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Original article

Standardizing PaO2 for PaCO2 in P/F ratio predicts in-hospital mortality in acute respiratory failure due to Covid-19: A pilot prospective study

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ABSTRACT

Introduction: Up to fifteen percent of patients with novel pandemic coronavirus disease (Covid-19) have acute respiratory failure (ARF). Ratio between arterial partial pressure of oxygen (PaO2) and fraction of inspired oxygen (FiO2), P/F, is currently used as a marker of ARF severity in Covid-19. P/F does not reflect the respiratory efforts made by patients to maintain arterial blood oxygenation, such as tachypnea and hyperpnea, leading to hypocapnia. Standard PaO2, the value of PaO2 adjusted for arterial partial pressure of carbon dioxide (PaCO2) of the subject, better reflects the pathophysiology of hypoxemic ARF. We hypothesized that the ratio between standard PaO2 over FiO2 (STP/F) better predicts Covid-19 ARF severity compared to P/F.

Methods: Aim of this pilot prospectic observational study was to observe differences between STP/F and P/F in predicting outcome failure, defined as need of invasive mechanical ventilation and/or deaths in Covid-19 ARF. Accuracy was calculated using Receiver Operating Characteristics (ROC) analysis and areas under the ROC curve (AUROC) were compared.

Results: 349 consecutive subjects admitted to our respiratory wards due to Covid-19 ARF were enrolled. STP/F was accurate to predict mortality and superior to P/F with, respectively, AUROC 0.710 versus 0.688, $p = 0.012$. Both STP/F and PF were accurate to predict outcome failure (AUROC respectively of 0.747 and 0.742, $p = 0.590$).

Discussion: This is the first study assessing the role of STP/F in describing severity of ARF in Covid-19. According to results, STP/F is accurate and superior to P/F in predicting in-hospital mortality.

1. Introduction

Novel coronavirus disease SARS-CoV-2 emerged in December 2019, rapidly became pandemic and it was the cause of the so-called severe acute respiratory coronavirus disease (Covid-19). So far, more than 127 million cases were confirmed worldwide, with more than 2.7 million deaths [1]. Covid-19 typically affects respiratory tracts, leading to pneumonia and acute respiratory failure (ARF). [2] Morbidity and mortality related to Covid-19 are due to complications, especially acute respiratory distress syndrome (ARDS), which occur in up to 15% of cases. [3,4].

The ratio of arterial (PaO2) to inspired (FiO2) partial pressure of oxygen (P/F ratio), is currently utilized to assess the severity of respiratory failure in patients with ARDS [5] and correlates to mortality rate [6–8]. P/F ratio has been recently proposed as a prognostic marker in Covid-19 [9,10]. However, P/F ratio may be poorly representative of the severity of hypoxemia in patients with ARDS [11,12] and does not consider the level of respiratory muscles effort and hyperventilation of

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Table 1
A – Characteristics of the study population and arterial blood gas analysis data at the time of Emergency Room (ER) admission.

