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Coronavirus Pandemic

The PaO_2/FiO_2 ratio on admission is independently associated with prolonged hospitalization in COVID-19 patients

Angelo Zinellu[1], Andrea De Vito[2], Valentina Scano[3,4], Panagiotis Paliogiannis[3], Vito Fiore[2], Giordano Madeddu[2], Ivana Maida[2], Elisabetta Zinellu[4], Arduino A Mangoni[5], Luigi B Arru[6], Ciriaco Carru[1], Sergio Babudieri[2], Pietro Pirina[3,4], Alessandro G Fois[3,4]

[1] Department of Biomedical Sciences, University of Sassari, Sassari, Italy
[2] Infectious and Tropical Diseases Clinic, Department of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy
[3] Department of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy
[4] Unit of Respiratory Diseases, University Hospital Sassari (AOU), Sassari, Italy
[5] Department of Clinical Pharmacology, College of Medicine and Public Health, Flinders University and Flinders Medical Centre, Adelaide, Australia
[6] Operative Unit of Hematology, Center for Stem Cell Transplantation, San Francesco Hospital, Nuoro, Italy

Abstract

Introduction: The early identification of factors that predict the length of hospital stay (HS) in patients affected by coronavirus desease (COVID-19) might assist therapeutic decisions and patient flow management.

Methodology: We collected, at the time of admission, routine clinical, laboratory, and imaging parameters of hypoxia, lung damage, inflammation, and organ dysfunction in a consecutive series of 50 COVID-19 patients admitted to the Respiratory Disease and Infectious Disease Units of the University Hospital of Sassari (North-Sardinia, Italy) and alive on discharge.

Results: Prolonged HS (PHS, >21 days) patients had significantly lower PaO_2/FiO_2 ratio and lymphocytes, and significantly higher Chest CT severity score, C-reactive protein (CRP) and lactic dehydrogenase (LDH) when compared to non-PHS patients. In univariate logistic regression, Chest CT severity score (OR = 1.1891, $p = 0.007$), intensity of care (OR = 2.1350, $p = 0.022$), PaO_2/FiO_2 ratio (OR = 0.9802, $p = 0.007$), CRP (OR = 1.0952, $p = 0.042$) and platelet to lymphocyte ratio (OR = 1.0039, $p = 0.036$) were significantly associated with PHS. However, in multivariate logistic regression, only the PaO_2/FiO_2 ratio remained significantly correlated with PHS (OR = 0.9164; 95% CI 0.8479-0.9904, $p = 0.0275$). In ROC curve analysis, using a threshold of 248, the PaO2/FiO2 ratio predicted PHS with sensitivity and specificity of 60% and 91%, respectively (AUC = 0.780, 95% CI 0.637-0.886 $p = 0.002$).

Conclusions: The PaO_2/FiO_2 ratio on admission is independently associated with PHS in COVID-19 patients. Larger prospective studies are needed to confirm this finding.

Key words: COVID-19; hospital stay; PaO2/FiO2 ratio.

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Introduction

The novel coronavirus disease COVID-19 outbreak, caused by the severe acute respiratory syndrome coronavirus 2, was initially reported in Wuhan, China, in late 2019 [1]. In recent years, at least two other epidemics have been caused by coronaviruses, the SARS-CoV with about 8,000 cases in China and other 37 countries, and the Middle East Respiratory Syndrome (MERS-CoV) which affected about 2,500 people in Middle East countries [2,3]. Due to its high contagiousness, COVID-19 has rapidly spread across the world with more than 3.5 million cases and 250,000 deaths as of 7 May 2020 [4]. The clinical spectrum of COVID-19 disease is wide, ranging from asymptomatic infection or mild upper respiratory tract symptoms (80%) to severe viral pneumonia with respiratory failure and death (20%) [5-9]. Since the major route of transmission of SARS-CoV2 is via droplet spread, which requires close contact [10], many countries have adopted extraordinary physical distancing strategies to reduce diffusion and mitigate the impact of the pandemic on health care systems, particularly in terms of hospital staff and bed availability. In this context, the implementation of effective patient flow management strategies would benefit from a better understanding of the clinical progress of the disease and the factors that are associated with the length of hospital stay (HS). In

