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SHORT COMMUNICATION

Frailty as a predictor of mortality in COVID-19 patients receiving CPAP for respiratory insufficiency

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Abstract

Objective Exploring the association between frailty and mortality in a cohort of patients with COVID-19 respiratory insufficiency treated with continuous positive airway pressure.

Methods Frailty was measured using a Frailty Index (FI) created by using the baseline assessment data on comorbidities and body mass index and baseline blood test results (including pH, lactate dehydrogenase, renal and liver function, inflammatory indexes and anemia). FI > 0.25 identified frail individuals.

Results Among the 159 included individuals (81% men, median age of 68) frailty was detected in 69% of the patients (median FI score 0.3 ± 0.08). Frailty was associated to an increased mortality (adjusted HR 1.99, 95% CI 1.02–3.88, $p = 0.04$).

Conclusions Frailty is highly prevalent among patients with COVID-19, predicts poorer outcomes independently of age. A personalization of care balancing the risk and benefit of treatments (especially the invasive ones) in such complex patients is pivotal.

Keywords Frailty · Non-invasive ventilation · COVID-19 · Mortality

Introduction

Coronavirus disease (COVID-19) can have heterogeneous manifestations [1]; however, a more severe course is expected in older people due to the combined effect of immune-aging and accrual of comorbidities over time [2, 3]. In addition, the exhaustion of physiological reserves, usually known as frailty [2], augments the vulnerability to stressors and enhances the risk of developing negative health outcomes [4].

High mortality rates were reported during the first stages of the current COVID-19 pandemic, possibly as the result of limited preparedness by the public health to deal with a novel disease with unprecedented epidemiological and pathophysiological features [5, 6]. Failure to identify older people as the main at-risk category for a poor COVID-19 course caused a delayed and defective implementation of enhanced control measures among low-intensity care facilities such as nursing care homes eventually leading to a disproportionately high number of deaths. A second major weakness in response to the crisis was the inability of health care services to provide respiratory support to a wide number of patients concentrated in very short timeframes coinciding with contagion surges. Non-invasive mechanical ventilation (NIV) proved successful as an alternative life support tool, even in patients with acute respiratory distress syndrome (ARDS), when intensive care units were

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overwhelmed [7, 8]. Little is however known to date about the potential predictors of poor respiratory and survival outcome in patients with COVID-19 treated with NIV. The aim of this study was exploring the association between frailty and mortality in a cohort of patients with COVID-19 treated with continuous positive airway pressure (CPAP) in Medical Wards of a tertiary hospital of Milan from February 25th to April 15th 2020.

Methods

This was a cohort study, part of the COVID-BioB protocol and was approved by the local review board. Upon informed consent, patients with COVID-19 treated in two General Wards of a tertiary hospital in Milan, Italy and starting CPAP for respiratory insufficiency from February 25th to April 15th 2020 were consecutively enrolled and followed up till May 5th. We excluded patients: (i) chronically receiving CPAP for obstructive sleep apnoea; (ii) previously intubated or requiring an intensive care unit (ICU) stay during the same admission; (iii) enrolled in a concomitant randomized trial on the use of early CPAP; (iv) with severe contraindications to CPAP (e.g. coma or hemodynamic instability).

COVID-19 was defined as the presence of signs and symptoms of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection together with a positive reverse-transcriptase polymerase chain reaction test from a nasal and/or throat swab and/or radiological findings consistent with COVID-19 pneumonia. We recorded patients' demographic features, anthropometrics and comorbid diseases, along with vital signs, oxygen requirements, CPAP treatment and routine blood tests at hospital admission and during the subsequent course of hospitalisation.

The degree of radiologic lung alterations observed at chest X-rays was quantified through the Radiographic Assessment of Lung Edema (RALE) score [9].

The decisions to start a ventilation support with CPAP were taken by a dedicated Medical Emergency Team performing a global evaluation of patients' age and comorbidities and taking into account the emergency setting of the first wave of the COVID-19 pandemic. In particular CPAP was offered as respiratory support in patients with an oxygen saturation (SO_2) < 94% in spite of high flow oxygen supply (through Venturi Mask or reservoir). Initially Positive End Expiratory Pressure (PEEP) was set at 10 cm H_2O and FiO_2 at 60% with 4 daily cycles of the duration of 3 h. Integration of CPAP cycles with mobilization manoeuvres encompassing pronation, lateral recumbent or seated positioning was offered to all patients unless not tolerated or contraindicated.

If FiO_2 remained < 94% despite CPAP treatment, PEEP was increased (but never over 15 cm H_2O). Instead, if SO_2 tended to significantly drop at the end of CPAP cycles, the duration of the cycles was prolonged up to 12 or 24 h. In cases of hypotension during CPAP treatment, PEEP was reduced or NIV was temporally interrupted until optimization of fluid balance and revaluation of the cardiac function [7, 10].

Pharmacological treatments for COVID-19 included antiviral and/or immunomodulatory agents as per national guidelines.

Frailty was measured using a Frailty Index (FI) created by using the standardization criteria described by Searle et al [11] (Supplementary Table S1). FI score > 0.25 identifies frail individuals.

