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TESI DI DOTTORATO DI RICERCA

COPD exacerbations in the emergency department: epidemiology, related costs, and validation of the risk assessment model BAP-65.

Settore disciplinare MED/09

TUTOR:

Prof. Nicola Montano

DOTTORANDO

Dr. Federico Germini

COORDINATORE DEL DOTTORATO

Prof. Emilio Berti

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Abstract/Sintesi

Sintesi in lingua italiana – Parte prima

Nei pazienti con BPCO, le riacutizzazioni sono una frequente causa di accesso in pronto soccorso e possono condizionarne negativamente la prognosi. Obiettivi dello studio erano: 1) descrivere le caratteristiche socio-demografiche e cliniche, nonché la gestione in pronto soccorso dei pazienti con riacutizzazione di bronco-pneumopatia ostruttiva cronica (BPCO); 2) stimarne i costi. Abbiamo condotto uno studio di coorte retrospettivo in Italia, raccogliendo dati su 4,396 pazienti da 34 centri. I pazienti avevano un'età media (deviazione standard [DS]) di 77 (11) anni, ed erano femmine nel 39% dei casi. Oltre il 70% dei pazienti presentava un indice di comorbidità moderato o severo, e nel 26% dei casi era presenta anche una diagnosi di scompenso cardiaco. Il 65% dei pazienti è stato ospedalizzato, per una durata media (DS) di 11 (10) giorni. Il costo stimato per paziente è 2.617 €. In conclusione, I pazienti che afferiscono in pronto soccorso con una riacutizzazione di BPCO sono anziani e gravate da importanti comorbidità. Il tasso di ricovero in questi pazienti è alto, e i costi onerosi.

Sintesi in lingua italiana – Parte seconda

Le riacutizzazioni di BPCO esitano frequentemente in ospedalizzazione, possono richiedere il trattamento con ventilazione invasiva e sono associate a elevata mortalità intraospedaliera. Il BAP-65 è modello di predizione del rischio di eventi avversi per pazienti con riacutizzazione di BPCO. Il BAP-65 è semplice da utilizzare e, se la sua accuratezza prognostica fosse confermata, potrebbe essere utilizzato per guidare la gestione dei pazienti. Abbiamo condotto uno studio retrospettivo, multicentrico in pazienti che afferivano in pronto soccorso per una riacutizzazione di BPCO durante il 2014. Lo scopo dello studio era validare il modello BAP-65 per la predizione dell'outcome combinato mortalità intraospedaliera e ricorso alla ventilazione invasiva. Abbiamo arruolato 2.908 pazienti da 20 centri Italiani. L'età media (DS) era 76 (11) anni, e il 38% dei pazienti

era femmina. L'outcome combinato si è verificato nel 5% dei pazienti. L'area sotto la curva (AUROC) stimata per l'outcome combinato è risultata pari a 0,64 (95%CI 0,59-0,68). Un punteggio BAP-65 ≥ 4 ha mostrato una sensibilità pari a 44% (95% CI 34%-55%) nel predire la mortalità intraospedaliera, con specificità 84% (95% CI 82%-85%), valore predittivo positivo 9% (95% CI 6%-12%) e valore predittivo negativo 98% (95% CI 97%-98%). In conclusione, il modello BAP-65 non ha dimostrato accuratezza sufficiente per un'efficacie stratificazione del rischio di prognosi infausta nella popolazione studiata.

Abstract part 1

Acute exacerbations of chronic obstructive pulmonary disease (AECOPDs) frequently cause patients with COPD to access the emergency department and have a negative impact on the course of the disease. The objectives of our study were: 1) describing the socio-demographic and clinical characteristics, and the clinical management, of patients with AECOPD, when they present to the emergency department; and 2) estimating the costs related to the management of these patients. We conducted a retrospective cohort study in Italy, collecting data on 4,396 patients, from 34 centres. Patients had a mean (SD) age of 76,6 (10.6) years, and 61.2 % of them where males. More than 70 % of the patients had a moderate to very high comorbidity burden, and heart failure was present in 26.4 % of the cohort. The 64.6 % of patients were admitted to hospital wards, with a mean (SD) length of stay of 10.8 (9.8) days. The estimated cost per patient was 2617 €. Conclusions: Patients attending the ED for an AECOPD are old and present important comorbidities. The rate of admission is high, and costs are remarkable.

Abstract part 2

Exacerbations of chronic obstructive pulmonary disease (AECOPD) frequently require hospitalizations, may necessitate of invasive mechanical ventilation (IMV), and are associated with a remarkable in-hospital mortality. The BAP-65 score is a risk assessment model (RAM) based on simple variables, that has been proposed for the prediction of these adverse outcomes in patients with AECOPD. If showed to be accurate, the BAP-65 RAM might be used to guide the patients management, in terms of destination and treatment. We conducted a retrospective, multicentre, chart-review study, on patients attending the ED for an AECOPD during 2014. The aim of the study was the validation of the BAP-65 RAM for the prediction of in-hospital death or use of IMV (composite primary outcome). We assessed the discrimination and the prognostic performance of the BAP-65 RAM. We enrolled 2908 patients from 20 centres across Italy. The mean (standard

deviation) age was 76 (11) years, and 38% of patients were female. The composite outcome occurred in 5.3% of patients. The AUROC of BAP-65 for the composite outcome was 0.64 (95%CI 0.59-0.68). The sensitivity of BAP-65 score ≥ 4 to predict in-hospital mortality was 44% (95% CI 34%-55%), the specificity was 84% (95% CI 82%-85%), the positive predictive value was 9% (95% CI 6%-12%), and the negative predictive value was 98% (95% CI 97%-98%).

Conclusions: In patients attending Italian EDs with an AECOPD, we found that the BAP-65 score did not have sufficient accuracy to stratify patients upon their risk of severe in-hospital outcomes.

List of abbreviations

AECOPD: acute exacerbations of chronic obstructive pulmonary disease

AUROC: area under the receiver operating characteristic

BAP-65: Blood urea nitrogen, altered mental status, Pulse > 109 beats/min, age > 65 years

BUN: Blood urea nitrogen

CI: confidence interval

CCI: Charlson Comorbidity Index

COPD: chronic obstructive pulmonary disease

DRG: diagnosis related group

ED: emergency department

GOLD: Global Initiative for Chronic Obstructive Lung Disease

ICD-9: International Classification of Diseases, Ninth Revision

ICU: intensive care unit

IMV: invasive mechanical ventilation

NIV: non-invasive ventilation

RAM: risk assessment model

SD: standard deviation

SIMEU: Italian Society of Emergency Medicine

USA: United States of America

Part 1: Epidemiology and costs of COPD exacerbations in the emergency department

Introduction

Background

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are one of the most frequent reasons for patients with COPD to access the emergency department (ED) and be hospitalized. Moreover, AECOPD may require invasive mechanical ventilation (IMV), and are associated with increased in-hospital mortality.[1] In Italy, COPD has a prevalence of between 2 and 11 %.[2,3] The care of these patients requires a remarkable amount of health resources, largely because of acute exacerbations.[4] Despite the burden of the disease, little is known about the demographic and clinical characteristics of patients with AECOPD when thy present to the ED, and about how they are managed in the first hours. Understanding the characteristic of patients attending the ED for an AECOPD and how they are managed in that setting can help improving the quality of their care.

Objectives

The present study aimed to describe the socio-demographic characteristics of patients presenting to the ED for an AECOPD, and their clinical management in the ED. Moreover, an estimation of the costs of resources utilization in relation to ED patients with AECOPD has been performed.

Material and methods

Study Design

This was a retrospective cohort, multicentre study. The present section of the manuscript has been prepared according to the RECORD[5] statement.

Study population and data collection

Patients accessing the ED for an AECOPD were eligible to the study. People aged < 40 years were excluded from the study, to omit those likely to have asthma rather than COPD.[6] Patients were recruited in 34 teaching and non-teaching hospitals, in different areas of Italy, from January the 1st to December the 31th, 2014. Figure 1 shows the geographical distribution of the participating centres. The ED databases were used for the selection of patients and for data extraction. Patients with an either primary or secondary ED discharge diagnosis of "AECOPD" (code 491.21), according to the International Classification of Diseases, 9th Revision, were identified. Moreover, the term "BPCO" (COPD in Italian) was searched in the textual diagnosis (if a free space for written diagnosis was provided by the ED management software of the participating centres). Since this was a broad search strategy, two authors (FG and GV) performed a first selection of retrieved cases to exclude those cases for which the primary diagnosis was unrelated to AECOPD (e.g. atrial fibrillation in patient with COPD). This selection process was performed independently by the two authors for the first 1503 cases (data from the first 5 centres). Disagreements were solved via discussion, in order to increase accuracy and consistency between reviewers for case selection in the remaining retrieved cases, which were screened only by one author. To further enhance specificity, an additional selection of retrieved cases was performed, after a training, by centre-level study contributors. This selection was based on the clinical chart data, to ensure that the ED access was actually due to an AECOPD.

