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FRAILTY INDEX AS A PROGNOSTIC TOOL: THE FRA-COVID STUDY AND THE ROLE OF FRAILTY IN COVID-19 IN-HOSPITAL MORTALITY

Tesi di Specializzazione di

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Chapter 1

Frailty Index as a prognostic tool

Frailty is defined as a nonspecific state of increasing risk, highly age-associated, which derives from multisystem physiological change[1]. The underlying changes do not by themselves always achieve disease status, so that some people, usually very elderly, are frail without having life-threatening illness.

A quantitative way to define frailty has been defined by Rockwood et other researchers[2] [3] [4] [5] [6] [7], considered in relation to the accumulation of deficits: namely, as Frailty Index (FI). The FI score is calculated as the proportion of potential deficits that are present in an individual, considering symptoms, signs, disabilities, diseases and laboratory measurements. Single deficits can be combined by addition, either considering 1 if present and 0 if absent, or utilizing fractions when a deficit is present to a limited extent.

[1] Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci. 2007 Jul;62(7):722-7. doi: 10.1093/gerona/62.7.722.

[2] Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal. 2001 Aug 8;1:323-36. doi: 10.1100/tsw.2001.58.

[3] Goggins WB, Woo J, Sham A, Ho SC. Frailty index as a measure of biological age in a Chinese population. J Gerontol A Biol Sci Med Sci. 2005 Aug;60(8):1046-51. doi: 10.1093/gerona/60.8.1046.

[4] Woo J, Goggins W, Sham A, Ho SC. Social determinants of frailty. Gerontology. 2005 Nov-Dec;51(6):402-8. doi: 10.1159/000088705.

[5] Woo J, Goggins W, Sham A, Ho SC. Public health significance of the frailty index. Disabil Rehabil. 2006 Apr 30;28(8):515-21. doi: 10.1080/09638280500215867.

[6] Kulminski A, Yashin A, Ukraintseva S, Akushevich I, Arbeev K, Land K, Manton K. Accumulation of health disorders as a systemic measure of aging: Findings from the NLTCS data. Mech Ageing Dev. 2006 Nov;127(11):840-8. doi: 10.1016/j.mad.2006.08.005.

[7] Kulminski A, Yashin A, Arbeev K, Akushevich I, Ukraintseva S, Land K, Manton K. Cumulative index of health disorders as an indicator of aging-associated processes in the elderly: results from analyses of the National Long Term Care Survey. Mech Ageing Dev. 2007 Mar;128(3):250-8. doi: 10.1016/j.mad.2006.12.004.

An interesting feature of the FI is that the variables included in it can be selected at random between those theoretically eligible, and yet the resulting FIs still yield comparable results in terms of risk of adverse outcomes, as long as a sufficiently large number of variables is considered (~40)[8].

The frailty likelihood described by the FI is associated with a greater risk of adverse outcomes, being institutionalization, further deficit accumulation of death; it must be stressed nevertheless that frailty is neither necessary for adverse outcomes to happen, nor it is sufficient.

A different, popular approach to frailty assessment is the Clinical Frailty Scale (CFS), through which an experienced clinician summarizes the overall level of fitness or frailty of an individual according to a clinical and anamnestic examination. The first version of the tool[9] comprised of 7 levels, from "very fit" to "severely frail", and was later expanded to 9 levels.

[8] Rockwood K, Mitnitski A, Song X, Steen B, Skoog I. Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. J Am Geriatr Soc. 2006 Jun;54(6):975-9. doi: 10.1111/j.1532-5415.2006.00738.x.

[9] Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005 Aug 30;173(5):489-95. doi: 10.1503/cmaj.050051.

A great advantage of the CFS is its handiness, since it can be performed relatively quickly and inexpensively, provided that the health professional is well trained in the tool usage.

Frailty has become of particular relevance in the coronavirus pandemic of 2020: the presence of comorbidities alone in a patient, along with chronological age, do not account for the heterogeneity observed in individual prognoses[10]. In fact, for older patients features like functional and cognitive status, and lifestyle habits, have been observed to relate with the individual's survival, even when comorbidities are absent[11].

For these reasons, it has been proposed to utilize frailty in order to guide the clinical decisions about older patients hospitalized with COVID-19[12], keeping in mind that frailty alone can not entirely determine the patient's likely prognosis[13].

[10] Cesari M, Marzetti E, Thiem U, Pérez-Zepeda MU, Abellan Van Kan G, Landi F, Petrovic M, Cherubini A, Bernabei R. The geriatric management of frailty as paradigm of "The end of the disease era". Eur J Intern Med. 2016 Jun;31:11-4. doi: 10.1016/j.ejim.2016.03.005.

[11] Dent E, Martin FC, Bergman H, Woo J, Romero-Ortuno R, Walston JD. Management of frailty: opportunities, challenges, and future directions. Lancet. 2019 Oct 12;394(10206):1376-1386. doi: 10.1016/S0140-6736(19)31785-4.

[12] Excellence NIFHaC. *COVID-19 rapid guideline: critical care in adults*. 2020. 20 March 2020. www.nice.org.uk/guidance/ng159

[13] Cosco TD, Best J, Davis D, Bryden D, Arkill S, van Oppen J, Riadi I, Wagner KR, Conroy S. What is the relationship between validated frailty scores and mortality for adults with COVID-19 in acute hospital care? A systematic review. Age Ageing. 2021 May 5;50(3):608-616. doi: 10.1093/ageing/afab008.

The aim of the FRA-COVID study is to investigate the association between frailty, measured as FI or as CFS, and in-hospital mortality in cohorts of adult patients admitted with COVID-19 in two large hospitals in northern Italy in 2020.

Chapter 2

FRA-COVID: a multi-center observational prospective study. Study design and methods

The project “Frailty and clinical outcome in elderly COVID-19 patients” (FRA-COVID) is a multi-center, prospective observational study conducted across three hospitals in northern Italy, aimed to investigate the association between frailty and mortality in patients admitted with COVID-19.