		n	Tot.	% of n	Mean	DS
Age	349			69,20	13,40	
Sex	349					
	Male		232	66,5%		
	Female		117	33,5%		
Smoking	277					
	Never		235	84,8%		
	Former/current		42	15,2%		
Comorbidities	349					
	Systemic arterial hypertension or Chronic Atrial fibrillation		239	68,5%		
	Diabetes mellitus		69	19,8%		
	Cerebrovascular accidents and/or ischemic heart disease		58	16,6%		
	Chronic obstructive pulmonary disease (COPD) or asthma		45	12,9%		
	Chronic kidney failure		35	10,0%		
	Active neoplasm (or diagnosis <5 years)		31	8,9%		
	Obesity		29	8,3%		
	Immunodepression and/or autoimmune disease		21	6,0%		
	Venous thromboembolism		7	2,0%		
	Obstructive sleep apnea syndrome (OSAS)		7	2,0%		
	Interstitial lung disease		2	0,6%		
	Miscellaneous		139	39,8%		
≥2 comorbidities	349	172	49,3%			
Symptoms	349					
	Fever		291	83,4%		
	Dyspnea		224	64,2%		
	Cough		159	45,6%		
	Dysgeusia/ageusia		32	9,2%		
	Anosmia		39	11,2%		
	Diarrhea		52	14,1%		
	Abdominal pain		26	7,1%		
	Headache		36	9,8%		
	Fatigue Mental confusion/delirium		132 29	35,9% 8,3%		
ER admission						
FiO_2	349			0,24	0,11	
$FiO_2 > 0,21$	349	25	7,2%			
SpO_2	260			91,8	5,9	
ABG/PaO_2 and P/F available	308		88,3%			
ABG/PaO_2, $PaCO_2$ and P/F available	305		87,4%			
	pH				7,47	0,05
	PaO_2 (mmHg)				63,8	16,4
	$_{ST}PaO_2$ (mmHg)				50,6	18,5
	$PaCO_2$ (mmHg)				32,1	5,0
	HCO^{3-} standard (mmol/L)				24,0	3,2
	PF				286,7	79,3
	$_{ST}P/F$				225,8	80,5
	PF<200	308	31	10,1%		
	$_{ST}P/F$ <200	305	117	38,4%		
Days from symptoms start to ER admission				6,1	2,0	
Days from symptoms start to Pulmonology Unit admission				9,6	7,7	
Days from ER admission to Pulmonology Unit admission				3,5	5,7	

Table 1. B – Arterial blood gas analysis data at the time of Pulmonology Unit admission and outcomes of the study population.

		n	Tot.	% of n	Mean	DS
Pulmonology Unit admission						
Previous hospital setting	349					
	ER		201	57,6%		
	General Medicine Units		70	20,1%		
	Infectious diseases Unit		44	12,6%		
	Other units		34	9,7%		
Respiratory treatment/support applied	349					
	Standard oxygen therapy		202	57,8%		
	High flow nasal oxygen		106	30,4%		
	Continuous positive airway pressure		31	8,9%		
	Non invasive ventilation		7	2,0%		
Thoracic high Resolution Computed Tomography/ pattern	333					
	Ground glass opacities		146	43,8%		
	Consolidation ± Ground glass opacities		187	56,2%		
FC (bpm)	337			80,1	13,4	
FR (breaths/minute)	322			22,3	5,4	
FiO_2	349			0,51	0,20	
SpO_2 (%)	344			95,8	2,7	
ABG available	349					
	ph				7,44	0,40

(continued on next page)

Table 1 (*continued*)

		n	Tot.	% of n	Mean	DS
	PaO_2 (mmHg)				85,7	25,4
	$_{ST}PaO_2$ (mmHg)				78,3	26,8
	$PaCO_2$ (mmHg)				35,5	5,0
	$PaCO_2 \leq 40$ mmhg		309	88,5%		
	HCO3 (mmol/L)				25,6	3,4
	P/F	349			189,4	61,9
	$_{ST}$P/F	349			172,4	80,1
	P/F<200	349	196	56,2%		
	$_{ST}$P/F <200	349	249	71,3%		
Outcomes						
Outcome failure	349	113	32,4%			
Deaths	349	58	16,6%			
Need for Invasive mechanical ventilation (IMV)	349	77	22,1%			
Need for respiratory treatment step up Survival, from symptoms start to date of death (days)	349 58 58	172	49,3%	21,0	13.4	
Survival, from ER admission to date of death (days)				16,8	13,3	
Days from ER Admission to recovery from ARF	291			21,6	9,9	

hypoxemic patients and do not discriminate patients according to their degree of hypocapnia [13]. In addition, considerable evidence supports that alteration of ventilation perfusion rate assessed as pulmonary dead space fraction [14] or ventilatory ratio [3] are associated with mortality in ARDS [15] and severity of COVID-induced ARDS [3].