particular, the identification of specific patient characteristics that predict a prolonged HS (PHS) might assist with specific therapeutic decisions and early transfer to appropriately equipped wards. We sought to address this issue by investigating the capacity of routine clinical, laboratory, and imaging parameters of hypoxia, lung damage, inflammation, and organ dysfunction, to predict PHS in COVID-19 patients.

Methodology

We retrospectively studied a consecutive series of 50 COVID-19 patients admitted to the Respiratory Disease and Infectious Disease Units of the University Hospital of Sassari, a tertiary COVID-19 referral centre based in North-Sardinia, Italy, between 15 March and 30 April 2020 and alive on discharge. COVID-19 patients were diagnosed according to the World Health Organization (WHO) interim guidance and had radiologic evidence of pneumonia or infiltrates on chest CT scan. The criteria for patient discharge included absence of fever for at least three days, significant improvement on chest CT, resolution of respiratory symptoms, and two consecutive negative throat-swab samples for viral RNA collected at least 24 hours apart. The data regarding demographic, clinical, laboratory, and imaging investigations performed within the first 24 hours of admission, and length of hospital stay (HS), were retrieved from individual clinical records and recorded into an electronic database. Specifically, we collected established parameters of comorbidity (Charlson Comorbidity Index), hypoxia (PaO2/FiO2), extent and severity of lung inflammation (Chest CT severity score), coagulation (D-dimer), inflammation and organ dysfunction [C-reactive protein (CRP), ferritin, white blood cell count (WBC), monocytes, lymphocytes, neutrophils, platelets, mean corpuscular volume (MCV), red cell distribution width (RDW), mean platelet volume (MPV), albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and procalcitonin (PCT)]. Furthermore, using available data, we calculated combined blood cell indexes of systemic inflammation, such as the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and lymphocyte to monocyte ratio (LMR), which have been shown to predict outcomes in patients suffering from specific infections, including COVID-19 [11-13]. We also collected information regarding the intensity of care received, specifically in terms of respiratory support (oxygen supplementation, non-invasive or invasive respiratory support) during the hospitalization. The study was conducted in accordance with the declaration of Helsinki and was approved by the ethics committee of the University Hospital (AOU) of Cagliari. Data are expressed as mean values (mean ± SD) or median values (median and IQR).

Table 1. Demographic, clinical, haematological and serological characteristics of the study population.