We recruited all COVID-19 patients hospitalized in COVID+ wards in Hospital St. Gerardo (Monza) and ASST Spedali Civili (Brescia), the latter hospital comprising two separated structures. We recruited patients in two acute wards in both hospitals, Geriatrics and Infectious Diseases. Patients’ admissions occurred either by transfer from other hospitals, or by Emergency Department.

Inclusion and exclusion criteria were diagnosis of COVID-related pneumonia and age below 18 years, respectively. COVID-19 diagnosis was determined by positive polymerase chain reaction nasopharyngeal swab test; informed consent for the participation to the study was obtained orally from patients or, if unable to provide it, from proxy respondents.

Study data was collected using structured electronic case report forms, through the online platform Research Electronic Data Capture (REDCap).

The information collected for each patient included sociodemographic data, smoking habits, comorbidities, information pertaining subject's functional autonomy, need for supplemental oxygen, onset of acute symptoms, delirium, blood panel and vital signs at admission, administered therapies, ventilation support, complications and patient outcome (either discharged, transferred to another structure, or dead). When appropriate, the anamnesis was completed by telephone interviews with family members of caregivers.

An assessment of frailty through the Clinical Frailty Scale (CFS) was also performed, evaluating in a nine-point scale patient's mobility, physical activity and function referred to the two weeks preceding symptoms' onset. A value of 1 indicates a very fit individual, while a value of 9 a terminally ill patient.

Statistical methods

Continuous variables were described using median and quartiles (Q1-Q3), while categorial ones were expressed as frequency and percentage. All variables were listed overall and divided by age class (<70, 70-79, >79 years of age).

Crude cumulative incidence of mortality was estimated by Aalen-Johansen, accounting for the competing events discharge or transfer to other facilities, and compared in patients with high and low frailty index by the Gray test. The cutoff used to divide patients in high- and low-frailty was set by the Youden index, in order to maximize specificity and sensitivity on Receiver Operating Characteristic (ROC) curve on in-hospital mortality.

In order to evaluate the association between frailty and in-hospital mortality we applied a multivariable Cox regression model stratified for center and ward, including potential confounders. Confounders were chosen a priori by a clinical point of view and were confirmed by the least absolute shrinkage and selection operator (LASSO) conditional logistic regression model with a 10-fold cross-validation in order to avoid overfitting.

Data elaboration and statistical analysis were performed using SAS (version 9.4) and R software (version 3.5.2).

Chapter 3

FRA-COVID: Results

We recruited a total of 1377 patients across the two centers; we then excluded 31 of them since they had been admitted to an intensive care unit before having been recruited, leaving 1346 patients. This was decided on the ground of a presumable dishomogeneity with the main sample, patients from ICU being more likely to incur in an adverse outcome.

Collected variables and their frequencies are shown in table 1, overall and stratified by age (<70, 70-79, >79 years). Patient median age was 68 years (Q1-Q3 56-79), and 859 of them (64%) were men. 240 (18%) patients died during hospitalization, 883 (66%) were discharged alive and the remaining 221 were transferred to other hospitals (188 to post-acute care settings, 28 to acute hospitals and 5 patients with destination not recorded). The median length of stay was 11 days (1st -3rd quartile 7-18 days). The FI distribution included in table 1 refers to the FI calculated using 36 items (see below).

Table 1: Patients' characteristics on admission overall and by age class (n=1346)

	Overall	<70 y	70-79 y	>79 y	Missing %
Total patients	*1346*	*706*	*311*	*329*	
Demographics					
Age (median, Q1, Q3)	68 [56, 79]	57 [50, 63]	75 [72, 77]	84 [82, 88]	0
Male sex	859 (64)	479 (68)	194 (62)	186 (57)	0
Living alone	276 (26)	96 (17)	50 (21)	130 (50)	22.2
Living with caregiver or in nursing home	107 (9)	12 (2)	17 (6)	78 (27)	12.6
Smoke					38.7
Current	42 (5)	27 (6)	10 (5)	5 (3)	
Previous	221 (27)	106 (22)	69 (37)	46 (29)	
Admission after 1st of July 2020	642 (48)	314 (44)	145 (47)	183 (56)	0
Comorbidities					
Hypertension	706 (52)	250 (35)	198 (64)	258 (78)	0.1
Cardiopathy	334 (25)	67 (9)	100 (32)	167 (51)	0.2
Atrial fibrillation	123 (9)	17 (2)	29 (9)	77 (23)	0.1
Peripheral vascular disease	139 (10)	13 (2)	48 (15)	78 (24)	0.3
Heart failure	58 (4)	5 (1)	15 (5)	38 (12)	0.1
Stroke	73 (5)	12 (2)	22 (7)	39 (12)	0.1
Diabetes mellitus	294 (22)	98 (14)	109 (35)	87 (27)	0.1
Depression	70 (5)	30 (4)	18 (6)	22 (7)	1
Osteoarthritis	115 (9)	13 (2)	26 (8)	76 (24)	1
Osteoporosis	70 (5)	9 (1)	13 (4)	48 (15)	1.2
Chronic Obstructive Pulmonary Disease	144 (11)	47 (7)	47 (15)	50 (15)	0.1
Renal failure	121 (9)	19 (3)	26 (8)	76 (23)	0.1
Hepatic disease	73 (5)	41 (6)	20 (6)	12 (4)	0.1
Hypo or hyperthyroidism	114 (8)	39 (6)	37 (12)	38 (12)	0.1
Visual impairment	87 (6)	3 (0)	25 (8)	59 (18)	0.3
Hearing impairment	72 (5)	7 (1)	17 (6)	48 (15)	1.6
Dementia	138 (10)	9 (1)	36 (12)	93 (28)	0.1
Parkinson's disease	28 (2)	6 (1)	8 (3)	14 (4)	0.1
Cancer	140 (10)	56 (8)	44 (14)	40 (12)	0.1
Hematological malignancy	47 (3)	19 (3)	16 (5)	12 (4)	0.1
Peptic ulcer	25 (2)	5 (1)	8 (3)	12 (4)	0.3
Rheumatic disease	55 (4)	25 (4)	15 (5)	15 (5)	0.1
Anemia	494 (37)	194 (27)	163 (50)	137 (44)	0
Polypharmacy (≥7 drugs)	283 (22)	51 (7)	90 (30)	142 (45)	2.5
Nutritional status					19.9
Malnutrition	56 (5)	5 (1)	11 (5)	40 (17)	
Obesity	164 (15)	107 (18)	37 (16)	20 (8)	
Functional status (independence)					