In a seminal paper, Mays emphasized the axiom that PaO2 and arterial carbon dioxide tensions (PaCO2) are inversely related [16] and suggested that estimation of the severity of ventilation/perfusion mismatch may be optimized standardizing PaO2 for PaCO2 by using the formula: standardized PaO2 ($_{ST}$PaO2) = 1.66*PaCO2 + PaO2 - 66.4 [17]. In the current pilot observational study we evaluated if substituting PaO_2 with $_{ST}PaO_2$ in calculating P/F ratio may better stratify patients according to outcome failure, defined as needs of invasive mechanical ventilation (IMV) and/or death in patients with COVID-19.

2. Material and methods

The Institutional Ethical Committee approved the study protocol and patients had to sign written informed consent before enrollment. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [18].

Patients were prospectively recruited in the period October 31th 2020-January 31th 2021 after admission to pulmonology wards of the following hospitals: IRCCS S.Orsola-Malpighi (Alma Mater University of Bologna); Policlinico Umberto I, (Sapienza University of Rome) and Central Hospital of Bolzano. Inclusion criteria were laboratory-confirmed SARS-CoV-2 infection (positive result of real-time reverse transcriptase-polymerase chain reaction assay from either nasal or pharyngeal swabs, or lower respiratory tract aspirates); presence of consolidation and/or ground glass opacities at Chest X-ray and/or at computed tomography of lungs [19] and presence of acute respiratory failure. Acute respiratory failure was identified when pO2 was <60 mmHg at FiO2 = 21%. [20] Exclusion criteria were needs of endotracheal intubation and invasive mechanical ventilation before Pulmonology wards admission and history of chronic respiratory failure. For each study subject we collected clinical history, arterial blood gas analysis (ABGs) data (PaO_2, $PaCO_2$, pH, HCO_3, FiO_2) at hospital admission and at the time of admission to the Pulmonology Unit, respiratory supports applied throughout hospital stay and date of death or recovery from respiratory failure. PaO2 was standardized for PaCO2 by using the formula: standardized PaO2 (STPaO2) = 1.66*PaCO2 + PaO2 - 66.4 [17]. P/F, $STPaO_2$ and STP/F were calculated for each subject. For $_{ST}$P/F and P/F, we use data from ABG collected on the first day of admission in Pulmonology Unit with the study subject that had inspired oxygen at a fixed FiO_2 for at least 10 minutes [21–25]. Occurrence of ARF, was identified when PaO_2 was < 60 mmHg with FiO_2 = 0.21. Outcome failure was defined as needs of invasive mechanical ventilation (IMV) and/or death. We also evaluated the relationship between duration of ARF and P/F and STP/F. Recovery from ARF occurred before pulmonology ward discharge of the study subjects. Duration of ARF was expressed in days from emergency room (ER) admission to the first day of recovery from ARF (subjects died during hospital stay were censored). End of follow-up for each study subject was fixed hospital stay discharge (for survivors) or date of death.

Continuous variables are presented as mean value and standard deviation (±SD), median, minimum and maximum values. Categorical ones are expressed by frequencies and percentages. To define accuracy of PF and $_{ST}$PF to predict study outcomes we used the receiver-operating characteristic (ROC) curve and compared the area under curve (AUROC) deriving from the use of conventional P/F vs. STP/F ratio. Comparisons between AUROC of PF and $_{ST}$PF for the study outcomes were made by De Long's test [26] and Best threshold for the ROC analysis was calculated using the Youden index point [27]. Categorical variables were analyzed using one-way analysis of variance (ANOVA) or χ2-square test, when appropriate. Associations between parameters were calculated using Spearman correlation test. $P \leq 0.05$ was considered statistically significant. Analysis was performed using IBM SPSS Statistics version 21. Using Buderer's formula, we empirically calculated a minimum sample size of 284 subjects to reach 70% of sensitivity and 70% of specificity [28]. In previous studies the average prevalence of outcome failure and mortality, respectively, were 43,7% and 19,6%. [[29–32],].

