Italy, being first- or second-generation immigrant), clinical characteristics at MS onset, clinical, radiologic and laboratory characteristics at the diagnosis, and clinical characteristics at follow-up.

Summary statistics were counts and percentages for categorical variables and either mean (standard deviation) or median (interquartile range) for quantitative variables. Crude odds ratios (OR) were computed together with 95%CI.

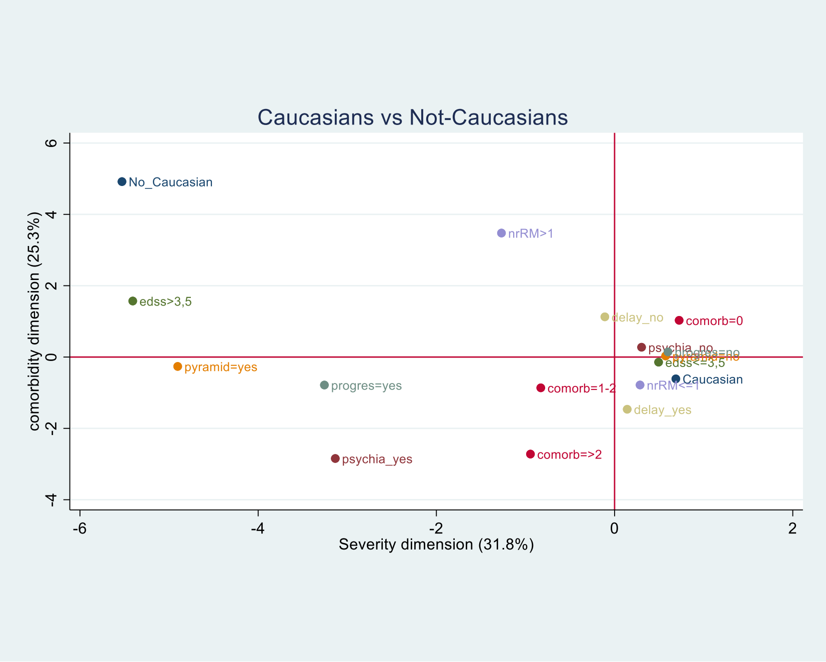
Statistically significant variables at univariable analysis were graphically displayed through the multiple correspondence analysis (MCA). Due to the large number of missing data, multiple imputation was performed preliminary to multiple logistic regression. Specifically, we used the Multivariate Imputation by Chained Equations (MICE) method [5], [6] We addressed the issue of perfect prediction that is frequent in the presence of categorical explanatory variables. We excluded variables occurring less than 1% in either of the outcome categories and we used the augmented-regression approach, which consists of adding a few extra pseudo-observations to the dataset, giving them small weights [7]. A multiple regression model was fitted on thirty imputed datasets and results were pooled into a single multiple-imputation result. Data were analysed using Stata IC/15.1 software [8], and a p-value < 0.05 was chosen as the statistical significance cut-off.

Results

The sample included 1077 (82.9%) Caucasians, of which 215 (20%) born in a foreign country, and 222 (10.1%) Not-Caucasians, all of these born abroad. Looking at the country of origin, 1092 (82.6%) patients were from a high income country and 230 (17.4%) were from low-middle income country and 89.8% of Non-Caucasians were from a Low-middle income (LMI) country.

Non-Caucasians showed more prevalence of psychiatric comorbidity (OR=1.74 (1.04-2.91)), more severe Expanded Disability Status Scale (edss) class at onset (OR=1.69 (1.10-2.57) for 3-4.5 class and OR= 3.06 (1.42-6.60) for >5, assumed 0-2.5 as reference), more frequent pyramidal and sphincteric involvement at onset (OR=1.99 (1.21-3.27) and OR=4.69 (1.04-21.20), respectively), magnetic resonance at the diagnosis (OR= 22.68 (3.15-163.46)), major risk of persistent Gadolinium lesions (Gad+) (OR= 2.79 (1.37-5.69)) and of progression since onset (OR= 1.45 (1.01-2.08)).

Figure - MCA plot of demographic and clinical characteristics of MS patients by ethnicity based on disease severity and comorbidity



Looking at edss at onset>=3.5, located on the extreme left of the MCA plot, helped us to interpret the x-axis as *Severity-related dimension*, while the y-axis was the *comorbidity-related dimension* (the lowest y-coordinates were found for number of comorbidities>2 and occurrence of psychiatric comorbidity). Of note, Non-Caucasians showed a more severe profile than Caucasians (x =-0.529 and x=0.688, respectively), but suffered a minor number of comorbidities (y=4.919 and y=-0.619, respectively, for Non-Caucasians and Caucasians). The first two principal axes accounted for 57.1% of total inertia, 31.8% the first axis alone (Figure).

Multivariate logistic regression after MICE imputation revealed that Non-Caucasians showed an increased risk of psychiatric comorbidity (AdjOR=1.88; 95%CI=(1.05-3.36)) and edss at onset>3.5 (AdjOR=2.65; 95%CI=(1.36-5.14)) and a minor risk of a number of comorbidities between 1 and 2 (AdjOR=0.65; 95%CI=(0.46-0.93)). However, they were more likely to take higher number of MR exams (AdjOR=1.65; 95%CI=(1.08-2.53)).

Conclusions

Our study found more severe MS profile for Non-Caucasian patients compared to Caucasians, characterized by higher disability levels at onset and the occurrence of psychiatric comorbidity. In Italy, the same healthcare is guaranteed to all patients regardless of ethnicity.

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IL MONITORAGGIO DEI TAGLI CESAREI: ANALISI ESPLORATIVA DELLA DISTRIBUZIONE DEGLI EVENTI NELL'ARCO DELLA GIORNATA NEGLI ANNI 2019 E 2020.

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INTRODUZIONE

L'utilizzo inappropriato del taglio cesareo (Tc) può essere associato, secondo le linee guida dettate dall'OMS, ad un aumento della morbilità [1,2]. L'evento gravidanza-parto è sottoposto a sorveglianza attraverso il flusso informativo obbligatorio dei Certificati di assistenza al parto (CedAP) che consente l'elaborazione di rapporti annuali nazionali e regionali in cui sono descritti indicatori di qualità dei punti nascita che, insieme alla classificazione di Robson (CR), consentono di valutare l'appropriatezza della pratica chirurgica, la qualità dei servizi ostetrici e la sicurezza materno-infantile [3,4]. Attraverso la CR è possibile stratificare i parti in dieci classi mutuamente esclusive definite da parità, n° dei feti, presentazione fetale, età gestazionale, modalità del travaglio e modalità del parto. L'appropriato ricorso al taglio cesareo può essere valutato attraverso la descrizione della percentuale dei Tc nelle diverse sottopopolazioni descritte dalla CR, ma anche attraverso il calcolo e il monitoraggio di alcuni importanti indicatori: la "proporzione di Tc primari" (Tcpr) ovvero i parti cesarei effettuati per la prima volta in una popolazione di parti in cui non è stato mai effettuato il Tc in precedenza; la "percentuale depurata di Tc NTSV" (TcNTSVd) che consente di valutare i Tc eseguiti, per la prima volta, in una popolazione ristretta corrispondente alle prime due classi di Robson (donne Nullipare, a Termine, feto Singolo, con presentazione Vertice) che sono a basso rischio di Tc [3-5-6]. TcNTSVd è un indicatore di valutazione di qualità del centro nascita utile per il monitoraggio dei Tc primari in una fascia di gravide a basso rischio che rappresentano circa il 40% di tutte le partorienti. E' quindi uno strumento idoneo a monitorare l'obiettivo di ridurre la quota di Tc primari e indirettamente la quota di Tc successivi al primo. La pandemia e le modifiche di accesso ai servizi sanitari, imposte dalle misure restrittive, potrebbero aver interrotto il circuito virtuoso di monitoraggio e miglioramento finalizzato alla riduzione della quota di TcNTSVd.

OBIETTIVI

Scopo dello studio è confrontare la distribuzione dei parti nelle ore della giornata tra il 2019 e il 2020. Tale confronto è finalizzato a valutare sia la quota dei Tc primari, elettivi (Tce) e in travaglio (Tcu), nella popolazione generale ed in quella specifica NTSV, sia eventuali cambiamenti organizzativi soprattutto per i Tc programmati tra il periodo pre-pandemico e quello pandemico.

METODI

L'analisi è stata condotta utilizzando i CedAP 2019 e 2020 di tutta la regione Puglia che sono risultati rispettivamente pari a 27.539 e 26.395. Al fine di valutare gli indicatori relativi alla percentuale di Tc sono state prese in considerazione le seguenti variabili presenti nel CEDAP: parità, età gestazionale, n° di feti presenti nel parto, modalità del travaglio, modalità dell'induzione e modalità del parto, la presenza di pregressi Tc e l'ora del parto. L'indicatore 'Proporzione di Tc primari' (TC pr) è determinato dalla formula [7]:

$$\text{Tc pr}=\frac{\text{Tc totali-Tc pregressi}}{\text{Nascite totali-Tc pregressi}}$$

L'indicatore 'Percentuale depurata di Tc NTSV' (Tc NTSVd) è determinato da [8]:

$$\text{Tc NTSVd}=\frac{\text{Tc Nullipare, a Termine, Feto Singolo, Vertice}}{\text{Tutti i parti delle prime due classi di Robson}}$$

La percentuale depurata di Tc NTSV rimuove i fattori di confondimento dovuti a presentazioni fetali anomale e a parti plurimi e limita l'analisi a fasce di popolazione più omogene, rendendo confrontabili tra loro punti nascita diversi [9]. Per valutare se le strutture ospedaliere pugliesi hanno medicalizzato eccessivamente il parto è stata calcolata la distribuzione di frequenza per tutte le modalità di parto nelle prime due classi di Robson e per i Tc primari in base all'ora del parto.

RISULTATI

In generale tra 2019 e 2020 la distribuzione dei parti rispetto alla modalità con la quale sono stati espletati si è modificata (χ^2=23.7, p<,001), con un aumento dei Tc in urgenza a sfavore dei Tc elettivi. Nel 2019, il 26,7% (6.015 / 22.531) dei parti rappresentano Tc primari, suddivisi in 11,51% Tce e 15,19% Tcu. Per il 2020, i Tc primari osservati sono il 26,8% (5.842 / 21.796), 11,07% Tce e 15,74% Tcu. I Tc primari in urgenza seguono un andamento casuale nell'arco della giornata, mentre quelli in elezione sono naturalmente concentrati tra le 8.00 e le 14.00, e non vi sono differenze evidenti tra 2019 e 2020 (Fig.1a). Tra i parti NTSV, nel 2019, si evidenzia una percentuale maggiore di parti spontanei (Ps) pari al 68,47% (6.096 / 8903), i Tce rappresentano il 12,78% (1.138 / 8.903) e i Tcu il 15,95% (1420 / 8.903); si riscontra il 2,79% di parti operativi (Po), espletati con ventosa, forcipe e altra metodica. Per l'anno 2020, i Ps sono il 67,43% (5.625 / 8.342) di tutti i parti NTSV, i Tce sono l'11,98% (999 / 8.342), i Tcu il 17,09% (1.426 / 8.342) e i Po sono il 3,5% (Fig.2b).

CONCLUSIONI

L'analisi evidenzia, per entrambi gli anni, una distribuzione casuale dei Tcu nell'arco delle 24 ore, sia tra i Tc primari che nei parti NTSV. Nelle ore del mattino, in particolare tra le 9:00 e le 10:00, è svolta l'attività programmata con alta frequenza di Tce e una drastica riduzione dei PS. La quota di inappropriatezza di TC, quindi, è probabilmente annidata tra gli eventi verificatisi in tale fascia oraria, e su questi andrebbero svolti ulteriori approfondimenti. La modalità di gestione degli eventi parto appare sovrapponibile nei due anni presi in esame. Ciò lascia ipotizzare che gli istituti di ricovero durante la pandemia hanno adottato misure organizzative che hanno consentito di gestire l'evento parto secondo i consueti standard.

Figura 1. Distribuzione dei Tc primari per ora del giorno e anno (a). Distribuzione dei parti NTSV per modalità di espletamento, ora del giorno e anno (b).

Tce= Taglio Cesareo in elezione; Tcu=Taglio Cesario in urgenza; Ps=Parto Spontaneo; PoV=Parto operativo con Ventosa; PoF=Parto operativo con Forcipe; Po-altro=altro Parto operativo.

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DISTRIBUZIONE GEOGRAFICA E DETERMINANTI CLIMATICI
DELL'INCIDENZA DI LEISHMANIOSI VISCERALE IN ITALIA

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Introduzione: Storicamente la Leishmaniosi Viscerale (LV), una malattia infettiva trasmessa da vettore, era limitata alle aree italiane con clima mediterraneo. Negli ultimi 20 anni, tuttavia, organismi vettore (*Phlebotomus Perniciosus*), casi di Leishmaniosi canina e casi di LV umana sono stati osservati nelle regioni del Nord Italia, tradizionalmente classificate come aree a clima continentale e inadatte alla sopravvivenza del vettore e alla trasmissione della patologia[1].

Obiettivi: Questo studio ambisce a studiare la distribuzione geografica e i determinanti climatici dell'incidenza di casi di Leishmaniosi Viscerale osservati in Italia tra il 2010 e il 2017.

Metodi: La banca dati nazionale delle Schede di Dimissione Ospedaliera (*Ministero della Salute-Direzione Generale della Programmazione Sanitaria-Banca dati SDO*) è stata utilizzata per identificare i casi incidenti di LV tra il 2010 e il 2017 tra i soggetti con cittadinanza italiana. Dati di temperatura e precipitazione ad elevata definizione (9x9 km) riferiti al periodo di studio sono stati ottenuti dal database ERA5-Land ed espressi, per ogni provincia, come temperature medie e precipitazioni cumulative stagionali. Inoltre, sono stati ottenuti, per ogni provincia, l'indice medio di vegetazione NDVI (Normalized Difference Vegetation Index), l 'asperità media e il tasso di ospedalizzazione per HIV (noto fattore di rischio per LV). Sono stati stimati i Rapporti Standardizzati di Incidenza (SIR) provinciali per sesso e classe di età, utilizzando come riferimento la popolazione residente in Italia nel 2011. I SIR sono stati analizzati tramite modelli spaziali auto-regressivi Bayesiani per quantificare come il rischio di LV sia influenzato dai parametri climatici. I risultati riportati sono aggiustati per NDVI, asperità e tasso di ospedalizzazione per HIV. L'inferenza statistica è stata condotta tramite simulazioni Monte Carlo basate sulle Catene di Markov (MCMC)[2].

Risultati: Durante il periodo di studio (8 anni) sono stati identificati 1123 casi di LV (tasso di incidenza: 2,4 casi /1.000.000 anni-persona). Il rischio di LV risulta essere maggiore nel Sud Italia, anche se un rischio elevato è stato osservato in alcune aree del Nord Italia. L'incidenza di LV è risultata positivamente associata alla temperatura atmosferica estiva (rischio relativo (RR) per 1°C di aumento della temperatura media estiva: 1.14, 95% Intervallo di Credibilità (ICr): 1.01-1.29) e inversamente associato alle precipitazioni cumulative primaverili ed estive (RR per un aumento di 10 mm delle precipitazioni cumulative primaverili: 0.93, 95% ICr: 0.89-0.97; RR per un aumento di 10 mm delle precipitazioni cumulative primaverili: 0.94, 95% ICr: 0.92-0.96).

Conclusioni: I risultati attuali indicano che la LV è ormai endemica in diverse aree della penisola italiana e che i fattori climatici, come la temperatura atmosferica e le precipitazioni possano svolgere un ruolo rilevante nel modellare la sopravvivenza del vettore e la trasmissione della malattia. Questi risultati suggeriscono inoltre che il cambiamento climatico potrebbe influenzare la futura diffusione della distribuzione della Leishmaniosi in Italia.

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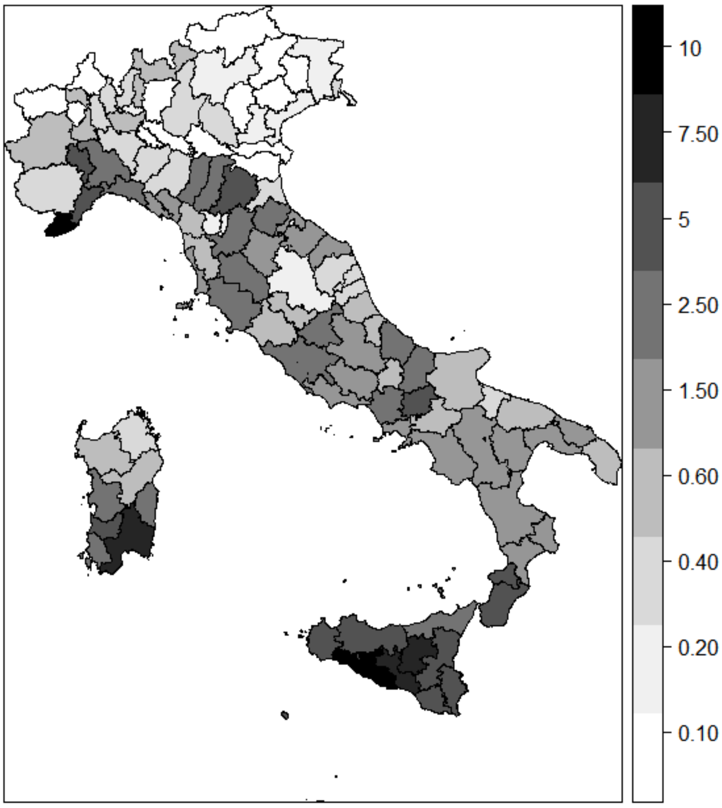
Fig1: Distribuzione dei Rapporti Standardizzati di Incidenza di Leishmaniosi Viscerale in Italia nel periodo 2010-2017



PREVALENCE AND ECONOMIC BURDEN OF MAJOR COMORBIDITIES IN MULTIPLE SCLEROSIS

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Background

Comorbidity is common in the general population, is associated with higher mortality and increased health care utilization and may account for some of the observed heterogeneity and severity in outcomes in people with Multiple Sclerosis (pwMS); yet its effect has only recently received attention [1]. The reported prevalence of comorbidity in pwMS varies widely depending on specific comorbid conditions, population evaluated, socio-demographic factors and assessment method. The identification of comorbidity through the review of medical records is a time consuming and costly process; the use of population-based administrative data is one of the few validated assessment alternatives [2]. It is also well known that medication and total healthcare costs are generally increased in persons with comorbidities; anyway, despite evidence that comorbidity is common in pwMS, data on healthcare costs in pwMS are sometimes confusing and partly inconsistent [3,4].

Aims

Our aims are to estimate the prevalence and economic burden of major comorbidities in people with MS (pwMS) in two Northern Italy study areas (Pavia, PV and Genoa, GE) and to analyse demographic factors related to presence of comorbidity in pwMS using routinely collected healthcare data.

Methods

We estimated prevalence of the following comorbid conditions in pwMS in the period 2012-2017: anxiety, depression, cancer, leukemia, lymphoma, hypertension, heart disease, cerebrovascular diseases, vascular diseases, ischemic stroke, hyperlipidaemia, bronchopathy, diabetes, gastropathy, gastric ulcer, autoimmune diseases, chronic renal failure, connective tissue diseases and HIV/AIDS.

They were identified by a specific algorithm currently used for monitoring prevalence of chronic diseases by Italian Local Health Authorities; such algorithm is implemented in the BDA (*Banca Dati Assistiti)* system and is based on hospital discharge records, active payment exemptions, drug prescriptions and ambulatory care claims.

Direct healthcare costs were defined by regional and governmental contracts; the aggregated healthcare expenditure was compared between pwMS with/without comorbidity.

Logistic regression models were used to evaluate the risk of having at least a comorbidity considering age class, sex, and study area.

Results

The MS cases identified were 2983, 2035 in Genoa and 948 in Pavia. 55.6% of pwMS had at least one comorbidity (50.6% GE and 66.5% PV, p<0.001), 64.5% were females (without significant differences between GE and PV, p>0.05), and pwMS in Genoa were slightly older (GE median=50 and IQR: 41-60 vs PV median=49 years and IQR: 39-58, p=0.005). The most prevalent comorbidities were depression (32.9%), hypertension (18.0%), cancer (10.9%), heart disease (7.8%), cerebrovascular diseases (7.0%) and hyperlipidaemia (6.1%). Comorbidity ranking was similar in the two provinces, although we observed significant differences considering specific prevalence rates.

The mean direct healthcare costs of MS were substantially higher for individuals with comorbidity (36,463 € vs 26,284 €, p<0.001), showing 39% of additive costs.

Presence of comorbidities were significantly less likely among males (OR 0.8, p=0.002) and more likely in the Pavia area (OR=2.3, p<0.001) and among older age groups (ORs increased from 1.5 to 11.0 considering the different age classes compared with the youngest, p<0.001) (Figure 1).

Conclusions

Our study provides evidence of the burden of comorbidities in MS. Comorbidity is common in MS and produce additive costs. Moreover, our study shows the importance of considering population-based characteristics when evaluating the impact of comorbidities in MS, as prevalence may vary based on age, sex and geographic area. The use of administrative data for tracking the MS comorbidity could help to improve knowledge' gaps. Moreover, when an additivity situation is involved, preventive policies could lead to monetary savings.

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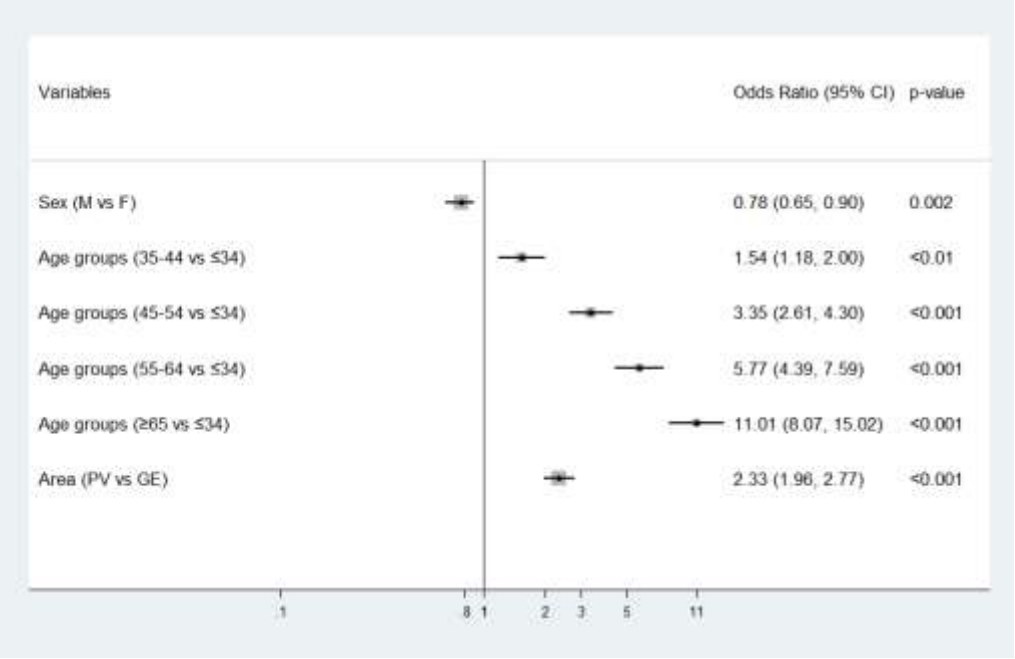
Figure 1. Forest plot of the multivariable logistic regression model to estimate the risk of having at least a comorbidity considering age class, sex and study area.



Variables	Odds Ratio (95% CI)	p-value
Sex (M vs F)	0.78 (0.65, 0.90)	0.002
Age groups (35-44 vs ≤34)	1.54 (1.18, 2.00)	<0.01
Age groups (45-54 vs ≤34)	3.35 (2.61, 4.30)	<0.001
Age groups (55-64 vs ≤34)	5.77 (4.39, 7.59)	<0.001
Age groups (≥65 vs ≤34)	11.01 (8.07, 15.02)	<0.001
Area (PV vs GE)	2.33 (1.96, 2.77)	<0.001

ASSESSING PHYSICAL HEALTHCARE GAP AMONG PATIENTS WITH SEVERE MENTAL ILLNESS: A LARGE REAL-WORLD INVESTIGATION FROM ITALY

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BACKGROUND

Mental health professionals and epidemiologists are recently moving beyond traditional measures of incidence and prevalence to include treatment gap [1] and assessment of unmet needs in psychiatry [2]. A main issue in this field, and one of the critical barriers to the uptake of mental health programs, is the so-called *physical healthcare gap*, a concern raised by the frequent unattended physical comorbidity [3] and early mortality of persons with severe mental illness (SMI) [4]. Indeed, patients with other chronic conditions may be noncompliant to recommended care for several reasons, including their disbelief in the efficacy of treatment, the presence of barriers such as adverse effects, and lack of help and support from family members or from health professionals. Furthermore, mental health disorders might also affect patients' willingness and ability to follow through with treatment. Thus, assessing the extent to which noncompliance might be a concomitant effect of a treatable condition like SMI may be an important step in improving patient adherence and the outcomes of medical treatment.