Descriptive statistics were used to characterize the study sample. A comparison between frail and non-frail COVID-19 patients' characteristics was performed through the Chi squared test for categorical variables and through the U-Mann–Whitney test or t test for continuous variables. Cox regression analysis was used to study the association between mortality and frailty. Unadjusted and adjusted models (for the significant predictors of the unadjusted analysis) were employed. Statistical analyses were performed with SPSS version 25 (SPSS Inc. Chicago, IL, USA).

Results

Among the 159 individuals enrolled 81% were men. The median age was 68 (IQR 56–75) (Table 1). The nadir of pO2/FiO2 during the course of their hospital stay was 78.5 (IQR 63.5–95). The RALE score on admission was 12.7 ± 8.30 with 94 (59.1%) patients with a high (≥ 9) RALE score. The median duration of hospitalization was 16 days (IQR 7–25) with a median CPAP treatment of 9 days (IQR 4–15). Fifty-one patients died after a median (IQR) time of 10 (5–25) days. The mean ± standard deviation (SD) FI was 0.3 (± 0.08) and 69% of the subjects had FI > 0.25 and could thus be considered as frail. Frail patients were older ($p < 0.001$), and presented lower haemoglobin levels ($p = 0.009$) and higher creatinine ($p < 0.001$) at hospital admission. Moreover, mortality was higher in frail patients compared to robust ones: 37.6% vs 17% (Table 1). Table 2 illustrates the results of the Cox unadjusted analysis. Frailty (defined by a FI > 0.25) confirmed to be a significant predictor of in-hospital mortality in the multivariable model (adjusted HR 1.99, 95% CI 1.02–3.88, $p = 0.04$). These results were confirmed also when considering FI as a continuous variable: adjusted HR 86.49, 95% CI 1.52–4919.53, $p = 0.03$.

Table 1 Main characteristics of the study population

Variables	Total sample ($n=159$)	Frail ($n=109$)	Robust ($n=47$*)	p
Age (years)	68 (IQR 56–75)	69 (SD ± 10)	56.3 (IQR 48.36–69.81)	**< 0.001**
Males	129 (81.1%)	88 (80.7%)	38 (80.9%)	0.99
Active smokers	5 (3.2%)	5 (4.6%)	0 (0%)	0.16
Weight (kg)	80.4 (SD ± 14.29)	80 (SD ± 4.22)	81.5 (SD ± 16.87)	0.59
Height (cm)	170.2 (SD ± 8.74)	170 (SD ± 8.3)	171.1 (SD ± 9.58)	0.44
BMI (kg/m2)	27.3 (IQR 24.6–30.5)	27.7 (SD ± 4.22)	26.9 (IQR 23.8–30.46)	0.72
Frailty Index	0.3 (SD ± 0.08)	0.33 (SD ± 0.07)	0.2 (SD ± 0.03)	**< 0.001**
Lenght of hospital stay (days)	16 (IQR 7–25.25)	17 (IQR 7–26)	16 (IQR 9–24)	0.62
Lenght of CPAP treatment (days)	9 (IQR 4–15)	8 (IQR 4–15)	10.3 (SD ± 6.60)	0.72
Worst pO2/FiO2 during hospital stay	78.5 (IQR 63.5–95)	78 (IQR 62.25–95.75)	81 (IQR 69–95)	0.58
RALE score at hospital admission	12 (IQR 6–18)	12 (IQR 6–17)	11 (IQR 6–18)	0.81
CRP at hospital admission (mg/l)	146.2 (SD ± 93.15)	135.4 (SD ± 97.26)	131 (SD ± 83.71)	0.17
WBC at hospital admission (10^3cells/mmc)	13.4 (SD ± 2.1)	8.8 (SD ± 4.30)	7.3 (IQR 5.6–9.8)	0.66
Hb at hospital admission (gr/dl)	13.4 (SD ± 2.10)	13.1 (SD ± 2.12)	14.5 (IQR 13.3–15.2)	**0.009**
Platelet at hospital admission (10^3cells/mmc)	222 (IQR 153–275)	218 (IQR 152 -284.5)	217.7 (SD 71.76)	0.80
LDH at hospital admission (U/l)	452.5 (IQR 377.5–576.0)	466.5 (IQR 390.25–635.50)	425 (IQR 350.50–515.50)	**0.02**
AST at hospital admission (U/l)	55 (IQR (40–90)	57.5 (IQR 41.75–93.25)	51 (IQR 36–71)	0.21
ALT at hospital admission (U/l)	40 (IQR 26–67.25)	41 (IQR 26–71.25)	40 (IQR 27–59)	0.63
Creatinine at hospital admission (mg/dl)	1.1 (IQR 0.88–1.36)	1.2 (IQR 0.91–1.65)	0.94 (IQR 0.82–1.07)	**< 0.001**
Deaths	51 (32.1%)	41 (37.6%)	8 (17%)	**0.01**

Bold means p value < 0.05

Results are presented as mean (SD), median (IQR) or number (percentage)

