Predictors of in-hospital mortality AND death RISK STRATIFICATION among COVID-19 PATIENTS aged ≥ 80 YEARs OLD

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A B S T R A C T

Introduction: : To date, mainly due to age-related vulnerability and to coexisting comorbidities, older patients often face a more severe COVID-19. This study aimed to identify at Emergency Department (ED) admission the predictors of in-hospital mortality and suitable scores for death risk stratification among COVID-19 patients ≥ 80 years old.

Methods: : Single-centre prospective study conducted in the ED of an university hospital, referral center for COVID-19 in central Italy. We included 239 consecutive patients ≥ 80 years old with laboratory-confirmed COVID-19.

The primary study endpoint was all-cause in-hospital mortality. Multivariable Cox regression analysis was performed on significant variables at univariate analysis to identify independent risk factor for death. Overall performance in predicting mortality of WHO severity scale, APACHE II score, NEWS score, and CURB-65 was calculated.

Results: : Median age was 85 [82-89] and 112 were males (46.9%). Globally, 77 patients (32.2%) deceased. The presence of consolidations at chest x-ray and the hypoxemic respiratory failure were significant predictors of poor prognosis. Moreover, age ≥ 85 years, dependency in activities of daily living (ADL), and dementia were risk factors for death, even after adjusting for clinical covariates and disease severity. All the evaluated scores showed a fairly good predictive value in identifying patients who could experience a worse outcome.

Conclusions: : Among patients ≥ 80 years old hospitalized with COVID-19, not only a worse clinical and radiological presentation of the disease, but also the increasing age, dementia, and impairment in ADL were strong risk factors for in-hospital death, regardless of disease severity.

1. Introduction

Since the first case identified in December 2019, the novel coronavirus designated SARS-CoV-2, has determined the current tragic pandemic of respiratory illness named COVID-19.(W. Guan et al. 2020; Huang et al. 2020; Chen et al. 2020; Jin et al. 2020) Most countries in the world experienced an un-precedent pressure on health care systems, and the number of affected patients and death toll is still on the rise (WHO Coronavirus Disease (COVID-19) Dashboard, 2021). To date, despite the aggressive effort of containment, Italy has been facing one of the largest and most serious COVID-19 cluster, and the number of affected and deceased patients continue to increase (Livingston & Bucher, 2020;

Ministero della Salute, 2021).

Older people, and those with comorbidities, are at higher risk of both severe infection (Wu & McGoogan, 2020) and death as a result of the disease (Gao et al. 2020; Zhou et al. 2020; Cheng et al. 2020) with a high fatality rate in patients aged 80 and above (Wu & McGoogan, 2020). Moreover, in older patients with COVID-19 emerged that not only the severity of COVID-19-related pneumonia or impairment of respiratory function, but also frailty and vulnerability are crucial determinant of poor prognosis (Lithander et al. 2020). However, routine medical assessment of COVID-19 patients seldom contemplated some of the key elements of risk in older persons, including dementia, or any degree of functional decline.

Up to now, although several efforts have been expended to determine the severity and prognosis of COVID-19 cases (W. Guan et al. 2020; Huang et al. 2020; Chen et al. 2020; Livingston & Bucher 2020; Gao et al. 2020; Zhou et al. 2020; Cheng et al. 2020) risk stratification and identification of predictors for in-hospital mortality in acutely ill patients aged over 80 years remains a challenge.

Thus, the aim of this study was to identify at ED admission the predictors of in-hospital mortality and suitable scores for death risk stratification among COVID-19 patients $\geq$ 80 years.

2. Methods

2.1. Study design

This is a single-centre, prospective observational study, conducted in the ED of an university hospital [Fondazione Policlinico A.Gemelli IRCCS, Rome], which is a referral centre for COVID-19, in central Italy.

We evaluated all the patients $\geq$ 80 years, consecutively admitted to our ED with confirmed COVID-19 over a three-months period (September 1st to November 30th, 2020). COVID-19 was diagnosed on the basis of the WHO interim guidance. We included in the analysis only patients with positive result on real-time reverse-transcriptase–polymerase-chain-reaction assay of nasal and pharyngeal swab specimens.

We excluded patients already on orotracheal intubation at ED arrival, and patients for whom a do not resuscitate order was in place.