OBJECTIVES

To assess the extension of physical healthcare gap among persons with severe mental illness needing chronic drug therapies.

METHODS

A retrospective cohort study was conducted using computerized Healthcare Utilization (HCU) databases of Lombardy region, overall covering nearly for the 16% of the whole italian population. HCU data include a variety of information on residents, such as hospital diagnosis, drug prescriptions, outpatient visits, and specific diagnostic and therapeutic codes for patients receiving specialist mental healthcare.

Beneficiaries of the NHS who on December 31st, 2016 (index date) were aged 18 years or older and were resident in Lombardy from at least two years, and who during the years 2015-2016 had at least three consecutive drug dispensations of blood pressure-lowering, lipid-lowering, or antidiabetic agents were included. 2,008,055, 723,694 and 391,773 prevalent users of, respectively, blood pressure-, lipid- or glucose-lowering agents were identified. Of those, prevalent users taken-in-care by a mental health service with diagnosis of depression, schizophrenia, bipolar or personality disorder formed the study-cohort. For each study-cohort member, up to three patients without signs of SMI were randomly selected to be matched for gender, age (± 1 year), and number of contacts with the NHS in the two years prior the index date. Individuals without SMI (the reference cohort) were identified according to whether no diagnosis of mental illness was experienced any time prior the index date and used as comparators. Patients who did not reach at least one year of follow-up were excluded from the study.

One-year adherence with healthcare was measured through the Proportion Days Covered (drug-adherence). Limited to patients on treatment with glucose-lowering agents, exposure to selected recommendations (clinical control adherence) [5]. was also evaluated. Multivariable conditional logistic regression was fitted for modelling the odds ratio (OR), and 95% confidence interval (CI), for the association between the exposure (being affected by a severe mental disorder) and the outcome(s) of interest. The outcome(s) was having experienced high adherence with recommended healthcare, i.e., a patient was considered having experienced the outcome whether, during the year of follow-up, (i) at least 75% of specific drugs was available or (ii) at least 4 of the 5 recommended controls for diabetes were performed (only for the diabetic patients).

RESULTS

The 55,162 patients with SMI experienced lower adherence with the corresponding drug therapy with respect to comparators. Patients affected by severe mental disorders had a likelihood to be well adherent with blood pressure-lowering, lipid-lowering, or antidiabetic agents respectively 24% (95% CI, 22% to 26%), 10% (6% to 14%), 25% (21% to 29%) lower than patients without signs of SMI. Concerning the 9,250 diabetic patients with SMI, they showed a 18% (13% to 22%) lower likelihood to meet recommendations for the clinical management of diabetes with respect to diabetic patients without SMI.

Stratified analysis showed that type of mental disorder, gender and clinical profile were significant effect modifiers.

CONCLUSIONS

Our study showed, using HCU data, that patients living with mental illness and needing chronic drug therapy with blood pressure-lowering, lipid-lowering or antidiabetic agents, were treated worse than patients without any sign of SMI but the same need of chronic drug therapies.

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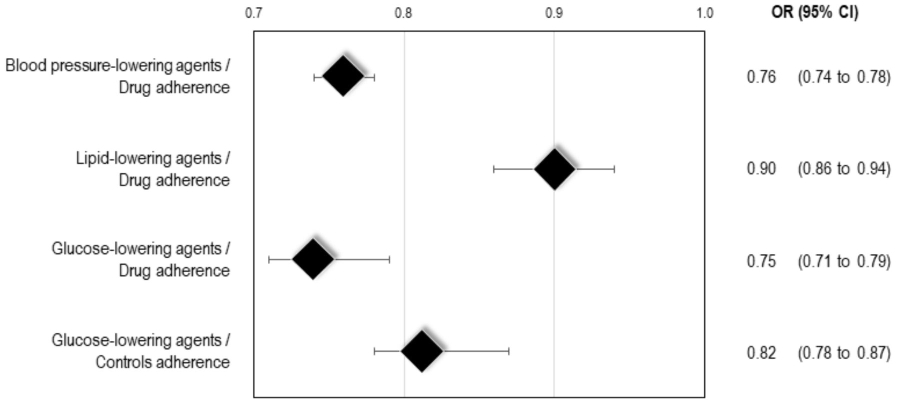
Figure 1. Forest plot for the association between exposure to mental disorders and high adherence with recommended healthcare. Lombardy, Italy, 2016-2017



Footnote. Odds ratio, and 95% confidence interval, estimated with conditional logistic regression.

FROM CONTACT COVERAGE TO EFFECTIVE COVERAGE OF COMMUNITY CARE FOR PATIENTS WITH SEVERE MENTAL DISORDERS: A REAL-WORLD INVESTIGATION FROM ITALY

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BACKGROUND

Provision of appropriate care through delivery of quality health services to people in need is a core function of health systems. Thus, accurate measurement of health service outputs and related outcomes is essential for tracking performance and addressing decision processes, and one measure to determine how a program is performing is the coverage level it achieves [1]. The WHO includes the provision of mental healthcare in community-based settings as a key objective of Mental Health Care (MHC) systems [2]. However, it has been found that increasing use of health services do not always translate into health gains. Indeed, simple assessment and reporting of rates of contact with MHC potentially overestimates the full expected health benefits of mental services. Distinct from the measurement of contact coverage with which provision of care is usually monitored, it is therefore useful to identify the rate of effective coverage [3]. This latter concept introduces the dimension of service quality and captures improvements in health achieved by patients who receive care [4].

OBJECTIVES

To measure the gap between contact and effective coverage of MHC.

METHODS

This study is based on computerized Healthcare Utilization (HCU) databases from four Italian regions involved in the QUADIM ("Clinical pathways in patients with severe mental disorders in Italy") project: Lombardy, Emilia-Romagna, Lazio, Sicily. Overall, data covered nearly 37% of the entire Italian population. HCU data include a variety of information on residents, such as hospital diagnosis, outpatient drug prescriptions, outpatient visits and diagnostic exams. In addition, a specific automated system concerning mental health care gathers data from regional Departments of Mental Health (DMHs) accredited by the NHS. This system provides demographic information and diagnostic and therapeutic codes for patients receiving specialist MHC.

NHS beneficiaries of these regions, aged 18-40, who during 2013-2016 had a diagnosis of depression, schizophrenia, bipolar or personality disorder, were identified. Patents who received a prior diagnosis of mental disorder at any time or received two prescriptions of psychotropic drugs in the 2 years prior the index date, were excluded. Newly taken-into-care patients were followed-up until the 06/30/2018.

Emergency admissions to psychiatric wards during follow-up were recorded as outcome episodes and considered as surrogates of relapse. Exposure to two broad categories of MHC, specific therapies with psychotropic drugs (i.e., antidepressants, antipsychotics, mood stabilizers) and community care (generic care, psychosocial and psychotherapy) interventions, were considered.

To control for patient specific characteristics while investigating the risk of relapse, we used a self-controlled case series (SCCS) design, a within person approach to compare the rates of relapse while a patient was covered or uncovered by specific MHC. To account for the possibility that exposure and relapses are time-correlated, estimates generated from the SCCS were compared with those generated from a self-controlled referent series (matched with the case series individuals for gender, age, date of mental diagnosis).

Conditional Poisson regression was used for estimating incidence rate ratios, and corresponding 95% confidence intervals (CI), for both case (IRRc) and referent (IRRr) series. Because referent patients did not experience relapse, IRRr estimates the portion of IRRc due to change in therapeutic strategy. Dividing IRRc by IRRr, the time-trend adjusted IRRa was obtained.

RESULTS

Among the 227,751 eligible prevalent cases, 45,761 individuals met the inclusion criteria and were included into the study cohort as newly taken-into-care patients with diagnosis of depression (73%), personality disorder (12%), schizophrenia (10%) or bipolar disorder (4%). 11,500 relapse episodes occurred. Relapse risk was reduced during periods covered by (i) psychotherapy for patients with diagnosis of depression (IRR 0.67; 95% CI, 0.49-0.91), and bipolar disorder (0.64; 0.29-0.99) ;(ii) psychosocial interventions for those with diagnosis of depression (0.74; 0.56-0.98), schizophrenia (0.83;0.68-0.99), and bipolar disorder (0.55; 0.36-0.84), (iii) pharmacotherapy for those with diagnosis of schizophrenia (0.58; 0.49 to 0.69), and bipolar disorder (0.59; 0.44 to 0.78). Coverage with generic MHC, in the absence of psychosocial interventions, did not affect the relapse risk.

CONCLUSIONS

Community MHC showing evidence of effectively prevent the onset of relapse were psychosocial interventions and psychotherapy for depression, antipsychotics and psychosocial intervention for schizophrenia, and mood stabilizers, psychosocial intervention, and psychotherapy for bipolar disorder. This study ascertained the gap between utilization of mental healthcare and effective coverage, showing that administrative data can usefully contribute to assessing the effectiveness of a mental health system.

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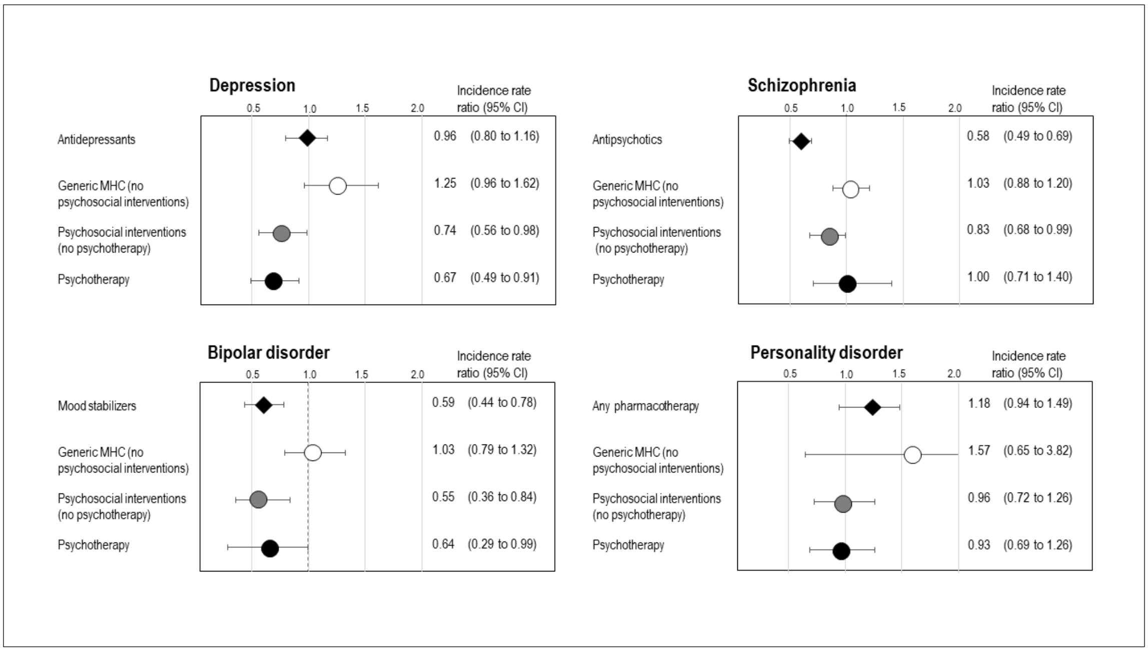
Figure 1. Self-controlled case-referent series estimates of the incidence rate ratio of relapse episodes associated with categories of mental care, according with the main diagnosis of depression, schizophrenia, bipolar disorder, and personality disorder. Italy, QUADIM-MAP project, Italy, 2013-2018



Footnote. Self-controlled case-referent series incidence rate ratio, and 95% confidence interval, estimated with Poisson regression contrasting within-patient incidence of relapse onset observed during mental care coverage and no coverage person-time. Relapse was emergency hospital admissions in a psychiatric ward. Time-windows with width of 180 and 90 days respectively prior and following the relapse onset were removed for mitigating the effect of incorrect allocate person-time of MHC coverage.

INCIDENCE OF SARS-COV-2 AND RISK FACTORS FOR SEVERE OUTCOMES IN PEOPLE WITH CYSTIC FIBROSIS IN EUROPE

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Introduction

Cystic fibrosis (CF) arises from gene mutations in cystic fibrosis transmembrane conductance regulator (CFTR), which lead to chronic CF lung disease and compromised function of multiple other organ systems [1]. Repeated cycles of respiratory infection and chronic inflammation cause progressive lung function decline. Viral infection such as influenza can trigger pulmonary exacerbations and can contribute to increased mortality in CF. Therefore, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic deserved great attention in the CF community.

Aims

This observational study aims to estimate the incidence of SARS-CoV-2 infection in people with Cystic Fibrosis (pwCF) in 2020 in Europe, to characterize morbidity of CF patients infected by SARS-CoV-2 and to identify risk factors associated with more severe symptoms and poorer outcomes.

Methods

This observational study included pwCF with a diagnosis of SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) between February and December 2020. Anonymized data on demographic and pre-infection characteristics of CF patients infected by SARS-CoV-2 and data on the course of the disease were collected from 38 countries through the European Cystic Fibrosis Society Patient Registry (ECFSPR) based on a defined data governance structure.

To compute incidence, the total number of pwCF in the different countries was retrieved from the most recent ECFSPR annual report (2018 data for the majority of countries, 2017 for France) [2].

To evaluate the association of demographic and pre-infection clinical characteristics of pwCF with symptoms and outcomes of SARS-CoV-2 infection, two multiple logistic regression models were fitted, considering presence of symptoms and hospitalization during SARS-CoV-2 infection as response variables. Demographic and pre-infection characteristics of pwCF were included in the model as explanatory variables (retaining variables with <5% missing data). To account for the effect of health system within the same country, generalized estimation equations models including the country of residence have been used.

Data analysis was performed using SAS 9.4 and R 4.0.3 with the additional package geepack.

Results

In 2020, 26 countries reported information on 828 pwCF and SARS-CoV-2 infection confirmed by PCR test. The overall incidence was estimated as 17.2 per 1000 pwCF (95% CI: 16.0-18.4). Incidence was notably higher in lung-transplanted pwCF (28.6 per 1000) versus non-lung transplanted pwCF (16.6 per 1000), p<0.001. Moreover, incidence increased along with age group (p<0.001) and was notably higher in all adult age groups compared to pediatric age groups.

Of the 828 cases, 48.4% were male and median age was 24 years. Most patients had normal body mass index (BMI) (90.6%), pancreatic insufficiency (80.6%), and mild lung disease (59.9%). 26.1% had CF-related diabetes (CFRD) and 26.6% had chronic liver disease. 57.7% were colonized by *Staphylococcus aureus* and 43.4% by *Pseudomonas aeruginosa*.

Three quarters of pwCF had symptoms, in particular general (64.8%) and pulmonary symptoms (54.0%). The most common individual symptoms were fever (43.6%), increased cough (43.2%), fatigue (34.2%).

Of the 828 cases, 11.7% needed extra oxygen and 3.9% needed respiratory support, 23.7% were admitted to hospital and 2.5% to intensive care. Regretfully, 11 pwCF (1.4%) died.

Factors mostly associated with hospitalization were lung transplant (OR 3.2, 95% CI: 1.7 - 6.1, p<0.001), moderate or severe lung function (OR 2.4, 95% CI: 1.6 - 3.6, p<0.001 and OR 5.4, 95% CI: 2.2 - 13.0, p<0.001), CFRD (OR 1.7, 95% CI: 1.1 - 2.6, p=0.027), azithromycin use (OR 1.8, 95% CI: 1.1 - 2.9, p=0.017).

Factors mostly associated with symptomatic disease were age >40 years (OR 2.6, 95% CI: 1.2 - 5.3, p=0.010) and the presence of at least one F508del mutation (OR 2.1, 95% CI: 1.3 - 3.5, p=0.004).

Conclusions

This is the first prospective study in a large cohort of pwCF infected with SARS-CoV-2 in Europe during the pandemic until the end of 2020. Incidence of SARS-CoV-2 in pwCF was estimated as 17.2 per 1000 and it was higher in lung-transplanted and in older patients. Accounting for the age distribution, the incidence of SARS-CoV-2 in pwCF was higher than in the general population [3]. Moreover, the real incidence of SARS-CoV-2 in pwCF could be even higher with underestimation due to incomplete surveillance, difficulties of clinicians and healthcare staff to collect information during pandemic and to failure to diagnose of mild and asymptomatic cases.

SARS-CoV-2 infection yielded high morbidity in pwCF, with 75.7% of patients having symptomatic illness and older individuals (>40 years) with at least one F508del mutation being more prone to become symptomatic.

Severe outcomes as hospitalization were quite common, with higher risk for pwCF with lung transplant, moderate or severe lung disease, CFRD and long-term azithromycin (often considered a surrogate for worse lung disease).

Future work includes long term follow-up of lung function in pwCF with SARS-CoV-2, and follow-up of incidence and severity following vaccination.

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CARDIOLOGICAL FACTORS ASSOCIATED WITH IN-HOSPITAL MORTALITY IN A COHORT OF PATIENTS WITH COVID-19. RESULTS OF A MULTICENTER STUDY.

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Introduction

The Coronavirus disease (COVID-19) pandemic was an unexpected crisis that has dramatically affected health systems worldwide. A major reorganization of the healthcare system took place in the most affected areas to cope with the increasing pressure on the hospitals: cardiology units began to deal almost exclusively with COVID-19 patients, mostly those with associated cardiac disorders[1],[2].

Aims

We aimed at investigating several hypotheses on the cardiological risk factors associated with in-hospital mortality in a cohort of patients with COVID-19, focusing on markers of myocardial injury (MI) (i.e., troponin I and T) and of cardiac disease (i.e., natriuretic peptides), as well as on cardiac comorbidities. Sex was also evaluated as an important mediator.

Methods

A multicenter register of COVID-19 patients hospitalized in 13 Italian cardiology units from March 1 to April 9, 2020, promoted and coordinated by the Cardiology Unit of ASST Spedali Civili of Brescia, was created. Patients were followed-up after the hospital admission until in-hospital death, discharge, or 23rd April 2020, whichever came first. The database included data on patients' demographics, medical history, and in-hospital clinical course, including laboratory findings collected within the first 48 hours of hospitalization and therapy.

Each center performed blood examinations as usual, meaning that the type of troponin (either I or T) and of natriuretic peptide (either BNP or NT-proBNP) were heterogeneous between centers. Moreover, different assays were used in different laboratories. For these reasons, we standardized our main clinical markers of interest as "normal" or "elevated".

Survival analyses were conducted building different models according to clinical hypotheses. Cumulative incidence function (CIF) of death was computed taking into account hospital discharge as a competing event. Comparisons of CIFs among subgroups were performed by the Gray's test. Variables clinically relevant and significantly associated with the risk of death at the univariable analysis were tested via selection methods in a multiple Cox regression model to identify independent risk factors. A 2-tailed p-value less than 0.05 was considered statistically significant. All analyses were performed using SAS software v. 9.4.

Results

701 patients were enrolled (mean age 67.2±13.2 years, 69.5% males) of whom 165 (23.5%) died during a median hospitalization of 15 (IQR, 9-24) days. Patients with preexisting cardiac disease had a higher mortality rate and having a history of HF was an independent predictor of in-hospital mortality even after adjusting for clinical variables related to COVID-19, age, and HF severity[3].

Regarding cardiac biomarkers, among patients with a troponin measurement within the first 24 hours of admission (N=614), 278 (45.3%) had elevated troponin and therefore a MI. This condition was found to be associated with an increased in-hospital mortality (adjusted HR 1.71, 95%CI 1.13-2.59, p=0.01) and was independent from concomitant cardiac comorbidities[1].

Considering patients who had a second troponin evaluation on day 2 of hospitalization (N=197), the majority (44%) had persistently elevated troponin, but in a small group of patients some changes were noticed: 8% transitioned from normal to elevated, and 7% from elevated to normal. We found that patients with at least one elevated assay had a higher risk of death compared to those with normal troponin at both evaluations. Interestingly, patients with MI detected on day 2 had the highest mortality risk (adjusted HR 3.78, 95%CI 1.10-13.09, p=0.035)[4].

Natriuretic peptides (NP) were also found to provide an additional risk stratification in patients with normal troponin values at admission. Indeed, for patients with both NPs and troponin assay at admission (N=341), elevated levels of both biomarkers were associated with a 3-fold increase of in-hospital mortality as compared to patients with normal values of both biomarkers. This risk remained similarly increased in patients with NPs value elevations and normal troponin, and 2-fold increase in those with high troponin and normal NPs.

Finally, sex was not found to be an independent predictor for mortality, however there was a sex-based heterogeneity in the association between baseline variables and the patients' risk of death. For example, the risk was more than double in men with low vs high lymphocytes count, whereas there was no effect in women (p for heterogeneity=0.03), and platelets count was associated with better outcome in men but not in women (p=0.03).

Conclusions

In severe COVID-19 infection, it is mandatory to perform an adequate and prompt prognostic stratification of patients hospitalized to identify those who may benefit most from intensive and specific care. From our cohort of patients hospitalized in cardiology units emerged that those with a history of HF have an extremely poor outcome. MI detection through serum troponin evaluation is highly recommended both at admission and within the first 48 hours of in-hospital stay as it accurately identifies patients at higher risk of death. NPs can further improve the prognostic stratification as they detect high-risk patients also among those with normal troponin. Patient's sex should also be considered.

A 12-month follow-up is currently underway to gather information about 1-year mortality and hospital readmission for any cause after the first COVID-19 hospitalization.

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L'IMPATTO DELLA PANDEMIA DI COVID-19 SULL'ASSISTENZA PRENATALE E SUGLI ESITI **PERINATALI**

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INTRODUZIONE:

L'assistenza prenatale mira a monitorare e migliorare il benessere della madre e del feto, rilevare le complicanze, prepararsi al parto e promuovere un corretto stile di vita durante la gravidanza. La mancanza di aderenza agli indicatori del percorso assistenziale per la nascita è associata a diversi esiti avversi materni e neonatali. Uno tra i più importanti è quello relativo alla nascita pretermine (nascita a <37 settimane di gestazione). Ogni anno nel mondo nascono 15 milioni di bambini prematuri e in due terzi dei casi non è possibile identificare fattori di rischio riconoscibili. Non è ancora chiaro quali siano le misure realmente efficaci per la prevenzione del parto pretermine, ma è importante ricercare i fattori di rischio e agire specialmente su quelli modificabili e sullo stile di vita della madre.

Dall'inizio del 2020 in tutto il mondo si è diffusa la pandemia da SARS-CoV-2, la quale ha causato un'emergenza sanitaria senza precedenti nella storia recente. La maggior parte degli Stati ha imposto restrizioni per ridurre il contagio che hanno modificato in modo radicale lo stile di vita e le abitudini quotidiane di tutta la popolazione. Alcuni studi europei hanno evidenziato una riduzione di parti pretermine nel 2020 e l'ipotesi è che tale evento sia stato determinato dalla modifica dello stile di vita delle donne a causa delle restrizioni imposte dai governi.

OBIETTIVI:

Lo scopo del presente studio è di valutare l'impatto della pandemia da SARS-CoV-2 (i) sull'aderenza al percorso assistenziale per la nascita e (ii) sulla nascita pretermine in Lombardia.

METODI:

I dati utilizzati sono stati ottenuti dai database amministrativi della regione Lombardia. Per valutare l'impatto di Covid-19 sul percorso assistenziale per la nascita sono state identificate delle coorti specifiche per il calcolo di ogni indicatore di aderenza al processo assistenziale relativamente al periodo del primo lock down (marzo-maggio 2020). Come riferimento sono state prese coorti retrospettive, applicando gli stessi criteri di inclusione/esclusione ma anticipando di un anno il reclutamento, e prospettiche, ove possibile. Sono stati calcolati i valori degli indicatori di aderenza al processo assistenziale prima e durante la pandemia. Successivamente è stato valutato l'andamento degli indicatori nei tre periodi d'interesse (no covid (gennaio/febbraio), covid lock down (marzo/maggio), e covid no lock down (giugno/ottobre)) attraverso l'interpolazione di un modello di Cox considerando l'esposizione alle misure restrittive come variabile tempo-dipendente. Le stime sono state inoltre corrette per una eventuale tendenza temporale dell'aderenza all'indicatore in studio.

Per valutare l'impatto della pandemia di Covid-19 sulla nascita pretermine sono stati considerati tutti i parti avvenuti dal 2015 al 2020. Il *trend* delle nascite pretermine negli anni in tutta la popolazione e stratificato per le province maggiormente colpite dalla pandemia (Bergamo, Brescia, e Cremona) è stato valutato attraverso il test del trend di Armitage.

RISULTATI:

Dai risultati si evince una minor aderenza alla continuità assistenziale territorio-ospedale durante il periodo di covid lock down: l'indicatore risultava del 20% inferiore nel periodo di covid lock down rispetto al periodo no covid. Per tutti gli altri indicatori non si è evidenziato nessun effetto della pandemia.

Analizzando i dati dal 2015 al 2020 si nota un decremento del numero di parti progredendo con gli anni (p trend=0.0048), mentre la prevalenza delle nascite pretermine ha un andamento costante (p trend=0.1885). La prevalenza dei parti pretermine rimane stabile nelle singole province, anche se si evidenzia un leggero aumento nella provincia di Cremona.