Self-bathing	940 (82)	593 (96)	217 (84)	130 (47)	14.4
Self-dressing	932 (86)	587 (97)	201 (86)	144 (57)	19.1
Walking indoor *without aids*	919 (80)	594 (96)	207 (81)	118 (43)	14.6
Walking outdoor *without aids*	874 (76)	586 (96)	195 (77)	93 (34)	14.8
Shopping	795 (75)	568 (95)	162 (75)	65 (27)	21.5
Driving a car	638 (73)	492 (95)	102 (68)	44 (21)	34.8
Managing money	745 (79)	523 (95)	135 (79)	87 (39)	30.1
Managing drugs	739 (78)	522 (95)	131 (76)	86 (39)	29.9
Laboratory data					
Sodium (mmol/L)	138 [135, 140]	138 [136, 140]	138 [135,140]	138 [135, 141]	1.3
Potassium (mmol/L)	4.0 [3.7, 4.4]	4.0 [3.7, 4.3]	4.0 [3.7, 4.3]	4.1 [3.7, 4.4]	1.4
Leucocyte (10^3 U/L)	6.2 [4.6, 8.5]	6.0 [4.5, 8.1]	6.3 [4.7, 8.4]	6.8 [4.7, 9.0]	1.5
Lymphocyte (10^3 U/L)	1.0 [0.7, 1.4]	1.1 [0.8, 1.5]	0.9 [0.6, 1.2]	0.8 [0.6, 1.2]	5.8
Platelets (10^3 U/L)	201.0 [154.0, 270.0]	211.0 [162.0, 283.0]	193.5 [151.0, 253.5]	183.5 [142.0, 252.2]	0.7
CRP (mg/dl)	4.9 [1.4, 9.4]	4.2 [1.3, 8.9]	4.9 [1.7, 8.9]	6.0 [2.0, 10.2]	5
Creatinine (mg/dl)	1.0 [0.8, 1.2]	0.9 [0.8, 1.1]	1.0 [0.8, 1.3]	1.1 [0.9, 1.5]	0.8
Frailty					
CFS class					17.3
1-3	696 (63)	505 (82)	132 (54)	59 (23)	
4-6	316 (28)	96 (16)	91 (37)	129 (51)	
7-9	101 (9)	13 (2)	21 (9)	67 (26)	
CFS (median [IQR])	3 [2, 5]	2 [2, 3]	3 [3, 4]	5 [4, 7]	17.3
FI (median [IQR])	0.09 [0.03, 0.20]	0.06 [0.03, 0.09]	0.13 [0.06, 0.22]	0.3 [0.20, 0.40]	0
Other data on admission					
Chest X-Ray					1.4
Unilateral consolidation	295 (22)	158 (23)	56 (18)	81 (25)	
Bilateral consolidations	886 (67)	463 (67)	209 (68)	214 (66)	
Ventilation support at admission					0
None	351 (26)	231 (33)	67 (22)	53 (16)	
Nasal cannula	346 (26)	192 (27)	69 (22)	85 (26)	
Venturi Mask	275 (20)	132 (19)	76 (24)	67 (20)	
Reservoir mask	245 (18)	86 (12)	61 (20)	98 (30)	
CPAP	129 (10)	65 (9)	38 (12)	26 (8)	
Heart rate					3.6
> 110	52 (4)	36 (5)	6 (2)	10 (3)	
Oxygen saturation					13.5
< 91	94 (8)	40 (7)	20 (8)	34 (11)	
91-94	243 (21)	119 (20)	64 (24)	60 (20)	
Systolic blood pressure					3.4
71-100	100 (7)	61 (9)	20 (7)	19 (6)	
Body temperature					3.4
≥37.5	322 (25)	198 (29)	65 (23)	59 (18)	

Days from symptoms onset to admission (median [IQR])	7.0 [4.0, 10.0]	7.0 [5.0, 11.0]	7.0 [4.0, 11.0]	6.0 [3.0, 9.0]	0.7

FI construction

Focus of the study was to establish the predictive value of a FI constructed according to Rockwood (accumulation of deficits), by combining disabilities, functional autonomy and laboratory data. The FI is calculated as the ratio of the number of deficits the subjects have, over the total possible number of deficits. This way, the FI is a continuous variable that can assume any value between 0 and 1, where 0 represents absence of any deficits, and 1 presence of all of them. A tentative index was constructed from 42 elements:

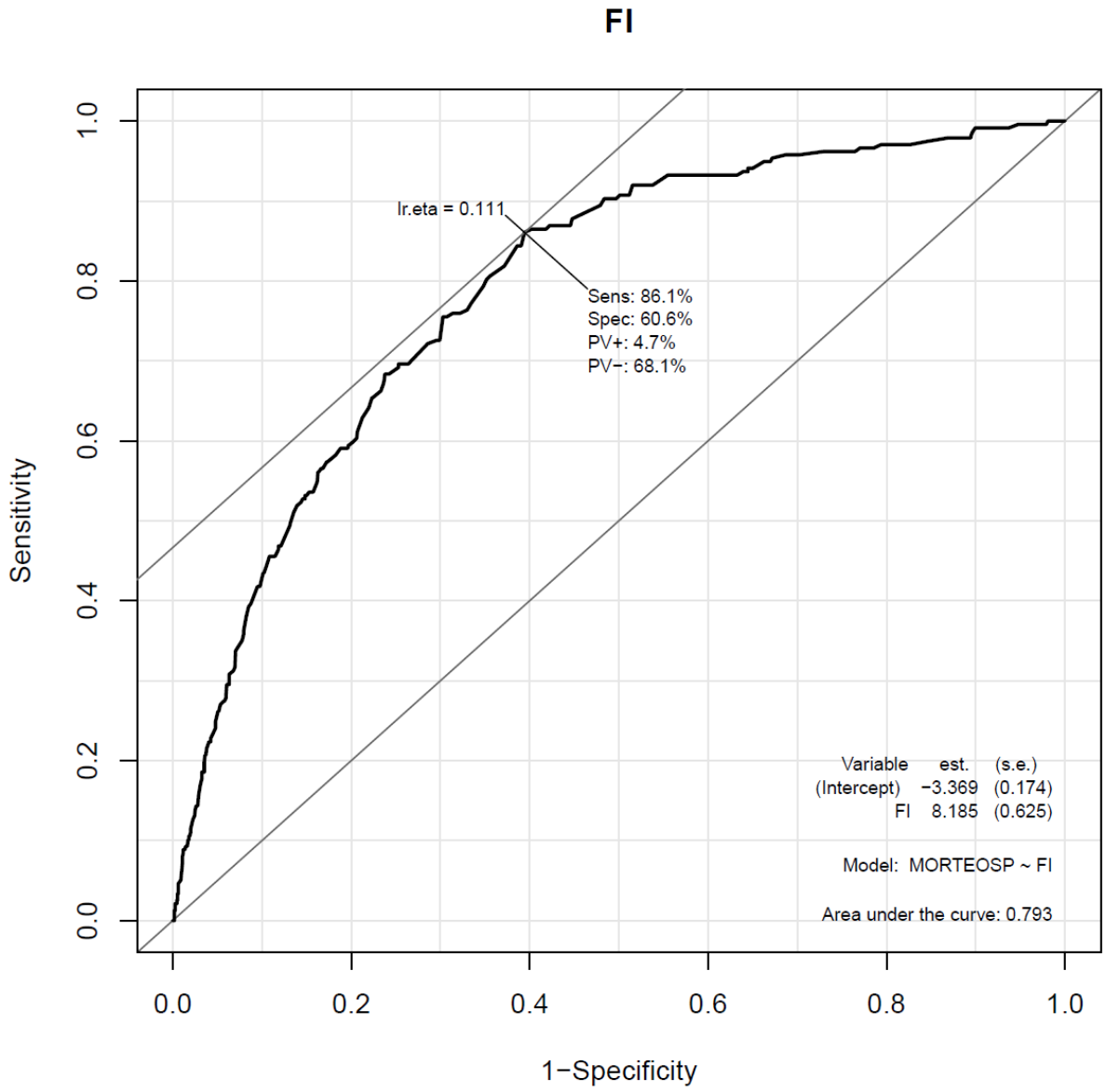
- 23 comorbidities: hypertension, cardiopathy, atrial fibrillation, peripheral vascular disease, heart failure, stroke, diabetes mellitus, depression, osteoarthritis, osteoporosis, chronic obstructive pulmonary disease, renal failure, hepatic disease, hypo or hyperthyroidism, visual impairment, hearing impairment, dementia, Parkinson's disease, cancer, hematological malignancy, peptic ulcer, rheumatic disease, anemia;

- 9 elements of functional autonomy: self-bathing, self-dressing, walking indoor, walking outdoor, shopping, driving a car, managing money, managing drugs, living in nursing home;
- 7 laboratory elements: sodium, potassium, leucocytes, lymphocytes, platelets, CRP, creatinine;
- 3 miscellaneous elements: therapy with 7+ medications, current/past smoking habit, nutritional status.

Evaluation of FI through ROC curve

A first evaluation of FI's sensitivity and specificity in predicting in-hospital mortality returned the following ROC curve (fig. 1):