2.2. Study variables

The following information were evaluated:

- Demographics: age, sex.
- Clinical presentation at ED admission: fever, dyspnea, cough, diarrhea, headache, ageusia/anosmia, myalgia, confusion, syncope/presyncope.
- Clinical history and comorbidities: hypertension, severe obesity (defined as BMI >40), history of coronary artery disease (CAD), congestive heart failure, cerebrovascular disease, dementia, diabetes, chronic obstructive pulmonary disease (COPD), chronic kidney disease, malignancy. For each patient was also recorded if living in residential nursing facility and if had any impairment in activities of daily living (ADL) according to the Katz index of independence in activities of daily living (Katz et al. 1970). Overall comorbidity presence was assessed by Charlson Comorbidity index.
- Physiological parameters at ED admission: body temperature, heart rate (HR), respiratory rate (RR), blood pressure (BP), Glasgow Coma Scale (GCS) peripheral oxygen saturation (SpO$_2$).
- Laboratory evaluation: For all patients we evaluated total white cell blood (WBC) count, lymphocyte count, lymphocyte to WBC ratio, blood glucose, creatinine, blood urea nitrogen (BUN), lactate dehydrogenase (LDH), sodium, potassium, C reactive protein (CRP), and serum lactic acid.
- Blood gas evaluation: All patients had a blood gas evaluation at ED admission. Blood gas was obtained in room air when possible, and in

case of severe respiratory distress at a FiO$_2$ adequate for keeping peripheral oxygen saturation at least $\geq$ 90%. In cases needing ventilator support, first blood gas sample obtained before ventilation or soon after ventilation start was considered.

- Radiological findings: defined as negative, interstitial involvement, and consolidative pneumonia.
- Early warning scores: Different scores for patient evaluation and outcome prediction were calculated for patients in our cohort: World Health Organization (WHO) severity scale based solely on respiratory evaluation (SpO$_2$, RR, presence of pneumonia); the National Early Warning Score (NEWS) severity score based on several physiological parameters (HR, RR, BP, GCS, SpO$_2$, Temperature) (Smith et al. 2013); the CURB-65 score for pneumonia severity (confusion, blood urea nitrogen, BP, RR, Age)(Lim, 2003); the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score (based upon initial values of 12 routine physiologic measurements, age, and previous health status)(Knaus et al. 1985) [Supplementary material, Table S1].

2.3. Study endpoints

The end-point of the study was the all-cause in-hospital death.

2.4. Statistical Analysis

Continuous variables are reported as median [interquartile range], and are compared at univariate analysis by Mann-Whitney U test. Categorical variables are reported as absolute number (percentage), and are compared by Chi-square test (with Fisher's test if appropriate).

Receiver operating characteristic (ROC) curve analysis was used to evaluate the overall performance of the evaluated scores in predicting the defined adverse outcome. The comparison between the ROC AUCs was made according to DeLong method.

Follow up and length of hospital stay were calculated from the time of ED admission to discharge or death. Evaluated parameters were assessed for association to all-cause in-hospital death by a univariate Cox regression analysis. Significant variables at univariate analysis were entered into a multivariate Cox regression model to identify independent risk factor for survival. For a better model fitting and hazard estimation, we categorized the continuous variables into dichotomous parameters (i.e. low/high). For each variable, we obtained the optimal dividing cut-off by Youden's index, performing a ROC curve analysis with respect to association with death. To avoid model redundancy or overfitting, some variables were excluded from the analysis, since they were derived (like Charlson Index, early warning scores, lymphocyte/WBC ratio). Similarly, for blood gas sample we considered PaO$_2$/FiO$_2$, and excluded from multivariate model PaO$_2$ and FiO$_2$ as single items. Survival curves were estimated by the Kaplan-Meier methods. Association of factors to risk of intra hospital death is expressed as Hazard Ratio (HR) [95% confidence interval]. We considered significant a two-sided p $\leq$ 0.05. Data were analyzed by SPSS v25® (IBM, Armonk NY, USA).

2.5. Statement of ethics

The study was conducted in accordance with the Declaration of Helsinki and approved by the Local Ethical Committee. All patients gave their informed consent to collect clinical and laboratory data.

3. Results

Overall, 239 patients aged between 80 and 100 years met the inclusion criteria and were included in the study cohort. Thirteen patients (5.4%) were transferred to residential COVID facility for quarantine. Twelve patients (5.0%) were discharged home from ED.

Globally, 77 patients (32.2%) deceased. Four patients (1.7%) died in ED prior than ward admission. Median time from ED admission to death

was 9.9 [3.5 – 15.4] days.