CONCLUSIONI:

Dal presente studio risulta che la pandemia non ha impattato sull'aderenza al processo assistenziale per il percorso nascita in Lombardia ad eccezione dell'indicatore relativo alla continuità assistenziale territorio-ospedale. Nonostante le restrizioni imposte per il contenimento della pandemia, non sembra che si sia modificata la prevalenza del parto pretermine. Gli effetti migliorativi e peggiorativi del diverso stile di vita si sono verosimilmente controbilanciati determinando un andamento costante delle nascite pretermine rispetto agli anni precedenti.

FIRST WAVE OF COVID-19 PANDEMIC: CONCERN AND SLEEP DISTURBANCES IN ITALIAN HEALTHCARE WORKERS

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Background

The ongoing Covid-19 pandemic has had an extensive impact on public health all over the world. Italy was one of the most affected countries with the occurrence of the first European full-blown outbreak [1]. During the pandemic, many healthcare workers (HCWs) fulfilled their duties in extremely harsh, high-pressure environments; their exposure to Covid-19 may be an important risk factor for psychological distress and even full-blown psychiatric disorders [2]. In addition, during an emergency such as either an epidemic/pandemic, HCWs can develop distress and concerns about their own health and for people around them [3,4,5]. However, it is known that a stressful workplace has negative effects on both the quality of life and the professional activity, in terms of limited efficiency and ability in providing high-quality health services [6,7]. Identifying the factors that may be a cause of concern in the healthcare environment regarding the Covid-19 pandemic can be useful in order to guarantee the most favorable conditions of professional and psychological well-being of workers, especially in situations of extreme pressure.

Aim

To explore and describe concerns and factors related to stress-induced sleep disturbances among Italian healthcare workers during the first wave of Covid-19 pandemic.

Methods

Cross-sectional survey design. Study population included physicians, nurses, medical staff (radiologic technologists, rehabilitation technicians, physiotherapists and midwives), health care support and administrative personnel working in hospitals, nursing homes and therapeutic communities in Italy during the first wave of the pandemic period (February–May 2020). Participants were recruited by using a "snow-ball" sampling, by email, newsletters and social media (Facebook and LinkedIn). An ad hoc questionnaire was administered to participants by Google platform, trainee students were excluded. Either the Chi-square test or the Fisher exact test was applied to compare qualitative variables and the Kruskal–Wallis nonparametric test for quantitative ones. Multivariable logistic regression model was implemented to evaluate the association between sleep disturbances and some variable of interest. Homer-Lemeshow (HL) test for goodness of fit was performed. The level of $p < 0.05$ was considered significant for all the analysis, except for multiple comparisons, for which the Bonferroni correction was used.

Results

A total of 2103 HCWs filled-up the questionnaire but only 2078 met inclusion criteria. Mean age was 42 ± 11 years and 78.80% were females. The highest percentage of respondents were physicians (40.75%) and nurses (32.15%), followed by medical (18.00%), health care support (4.50%) and administrative (4.60%) staff. 15.80% reported having been infected with SARS-CoV-2. The most frequent worry was about "*The risk of infection for the surrounding people*" (55%). Participants declared that they were worried about the COVID-19 infection with a median score of 3 (IQR 2-3) (score ranged from 0 "I'm not worried" to 4 "I'm very worried"). 58.85% of the sample declared that perceived high risk of being infected (25.30% low and 15.78% medium).HCWs reported they suffered from sleep disturbances were 63.43%. Results from multivariable logistic regression model shows that to be a female (OR= 1.565; 95%CI: 1.240-1.975), higher risk perception of being infected (OR=1.603; 95%CI: 1.156-2.221), to be a nurse (OR=1.664; 95%CI: 1.290-2.146) and high score of worry (OR=1.680; 95%CI: 1.476-1.913) were significantly associate with presence of sleep disturbances (HL test p=0.4375) (Table 1).

Table 1. Factors associated to a presence of sleep disturbances: results from multivariable logistic regression model.

	OR	95% CI		P-value
		Lower	Upper	
Sex				
Female vs Male	1.565	1.240	1.975	0.000
Perception of risk of being infected				
Medium vs low	1.250	0.957	1.633	0.101
High vs low	1.603	1.156	2.221	0.005
Professional Group				
Nurses vs medical/healthcare support/administrative staff	1.664	1.290	2.146	0.000
Physicians vs medical /healthcare support /administrative staff	1.202	0.951	1.518	0.124
Degree of worry (score)	1.680	1.476	1.913	0.000

Conclusion

HCWs involved in Covid-19 emergency have worked in one of the most challenging contexts of the last thirty years. This impendent emergency has caused some concerns among HCWs and lifestyle changes affecting all aspects of life, such as sleep quality.

Understanding better factors associated with this issue is very important and can be useful to provide them the right support to avoid the onset of psychological disorders and consequently to ensure high quality health services provision: work performance is highest when personnel report a good physical and psychological well-being level. Health authorities and policymakers can play an active role in maintaining the psychological well-being of their employees: this research, based on real-world data, may help them to address the most appropriate interventions during a public health emergency.

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L'EFFETTO INDIRETTO DELL'EPIDEMIA DA COVID-19 SUL MONITORAGGIO ED IL TRATTAMENTO DEI PAZIENTI CRONICI: RISULTATI DEL PROGETTO MOVID

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INTRODUZIONE

L'epidemia da Covid-19 ha avuto e sta avendo una notevole influenza sui pazienti cronici. Innanzitutto, gli individui caratterizzati da un profilo clinico più compromesso, perché affetti da diverse patologie e/o in trattamento con diverse terapie farmacologiche, sono a maggior rischio di contrarre l'infezione e di sviluppare forme severe della malattia. In secondo luogo, le misure restrittive adottate per contenere la diffusione del virus incentivano stili di vita (ad esempio, una ridotta attività fisica) che incrementano il rischio di sviluppare o di esacerbare malattie croniche. Infine, queste misure hanno anche ridotto le capacità dei sistemi sanitari di diagnosticare precocemente, monitorare e trattare i pazienti affetti da malattie e condizioni croniche.

OBIETTIVI

Il progetto MoViD (Monitoraggio e Valutazione dei Livelli Essenziali di Assistenza nel corso dell'epidemia da CoViD-19) ha l'obiettivo di valutare come si è modificato durante l'epidemia da Covid-19 l'accesso ai livelli essenziali di assistenza (LEA) utilizzando un approccio basato sui pazienti.

METODI

Mediante l'analisi dei database amministrativi della Regione Lombardia, si sono identificate coorti di pazienti affetti da diverse condizioni, tra cui il diabete ed il tumore della mammella. Il periodo di reclutamento della coorte è stato fatto variare in funzione della condizione indagata e dell'indicatore in studio, in modo tale che il controllo/trattamento dovesse svolgersi durante il periodo del primo lockdown (marzo-maggio 2020). Una coorte di riferimento è stata poi identificata applicando gli stessi criteri di inclusione/esclusione ma anticipando di un anno il reclutamento.

Per valutare il ritardo nel monitoraggio e nell'inizio del trattamento, sono state innanzitutto applicate metodologie di analisi di sopravvivenza, quali curve Kaplan-Meier, curve hazard e Restricted Mean Survival Time (RMST) nella coorte in esame ed in quella di riferimento. Inoltre, i mesi del 2020 sono stati classificati in tre periodi: no covid (gennaio/febbraio), covid lockdown (marzo/maggio) e covid no lockdown (giugno/ottobre). Per quantificare la diversa propensione allo svolgimento dell'esame/trattamento in questi tre periodi (ossia l'esposizione di interesse), due approcci sono stati adottati. Quando il periodo di valutazione dell'indicatore è breve (non permettendo quindi al paziente di attraversare i tre livelli di esposizione durante il follow-up) ed il tempo allo svolgimento dell'esame/trattamento è di interesse (ad esempio, nella valutazione della tempestività dell'inizio della terapia medica nelle donne operate per tumore della mammella), un modello di Cox è stato interpolato inserendo l'esposizione come variabile tempo-dipendente. Invece, quando il follow-up è lungo ed il paziente attraversa tutti i periodi dell'anno, un disegno Self-Controlled Case Series è stato adottato. Una coorte di riferimento è stata identificata al fine di aggiustare le stime per il trend temporale nello svolgimento degli esami.

RISULTATI

Tra i pazienti diabetici, vi è stato un ritardo di un mese nell'esame dell'emoglobina glicata. Infatti, la RMST nel 2019 era di 175 giorni (ossia, un paziente diabetico spendeva in media 175 giorni senza questo controllo), ed è salita a 205 giorni nel 2020. Anche gli altri controlli sono stati posticipati, con un range tra 17 (microalbuminuria) e 27 (controllo della funzionalità renale) giorni. Nel sottogruppo di pazienti in trattamento, la proporzione media di pazienti coperti dal trattamento farmacologico antidiabetico si è ridotta dal 78% al 68%. Durante il lockdown, lo svolgimento delle raccomandazioni si è dimezzato, mentre è tornato ai livelli pre-covid da giugno in poi. Ad esempio, rispetto al periodo no covid, il rapporto tra i tassi di svolgimento dell'emoglobina glicata durante il lockdown e dopo il lockdown era di 0.45 (intervallo di confidenza al 95%, 0.41-0.50) e 0.95 (0.88-1.03), rispettivamente.

Le donne operate per tumore della mammella nel periodo maggio-giugno 2020 hanno sperimentato un ritardo nella tempestività dell'intervento chirurgico di 12 giorni rispetto a quanto osservato nel 2019. L'inizio della radioterapia complementare così come il controllo mammografico post-chirurgico hanno rispettivamente sperimentato un ritardo di 12 e 20 giorni durante il lockdown rispetto allo stesso periodo dell'anno precedente. Il monitoraggio ed il trattamento delle donne ha subito un ritardo durante il lockdown ma ha avuto una ripresa successivamente. Infatti, la tempestività dell'intervento chirurgico ha subito una riduzione del 24% (16-31%) durante il lockdown, ed una ripresa del 18% (10-25%) da giugno in poi.

CONCLUSIONI

Il progetto ha permesso di valutare il ritardo e la riduzione nell'accesso ai LEA durante lo shock epidemico nei pazienti affetti da diverse condizioni croniche. I risultati di questo progetto possono contribuire a programmare gli interventi atti a recuperare l'assistenza ritardata, prevedere gli esiti clinici che ci si aspetta aumentare a seguito del rilassamento delle cure e dei controlli, e allocare risorse al fine di gestire questi nuovi esiti.

Θ-SI(R)D: A NEW 6-COMPARTMENT MODEL FOR COVID-19 PANDEMIC

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Introduction

Many models of the current Covid-19 epidemic have been made in the recent past, mostly SIR and SEIR. We have already proposed a SI(R) model [1]. In this contribution, we propose a 6-compartment θ-SI(R)D model.

Objectives

The principal objective of the present study is to provide an epidemic model for Covid-19 that takes in account both the possibility of re-infection and the differentiation between asymptomatic and symptomatic infected subjects.

Materials and methods

The model, denoted as θ-SI(R)D, is a 6-compartment model, described by as many ordinary differential equations. The six compartments are represented by Susceptible (S), Symptomatic Infected (I_s), Asymptomatic Infected (I_a), Recovered from Asymptomatic fraction (R_a), Recovered from Symptomatic fraction (R_s), Deceased (D). The compartmental structure of the model is presented in Fig.1.

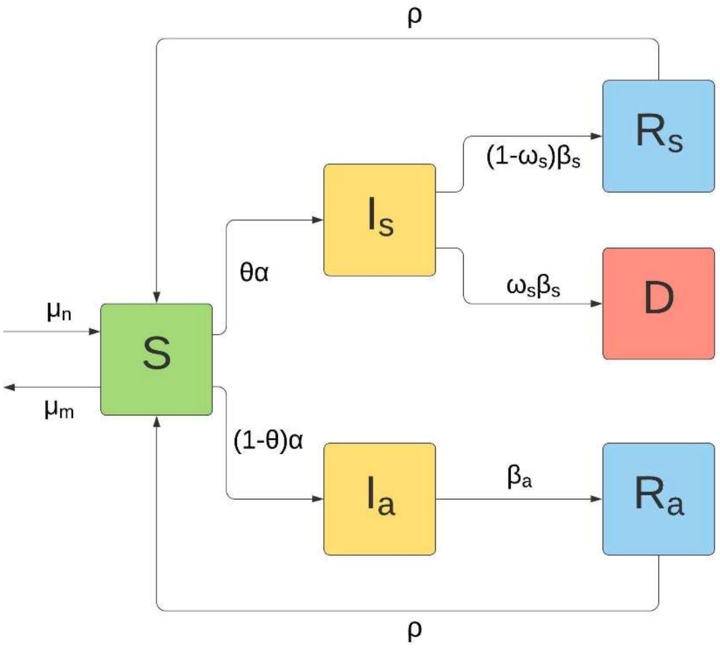

Fig.1: Compartmental structure of the model

The biological assumptions are as follows: (i) no entry or exit from the territory (closed territory); (ii) the contagiousness of the infected is immediate (therefore the compartment of the Exposed is not considered);

(iii) a loss of immunity is considered (in this version of the model it is considered at a constant rate); (iv) mortality and birth rate affect, as a first approximation, only the Susceptible compartment; (v) the Asymptomatic Infected compartment includes both the fraction identified by laboratory diagnostic evaluation and the unidentified one; (vi) there is no lethality in the Asymptomatic Infected fraction.
The model is the following

$$\begin{cases} \dfrac{dS}{dt} = \mu_n S - \mu_m S - \theta\alpha S I_s - (1-\theta)\alpha S I_a + \rho(R_a + R_s) \\ \dfrac{dI_a}{dt} = (1-\theta)\alpha S I_a - \beta_a I_a \\ \dfrac{dI_s}{dt} = \theta\alpha S I_s - \beta_s I_s \\ \dfrac{dR_a}{dt} = \beta_a I_a - \rho R_a \\ \dfrac{dR_s}{dt} = (1-\omega_s)\beta_s I_s - \rho R_s \\ \dfrac{dD}{dt} = \omega_s \beta_s I_s \end{cases}$$

Where: α is the disease contact rate; β_a, β_s are the transition rates ($I_a \rightarrow R_a$, $I_s \rightarrow R_s$, respectively); ρ is the rate of loss of immunization, ω_s is the fatality rate in I_s compartment; θ is the proportion of asymptomatic infected; μ_n is the natality rate; μ_m is the mortality rate.
Concerning the parameters, we assumed (taking them from biological literature and pandemic official data) the following values: α = 0.6, β_a = 0.143; β_s = 0.055, ρ = 0.003, μ_n=0.007, μ_m=0.011, θ=0.1, ω_s=0.14.

Results

From the above considerations, we have simulated (through MatLab) the evolution of pandemic through the model; it seems to converge towards a steady state.

Discussions and Conclusions

This model represents a new step towards the complete comprehension of Covid-19 pandemic evolution. However, given the low reliability of the epidemiological data provided by the Institutions, it is currently impossible to verify the validity of the model on real data, except for the deaths data. This fitting provided positive and encouraging indications. This model can be easily adapted to new acquisitions both on transmissibility parameters and on those concerning lethality and time of loss of immunity. Moreover, we plan to modify the model, taking into account the characteristics of the vaccinations currently used.

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Immunosuppressive therapy after solid organ transplantation in Italy: a pilot study of the CESIT project

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Introduction

Post-transplant immunosuppressive therapy represents the most effective strategy to ensure graft survival and prevent rejection. These interventions are commonly associated with multidrug approach involving medications with different mechanisms of action.[1] A pilot study was performed to explore immunosuppressant prescription patterns and trends in the last decade across different transplant settings in Lazio region. This analysis will be replicated in three other Italian regions (Veneto, Lombardy and Sardinia) involved in a multi-database network for post-marketing surveillance of immunosuppressive drugs in transplant patients (CESIT project).

Objectives

To describe immunosuppressive maintenance therapy for kidney, liver, and heart transplantation.

Methods

The present pilot study is a cornerstone to develop a multicentre retrospective observational study. The Lazio transplant cohort was based on the national Transplant Information System (SIT) and regional healthcare claims data. In particular, regional analytical dataset was created using an open-source tool for distributed analysis, "The ShinISS", that was customized for the purpose of the study. [2,3] To link SIT data to transplant cohort, a semi-deterministic record linkage procedure was performed within the tool.

Patients underwent to kidney, liver and hearth transplant for the first time in the years 2009-2019 were identified. On the basis of immunosuppressive treatment regimen prescribed in the first month after discharge, patients were defined in calcineurin inhibitor mono or multi-therapy: ciclosporin (CIC) or tacrolimus (TAC) based. In particular, the combination with an antimetabolite: [mycophenolate mofetil/mycophenolic acid (MMF) or azathioprine (AZA)] or an mTOR inhibitor [i.e. sirolimus, SIR or everolimus, EVE] as well as the use of steroids were investigated. Maintenance therapy was presented using sunburst chart [Figure 1].

Results

Overall, 2,017 transplant patients were identified: 61.7% in kidney (K), 32.7% liver (L), 5.6% hearth (H); the percentage of male were 61.6%, 76.8%, 64.6% respectively. Median age was 55 years for K-cases, 54 years for L-cases and 36 years for H-cases; in this last setting the low median age was due to the contribution of paediatric heart transplants.

In the first two settings, the most patients received TAC-based therapy (K: 75.6%; L: 92.6%) while patients with H-transplant received mainly CIC-based therapy (78.8%). The percentage of K and L patients treated with TAC-based therapy increased over time (K: 2009: 52.7% 2019: 94.4%; L: 2009: 84.9% 2019: 97.3%). The percentage of H-transplant patients treated with CIC remained stable (2009: 81.0% 2019: 83.3%).

The most frequent drug combination was calcineurin inhibitor plus MMF, observed in 65.9% of K-cases, 60.7% of L-cases, 63.7% of H-cases.

Among K-transplant patients, triple therapy including TAC, MMF and steroids was prescribed for 55.5 % of cases versus 51.0% in L-setting; while in H-setting triple therapy CIC-based was 49.6%.

Conclusions

In the study period, an increase of TAC-based therapy in K and L setting was observed; on the contrary, the most widely prescribed therapy for H transplants was based on CIC. For all settings, the most frequent drug combination was calcineurin inhibitor plus MMF, mostly associated with steroids. Further studies are necessary to explore maintenance therapy and its determinants in a larger multicentre sample.

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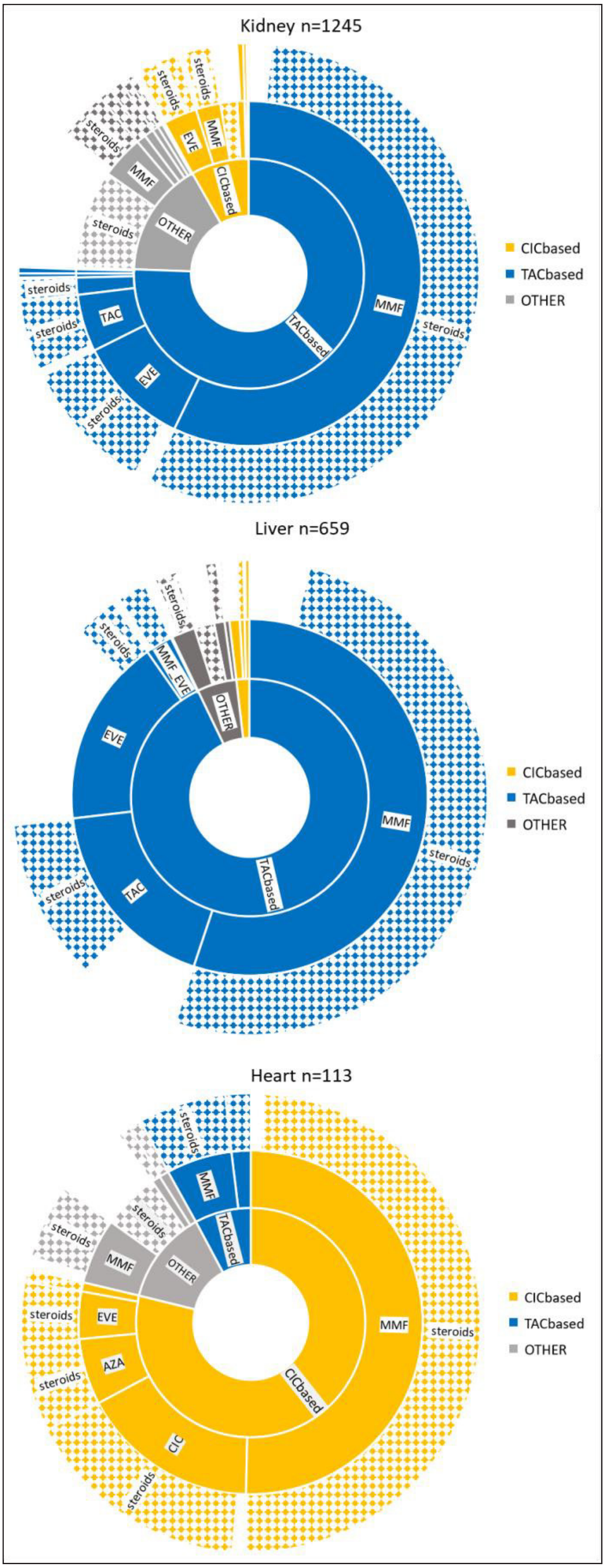
Figure1. Sunburst Chart. The inner circle (the CIC/TAC based therapy) is surrounded by rings of deeper hierarchy levels (multi-therapy: MMF, AZA, EVE, SIR, steroids).



STUDIO EPIDEMIOLOGICO IN UNA COORTE DI ADDETTI PRESSO CENTRALE NUCLEARE E.FERMI IN TRINO:MORTALITA' DAL 1974 AL 2019.

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INTRODUZIONE

Conoscere il territorio attraverso un'appropriata promozione d'indicatori dell'ambiente e della salute, diviene un requisito inderogabile per ogni comunità per tutelare la salute di tutti e per preservare le risorse ambientali esistenti: ciò può avvenire attraverso l'analisi dei diversi pressanti siti in Trino sia di natura ambientale sia occupazionale. (**1-3**)
Tra i vari siti produttivi costruiti negli anni 60 nel Comune di Trino , vi è certamente quello delle Centrale Elettronucleare E.Fermi entrata in funzione nel 1964 e chiusa alla fine degli anni 80 a seguito dell'esito referendario del 1987(**4**). Dai primi anni 2000 è in corso per tutti gli impianti nucleari italiani la fase di decomissing con relativo smantellamento e allontanamento del materiale radioattivo. (**5-7**)

METODI

Grazie alla collaborazione di SOGIN S.P.A. e dai dati raccolti da Osat (Osservatorio Ambientale Trinese) in questi anni, si sono estratte le informazioni occupazionali degli addetti presso la Centrale E.Fermi e seguiti in follow-up fino alla stesura della relazione qui presentata. Una piccola parte dei dati sono stati anche raccolti presso la Camera del Lavoro CGIL di Vercelli. (**8**)
L'SMR è stato ricavato impiegando i tassi specifici di mortalità per fasce di età quinquennali della Regione Piemonte dal 1980 al 2018; in particolare i tassi 80/81 sono stati estesi al periodo 78/79 anni del primo decesso osservato in centrale come pure i tassi del 2016/2018 sono stati applicati agli anni 2019/2020 sino al termine del follow up.
La conferma significativa è avvenuta tramite il calcolo degli intervalli di confidenza al 95% attraverso il metodo di Byar.
Come fonti dati si_sono adoperati i registri di mortalità creati da OSAT grazie ai differenti flussi dati adoperati quali i certificati di morte di coloro che sono deceduti in Trino, dati di mortalità ISTAT e i questionari epidemiologici raccolti in maniera pressochè continuativa presso il comune di Trino.

RISULTATI

La coorte risulta costituita da 319 addetti di cui 288 uomini e 31 donne con il maggior numero di soggetti collocati nelle fasce 65-69 anni (61 soggetti) , 70-74 (45 addetti) e 60-64 (41 soggetti) Ovviamente si tratta di soggetti, limitatamente a questi gruppi di età, in follow-up con cessazione dell'attività lavorativa all'interno del sito produttivo.

