The PaCO2/FiO2 ratio as outcome predictor in SARS-COV-2 related pneumonia: a retrospective study

Stefano De Vuono, Pasquale Cianci, Sokol Berisha, Patrizia Pierini, Gaia Baccarini, Francesco Balducci, Alessandra Lignani, Laura Settimi, Maria Rita Taliani, Paolo Groff

Emergency Department, Santa Maria della Misericordia Hospital, Perugia, Italy

Abstract. *Background and aim:* Respiratory failure in SARS-CoV-2 patients is characterized by the presence of hypoxemia and hypocapnia without relevant dyspnea. To date, the use of respiratory parameters other than PaO2/FiO2 ratio to stratify the risk of worsening of these patients has not been sufficiently studied. Aim of this work was to evaluate whether the ratio between partial pressure levels of carbon dioxide (PaCO2) and the fraction of inspired oxygen (FiO2) measured at emergency department (ED) admission is predictive of the clinical course of patients suffering from SARS-CoV-2 pneumonia. *Methods:* We retrospectively studied 236 patients with SARS-CoV-2 pneumonia evaluated at the ED of the Perugia Hospital. The end-points were: in-hospital mortality, need for invasive mechanical ventilation (IMV) and length of in-hospital stay (LOS). Clinical, blood gas and laboratory data were collected at ED admission. *Results:* Of the 236 patients 157 were male, the mean age was 64 ± 16. Thirtythree patients (14%) needed IMV, 49 died (21%). In the univariate analysis, the PaCO2/FiO2 ratio was inversely associated with the need for IMV (p <0.001), mortality (p <0.001) and LOS (p = 0.005). At the multivariate analysis the PaCO2/FiO2 ratio was found to be predictive of the need for IMV, independently from age, gender, number of comorbidities, neutrophils, lymphocytes, glomerular filtrate, d-dimer, LDH and CRP. *Conclusions*: the PaCO2/FiO2 ratio is predictive of the risk of respiratory failure worsening in patients with SARS-CoV-2 pneumonia, independently from other several confounding factors. (www.actabiomedica.it)

Key words: PaCO2/FiO2 ratio, SARS-CoV-2 , pneumonia, respiratory failure, outcome predictors

Introduction

In early December 2019 a new coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China (1). Subsequently, it rapidly spread worldwide producing millions of victims and deaths and WHO officially declared the pandemic on March 2020 (2). SARS-CoV-2 outbreaks caused an important increase in the need for hospital beds and medical equipment and despite the great efforts of public health for containing the disease and delaying the spread, SARS-CoV-2 diffusion is an important threat to global health (1).

The clinical spectrum of coronavirus disease 19 (Covid-19) can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome and death (3). A major clinical characteristic of SARS-CoV-2 related pneumonia is that despite the pronounced arterial hypoxemia there are not proportional signs of respiratory distress (4). This phenomenon is called "happy hypoxemia" or "silent hypoxemia" and early reports revealed that one third of patients did not have dyspnea (5). In other series dyspnea has been reported in only 18.7% of Covid-19 patients hospitalized with an abnormal CT scan (6). Huang et al. showed that only 50% of patients with objective

radiographic findings consistent with Covid-19 pneumonia reported shortness of breath (1). Often happy hypoxemia is associated with hypocapnia. Experiments in hypobaric chambers have revealed that hypocapnic hypoxia is not usually accompanied by air hunger (7). The causes of this phenomenon in Covid-19 are not yet fully understood. Probably ventilation/perfusion mismatch without a concomitant increase in pulmonary airway resistance and pulmonary compliance reduction allow an increase in respiratory rate and in tidal volume without a need of carrying out a great respiratory effort and with consequent hypocapnia development (8). Hypocapnia cause respiratory alkalosis with a consequent shift of the oxyhaemoglobin dissociation curve to the left, thus increasing haemoglobin's oxygen affinity and an increase in arterial oxygen saturation (9). Moreover the alveolar gas equation predicts that hyperventilation and the resulting drop in the alveolar partial pressure of alveolar CO_2 tension leads to an increase in the alveolar partial pressure of oxygen and ultimately an increase in SpO_2 (9). In conclusion caution should be made interpreting SpO_2 values in patients with Covid-19 and performing a blood gas analysis allow to better recognize the presence of hypoxemia and its hypocapnia. Prompt Covid-19 patients risk stratification in the emergency department could ameliorate the referral to the appropriate care setting, improving patient outcome and healthcare resource utilization (10). To our knowledge no studies have evaluated the potential role of hypocapnia as a predictor of respiratory failure deterioration in subjects with SARS-CoV-2 related pneumonia.