3.1. Demographic, ED presentation and clinical history

Median age was 85[82-89], 112 were males (46.9%). Figure 1 describes age distribution in our cohort. Most of patients reported fever (82.8%), dyspnea (59.0%), and cough (45.1%) as main symptoms. Interestingly, anosmia/ageusia were reported only by few subjects (1.3%) (Table 1).

Most of patients admitted to ED had some alteration of physiological parameters. However, a significant difference between deceased and survived patients emerged only for peripheral oxygen saturation at admission (Table 1).

Not surprisingly, most of the enrolled patients (63.9%) had impairment in ADL, and about half of them lived in a residential nursing facility. Major comorbidities included hypertension (40.2%), dementia (16.7%), diabetes (14.6%), and congestive heart failure (10%). Median Charlson comorbidity index was 4 [4 – 5] (Table 1).

Deceased patients were significantly older and had higher Charlson comorbidity index. Living in institution and being dependent in ADL was significantly associated to poor prognosis. Among comorbidities considered in Charlson comorbidity score, dementia, cerebrovascular disease and congestive heart failure were significantly associated to death at univariate analysis (Table 1).

3.2. Laboratory findings

Considering laboratory values, many were associated with poor prognosis at univariate analysis. In particular, deceased patients showed a higher WBC count, lower lymphocyte count and lower lymphocyte/WBC ratio. Moreover, a significantly higher BUN, blood glucose, LDH, CRP, and lactic acid, were associated to death in our cohort (Table 1).

3.3. Blood gas evaluation

Higher need of oxygen supplement was associated to worse prognosis (Table 1). Similarly, a lower PaO_2, PaO_2/FiO_2 ratio, and HCO_3- were associated to death in our cohort.

3.4. Radiological findings

Most of the enrolled patients (>80 %) had the pulmonary involvement of the disease, as confirmed by chest x-ray findings. A more severe pulmonary involvement at chest x-ray was associated to a significant worse prognosis (Table 1).

3.5. Risk Scores evaluation

All the four scoring system evaluated in our cohort showed a fair predicting ability for death prediction. The WHO severity scale had a slightly higher ROC AUC among them, although it was not significantly different from APACHE II score, NEWS score, and CURB-65 index (Table 2). However, while NEWS, WHO scale, and APACHE performed pretty similar, CURB-65 showed a slightly lower ROC AUC.

3.6. Multivariate analysis

When entered into a multivariate COX regression model, several factors emerged as independent risk factors for death. Among demographic factors, increasing age played a significant role, being death hazard ratio more than doubled for age ≥ 85 years (Table 3). Among the clinical history covariates, dependency in ADL, dementia, and congestive heart failure were the strongest risk factor for death with respectively 2.57, 2.37, and 2.09 hazard ratios, respectively (Table 3).

As expected, chest x-ray findings were significantly associated to increased death risk, and patients with pulmonary consolidation had almost fourfold risk of death, when compared to negative chest x-ray. Patients with interstitial involvement showed a tendency toward a hazard risk increase, although not reaching statistical significance (Table 3).

Among the laboratory values evaluated a higher CRP, LDH, and lactic acid were independent risk factors for death. As expected, a lower PaO_2/FiO_2 at admission was a significant risk factor for poor prognosis.

4. Discussion

The main finding of this study is that among patients ≥ 80 years old hospitalized with COVID-19, in addition to worse clinical and radiological presentation of the disease, also the increasing age, dementia, and impairment in ADL were strong risk factors for all cause in-hospital death, even after adjusting for clinical covariates and disease severity. Moreover, in this population the WHO severity scale, APACHE II score, NEWS score, and CURB-65 showed a fairly good predictive value in identifying at ED admission patients who could experience a worse
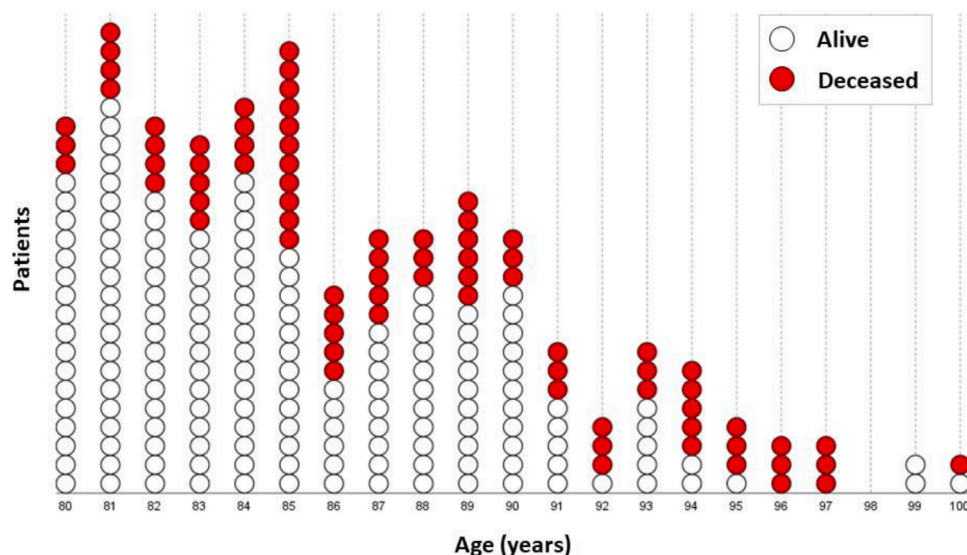