RISCHI DI MORTALITA' (SMR) E I.C. 95% PER COMPARTO E PRINCIPALI CAUSE DI DECESSO-**						
COMPARTO	**Totale cause**	**Totale tumori**	**T.Polmone**	**Tot. T. App.digere.**	**Mesotelioma**	**Cardiovascolare**
MANUTENZIONE	0,82	**1,87****	1,69	1,69	**30,0** (3oss)**	0,34
FISICA-CHIMICA	0,79	1 SOLO CASO	N.C.	N.C.	N.C.	N.C.
DIRIGENZA	NESSUN DECESSO	-	-	-	-	-
PORTIERE/AUTISTA/FATTOR.	**2,40****	1,68	2,15	**4,28****	N.C.	1,10
ESTERNO	1 SOLO DECESSO	1 SOLO CASO	N.C.	NC.	N.C.	N.C.
PROGRAMMAZ.SICUREZZA	1 SOLO DECESSO	N.C.	N.C.	N.C.	N.C.	1 SOLO CASO
UNITA TECNICA	1,19	N.C.	N.C.	N.C.	**200,0** (2oss)**	N.C.
REATTORE	0,34	N.C.	N.C.	N.C.	N.C.	0,55
PERSONALE	0,84	1,21	N.C.	1 SOLO CASO	1 SOLO CASO	0,82

I rischi di mortalità per settori (vedi tabella) evidenziano due comparti con le maggiori criticità: il reparto manutentivo con eccessi statisticamente significativi dell'87% per le totali neoplasie e mesotelioma (eccesso 30 volte superiore rispetto all'atteso con 3 osservazioni). Meritevoli d'attenzione gli eccessi senza conferma statistica per neoplasie del polmone (organo potenzialmente sensibile alle radiazioni) e totale apparato digerente.
A seguire il settore portineria/autista e fattorino con rischi più che doppi e significativi per la mortalità totale e l'insieme delle neoplasie dell'apparato digerente.
Incrementi senza significatività statistica per totale neoplasie e tumori del polmone.
Infine si segnala un eccesso sensibilmente alto rispetto all'atteso per mesotelioma negli addetti dell'unità tecnica; un incremento non statisticamente significativo (4 decessi) del 21% per totale neoplasie tra il personale amministrativo.

CONCLUSIONI

Per la prima volta in Italia si è condotta un'indagine epidemiologica su addetti (ed ex) impiegati in una delle quattro ex centrali nucleari attive sul territorio nazionale dalla fine degli anni 50 al 1987. (**11-13**)
La situazione sanitaria da questo iniziale studio preliminare risulta essere soddisfacente nei dati complessivi della coorte con un solo eccesso statisticamente significativo per mesotelioma e valori protettivi per il totale cause e apparato cardiovascolare**.**
Questi primi risultati confermano con dati scientifici quello che già si era osservato negli anni passati con diversi decessi per patologia amianto correlata perciò dovuta ad un'esposizione occupazionale a tale fibra di una parte degli addetti. (**14-15**)
La successiva divisione per comparti ha permesso d'indentificare e confermare che gli occupati del reparto manutentivo e dell'unità tecnica erano, proprio per la tipologia di lavoro svolto, i più esposti al materiale amiantifero rispetto ai colleghi impiegati in altri settori. Inoltre è verosimile che l'esposizione all'amianto per il comparto manutentivo possa aver inciso anche nell'insorgenza di altre forme tumorali.

La ricerca qui presentata, è caratterizzata da diversi limiti quali ad esempio l'assenza del controllo dei confondenti individuali (fumo, alcool, alimentazione), eventuali esposizioni ad altre occupazioni precedenti e la non conoscenza dei valori di esposizione durante l'attività lavorativa a possibile fonti radioattive. Inoltre per eseguire modelli di analisi più complessi e raffinati sarebbe stato utile disporre della durata del periodo trascorso all'interno della centrale per ogni addetto per permettere un'analisi del rischio stratificata per durata anni –lavoro

In conclusione crediamo che tale indagine, seppur con i diversi limiti qui elencati, possa contribuire a comprendere al meglio come si è sviluppato il nucleare in Italia e i suoi effetti/conseguenze eventuali non solo a livello ambientale ma anche per coloro che ci hanno lavorato/lavorano quotidianamente

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COMPARING MEDICATION PERSISTENCE AMONG PATIENTS WITH TYPE 2 DIABETES USING SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS OR GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS IN REAL-WORLD SETTING

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Introduction

Because of its high and growing prevalence [1], and the associated macro- and micro-vascular complications and mortality, diabetes is a major public health issue worldwide [2].

Although metformin was the recommended first-line drug treatment, patients often require multiple antidiabetic agents to achieve and maintain glycaemic control [3]. Recently, randomized controlled trials showed that some classes of antidiabetic drugs, i.e., glucagon-like peptide-1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2-I), are able to reduce the incidence of cardiovascular (CV) events among patients with type 2 diabetes [4-6]. As such, recent guidelines recommend them as the preferential add-on therapy to metformin in patients with or at high risk for CV events [7] or the first-choice treatment in patients naïve to the treatment with metformin [8]. However, low adherence because of side effects could potentially affect their protective action in routine clinical practice, with significant clinical and public health implications [9,10].

To address the gap in knowledge, a very large investigation in the real-world setting of the Italian Lombardy Region was carried out.

Aim

To assess and compare the persistence with drug therapy between patients treated with GLP1-RA and SGLT2-I therapy in a large cohort of patients with type 2 diabetes.

Methods

The 126,493 residents of the Lombardy Region (Italy) aged ≥40 years newly treated with metformin during 2007-2015 were followed until 2017 to identify those who started therapy with GLP1-RA or SGLT2-I. 1-year persistence was measured as days of continuous therapy with no gaps >60 days between consecutive refilled prescriptions. Two outcomes were considered: discontinuation from antidiabetic drug of interest (GLP1-RA or SGLT2-I) and from any antidiabetic drug therapy. To make GLP1-RA and SGLT2-I users more comparable, a 1:1 matched cohort design was adopted. Matching variables were sex, age, and adherence to the first-line therapy with metformin.

Log-binomial regression models were fitted to estimate the propensity to 1-year treatment persistence in relation to the therapeutic strategy. Adjustments were made for baseline covariates, such as comorbidities and co-treatments. The association of interest was also assessed after patient stratification for gender and age and cardiovascular disease. In addition, GLP1-RA users were stratified according to the treatment regimen, i.e., once-weekly vs. once-daily regimens.

Two sensitivity analyses were performed. First, to avoid the arbitrary nature of the threshold used to assess treatment persistence (i.e., 60 days), in a secondary analysis we used more permissive (90 days) and more restrictive (30 days) thresholds to define drug discontinuation. Second, to account for the possible difference in the clinical status and other characteristics between patients on GLP1-RA and SGLT2-I, data were also analysed according to the high-dimensional propensity score matching approach [11].

Results

The final matched cohort was composed by 1,276 GLP1-RA─SGLT2-I pairs. About 24% (307 patients) and 29% (368 patients) of cohort members respectively on GLP1-RA and SGLT2-I discontinued initial antidiabetic drug during the first year after the index date. As shown in **Figure 1**, compared with patients starting on SGLT2-I, those on GLP1-RA had 15% (95% CI, 3% to 25%) lower risk of discontinuation of the treatment. This was also the case in female patients and for patients younger than 65 years, and irrespectively of the presence of cardiovascular disease. Stratified analyses for the treatment regimen showed that, compared with patients starting on SGLT2-I, the risk of discontinuation was lower among GLP1-RA users who received a once-weekly administration (RR: 0.72, 95% CI: 0.54-0.96) but not among those on a daily administration (RR: 0.90, 95% CI: 0.76-1.06).

About 6.2% (79 patients) and 12.5% (160 patients) of cohort members respectively on GLP1-RA and SGLT2-I interrupted any antidiabetic drug therapy during the first year after the index date. Compared with patients starting on SGLT2-I, those on GLP1-RA had 45% (95% CI, 28% to 57%) lower risk of discontinuing antidiabetic drug therapy. Persistence was better in patients on GLP1-RA in each stratum of age, sex, and cardiovascular disease. Finally, there was evidence that the risk of discontinuation was lower among GLP1-RA users who received a once-weekly administration (RR: 0.31, 95% CI: 0.22-0.47), whereas there was no difference between those on a GLP1-RA daily administration and patients on SGLT2-I (RR: 0.80, 95% CI: 0.55-1.14).

The main findings did not change substantially by modifying the threshold used to define treatment discontinuation and adopting the high-dimensional propensity score algorithm.

Conclusions

In conclusion, our observational investigation confirms that persistence to GLP1-RA and even more to SGLT2-I is suboptimal in clinical practice. Understanding the reasons underlying this issue will likely help to develop interventions aimed to improve the management of the disease. These efforts would most likely substantially reduce long-term outcomes, healthcare resource utilization and costs.

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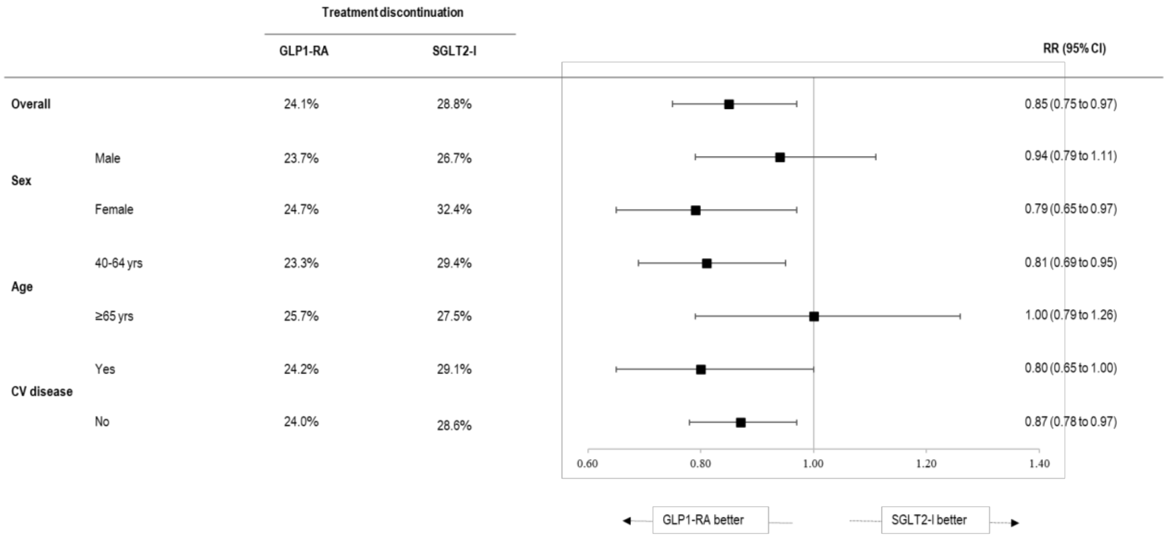
Figure 1. Adjusted risk ratio (RR), and 95% confidence intervals (CI), of treatment discontinuation with the drug started at the index date (i.e., GLP1-RA or SGLT2-I) in the whole cohort and according to sex, age and cardiovascular (CV) disease.



Durata della ventilazione non invasiva somministrata come pressione positiva continua delle vie aeree e rischio di decesso in pazienti ricoverati per COVID-19 che hanno rischiesto una successiva intubazione endotracheale

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Introduzione

Il Piemonte è stata una delle regioni italiane più colpite dalla pandemia di coronavirus 2019 (COVID-19). A causa dell'eccezionale richiesta di risorse per le unità di terapia intensiva, gli ospedali hanno aumentato il numero di posti letto in terapia intensiva e hanno convertito molti reparti generali in unità di cure intermedie respiratorie per il trattamento di pazienti con polmonite grave e insufficienza resporatoria acuta (ARF) che necessitano di supporto e monitoraggio respiratorio continuativo [1]. La ventilazione non invasiva (NIV) frequentemente somministrata come pressione positiva continua delle vie aeree (CPAP) è stata considerata come supporto di prima linea per i pazienti che necessitavamo della ventilazione [2] in quanto può essere effettuata in reparti diversi dalla terapia intensiva [3] ed è una tecnica meno invasiva dell'intubazione endotracheale che è stata utilizzata in caso di aggravamento delle condizioni respiratorie dei pazienti. Tra coloro che sono stati intubati, è di interesse valutare l'impatto della durata della NIV, considerata come un ritardo nell'intubazione, sulla mortalità.

Obiettivi

Valutazione dell'effetto della durata del trattamento con CPAP sul rischio di morte in pazienti affetti da COVID-19 che sono stati successivamente intubati.

Metodi

I dati utilizzati per questo studio provengono da uno studio osservazionale multicentrico retrospettivo condotto in sei ospedali del Piemonte Orientale Italia (Novara, Vercelli, Alessandria, Borgomanero, Domodossola e Biella) che aveva come obiettivo principale quello di descrivere le caratteristiche cliniche dei pazienti con COVID-19, confermato in laboratorio, trattati con CPAP al di fuori della terapia intensiva, per valutare la mortalità intraospedaliera a 60 giorni e la durata della degenza ospedaliera. Tutti i pazienti ricoverati in uno degli ospedali partecipanti tra l' 1 marzo e il 15 aprile 2020 con ARF ipossiemica secondaria a SARS-CoV-2 confermato sono stati inclusi nello studio. I criteri di inclusione erano: 1) età ≥18 anni, 2) distress respiratorio e pressione parziale di ossigeno arterioso per frazione del rapporto di ossigeno inspirato < 200 mmHg durante l'ossigenoterapia con maschera Venturi, 3) inizio della CPAP al di fuori della terapia intensiva. I pazienti sottoposti a CPAP post-estubazione sono stati esclusi. I pazienti sono stati seguiti dalla data di ricovero fino alla prima data tra decesso e dimissione in vita o termine del follow-up (15 Maggio 2020). Per tutti i pazienti inclusi nello studio sono state rilevate: i) le caratteristiche demografiche, ii) l'indice di massa corporea, iii) l'indice di comorbidità di Charlson (CCI), iv) i risultati degli esami ematologici eseguiti al momento del ricovero e v) dell'emogasanalisi arteriosa ottenuti prima dell'inizio della CPAP e da 2 a 24 ore dopo e vi) le comorbidità concomitanti. Sono state inoltre valutate la durata dell'uso della CPAP, la durata della degenza ospedaliera e l'intubazione.

Statistiche descrittive sono state utilizzate per sintetizzare le principali caratteristiche demografiche e cliniche dei pazienti inclusi nello studio. Modelli multivariabili di Fine e Gray sono stati utilizzati per stimare i subdistribution hazard ratio (sHR) e i corrispondenti intervalli di confidenza al 95% (95% CI) per l'associazione tra durata della CPAP e il rischio di morte nei pazienti intubati, considerando la dimissione come evento competitivo. Per l'analisi il follow-up dei soggetti iniziava alla data dell'intubazione. Il modello multivariabile includeva come variabili di aggiustamento età, sesso, l'indice di comorbidità Charlson e ipertensione, lattato deidrogenasi (LDH), livelli di proteina C-reattiva e conta dei linfociti e centro. Le variabili di aggiustamento sono state selezionate in base alla loro rilevanza clinica. L'analisi principale è stata effettuata sui soli soggetti con dati complete mentre un'analisi secondaria è stata effettuata utilizzando la multiple imputation per valutare l'impatto dei valori mancanti sulle stime dell'associazione calcolate nell'analisi principale.

Risultati

2845 pazienti sono stati ricoverati tra l'1/3/2020 e il 15/4/2020. Di questi 537 sono stati trattati con CPAP al di fuori della terapia intensiva e 180 sono stati successivamente intubati. L'81% dei pazienti intubati era maschio e l'età mediana era pari a 68 anni. Il modello, aggiustato per età, sesso, CCI, LDH, valori della proteina C-reattiva e conta dei linfociti, indica un aumento del 9,4% (sHR 1,094, 95% CI 1,010-1,184) del rischio di morte all'aumentare unitario dei giorni di trattamento con CPAP. L'associazione tra durata della CPAP e mortalità non cambia sostanzialmente nell'analisi secondaria utilizzando l'imputazione multipla.

Conclusioni

Si conferma che il ritardo nell'intubazione è un fattore di rischio per la mortalità. Sono necessari ulteriori studi per accertare il potenziale rischio infettivo correlato al trattamento con CPAP al di fuori della terapia intensiva tra gli operatori sanitari.

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Monitoring the incidence of COVID19 in the Metropolitan City of Naples

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Introduction

The COVID19 epidemic evolution has been extensively evaluated at national and regional level, but little has been studied and presented at local level, intended as large municipalities (metropolitan cities).

Aim

To monitor the incidence of COVID19, by age group and District/Municipality, in the Metropolitan City of Naples.

Methods

At the request of the City of Naples, a Task Force was set up to monitor the epidemiological trends of COVID19. The data were provided by ASL NA1 (about 1 million inhabitants). For each incident case of COVID19, information was collected on gender, age, address of residence, presence of symptoms, admission to hospital and/or intensive care, and date of death. The address of residence was used to geocoding the case and assign the neighbourhood/municipality to which it belonged. Weekly incidence rates per 100,000 inhabitants were calculated and further characterised by neighbourhood/municipality and age group. A comparison of incidence and mortality between the Municipality of Naples and the Campania Region (Campania Civil Protection data) was also carried out using time series graphs with a 7-day moving average.

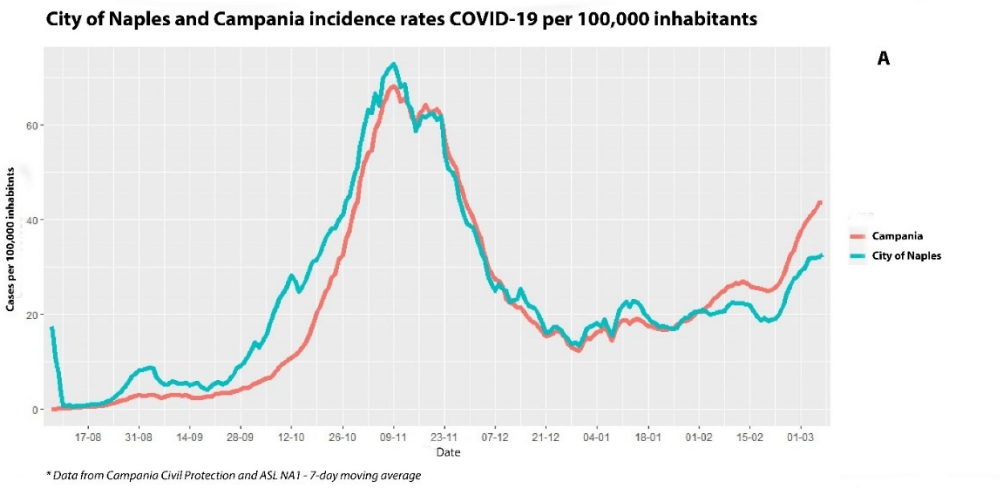
Results

The analysis of the epidemiological trend of the second wave starts from 1 August 2020. As of 7 March 2021, the date of the last update, the total number of COVID19 infections in the city of Naples was 49,323, while the number of cases diagnosed in 2021 was 14,053. The evaluation of incidence rates showed significant differences in the epidemiological trend by age group and neighbourhood/municipality. The comparison between the City of Naples and Campania showed, especially in the first part of the second wave, a higher incidence of COVID19 in the City of Naples (**Figure 1A**), while in the last period it is the Campania Region that presents higher incidence values. The comparison of COVID19 mortality rates showed during the second wave a significantly higher mortality in Naples than in Campania (in some periods more than double), with a greater difference than expected due to the difference observed in the comparison of the incidence of cases (**Figure 1B**). Higher mortality in Naples is also observed in the current period. A short report was published weekly (monthly with information on Neighbourhood/Municipality) on the Naples Municipality website www.comune.napoli.it/emergenza-covid19.

Conclusions

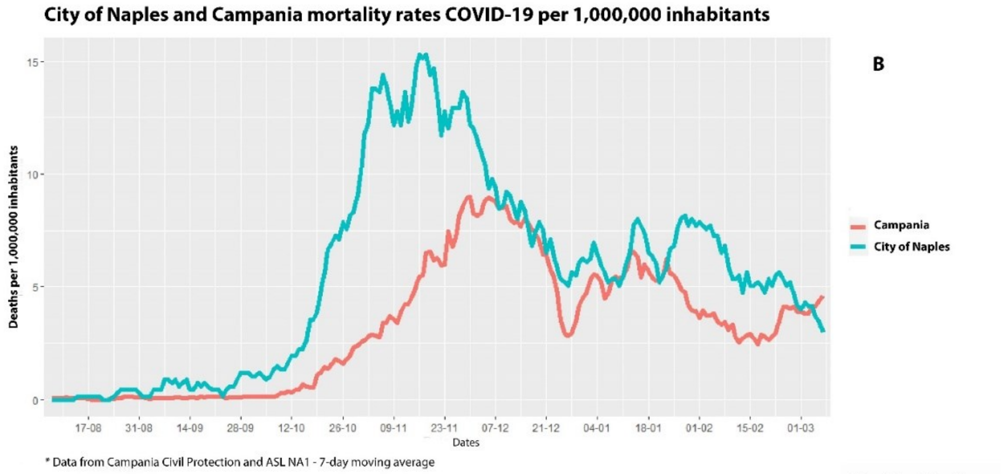
The monitoring and the published reports allowed the Municipality of Naples and the Presidents of the 10 Municipalities to have detailed information on the population groups most involved in the spread of the infection and to contribute to a better management of the epidemic.

Figure 1 - COVID19 epidemic evolution: comparison between the City of Naples and Campania Region



City of Naples and Campania incidence rates COVID-19 per 100,000 inhabitants

* Data from Campania Civil Protection and ASL NA1 - 7-day moving average



City of Naples and Campania mortality rates COVID-19 per 1,000,000 inhabitants

* Data from Campania Civil Protection and ASL NA1 - 7-day moving average

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A HEALTHY HUMAN “SCAFFOLD” OF ITALIAN ADULTS’ MICROBIOTA: A PROPOSAL FOR REFERENCE INTERVALS

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Introduction: Several factors, from genetic background, age, lifestyle, dietary habits to local environments, contribute to microbiota heterogeneity in humans. Understanding the variability of the "healthy microbiome" is a major challenge in microbiome research. Recent studies underlined the emerging differences in microbiota composition even in population cohorts with a similar genetic and cultural background. Scientists are focusing their attention on how to manipulate microbiota to improve health status; however, the scientific community also agrees on studying the factors constituting the normal ranges of these features in healthy populations as a first step. Previously, some papers have been published about microbiota composition of Italians in specific diseases, or as a changing ecosystem, just a few data were reported about microbiota of healthy population.

Objective: This study aimed to define the reference intervals of the gut microbiota of a healthy Italian people sample with relatively homogeneous physiological features.

Methods: 148 healthy control subjects of seventeen Italian regions, with a gender ratio of 69 male / 79 female and an age ranging from 23 to 57 years, were recruited by the medical board constituting part of the authors of this work, in different Italian university sites. A questionnaire has been administered to each participant to collect information regarding the demographic and anthropometric variables, dietary habits and physical activity. For 16SrDNA sequencing, the total microbial DNA of the samples was extracted. After assessing DNA concentration and purity, samples were stored at -80° until processing. K means clustering was performed; Elbow and Silhouette methods were used for determining the optimal cluster numbers. PERMANOVA was performed on the Bray-Curtis distance matrix to assess if the gut microbiota structure differed between the two clusters, considering phyla, families and genera. To calculate the reference intervals related to phyla, families and genera, a non-parametric method was used. The 90% confidence intervals relative to the 95% lower and upper limits of the reference intervals have been calculated using the bootstrap method, according to the NCCLS Guidance Document C28A2.

Results: The analysis performed using Elbow and Silhouette methods showed that the best clustering solution was the one with two clusters of subjects; both methods showed the same results. The two different clusters are clearly defined; Cluster 1 (C_1) assembles 108 subjects, while Cluster 2 (C_2) includes 40 subjects. Differences in phyla (F = 106.89), families (F = 16.67) and genera (F = 13.98) among the two clusters were observed (PERMANOVA, Bray–Curtis dissimilarity index, Bonferroni corrected; $p < 0.001$ for all comparison). Heatmap was used to represent the abundance of the nine more prevalent phyla. *Firmicutes* and *Bacteroidetes* reached together about 85% of the total phyla abundance. The division between the two clusters can be easily noticed: C_1 (Figure 1, right) and C_2 (Figure 1, left). *Bacteroidetes* were prevalent in C_2, while in C_1, *Bacteroidetes* and *Firmicutes* have a similar abundance. Mean, upper and lower limits of 95% reference intervals are calculated for phyla, families and genera with abundance > 0.1% for each clusters' abundance.

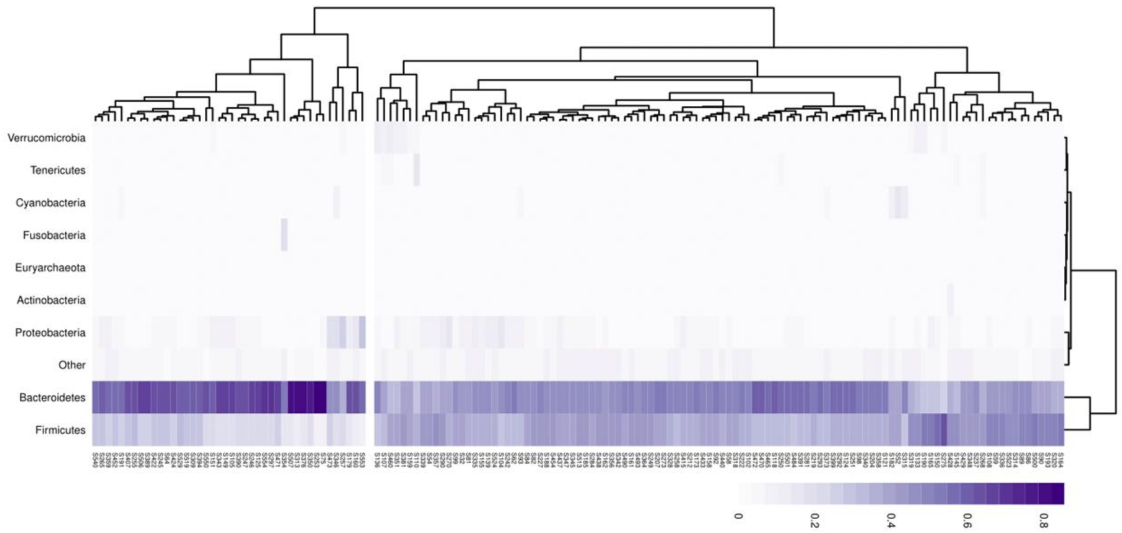

Figure 1. Heatmap of the most represented 9 phyla. Each row represents a single phylum, with each column representing a different subject. Bray-Curtis distance has been used as a clustering method. Two different clusters of subjects have been selected as the best solution.