Data collected for epidemiological purposes were as follows: patient demographic characteristics, home treatment for COPD, comorbidities, use of ambulance for ED access, ED treatment for COPD, ED disposition (i.e. discharge, short term observation, or admission), the occurrence of in-hospital death, the need for invasive mechanical ventilation, and, in case of admission, duration of the hospital stay and ward of admittance. Information regarding sex, blood pressure at presentation, the presence of pneumonia or respiratory failure, and the variables included in the Charlson Comorbidity Index (CCI)[7] was recorded. Respiratory failure was considered present if explicitly reported among the diagnosis or in case of $SpO2 < 90$ %.

Costs: For the estimation of resources consumption, in addition to the use of ambulance for ED access and the ED disposition, the diagnosis related group (DRG) and relative costs have been recorded.

Ethical considerations

The Research Ethics Committee approved the study, and the research was conducted according to the principles of the Declaration of Helsinki. In consideration of the retrospective nature of the study and the fact that data were anonymized before being entered the general database, no informed consent was required.

Analysis

To assess agreement between authors for cases selection, we used the k statistic, which measures agreement beyond chance.[8] Quantitative variables were reported as mean and standard deviation, qualitative variables as frequencies.

Costs were estimated as follow: €118 in case of ambulance call, plus €242 per ED visit followed by discharge,[9] or the mean of recorded costs according to the DRG in case of admittance.

Results

Data on 4,396 patients presenting to the ED for an AECOPD from January the 1st, 2014 to December the 31th, 2014 were obtained from 34 centres. Agreement for patient selection among authors was substantial (k = 0.78). Table 1 shows the baseline characteristic and Table 2 the ED management and outcome of included patients. The mean (SD) age was 77 (11) years, and 40% were female. The comorbidity burden according to the CCI was low (CCI 0) in 1,242 (28%) cases, moderate (CCI 1-2) in 1,890 (43%), high (CCI 3-4) in 833 (19%), and very high in 431 (10%). The most common comorbidities were heart failure (26%) and coronary artery disease (23%). A diagnosis of respiratory failure was associated to AECOPD in 1241 (30%) patients, and a diagnosis of pneumonia in 448 patients (11%). Treatments mainly adopted in EDs were oxygen therapy (60%), bronchodilators (61%), inhaled steroids (58%), steroids (71%), and antibiotics (23%). Systemic steroids where used in 2,302 (53%) patients, and inhaled steroids in 2,467 (57%), with an overlap between systemic and inhaled steroids in 1700 (39%) patients. Following the ED visit, 1,192 patients (27%) were discharged; 115 (3%) received a short-term observation; 2,839 (65%) were admitted to hospital wards. The main wards of admission were Internal Medicine/Geriatrics (65%), and Pulmonology (18%), while forty-two patients (2%) were admitted to Critical Care. In-hospital death occurred in 159 patients (4%), IMV was deemed necessary in 83 (2%) cases. The mean (SD) length of stay for an admitted patient was 10.8 (9.8) days. AECOPD accounted for 0.5 % of overall ED access, and 37% of cases occurred in the first 3 months of the year.

The mean (SD) reported cost for an admitted patient was €3,820 (3,437). Given that 1) 55% of patients reached the ED by ambulance (estimated cost €118), 2) 65% of patients were admitted to the hospital, and 3) the rest of them received an ED visit (estimated cost €242), we calculated an average cost of €2617 per patient attending the ED for an AECOPD.

Discussion

In our study, patients attending the ED for an AECOPD were on average older than 75, mainly males, and they often presented comorbidities, commonly heart failure. The therapy administered in the ED diverged from guidelines on the use of bronchodilators and steroids[10] in one third of cases, with bronchodilators being used in 61% of patients, steroids in 71%, and with an overlap of inhaled and systemic steroids in 39%. The rate of admissions was high, and costs were remarkable. To our knowledge, the characteristics of patients with AECOPD have never been described using data directly from the ED in Italy. The large number of contributing centres (34) corroborates our confidence in the study results. Despite these strengths, our study had some limitations. First, the retrospective nature of the study and the fact that we relied on administrative data, could have disturbed the correct identification of patients with AECOPD. In an effort to address this problem, we combined two search strategies, one based on ICD-9 classification and one based on descriptive diagnosis. Moreover, we carefully selected cases through a 2-step process. Also, the retrospective nature of the study could have affected the quality of some data, in particular those relating to medical history and medications.[11] Unfortunately, no data on the smoking habits and the results of arterial blood gas analysis were available. Furthermore, the in-hospital follow-up period could have been too short, especially for patients not admitted to the hospital (35%). For these patients, an adverse outcome was less probable, but still possible. Unfortunately, despite our efforts, we had no chance to retrieve reliable data on follow-up after hospital discharge. Eleven percent of the included patients had a concomitant diagnosis of pneumonia. It is indeed true that some studies excluded pneumonia when defining a COPD exacerbation,[12] and the GOLD 2017 guidelines adhere to this definition: “As comorbidities are common in COPD patients, exacerbations must be differentiated clinically from other events such as […] pneumonia”.[13] However, at the time we planned the study and started the data collection, this was still matter of

discussion,[14] and in GOLD 2014 it is stated that: “Other conditions (pneumonia […]) may mimic or aggravate an exacerbation of COPD.”[10] For this reason, and to be consistent with our inclusion criteria and the everyday clinical practice, we decided not to exclude these patients.

Our estimate of the costs related to the emergency care of patients with AECOPD is limited by the fact that the distribution of the reported costs for admitted patients is wide, and by the use of a general cost of the ED visit of discharged patients, not specific to AECOPD. It is reasonable to assert that the ED management of a patient with an AECOPD requires more resources than the average of ED patients, in terms of diagnostic efforts, monitoring, and therapeutic measures. Still, we think that our approximation can be useful to have an idea of the costs of the resources used in this setting.

The low adherence to treatment guidelines, in terms of bronchodilators and steroids, confirms the results of a previous study conducted in 29 EDs in North America.[15] In particular, in this study, a median of 1 short-acting beta-agonist treatment was received across the cohort, only 1 patient was treated with anticholinergic aerosol, and only 62% of patients received systemic corticosteroids. Notably, even if this was a study on elderly patients, and age > 55 years was an inclusion criteria, the mean age of the population was 71 years, well below the mean of 77 found in our population. This difference might be due to the fact that the study described was conducted in a different setting and was prospective. It is known that retrospective studies, despite limitations like the lower quality of data and a higher proportion of missing data, can better represent the usual clinical practice.[16] The time lag in translational research is about 17 years,[17] but this does not justify the low adherence to guidelines for the management of a disease which remained unchanged in more than 25 years.[18] A previous survey among Italian outpatients with respiratory diseases (15% of which had COPD) revealed the poor patients' disease awareness and adherence to therapy, associated with a lack of diagnostic and follow up

efficacy (<2% of patients had performed a blood gas analysis in the previous year).[19] This, together with the results of our study, reflects the need for a "call for alignment" with the current recommendations and guidelines. The present study might represent the occasion to work on the implementation of available evidences in the management of AECOPD. Finally, we believe that our study succeeded in representing the complex picture composed by the so-called real-life patients and their real-life physicians, and the difficulties faced daily in our EDs.

Conclusions

AECOPDs accounts for 0.5% of ED visits and are economically onerous. Patients with AECOPD attending the EDs are old, frequently affected by several comorbidities, and are burdened by a high prevalence of an adverse outcome.

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Tables and Figures

Table 1. Baseline characteristics of patients with exacerbation of chronic obstructive pulmonary disease seen in the emergency department

Characteristic	**Overall (*n* = 4,396, 34 centres)** N. (%)/mean(SD)
Demographics	
Female	1,706 (38.8)
Age, years	76.6 (10.6)
Medical history	
Heart failure	1,162 (26.4)
Coronary artery disease	995 (22.6)
Peripheral vascular disease	502 (11.4)
Cerebrovascular disease	634 (14.4)
Diabetes without end organ damage	774 (17.6)
Diabetes with end organ damage	228 (5.2)
Moderate or severe renal disease	531 (12.1)
Connective tissue disease	97 (2.2)
Dementia	490 (11.2)
Peptic ulcer disease	245 (5.6)
Mild liver disease	177 (4.0)
Moderate or severe liver disease	25 (0.6)
Cancer	578 (13.2)
Metastatic cancer	88 (2.0)
CMI	
Class 1 (CMI 0)	1,242 (28.3)
Class 2 (CMI 1-2)	1,890 (43.0)
Class 3 (CMI 3-4)	833 (19.0)
Class 4 (CMI ≥ 5)	431 (9.8)
Current respiratory medications	
Oxygen therapy	1,048 (24.8)
Inhaled beta agonists	2,080 (49.9)
Inhaled anticholinergic	1,454 (34.9)
Inhaled steroid	1,844 (44.2)
Systemic steroids	718 (17.2)
Theophylline	312 (7.5)
Antibiotics	662 (15.8)
Non invasive ventilation	115 (2.7)
CPAP	86 (2.0)

SD: standard deviation, CMI: Charlson comorbidity index, CPAP: Continuous Positive Airway Pressure

Table 2. ED management and outcome of patients with exacerbation of chronic obstructive pulmonary disease