3. Results

We enrolled 349 consecutive patients. Characteristics of the study population and outcomes are described in Tables 1A and 1B. Outcome failure was observed in 113 patients (32,4%) and 58 patients died (16.6%). Median survival was 18.5 days (range 4-65, mean 21.0 ± 13.4) and 13.0 days (range 0-65, mean 16.6 ± 13.3) calculated, respectively, from symptoms start to date of death and from ER admission to date of death. All deaths were caused by acute respiratory failure due to Covid-19. Median duration of ARF was 23 days (range 2-58, mean 21.6 ± 9.9).

Considering outcome failure, AUROC was 0.747; (95% CI 0.693-0.801) for $_{ST}$P/F and 0.742 for P/F (95% CI 0.687-0.797), with an advantage for $_{ST}$P/F comparing to P/F, but not statistically significant (p = 0.59), as shown on Fig. 1A. Analyzing only in-hospital mortality as outcome (Fig. 1B), only AUROC of $_{ST}$P/F showed enough accuracy comparing to AUROC of PF (0.710; 95% CI 0.638-0.782 vs. 0.688; 95% CI 0.650-0.846); this difference was statistically significant, p = 0.0189.

PaO_2, $_{ST}PaO_2$ and $PaCO_2$ showed not enough accuracy according to the ROC curve both by outcome failure and deaths (AUC<0.7). By outcome failure, PaO2, $_{ST}$PaO2 and PaCO2 showed AUC of, respectively, 0.533 (95% CI 0.491-0.616), 0.582 (95% CI 0.520-0.645), and 0.574 (95% CI 0.509-0.639). By deaths, AUROC of PaO_2 was 0.599 (95% CI 0.520-0.677), AUC for $_{ST}PaO_2$was 0.623 (95%CI 0.544-0.701) and AUC