Conclusions: Our study may contribute to primarily identify the existence, within the healthy Italian population, of a commonly distributed, constantly present, main microbiological pattern, thus suggesting the presence of a short of a microbiological scaffold. Taken together, our data highlights the significance of studies on population-specific variations in human microbiota composition. Nevertheless, at the same time, it can be highlighted here how the variability studies must be able to take into account even minimal variations in the intestinal microbiological population, given that, at least in the healthy population, there is a significant and reproducible presence of well-defined groups of bacteria.

Meta-analysis of association between visit-to-visit blood pressure variability and death: a linear relationship?

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Introduction

While the association between mean levels of blood pressure (BP) and the risk of mortality is well known, in the last decades many studies suggested that visit-to-visit BP variability (BPV) may significantly improve the prediction of all cause and cardiovascular mortality. It should be noticed, however, that the available studies are characterized by large heterogeneity in their design (e.g. cross sectional vs. prospective cohorts, population based vs. clinical trial), low standardization in terms of BP measurements (e.g. differences in intervals between measurements, number of measures) and by different statistical approaches to data analysis (e.g. choice of BPV category, adjustment for mean BP level). This limits the possibility of meaningful comparison among their results, the applicability of visit-to-visit BPV in clinical practice and the definition of the type of association (e.g. linear or non linear) linking BPV with prognostic outcomes. Moreover, because of such heterogeneity, no agreement has been reached on the existence of a BPV threshold above which this phenomenon could be defined as dangerous.

Aim

The main purpose of this meta-analysis was to investigate the linear or non-linear nature of the BPV-outcome relationship and to explore the existence of threshold values for visit-to-visit BPV, above which this phenomenon could be responsible for cardiovascular damage

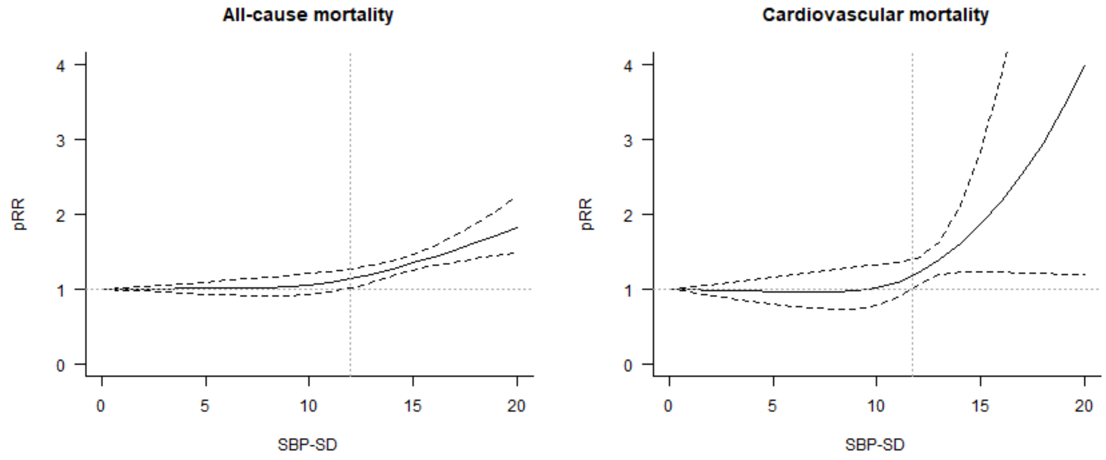
Methods

A Medline search was performed up to 21 April 2021 to identify all studies reporting the association between BPV and risk of death. Studies were included in the meta-analyses if: i) post-hoc analyses of randomized controlled trials (RCT) or original observational studies, ii) considered as exposure visit to visit systolic (SBPV) or diastolic (DBPV) blood pressure variability expressed in mmHg and categorized in at least three levels of at least one of the following BPV indices (Standard deviation (SD), Average Real Variability (ARV), Coefficient of variation (CV), Residual, Variability independent of the mean (VIM)), iii) evaluated mortality outcomes (all-cause mortality, cardiovascular mortality, fatal/non-fatal specific cardiovascular events), iv) reported the association measurements between exposure and outcome (i.e. relative risk (RR), odds ratio (OR), hazard ratio (HR)) and the corresponding 95% confidence intervals or data allowing the estimation of standard error of association measurement. Studies were excluded from the analyses if the study's sample included patients affected by acute cardiovascular disease or stage 5 chronic kidney disease because these conditions could affect themselves variation in blood pressure levels. Selected papers were analysed separately for type of blood pressure, BPV index and outcome to assess heterogeneity. To address the problem of functional relationship between BPV index and risk of death, we considered only papers reporting associations relative to a given BPV index categorized in two or more levels and transformed on log-scale. Following the approach by Orsini et al, restricted cubic spline random effects meta-regression models were applied with knots at 5th, 50th and 95th percentile of the BPV index distribution [2]. Correlation between estimates belonging to the same study was taken into account using the Greenland and Longnecker approach [3]. The analyses were performed when at least 3 studies exploring the association of interest were available.

Results

Bibliography search identified 4268 studies, 44 of them were included. 18 studies reported the association between categorized BPV index and outcome, as well as the extreme and mean value of each category and the corresponding number of events. Only for SBPV SD index there were sufficient data to perform the analysis. The figure shows a non-linear functional relationship of SBPV SD with all-cause mortality and cardiovascular mortality. We could also define specific SBPV SD thresholds above which the risk of these outcomes becomes statistically significant (12.0 and 11.8 mmHg, respectively).

Figure Non-linear relationship between SBPV SD and all-cause mortality and cardiovascular mortality



Conclusions

Our results show a non-linear relationship between BPV and death and indicate a value of SBPV SD around 12 mmHg as the threshold above which visit-to-visit SBPV may increase the risk of mortality. Our findings, derived from heterogeneous studies in term of type of population and number of BPV measurements, would need to be confirmed by additional evidences.

WHAT IS NEW ABOUT EXTENSION OF LYMPHADENECTOMY FOR GASTRIC CANCER? A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: The most appropriate extension of lymphadenectomy has been a hot topic for several decades. In the Nineties, two randomized clinical trials, performed in the UK and the Netherlands, found no survival advantage after extended (D2) lymphadenectomy with respect to limited (D1) lymphadenectomy. D2, on the other hand, was burdened by a very high post-operative mortality. However, eastern surgeons, as well as the Italian Research Group for Gastric Cancer (GIRCG) [1], supported routine use of D2 lymphadenectomy. The latter view was progressively adopted by most international and national guidelines [1-5]. Only the National Comprehensive Cancer Network guidelines, produced in the US, just mention three different types of lymphadenectomies (D0 (very limited), D1, D2), with the only recommendation to remove at least 15 lymph nodes.

Aim: To update current evidence on extension of lymphadenectomy and the most recommended lymphadenectomy according to international guidelines.

Methods: A systematic review was carried out on Web of Science database and meta-analyses were separately performed on RCTs. Research included publications 2010 to 2021 and combined the following Medical Subject Headings (MeSH) terms: "Lymphadenectomy and gastric cancer and RCT" or "Lymphadenectomy and gastric cancer and guidelines". Meta-analysis of overall survival and recurrence-related survival was also performed.

Results: In the last ten years, no new RCT comparing D1 and D2 was found. Only two articles reported the late results of a Dutch [6] and Italian [7] trials. No difference emerged between D1 and D2 treatments as regards overall survival (OS) (RR of D2 vs D1=0.98, 95% CI 0.82-1.16; p=0.808) while D2 treatment was significantly favored as regards recurrence-related survival (RR=0.81, 95% CI 0.69-0.95; p=0.008) (Figure 1.), i.e. when neglecting postoperative mortality and other causes of death. Interestingly the Italian trial found that OS and Disease-Specific Survival (DSS) was better after D1 in elderly patients and in early stages, while DSS was better after D2 in advance stages (pT>1 N+).

Conclusions: New RCTs comparing D1 or D2 were lacking during the observation period, and this likely reflects the absence of equipoise concerning the two procedures according to most international guidelines (ESSO-ESMO-ESTRO) [4]. Only 15-year results of previously performed trials were published as an update, and they support an advantage of D2 over D1 if performed with no or minimal postoperative mortality. In addition, the need to tailor treatment to patient and tumor's characteristics emerged. The scientific surgical community is moving from an Eastern-Western confrontation about D1/D2 to a more sensible tailored approach.

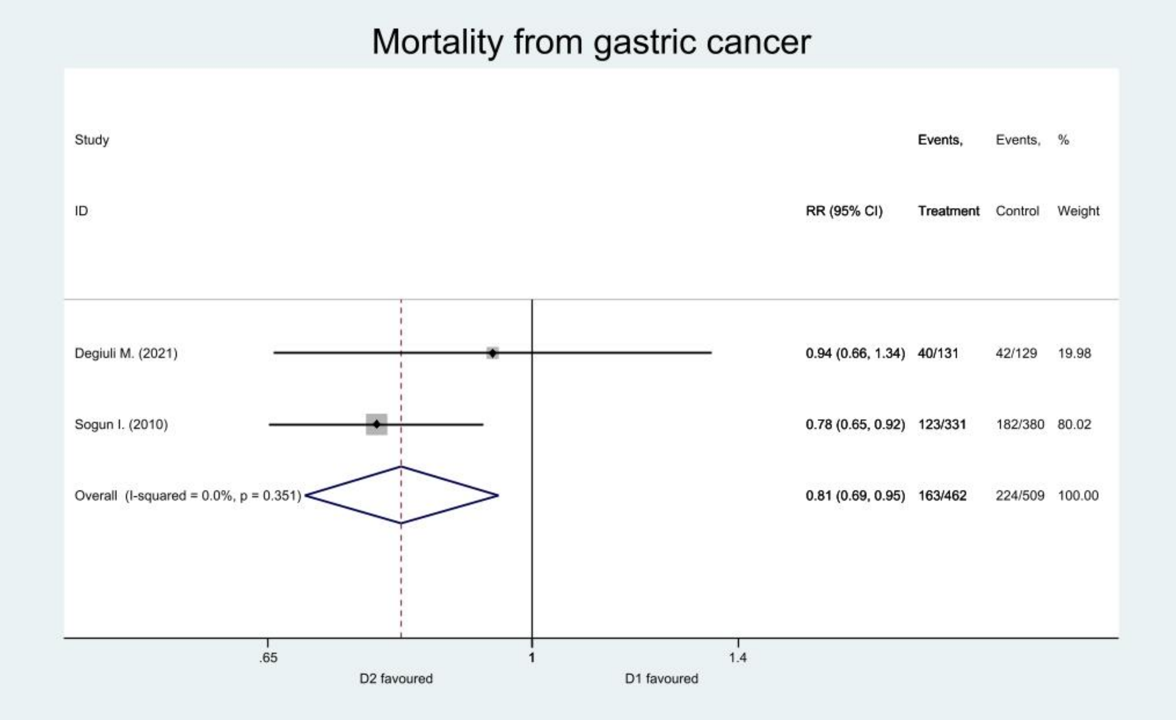

Figure 1.

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POSTER

METODI BIOSTATISTICI

CHAID analysis and Logistic Regression for identification of predictive scores in Post-Covid-19 Syndrome

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Introduction

From the beginning of the SARS-CoV-*2* pandemic, descriptions of the symptomology and underlying mechanisms have been focused on acute Coronavirus Disease 2019 (COVID-19) and short-term outcomes. However, the so-called "post-COVID-19 syndrome" or "chronic COVID-19 syndrome", describing the experience of persistent symptoms after recovering from the initial acute COVID-19, has recently attracted attention [1]. Main interest of current research is to assess factors associated with this syndrome some months after the onset.

The aim of this work is to compare two scores created for predicting the presence of symptoms after six months from recovery. The first score is created using a model of multivariable logistic regression, while for the second one the chi-squared automatic interaction detection (CHAID) analysis method is used [2]. CHAID is a decision tree technique, based on adjusted significance testing (Bonferroni testing), that divides a data set in segments that differ with respect to the response variable. This algorithm offers an alternative method from the classical one, being able to create scores considering interactions between variables.

Aim

Create and compare the performance of two scores predicting the presence of symptoms six months after the recovery from COVID-19, applying multivariable logistic regression and CHAID analysis.

Methods

The analysis includes 599 in- and out-patients (≥ 18 years) attending the Infectious Disease Department with a diagnosis of COVID-19 from 1 March to 30 May 2020. Their demographic, clinical and laboratory information were collected. Six months after acute disease onset, between September and November 2020, patients were telephone interviewed by trained nurses about specific persistent or emerging symptoms potentially associated with COVID-19. Factors included in the analysis were: sex (0 male, 1 female), group of age (18-40, 41-60, >60), number of symptoms during acute onset disease (0 or 1, 2, 3, 4, ≥ 5), management of the patient (outpatients, hospital-ward and intensive care unit). The first score was created using a multivariable logistic regression model and the estimated odds ratios led to the assignment of different weights depending on the variables considered. The second score was created using CHAID analysis, using the same variables considered in the logistic model.

The performance of these two models has been evaluated using the index AUC (area under the curve), presented with its 95% confidence interval and obtained through ROC analysis.

Results

The logistic univariable analysis has highlighted that the following variables are significantly associated with post-Covid-19 syndrome: sex (OR 1.55, 95% CI 1.05-2.27); number of symptoms during acute onset disease: 2 *vs.* 0 or 1 (OR 2.41, 95% CI 1.32-4.39), 3 *vs.* 0 or 1 (OR 5.79, 95% CI 3.23-10.38), 4 *vs.* 0 or 1 (OR 8.05, 95% CI 4.34-14.93), ≥ 5 *vs.* 0 or 1 (OR 11.85, 95% CI 6.58-21.36); intensive care unit *vs.* hospital-ward (OR 1.91, 95% CI 1.21-3.04). Based on these results, each significant predictor was weighted according to the odds ratio: female sex (1 point); 2 symptoms during acute phase (1 point), 3 (2 points), 4 (3 points), at least 5 (4 points); patient in hospital-ward (1 point), patient in intensive care unit (2 points). Consequently, a score ranging from 0 to 7 was assigned to each patient. On the other hand CHAID analysis led instead to the creation of 4 groups, due mainly to the number of symptoms in the acute phase.
The first score reported an AUC of 0.762 (95% CI 0.725-0.800), while the second score 0.741 (95% CI 0.703-0.779). However, the two areas resulted to be significantly different (p=0.014), which is probably due the size of the sample.

Conclusion

CHAID procedure could represent an optimal method to create predictive scores, even if it has some limitations due to the fact that the variables considered in the analysis have to be categorical.
In this peculiar population, CHAID analysis and logistic model showed a similar predictive performance, easy use in clinical practice should guide the final score selection.

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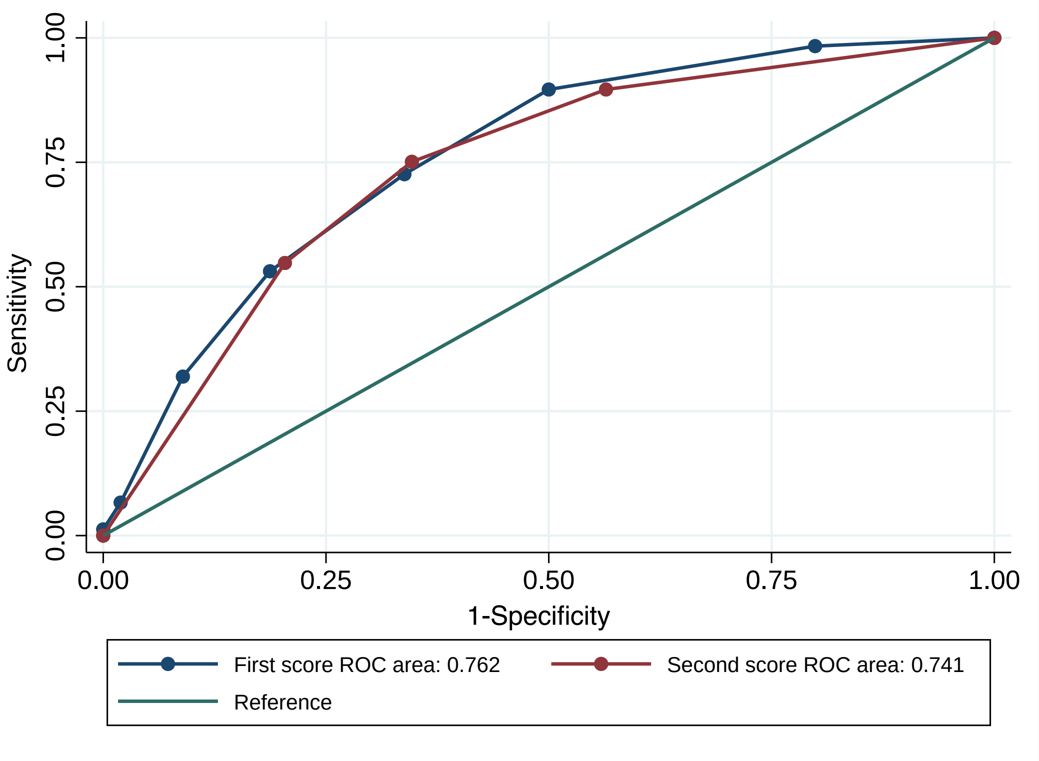

Figure 1: ROC curves referred to the two methods

Environmental Asbestos Exposure and Clustering of Malignant Mesothelioma in Community: a Spatial Analysis in a Population-Based Case-Control Study.

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Background

Neighborhood exposure to asbestos increases the risk of developing malignant mesothelioma (MM) in residents who live near asbestos mines and asbestos product plants. The area of Casale Monferrato (Northwest Italy) was interested by several sources of asbestos environmental pollution, due to the presence of the largest Italian asbestos cement (AC) plant.

Aims

In the present study, we examined the spatial variation of MM risk in an area with high levels of asbestos pollution and secondly, and we explored the pattern of clustering.

Methods

A population-based case–control study conducted between 2001 and 2006 included 200 cases and 348 controls. Demographic and occupational data along with residential information were recorded. Bivariate Kernel density estimation was used to map spatial variation in disease risk while an adjusted logistic model was applied to estimate the impact of residential distance from the AC plant. Kulldorf test and Cuzick Edward test were then performed.

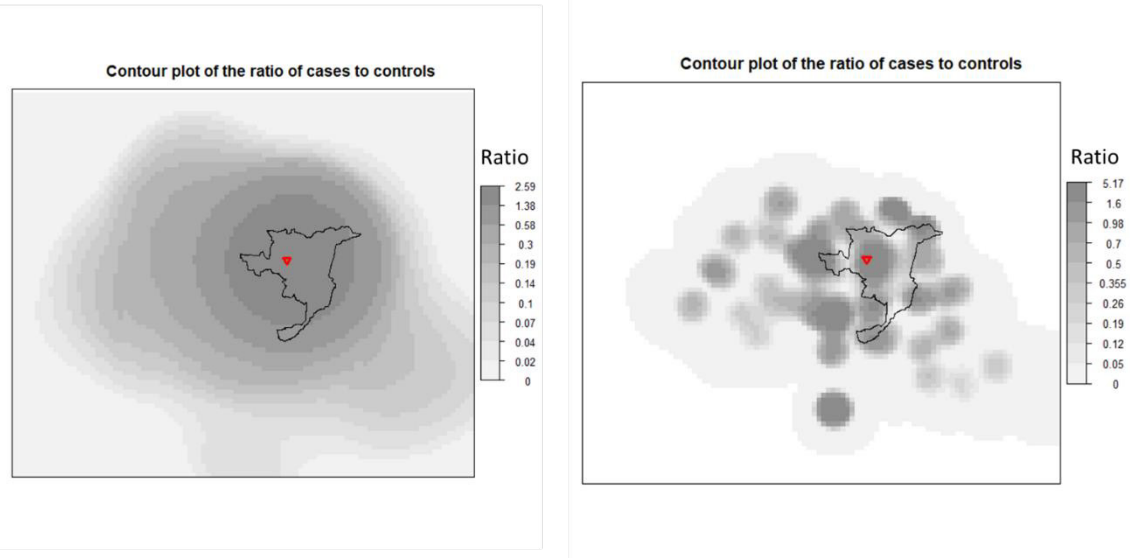
Results

One hundred ninety-six cases and 322 controls were included in the analyses. The contour plot of the cases to controls ratio showed a well-defined peak of MM incidence near the AC factory, and the risk decreased monotonically in all directions when large bandwidths were used. However, considering narrower smoothing parameters, several peaks of increased risk were reported [Figure 1]. A constant trend of decreasing OR with increasing distance was observed, with estimates of 10.9 (95% CI 5.32-22.38) and 10.48 (95%CI 4.54-24.2) for 0-5 km and 5-10 km, respectively (reference >15 km). Finally, a significant ($p<0.0001$) excess of cases near the pollution source was identified and cases are spatially clustered relative to the controls until 13 nearest neighbours.

Conclusions

In this study, we found an increasing pattern of mesothelioma risk in the area around a big AC factory and we detected secondary clusters of cases due to local exposure points, possibly associated to the use of asbestos materials.

Figure 1. Case control study on MM in Casale Monferrato area. Contour plot of the kernel density surfaces of the case to control ratio, including occupationally and non-occupationally exposed individuals in an area of approximately 2500 km2 around Casale Monferrato (solid line). Bivariate Gaussian Kernels with smoothing parameters set to 10 and 20 km for cases and controls, respectively, in the left panel and 2 and 4 km in the right panel. The location of the AC plant (red triangle) is indicated. The legend reports the value of ratio and the corresponding grey shades.



STUDIO OSSERVAZIONALE SUL COVID-19 NEGLI ANZIANI: CARATTERISTICHE LABORATORISTICHE E FATTORI PROGNOSTICI

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INTRODUZIONE

La Società Italiana di Gerontologia e Geriatria nel 2018 ha presentato una nuova definizione di anziani. Infatti precedentemente era considerato anziano un soggetto con età maggiore o uguale ai sessantacinque anni, ma considerato l'allungamento della vita media è stata stesa una classificazione nuova di anzianità51:

- Giovani anziani dai sessantacinque ai settantaquattro anni;
- Anziani dai settantacinque agli ottantaquattro anni;
- Grandi vecchi dagli ottantacinque ai novantanove anni;
- Centenari dai 100 anni in su.

Da qui deriva quindi la proposta di reputare anziano un soggetto con età maggiore o uguale ai settantacinque anni.

Per comprendere quale fascia della popolazione risulta essere più colpita da un punto di vista di mortalità, basta guardare il tasso di mortalità del COVID 19 per fascia di età.

La grande quantità di decessi dovuti al COVID 19 nella fascia di età avanzata ci porta a considerare maggiormente gli aspetti clinici, laboratoristici e strumentali della popolazione con età maggiore o uguale ai settantacinque anni. Da qui arriva il bisogno di analizzare tutti questi aspetti legati alla popolazione anziana per aumentare le conoscenze specifiche per poter quindi migliorare l'approccio diagnostico e terapeutico.

Il bollettino dell' Istituto Superiore di Sanità del 23 giugno 2021, che riporta 126.402 decessi di pazienti che erano risultati positivi al SARS CoV 2, ci mostra il numero di pazienti deceduti per fascia d'età:

- Dai 60 ai 69 anni i decessi sono 13.029 ovvero il 10,3% dei morti totali;
- Dai 70 ai 79 anni sono 31.895 i decessi, ovvero il 25,2%;
- Dagli 80 agli 89 anni i decessi sono 51.039 ovvero il 40,4%;
- Dai 90 anni in su i decessi sono 24.488 ovvero il 19,4%.

Da questo bollettino è tangibile come i decessi causati dal COVID-19 si raggruppano nelle fascie di età avanzate, infatti è possibile notare come i decessi che riguardano pazienti con età inferiore ai sessant'anni riusltano essere solo il 4,9% delle morti totali.