Characteristic	**Overall (*n* = 4,396, 34 centres)** N. (%)/mean(SD)
Arrival status	
Ambulance call	2,395 (54.7)
Tachycardia (>109 bpm)	771 (18.5)
Tachypnea (>20)	1,779 (51.2)
Systolic blood pressure < 90 mmHg	58 (1.4)
Sat02 <90%	1,116 (26.2)
ED therapy	
Oxygen therapy	2,570 (59.9)
Bronchodilators	2,636 (60.8)
Inhaled beta agonists	2,581 (59.6)
Inhaled anticholinergic	1,877 (43.3)
Steroids	3,079 (71.0)
Inhaled steroids	2,467 (56.9)
Systemic steroids	2,302 (53.1)
Both inhaled and systemic	1700 (39.2)
Systemic beta agonists	19 (0.4)
Theophylline	186 (4.3)
Antibiotics	991 (22.8)
Non invasive ventilation	274 (6.3)
CPAP	102 (2.3)
Associated conditions	
Respiratory failure	1,241 (30.4)
Pneumonia	448 (11.0)
Altered mental status	316 (7.9)
ED disposition	
Discharged	1,192 (27.1)
Short-term observation	115 (2.6)
Admitted to hospital	2,839 (64.6)
Others	249 (5.7)
Department of admittance	
Critical care	42 (1.7)
Internal Medicine & Geriatrics	1944 (78.6)
Pulmonology	448 (18.1)
Others	41 (1.5)
Outcomes	220 (5.0)
Invasive mechanical ventilation	83 (2.0)
In hospital death	159 (3.6)

SD: standard deviation, ED: Emergency Department, CPAP: Continuous Positive Airway Pressure

Figure 1: geographical distribution of the participating centres

References - Part 1

1. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, Salcedo E, Navarro M, Ochando R (2005) Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 60 (11):925-931. doi:10.1136/thx.2005.040527
2. Cazzola M, Puxeddu E, Bettoncelli G, Novelli L, Segreti A, Cricelli C, Calzetta L (2011) The prevalence of asthma and COPD in Italy: a practice-based study. Respiratory medicine 105 (3):386-391. doi:10.1016/j.rmed.2010.09.022
3. Rycroft CE, Heyes A, Lanza L, Becker K (2012) Epidemiology of chronic obstructive pulmonary disease: a literature review. International journal of chronic obstructive pulmonary disease 7:457-494. doi:10.2147/COPD.S32330
4. Dal Negro R, Rossi A, Cerveri I (2003) The burden of COPD in Italy: results from the Confronting COPD survey. Respiratory medicine 97 Suppl C:S43-50
5. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sorensen HT, von Elm E, Langan SM, Committee RW (2015) The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS medicine 12 (10):e1001885. doi:10.1371/journal.pmed.1001885
6. Shorr AF, Sun X, Johannes RS, Derby KG, Tabak YP (2012) Predicting the need for mechanical ventilation in acute exacerbations of chronic obstructive pulmonary disease: comparing the CURB-65 and BAP-65 scores. Journal of critical care 27 (6):564-570. doi:10.1016/j.jcrc.2012.02.015
7. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40 (5):373-383
8. McGinn T, Wyer PC, Newman TB, Keitz S, Leipzig R, For GG, Evidence-Based Medicine Teaching Tips Working G (2004) Tips for learners of evidence-based medicine: 3. Measures of observer variability (kappa statistic). CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 171 (11):1369-1373. doi:10.1503/cmaj.1031981
9. Proposta metodologica per la valutazione dei costi dell'emergenza. (2007) Ministero della Salute. Accessed 09/14/2017 2017
10. Decramer M (2014) Global Strategy for the Diagnosis,Management, and Prevention of Chronic Obstructive Lung Disease (GOLD) 2014. http://goldcopd.org/. Accessed 01/20/2015
11. Kern LM, Malhotra S, Barron Y, Quaresimo J, Dhopeshwarkar R, Pichardo M, Edwards AM, Kaushal R (2013) Accuracy of electronically reported "meaningful use" clinical quality measures: a cross-sectional study. Annals of internal medicine 158 (2):77-83. doi:10.7326/0003-4819-158-2-201301150-00001
12. Sethi S, Evans N, Grant BJ, Murphy TF (2002) New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. The New England journal of medicine 347 (7):465-471. doi:10.1056/NEJMoa012561
13. From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. (2017). http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/.
14. Evensen AE (2010) Management of COPD exacerbations. Am Fam Physician 81 (5):607-613
15. Cydulka RK, Rowe BH, Clark S, Emerman CL, Camargo CA, Jr., Investigators M (2003) Emergency department management of acute exacerbations of chronic obstructive pulmonary disease in the elderly: the Multicenter Airway Research Collaboration. J Am Geriatr Soc 51 (7):908-916

16. Sorensen HT, Sabroe S, Olsen J (1996) A framework for evaluation of secondary data sources for epidemiological research. Int J Epidemiol 25 (2):435-442
17. Morris ZS, Wooding S, Grant J (2011) The answer is 17 years, what is the question: understanding time lags in translational research. J R Soc Med 104 (12):510-520. doi:10.1258/jrsm.2011.110180
18. Aaron SD (2014) Management and prevention of exacerbations of COPD. Bmj 349:g5237. doi:10.1136/bmj.g5237
19. Santus P, Picciolo S, Proietto A, Falcone F, Mangiacavallo A, Pellegrino G, Sereno F, Radovanovic D, Blasi F, Girbino G, Centanni S (2012) Doctor-patient relationship: a resource to improve respiratory diseases management. Eur J Intern Med 23 (5):442-446. doi:10.1016/j.ejim.2012.04.004

Part 2: Validation of the BAP-65 score for prediction of in-hospital death or use of mechanical ventilation in patients presenting to the emergency department with an acute exacerbation of COPD.

Introduction

Background and rationale

"Chronic Obstructive Pulmonary Disease (COPD) is defined as a "common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases." in the 2017 report from the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[1] Patients with COPD often experience acute exacerbations (AECOPDs), defined as "acute worsening of respiratory symptoms that result in additional therapy".[1] The spectrum of clinical presentation of AECOPDs is wide: in some case they can be treated at home, but they often induce the patients to access the emergency department (ED), and might require hospitalization. In severe cases, invasive mechanical ventilation (IMV) is necessary, and the incidence of in-hospital mortality is not negligible.[2] We recently conducted a research project under the auspices of the Italian Society of Emergency Medicine (SIMEU), aimed at collecting epidemiological data on patients accessing 34 Italian EDs with a suspect of AECOPD.[3] In summary, we found these patients to have a mean age of 77 years and to experience an important burden of comorbidity. The admission rate was 65%, and the estimated cost per patient was € 2617. The use of a risk assessment model (RAM) to predict patients prognosis and therefore guide decisions on the patients' destination (discharge, short-term observation, hospital medical ward or intensive care), and on type and intensity of monitoring, treatment and follow up during and after the acute episode can represent a step toward the improvement of the efficiency of care for AECOPD in the

ED. Among several RAMs proposed for patients with AECOPD, the BAP-65[4] is based on information which is easily available (elevated blood urea nitrogen [BUN], altered mental status, pulse > 109 beats/min, age > 65 years) and may serve emergency clinicians as a simple and rapid risk-stratification tool. The BAP-65 RAM has been derived and validated in cohorts of inpatients, admitted for AECOPD in the United States of America (USA). In these patients, the BAP-65 RAM showed a good accuracy for the prediction of the risk of mortality and the use of IMV during the hospital stay.[4,5] In particular, in the derivation and internal validation study, Tabak and colleagues[4] found an AUROC for mortality of 0.72 (95% confidence interval [CI], 0.70-0.74) in the derivation and 0.71 (95% CI, 0.70-0.73) in the internal validation cohort, respectively. The AUROC for IMV was 0.77 (95% CI, 0.75-0.79) for both the cohorts. The same research group, further validated the model with data from the same database on a different time period,[5] estimating an AUROC of 0.77 (95% CI, 0.76-0.78) for mortality, of 0.78 (95% CI, 0.78-0.79) for the use of IMV, and of 0.79 (95% CI, 0.78-0.80) for the composite outcome death and IMV.

However, to the best of our knowledge, the BAP-65 RAM has never been validated in the ED setting, where it could help to make decisions about the intensity of care and destination based on patient risk. Moreover, it has never been validated in Europe. If showed to be accurate for the prediction of poor prognosis in an ED population, the BAP-65 RAM could help the physicians in the management of patients with AECOPD.

Objectives

The present study aimed at the validation of the BAP-65 RAM for the prediction of in-hospital mortality and/or the use of IMV in an Italian cohort of patients attending the ED for an AECOPD. This was a pre-specified objective of the above-mentioned COPD-SIMEU research project.[3] Secondary objectives were the prediction of in-hospital mortality, use of IMV or non-invasive mechanical ventilation (NIV), separately.

Material and methods

Study Design

This was a retrospective cohort, multicentre, validation study. The present manuscript has been prepared according to the RECORD[6] and the TRIPOD[7] statements.

Study population and data collection

The study population, with inclusion and exclusion criteria, is described in detail in a previous manuscript (Part 1 of this thesis).[3] In brief, patients aged > 40 years attending the ED of one of the included centres during 2014 and discharged from the ED (to the ward, ICU or home) with a diagnosis of AECOPD were eligible. The EDs databases were used for patients' selection and for data extraction. The diagnosis of AECOPD was based on the International Classification of Diseases, 9th Revision (ICD9) code 491.21 or on the textual diagnosis, and further confirmed checking the data in the clinical chart. The researchers of each participating centre manually reviewed the charts to extract the data, following a detailed data extraction manual created ad hoc. FG, GV, and DA centrally reviewed the data quality and, when needed, local investigators were contacted for clarifications.