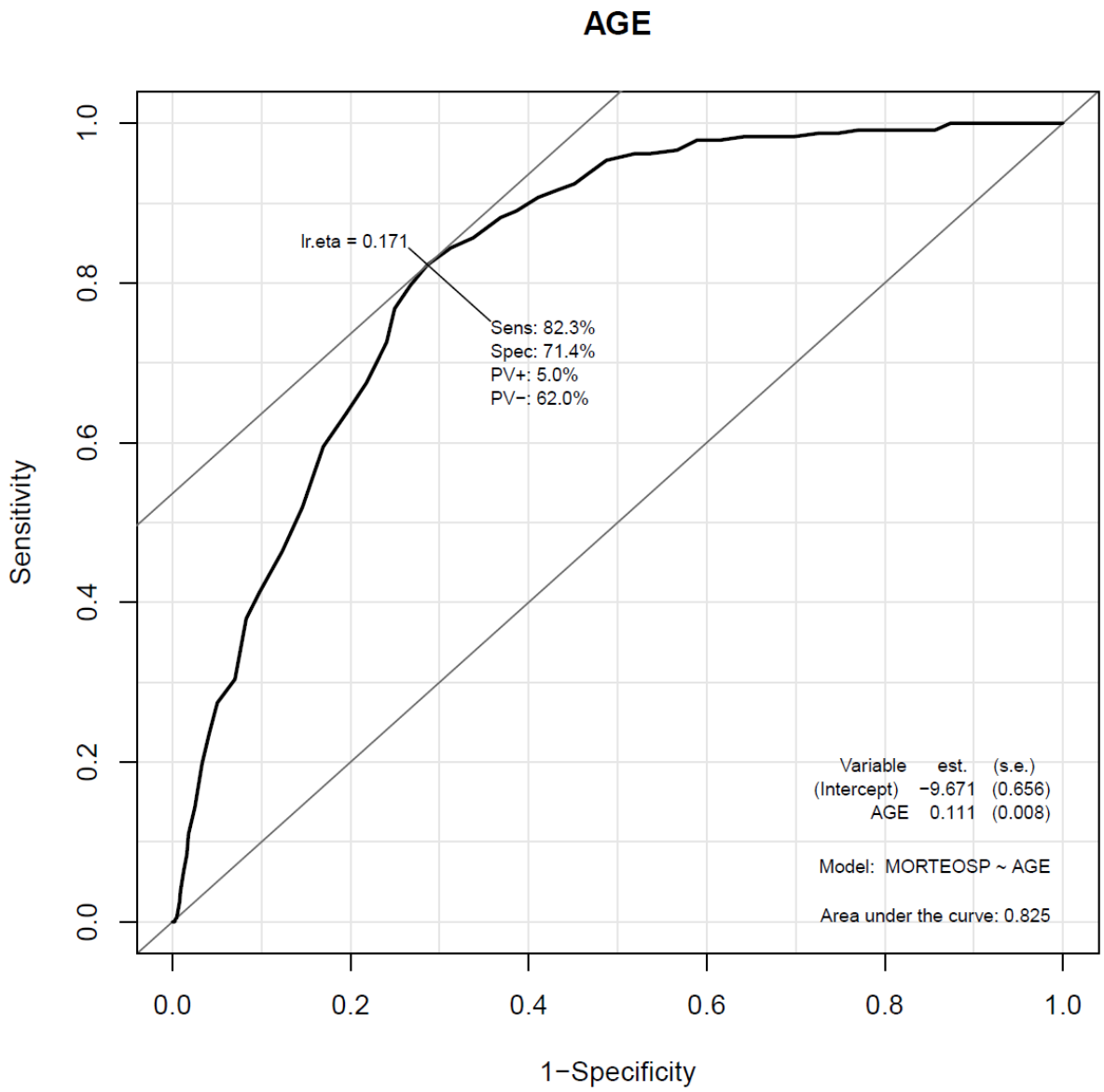
Figure 1: ROC curve for in-hospital mortality ~ FI



The AUC for the whole population was 0.79, while a stratification for age classes showed a decreasing model performance: >70y = 0.76, 70-79y = 0.75, >79y = 0.62.

An analogous model constructed in function of age showed a similar performance (AUC = 0.82) (fig. 2):

Figure 2: ROC curve for in-hospital mortality ~ age



In order to ascertain if a different combination of FI components produced more satisfactory results, we experimented with three variations of the index:

- FI1 (multimorbidity): all 23 comorbidities plus obesity

- FI2 (functionality): all 9 elements of functional autonomy plus malnutrition and life alone (deduced from marital status)
- FI3 (condition at admission): abnormalities in the 7 laboratory elements plus lung consolidations, need for artificially administered oxygen, tachy- or bradyarrhythmia, blood O2 saturation below 94%, hyper- or hypotension, body temperature over 37.5 °C, presence of delirium.

Table 2 shows the AUC of the ROC curves calculated for the three models predicting in-hospital mortality in function of those indexes:

Table 2: AUC for ROC curves calculated for FI, FI1, FI2, and FI3 (95%CI)

FI	AUC
Overall	0.79 (0.78-0.80)
< 70	0.76 (0.72-0.80)
70-79	0.75 (0.74-0.76)
> 79	0.62 (0.58-0.64)

FI1	AUC
Overall	0.77 (0.76-0.78)
< 70	0.66 (0.60-0.72)
70-79	0.68 (0.65-0.71)
> 79	0.58 (0.54-0.62)

FI2	AUC
Overall	0.76 (0.74-0.78)
< 70	0.63 (0.57-0.69)
70-79	0.64 (0.61-0.67)
> 79	0.60 (0.56-0.64)

FI3	AUC
Overall	0.74 (0.73-0.75)
< 70	0.79 (0.74-0.83)
70-79	0.67 (0.65-0.69)
> 79	0.69 (0.66-0.72)

The performance of the three combined indexes is somewhat inferior to the original model. A combined index built adding all elements of F1, F2, and F3 seemed to have a more satisfactory performance (whole population = 0.83; >70y = 0.81, 70-79y = 0.74, >79y = 0.63), but it should be noted that, despite the good AUC values, the F3 component goes beyond the scope of a FI, capturing health-impacting features which can reasonably spur from the acute condition of the patient, rather than describing a chronic state of frailty. For these reasons, the tripartition of the index was judged not worth pursuing.

Lastly, we observed that a more parsimonious FI of 36 items, which excluded the 7 laboratory elements and added the variable "living alone", showed a very similar (or better) ROC performance in terms of AUC (table 3):

Table 3: comparison of 42- and 36-items FIs

36-items FI	AUC
Overall	0.79
<70	0.76
70-79	0.75
>79	0.62

42-items FI	AUC
Overall	0.79
<70	0.73
70-79	0.69
>79	0.57

The exclusion of the laboratory components of the FI is also motivated by last paragraph's observation, since blood panel alterations can derive from the infection that caused the hospitalization, not from frailty per se. For its better clinical manageability, we then chose to utilize the 36-items FI in all subsequent analysis, summarized in table 4.