SD standard deviation; *IQR* inter quartile range; *BMI* body mass index; *RALE* Radiographic Assessment of Lung Edema; *CRP* C reactive protein; *WBC* white blood cells; *Hb* haemoglobin; *LDH* lactate dehydrogenase; *AST* aspartate aminotransferase; *ALT* alanine transaminase

*3 missing data on Frailty Index

Table 2 Predictors of mortality at the Cox unadjusted analysis

Mortality			
	HR	95% CI	p
Age	1.06	1.02–1.10	**< 0.001**
Gender	1.16	0.61–2.24	0.65
Active smoker	3.49	1.06–11.46	**0.04**
WHO scale	3.36	1.84–6.13	**< 0.001**
Worst pO2/FiO2 during hospital stay	0.99	0.97–1.001	0.07
LDH at hospital admission	1.001	1.00–1.003	0.06
CRP at hospital admission	1.003	1.00–1.006	**0.03**
RALE score	1.05	1.01–1.08	**0.005**
Frailty (FI > 0.25) Index	2.973409.74	105.35–110390.571.68–5.25	**< 0.001**

Bold means p value < 0.05

WHO World Health Organization; *LDH* lactate dehydrogenase; *CRP* C reactive protein; *RALE* Radiographic Assessment of Lung Edema, *FI* Frailty Index

Discussion

Among patients suffering from COVID-19 ARDS treated with CPAP in a non-ICU setting, frailty measured through the FI was associated with an increased in-hospital mortality.

In this study, we expanded the findings of Ramirez et al. [7] on non-invasive mechanical ventilation outside the ICU setting [7]. Moreover, we specifically focused on the role of frailty in predicting the outcomes of older patients treated with CPAP. Our results are in line with those of

Zampieri et al. [12] who consistently demonstrated an association between frailty and mortality in a pre-pandemic cohort of critically ill patients. We confirmed also the data of De Smet who found that frailty was associated with increased mortality in older COVID-19 patients hospitalized in a General Hospital in Belgium but not specifically treated with CPAP [13]. Moreover, we described a wider sample of frail patients treated with NIV compared to Burns et al. [8] who assessed the benefit of NIV in only 28 COVID-19 patients. Frailty is a cornerstone of geriatric medicine because of its ability to capture the health status of older individuals [14]. However, our data suggest that frailty assessment might be a valuable tool for clinicians with other expertise and might be particularly useful for reliable risk stratification in patients with COVID-19, who might also be younger than the average population of patients hospitalised in an Internal Medicine setting.

Furthermore, frailty is a predictor of negative outcomes [2], even in the short-term period, and it is associated to an increase of resource use in critically ill patients [14]. Consequently, frailty assessment might be additionally helpful to correctly estimate the resource to be allocated according to patients' specific needs.

Indeed, both Lagolio [15] and Pilotto [16] showed that prognostic tools based on the assessment of social and functional aspects (that are part of the frailty syndrome) [15] or on a multidimensional evaluation [16] were able to predict relevant outcomes (like mortality), independently from chronological age, in COVID-19 patients.

However, the study of Lagoglio [15], was retrospective and his findings on the predictive values of a composite score (including LDH, pO_2/FiO_2 and Braden score) need further confirmations. Moreover, the Braden score used to compute the predictive index, though including social and functional aspects, was originally designed to assess the risk of pressure sores. Therefore, it does not to capture the general proprieties of ageing and the vulnerability of the organism complex systems as the FI does.

Instead, the multidimensional prognostic index of Pilotto [16], is extremely complete (including comorbidities, pressure sores risk, information on pharmacological therapy, functional, social, cognitive and nutritional domains) but it requires between 15 and 25 min to be completed. This time could not always be available during the busy routine clinical practice of an emergency setting until the models of care will change. Anyway these studies and ours demonstrated how including geriatric and multidimensional evaluations, maybe with a dedicated personnel, would be a pivotal part of the care of critically ill patients.

In particular, frailty should be considered when evaluating the possibility to escalate treatments. A balanced viewpoint on the chances of the patient and the risks of intervention would avoid both unnecessary suffering and resource consumption.

Our study has the merit of having described a Real-Word complex population afferent to an Italian Hospital during the first wave of the COVID-19 pandemic. However, some limitations are worth to be mentioned. The observational design of the study prevents to demonstrate causality in the studied relationship. Moreover, we lack information on the functional abilities of the hospitalized patients and these data could not have been included as deficits in the computation of the FI. However, the redundancy of the other variables composing the index and its mathematical proprieties could have adequately compensated for this missing datum. Finally, the monocentric nature of the study suggests that further data are needed for the generalization of our findings to other contexts.

Changing the traditional medical thinking by taking into account frailty in the decision making would be necessary in the future years. The global aging of the World population, would inevitably increase the number of frail people accessing hospitals. A redesign of the traditional models of care, with a prioritization and personalization of the interventions and the expansion of home care services, could reduce inappropriate hospitalizations and their negative consequences.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the local review board of the San Raffaele Hospital.

Informed consent Obtained.

Human and animal rights statement The study will follow the principles of the Declaration of Helsinki. No animal was included in the study.

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