Thus, in this study we wanted to evaluate if the $PaCO_2/FiO_2$ ratio, measured at the beginning of the in-hospital route, is a predictor of worse outcome in patients with SARS-CoV-2 related pneumonia

Patients and methods

We retrospectively included in our study all subjects with severe or critical SARS-CoV-2 related pneumonia admitted to our II-level Emergency Department (ED) between October 2020 and April 2021. The Institutional Board of our Hospital approved the study with the prescription of the use of data in a strictly anonymous form, given the retrospective design of the study informed consent was waived.

The end-points of the study were in-hospital death, need for invasive mechanical ventilation (IMV) and length of in-hospital stay. Also vital signs were registered at admission and we included: systolic and diastolic blood pressure (SBP and DBP, *mmHg*), heart rate (*beats per minute*) and body temperature (*°C*)

Clinical medical history, laboratory and blood gas data were obtained at the same time at the time of emergency room admission.

At admission we took note of the following comorbidities: hypertension (HTN), diabetes, dyslipidemia, obesity, chronic ischemic cardiomyopathy (CIC), previous cerebrovascular disease (CVD), peripheric obliterative arteriopathy (PAOD), atrial fibrillation (AF), chronic obstructive pulmonary disease (COPD); we also reported the sum of them as number of comorbidities (NOC).

The following laboratory parameters were included: white blood cells count (WBC) with its relative formula (neutrophils, lymphocyte, monocyte, eosinophils, basophils), haemoglobin (Hb), platelets (PTL), glycemia, urea, creatinine, glomerular filtration rate (GFR) (calculated with MDRD formula), INR, RATIO, d-dimer, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum lactic dehydrogenase (LDH), creatine phosphokinase (CPK), C-reactive protein (CRP).

Blood gas analysis was performed at admission without changing the oxygen supplementation set during ambulance transport; oxygen was mainly administered through Venturi-mask and rarely through nasal-canula. If oxygen was supplied with nasal-canula we assumed that for every liter of oxygen supplied FiO_2 increased by 4%. If oxygen was administered through Venturi-mak the FiO_2 was estimated based on the valve used.

SARS-CoV-2 infection diagnosis was based on a positive nucleic acid amplification test made on nasopharyngeal swab. Pneumonia diagnosis was based on a positive chest-x-ray or lung ultrasound.

Severe Illness was defined by: SpO_2 <94% on room air or a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg. Critical Illness was defined by respiratory failure, septic shock, and/or multiple organ dysfunction (11).

As many patients already were on oxygen supplementation at the time of the emergency room admission we believed that using the ratio between carbon dioxide values and fraction of inspired oxygen ($PaCO_2/FiO_2$) was more accurate and informative than carbon dioxide values itself, with the assumption that administered O_2 could affect respiratory pattern and consequently $PaCO_2$.

We followed The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.

Statistical analysis

We used binary logistic regression analysis and Spearman's rank correlation coefficients for testing the univariate relations between the variables. Binary logistic regression and multistep regression analysis were used for testing the effect of possible confounding factors on the considered end-points. To define the accuracy of the $PaCO_2/FiO_2$ ratio we used the receiver-operating characteristic (ROC) curve analysis. Analysis were performed with SPSS software (version 19.0; SPSS, Inc., Chicago, IL), with statistical significance set at $p < 0.05$.