	COVID 19 global cohort (*n = 50*)
Demographic and clinical parameters	
Age, years	66.9 ± 14.7
Gender (F/M)	18/32
Smoking status (no/yes)	33/17
BMI, (non-obese/obese)	33/12
P/F ratio	295 ± 68
Interval between disease onset and admission, (days)	6 (3-9)
Intensity of care (no, OT, RSni, RSi)	11/26/4/9
Chest CT severity score	10.9 ± 7.4
Charlson Comorbidity Index	4 (2-5)
Cardiovascular disease, (no/yes)	26/24
Respiratory disease, (no/yes)	41/9
Kidney disease, (no/yes)	41/9
Diabetes, (no/yes)	38/12
Cancer, (no/yes)	43/7
Autoimmunity, (no/yes)	47/3
Hospital stay, (days)	18 (12-24)
Haematological Parameters	
WBC, ($\times 10^9$ L)	6.87 ± 2.46
Monocytes, ($\times 10^9$ L)	0.30 (0.20-0.40)
Lymphocytes, ($\times 10^9$ L)	1.00 (0.70-1.20)
Neutrophils, ($\times 10^9$ L)	4.90 (3.40-6.70)
Platelets, ($\times 10^9$ L)	213 (150-264)
NLR	4.41 (3.25-8.80)
PLR	217 (142-331)
LMR	3.00 (2.00-4.25)
MCV, (fL)	86.1 ± 10.6
RDW, (%)	15.6 ± 3.7
MPV, (fL)	8.4 (8.2-8.8)
Serological parameters	
CRP, (mg/dL)	5.79 (2.08-13.14)
Albumin, (g/dL)	3.50 (3.12-3.87)
PCT, (μg/L)	0.08 (0.035-0.190)
Ferritin, (ng/mL)	366 (186-1874)
ALT, (IU/L)	23.5 (15.0-39.0)
AST, (IU/L)	31.5 (21.0-47.0)
LDH, (IU/L)	273 (197-359)
D-dimer, (μg/mL)	1.11 (0.58-3.38)
Fibrinogen, (mg/dL)	558 (458-694)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index, COVID-19: coronavirus disease 2019; CRP: C-reactive protein; LDH: lactate dehydrogenase; LMR: lymphocyte to monocyte ratio; M: male; MCV: mean corpuscular volume; MPV: mean platelet volume; NLR: neutrophil to lymphocyte ratio; PCT, Procalcitonin; P/F: PaO_2/FiO_2; PLR: platelet to lymphocyte ratio; OT: oxygen therapy; RDW: red blood cells distribution width; RSi: invasive respiratory support; RSni: non-invasive respiratory support; WBC: white blood cells. Statistical significance at 0.05.

Table 2. Correlations between hospital length of stay and demographic, clinical and laboratory parameters.

	Kendall rank correlation coefficient (Tau)	p value
PaO_2/FiO_2	- 0.304	0.023
Intensity of care	0.339	0.005
Chest CT severity score	0.344	0.003
Monocytes	- 0.259	0.008
Lymphocytes	- 0.205	0.035
PLR	0.210	0.032
CRP	0.237	0.017
PCT	0.227	0.024
Ferritin	0.296	0.004
AST	0.211	0.031
LDH	0.321	0.001

AST: aspartate aminotransferase; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; LDH: lactate dehydrogenase; PCT, Procalcitonin; P/F: PaO2/FiO2; PLR: platelet to lymphocyte ratio; WBC: white blood cells. Statistical significance at 0.05.

Table 3. Demographic, clinical and haematological and serological characteristics in patients with prolonged (PHS) and non-prolonged (non-PHS) hospital stay.