Figure 1. Age distribution of the enrolled patients. Dividing our patients in 5 year age groups, death ratio is 19% in 80-84 years old, 38% in 85-89 years old, 41.5% in 90-94 years old, 71.4% in ≥ 95 years old (p<0.001)

Table 1
Demographic and clinical characteristics of enrolled patients at ED admission

Characteristics	All cases N 239	Survived N 162	Deceased N 77	*P-value*
Age	85 (82 – 89)	84 (82 – 88)	87 (84 – 92)	<0.001
Sex (male)	112 (46.9%)	74 (45.7%)	38 (49.7%)	0.595
Clinical presentation				
Fever	198 (82.8%)	137 (84.6%)	61 (79.2%)	0.306
Dyspnea	141 (59.0%)	94 (58.0%)	47 (61.0%)	0.658
Cough	102 (45.1%)	73 (45.1%)	29 (37.7%)	0.280
Diarrhea	10 (4.2%)	9 (5.6%)	1 (1.3%)	0.174
Headache	15 (6.3%)	8 (4.9%)	7 (9.1%)	0.216
Ageusia/anosmia	3 (1.3%)	1 (0.6%)	2 (2.6%)	0.244
Myalgia	17 (7.1%)	15 (9.3%)	2 (2.6%)	0.103
Confusion	11 (4.6%)	8 (4.9%)	3 (3.9%)	0.977
Syncope/pre-syncope	10 (4.2%)	7 (4.3%)	3 (3.9%)	0.878
Physiological parameters				
Heart Rate (beats/min)	85 (82 – 89)	84 (82 – 88)	87 (84 – 92)	0.678
SpO2 (%) in ambient air	94 (90 – 97)	94 (91 – 97)	93 (87 – 96)	0.037
Respiratory rate (breaths/min)	25 (21 – 28)	24 (20 – 28)	26 (22 – 28)	0.124
SBP (mmHg)	128 (115 – 140)	129 (120 – 141)	124 (110 – 140)	0.075
DBP (mmHg)	76 (66 – 84)	77 (69 – 85)	70 (60 – 81)	0.110
MBP (mmHg)	93 (84 – 102)	95 (86 – 103)	90 (80 – 100)	0.021
GCS	15 (14 – 15)	15 (14 – 15)	15 (14 – 15)	0.762
Body Temperature (°C)	36.0 (36.0 – 37.2)	36.5 (36 – 37.3)	36.5 (36.0 – 37.0)	0.730
Clinical history and comorbidities				
Charlson comorbidity index	4 (4 – 5)	4 (4 – 5)	5 (4 – 6)	0.007
Dependent in ADL	145 (63.9%)	82 (53.9%)	63 (84.0%)	<0.001
Living in institution	117 (49.0%)	68 (42.0%)	49 (63.6%)	0.002
Hypertension	96 (40.2%)	64 (39.5%)	32 (41.6%)	0.762
Dislipidemia	16 (6.7%)	13 (8.0%)	3 (3.9%)	0.233
Severe obesity	2 (0.8%)	1 (0.6%)	1 (1.3%)	0.541
History of CAD	18 (7.5%)	10 (6.2%)	8 (10.4%)	0.248
Congestive heart failure	24 (10.0%)	10 (6.2%)	14 (18.2%)	0.004
Cerebrovascular disease	12 (5.0%)	5 (3.2%)	7 (9.1%)	0.047
Dementia	40 (16.7%)	21 (13.0%)	19 (24.7%)	0.023
COPD	32 (13.4%)	22 (13.6%)	10 (13.0%)	0.900
Diabetes	35 (14.6%)	23 (14.2%)	12 (15.6%)	0.777
Chronic kidney disease	10 (4.2%)	7 (4.3%)	3 (3.9%)	0.878
Malignancy	5 (2.1%)	1 (0.6%)	4 (5.2%)	0.038
Laboratory evaluation				
WBC count (cells/mm3)	7190 (4940 – 10100)	6910 (4867 – 9455)	7840 (5305-11735)	0.042
Lymphocyte (cells/mm3)	990 (710 – 1340)	1020 (757 – 1370)	860 (650 – 1270)	0.016
Lymphocyte/WBC ratio	0.14 (0.08 – 0.23)	0.17 (0.11 – 0.24)	0.11 (0.06 – 0.19)	<0.001
Blood glucose (mg/dL)	109 (91 – 138)	104 (89 – 129)	122 (99 – 172)	0.002
Creatinine (mg/dL)	1.01 (0.76 – 1.46)	0.97 (0.71 – 1.38)	1.13 (0.79 – 1.83)	0.104
BUN (mg/dL)	24 (18 – 37)	22 (16 – 30)	31 (23 – 46)	<0.001
LDH (UI/L)	280 (200 – 379)	267 (198 – 373)	295 (225 – 503)	0.023
Sodium (mEq/L)	136 (129 – 141)	137 (130 – 140)	134 (127 – 138)	0.378
Potassium (mEq/L)	4.1 (3.8 – 4.5)	4.1 (3.9 – 4.4)	4.3 (3.9 – 4.6)	0.435
CRP (mg/L)	65 (27 – 133)	53 (20 – 110)	102 (51 – 161)	<0.001
Serum Lactate (mmol/L)	1.2 (0.8 – 1.8)	1.1 (0.8 – 1.5)	1.4 (1.1 – 2.2)	<0.001
Blood gas evaluation				
FiO2 (%)	24 (21 – 31)	21 (21 – 27)	28 (21 – 40)	<0.001
pH	7.45 (7.41 – 7.48)	7.45 (7.40 – 7.48)	7.45 (7.41 – 7.50)	0.304
PaO2 (mmHg)	66 (57 – 80)	67 (60 – 82)	63 (52 – 76)	0.037