Outcomes

The primary outcome of the study was the composite of in-hospital death and the use of IMV. Secondary outcomes were separately the occurrence of in-hospital death the use of IMV, and the use of NIV.

Predictors

The BAP-65 RAM refers to information available on initial hospital presentation. The three main variables are BUN level > 25 mg/dL, altered mental status, and pulse > 109 beats/min. Patients who have none of these risk factors and are aged < 65 are designated as class I, while patients

with no risk factors who are aged 65 years or more are classified as class II. Patients who have one, two, or three main risk factors are designated into risk classes III, IV, and V, respectively. The occurrence of altered mental status was defined as a Glasgow Coma Score < 14 or a description by the physician of disorientation, stupor, or coma.[4]

As possible pre-specified confounders, we recorded information regarding sex, blood pressure at presentation, the presence of pneumonia or respiratory failure, and the variables included in the Charlson Comorbidity Index (CCI).[8] Respiratory failure was defined as SpO2 < 90% presence of respiratory failure among the discharge.

Respect to the derivation study,[4] the population of this study differed for the setting, as we enrolled patients presenting to the ED for an AECOPD either being admitted or discharged, while the derivation cohort was only composed of hospitalized patients. Besides that, eligibility criteria, outcome, and predictors of the validation cohort matched the derivation study.

Ethical considerations

The research was conducted according to the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee. A waiver for informed consent was obtained, given the retrospective nature of the study and the fact that data were anonymized before being entered in the general database.

Analysis

The baseline characteristics of the population were tabulated using standard descriptors of central tendency and variability (mean and standard deviation [SD] or ranges, as appropriate). We assessed the association between the BAP-65 score, other pre-specified variables, and the composite outcome using logistic regression, both univariate and multivariable, considering the centers as clusters. We included in the multivariable analysis the variables that showed a statistically significant association with the composite outcome at the univariate analysis. The

calibration of the risk score predictions was evaluated by plotting observed proportions versus predicted probabilities and by calculating the calibration slope and intercept.[7] The AUROC was used to assess the model's discrimination. Moreover, we derived sensitivity, specificity, positive predictive value, and negative predictive value of a BAP-65 ≥ 4 for the primary outcome. The AUROC, sensitivity, specificity, positive and negative predictive values were calculated also for the secondary outcomes. As a sensitivity analysis, we conducted the same analyses excluding patients with Pneumonia. The rationale for this sensitivity analysis is that some studies and recent guidelines exclude pneumonia when defining a COPD exacerbation.[1,9]

Sample size: The composite outcome was expected to occur in at least 5% of the study population.[5,10,11] We estimated a sample size of 2000 patients, since 100 patients with the outcome of interest have been suggested for validation studies to be able to reliably detect different types of model invalidity.[12]

Missing data: In some centres participating in the COPD-SIMEU project, the study collaborators were not able to retrieve data concerning the outcome or the variables included in the BAP-65 RAM. If the percentage of missing data for one of these variables was > than 25%, we decided to exclude the centre from the present analysis. We compared the characteristics of these two groups (included and excluded patients) using the t test for continuous variables and either the Pearson's chi-squared or the Fisher's exact test for proportions, as appropriate. For the remaining centres, we assumed missing data occurred at random and performed multiple imputations using the chained equations method, creating twenty different imputed data sets.[13]

Results

The BAP-65 score was calculated on 2,908 patients from 20 centres. Other 14 centres (1488 patients) were not able to provide the data required for the calculation of BAP-65 score (i.e. missing data for one or more variable were > 25%) and were excluded from the analysis. The most commonly missing data was urea, not measured in 1244 of the 1488 patients (84%). Table 3 shows the characteristics of the study population. The mean (SD) age was 76 years and 38% were female. A comparison with the characteristic of the patients excluded from this analysis is shown in eTable 1. In the validation cohort, data on the calculation of the BAP-65 score were missing in 10.7% of the cases. For all the other predictive and outcome variables, missing data were lower than 5% (see eTable 2). Table 4 shows a comparison of the distribution of demographics, predictors and outcomes among the derivation[4] and validation cohorts. Patients' distribution and outcomes frequencies among the 5 BAP-65 classes are reported in Table 5. Table 6 shows the unadjusted and adjusted association between each candidate predictor and outcome. The distribution of each predictor according to the occurrence of the composite outcome is shown in eTable 3. The multivariable analysis showed a statistically significant association ($p<0.05$) between BAP-65 score (OR 1.74, 95% CI 1.29-2.11) and hypotension (3.12, 95% CI 1.21-8.00), and the composite outcome.

The calibration plot for the composite outcome is shown in Figure 2 (slope = 0.69, intercept 1.7). Figure 3 shows the ROC curve of BAP-65 for the composite outcome. The AUROC was 0.64 (95% CI 0.59-0.68). The sensitivity of BAP-65 score ≥ 4 to predict the composite outcome was 40% (95% CI 32%-49%), the specificity was 84% (95% CI 82%-85%), the positive predictive value was 12% (95% CI 9%-15%), and the negative predictive value was 96% (95% CI 96%-97%).

For the outcome in-hospital mortality, the AUROC for BAP-65 was 0.66 (95% CI 0.60-0.71). The sensitivity of BAP-65 score ≥ 4 to predict in-hospital mortality was 44% (95% CI 34%-55%), the

specificity was 84% (95% CI 82%-85%), the positive predictive value was 9% (95% CI 6%-12%), and the negative predictive value was 98% (95% CI 97%-98%).

The AUROC for BAP-65 was 0.61 (95% CI 0.54-0.69) for IMV. The sensitivity of a BAP-65 score ≥ 4 to predict the use of IMV was 36% (95% CI 23%-52%), the specificity was 83% (95% CI 82%-85%), the positive predictive value was 4% (95% CI 2%-6%), and the negative predictive value was 99% (95% CI 98%-99%).

At the sensitivity analysis conducted excluding patients with pneumonia (2242 patients analysed), the AUROC for the BAP-65 score was 0.64 (95% CI 0.59-0.70) for the composite outcome. The sensitivity of a BAP-65 score ≥ 4 to predict the composite outcome was 42% (95% CI 32%-52%), the specificity was 85% (95% CI 83%-86%), the positive predictive value was 12% (95% CI 9%-16%), and the negative predictive value was 97% (96% CI 96%-97%).

Discussion

We assessed the accuracy of the BAP-65 score for the prediction of adverse outcomes on over two-thousand and nine-hundred patients. The AUROC of the BAP-65 RAM for the composite outcome (in-hospital mortality and/or use of IMV) was 0.64 (95% CI 0.59-0.68), with a sensitivity of 40% and a specificity of 84%. The AUROC for mortality was 0.66 (95% CI 0.60-0.71) and the AUROC for the use of IMV was 0.61 (95% CI 0.54-0.69). These results did not meaningfully change when patients with pneumonia were removed from the analysis. To our knowledge, this is the first attempt of validation of the BAP-65 RAM in the ED setting and the first one in general in a European cohort. We believe that this is important, because the model has been derived in an inpatient setting, while it is mainly meant to be used in the ED. It would not be appropriate to use the model in a setting different from the one in which it has been derived, without a new validation. Moreover, it is common in clinical research not to assume generalizability across populations differing for geographical, ethnical, and socio-cultural reasons, and across health systems. In particular, in this specific case, it is reasonable to think that the differences in the health system between the USA and Italy could affect the case mix of patients accessing ED with AECOPD in terms of severity of the index disease and comorbidities, and physicians' behaviours (e.g. attitude to use IMV).[14,15] Another strength of the study is the large number of contributing centres, which supports the generalizability of the results.