Results

General population characteristics

In the considered period 236 patients met the characteristics of severe pneumonia as previously defined. Mean age of our study population was 64 ± 13 years old and there was a prevalence of males (157 males and 79 females). The main represented comorbidity of our study population was hypertension, followed by diabetes and dyslipidemia (Figure 1).

Laboratory data collected at admission in the emergency room and blood gas analysis data are shown in Table 1.

Mean PaO_2/FiO_2 suggests that most subjects were affected by mild to moderate ARDS. Indeed, during in-hospital stay many patients needed support with high-flow nasal canula (HFNC) oxygen administration (37%) and many needed non-invasive mechanical ventilation (NIMV) support (62%); 33 (14%) patients needed IMV and 49 (21%) died during in-hospital stay. Mean length of in-hospital stay was $14,6 \pm 10,4$ days.
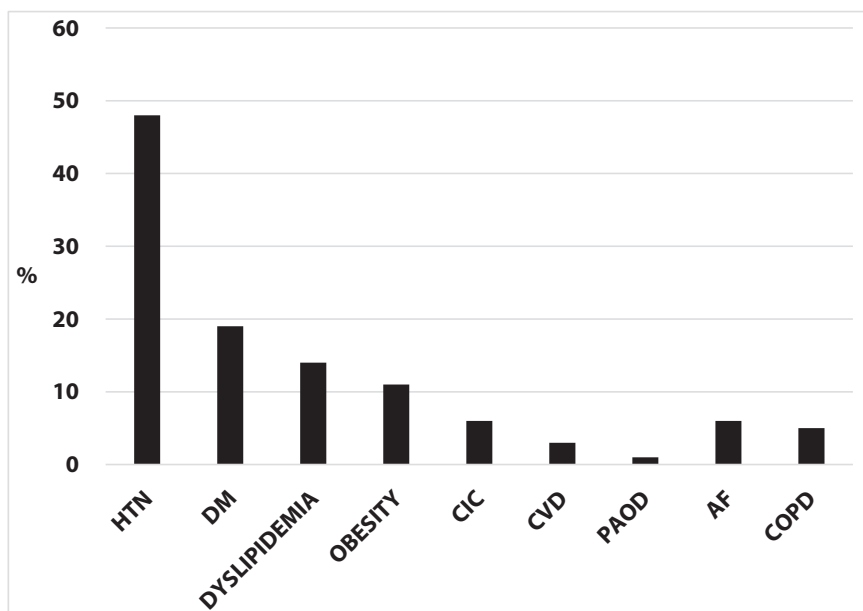

Figure 1. Comorbidities in our population study.

Table 1. General characteristics and laboratory data at ER admission.

	Mean (± DS)
Age, *yrs*	64 ± 13
Gender, *M/F*	157/79
WBC, $10^3/mmc$	5673 ± 4918
N, %	82 ± 10
L, %	12 ± 9
M, %	5 ± 2
E, %	0,1 ± 0,5
B, %	0,1 ± 0,2
Hb, *mg/dl*	13,8 ± 1,8
PTL, $10^3/mmc$	224 ± 79
Glycemia, *mg/dl*	153 ± 57
Urea, *mg/dl*	50 ± 32
Creatinin, *mg/dl*	1,01 ± 0,8
GFR, *ml/min/1,73 m^2*	80 ± 24
D-dimer, *µg/ml*	1171 ±1412
AST, *IU/L*	61 ± 84
ALT, *IU/L*	49 ± 57
LDH, *IU/L*	423 ± 292
CPK, *IU/L*	278 ± 963
CRP, *mg/ml*	13,3 ± 23
Blood gas analysis	
pH	7,47 ± 0,5
pO_2, *mmHg*	64,7 ± 16,5
pCO_2, *mmHg*	31,1 ± 6,3
HCO_3^-, *mmol/L*	23,2 ± 4,0
PaO_2/FiO_2	244 ± 100
$PaCO_2/FiO_2$	121 ± 92