Table 1 (*continued*)

Characteristics	All cases N 239	Survived N 162	Deceased N 77	*P-value*
PaCO2 (mmHg)	35 (31 – 40)	35 (31 – 39)	35 (30 – 39)	0.480
HCO3- (mmol/L)	26 (23 – 28)	26 (24 – 28)	25 (22 – 27)	0.015
PaO2/FiO2	276 (214 – 333)	297 (229 – 345)	233 (173 – 295)	<0.001
Radiological findings				
Negative	40 (16.7%)	35 (21.6%)	5 (6.5%)	
Interstitial involvement	98 (41.0%)	76 (49.9%)	22 (28.6%)	<0.001
Consolidation	101 (42.3%)	51 (31.5%)	50 (64.9%)	

Abbreviations: SpO2, peripheral oxygen saturation; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; GCS, Glasgow Coma Scale; ADL, Activities of daily living; CAD, Coronary artery disease; COPD Chronic Obstructive Pulmonary Disease; WBC, white blood cells; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; CRP, C reactive protein; FiO2, fraction of inspired oxygen; PaO2, partial pressure of oxygen; PaCO2, partial pressure of carbon dioxide

Table 2
Sensitivities, specificities, negative and positive predictive values, positive and negative likelihood ratios for WHO severity scale, NEWS, CURB-65 and APACHE scoring systems for predicting death of COVID-19 patients ≥80 years old.

SCORE	ROC AUC	Value	Sensitivity	Specificity	PPV	NPV
WHO scale	0.654 (0.590 – 0.714)	≥ 2	75 (64 – 84)	49 (41 – 57)	41 (37 – 46)	81 (73 – 86)
NEWS	0.649 (0.584 – 0.709)	≥ 5	69 (57 – 79)	52 (44 – 60)	41 (36 – 46)	78 (71 – 84)
CURB-65	0.591 (0.526 – 0.654)	≥ 5	32 (22 – 44)	78 (71 – 84)	41 (31 – 57)	71 (67 – 74)
APACHE II	0.651 (0.587 – 0.712)	≥ 26	62 (51 – 73)	67 (59 – 74)	47 (41 – 54)	79 (73 – 84)

Abbreviations: WHO, World health organization; NEWS, National early warning score; APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II

outcome.