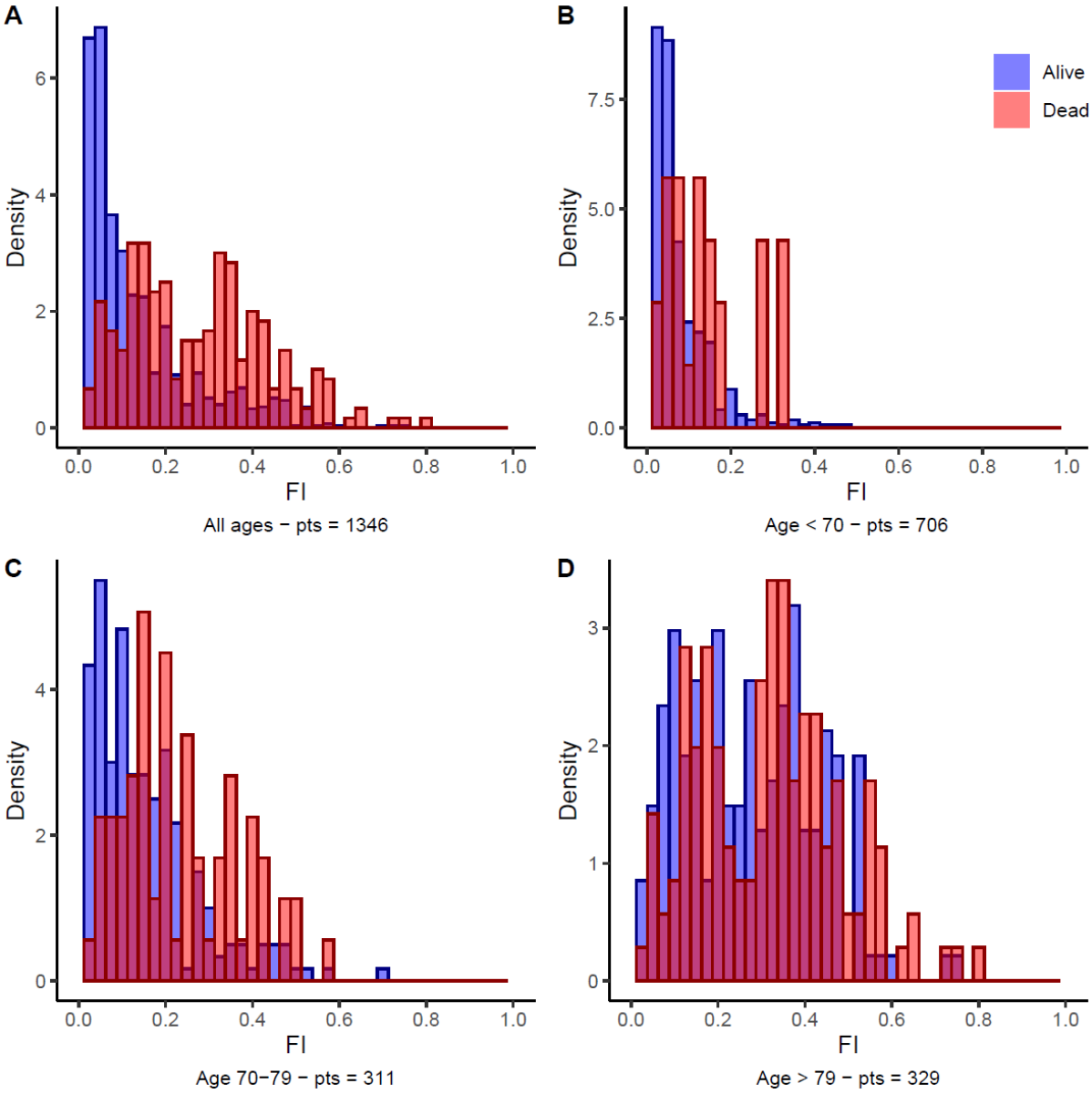
Table 4: Variables included in the 36-items frailty index

	Overall	Missing %
Total patients	*1346*	
Marital status		22.2
Living alone	276 (26)	
Not alone	771 (74)	
Has a caregiver or in nursing home	107 (9)	12.6
Smoker		38.7
Ongoing	42 (5)	
Never been	562 (68)	
Past	221 (27)	
Hypertension	706 (52)	0.1
Cardiopathy	334 (25)	0.2
Atrial fibrillation	123 (9)	0.1
Peripheral vascular disease	139 (10)	0.3
Heart failure	58 (4)	0.1
Stroke	73 (5)	0.1
Diabetes mellitus type 2	294 (22)	0.1
Depression	70 (5)	1
Osteoarthrosis	115 (9)	1
Osteoporosis	70 (5)	1.2
COPD	144 (11)	0.1
Renal failure	121 (9)	0.1
Hepatopathy	73 (5)	0.1
Dysthyroidism	114 (8)	0.1
Hypoacusis	87 (6)	0.3
Hypovisus	72 (5)	1.6
Dementia	138 (10)	0.1

Parkinson's disease	28 (2)	0.1
Solid neoplasm	140 (10)	0.1
Liquid neoplasm	47 (3)	0.1
Peptic ulcer	25 (2)	0.3
Rheumatic disease	55 (4)	0.1
Anemia	494 (37)	0
Polytheraphy (>=7 drugs)	283 (22)	2.5
Nutritional status		19.9
Denutrition	56 (5)	
Normal weight	858 (80)	
Obese	164 (15)	
Autonomous in hygene	940 (82)	14.4
Autonomous in-home deambulation *without aids*	919 (80)	14.6
Autonomous out-of-home deambulation *without aids*	874 (76)	14.8
Autonomous shopping	795 (75)	21.5
Autonomous dressing	932 (86)	19.1
Autonomous driving	638 (73)	34.8
Autonomous management of money	745 (79)	30.1
Autonomous management of drugs	739 (78)	29.9

Figure 3 shows the distribution of the FI by age and in-hospital mortality:

Figure 3. Frailty index distribution, by age and in-hospital mortality (n=1346).



It is clearly visible the gradient of mortality across the three age groups, as well as the rising prevalence of higher FIs. As expected, patient death density tends to be lower for smaller values of FI, overall and for ages below 79 years old. Interestingly, for patients of 80 years and older the difference in density between

death and survival across various ranges of FI does not appear to be as evident, with relatively more frail patients being alive at discharge from hospital. This suggests a more important role of the FI in the prognosis of frail, but not very old patients.