WBC: white blood cells; **N**: neutrophils; **L**: lymphocyte; **M**: monocyte; **E**: eosinophils; **B**: basophils; **Hb**: haemoglobin; **PTL**: platelets; **GFR**: glomerular filtration rate; **AST**: aspartate aminotransferase; **ALT**: alanine aminotransferase; **LDH**: serum lactic dehydrogenase; **CPK**: creatine phosphokinase; **CRP**: C-reactive protein

Table 2. Univariate correlations among PaCO2/FiO2 ratio and other variables.

	β	**p**
Age	–.209	**.001**
Gender	–.005	.067
Number of comorbidities	–.004	.953
SBP	–.006	.940
DBP	–.011	.892
Heart rate	–.069	.312
Body temperature	–.090	.194
WBC	.082	.215
N	–.342	**<.001**
L	.307	**<.001**
M	.315	**<.001**
E	–.001	.994
B	–.180	**.007**
Hb	.008	.907
PTL	–.048	.471
Urea	–.294	**<.001**
Creatinin	–.146	**.028**
GFR	.165	**.013**
D-dimer	–.286	**<.001**
AST	–.090	.178
ALT	–.114	.087
LDH	–.239	**<.001**
CRP	–.281	**<.001**

SBP: systolic blood pressure; **DBP:** dyastolic blood pressure; **WBC:** white blood cells; **N:** neutrophils; **L:** lymphocyte; **M:** monocyte; **E:** eosinophils; **B:** basophils; **Hb:** haemoglobin; **PTL:** platelets; **GFR:** glomerular filtration rate; **AST:** aspartate aminotransferase; **ALT:** alanine aminotransferase; **LDH:** serum lactic dehydrogenase; **CRP:** C-reactive protein

Variables influencing the PaCO2/FiO2 ratio

As to our knowledge the PaCO2/FiO2 ratio was not used in previous studies, we wanted to evaluate which variables could influence the PaCO2/FiO2 ratio, thus considering them as possible confounding variables at multivariate analysis. As shown in Table 2 we found a statistically significant inverse association among the PaCO2/FiO2 ratio and age, neutrophils, basophils, blood urea, creatinin, d-dimer, LDH and CRP; moreover the PaCO2/FiO2 showed significant direct association with lymphocytes, monocytes and GFR.

Univariate and multivariate analysis between the PaCO2/FiO2 ratio end the end-points

At univariate analysis we observed a significant inverse correlation between PaCO2/FiO2 and need of IMV (p < .001, OR 0,979, 95% CI 0,970-0,989),

between PaCO2/FiO2 and mortality (p < .001, OR 0,987, 95% CI 0,979-0,994) and between PaCO2/FiO2 and length of in-hospital stay (p .005, β -0,187) (Table 3).

At multivariate analysis we observed that PaCO2/FiO2 predicted the risk of IMV independently from age, gender, number of comorbidities, neutrophil and lymphocyte count, GFR, d-dimer, LDH and CRP (p .021, OR 0,985, 95% CI 0,972-0,998). Correcting for the same confounding factors the associations between PaCO2/FiO2 and mortality and between PaCO2/FiO2 and length of in-hospital stay were lost. The independent predictors of in-hospital mortality were age and d-dimer, while the independent predictors of length of in-hospital stay were age, GFR and d-dimer (Table 4).

Table 3. Univariate correlation analysis.