È possibile presumere quali possano essere le principali motivazioni per cui gli anziani affrontano il virus in modo peggiore; seguono gli aspetti principali della risposta al COVID -19 dell'anziano:

- Le caratteristiche fisiche o pregresse patologie polmonari che modificano la barriera e la funzionalità dell'apparato respiratorio (esempi possono essere la diminuzione del riflesso della tosse, diminuzione dell'attività ciliare della mucosa respiratoria);
- L'inflammaging, quindi il background infiammatorio che presentano i pazienti anziani anche senza la presenza di un'effettiva infezione. Questo si collega alla fragilità e quindi ad una sindrome fisiologica definita dalla diminuzione delle riserve funzionali e dalla riduzione della resistenza agli stressor che deriva dal decadimento di sistemi fisiologici multipli che portano a vulnerabilità ed avversità;
- Una diminuzione della risposta immune di macrofagi che presentano una diminuita capacità di fagocitosi dei detriti cellulari, tutto ciò porta al richiamo di altri macrofagi , venendosi a creare un intasamento polmonare ed all'aumento dell'infiammazione; le cellule dendritiche hanno una capacità ridotta di attivare i linfociti T54.

OBIETTIVO

Uno studio osservazionale monocentrico è stato condotto presso il Policlinico Universitario G. Martino di Messina, UOC di Malattie Infettive, centro di riferimento per il COVID-19 da marzo 2020 a giugno 2021. In questo periodo sono stati ricoverati più di 450 pazienti affetti da COVID-19 con età maggiore a 18 anni.
Obiettivo dello studio era analizzare gli aspetti clinici, laboratoristici e i fattori di rischio dei pazienti positivi al COVID 19 di età maggiore o uguale ai settantacinque anni, individuando le caratteristiche tipiche dei soggetti anziani. Per la raccolta dati ci si è avvalsi di un homemade database che raccoglieva dati clinici, anamnestici, laboratoristici e microbiologici. Tutti i pazienti all'ingresso hanno firmato un consenso informato. Il protocollo dello studio è stato approvato dal Comitato etico dell'AOU "G. Martino" di Messina.

METODI

In fase analitica sono stati utilizzati test di permutazione[1] (NPC test) per il confronto tra i gruppi di pazienti, identificati dalla diversa fascia di età (ovvero giovani anziani, anziani e grandi vecchi).
È stato utilizzato un modello di regressione di Cox[2] al fine di individuare i fattori prognostici; tra le tante variabili raccolte, sono state inserite nel modello quelle ritenute più cogenti (Età, Sesso, Ipertensione, Tosse, Cardiopatia, Diabete, BPCO, IRC, Obesità, Febbre, P/F minore di 200, D-Dimero, LDH, Na (sodio), K (potassio), PCR, PCT, IL-6, Leucociti, INR). Il metodo kaplian Meier[3] è stato utilizzato per la realizzazione di curve di sopravvivenza, considerando come fattore l'appartenenza alle diverse fasce di età (giovani anziani, anziani e grandi vecchi); il Log Rank test è stato utilizzato per confrontare le relative curve.

RISULTATI

Dalla stima del modello, sono stati identificati come fattori prognostici l'età, le alterazioni elettrolitiche di Sodio (Na +) e Potassio (K +) e una concentrazione sierica di LDH al di sopra della norma. In particolare una concentrazione di sodio sierico al di fuori del range di normalità, all'ingresso in reparto, è risultato essere un fattore che esponeva i pazienti a un rischio di mortalità 2,7 volte maggiore, con una elevata significatività statistica. Inoltre, una concentrazione anormale di potassio sierico è risultato essere un fattore che esponeva i pazienti a un rischio di mortalità 3,2 volte maggiore. Altresì, un valore elevato di LDH, all'ingresso in reparto, è risultato essere un fattore che esponeva i pazienti a un rischio di mortalità 2,003 volte maggiore.

CONCLUSIONI

Il prepotente arrivo del Sars- Cov 2 ha messo in ginocchio l'intero sistema sanitario mondiale. Gli operatori sanitari in ambito internazionale si sono ritrovati a cercare di capire quali fossero gli effetti nell'immediato di questo nuovo virus e ad identificare i fattori di rischio di complicanze gravi per portare poi al decesso.
Si è da subito visto come i soggetti che rispondevano peggio al COVID 19 fossero quelli con età maggiore ai 75 anni. Abbiamo verificato come l'età in particolare rivesta un ruolo importante nella risposta immunitaria, Anche il sodio e il potassio sono risultati essere fattori prognostici negativi. Infine l'LDH, che è un fattore prognostico negativo per le polmoniti virali, risulta essere elevato in una elevata percentuale dei pazienti in esame e risulta essere riconducibile all'evento morte, pertanto anche l'LDH sembra rivesta il ruolo di fattore prognostico negativo.

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Cluster Analysis of Renin-Angiotensin-Aldosterone System (RAAS) hormones in general population individuals under anti-hypertensive treatment

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Introduction

Hypertension is a leading cause of death worldwide and a primary risk factor for coronary artery disease, stroke and chronic kidney disease (1). These complications could be largely avoided with an effective anti-hypertensive drug (AHD) treatment. The Renin-Angiotensin-Aldosterone System (RAAS) is a critical pathway responsible for the long-term control of blood pressure (2). The main hormones of RAAS are angiotensin II that is generated from angiotensin I via c-terminal cleavage by angiotensin-converting enzyme (ACE) and aldosterone, a mineralocorticoid hormone whose production is stimulated by the binding of angiotensin II to angiotensin II type 1 receptor. The RAAS pathway is widely therapeutically targeted by either ACE inhibitors (ACEi) or angiotensin II receptor blockers (ARB). Combinations of an ACEi or an ARB with a calcium channel blocker or a diuretic is the recommended first-line treatment for hypertension (3). Despite the availability of a number of AHDs, hypertension remains poorly controlled. The complexity of the blood pressure regulation, characterized by multiple levels of controls and based on different molecular mechanisms (4) can result in poor AHD efficacy. This highlights the importance and need to investigate the molecular pathways in their complexity rather than one hormone at a time. Additionally, due to technical difficulties in the simultaneous and accurate measurement of angiotensin I, angiotensin II and aldosterone, there are currently insufficient studies about the distribution of these RAAS hormones in the general population.

Aim

Aim of this study was the joint characterization of the three functionally related RAAS hormones using cluster analysis in participants under different types of AHD treatment, and the assessment of cluster-specific clinical features.

Methods

This study was based on the Cooperative Health Research in South Tyrol (CHRIS) study, which consists of 13393 participants from the general population recruited between 2011 and 2018 (5). The current study focused on 800 CHRIS participants (aged between 43 and 90 years; 54% females); of them 300 were not taking any AHD and 500 had a documented history of AHD. AHDs groups were ACEI or ARB plain or in combination with a diuretic (N=100 each), and beta blocker (N=100). We used the novel RAAS Triple-A assay (6) to obtain high quality RAAS data from standard clinical serum samples: Angiotensin I, Angiotensin II and Aldosterone were simultaneously quantified by liquid chromatography combined with tandem mass spectrometry (LC-MS/MS) analysis.

The K-means unsupervised clustering technique was adopted to explore subgroups of participants based on age and gender corrected RAAS hormones. The clustering algorithm assigns each data point to one of K groups based on a similarity feature computed from the covariance matrix of the three hormones. The hormones were first turned into three independent principal components, which were then used to stratify the 800 CHRIS participants into the K clusters. The quality of the separation of the clusters was assessed using the proportion of the between cluster variability and total explained variability. Clinical and laboratory variables were evaluated according to the cluster analysis. ANOVA and Chi-square tests were used to assess the differences of continuous and categorical variables across clusters at a significance level of 0.05.

Results

The principal component analysis indicated that the first component explained 62% of the RAAS total variability, while the second and the third components explained 28% and 10% of the variation, respectively. All the individuals were eventually stratified into K=3 clusters. The widest cluster comprised 55% of all participants, whereas the remaining clusters included 30% and 15% participants, respectively. The first cluster comprised participants with no active AHDs treatment or taking plain beta blocker only. The second cluster comprised participants with a single AHD treatment (either ACEi or ARB). Participants with combined treatments, which included diuretics, characterized the third cluster.

Among the clinical characteristics, individuals included in cluster 2 had higher average BMI than those in cluster 1 and cluster 3 (P-value<0.0001). The three clusters were also heterogeneous by systolic blood pressure, although the differences across the clusters were not statistically significant (P-value=0.0614). Cluster 1 and cluster 3 individuals had mean glycated hemoglobin (HbA1c) level > 6%, substantially higher than for individuals in cluster 2 (mean=5.7%, P-value=0.0028).

Conclusions

This study indicated that cluster analysis based on RAAS system is a feasible approach for investigating the heterogeneity of participants with hypertension in a population-based study. In particular, the cluster analysis reliably identified individuals under different AHD treatment. Finally, cluster analysis indicated differences in important clinical characteristics across groups.

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TITOLO:

Un modello ad effetti misti per analizzare la variazione dei livelli di emoglobina glicata in donne con diagnosi di cancro alla mammella.

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Introduzione

Gli studi clinici d'intervento anche se randomizzati possono subire l'effetto di vari confondenti e le misurazioni multiple degli end points possono fornire informazioni importanti sull'effetto del trattamento. Le analisi della varianza anche a misure ripetute non riescono a captare l'intensita' della risposta individuale al trattamento. Il Mixed effect Model (MEM) è un metodo di stima simile a quello della regressione lineare multipla ma consente di misurare la relazione tra variabile dipendente e un set di variabili indipendenti nel tempo tramite l'aggiunta di un effetto random al modello. Uno dei principali vantaggi di questa metodologia è che si adatta al complessità dei dataset di tipo longitudinali e consente la specificazione di modelli determinati da caratteristiche assunte dall'individuo piuttosto che da limitazioni definite a priori.
Inoltre il modello consente di misurare sia l'analisi della variazione tra soggetti che all'interno dei soggetti e questo permette di notare ad esempio l'intensità della risposta individuale al trattamento.

Obiettivi

L'obiettivo è di paragonare le differenze di emoglobina glicata tra due trattamenti di lifestyle nei 5 tempi di osservazione e confrontare la risposta dei due trattamenti utilizzando il metodo MEM.

Metodi

I dati derivano dalle visite ai tempi 0, 3, 6, 9 12 mesi da 129 pazienti sovrappeso (BMI>25 kg/m^2), partecipanti ad uno studio d'intervento con dieta, attivita' fisica e vitamina D, randomizzati in uno dei due bracci d'intervento: gruppo A (alta intensita', n=67) e gruppo B (bassa intensita', n=62). Ogni tre mesi sono stati raccolti dati clinici, ematici, antropometrici, nutrizionali e di attivita' fisica (passi al giorno). L'equazione del modello finale comprende come variabile dipendente l'emoglobina glicata (misurata in mmol/mol) e come variabili esplicative il glucosio, il colesterolo LDL, l'insulina, la circonferenza fianchi, la circonferenza vita, la media dei passi giornalieri, eventuali comorbidità, l'assunzione di vitamina D, l'abitudine al fumo, l'eventuale trattamento adiuvante in corso. L'effetto random è misurato per i diversi soggetti nell'intercetta e nelle variabili d'intervento; quali vitamina D, insulina e media passi. Si è inserito infine un regressore di interazione tra il trattamento ed il tempo.

Risultati

Nel modello longitudinale ad effetti misti, abbiamo valutato l'effetto di ogni trattamento sul livello di HbA1c nel tempo. Il valore dell'intercetta è 13.53, quando tutte le altre covariate sono uguali a 0. Al passaggio dal trattamento A al trattamento B non si notano differenze significative dei livelli di HbA1c (beta = -0.12, p = 0.90). Rispetto al basale si evidenzia un incremento significativo nel trattamento B al mese 6 (beta = 2.17, p<0.01), il quale si mantiene costante al mese 9 (beta = 2.15, p<0.01, vs basale) per poi crescere (rispetto al mese 9 di circa 22%) al mese 12 (beta = 2.62, p<0.001, vs basale). Si rileva un'associazione positiva significativa (p<0.001) tra l'HbA1c e le pazienti affette da diabete di tipo 2, i livelli di colesterolo LDL, la circonferenza dei fianchi.

Conclusioni

Non è stata osservata alcuna differenza significativa dei livelli di HbA1c tra i due trattamenti ma delle variazioni durante i tempi intermedi che permettono di valutare l'aderenza al trattamento ed intervenire per aumentare l'aderenza. Gli studi clinici d'intervento anche se randomizzati possono subire l'effetto di vari confondenti e le misurazioni multiple possono fornire informazioni importanti sull'effetto del trattamento. Nell'analisi di tali valori si è infatti rimossa un'eventuale modificazione d'effetto dovuta alla riduzione della circonferenza fianchi e presenza di diabete. Altri metodi come l'analisi della varianza anche a misure ripetute sono fortemente influenzate dagli effetti mediati, inoltre non sono sensibili all'intensità della risposta individuale al trattamento. Dati questi aspetti, il MEM permette una ampia visione dei risultati. Nel caso in esame si è in grado di distinguere il trend dell'HbA1c a seconda del trattamento. La variazione individuale dipende anche dalle covariate trattate come effetti random in quanto ogni individuo ha una risposta al trattamento che si discosta da quella generale (descritta dagli effetti fissi) fornita dal modello di regressione classico. I risultati mostrano come sia possibile osservare la differenza media di reazione al trattamento. Con la suddivisione del periodo in più misurazioni è possibile studiare eventuali change point di tale reazione e valutarne significatività, modulo e direzione. Uno dei maggiori vantaggi di tale metodologia è che ingloba e sfrutta la complessità tipica dei dati longitudinali. Quindi consente l'analisi della variazione tra individui e negli individui.

QUANTILE COMPOSITE-BASED PATH MODELING: AN APPLICATION TO A STUDY OF CHRONIC KIDNEY DISEASE

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Introduction

Composite–based path modeling aims to study relationships among a set of composites, i.e., linear combinations of observed or manifest variables (MVs). Prior knowledge is used to specify the theoretical model and to partition data in blocks of manifest variables, in order to establish which manifest variable is related to which composite (through the so-called measurement model) and to define the relations among composites (through the so-called structural model). Two are the main parameters of the models: the path coefficients (β), which measure the relationships between composites, and the loadings (λ), which measure the relationship between each composite and the corresponding MVs.

Partial Least Square Path Modeling (PLS–PM) [1] is the traditional method for composite–based path modeling. Being based on iterative alternating Ordinary Least Squares (OLS) algorithms, it focuses on the conditional means of the distributions. However, limiting to the mean may not reveal interesting effects at other locations of the outcome variable distributions, especially when response variables are highly skewed, the analysis is concerned also about the tail part of the distributions, heteroscedastic variance of the errors is present, distributions are characterized by outliers. In such cases, a quantile regression approach to path modeling, which consider the entire distribution of outcome variables, is a valuable tool to complement the PLS-PM.

Objectives

To provide a description of a recent proposal, called Quantile Composite-based Path Modeling (QC-PM) [2,3], illustrating the potentialities of the method to detect heterogeneity in the variable relationships, and the benefit of using QC-PM as a supplement of PLS-PM, through an application on Chronic Kidney Disease (CKD) in diabetic patients.

Methods

Artificial data were generated mimicking a study proposed by Wang et al. [4] who examined the potential risk factors of CKD through a quantile approach to factor-based structural equation modeling. Data were simulated because the original data were not available. However, since data were generated considering the same model and the obtained estimates, the involved variables and their relations are in line with the study by Wang et al.

The study investigates Type 2 diabetic patients who have experienced CKD. Diagnosis and staging of CKD were based on urinary albumin-creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR). These two variables are the MVs of the outcome block named Kidney disease. The considered risk factors were Blood pressure and Lipid. The former was measured by systolic blood pressure (SBP) and diastolic blood *pressure (DBP), while the latter by total cholesterol (TC), high-density lipoprotein (HDL), and triglycerides (TG). Therefore, the structural model consists of two explanatory composites, Blood pressure (ξ_1) and Lipid (ξ_2), and one dependent composites, Kidney disease (ξ_3) (see Figure 1).*

In the study by Wang et al. Blood pressure and Lipid were positively correlated with the severity of Kidney disease, and these relations were stronger for higher quantiles. Thus, heterogeneity in the structural model was introduced in the artificial data assuming that ξ_1 and ξ_2 exert a different effect on the different parts of the ξ_3 distribution. According to such data generation process, we expect that QC–PM provides estimates of path coefficients that differ across quantiles.

PLS-PM and QC-PM were applied to analyze the data. The numerical solutions of all these methods are obtained through an iterative algorithm, which is the first stage of the procedure where the weights used to define the composites are computed. Partial Least Squares (PLS) refers to a set of iterative alternating Ordinary Least Squares (OLS) algorithms, thus a least squares criterion is adopted to estimate the parameters in each step. In the second stage of the procedure, loadings and path coefficients are estimated through simple and multiple OLS regressions. The QC–PM algorithm follows the same steps of the PLS-PM algorithm, but replacing the OLS regression with quantile regression in all the stages of the procedure [5].

The use of quantile-based tools in all phases of the algorithm shifts the focus to the entire conditional distributions of the involved response variables, allowing to estimate partial conditional quantiles. Therefore QC–PM is a valuable complement to PLS–PM, as much as quantiles are a complement to the average.

Results

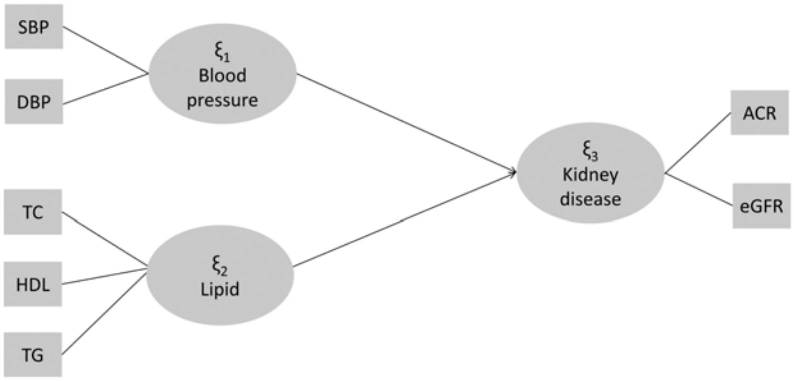
QC–PM was able to detect the structure underlying the data, since it properly distinguished the different effects in the different parts of the kidney disease distribution: both path coefficients increase with quantiles. Both Blood pressure and Lipid have a positive impact on Kidney disease, which increases for patients with higher levels of CKD. In particular, the effect of Blood pressure on Kidney disease (β_1) estimated by PLS-PM is equal to 0.32 ($p<0.05$), while using QC-PM and considering the quantiles $\theta \in \{0.25, 0.50, 0.75\}$, the estimate of β_1 is equal to 0.19 ($p<0.05$) for the $\theta=0.25$, 0.29 ($p<0.05$) for the $\theta=0.50$ and 0.42 ($p<0.05$) for the $\theta=0.75$. The effect of Lipid on Kidney disease (β_2) estimated by PLS-PM is equal to 0.43 ($p<0.05$), while using QC-PM the estimate of β_1 is equal to 0.26 ($p<0.05$) for the $\theta=0.25$, 0.55 ($p<0.05$) for the $\theta=0.50$ and 0.59 ($p<0.05$) for the $\theta=0.75$.

Conclusion

QC–PM complements the well-known and consolidated PLS–PM by exploring heterogeneous effects of explanatory composites over the entire conditional distributions of the response composites.

A description of QC–PM and the applicative potentialities of QC–PM is provided through the analysis of an artificial data set on chronic kidney disease in diabetic patients, highlighting the capability of the method in detecting the heterogeneity in the variable relationships.

Fig.1 Theoretical Model for Chronic Kidney Disease Data, following Wang et al. [60]



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Can response in patients with HCC after transarterial embolization be predicted by Radiomics on gadoxetate disodium MRI? A two-step selection procedure for a prediction model.

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Introduction

Hepatocellular carcinoma (HCC) accounts for about 90% of all primary liver malignancy in cirrhotic patients. In patients with localized HCC, accurate prediction of response to treatment with transarterial embolization (TAE) is crucial for treatment planning. Nevertheless, response to TAE can be heterogeneous according to pre-treatment tumors and patients' characteristics. Additionally, some studies evaluated pre-treatment qualitative imaging features of HCC on magnetic resonance imaging (MRI) to predict tumor response [1,2]. Qualitative imaging features may be affected by subjective interpretation, readers experience, and different definition among HCC guidelines. Therefore, reliable prediction of response on pre-treatment MRI remains an unsolved challenge in clinical practice.

Radiomics is as emerging as a promising tool providing many quantitative features from radiological images. Radiomics features can be combined with clinical and imaging data to construct predictive models for lesion characterization, prediction of treatment response, and patients' prognosis [3]. Initial studies have explored the potential of radiomics and texture analysis for the prediction of treatment response and prognosis of localized HCC patients after TAE on pre-treatment contrast-enhanced CT [4,5,6,7] and MRI with extracellular contrast agents [8] with high performances. None of these studies have investigated the accuracy of radiomics on gadoxetate disodium as MRI contrast agent in combination with both clinical and semantic imaging features. We hypothesize that radiomics may provide an added value for the prediction of treatment response by quantifying lesions heterogeneity related to tumor aggressiveness that cannot be perceptible by the radiologist eyes.

Aims

The aim of this study was to explore the potential of radiomics on gadoxetate disodium-enhanced MRI in comparison with clinical variables and qualitative imaging features for the prediction of hepatocellular carcinoma response after transarterial embolization.

Methods

The study population consisted of 51 patients (37 males, 14 females, median age 73 years, range 44-85 years) with unifocal HCC treated with TAE and available pretreatment gadoxetate disodium MRI. Patient-related clinical and laboratory variables were collected using the electronic data repository systems, including age at the time of treatment, sex, laboratory and tumor markers, history of ascites or varices, and Child-Pugh score. 854 radiomics features, categorized into three main categories (i.e. intensity, shape, and texture radiomics features) were analyzed. Six different radiomics models were constructed for the prediction of complete response and objective response in each analyzed phase (PVP, 3' TP, and HBP). Each model was fitted on the combined dataset of 12 clinical variables, 19 LI-RADS qualitative imaging features, and 854 radiomics features. A two-step model selection and fitting procedure was performed to avoid overfitting by also taking into account for correlation among the variables. In the first step, a logistic model with elastic net penalty [9,10,11] and a high alpha-parameter (i.e. close to the lasso solution) was used to select the variables, while the tuning parameters were chosen by 5-fold cross-validation. Then, a new logistic model with ridge penalty was fitted based on the selected variables to take into account for the correlation among the selected variables. All models were fitted on a training set, and validated on a test set, according to 80-20% random split of the original dataset.

Results

Table 1 reports some prediction accuracy measures in six test sets (the two responses, complete and objective, in each of the three phases of the gadoxetate disodium contrast agent administration for MRI), using the proposed two-step procedure.

Table 1: Performance of the two-step procedure for the prediction, on the test set, of complete response and objective response after TAE, on three phases of the gadoxetate disodium contrast agent administration for MRI.

	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUROC (95% CI)	p value
	Prediction of complete response				
PVP	87.5	33.3	72.7	0.667 (0.251-1.000)	0.431
3' TP	75.0	33.3	63.6	0.750 (0.429-1.000)	0.127
HBP	100.0	100.0	100	1.000 (1.000-1.000)	<0.001
	Prediction of objective response				
PVP	100	40	72.7	0.733 (0.405-1.000)	0.163
3' TP	40.0	66.7	54.5	0.667 (0.305- 1.000)	0.367
HBP	20.0	100.0	63.6	0.600 (0.1936-1.000)	0.630

Abbreviations: PVP: Portal Venous Phase; 3' TP: 3 minutes Transitional Phase; HBP: Hepatobiliary Phase.

Conclusions

The prediction accuracy of HCC response predictions after TAE using Radiomics on gadoxetate disodium MRI, in conjunctions with clinical variables and qualitative imaging features, resulted to be moderate on 5 out six of the test sets. Predictions on the complete response in hepatobiliary phase resulted to be highly accurate. As expected, a very high prediction accuracy was instead obtained in all phases and responses on the six training sets. Before using the proposed procedure of analysis, several supervised machine learning techniques such as classification trees, bagging, random forests, boosting, support vector classifiers [12] were employed, but with poorer prediction accuracy than the proposed procedure.

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Development of a predictive model for new onset of atrial fibrillation in a hospital cohort

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Introduction

Atrial fibrillation (AF) is a type of cardiac arrhythmia with a prevalence around 1%-2%, that represents a major problem of public health. Given the association between the disease and adverse events, like hospitalizations and even death, tools and techniques for the prediction of AF are required to identify high-risk individuals. Currently, the most used tool for this aim is the CHARGE-AF risk model [Alonso 2013], which is a standard survival model based on a small number of variables readily available in primary care setting.

Aims

The present work has two main objectives: 1) the development of a predictive risk score based on machine learning (ML) algorithms applicable in the clinical context, in particular for risk stratification among the cohort under study; 2) performing an extensive comparison between standard and ML methods, in particular benefits coming from the usage of a large number of input features and possible drawbacks in using black-box models.