COVID-19 pandemic is posing an outstanding challenge on health care systems worldwide, and the number of affected patients and deaths is still on the rise. Older people, and those with comorbidities, are at greater risk of requiring hospitalization or dying if they are diagnosed with COVID-19(Wu & McGoogan, 2020; Becerra-Muñoz et al. 2020). Indeed, in older patients with COVID-19 emerged that not only the severity of COVID-19-related pneumonia or impairment of respiratory function, but also frailty and vulnerability are crucial determinant of poor prognosis (Aliberti et al. 2021; Hwang et al. 2020). Consequently, mainly due to age-related vulnerability and to the several complications, the older patients are facing a more severe COVID-19.

This study was focused on a cohort of older patients with COVID-19 aged ≥80 years old. To the best of our knowledge, the proportion of these patients in the current study is one of the largest analysed to date. Thus far, clear evidence exists about the role of age as a risk factor of death in patients with COVID-19(W. Guan et al. 2020; Huang et al. 2020; Chen et al. 2020; Jin et al. 2020; WHO Coronavirus Disease (COVID-19) Dashboard 2021; Livingston & Bucher 2020; Ministero della Salute 2021). However, most of reported data included only few hospitalized patients older than 80 or 85 years. In this study we confirmed that even considering only patients older than 80 years, the increasing age was by itself an independent risk factor for death. In our cohort, dividing our patients for 5-year group, death ratio ranged from 19% in 80-84 years old, to 71.4% in ≥ 95 years old (Figure 1). It is arguable that the overall reduced physical fitness associated to older age could play a significant

Table 3
Multivariate Cox regression model for survival.

	β	Standard Error	Hazard ratio (95% CI) *Adjusted model*	*P-value*
Age ≥ 85	0.876	0.303	2.40 [1.32 – 4.35]	0.004
Dependency in ADL	0.945	0.416	2.57 [1.14 – 5.82]	0.023
Resident in nursing facility	-0.187	0.329	0.83 [0.44 – 1.58]	0.570
Dementia	0.852	0.288	2.34 [1.33 – 4.12]	0.003
Cerebrovascular disease	0.067	0.486	1.07 [0.41 – 2.77]	0.891
Congestive heart failure	0.661	0.306	1.94 [1.06 – 3.53]	0.031
Chest X ray findings				
• Negative			*Reference*	0.047
• Interstitial involvement	0.955	0.552	2.59 [0.88 – 7.67]	0.084
• Consolidation	1.300	0.551	3.67 [1.24 – 10.81]	0.018
WBC > 8860 (cells/mm3)	0.280	0.271	1.32 [0.78 – 2.25]	0.302
Lymphocyte ≤ 790 (cells/mm3)	0.437	0.253	1.55 [0.94 – 2.54]	0.085
Blood glucose > 101 (mg/dL)	0.461	0.272	1.58 [0.93 – 2.70]	0.091
BUN > 20 (mg/dL)	0.306	0.382	1.36 [0.64 – 2.88]	0.424
LDH > 489 (UI/L)	0.731	0.286	2.08 [1.19 – 3.64]	0.011
CRP > 121 (mg/L)	0.876	0.279	2.40 [1.39 – 4.15]	0.002
Serum Lactate > 1.5 (mmol/L)	0.508	0.251	1.66 [1.02 – 2.72]	0.043
SpO2 < 88% in ambient air	0.354	0.314	1.42 [0.77 – 2.63]	0.261
PaO2/FiO2 < 261	0.516	0.347	1.67 [1.03 – 2.72]	0.037

Abbreviations: ADL, Activities of daily living; WBC, white blood cells; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; CRP, C reactive protein; SpO2, peripheral oxygen saturation; FiO2, fraction of inspired oxygen; PaO2, partial pressure of oxygen

role for death risk. Similarly, other conditions that reduce overall physical fitness, as expressed by impairment in ADL and low Barthel index, were already found to be associated to an increased hazard for death in COVID-19 patients (Laosa et al. 2020; Heras et al. 2020). Nevertheless, no final clues are available to explain why COVID-19 is disproportionately killing older people(Mueller, McNamara, & Sinclair 2020; Blagosklonny, 2020).