	Non-PHS (*n = 35*)	PHS (*n =15*)	p value
Age, years	70.4 ± 14.7	65.4 ± 17.4	0.27
Gender (F/M)	11/24	7/8	0.35
Smoking status (no/yes)	23/12	10/5	1.00
BMI, (non-obese/obese)	23/7	10/5	0.50
PaO2/FiO2 ratio	314 ± 66	252 ± 51	**0.002**
Illness onset to first hospital, (days)	6 (3-10)	6 (2-8)	0.57
Intensity of care (no, OT, RSni, RSi)	10/19/2/4	1/7/2/5	0.11
Chest CT severity score	8.1 ± 6.8	15.9 ± 6.0	**0.001**
Charlson Comorbidity Index	4 (2-5)	4 (2-6)	0.73
Cardiovascular disease, (no/yes)	19/16	7/8	0.76
Respiratory disease, (no/yes)	27/8	14/1	0.27
Kidney disease, (no/yes)	27/8	14/1	0.27
Diabetes, (no/yes)	27/8	11/4	0.74
Cancer, (no/yes)	28/7	15/0	0.09
Autoimmunity, (no/yes)	32/3	15/0	0.54
Hospital stay, (days)	15 (10-18)	34 (25-37)	--
WBC, ($x10^9$ L)	7.10 ± 2.57	6.36 ± 2.15	0.34
Monocytes, ($x10^9$ L)	0.40 (0.30-0.40)	0.3 (0.2-0.4)	0.12
Lymphocytes, ($x10^9$ L)	1.00 (0.82-1.30)	0.70 (0.60-1.10)	**0.042**
Neutrophils, ($x10^9$ L)	5.00 (3.25-6.67)	4.80 (3.52-7.00)	0.88
Platelets, ($x10^9$ L)	196 (146-255)	220 (170-324)	0.32
NLR	4.19 (3.28-7.41)	8.00 (3.26-12.11)	0.20
PLR	185 (137-280)	317 (219-494)	**0.012**
LMR	3.00 (2.99-4.19)	2.75 (1.75-5.12)	0.67
MCV, (fL)	86.6 ± 11.1	82.5 ± 8.8	0.21
RDW, (%)	16.4 ± 3.7	15.1 ± 3.7	0.27
MPV, (fL)	8.4 (8.2-9.2)	8.40 (8.12-8.70)	0.40
CRP, (mg/dL)	3.32 (1.89-12.01)	10.82 (5.62-14-99)	**0.047**
Albumin, (g/dL)	3.60 (3.18-3.90)	3.40 (3.00-3.70)	0.33
PCT, (μg/L)	0.07 (0.02-0.18)	0.014 (0.08-0.25)	0.14
Ferritin, (ng/mL)	352 (111-1374)	971 (252-2401)	0.08
ALT, (IU/L)	23.0 (12.0-35.0)	26.0 (19.5-52.5)	0.21
AST, (IU/L)	30.0 (17.8-43.3)	37.0 (25.5-48.8)	0.12
LDH, (IU/L)	257 (173-325)	354 (272-418)	**0.017**
D-dimer, (μg/mL)	1.09 (0.54-4.39)	1.12 (0.74-2.29)	0.83
Fibrinogen, (mg/dL)	592 (359-684)	608 (476-742)	0.65

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index, COVID-19: coronavirus disease 2019; CRP: C-reactive protein; LDH: lactate dehydrogenase; LMR: lymphocyte to monocyte ratio; LTBSOAH: lag time between symptoms onset and hospitalization; M: male; MCV: mean corpuscular volume; MPV: mean platelet volume; NLR: neutrophil to lymphocyte ratio; PCT, Procalcitonin; P/F: PaO2/FiO2; PLR: platelet to lymphocyte ratio; OT: oxygen therapy; PHS: prolonged hospital stay; RDW: red blood cells distribution width; RSi: invasive respiratory support; RSni: non-invasive respiratory support; WBC: white blood cells. Statistical significance at 0.05.

Variables distribution was assessed by the Kolmogorov-Smirnov test. Between group differences of continuous variables were compared using unpaired Student's t-test or Mann–Whitney rank sum test, as appropriate. Differences between categorical variables were evaluated by Fisher test or chi-squared test, as appropriate. The Kendall rank correlation test was used to assess correlations between length of HS and other variables. Univariate and multivariate linear regression analysis was used to assess independent associations between length of HS and baseline demographic, clinical and laboratory parameters. Only variables with significant ($p < 0.05$) associations in univariate correlation analysis were entered in multivariate analysis. Non-normally distributed variables were log10-transformed prior to being entered in parametric tests. Normal distribution of the residuals was checked to assess the goodness of fit of the transformations. Logistic regression analysis was performed to assess independent associations between PHS (defined as the upper HS tertile, > 21 days) and baseline demographic, clinical, laboratory, and imaging parameters. Only variables with significant ($p < 0.05$) associations in univariate logistic analysis were entered in multivariate analysis. The ability of specific parameters to predict PHS was assessed using receiver operating characteristics (ROC) curve analysis. Selection of optimal cut-off values for sensitivity and specificity was assessed according to the Youden Index. Statistical analyses were performed using MedCalc for Windows, version 19.1 64 bit (MedCalc Software, Ostend, Belgium).