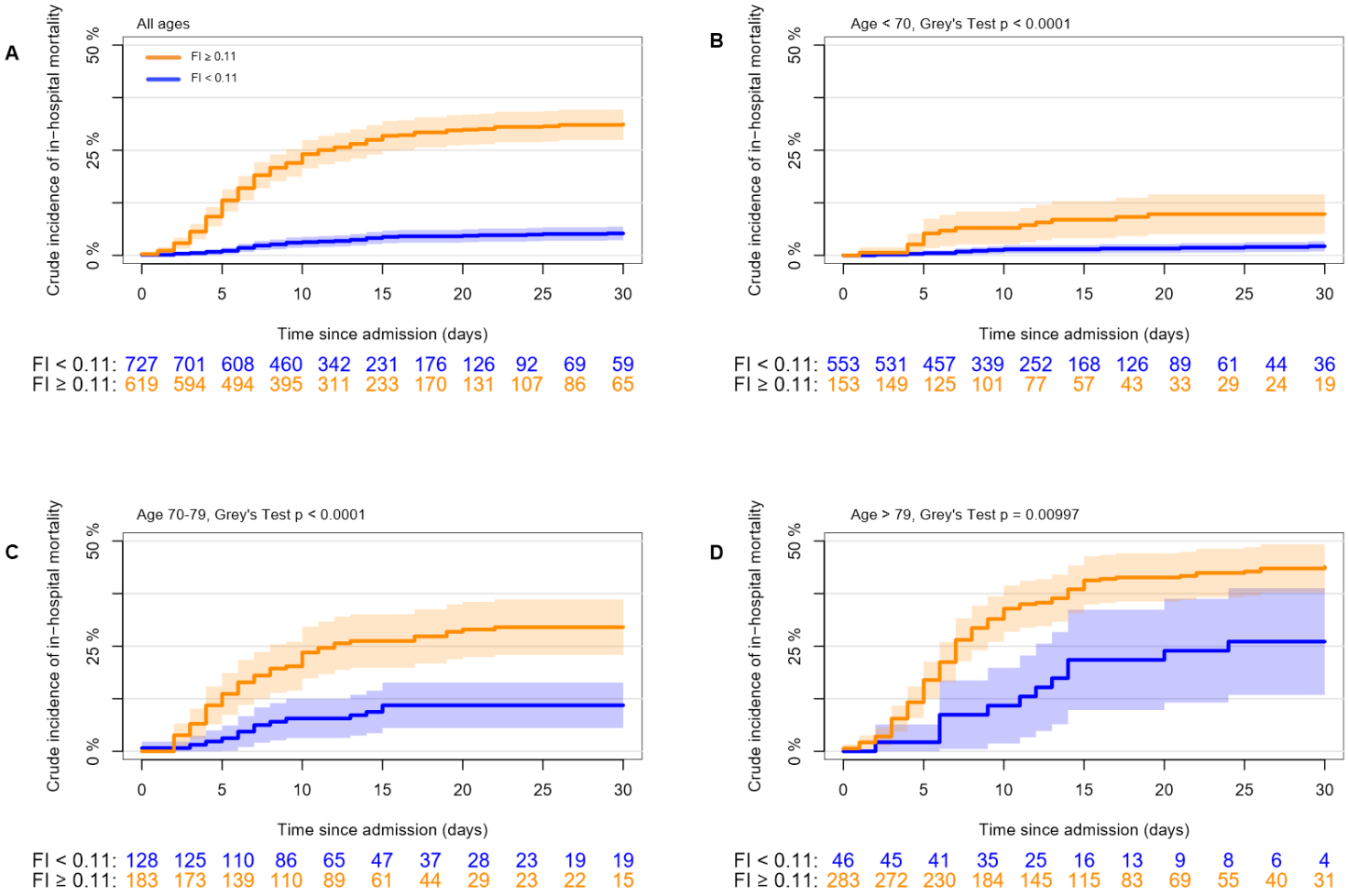
Crude cumulative incidence

The crude cumulative incidence of mortality was estimated by Aalen-Johansen accounting for the competing events discharge or transfer to other facilities and compared in patients with high and low frailty index by the Gray test. For descriptive purposes a cut-off of 0.11 was used to define patients with low and high frailty. The cut-off was chosen by the Youden index to maximize both specificity and sensitivity on Receiver Operating Characteristic (ROC) curve on in-hospital mortality (fig. 1).

Figure 2 depicts the crude cumulative incidence of in-hospital mortality over time, overall (panel A) and by age strata (panel C to E) and the dichotomized FI score.

At 20 days from admission, the in-hospital mortality was 30% (95%CI 26-34%) in patients with FI ≥ 0.11 and 5% (95%CI: 3-6%) in patients with FI<0.11 ($p<0.0001$). The difference between in-hospital mortality was significant across all the age groups. In patients with age less than 70 years, the in-hospital mortality at 10 days from admission was 7% (3-11%) in frails and 1.5% (0.5-2.4%) in others; in those aged 70-80 years, it was 24% (17-30%) in frails and 8% (3-13%) in others; and in patients aged 80 years and above, it was more than three times the one in less frail patients (34%, 95%CI 28-39% with FI ≥ 0.11 versus 11%, 95%CI: 2-20%).

Figure 2. Crude cumulative incidence of in-hospital mortality overall and by age class and frailty index. Shaded area represents confidence intervals.



Regression model

In order to evaluate the association between frailty and in-hospital mortality, we chose to apply a multivariable Cox regression model, stratified by center and ward. Included confounders were both chosen clinically and confirmed by the LASSO conditional logistic regression model with a 10-fold cross-validation, and

they included age, sex, chest X-ray or CT, CRP, ventilation support, date of admission (before or after 1st July 2020), heart rate, sodium, potassium, leucocytes, platelets, creatinine.

Model coefficients are shown in table 5

Table 5. Multivariable stratified Cox model on in-hospital mortality, selected by LASSO. Center and ward included as strata.