	OR	95% CI	p
IMV	0,979	O,970-0,989	**<.001**
In-hospital death	0,987	0,979-0,994	**<.001**
		β	p
Length of in-hospital stay		-0,187	**.005**

IMV: invasive mechanical ventilation

ROC curve analysys

Regarding the end-point need for IMV the PaCO2/FiO2 ratio showed to have moderate accuracy, with an AUROC of 0.761 (95% CI 0.664-0,858, p <.001) (Figure 2)

Discussion

The aim of our study was to evaluate if the PaCO2/FiO2 ratio, measured at the beginning of the in-hospital route, could be a predictor of worse outcome in patients with SARS-CoV-2 related pneumonia and actually our results show that PaCO2/FiO2 ratio could predict the need of IMV in these patients confirming our hypothesis. Thus the PaCO2/FiO2 ratio could help physicians working in the ED in choosing the better allocation of covid patients. 3-5% of patients with COVID-19 related pneumonia require intensive care, thus the stress on health systems all over the world caused by the pandemic waves stimulated the search for predictors of unfavorable outcome that can be applied early in the treatment process and capable of guiding physicians in the correct allocation of resources. A large number of papers already showed that epidemiological factors, number

Table 4. Binary logistic and multistep regression analysis.

	IMV			Death			Length of in-hospital stay	
	OR	95% CI	p	OR	95% CI	p	β	p
PaCO$_2$/FiO2	**0,984**	**0,972-0,996**	**.011**	1,003	0,993-1,013	.556	0,028	.668
Age	0,995	0,946-1,047	.848	1,108	1,044-1,175	**.001**	0,259	**.002**
Gender	3,465	0,912-13,165	.068	2,344	0,787-6,984	.0,89	0,089	.153
NOC	0,926	0,551-1,559	.774	0,964	0,609-1,524	.874	-0,040	.532
N	1,073	0,842-1,367	.568	1,217	9,959-1,546	.107	0,500	.061
L	1,022	0,758-1,376	.888	1,158	0,871-1,539	.313	0,405	.130
GFR	0,994	0,969-1,018	.604	0,980	0,956-1,005	.112	-0,188	**.017**
D-Dimer	1,000	1,000-1,000	.303	1,000	1,000-1,001	**.018**	0,277	**<.001**
LDH	1,000	0,998-1,002	.911	1,002	0,999-1,004	.188	0,093	.147
CRP	1,004	0,980-1,027	.766	0,992	0,959-1,026	.632	-0,051	.395