Results

The baseline demographic, clinical, laboratory and imaging parameters are described in Table 1. Median age was 66.9 ± 14.7 years and the majority of patients were males (64%). The median length of HS was 18 days (IQR: 12–24 days). No respiratory support was required in 11 patients while the rest required some form of support during the hospitalization. Univariate correlation analysis showed significant negative relationships between length of HS and PaO_2/FiO_2 ratio (Tau = -0.304, $p = 0.023$), monocytes (Tau = -0.259, $p = 0.008$) and lymphocytes (Tau = -0.205, $p = 0.035$) and positive relationships with intensity of care (Tau = 0.339, $p = 0.005$), chest CT severity score (Tau = 0.344, $p = 0.003$), PLR (Tau = 0.210, $p = 0.032$), CRP (Tau = 0.237, $p = 0.017$), PCT (Tau = 0.227, $p = 0.024$), ferritin (Tau = 0.296, p = 0.004), AST (Tau = 0.211, p = 0.031) and LDH (Tau = 0.321, $p = 0.001$) (Table 2). In multiple regression, only the PaO_2/FiO_2 ratio was significantly and negatively associated with the length of HS (r = -0.47, $p = 0.03$). The comparison between the characteristics of PHS (> 21 days) and non-PHS patients is described in Table 3. When compared with non-PHS patients, PHS patients had significantly lower PaO_2/FiO_2 ratios (252 ± 51 vs 314 ± 66, $p = 0.002$) and lymphocytes (median: 0.70 $\times 10^9$ L; IQR: 0.60 - 1.10 $\times 10^9$ L vs 1.00 $\times 10^9$ L; IQR: 0.82-1.30 $\times 10^9$ L, $p = 0.042$), and significantly higher chest CT severity scores (15.9 ± 6.0 vs 8.1 ± 6.8), PLR (317; IQR: 219 - 494 vs 185; IQR: 137-280, $p = 0.012$), CRP (10.82 mg/dL; IQR: 5.62-14-99 mg/dL vs 3.32 mg/dL; IQR: 1.89-12.01 mg/dL, $p = 0.047$) and LDH (354 IU/L; IQR: 5272-418 IU/L vs 257 IU/L; IQR: 173-325 IU/L,

Figure 1. ROC curve of P/F ratio in prolonged hospital stay COVID-19 patients.

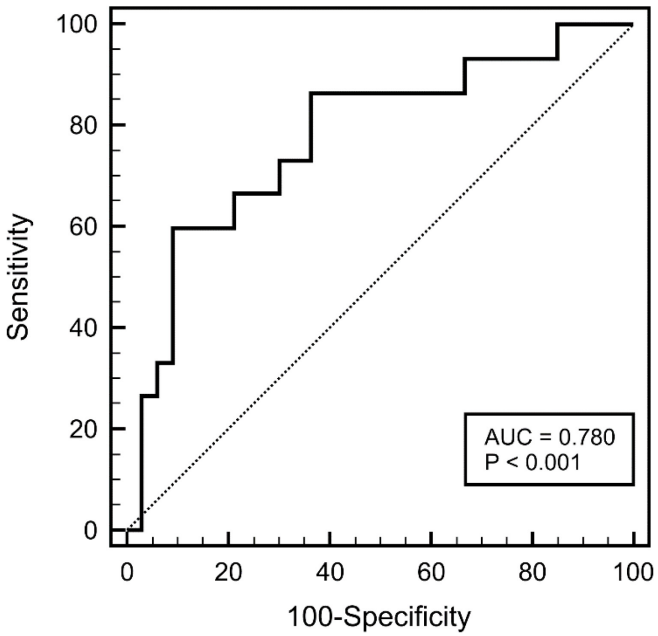

Table 4. Univariate logistic regression assessing the association between patient characteristics and prolonged hospital stay.