Methods

In this study we analysed data of 18295 patients examined at the Cardiovascular Observatory of Trieste [Iorio 2019] between 2009 and 2014 with no previous history of AF. Information consists of Electronic Health Records (EHRs) that includes a wide variety of variables: demographics, clinical parameters measured during the cardiological visit, ECG parameters, prescriptions, previous diagnosis, comorbidities. We investigated two approaches for the prediction of AF onset within 1 year from the visit date: the application of CHARGE-AF and development of prediction models based on 95 features extracted from EHRs. We implemented two algorithms: the penalised logistic regression (LR) and the gradient boosting (XGB), an ensemble method based on tree weak learners.

Results

In our preliminary analysis we observe a modest increase in the performance of machine learning approaches. Using CHARGE-AF we obtain an area under the ROC curve (AUC) of 0.696 ([0.660 , 0.747] 95% CI), whereas for LR model and XGB model we obtain AUC=0.736 ([0.682 , 0.771] 95% CI) and AUC=0.720 ([0.679 , 0.760] 95% CI) respectively. As for the variable having more impact in the model, for XGB we identify an interesting overlap with factors involved in the CHARGE-AF score and, in addition, a major role for hemoglobin, which could be linked to recent findings suggesting that a normal level of hemoglobin is an important protective factor in AF [Lim 2020].

Conclusions

Our preliminary results suggest the use of EHRs could useful for the development of a risk score for AF. Further analyses are required to understand the benefit in using ML algorithms in this context. Next developments of the work will include: oversampling strategies to handle the unbalanced classes that are target of our classification problem; implementation of more advanced tuning techniques for model's hyper-parameters; analysis of models calibration; analysis of variables impact.

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Title:

Long-term effect of adjuvant tamoxifen: adherence-based analysis

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Introduction:

Despite meaningful, incremental improvements in screening, in local treatment and in adjuvant systemic therapies for breast cancer, there remains a significant risk of late relapse in hormone receptor (HR)-positive disease. Tamoxifen adjuvant treatment in early breast cancer has proved to be efficient on increasing Invasive Disease-Free Survival (iDFS) and Overall Survival (OS) compared to placebo [1]. Five years of tamoxifen or an aromatase inhibitor for all patients with HR-positive early breast cancer is considered standard; however, there are data to support an improvement of survival outcomes extending tamoxifen treatment up to 10 years [2].

Although randomized clinical trials (RCTs) often suffer from non-adherence or noncompliance of trial participants to the intervention(s) protocol to which they are randomized, the analyses are usually performed according to intention-to-treat (ITT) principle. These analyses do not provide the answer to the key question of the true benefit of the experimental drug when appropriately undertaken.

Several commonly used statistical methods are available to estimate survival benefit while adjusting for treatment switching ranging from naive exclusion or censoring approaches, to time-dependent Cox regression models. However, all these methods are prone to serious selection bias and cannot claim causal treatment effect.

More complex methods are required to improve upon the ITT analysis and correctly account for treatment switching.

Aims: This study aims at estimating the switching-adjusted treatment effect of tamoxifen for OS and iDFS using several causal inference methods, performing simulation study to assess the operational characteristics of each method.

Methods: The analysis was based on data from TAM1 trial: the design and conduct of trial have been described elsewhere [3]. The cohort includes 3830 women with breast cancer and 2 to 3 years of tamoxifen exposure at randomization, of whom 1969 were allocated to short term tamoxifen (ST) (tamoxifen was immediately stopped after randomization) and 1861 to long term tamoxifen (LT) (patients continued tamoxifen for further 10 years). In addition to the standard statistical methods (ITT, per protocol, censorship of switchers, exclusion of switchers and use of time-varying treatment variable), we applied complex methods: Inverse Probability of Censoring Weights (IPCW), Marginal Structural Models (MSM) and Rank-Preserving Structural Failure Time Models (RPSFTM) to account for confounding associated with treatment switching [4-5]. The 2 first methods rely on the counterfactual framework, whereas the last one relies on g-computation. Several sensitivity analyses were performed to evaluate robustness of the complex models.

Results:

Overall non-adherence rate in LT arm was 27 %. ITT analysis estimated a 6% reduction in the hazard of death and a 10% reduction of hazard of relapse with tamoxifen treatment (hazard ratio (HR) respectively, 0.94 (0.84-1.07) and 0.90 (0.81-0.99)). All causal inference methods adjusted for switching showed that a significant survival benefit would have been observed had there been no selective switching (see Table 1). Results from counterfactual and RPSFTM methods differ on iDFS endpoint, which underlines the need for careful assessment of underlying assumptions in each method. Discussion elements are provided for guidance in implementation of these methods, overall and in the specific case of breast cancer and tamoxifen exposure

Conclusion

The ITT method remains the established method to evaluate efficacy of a treatment; however, additional analyses should be considered to assess the on-treatment effect when substantial non-adherence to study drug is expected or observed. IPCW, MSM and RPSFTM are well-established methods to deal with this issue, however their use remains still uncommon, notably when dealing with a time-to-event outcome. This could be explained at least partially because of the difficulty in implementation given the need to adapt existing software programs to treatment stop, rather than to treatment crossover. In conclusion, in the presence of switching treatment, it is important to perform a detailed analysis as suggested by a recently review [6]. No method is universally "best": results are sensitive to the assumptions associated with each adjustment method and their applicability depends on the characteristics of the trial in question. For this reason, assessment of the plausibility of assumptions' methods and implementation of a range of sensitivity analyses are fundamental.

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Table1: IPCW, MSM and RPSFTM estimates of overall survival and invasive disease free survival treatment effect

Outcome: Overall Survival			*Outcome: Invasive Disease Free Survival*		
NAIVE METHODS			*NAIVE METHODS*		
Method	*HR (95% CI)*	*p-value*	*Method*	*HR (95% CI)*	*p-value*
ITT ANALYSIS (unadjusted)	*0.94 (0.84-1.07)*	*0.352*	*ITT ANALYSIS (unadjusted)*	*0.90 (0.81-0.99)*	*0.045*
PP ANALYSIS	*1.14 (1.00-1.30)*	*0.005*	*PP ANALYSIS*	*0.99 (0.89-1.18)*	*0.95*
*Censoring switchers**	*0.96 (0.84-1.09)*	*0.506*	*Censoring switchers**	*0.94 (0.84-1.05)*	*0.283*
*Switching as time-dependent covariate**	*0.95 (0.84-1.08)*	*0.459*	*Switching as time-dependent**	*1.08 (0.97-1.21)*	*0.159*
COMPLEX-METHODS			*COMPLEX METHODS*		
Method	*HR (95% CI)*	*p-value*	*Method*	*HR (95% CI)*	*p-value*
IPCW	*0.73 (0.63-0.84)*	*<0.001*	*IPCW*	*0.45 (0.38-0.51)*	*<0.001*
MSM	*0.73 (0.62-0.84)*	*<0.001*	*MSM*	*0.48 (0.42-0.56)*	*<0.001*
RPSFTM (with re-censoring)	*0.75 (0.57-0.99)*	*//*	*RPSFT (with re-censoring)*	*0.70 (0.53-0.92)*	*//*
RPSFT (without re-censoring)	*0.80 (0.65-0.99)*	*//*	*RPSFT (without re-censoring)*	*0.83 (0.72-0.96)*	*//*

** HR adjusted for age, year of initial treatment, surgery, nodal status, radiotherapy and dose of Tamoxifen.*

ETHICS COMMITTEES REVIEWS OF CLINICAL RESEARCH STUDIES APPLICATIONS IN ITALY DURING THE COVID-19 PANDEMIC

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Introduction.

Since the first identification in December 2019, the coronavirus disease 2019 (Covid-19) pandemic has spread from, the city of Wuhan in China all over the world. The virus, was first confirmed to have spread to Italy on 31 January 2020 and since then, as of April 2021, Italy results to be the 8th country in the world for absolute count of confirmed cases. Since the beginning of the pandemic, scientists and physicians from all over the world, Italy included, have been conducting many clinical studies involving affected patients in order to overcome the lack of information necessary in the battle against the newcoming virus. Indeed, the haste determined by the situation and the struggle for information threatened the possibility of lowering study quality as well as Ethical Committees review standards during the outbreak [4, 3]. Our investigation aimed to assess the impact of Covid-19 on clinical research studies quality submitted to Italian Ethics Committees in the period between April and July 2020.

Materials and Methods

All 91 Italian Ethics Committees have been contacted via email in order to collect information on the type and quality of Covid-related studies submitted to each Committee in the period between April and July 2020. Among the 91 Committees, 19 agreed to participate to the study (4 of them specified to have reviewed no Covid-related study), 64 did not answer to the survey, 8 resulted not reachable despite repeated telephone and email attempts at contact. In summary, 15 Ethical Committees from 7 different Italian Regions agreed to participate to the study and contributed with at least one case of Covid-related study, collecting an overall total of 184 study applications. Additional information on Italian Ethics Committees participation to the study are shown in Table 1. The Committees have been requested to fill in the information of the Covid-related reviewed studies in a spreadsheet file containing drop-down predefined options for any given column. The defined variables were: anonymous study Id, study design, mono or multicentric organization, choice of the comparison group, method of groups creation, study population, study objective and outcome, presence of sample size calculation and appropriateness with respect to the study objective, description of statistical analysis and appropriateness with respect to the study outcome, Ethics Committee final decision on study application.

Results

The 184 study applications included for the vast majority observational studies of various kind (n = 164; 89.2%) against 19 experimental studies, accounting for only 10.3% of the total; moreover, a meaningful percentage (39.5%) of the reviewed applications were part of multicentric studies. The main study population resulted to be adults (n=145; 78.8%) followed by pediatric (12.0%) and healthcare professionals (6.5%). 139 studies (75.5%) were designed as single-arm, thus the results obtained were mainly determined without comparison group. Furthermore randomization have been rarely used as comparison group creation method (2.7%) and in general information on this specific topic resulted quite unclear, especially because biased by a consistently high percentage of missing answer (18.5%). The information relative to study objectives and outcomes, probably due to its intrinsic variability, resulted difficult to coerce into few predefined categories, as proven by the high percentages of ”Other” responses collected (respectively 42.9% and 28.8%). Regarding study quality information we requested each Ethic Committee to declare if statistical analysis and sample size estimations were available and establish if the aforementioned were appropriate relatively to the single studies objective and outcome. The statistical analysis description was largely included in the applications (77.7% present; 73.4% present and appropriate) while the sample size calculation was in contrast very low represented (29.9% present; 25% present and appropriate). In summary, only 71 studies (22.4%) presented an appropriate statistical analysis description and a correct sample size determination. The vast majority of the studies were approved (n=127; 69.0%), while 34 (18.5%) were referred for modification and 6 (3.3%) were rejected; we highlight that for 17 studies this information was missing but can be traced back to the overall contribution of a single Ethic Committee. As an additional consideration, we tried to analyze whether rejection or referral for modification, both conditions proving the review effort of the Committees aimed at study quality, were influenced by any of the variables collected. Using Fisher's exact test, we found a statistically significant association both between application approval and study population, with pediatric population-based studies more frequently rejected or suspended in comparison with nonpediatric ones (OR=0.2, IC 95%: 0.1, 0.6; p-value = 0.001), probably due to the greater caution generally related with pediatric healthcare, and between application approval and accurate statistical analysis description, where studies reporting a good quality statistical analysis resulted more likely to obtain Ehtics Committees approval (OR=11.0, IC 95%: 4.5, 27.9; p-value < 0.001). All the reviewed study characteristics are shown in detail in Table 2 and Table 3.

Conclusions The main limitation of our study is the poor participation of the Italian Ethics Committees: we scored an already low overall 20.9% positive response rate, with only a raw 16.5% effectively involved in data contribution. Beyond the mere downsizing of the sample numerosity and the consequent poor representativity of the overall Italian situation, the scarce response in participation, against the Ethics Committees own self-interest, undermined the aim itself of the present study, making us unable to disprove the suspicion of quality review deterioration under the climate of urgency generated by Covid-19 pandemic in Italy. We understood that some not responding Committees could have been overwhelmed by the amount of work caused by the pandemic; nevertheless, in such challenging historical period, both from a scientific and political perspective, the need for clear and reliable information is crucial. The pursue for information quality instead of quantity has been a problem during the pandemic, resulting in multiple cases with retractions and withdrawals of scientific papers [3]. We believe that science must be clear and open in its methodology because the general public needs to trustfully rely on its methods in order to overcome the challenge of the Covid-19 [1, 2]. Its our hope future studies on study quality assessment could experience broader participation in order to achieve these fundamental common goals.

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COPING STRATEGIES, EMOTIONAL REGULATION, PSYCHOLOGICAL DISTRESS AND SUICIDE RISK IN TWO GROUPS OF SPANISH POPULATION DURING THE COVID-19 CONFINEMENT

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Introduction Understanding how people respond to emergency situations such as the COVID-19 pandemic can support public health policy makers during the crisis and propose long-term health prevention, promotion and intervention measures [1]. People with addictions are identified as a group with a higher socio-health risk and psychosocial vulnerability compared to the general population [2].

Objective To compare two groups of Spanish adult populations in terms of coping strategies, emotional regulation, psychological distress and suicide risk during the first phase of the COVID-19 lockdown and to identify if there are differences in the type of psychological response between the general population and the population under treatment for addictions.

Methods Multicentre and observational epidemiological study. Snowball non-probabilistic sampling. Web-based administration of tools: Coping Orientations to Problems Experienced (COPE), Emotion Regulation Questionnaire (ERQ), Symptom Check-List-90 Revised (SCL-90-R) and Okasha Suicidality Scale. Data analysis: Descriptive statistics, Alpha di Cronbach, Mann-Whitney U test, Multivariate Logistic Regression Model. The Hosmer –Lemeshow test was used to determine the goodness of fit of the Multivariate logistic regression Model. Software STATA 16.

Results 91 participants, 56 adults from the general population and 35 adults from an addiction treatment center, total 37 men (40.66%) and 54 women (59.34%), aged between 19 and 63 years (mean = 35.7; S.D. = 12.9).

The instruments have good internal consistency (Cronbach's Alpha: COPE = .86, ERQ = .76, SCL-90-R = .98, Okasha Suicidality Scale = .85).

The medians with interquartile range (IQR) for each of the variables in the total sample, in the general population and in treatment for addictions population, show significant differences only in the medians of the coping strategies: humor and distraction activities, and the symptoms of psychological distress: somatization, depression and hostility, all being higher in the general population.

To analyse the association among the variables, univariate and multivariate logistic models were performed, selecting as the most functional model the multivariate that correctly classifies 78.02%, has a sensitivity of 73.33%, specificity of 82.61%, AUC = 0.85, and includes direct (positive) association among psychological distress with the coping restraint strategy, and the risk of suicide, and inverse association with the emotional regulation strategy cognitive reappraisal and being in treatment for addictions (see Table).

Table. Multivariate Logistic Regression Model of psychological distress with coping strategies, emotional regulation, suicide risk and type of population

Psychological Distress	*Regression Coefficient*	*Standard Error*	*Odds Ratio*	*P>|z|*	*95% Confidence Interval*	
Coping restraint	*.32*	*.17*	*1.4*	*.001*	*1.0*	*1.8*
Cognitive reappraisal	*-.11*	*.03*	*.89*	*.003*	*.83*	*.96*
Suicide risk	*.37*	*.15*	*1.4*	*.000*	*1.18*	*1.79*
People in treatment for addictions	*-1.2*	*.17*	*.30*	*.039*	*.09*	*.94*
Constant	*-.16*	*1.3*	*.85*	*.902*	*.63*	*11.42*

Note: Hosmer-Lemeshow Goodness of Fit Test, p = .444

Conclusions Even though the pandemic and confinement have increased drug use in a large part of the population [3, 4] and the increase in addictive behaviors [5, 6], the fact of receiving some type of psychotherapeutic support or psychological treatment during the health crisis caused by COVID-19 it has proven to be a protective factor for mental health [7], also in people with addiction diagnoses [8], as found in the present study, where the general population shows less adaptive responses during confinement compared to people in treatment for addictions.

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Model-based reliability indexes: an application to rehabilitation

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Introduction

In the early 1960s, Chronbach et al [1] introduced the concept of generalizability (G) theory. G theory addresses the fact that measurements evaluated on persons vary not only due to individual differences in the personality, behaviors, symptoms, abilities, or skills measured, but also due to various sources of measurement error associated with "facets" of the measurement (e.g., different raters, time of recording). In multi-facet context the linear mixed models were proposed to estimate the contribution of different sources of variability and their interactions on total variance. The estimates of variance components are used to calculate two indexes: generalizability coefficient pertained to relative decisions and dependability coefficient for absolute decisions [2] which can be used to calculate the minimal detectable change (MDC) [3] that is the minimal amount of change that can be interpreted as a change exceeding the one expected by chance. Indeed, MDC is an extension of the Least Significant Difference (LSD) concept [4]. Availability of MDC value in any neuromotor test and, of interest here, in Head Repositioning Accuracy (HRA), is relevant to interpret change in outcome studies.

Aim

The main purpose of this study was to address the problem of reliability of Joint Position Error (JPE), a component of HRA, using linear mixed model based-generalizability indexes.

Methods

During period 2020-2021 the Department of neurorehabilitation sciences of Italian Auxologico Institute (Italy) recruited 26 healthy adults (both genders and range age 18 to 50 years) to perform neuromotor functional tests consisting in 4 exercises: the head was passively rotated 30° to the right or left (right and left axial rotation movements of the cervical spine, RR and, LR tests, respectively) and tilted 25°back or forth (extension and flexion, EXT and FL tests, respectively). Movements towards the targets took place at freely chosen speed, and required about 3-4 seconds each. No constraints were imposed to the intervertebral and the sub-occipital joints motions. For each movement the JPE was calculated as absolute difference in degrees between requested and reproduced positions. Tests were conducted in two sessions (T0 and T1), two weeks apart. The two-week period was chosen because it corresponds to the usual interval for outcome measurement in a typical rehabilitation program for neck or balance disorders. In each session, T0 and T1, the test was performed twice consecutively, by two operators. The sequence of operators was randomized. All subjects (*s*) were evaluated by both operators (*o*) at each time (*t*). Data from this fully crossed design (*s x o x t*) was analysed by means a linear mixed model including *s,o,t* and their pairwise interactions as random effects, separately for each exercise. This approach uses the restricted maximum likelihood (REML) to produce unbiased estimates of variance components.

Results

Subjects had a mean age of 33 (± 6). Thirteen out of 26 were males. For each movement the highest variance component was related to subjects, and ranged from 1.93 to 8.86 for movement EXT and RR respectively. This rank was confirmed for residual variance component. The variance component related to time, operator and interaction were generally much lower. Negative components of variance were put to 0 value from PROC MIXED of Statistical Analysis System (SAS) software. The dependability index, that is, the ratio of the variance components related to patients to the sum of all variance components, ranged from 0.49 to 0.71 for movement EXT and RR respectively.

	Movement			
Source of variance	RR	LR	EXT	FLEX
Subject	8.856	3.817	1.927	2.209
Time	0.038	0.154	0.035	0.000
Operator	0.185	0.049	0.000	0.036
Subject*Time	0.449	0.456	0.756	0.003
Subject*Operator	0.170	0.446	0.449	0.063
Time*Operator	0.000	0.000	0.023	0.000
Residual	2.621	2.448	0.716	1.292
Dependability index	0.712	0.518	0.493	0.613

Conclusions

Values of obtained dependability indexes suggested non negligible "bias" due to facets. Linear mixed models seem to be a feasible approach to estimate variance components needed to measure reliability in complex designs. Unbiased estimates of reliability index is the main prerequisite to obtain informative MDC values. The method adopted here matches general clinical needs, as far as it allows to interpret change in individual subjects and to estimate the probability of a "real" change in individuals, not only changes in means/medians across samples.

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MODELLO SIR E PANDEMIA COVID19: UNO STUDIO SUI DATI PIEMONTESI

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Obiettivi

Il modello SIR è stato criticato come non performante sui dati della pandemia COVID-19, in quanto non idoneo a tener conto di altri fattori come l'inquinamento, le condizioni socio-culturali, gli imprevisti (nell'articolo citato si considera il caso della Malesia in cui grandi festival religiosi si sono comunque svolti durante la pandemia) [1].
L'obiettivo di questo studio è sperimentare l'affidabilità del modello epidemiologico SIR per modellizzare i dati della pandemia in Piemonte.

Materiali e Metodi

Il modello SIR [2, 3] è un sistema di equazioni differenziali che vuole predire l'andamento di tre popolazioni, connesse fra loro, nel tempo. In particolare, le tre popolazioni sono gli **S**, i 'suscettibili', ovvero le persone a rischio di infezione, gli **I**, 'infetti', coloro che contraggono la malattia, gli **R**, 'rimossi', coloro che non possono più contrarre la malattia.
Le tre popolazioni si relazionano tra loro attraverso dei parametri, tra cui il tasso di contagio, il tasso di morte, il tasso di guarigione, dalla cui interazione è possibile stimare il coefficiente R_0 che è tra i parametri alla base delle analisi del Ministero della Salute per decidere il tipo di lockdown da applicare.
Il modello SIR utilizzato in questo studio è nella sua forma più semplice:

$$S' = -\rho SI$$

$$I' = \rho SI - (m+g)I$$

$$R' = mI$$

Dove S sono le persone a rischio di infezione, I gli infettati dal COVID19, R i deceduti per la malattia, ρ il tasso di contagio, m di morte e g di guarigione.
La base dati di riferimento del presente lavoro è costituita dai dati reali dei contagi (contagiati, attivi, morti, guariti) in Piemonte dal 24/02/2020 al 18/03/2021 [4] e su questi sono stati stimati i parametri ρ, m e g.
Dato che questi parametri variano nel tempo, si è deciso di stimarli ogni 10 giorni (intervallo di tempo simile a quello utilizzato dal Ministero della Salute) utilizzando l'Optimization Toolbox di Matlab. I dati dal 19/03/2021 al 20/04/2021 sono stati utilizzati per la validazione.
Sono stati inoltre raccolti i dati metereologici [5] quali temperatura, pressione e umidità medi di ogni giorno.

La bontà del modello è stata stimata come:

$$\chi^2 = \sum \frac{(S_s - S_t)^2}{S_t} + \sum \frac{(I_s - I_t)^2}{I_t} + \sum \frac{(R_s - R_t)^2}{R_t}$$

Dove S_t, I_t e R_t sono i dati veri e S_s, I_s e R_s i dati simulati dal modello.

Risultati

I risultati principali evidenziano che il modello SIR stimato riesce a fornire una buona stima di contagi e mortalità: il 75% delle simulazioni ottiene un errore χ^2 inferiore al 5% e il restante sotto il 10%.
I parametri in studio sono stati anche classificati per zona, temperatura, pressione, umidità al fine di valutare l'idoneità del modello SIR come previsione sui dati di validazione. Raggruppando per fasce di temperatura e umidità il modello SIR sembra presentare una buona conformità con i dati reali ($\chi^2 < 10\%$); le simulazioni non sembrano invece soddisfacenti nel caso di una classificazione per zona ($\chi^2 > 10\%$).

Conclusioni

Nonostante la presunta poca elasticità del modello SIR [1] le nostre simulazioni mostrano un'ottima concordanza tra osservato e stimato, sebbene l'applicazione di tale modello come previsionale non sia immediata. Sono sicuramente da sottolineare alcuni limiti, tra i quali l'assenza della popolazione dei vaccinati, in crescita da gennaio 2021, la mancanza di stratificazione per fasce d'età e per gravità, l'impossibilità di stimare la popolazione degli asintomatici. Altri autori [2] per ovviare a questi limiti hanno utilizzato versioni modificate, ad esempio inserendo due classi di infetti (riconosciuti con tampone e non riconosciuti). Questo approccio rende più accurato il modello, ma meno facile da validare.
Il risultati presentati sono le prime evidenze del nostro studio che stiamo sviluppando con l'obiettivo di approfondire la correlazione tra fattori esterni (es. temperature, stagionalità, inquinamento) e i parametri del modello (come suggerito già da altri autori [6]) e potrebbe trovare una utile applicazione nell'identificazione dei maggiori fattori di rischio responsabili del diffondersi della pandemia.

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A MACHINE LEARNING APPROACH FOR EVALUATING ANXIETY IN NEUROSURGICAL PATIENTS DURING THE COVID-19 PANDEMIC

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Introduction

In 2020, the COVID-19 pandemic forced Italy and many other countries over the world into lockdown. In that period, in Lombardy nonurgent neurosurgical procedures were rescheduled from the end of May 2020. Although stress and anxiety during the COVID-19 pandemic was investigated in general population[1], no studies explored anxiety in patients whose neurosurgery has been postponed. This study applied Machine Learning (ML) methods for understanding which features have a major impact on the latent construct of anxiety.

Aim

The aim of this study was to investigate anxiety in neurosurgical patients undergoing nonurgent surgical procedures in the post-lockdown phase of the COVID-19 pandemic. Moreover, the safety perception from SARS-CoV-2 infection during their hospitalization were inspected.

Methods

Inclusion criteria for the study were: adult patients (>18) undergoing nonurgent neurosurgical procedures who consented to study participation. Each patient filled in 3 questionnaires: 2 before surgery and 1 after. The first questionnaire collected demographic data (age, sex, and highest academic degree), days of postponement of the surgery, fear related to disease, COVID-19 and hospitalization (measured on a Likert scale from 1 (not at all) to 10 (very)).