Our study had also some limitations. The retrospective nature of the study can translate into a better representation of the usual clinical practice,[16] but can also affect data quality and completeness. The diagnosis of COPD should be clinical and instrumental, but in the emergency setting the lack of time and clinical documentation may lead to a misdiagnosis of COPD and its exacerbations, only based on suggestive but not specific symptoms (wheezing and/or respiratory acidosis) and incomplete medical history. We tried to minimize this issue with a careful patient

selection process, as previously described.[3] To address the problem of data completeness, we used data imputation. However, for centers with a high proportion of missing data, we felt it was safer to exclude them from the analysis. This implied excluding 1488 patients form 14 centers. Urea was the missing BAP-65 variable for most of the patients with missing data, as it is not necessarily included in the routine lab screening done in Italian EDs. The characteristics of excluded and included patients did not match exactly. In particular, in centers excluded from the analysis, bronchodilators and steroids were used more frequently, while antibiotics were used less. This can affect the generalizability of our findings. However, we could still base our analysis on a considerable sample of 2,908 patients from 20 different centres across the country. Retrieving data on the blood gas analysis of the included patients would have allowed us to better define the respiratory failure, and the need for NIV and IMV. We tried to extract these data in a pilot phase with the first 3 centers but, unfortunately, we realized that the BGA results were seldom reported, so we decided to drop the variable. A longer follow-up would have been appropriate, especially in patients not admitted to the hospital (34%), but it would have required either a prospective design or at least the link with other databases, and those options were not viable for the present study. Compared to the derivation study, the validation cohort was older, had a higher proportion of males, BUN levels were higher, a lower proportion of patients had pulse >109 bpm, and mortality was higher. [4] These differences can be partially due to the diverse geographical and clinical settings in which the studies have been performed. Concerning the gender distribution, in the derivation study the male/female ratio was 0.82, while we found a ratio of 1.58. However, our findings are more in line with the gender distribution of the disease (being COPD more frequent among men),[17] and perfectly match the findings of a previous Italian study, with a male/female ration of 1.57.[18] The older age of patients, the higher proportion of males, and the high prevalence of comorbidities (mainly heart failure), can contribute to explain the higher

level of blood urea in our patients as compared to the derivation cohort. As a consequence of the different variable distributions, patients in the validation cohort were less likely to be classified in BAP-65 class 1 or 2, and this affected the model's discrimination. These factors can contribute to explaining the lower accuracy of BAP-65 RAM for the prediction of the adverse composite outcome found in our study, compared to the derivation and validation cohorts. On the other end, it is also known that the estimate of the predictive ability of a model form the derivation and internal validation set is usually overoptimistic.[7] This low accuracy and the fact that 95% of patients are categorized in class 2 or higher, therefore having a risk of short term adverse composite outcome ≥ 3.3%, do not support the use of this RAM for the management of patients in the ED. Several other RAMs have been proposed to be used for patients with AECOPD. Among others, the DECAF[19] and the Ottawa prediction rule[20] seem more valuable. However, these rules may be problematic to use in the ED. The DECAF score requires that dyspnoea is assessed using the extended Medical Research Council Dyspnoea (eMRCD) Score.[21] The eMRCD Score is not of commonly used by non-respirologists and might be difficult to implement while dealing with older patients, often presenting dementia or altered mental status. The Ottawa prediction rule entails the execution of the 3 minute walking test, and this can hinder its use in everyday practice in a busy and often chaotic environment such as the ED. Moreover, some of the variables contained in these RAMs would not be retrievable retrospectively, making them not suitable for our study. For these reasons, we decided to test the performance of the BAP-65 score, which is based on variables commonly available in the ED setting and easy to calculate. Unfortunately, a simple solution seems not to be the best for a complex disease, affecting complicated patients.

Conclusions

In patients attending Italian EDs with an AECOPD, the accuracy of the BAP-65 score in the prediction of adverse clinical outcomes does not support its use for the management of patients attending the ED for an AECOPD.

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Tables and Figures

Table 3 (part 1 of 2). Characteristics of patients with exacerbation of chronic obstructive pulmonary disease seen in the emergency department

Characteristic	**BAP-65 validation cohort (n = 2,908, 20 centres)** N. (%)/mean (SD)
Demographics	
Female	1,112 (38.2)
Age, years	76.2 (10.7)
CCI	
Class 1 (CCI 0)	789 (27.1)
Class 2 (CCI 1-2)	1,230 (42.3)
Class 3 (CCI 3-4)	593 (20.4)
Class 4 (CCI ≥ 5)	296 (10.2)
Current respiratory medications	
Oxygen therapy	694 (24.7)
Inhaled beta agonists	1,403 (50.8)
Inhaled anticholinergic	933 (33.8)
Inhaled steroid	1,226 (44.4)
Systemic steroids	491 (17.8)
Theophylline	205 (7.4)
Antibiotics	409 (14.7)
Non-invasive ventilation (NIV)	79 (2.8)
CPAP	64 (2.3)
Arrival status	
Ambulance call	1,552 (53.6)
Tachycardia (>109 bpm)	492 (17.7)
Tachypnea (>20)	1,177 (47.4)
Systolic blood pressure < 90 mmHg	36 (1.3)
Sat02 <90%	747 (26.2)

SD: standard deviation, CCI: Charlson comorbidity index, CPAP: Continuous Positive Airway Pressure

Table 3 (part 2 of 2). Characteristics of patients with exacerbation of chronic obstructive pulmonary disease seen in the emergency department

Characteristic	**BAP-65 validation cohort (n = 2,908, 20 centres)** N. (%)/mean (SD)
ED therapy	
Oxygen therapy	1,701 (58.9)
Bronchodilators	1,652 (57.3)
Inhaled beta agonists	1,617 (56.1)
Inhaled anticholinergic	1,035 (36.0)
Steroids	2,003 (69.5)
Inhaled steroids	1,546 (53.7)
Systemic steroids	1,451 (50.4)
Both inhaled and systemic	994 (32.8)
Systemic beta agonists	15 (0.5)
Theophylline	169 (5.8)
Antibiotics	708 (24.5)
Non-invasive ventilation (NIV)	200 (6.9)
CPAP	68 (2.4)
Associated conditions	
Respiratory failure	918 (31.7)
Pneumonia	333 (11.5)
Altered mental status	227 (8.0)
ED disposition	
Discharged	764 (26.3)
Short-term observation	53 (1.8)
Admitted to hospital	1,913 (65.8)
Others	177 (6.1)
Department of admittance	
Critical care	27 (1.6)
Internal Medicine & Geriatrics	1,337 (80.9)
Pulmonology	254 (15.4)
Others	34 (2.1)
Outcomes	151 (5.3)
Mechanical ventilation	55 (1.9)
In hospital death	110 (3.8)

SD: standard deviation, ED: Emergency Department, CPAP: Continuous Positive Airway Pressure

Table 4. Comparison of the BAP-65 derivation and validation cohorts

Characteristics of patients	Validation cohort (present study), N. (%) (n = 2,908, 20 centres)	Derivation cohort,[4] N. (%) (n = 43,893, 191 centres)
Demographics		
Female	1,112 (38.2)	24,047 (54.8)
Age, years	78 (70-84)*	72 (63-79)*
BAP items		
Blood urea >25	1,948 (70.7)	8564 (19.5)
Age >65	2,459 (84.6)	NA
Pulse >109 beats/min	492 (17.7)	13 063 (29.8)
Altered mental status	227 (8.0)	3493 (8.0)
Outcomes		
Invasive mechanical ventilation	55 (1.9)	926 (2.1)
In hospital death	110 (3.8)	774 (1.8)

* Median (1st and 3rd quartile); NA: not available

Table 5 Distribution of BAP-65 class and corresponding observed outcome

BAP-65 class	Prevalence, N (%)	Composite outcome, N (%)	Mortality	IMV
Class 1	126 (4.9)	2 (1.6)	1 (0.8)	1 (0.8)
Class 2	431 (16.6)	14 (3.3)	9 (2.1)	5 (1.2)
Class 3	1,592 (61.3)	60 (3.9)	41 (2.6)	24 (1.6)
Class 4	403 (15.5)	44 (11.1)	33 (8.2)	15 (3.8)
Class 5	44 (1.7)	7 (16.3)	7 (15.9)	2 (4.7)

IMV: invasive mechanical ventilation

Table 6 Univariate and multivariable analysis for the composite outcome

Predictor	**Missing data not imputed**		**Missing data imputed**	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**
Univariate analysis				
BAP65 class	2.11 (1.64 - 2.72)	< 0.001	1.71 (1.35 - 2.16)	< 0.001
Age	1.04 (1.03 - 1.06)	< 0.001	1.01 (0.99 - 1.04)	0.184
Sex (female)	0.98 (0.72 - 1.32)	0.879	0.96 (0.76 - 1.23)	0.768
Respiratory failure	3.75 (1.99 - 7.06)	< 0.001	1.82 (0.92 - 3.61)	0.087
Systolic blood pressure < 90 mmHg	4.68 (1.74 - 12.61)	0.002	3.61 (1.42 - 9.24)	0.007
Pneumonia	1.73 (1.21 - 2.46)	0.003	1.40 (0.89 - 2.20)	0.144
CCI	1.10 (1-02 - 1.19)	0.015	1.00 (0.92 - 1.09)	0.927
Heart failure	1.53 (1.05 - 2.22)	0.025	1.08 (0.77 - 1.51)	0.654
Coronary artery disease	0.95 (0.60 - 1.50)	0.815	0.90 (0.63 - 1.27)	0.536
Peripheral vascular disease	0.86 (0.50 - 1.49)	0.595	0.82 (0.51 - 1.31)	0.400
Cerebrovascular disease	1.06 (0.61 - 1.83)	0.848	0.83 (0.53 - 1.28)	0.395
Diabetes without end organ damage	1.04 (0.73 - 1.47)	0.842	0.91 (0.65 – 1.28)	0.594
Diabetes with end organ damage	0.78 (0.50 - 1.21)	0.272	0.63 (0.40 - 1.01)	0.054
Moderate or severe renal disease	1.20 (0.99 - 1.45)	0.066	0.99 (0.83 - 1.19)	0.933
Connective tissue disease	1.00 (0.44 - 2.25)	0.999	0.66 (0.28 - 1.56)	0.344
Dementia	2.47 (1.61 - 3.81)	< 0.001	1.75 (1.18 - 2.61)	0.005
Peptic ulcer disease	1.62 (0.90 - 2.91)	0.110	1.14 (0.60 - 2.15)	0.694
Mild liver disease	1.78 (0.99 - 3.20)	0.054	1.36 (0.78 - 2.36)	0.281
Cancer	1.27 (1.04 - 1.54)	0.018	1.13 (0.98 - 1.30)	0.084
Metastatic cancer	1.07 (0.93 - 1.23)	0.337	1.07 (0.94 - 1.21)	0.293
Multivariable analysis				
BAP65 class	1.70 (1.29 - 2.25)	< 0.001	1.74 (1.34 - 2.25)	< 0.001
Age	1.03 (1.01 - 1.05)	0.002	Not included*	-
Respiratory failure	3.17 (1.82 - 5.51)	0.000	Not included*	-
Systolic blood pressure < 90 mmHg	2.32 (0.57 – 9.50)	0.242	3.12 (1.21 – 8.00)	0.018

OR: odds ratio, CI: confidential interval, CCI: Charlson comorbidity index, *variables not included in multivariable analysis, having not showed a statistically significant association at univariate analysis.