Our data also confirmed the negative impact of dementia on COVID-19 prognosis (Covino, De Matteis, et al. 2020) showing in our cohort an adjusted hazard risk of death in patients with dementia of 2.34. Similarly, in a recent meta-analysis on 56577 patients with COVID-19, dementia whose prevalence was about 10%, was associated with increased mortality in both pooled unadjusted and adjusted effect estimates, with about a two-fold risk of death (Hariyanto et al. 2021).

Likewise, a post-hoc analysis of the international, multicentre, 'real-world' HOPE COVID-19 registry on patients aged ≥65 years hospitalized for COVID-19, also including a group of 585 patients aged ≥80 years old, showed as dementia was an independent predictor of mortality in this population (Foley, Affoo, & Martin 2015). Although the link between dementia and death could not appear obvious for COVID-19 older patients, it is well known that the risk of pneumonia-associated mortality is significantly increased in patients with any form of cognitive impairment(Numbers & Brodaty 2021) . Moreover, a latest report describing the effects of the COVID-19 pandemic on people suffering dementia reported that these patients have a relatively high risk both of contracting severe disease and of neuropsychiatric disturbances and delirium, also as a result of lockdown measures and social isolation (Garcez et al. 2020). In addition, delirium itself has been reported to be an independent predictor for death in COVID-19 patients (Garcez et al. 2020).

These findings confirmed that special support is needed for older COVID-19 patients with impaired physical and cognitive function. First and foremost, these patients should be given extra care and prevention

to minimize exposure to the virus guaranteeing both strategies of monitoring and quick access to healthcare, also by implementing tele-medicine and virtual consultations. Second, hospitals should be equipped of COVID-19 geriatric care units with a multidisciplinary team of mental health professionals (doctors, nurses and psychologists), to provide a careful and comprehensive evaluation, and better care for these patients (Hariyanto, Putri, et al 2020). Lastly, also caregivers should be involved in close monitoring of COVID-19 older patients, promoting better medications adherence (Hariyanto & Kurniawan, 2020a) and contributing to a multi-component program including psychological strategies, lifestyle changes, nutrition habits, and cognitive stimulation exercises, aiming to reduce disease severity and mortality by preventing social isolation, physical and mental inactivity. Hence, these strategies could help to improve health status in older COVID-19 patients, particularly in those with frailty, associated comorbid conditions (Hariyanto & Kurniawan, 2020b) and dementia.

Moreover, not surprisingly, in our cohort of COVID-19 patients aged 80 years or more we found that several factors depicting a severe disease at ED admission were associated to an increased risk of poor outcome, as previously described both in younger populations and in those of similar age (Zhou et al. 2020). As expected, since in COVID-19 patients the acute hypoxia is the main determinant of disease progression and severity, the blood gas evaluation provides significant information and has a relevant role in risk prediction for death at ED admission. Our data confirmed that among the blood gas parameters the PaO2/FiO2 is the best predictor even after adjusting for other covariates, and that also in patients who are 80 years of age or older, hypoxia is the main determinant of disease severity (Grasselli et al. 2020).

Among laboratory values, we found that both an elevated LDH, CRP, and serum lactic acid were independent risk factors for death. An elevation of LDH in COVID-19 deceased patients was found in several studies(Zhou et al. 2020; X. Guan et al. 2021; Lv et al. 2020). These findings appear to be consistent with a previous report on the predictors of disease severity in SARS infection, where multivariate analysis identified elevated LDH as a marker associated with worse outcomes (Leong et al. 2006). Indeed, lactate dehydrogenase is a non-specific marker, and it is usually increased in critically ill patients. Similarly, serum lactic acid levels represent both a marker of illness severity and a therapeutic target, and the higher is the level, the greater is the risk of death. Hyperlactatemia usually occurs in inadequate tissue perfusion and oxygenation, and is common in Sars-CoV-2 infection, since hypoxia is the mainstay of severe COVID-19, also in older COVID-19 patients (Foucher & Tubben, 2020; Bahl et al. 2020). C-reactive protein level correlates to inflammation and its concentration is not affected by age, sex, and physical condition (Chalmers et al. 2019). CRP is also a well-known index of severe pulmonary infections, and CRP levels were found to positively correlate with disease severity in COVID-19 (X. Guan et al. 2021; Huang et al. 2020; Chen et al. 2020; Jin et al. 2020; WHO Coronavirus Disease (COVID-19) Dashboard 2021; Covino, De Matteis, et al. 2020; Chalmers et al. 2019; Wang 2020). These results confirmed that an elevated CRP could have a predictive role in patients ≥ 80 years with COVID-19 (Covino, De Matteis, et al. 2020).