The second questionnaire was the State Anxiety Inventory (STAI-State)[2] which contains 20 questions on a 4-point Likert scale. It measures the latent constructs of state anxiety related to an event in a specific moment, such as a surgical procedure. Each item belonging to this questionnaire has a range from a minimum of 1 to a maximum of 4 points, hence the score ranges from a minimum of 20 to a maximum of 80. In detail:

- $20 \leq$ STAI-State score < 48: Normal
- $48 \leq$ STAI-State score ≤ 52: Mild
- $52 <$ STAI-State score ≤ 80: Severe

The last questionnaire collected patients' impressions (Likert scales from 1 (not at all) to 10 (very)) on safety from SARS-CoV-2 infection during hospitalization. First and third questionnaires were tested at the beginning of June 2020 on an external and independent sample of 30 subjects in order to improve the questions' semantics and their comprehension. Answers were collected with REDCap. Clinical data, provided by the neurosurgeon in charge of the patient, included among others, prolongation of time on the waiting list and postponement of hospital admission.

Two different models were used to identify which covariates (X) have the greatest impact on the outcomes (Y_1 and Y_2 which are ordinal variables). Since variables were qualitative and quantitative, mostly asymmetrical, and related to Y by nonlinear relationships, the Random Forest[3] (RF) was applied, and, for each model, 10,000 regression trees were grown. In detail:

RF_1: STAI-State (Y_1) was modeled to investigate which concerns (Table 1, column 1), in the preoperative questionnaire, have a primary role on it.

RF_2: The question "*How much did you feel protected from the risk of being infected with Coronavirus during your hospital admission in Neurosurgery?"* (Y_2), collected on a Likert scale from 1 (not at all) to 10 (very), was modeled using items in the post-operative questionnaire (Table 1, column 2).

To highlight which covariates have major impact on the prediction of the outcomes, the relative Variable Importance Measure[4] (relVIM) was computed.

Table 1: Covariates used in RF_1 (left), RF_2 (right) models

RF_1 covariates	RF_2 covariates
Worried for positivity to Coronavirus	Feeling of safety due to distance between beds
How worried are you about the pathology for which you have been admitted?	Feeling of safety due to hand sanitizer gel available in hospital
How much are you worried about the surgical procedure?	Feeling of safety due to health personnel following security protocols
How anxious were you about a possible worsening of your condition?	Feelings of safety due to the procedures to prevent infection from COVID-19
How stressed were you during the waiting time to admission?	Feeling of safety due to measure body temperature at hospital entrance
Age	Feeling of safety due to masks
Becoming positive to COVID-19 during hospitalization	Feeling of safety due to a reassuring behavior of health personnel
How many days would you have been willing to post-pone your admission?	Feeling of safety due to sanitization of hospital environments
How safe do you feel in Neurosurgical ward?	In the operating room, did you feel safe from Coronavirus
Perception of time from neurosurgical evaluation to admission	Did the health personnel seem prepared for the post-operative period
How much COVID-19 increased concern about Neurosurgery admission?	
How useful is the screening on COVID-19 performed pre-operatively?	
How safe is the screening on COVID-19 performed pre-operatively?	

Results

The study included 123 subjects (M/F: 64/59; mean age: 60.28 years SD=15.08) for 114 variables.

Modeling state anxiety, the patients' condition was significantly associated with the worry of being positive for SARS-CoV-2. This was the first variable identified by relVIM, followed by intuitive ones such as the concern for the primary pathology, surgery, and worsening of their condition, as well as waiting time. In fact, hospital admission to neurosurgery was postponed in mean of 49.72 days and it was due to organizational issues (83%) or, rarely, for positivity to SARS-CoV-2 (1.6%).

This study also investigated the feeling of safety conveyed by different features that were activated in all Italian hospitals during the pandemic. Interestingly, the increased distance between surgical beds was the first factor associated with a feeling of safety from SARS-CoV-2, followed by the availability of hand sanitizers.

Conclusions

This study used a ML approach for modeling latent constructs such as anxiety in patients whose neurosurgery has been postponed during the lockdown. Results confirmed that psychological support should be enhanced during outbreaks, possibly using novel solutions to provide follow-up care remotely during waiting times. Moreover, these data can be interpreted as a result of the social media communication on the importance of social distancing; this evidence might be important for hospital managers and to optimize communication with patients during pandemic situations.

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DECREASING THICKNESS AND ENHANCED THERAPY HAVE BOTH CONTRIBUTED TO THE 2010s INCREASE IN SURVIVAL FROM MELANOMA IN ITALY

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Introduction. After World War II, the incidence of cutaneous malignant melanoma (CMM) has increased for decades in the whole western world. The incidence increase has been primarily driven by early-stage CCM cases, defined as having a small tumour thickness. The incidence of thick CMM has also increased, but to a lesser extent. These trends have been paralleled by an increase in survival in many countries. As a low Breslow thickness is the single most favourable prognostic factor, researchers have generally related the survival increase to the rise in thin CMM incidence rates. This temporal correlation, however, is not necessarily evidence for a causal link.

Objectives. This study aimed to determine the relative role that the improvement in tumour thickness has played in the favourable trend in survival from CMM in Italy over the last two decades.

Methods. Eleven local cancer registries, covering a population of 8,056,608 (13.5% of the Italian population) on 1 January 2010, provided data for primary CMM cases registered between 2003 and 2017. Age standardized 5-year net survival (NS) was calculated with the non-parametric Pohar Perme estimator [1] using the *strs* [2] STATA [3] command and the International Cancer Survival Standard type 2 weights [4]. Multivariate analysis of 5-year NS was done by calculating the relative excess risk of death (RER). The relative contribution of the decrease in tumour thickness to the trend in RER was evaluated with a forward stepwise analysis, based on flexible parametric models fitted on the log cumulative excess hazard scale with the *stmp2* [5] STATA command.

Results. Over the study period as a whole, tumour thickness was inversely associated with 5-year NS and multivariate RER in both genders. The median tumour thickness was 0.90 mm in 2003-2007, 0.85 mm in 2008-2012 and 0.75 mm in 2013-2017 among men, and 0.78 mm, 0.77 mm and 0.68 mm among women. The 5-year NS was 89.4%, 90.7% and 95.2% among men and 92.9%, 93.5%, and 95.2% among women, respectively. For both genders, the increasing survival trend was more pronounced with increasing tumour thickness. Table 1 shows that, for men, the inclusion of tumour thickness into the forward stepwise flexible parametric model made the RER in 2013-2017 versus 2003-2007 to increase from 0.62 (95% confidence interval, 0.48-0.82) to 0.69 (0.54-0.87). A sensitivity analysis confirmed this finding. For women, the results were not significant. By including cases with unknown tumour thickness, the RER rose from 0.74 (0.59-0.94) to 0.86 (0.70-1.07).

Conclusions. The marked decrease in tumour thickness accounted for less than half of the improvement in survival observed in 2013-2017. The introduction of immunotherapy and targeted therapy in the last decade is the most likely explanation for the remaining component.

Table 1. Multivariate relative excess risk of death from cutaneous malignant melanoma according to time period of diagnosis, by sex. Italy, 2003-2017.

Sex	Model	Variable	LR Test	*P*	RERs and 95% CI		
					2003-2007	2008-2012	2013-2017
Men	A	Period		NA	1.00	0.93 (0.71-1.21)	0.64 (0.46-0.87)
	B	Model A plus age	B vs A	<0.001	1.00	0.89 (0.70-1.14)	0.60 (0.45-0.80)
	C	Model B plus histologic subtype	C vs B	<0.001	1.00	0.87 (0.69-1.10)	0.61 (0.46-0.80)
	D	Model C plus subsite	D vs C	0.034	1.00	0.86 (0.68-1.09)	0.62 (0.48-0.82)
	E	Model D plus thickness	E vs D	<0.001	1.00	0.93 (0.76-1.14)	0.69 (0.54-0.87)
Women	A	Period		NA	1.00	0.95 (0.66-1.37)	0.64 (0.40-1.01)
	B	Model A plus age	B vs A	<0.001	1.00	0.94 (0.69-1.29)	0.65 (0.44-0.97)
	C	Model B plus histologic subtype	C vs B	<0.001	1.00	0.97 (0.72-1.30)	0.78 (0.55-1.12)
	D	Model C plus subsite	D vs C	0.077	1.00	0.96 (0.71-1.29)	0.78 (0.55-1.12)
	E	Model D plus thickness	E vs D	<0.001	1.00	0.99 (0.77-1.27)	0.83 (0.62-1.11)

LR, likelihood ratio; RER, relative excess risk; CI, confidence interval.

Relative excess risk of death is from a flexible parametric model for relative survival. P-values are for the likelihood ratio test comparing each model with the previous one.

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A SYSTEMATIC REVIEW ON BREAST DEVELOPMENT WITH A FOCUS ON IN UTERO AND EARLY LIFE WINDOWS OF SUSCEPTIBILITY

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INTRODUCTION

Puberty is characterized by rapid growth, and changes in body composition, attainment of secondary sexual characteristics, and behavioural changes. It marks an important period in the dynamic of the individual development from childhood to adolescence. Over the last 20 years changes in age at puberty onset have been observed, affecting heterogeneously the different pubertal markers. Breast onset is the initial physical sign of puberty in girls, and is considered a better indicator than pubic hair growth because it is linked to gonadal functioning. Menarche is the endpoint of a complex sequence of developmental steps, and hence it is a late marker of puberty.

As the reproductive axis and its function are mainly determined in foetal life, and foetal and neonatal periods are essential for sexual differentiation, the intrauterine period can be relevant for programming the onset of puberty as a lifelong adaptive mechanism to environmental factors.

OBJECTIVES

We reviewed the evidence on the effects of in utero and early life events on subsequent breast onset and development, aiming to present and discuss their putative role during this susceptible developmental period.

METHODS

We identified relevant literature from Pubmed and Embase databases, up to 30 November 2020. We selected original studies in which female human (i) exposure during foetal or the first years of life (ii) was measured or estimated (iii), and associations with breast onset or development were evaluated (iv). We did not require breast development to be the main outcome of the study.

We then excluded studies if i) targeted premature thelarche, conceived as breast development in the first years of life, ii) assessed genetic features as potential risk factors, iii) subjects had diseases related with pubertal development (e.g., Mc Cune Albright, Turner syndrome) or neoplasms, iv) not used Tanner scale to assess the outcome, v) language was not English.

RESULTS

Forty-four original studies were identified [1-44]. Most were cohort studies while 4 studies were cross-sectional. Summary results are reported in Table 1. High maternal weight and primiparity, and daughter's early weight gain after birth were associated to an increased risk of early breast onset or development, almost uniformly across the studies. In some of the studies, positive associations were also reported for daughter's birth weight, maternal diabetes and smoking habits in pregnancy. Solid evidence emerged for breastfeeding as protective factor against early breast onset/development, and similar effects were also reported for preterm birth. Results for maternal hypertensive disorders and daughters born SGA were inconsistent. No association emerged for maternal age at delivery, alcohol drinking and specific drugs use in pregnancy across all the studies.

CONCLUSION

Maternal weight and primiparity, and daughter's early weight gain were associated with early thelarche and breast development, while breastfeeding and preterm birth reported and inverse association. Maternal parity and preterm birth act by modifying maternal hormones exposure in the daughter: preterm birth reduces the overall exposure in utero, while the concentration of specific maternal hormones in umbilical cord blood is higher in first born children. Maternal adiposity may act directly, for example through foetus/child exposure to leptin or other hormones, but also share a common genetic determinant with daughter's age at puberty onset. Rapid early weight gain is associated with the development of insulin resistance and an exaggerated adrenal androgen secretion. Moreover, low birth weight followed by rapid early weight gain is associated to an increased risk of central fat deposition and later obesity, i.e., the best recognized risk factor for early pubertal development. In contrast, breastfeeding has a beneficial role against weight gain in early infancy and childhood obesity in general. Thus, this combination of hormonal and metabolic changes, that are difficult to dissect, appears to affect the progression of puberty.

Breast development is a key physical marker of puberty onset, and early puberty development is linked to consequences that can reverberate throughout life. Answering the questions about the interconnections of environmental exposures during pre/postnatal period and their impact on puberty represents an important area of multidisciplinary research. This is useful to identify and target potential intervention to limit harmful effects of this complex combination of exposures in order to protect this delicate phase and preserve later metabolic and reproductive outcomes.

TABLE

Table 1. Summary of the associations between in utero and early life exposures and breast development reported in 40 cohorts [1, 2, 5-37, 39, 40, 42-44] and 4 cross-sectional studies [3, 4, 38, 41].

	NO ASSOCIATION	**EARLIER DEVELOPMENT**	**DELAYED DEVELOPMENT**
In pregnancy			
MATERNAL AGE AT DELIVERY	3 studies [11, 33, 36]		
MATERNAL PRIMIPARITY	1 study [11]	4 studies [12, 13] [21, 36]	
MATERNAL PREGRAVID WEIGHT	1 study [11]	6 studies [8, 12, 13, 28, 31, 36]	
MATERNAL GESTATIONAL WEIGHT		3 studies [2, 27, 31]	
MATERNAL DIABETES	3 studies [27, 28, 30]	1 study [18]	
MATERNAL HYPERTENSIVE DISORDERS		1 study [35]	3 studies [35, 37, 40]
MATERNAL SMOKING	2 studies [11, 44]	2 studies [9, 36]	
MATERNAL ALCOHOL DRINKING	2 studies [10, 11]		
MATERNAL DRUGS USE	3 studies [14, 16, 39]		
Perinatal			
DAUGHTER'S PRETERM **BIRTH**	3 studies [3, 4]*, [33]		2 studies [20, 21]
DAUGHTER BORN SMALL FOR GESTATIONAL AGE	4 studies [3, 4]*, [15, 24]	6 studies [6, 17, 22, 32, 36, 42]	2 studies [22, 34]
DAUGHTER'S BIRTH **WEIGHT**	7 studies [7, 25, 33, 36, 43], [38, 41]*	2 studies [6, 19]	
Early life			
MATERNAL BREASFEEDING			5 studies [1, 26, 29, 33, 40]
DAUGHTER'S EARLY **WEIGHT GAIN**		6 studies [5, 7, 23, 24, 36, 43]	

*Cross-sectional studies.

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COLORECTAL CANCER MORTALITY IN YOUNG ADULTS IS RISING

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Introduction

Rising trends in incidence from colorectal cancer (CRC) in young adults have been reported in various countries worldwide [1-3]. We previously examined trends and cohort patterns in CRC mortality between age 25 and 49 from 12 selected high-income countries and the EU and found rising trends in the USA, Canada, the UK and Australia [4]. Furthermore our cancer mortality predictions for Latin American countries reported rises in colorectal cancer in the young and middle aged [5].

Aim

To examine trends in CRC mortality at age 25-49 for all countries with over 20 million inhabitants with mortality data of sufficient quality.

Methods

We obtained official matrices of certified deaths and resident population from the WHO mortality database from 1970 to 2017 according to availability, for 19 countries worldwide and the the European Union [6].
We encoded CRC mortality according to the 10th Revision of the ICD (C17-C21, C26) [7].
From the matrices of certified deaths and resident populations, we derived Age Standardised Rates (ASR) per 100,000 person-years, using the world standard population [8].
We carried out a joinpoint regression analysis over the period 1980-2018. As a summary measure, we calculated the estimated annual percent change (EAPC) for each identified linear segment, and the weighted average EAPC (AAPC) from 2005 to the most recent available calendar period [9, 10].
To disentangle the effects of age, period of death and cohort of birth, we applied an age period cohort (APC) model to quinquennial age-standardized rates from 1970-74 to 2010-14, between 25 (25-29 years) and 79 (75-79 years) years of age and cohorts were defined according to their central year of birth. The age effects are interpretable as mean age-specific death rates per 100,000 persons over the analysed period, the period and cohort effects are expressed in relative terms against their weighted average set to unity [11, 12].

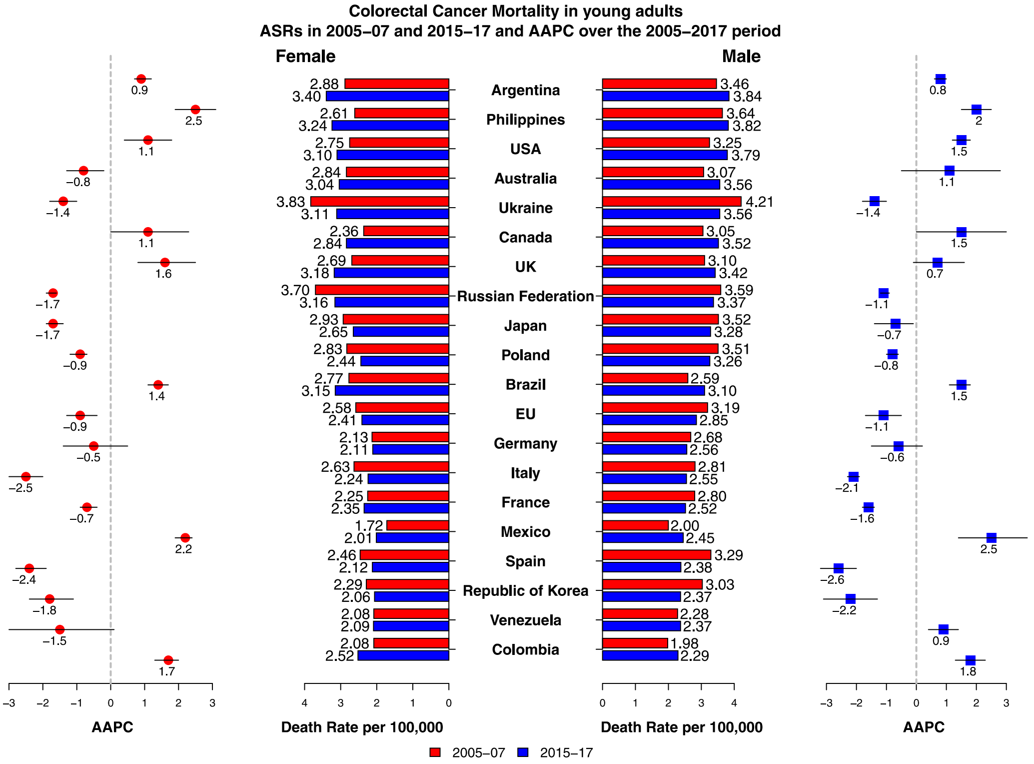

***Figure 1** Bar plots of male and female age-standardized mortality rates from CRC among young adults aged 25-49 years per 100 000, in 19 countries and the EU as a whole, in 2005-2007 (red) and 2015-2017 (blue), and the corresponding AAPC (males in blue and females in red, with 95% confidence intervals) for the period from 2005 to the most recent available year.*

Results

Considering the 1980-2017 period (Figure 1), the overall CRC mortality trends were favourable in the considered European, Asian and Pacific countries in both sexes, except for the UK, with a rising trend in women (1.6% year significant) and a stable one in men (0.7%), Germany stable in both sexes (-0.6% males, -0.5% females), the Philippines with significant rising AAPCs for both sexes (2% Males, 2.5% Females) and a stable AAPC in Australian men (1.1%). In the Americas trends were unfavourable in both sexes in all countries, with the exception of Canadian men (1.5% non significant) and Venezuelan Women (-1.5% not significant). ASRs in the 2015-17 triennium were between 2.3/100 000 in Colombian and 3.8 in Argentinian men and 2/100 000 in Mexican and 3.4 in Argentinian women.

Joinpoint modelling identified significant rising trends for recent calendar years in all the American countries in both sexes, except for Canadian men and Venezuelan women. Recent significant rising EAPCs were also recorded in UK women and the Philippines in both sexes.

APC analysis showed a common cohort pattern with descending effects up to those born in the 1950s or 1960s, with a trough and a subsequent rise in effects or plateau, in the USA, Canada, France, Germany, Australia and the UK, Italian men and Argentinian women. In Latin American countries and the Philippines recent cohorts showed rising trend in effects. The remaining examined countries displayed declining risks for successive recent cohorts.

Conclusions

In recent years trends in incidence for CRC in young adults have been rising in the USA, selected European and Asian countries [1-3]. In the EU, rises in incidence were reported for young adults aged 20 to 39 years in France, Germany, Poland and the UK, but not Italy. Our previous mortality analysis confirms the trends reported for incidence in the USA and Canada, and to a lesser degree in the UK particularly in women and Australia mainly in males [4]. Here we show that young onset CRC is rising in Latin American countries and the Philippines. Although differently from previous high income countries this pattern is part of a general rise in all the age groups and starting from comparatively low rates [5].

Overweight and obesity are recognized risk factors for colorectal cancer and the prevalence patterns recorded in most countries are coherent to the recorded CRC mortality trends; the USA, Canada, Australia and UK and the examined Latin American countries all show rising prevalences in overweight/obesity [13, 14]. Alcohol is also a confirmed risk factor in early onset CRC [13, 15], and among the countries that did not display a rising trend in mortality from these neoplasms, France and Italy had the greatest fall in total alcohol consumption since at least the 1960s with Germany and Spain showing similar falls in consumption since the 1980s, Canada and the USA did not have these falls in consumption, Brazil Mexico and the Philipines showed rising levels [16, 17].

As a result of these rising trends in incidence in early onset CRC, the American Cancer Association updated its guidelines on screening, recommending that subjects at average risk should start screening at 45 years instead of 50 [18]. In the USA screening has been recommended since the 1980s in Europe these have mostly been implemented from the early 2000s, In Latin America only Argentina had a national screening program [19, 20].

In conclusion, the rising trends in young adult colorectal cancer are confirmed by mortality data in the USA, Canada, Australia, the UK, and selected middle income countries. Due to their cohort nature, a smaller increase in overweight and obesity and declining alcohol drinking in some European and Asian countries may, at least in part explain the more favourable trends.

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NOVEL SCORING SYSTEM FOR THE DIAGNOSIS OF CREUTZFELDT-JAKOB DISEASE: A METHODOLOGICAL PROPOSAL

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Introduction

Prion diseases are a very rare group of neurodegenerative diseases which are all currently untreatable and ultimately fatal. Prion diseases can exist in different forms, but the most common is sporadic CJD (sCJD) and occurs worldwide causing around 1-2 deaths per million population per annum. There are also inherited forms of human prion disease linked to mutations of the prion protein gene (gCJD, FFI, GSS) and cases caused by transmission via medical or surgical treatments (iCJD). Both in Italy and internationally the CJD surveillance remains vital from a public health perspective in order to support essential research into disease pathophysiology [1], as well as directly contributing to the diagnosis and management of CJD patients. The most challenging aspect of this disease is its diagnosis and, although the gold standard for definitive diagnosis is considered to be histopathological confirmation, various tests are proven means for an antemortem diagnosis of the pathology [2]. CJD can pose a significant diagnostic challenge when accompanied by non-specific or atypical features which differ from known diagnostic criteria, however, EEG, MRI and CSF study are invaluable diagnostic tools when assessing for CJD [3]. Moreover Real-Time Quaking-Induced Conversion Testing (RT-QuIC) has high sensitivity and specificity for diagnosing prion diseases and greatly improves laboratory-based prion disease ascertainment for surveillance purposes [4,5]. However, current diagnostic criteria have limitations and may be enhanced in order to optimize the current diagnostic process of the disease.

Objectives

The primary objective of our study consists in the definition of an innovative diagnostic score capable of maximizing the diagnostic accuracy of Creutzfeldt-Jakob disease (CJD) through the definition of a threshold value capable of discriminating between CJD and non-CJD subjects starting from the population of patients reported as suspected cases by local physicians in Italy to the national register of Creutzfeldt-Jakob disease and related syndromes of Istituto Superiore di Sanità (ISS). Favorable results of this study would allow to overcome the limitations of a diagnostic classification based on classes of decreasing uncertainty (definite, probable, possible, ruled out) through a probabilistic quantification of the risk of a given patient, allowing to quantify which are the most important variables in determining an effective patient classification along the diagnostic process of the disease. Moreover such a system could serve as a diagnostic support resource potentially useful to physicians in need of evaluating the diagnostic suspicion of this extremely rare disease, of which only few healthcare professionals hold both the clinical and technical expertise necessary to perform an efficient diagnostic process, with particular attention to disadvantaged contexts of low and middle-income countries, where conducting the necessary tests is economically unfeasible and CJD surveillance does not even exist.

Methods

A logistic regression model will be developed using both clinical and diagnostic data of the patients collected by the ISS national register in order to obtain the beta coefficients of the model necessary to derive weighting factors for the new diagnostic score.

The diagnostic performance of the score will be assessed by the area under the curve (AUC) plotting receiver operating characteristic (ROC) curve that will be designed to differentiate between the patients with and without CJD. Optimal cut-off value will be chosen to maximize the sum of sensitivity and specificity (Youden's J statistic); internal validation will be obtained by means of bootstrap replicates and a k-fold cross-validation will be performed in order to estimate the model's classification accuracy. All tests will be two-tailed and a value of P < .05 will be considered as statistically significant. Analyses will be performed using R version 4.1.0 (The R Project for Statistical Computing).

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ed Epidemiologia Clinica

Indice dei nomi

ISBN 979-12-80503-24-4