Figure 2: Calibration plot and AUROC for mortality or invasive mechanical ventilation.

AUROC: area under the receiver operating characteristic curve

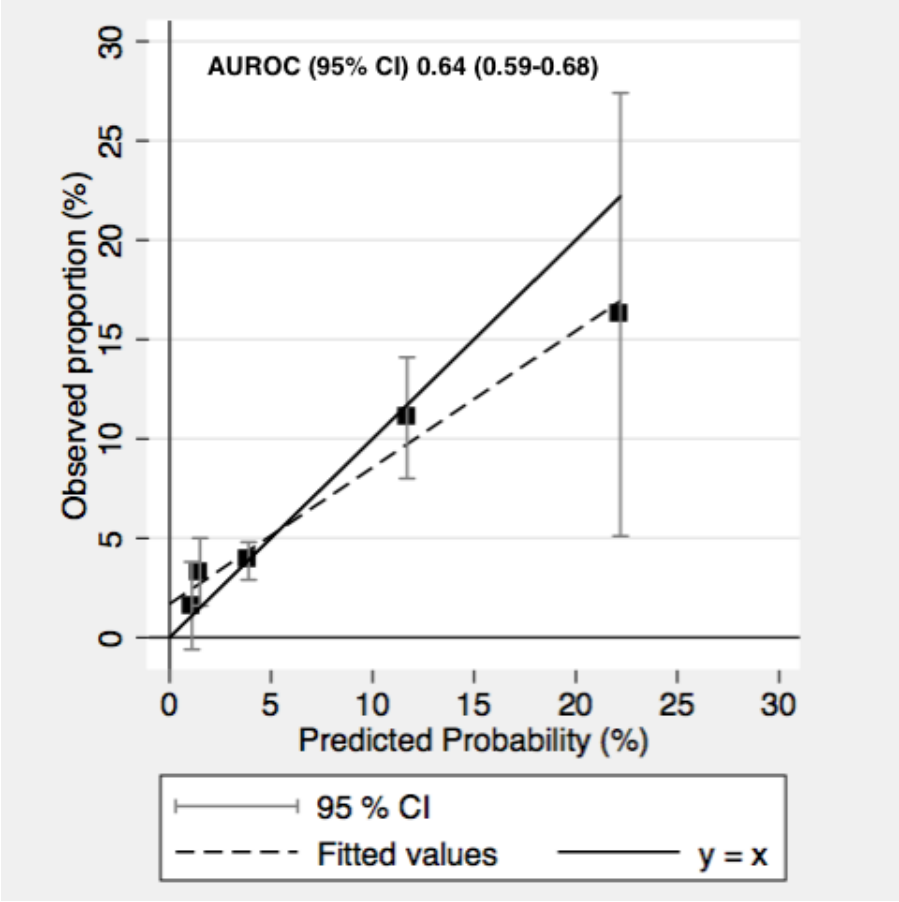
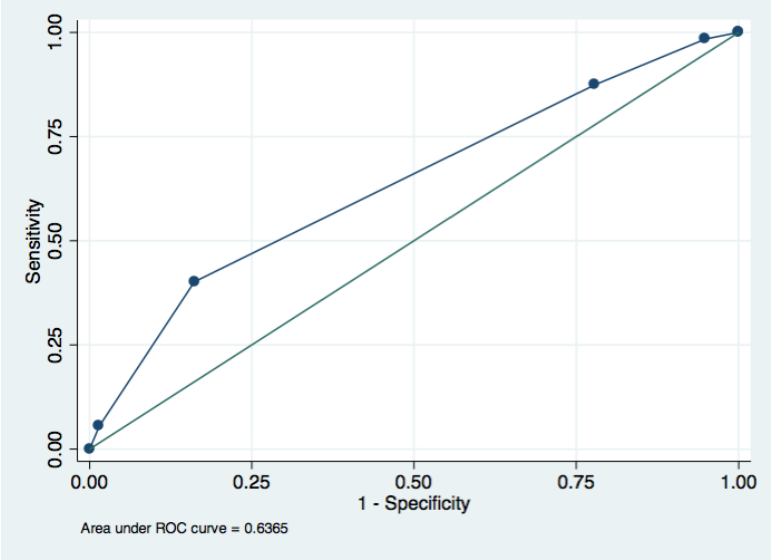


Figure 3: Receiver-operating characteristic (ROC) curve of the BAP-65 score for the prediction of the composite outcome in-hospital mortality and invasive mechanical ventilation



References – Part 2

1. Global Strategy for the Diagnosis, Management and Prevention of COPD - Global Initiative for Chronic Obstructive Lung Disease - GOLD 2017. https://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/. Published 2017. Accessed September 21, 2018.
2. Soler-Cataluna JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax*. 2005;60(11):925-931. doi:10.1136/thx.2005.040527
3. Germini F, Veronese G, Marcucci M, et al. COPD exacerbations in the emergency department: Epidemiology and related costs. A retrospective cohort multicentre study from the Italian Society of Emergency Medicine (SIMEU). *Eur J Intern Med*. 2018. doi:10.1016/j.ejim.2018.01.010
4. Tabak YP, Sun X, Johannes RS, Gupta V, Shorr AF. Mortality and need for mechanical ventilation in acute exacerbations of chronic obstructive pulmonary disease: development and validation of a simple risk score. *Arch Intern Med*. 2009;169(17):1595-1602. doi:10.1001/archinternmed.2009.270
5. Shorr AF, Sun X, Johannes RS, Yaitanes A, Tabak YP. Validation of a Novel Risk Score for Severity of Illness in Acute Exacerbations of COPD. *Chest*. 2011;140(5):1177-1183. doi:10.1378/chest.10-3035
6. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLOS Med*. 2015;12(10):e1001885. doi:10.1371/journal.pmed.1001885
7. Moons KGM, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): Explanation and Elaboration. *Ann Intern Med*. 2015;162(1):W1. doi:10.7326/M14-0698
8. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383. http://www.ncbi.nlm.nih.gov/pubmed/3558716. Accessed September 28, 2018.
9. Sethi S, Evans N, Grant BJB, Murphy TF. New Strains of Bacteria and Exacerbations of Chronic Obstructive Pulmonary Disease. *N Engl J Med*. 2002;347(7):465-471. doi:10.1056/NEJMoa012561
10. Shorr AF, Sun X, Johannes RS, Derby KG, Tabak YP. Predicting the need for mechanical ventilation in acute exacerbations of chronic obstructive pulmonary disease: Comparing the CURB-65 and BAP-65 scores. *J Crit Care*. 2012;27(6):564-570. doi:10.1016/j.jcrc.2012.02.015
11. CHANG CL, SULLIVAN GD, KARALUS NC, MILLS GD, MCLACHLAN JD, HANCOX RJ. Predicting early mortality in acute exacerbation of chronic obstructive pulmonary disease using the CURB65 score. *Respirology*. 2011;16(1):146-151. doi:10.1111/j.1440-1843.2010.01866.x
12. Vergouwe Y, Steyerberg EW, Eijkemans MJC, Habbema JDF. Substantial effective sample sizes were required for external validation studies of predictive logistic regression models. *J Clin Epidemiol*. 2005;58(5):475-483. doi:10.1016/j.jclinepi.2004.06.017
13. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med*. 2011;30(4):377-399. doi:10.1002/sim.4067
14. Ferré F, de Belvis AG, Valerio L, et al. Italy: Health system review. *Health Syst Transit*. 2014;16(4):1-168.
15. Rice T, Rosenau P, Unruh LY, Barnes AJ, Saltman RB, van Ginneken E. United States of