NOC: number of comorbidities; **N:** neutrophils; **L:** lymphocyte; **GFR:** glomerular filtration rate; **LDH:** serum lactic dehydrogenase; **CRP:** C-reactive protein
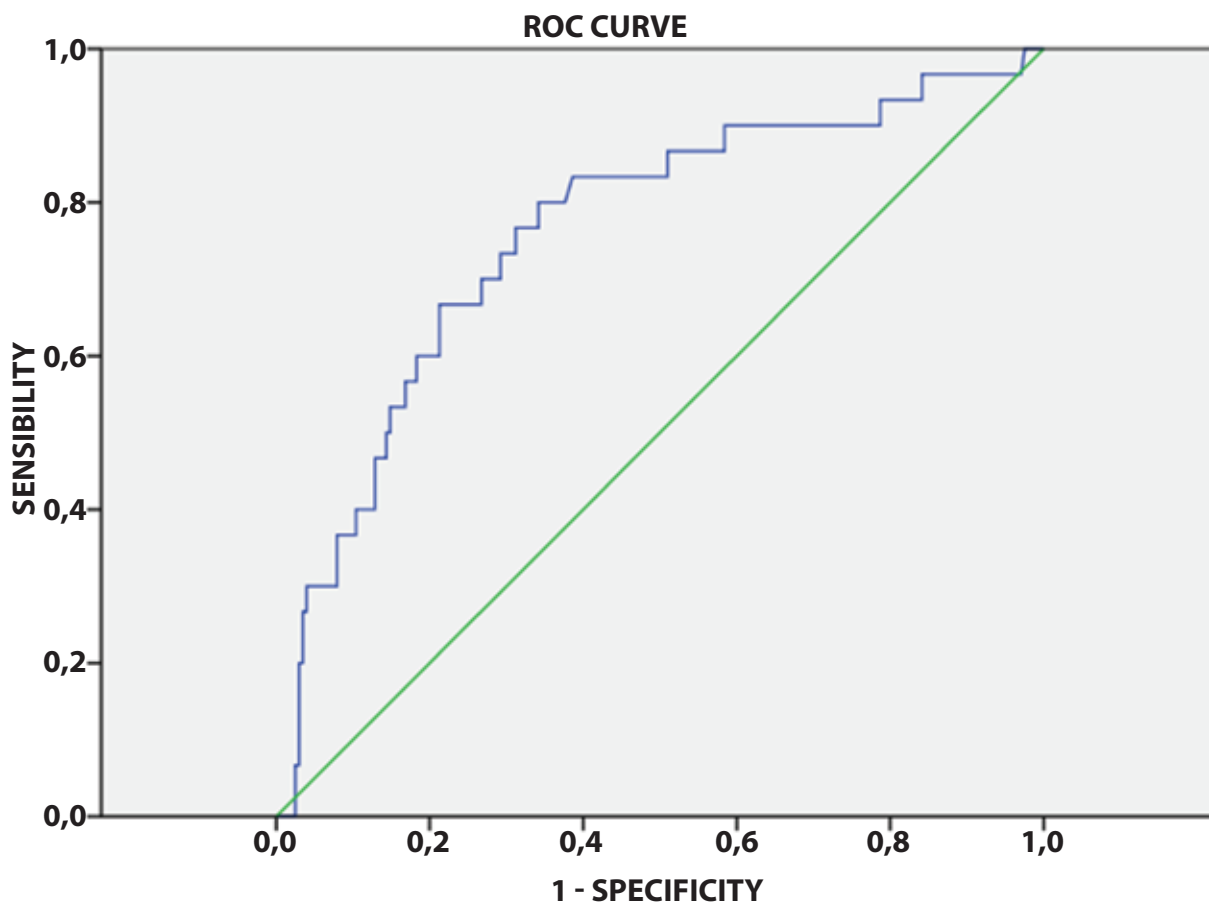
Figure 2. ROC curve for the need of IMV.

and type of comorbidities (12-14), clinical and laboratory factors detectable at the first evaluation of the patients (15-19) can help clinicians in risk stratification of COVID-19 patients. Some predictive scores, already validated or newly formulated, have been proposed (20-26). Unfortunately, as showed by Wynants et al. (27) in a systematic review, many of the proposed models are at high risk of bias and have not a good performance. Thus, the individuation of new predictors is needed. In our study we observed that the $PaCO_2/FiO_2$ ratio is associated with many variables considered in most of the proposed risk scores, i.e. age, pre-existent comorbidities, neutrophils, lymphocytes, GFR, d-dimer, LDH and CRP. Nevertheless $PaCO_2/FiO_2$ ratio was able to predict the need for IMV independently from them. The same cannot be applied for in-hospital death and length of in-hospital stay.

To our knowledge only one study indirectly explored the role of hypocapnia as a prognostic predictor (28). Studying a population of 349 patients with COVID-related acute respiratory failure consecutively admitted to a respiratory intensive care unit, Prediletto et al. observed that the ratio between the standard PaO_2 (which include $PaCO_2$ and therefore the respiratory work necessary to maintain a certain PaO_2) and FiO_2 ($STPaO_2/FiO_2$) is more accurate than the traditional PaO_2/FiO_2 ratio in predicting in-hospital mortality. Interestingly, in this study, the deceased patients had a significantly lower $PaCO_2$ value than the survivors, although the AUROC of $PaCO_2$ was not sufficiently accurate in predicting this outcome. Our study not only confirms these data, but explored more directly the association between $PaCO_2$ and adverse outcomes (need of invasive mechanical ventilation, in-hosptital

mortality) and supported this association after adjusting for other factors that were known to be correlated with adverse outcomes. ROC curve analysis on our study population confirmed that the PaCO2/FiO2 ratio has enough accuracy in predicting the need for IMV.