In addition, also in our cohort of older COVID-19 patients we strengthened the role of the worse clinical findings at chest x-ray as independent risk factor for a poor prognosis. Interestingly, after adjusting for other covariates, only the presence of consolidation was an independent predictor of death, whereas the interstitial involvement alone did not reach statistical significance. Although limited by the relatively small study cohort, our results are similar to those reported by several studies showing that the outcome in COVID-19 could be predicted by the radiological estimation of the residual ventilated lung area (Colombi et al. 2020).

Several early warning score have been evaluated and proposed for death risk prediction in COVID-19 both in general population (Covino, Sandroni, et al. 2020; Liang et al. 2020; Haimovich et al. 2020; Knight et al. 2020), and in older patients (Covino, De Matteis, Burzo, Russo,

et al. 2021). The WHO severity scale performs similar to other EWS in older adults, and could be evaluated without laboratory and radiological findings (Covino, De Matteis, Burzo, Franceschi, et al. 2021). At the same time, if already in use in the ED, the NEWS score performs fairly for COVID-19 patients (Covino, Sandroni, et al. 2020), and there is probably no meaning in the use of complicate calculation such as for APACHE II. CURB-65 could be used for risk stratification of COVID-19 patients (Bradley et al. 2020). However, since not every patient has pneumonia, we do not support the use of this latter score for all COVID-19. Present data, and previously published studies (Covino, Sandroni, et al. 2020; Liang et al. 2020; Haimovich et al. 2020; Knight et al. 2020; Covino, De Matteis, Burzo, Russo, et al. 2021; Covino, De Matteis, Burzo, Franceschi, et al. 2021) confirm that in older adults no EWS is really superior to others, and clinical implementation should be driven by simplicity in calculation and pre-existent local protocols. Hence, all the severity scores including a respiratory function evaluation showed a fairly good predictive value in identifying patients who could experience a worse outcome, also in this cohort of older patients.

Our study presents several limitations. Firstly, our sample is limited. Secondly, this study was conducted in a single institution which is a referral COVID-19 centre and therefore our result could not be generalizable. Thirdly, some important severity markers as D-Dimer and albumin, that a latest report suggested to use for predicting severe outcomes in COVID-19, were not included in this study (Hariyanto, Japar, Kwenandar et al. 2021). Finally, we included in our series only patients confirmed Sars-CoV2 positive at nasal and pharyngeal swab specimens. Indeed, while this could help to provide robust data on COVID-19, it excluded several patients with suggestive symptoms and radiological findings from our analysis.

5. Conclusions

Among patients $\geq$ 80 years old hospitalized with COVID-19, not barely the worse clinical and radiological presentation of the disease, but also the increasing age, dementia, and impairment in ADL were strong risk factors for all cause in-hospital death, regardless of disease severity. As expected, also in this population the severity scores including a respiratory function assessment, as well as WHO severity scale, APACHE II score, NEWS score, and CURB-65, showed a fairly good predictive value in identifying at ED admission patients who could experience a poor outcome.

These findings confirmed that special support is needed for older patients with impaired physical and cognitive function. Accordingly, caregivers and physicians should be aware of the peculiar characteristics of COVID-19 in patients aged $\geq$80 years old.

CRediT authorship contribution statement

Marcello Covino: Conceptualization, Methodology, Software, Data curtion, Formal analysis, Writing - review & editing. **Giuseppe De Matteis:** Conceptualization, Validation, Visualization, Writing - original draft, Writing - review & editing. **Davide Antonio Della Polla:** Validation, Visualization, Writing - original draft, Writing - review & editing. **Michele Santoro:** Software, Formal analysis. **Maria Livia Burzo:** Validation, Visualization, Writing - original draft, Writing - review & editing. **Enrico Torelli:** Software, Formal analysis. **Benedetta Simeoni:** Writing - review & editing. **Andrea Russo:** Writing - review & editing. **Claudio Sandroni:** Conceptualization, Methodology, Writing - review & editing. **Antonio Gasbarrini:** Conceptualization, Methodology, Writing – review & editing. **Francesco Franceschi:** Conceptualization, Methodology, Data curtion, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors have no financial or other personal conflict with this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.archger.2021.104383.

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