	Crude OR	95% CI	p
Chest CT severity score	1.1891	1.0495 to 1.3472	0.007
Intensity of care	2.1350	1.1166 to 4.0822	0.022
PaO_2/FiO_2	0.9802	0.9661 to 0.9944	0.007
CRP	1.0952	1.0035 to 1.1954	0.042
PLR	1.0039	1.0003 to 1.0076	0.036

CRP: C-reactive protein; P/F: PaO_2/FiO_2; PLR: platelet to lymphocyte ratio; Statistical significance at 0.05.

p = 0.017). In univariate logistic regression, chest CT severity score (crude OR = 1.1891, 95% CI 1.0495-1.3472, p = 0.007), intensity of care (crude OR = 2.1350, 95% CI 1.1166-4.0822, p = 0.022), PaO_2/FiO_2 ratio (crude OR = 0.9802, 95% CI 0.9661-0.9944, p = 0.007), CRP (crude OR = 1.0952, 95% CI 1.0035-1.1954, p = 0.042) and PLR (crude OR = 1.0039, 95% CI 1.0003-1.0076, p = 0.036) were significantly associated with PHS (Table 4). In multivariate logistic regression, only the PaO_2/FiO_2 ratio was significantly associated with PHS (OR = 0.9164; 95% CI 0.8479-0.9904, p = 0.0275). In ROC curve analysis, using a threshold of 248, the PaO_2/FiO_2 ratio identified PHS patients with sensitivity and specificity of 60% and 91%, respectively (AUC = 0.780, 95% CI 0.637-0.886 p = 0.002) (Figure 1).

Discussion

A WHO alert was issued in late December 2019 regarding several cases of pneumonia of unknown aetiology in Wuhan City, Hubei Province, People's Republic of China [1]. A novel Betacoronavirus named SARS CoV-2 was successively identified as the causative factor of the disease that rapidly spread from China to the rest of the world, generating a global pandemic [14]. COVID-19 has necessitated the development and implementation of nationwide public health prevention strategies to contain transmission and reduce the burden on health care systems, particularly in regard to the availability of acute and intensive care hospital beds. In this context, strategies are urgently required on how to best tackle the overflow of admissions and the patient journey during hospital stay, optimizing outcomes and, at the same time, managing existing resources. Such strategies would greatly benefit from the early identification of specific patient characteristics that are associated with the length of hospital stay, a leading indicator of healthcare utilization and associated costs. In order to address this pressing issue, we retrospectively studied a consecutive series of 50 COVID-19 patients admitted to a dedicated referral centre in north Sardinia (Italy), with clinical and demographic characteristics comparable to those recently described in other COVID-19 cohorts [5-7,14-16]. A key factor in the spreading of SARS-CoV2 across the community is the lag time between the onset of symptoms and hospital admission. The lag time period in our study (6 days, IQR 3-9) was within the range of previous studies, between 4 and 12 days [5-6, 15,16-19]. The median length of HS (18 days, IQR 12-24) was also within the range of that described in previous reports (between 12 and 22 days) [6,8,16,19]. Investigating a range of established clinical, laboratory, and imaging parameters of hypoxia, lung damage, inflammation, and organ dysfunction, collected at the time of admission, we found significant negative univariate correlations between the length of HS and the PaO_2/FiO_2 ratio, monocytes and lymphocytes and positive associations with intensity of care, chest CT severity score, PLR, CRP, PCT, ferritin, AST and LDH. However, in multiple regression, only the PaO_2/FiO_2 ratio remained significantly associated with the length of HS. To further investigate the latter, we categorized patients in those with or without prolonged HS (PHS). There were significant between-group differences in the PaO_2/FiO_2 ratio, lymphocytes, chest CT severity score, PLR, CRP and LDH. In particular, PHS patients had lower PaO_2/FiO_2 ratio and lymphocytes and higher chest CT severity score, PLR, CRP and LDH when compared to short HS patients. The association between low lymphocytes and PHS, as well as the observed relationships between disease severity and increased CRP and LDH concentrations, is consistent with previous observations [8,16,20-25]. In univariate logistic regression, chest CT severity score, intensity of care, PaO_2/FiO_2 ratio, CRP and PLR were significantly associated with PHS. In multivariate logistic regression, only the PaO_2/FiO_2 ratio remained significantly associated with PHS. PaO_2/FiO_2 ratio, also known as Horowitz index, is a measure of hypoxemia in respiratory failure widely known in clinical practice due to its easy to use: it is calculated as the ratio between the arterial oxygen partial pressure (PaO_2) and the fractional inspired oxygen (FiO_2). It is a good descriptor of respiratory failure tied to lung parenchymal damage with subsequent shunt effect, as occurs for example in pulmonary oedema, acute respiratory distress syndrome (ARDS) and pneumonia [26]. Valuated in 1974 as predictor of pulmonary dysfunction in injured patients admitted in trauma services [27], it was validated as a recommended criterion for acute lung injury and ARDS in the American-European Consensus Conference on ARDS [28] and lately incorporated in the Berlin definition of ARDS, in which PaO_2/FiO_2 ratio determines the degree of severity of ARDS itself [29]. Despite being widely used in clinical practice, only a few reports have previously investigated its capacity to predict the length of stay in non-COVID-19 patients in critical care settings [30-32]. In the context of COVID-19, the PaO_2/FiO_2 ratio has been primarily investigated as a marker of disease severity. Guan et al. [11] did not found any significant differences in the PaO_2/FiO_2 ratio between severe and non-severe COVID-19 patients. However, data were missing in 81.3% of cases.