America: health system review. *Health Syst Transit*. 2013;15(3):1-431. http://www.ncbi.nlm.nih.gov/pubmed/24025796.
16. Sorensen HT, Sabroe S, Olsen J. A framework for evaluation of secondary data sources for epidemiological research. *Int J Epidemiol*. 1996;25(2):435-442. http://www.ncbi.nlm.nih.gov/pubmed/9119571. Accessed September 28, 2018.
17. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J*. 2006;28(3):523-532. doi:10.1183/09031936.06.00124605
18. Cazzola M, Puxeddu E, Bettoncelli G, et al. The prevalence of asthma and COPD in Italy: A practice-based study. *Respir Med*. 2011;105(3):386-391. doi:10.1016/j.rmed.2010.09.022
19. Steer J, Gibson J, Bourke SC. The DECAF Score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. *Thorax*. 2012;67(11):970-976. doi:10.1136/thoraxjnl-2012-202103
20. Stiell IG, Clement CM, Aaron SD, et al. Clinical characteristics associated with adverse events in patients with exacerbation of chronic obstructive pulmonary disease: a prospective cohort study. *Can Med Assoc J*. 2014;186(6):E193-E204. doi:10.1503/cmaj.130968
21. Steer J, Norman EM, Afolabi OA, Gibson GJ, Bourke SC. Dyspnoea severity and pneumonia as predictors of in-hospital mortality and early readmission in acute exacerbations of COPD. *Thorax*. 2012;67(2):117-121. doi:10.1136/thoraxjnl-2011-200332

Appendix

eTable1 (part 1 of 2). Characteristics of patients with exacerbation of chronic obstructive pulmonary disease seen in the emergency department

Characteristic	**BAP-65 validation cohort (n = 2,908, 20 centres)** N. (%)/mean (SD)	**Excluded patients (n = 1488, 14 centres)** N. (%)/mean (SD)	**P value**
Demographics			
Female	1,112 (38.2)	594 (39.9)	0.279
Age, years	76.2 (10.7)	77.5 (10.3)	**0.0002**
CMI			**0.001**
Class 1 (CMI 0)	789 (27.1)	453 (30.4)	
Class 2 (CMI 1-2)	1,230 (42.3)	660 (44.4)	
Class 3 (CMI 3-4)	593 (20.4)	240 (16.1)	
Class 4 (CMI ≥ 5)	296 (10.2)	135 (9.9)	
Current respiratory medications			
Oxygen therapy	694 (24.7)	354 (24.8)	0.948
Inhaled beta agonists	1,403 (50.8)	677 (48.1)	0.097
Inhaled anticholinergic	933 (33.8)	521 (37.0)	**0.042**
Inhaled steroid	1,226 (44.4)	618 (43.9)	0.731
Systemic steroids	491 (17.8)	227 (16.6)	0.182
Theophylline	205 (7.4)	107 (7.6)	0.818
Antibiotics	409 (14.7)	253 (17.9)	0.007
Non invasive ventilation	79 (2.8)	22 (1.5)	0.246
CPAP	64 (2.3)	36 (2.5)	
Arrival status			
Ambulance call	1,552 (53.6)	843 (56.7)	**0.048**
Tachycardia (>109 bpm)	492 (17.7)	279 (20.0)	0.076
Tachypnea (>20)	1,177 (47.4)	602 (60.5)	**0.001**
Systolic blood pressure < 90 mmHg	36 (1.3)	22 (1.5)	0.495
Sat02 <90%	747 (26.2)	369 (26.2)	0.986

SD: standard deviation, CMI: Charlson comorbidity index, CPAP: Continuous Positive Airway Pressure

eTable1 (part 2 of 2). Characteristics of patients with exacerbation of chronic obstructive pulmonary disease seen in the emergency department

Characteristic	**BAP-65 validation cohort (n = 2,908, 20 centres)** N. (%)/mean (SD)	**Excluded patients (n = 1488, 14 centres)** N. (%)/mean (SD)[1]	**P value**
ED therapy			
Oxygen therapy	1,701 (58.9)	869 (61.9)	0.064
Bronchodilators	1,652 (57.3)	984 (67.7)	**<0.001**
Inhaled beta agonists	1,617 (56.1)	964 (66.3)	**<0.001**
Inhaled anticholinergic	1,035 (36.0)	842 (58.0)	**<0.001**
Steroids	2,003 (69.5)	1,076 (74.0)	**0.002**
Inhaled steroids	1,546 (53.7)	921 (63.4)	**<0.001**
Systemic steroids	1,451 (50.4)	851 (58.5)	**<0.001**
Both inhaled and systemic	994 (32.8)	696 (47.9)	**<0.001**
Systemic beta agonists	15 (0.5)	4 (0.8)	0.333
Theophylline	169 (5.8)	17 (1.1)	**<0.001**
Antibiotics	708 (24.5)	283 (19.4)	**<0.001**
Non invasive ventilation	200 (6.9)	74 (5.1)	0.058
CPAP	68 (2.4)	34 (2.33)	
Associated conditions			
Respiratory failure	918 (31.7)	323 (27.5)	**0.005**
Pneumonia	333 (11.5)	115 (9.7)	0.104
Altered mental status	227 (8.0)	89 (7.7)	0.702
ED disposition			**<0.001**
Discharged	764 (26.3)	428 (28.8)	
Short-term observation	53 (1.8)	62 (4.2)	
Admitted to hospital	1,913 (65.8)	926 (62.2)	
Others	177 (6.1)	65 (4.4)	
Department of admittance			**<0.001**
Critical care	27 (1.6)	15 (1.8)	
Internal Medicine & Geriatrics	1,337 (80.9)	607 (73.8)	
Pulmonology	254 (15.4)	194 (23.6)	
Others	34 (2.1)	7 (0.85)	
Outcomes	151 (5.3)	67 (5.0)	0.664
Mechanical ventilation	55 (1.9)	28 (2.1)	0.742
In hospital death	110 (3.8)	49 (3.3)	0.409

SD: standard deviation, ED: Emergency Department, CPAP: Continuous Positive Airway Pressure

eTable 2 Missing data in the BAP-65 validation cohort (2908 patients)

Variable	Missing, N (%)
Outcomes	76 (2.6)
Mechanical ventilation	1 (0.0)
In-hospital death	75 (2.6)
BAP-65 RAM	312 (10.7)
Blood urea	154 (5.3)
Age	2 (0.1)
Altered mental status	82 (2.8)
Heart rate	130 (4.5)
Pneumonia	11 (0.4)
Respiratory failure	9 (0.3)
Systolic arterial pressure	105 (3.6)
CCI	0 (0)

RAM: risk assessment model CCI: Charlson comorbidity index

eTable 3 Distribution of predictors according to the occurrence of the combined outcome.

	Combined outcome (%)	
	No	**Yes**
BAP65 class; median (Q1, Q3)	3 (3, 3)	3 (3, 4)
Age; mean (SD)	76.1 (10.7)	80.3 (9.2)
Sex (female)	61.7	62.3
Respiratory failure	30.6	62.3
Systolic blood pressure < 90 mmHg	1.1	4.9
Pneumonia	11.2	17.9
CCI class; median (Q1, Q3)	2 (1, 3)	2 (2, 3)
Heart failure	26.7	35.8
Coronary artery disease	23.5	22.5
Peripheral vascular disease	10.6	9.3
Cerebrovascular disease	14.6	15.2
Diabetes without end organ damage	20.0	20.5
Diabetes with end organ damage	6.3	4.0
Moderate or severe renal disease	14.7	19.9
Connective tissue disease	2.7	2.7
Dementia	7.4	16.6
Peptic ulcer disease	5.1	8.0
Mild liver disease	4.6	8.0
Cancer	12.9	19.2
Metastatic cancer	1.8	2.7

Q1: first quartile
Q3: third quartile
SD: standard deviation
CCI: Charlson comorbidity index

References - Appendix

1. Tabak YP, Sun X, Johannes RS, Gupta V, Shorr AF (2009) Mortality and need for mechanical ventilation in acute exacerbations of chronic obstructive pulmonary disease: development and validation of a simple risk score. Archives of internal medicine 169 (17):1595-1602. doi:10.1001/archinternmed.2009.270

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Authors

Federico Germini[1,2,3], Giacomo Veronese[4], Maura Marcucci[2], Daniele Coen[4], Deborah Ardemagni[5, 6], Nicola Montano[3, 6] Andrea Fabbri[7], and the SIMEU Study Group

Affiliations

[1] Department of Health Sciences, Università degli Studi di Milano, Milan, Italy;

[2] Department of Health Research Methods, Evidence, and Impact (formerly Clinical Epidemiology and Biostatistics), McMaster University, Hamilton, ON, Canada;

[3] Emergency Department, Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Milan, Italy;

[4] Department of Emergency Medicine, Grande Ospedale Metropolitano Niguarda Ca' Granda, Università di Milano-Bicocca, Milan, Italy;

[5] Geriatric Unit, Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Milan, Italy;

[6] Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy;

[7] Department of Emergency Medicine, Ospedale Morgagni-Pierantoni, Forlì, Italy

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Study collaborators:

Luigi Elio Adinolfi, Università della Campania Luigi Vanvitelli, Dipartimento di Scienze Mediche, Chirurgiche, Neurologiche, Metaboliche e dell'Invecchiamento, Ospedale Clinicizzato di Marcianise, Marcianise (CE), Italia;

Antonella Alvisi, Pronto Soccorso e Medicina D'urgenza Ospedale Civile di Vignola AUSL Modena

Pagano Antonio, U.O.C Ps-OBI A.O.R.N A. Cardarelli di Napoli, Italia;

Giulia Azin, Dipartimento di Scienza della Salute, Università degli studi di Milano Bicocca, Italia;

Andrea Balloni, Pronto Soccorso Ospedale A. Murri, Fermo, Italia;