Characteristic	HR	95% CI	p-value
FI (0.1-points increments)	**1.28**	**1.15, 1.42**	**<0.001**
Age	1.41	1.15, 1.72	<0.001
Age^2	1.00	1.00, 1.00	0.005
Sex (Male vs Female)	1.24	0.90, 1.71	0.2
Admission period after 1st of July 2020 vs before	0.55	0.39, 0.78	<0.001
Sodium	1.02	0.99, 1.04	0.2
Potassium	1.09	0.81, 1.45	0.6
Leucocytes	1.00	0.99, 1.01	0.4
Platelets	1.00	1.00, 1.00	0.10
CRP (for each mg/dl increment)	1.05	1.03, 1.07	<0.001
Creatinine	1.04	0.90, 1.20	0.6
Chest X-ray			
Both-lungs consolidations	2.46	1.23, 4.92	0.011
Single-lung consolidations	2.31	1.12, 4.77	0.024
Ventilation			
CPAP	2.30	1.30, 4.06	0.004
Other non-invasive ventilation	1.15	0.72, 1.84	0.5
Body Temperature (°C) <35.1 OR >38.4	0.89	0.46, 1.73	0.7
Heart rate >110	2.12	1.17, 3.84	0.013
Time between symptoms and admission (days)	0.98	0.96, 1.00	0.11

A second, simplified model included all variables with a p-value < 0.1, and those variables that were selected a priori on a clinical base before performing the LASSO.

Model is shown in table 6:

Table 6. Simplified multivariable stratified Cox model on in-hospital mortality (for FI). Center and ward included as strata.

Characteristic	HR	95% CI	p-value
FI (0.1-points increments)	**1.30**	**1.17, 1.44**	**<0.001**
Age	-		<0.001
Age ^{2}	-		0.004
Sex (Male vs Female)	1.28	0.95, 1.73	0.11
Admission period after 1st of July 2020 vs before	0.57	0.40, 0.80	0.001
CRP (for each mg/dl increment)	1.05	1.03, 1.06	<0.001
Chest X-ray			
Both-lungs consolidations	2.40	1.20, 4.79	0.013
Single-lung consolidations	2.37	1.15, 4.89	0.019
Ventilation			
CPAP	2.31	1.32, 4.05	0.003
Other non-invasive ventilation	1.14	0.72, 1.80	0.6
Heart Rate >110 bpm	2.06	1.14, 3.72	0.016
Time from first symptoms to admission (days)	0.98	0.96, 1.00	0.089

Each increment of 0.1 in the FI increased the hazard of in-hospital death by 30%, (HR= 1.30 95%CI 1.17-1.44); other significant variables (all measured at admission) were CRP serum levels higher than 0.5 mg/dl (HR 1.05, 95%CI 1.03-1.06), single and bilateral lungs consolidations (HR 2.40, 95%CI 1.20-4.79 and

2.37, 95%CI 1.15-4.89 respectively), CPAP use (HR 2.31, 95%CI 1.32-4.05), heart rate over 110 bpm (HR 2.06, 95%CI 1.14-3.72), and age in years ($p<0.0001$). Age showed a nonlinear relationship with log-mortality hazard due to a plateau of risk after age 85. Period of admission was also significantly associated with mortality, with patients admitted after July 2020 incurring in a hazard of death 43% lower than those admitted before.

Interestingly, when the same model was fitted including frailty measured as CFS, instead of FI, a significant association with in-hospital mortality was retained (HR=1.30, 95%CI 1.18-1.44), as shown in table 7.

Table 7. Simplified multivariable stratified Cox model on in-hospital mortality (for CFS). Center and ward included as strata.

Characteristic	HR	95% CI	p-value
CFS (for each category)	**1.30**	**1.18, 1.44**	**<0.001**
Age	-		0.002
Age ^{2}	-		0.008
Sex (Male vs Female)	1.26	0.89, 1.77	0.2
Admission period after 1st of July 2020 vs before	0.92	0.58, 1.44	0.7
CRP (for each mg/dl increment)	1.04	1.02, 1.06	<0.001
Chest X-ray			
Both-lungs consolidations	2.84	1.29, 6.24	0.010
Single-lung consolidations	2.75	1.20, 6.28	0.016
Ventilation			

CPAP	2.20	1.17, 4.14	0.014
Other non-invasive ventilation	1.01	0.60, 1.70	>0.9
Heart Rate >110 bpm	1.69	0.86, 3.32	0.13
Time from first symptoms to admission (days)	0.98	0.96, 1.01	0.13

Chapter 4

FRA-COVID: Discussion and conclusions

The FRA-COVID project was designed to investigate the association between frailty and mortality in patients admitted with COVID-19 in two large hospitals in northern Italy.

It was subsequently found that frailty, either measured with CFS or with a 36-item FI, is a strong predictor of in-hospital mortality, in the overall cohort and across all age groups. Ever for younger individuals (<70 years old) frailty, when present, was able to independently predict in-hospital mortality, capturing risks apart from those associated with age and severity of acute disease.

Of note, in this study both the FI and the CFS converged in demonstrating the association between frailty and higher in-hospital mortality, having similar predictive power in the multivariate analysis. In the Cox regression model, for an increase of 0.1 in the FI and for each point of CFS score the risk to die during hospitalization was shown to increase by an equal 30%. This finding is consistent across all age strata, suggesting that the assessment of frailty, performed with either method, can improve physicians' ability to triage patients admitted to acute hospitals with COVID-19.

Furthermore, having recruited patients from both the first and the second wave of the epidemic in Italy, this study is able to show that frailty is associated with poor survival regardless of the fatality rate of the disease in that moment, the latter being higher in the first months of the pandemic due to lower availability of hospital beds and less experience with effective treatment of COVID-19.

Frailty still maintains its prognostic relevance in the multivariate analysis even when taking into account severity of illness (extension of pneumonia), markers of inflammatory response (PCR serum levels) and use of ventilatory support.

The findings of this study strongly suggest the use of frailty measurement in all patients hospitalized with COVID-19, this being a better tool to estimate the vulnerability of infected patients than age alone and comorbidity.

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