In the results, PaCO2 (divided for FiO2) was an independent predictor of IMV, while it was not for in-hospital mortality. This data could indicate that, as better explained below, the production of excessively large tidal volumes in spontaneous breathing, responsible for hypocapnia, is a factor directly related to the worsening of lung damage, while other and more complex factors intervene on mortality. Indeed, in our multivariate analysis in-hospital mortality was predicted by age and d-dimer and length of in-hospital stay was predicted by age, GFR and d-dimer.

Early hypocapnia development in COVID-19 patients has several pathophysiological explanations. COVID-19 pneumonia is characterized by an initial phase of prevalent interstitial and microvascular involvement, which subsequently leads to a condition of diffuse alveolar damage with the formation of hyaline membranes, edema and fibrotic deposition (29). Therefore, it is possible to believe that, at least in the first phase, lung compliance is not significantly compromised and that hypoxemia depends on the loss of the physiological mechanism of hypoxic vasoconstriction secondary to a dysregulation of the microcirculation induced by inflammation and the formation of microthrombi (30). In this situation of hypoxemia associated with preservation of lung compliance, the patient develops a respiratory pattern characterized by greater depth of breaths and greater respiratory frequency with consequent development of hypocapnia (9).

Hypocapnia development could have itself a role in respiratory failure worsening, thus giving a possible pathophysiological explanation to the possible predictive role of PaCO2/FiO2 ratio. The occurrence of a spontaneous respiratory pattern characterized by deep and frequent breathing, typical of this phase of the disease, can generate an excessive swing of transpulmonary pressure inducing a real risk of producing a self-induced lung injury (PSILI) (31, 32) The concept of PSILI is more to a theoretical assumption than a concrete experimental evidence because this picture has never been directly observed in patients with COVID-19 related pneumonia and thus it has been criticized by distinguished authors, especially if the decision to intubate a patient would depend on it (33, 34). Nevertheless, excessive stretching of the lung parenchyma, which can occur in conditions of hyperventilation, remains an accredited hypothesis of inflammatory lung damage. In our study the PaCO2/FiO2 ratio is not only an early predictor of the need for IMV, but also independent by other already known but more generic predictors, such as age, sex, number of comorbidities, neutrophil and lymphocyte counts, blood urea, creatinine, GFR, d-dimer, and CRP. Given that the FiO2 level indirectly represents the degree of hypoxaemic respiratory failure, indeed FiO2 is already used for calculating the PaO2/FiO2 ratio which defines the severity of ARDS according to the Berlin criteria (35) and it is the parameter on which the decision to start IMV is based, almost part of the predictive ability of the PaCO2/FiO2 ratio could be explained by FiO2 itself. On the other hand, it should be considered that was mandatory calculating the ratio between PaCo2 and FiO2 in order to consider the potential effect of oxygen administration on the ventilatory pattern. It is easy to understand that being hypocapnic (and thus having a respiratory pattern characterized by deep and frequent breathing) on room air is not the same than being hypocapnic while receiving supplemental oxygen with elevated FiO2. In our opinion it is precisely the combination of PaCO2 and FiO2 that gives the ratio its good predictive performance.

Limitations

Our study has some limitations. It has a retrospective design, thus we cannot consider some possible confounding variables such as respiratory rate or the time from symptoms begin to hospital admission. However it should be considered that epidemiological, clinical, laboratory and imaging data of all patients were all homogeneously and simultaneously collected at the time of admission to the Emergency Department for institutional policy and this made it possible not to have missing data in the subsequent processing. The study is monocentric and therefore the results may

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Correspondence:
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Paolo Groff
Emergency Department, Ospedale Santa maria della Misericordia
Piazzale Menghini 1 - 06129 Perugia, Italy
E-mail: paolo.groff@ospedale.perugia.it
ORCID iD: 0000-0001-9941-619