Geminiano Bandiera, Pronto Soccorso OCSAE - Azienda Ospedaliero Universitaria Policlinico OCSAE Modena, Italia;

Marco Barchetti, Nuovo Ospedale di Sassuolo, Modena, Italia;

Alfredo Barillari, Pronto Soccorso, AAS2 Bassa Friulana-Isontina, Ospedale di Monfalcone (Go) Italia;

Marco Barozzi, U.O. Medicina d'Urgenza-Pronto Soccorso, Presidio Ospedaliero "Bufalini-Marconi-Angiloni", Cesena, Italia;

Giulia Belloni, Geriatria, Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Milano, Italia;

Eugenia Belotti, Emergenza Alta Specializzazione (Pronto soccorso), ASST Papa Giovanni XXIII di Bergamo, Italia;

Nicola Binetti, Unità Operativa di Pronto Soccorso ed Emergenza territoriale, Area Nord Bologna, Italia;

Miriam Bonora, Pronto Soccorso e Medicina d'Urgenza, Ospedale Madonna delle Grazie, Matera, Italia;

Rosamaria Bruni, Pronto Soccorso ospedale San Martino, Belluno, Italia;

Silvia Cacco, Pronto Soccorso, ASST Melegnano e Martesana, Presidio di Vizzolo Predabissi, Milano, Italia;

Daniele Camisa, Pronto Soccorso, ASST Melegnano e Martesana, Presidio di Vizzolo Predabissi, Milano, Italia;

Giorgio Carbone, S.C. di Medicina e Chirurgia d'Urgenza e Accettazione, Humanitas "Gradenigo", Torino, Italia;

Giuseppe Carpinteri, Azienda Ospedaliero Universitaria Policlinico Vittorio Emanuele, Catania, Italia;

Laura Catino, Università degli Studi di Modena e Reggio Emilia, Italia;

Massimo Cazzaniga, Pronto Soccorso, Ospedale A. Manzoni, Azienda Ospedaliera di Lecco, Lecco, Italia;

Patrizia Cenni, Pronto Soccorso e Medicina d'Urgenza, Ospedale di Imola (BO), Italia;

Vittorio Chelli, Dipartimento di Emergenza e Accettazione, Presidio Grosseto, Azienda Usl Toscana sud est, Italia;

Leonora Cicero, U.O. Medicina d'Urgenza-Pronto Soccorso, Presidio Ospedaliero "Bufalini-Marconi-Angiloni", Cesena, Italia;

Carlo Domenico Cottone, Responsabile PS, Ospedale di Petralia Sottana (PA), Italia;

Filippa Cuccia, Pronto Soccorso e Medicina d'Urgenza, Ospedale Madonna delle Grazie, Matera, Italia;

Luciano D'Angelo, Pronto Soccorso, Ospedale A. Manzoni, Azienda Ospedaliera di Lecco, Lecco, Italia;

Francesca Dalmonte, Pronto Soccorso e Medicina d'Urgenza, Ospedale di Imola (BO), Italia;

Fabio Daviddi, Medicina d'Accettazione e d'Urgenza P.O. Pescia (PT), Italia;

Anna De Vita, Università della Campania Luigi Vanvitelli, Dipartimento di Scienze Mediche, Chirurgiche, Neurologiche, Metaboliche e dell'Invecchiamento. Ospedale Clinicizzato di Marcianise. Marcianise (CE), Italia;

Fausto Famà, Human Pathology Department, University Hospital "G. Martino" of Messina, Messina (Italia);

Marta Fedele, Marta Fedele, Unità Operativa di Pronto Soccorso ed Emergenza territoriale, Area Nord Bologna, Italia;

Caterina Fonti, S.C. di Medicina e Chirurgia d'Urgenza e Accettazione, Humanitas "Gradenigo", Torino, Italia;

Marta Frigerio, Pronto Soccorso Ospedale A. Murri, Fermo, Italia;

Alan Gallingani, Nuovo Ospedale di Sassuolo, Modena, Italia;

Valeria Ghiglione, Pronto Soccorso, Ospedale S. Paolo, Savona, ASL 2 Liguria, Italia;

Maria Gioffrè-Florio, Human Pathology Department, University Hospital "G. Martino" of Messina, Messina (Italia);

Mauro Giordano, Università della Campania Luigi Vanvitelli, Dipartimento di Scienze Mediche, Chirurgiche, Neurologiche, Metaboliche e dell'Invecchiamento, Ospedale Clinicizzato di Marcianise, Marcianise (CE), Italia;

Fabrizio Giostra, Pronto Soccorso Ospedale A. Murri, Fermo, Italia;

Maria Giulia Galli, Dipartimento di Medicina Clinica e Sperimentale, Università degli Studi di Parma, Parma, Italia;

Maria Elena Greggi, Pronto Soccorso, Ospedale di Petralia Sottana (PA), Italia;

Paolo Groff, UO Pronto Soccorso e Medicina d'Urgenza, Ospedale "Madonna del Soccorso", San Benedetto del Tronto, Italia;

Stefano Guizzardi, Pronto Soccorso, Ospedali riuniti Padova Sud Madre Teresa di Calcutta, Azienda ULSS 6 Euganea, Schiavonia, Padova, Italia;

Chiara Lagasio, Pronto Soccorso, Ospedale S. Paolo, Savona, ASL 2 Liguria, Italia;

Giuseppe Lazzara, Pronto Soccorso, Ospedali riuniti Padova Sud Madre Teresa di Calcutta, Azienda ULSS 6 Euganea, Schiavonia, Padova, Italia;

Eloisa Lubini, Pronto Soccorso, AAS2 Bassa Friulana-Isontina, Ospedale di Monfalcone (Go) Italia;

Laura Magni, Pronto Soccorso, ASST di Vimercate, Ospedale di Vimercate (MB), Italia;

Sandro Mancarella, Pronto Soccorso, Ospedale Bassini, Cinisello Balsamo, ASST-Nord Milano, Italia;

Giuseppe Mangano, Azienda Ospedaliero Universitaria Policlinico Vittorio Emanuele, Catania, Italia;

Margherita Maragno, Pronto Soccorso e Medicina d'Urgenza, Ospedale Madonna delle Grazie, Matera, Italia;

Monia Menabue, Pronto Soccorso e Medicina D'urgenza, Ospedale Civile di Vignola, AUSL Modena, Italia;

Eleonora Meoni. Medicina d'Accettazione e d'Urgenza P.O. Pescia (PT), Italia;

Federica Molinaro, S.C. di Medicina e Chirurgia d'Urgenza e Accettazione, Humanitas "Gradenigo", Torino, Italia;

Alice Morelli, Pronto Soccorso, Medicina D'Urgenza e 118 - Ospedale Morgagni-Pierantoni di Forlì, Italia;

Francesco Moscariello, Pronto soccorso e medicina d'urgenza Pordenone, Italia;

Riccardo Nevola, Università della Campania Luigi Vanvitelli, Dipartimento di Scienze Mediche, Chirurgiche, Neurologiche, Metaboliche e dell'Invecchiamento, Ospedale Clinicizzato di Marcianise. Marcianise (CE), Italia;

Paola Noto, Azienda Ospedaliero Universitaria Policlinico Vittorio Emanuele, Catania, Italia;

Fiorella Paladino, U.O.C Ps-OBI A.O.R.N A. Cardarelli di Napoli, Italia;

Roberta Pancani, Medicina e Chirurgia d'accettazione e d'urgenza Azienda USL Toscana Nordovest, Italia;

Giuseppina Petrelli, UO Pronto Soccorso e Medicina d'Urgenza, Ospedale "Madonna del Soccorso", San Benedetto del Tronto, Italia;

Roberta Petrino, Medicina e Chirurgia d'Accettazione ed Urgenza (MeCAU) - Pronto Soccorso, Ospedale S. Andrea, Vercelli, Italia;

Carmine Sinno, Pronto Soccorso e Medicina d'Urgenza, Ospedale Madonna delle Grazie, Matera, Italia;

Aferdita Tafa, Dipartimento di Emergenza e Accettazione, Presidio Grosseto, Azienda Usl Toscana sud est, Italia;

Sergio Tartaglia, Medicina e Chirurgia d'Accettazione ed Urgenza (MeCAU) - Pronto Soccorso, Ospedale S. Andrea, Vercelli, Italia;

Chiara Taurino, Medicina e Chirurgia d'accettazione e d'urgenza Azienda USL Toscana Nordovest, Italia;

Martina Treleani, Pronto soccorso e medicina d'urgenza Pordenone, Italia;

Liliana Villari, Medicina e Chirurgia d'accettazione e d'urgenza Azienda USL Toscana Nordovest, Italia;

Alessandra Vitelli, U.O.C Ps-OBI A.O.R.N A. Cardarelli di Napoli, Italia;

Cinzia Zaccagni, Pronto Soccorso, Ospedale Bassini, Cinisello Balsamo, ASST-Nord Milano, Italia;

Bruna Zaccaro, Pronto Soccorso e Medicina d'Urgenza, Ospedale Madonna delle Grazie, Matera, Italia;

Massimo Zacchino, Dipartimento di Scienza della Salute, Università degli studi di Milano Bicocca, Italia