Colaneri *et al*. [22] found a univariate correlation between the PaO_2/FiO_2 ratio and disease severity, however this parameter was not included in multivariate analysis because it was available in a limited number of patients, thus precluding more definitive conclusions. The results of our study have potential clinical relevance as they suggest that a single PaO_2/FiO_2 ratio measurement within the first 24 hours of admission might independently predict PHS. As a consequence, this parameter might prove useful to rapidly divert some patients to management pathways characterized by specific management and monitoring protocols. Some limitations of our study must be acknowledged, particularly its retrospective design and the relatively small sample size. However, to the best of our knowledge, this is the first evidence of a significant and independent association between the PaO_2/FiO_2 ratio on admission and prolonged hospitalization in COVID-19 patients. Larger prospective studies are needed to confirm our results and further evaluate the use of the PaO_2/FiO_2 ratio is optimizing COVID-19 patient care and flow management in acute care.

Conclusions

The outbreak of the new pandemic caused by the betacoronavirus SARS-CoV-2 got in trouble several countries all over the world, even those whose health system was believed to be cutting-edge. The burden of patients affected with COVID-19 that needed hospitalization was in fact either heavy and sudden: this situation led to a necessary reorganization of the resources to increase survival chances of as many as possible patients. We propose to use PaO_2/FiO_2 ratio at the admission to make a decision on the intensity of treatment, as a single measurement of Horowitz index predicts a longer hospitalization. Even with the limitation of a limited number of patients analysed, our study possibly provides the first evidence of an independent association between PaO_2/FiO_2 ratio measured within 24 hours from the admission and a prolonged hospitalization in patients with COVID-19.

Authors' contributions

Conceptualization, A.Z.,S.B., P.P. and A.G.F..; methodology, A.Z., A.D.V. and Pa.P.; Data curation and investigation: A.D.V., V.S., V.F., G.M., I.M., E.Z. and L.B.A; formal analysis: A.Z., A.A.M., and C.C.; original draft preparation, A.Z., A.D.V. and A.G.F; review and editing, A.Z., A.G.F., S.B.,P.P.

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Corresponding author

Alessandro Giuseppe Fois, MD
Unit of Respiratory Disease, University Hospital Sassari (AOU), Department of Medical, Surgical and Experimental Sciences, v.le San Pietro 43, 07100 Sassari, Italy.
Phone: +39 079228370
Fax: +39 0792151104
Email: agfois@uniss.it

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