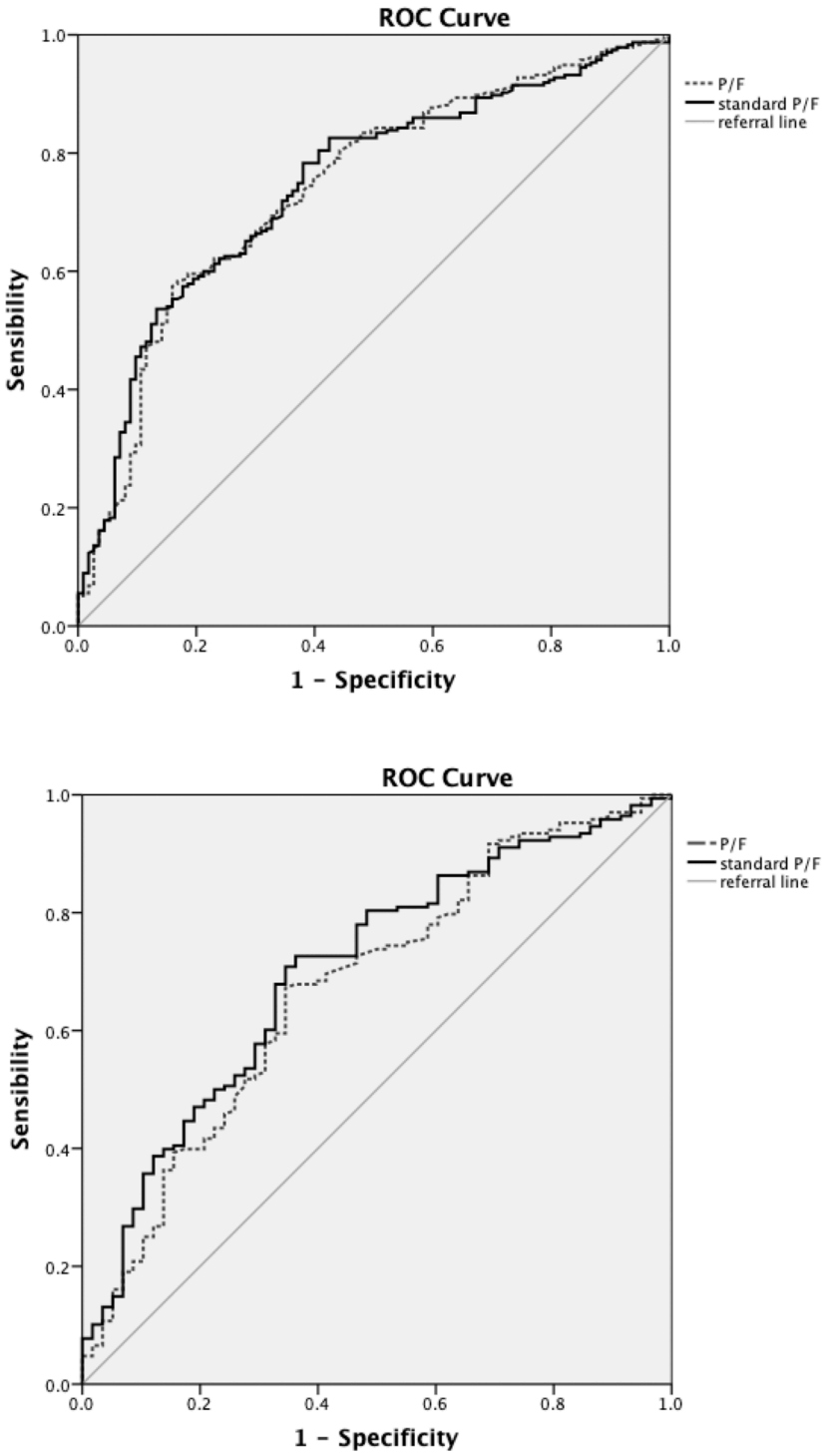

Fig. 1. Predictive receiver-operating characteristic (ROC) curve of the study population by outcome failure (A) and deaths (B) for $_{ST}$P/F and P/F.

of $PaCO_2$ was 0.617 (95% CI 0.532-0.702).

According to ROC analysis, the best cut-off for $_{ST}$P/F was, respectively, 170 for outcome failure and 125 for deaths. The best cut-off for P/F was, respectively, 180 for outcome failure and, even if AUROC was not enough accurate, 150 for deaths. Sensibility, specificity, positive predictive value and negative predictive value for $_{ST}$P/F and P/F are shown on Table 2. There were 146 subjects with $_{ST}$P/F $\leq$ 170 and 203 with $_{ST}$PF $>$ 170. Among subjects with sP/F $\leq$ 170, outcome failure rate was 46,8% and morality rate 23.2%. In comparison outcome failure rate and mortality rate were, respectively, 12.3% and 7.5% for the subgroup with $_{ST}$P/F $>$ 170. These differences were statistically significant (p = 0.000). There were 115 subjects with $_{ST}$P/F $\leq$ 125 and 234 with P/F $>$ 125. Among those with $_{ST}$P/F $\leq$ 125, outcome failure was 59.1% and mortality rate 33%. In comparison outcome failure rate and mortality rate were, respectively, 19,2% and 8,8% for the subgroup with $_{ST}$P/F $>$ 125. These differences were statistically significant (p = 0.000).

Stratifying by deaths (Table 3) mean value of both P/F and STP/F showed statistical significant differences between groups: patient died due to Covid-19 ARF had a mean P/F 149.9 $\pm$ 67.5, mean STP/F 129.8 $\pm$ 58.4 versus, respectively, 197.3 $\pm$ 83.3 and 181.0 $\pm$ 81.7 of survivors subgroup (p = 0.000 and p = 0.000). No differences between groups were observed according to PaO2, while the subgroup of patients who

Table 2
Predictive power of standard PF and PF in the study population according to outcomes (SE = sensibility; SP = specificity; PPV = positive predictive value; NPV = negative predictive value).

Outcome Failure (IMV or death)	AUROC	Cut-off	SE	SP	PPV	NPV
standard P/F PF	0.747	170 *	54%	87%	88,00%	47,00%
	0.747	125	81%	41%	81,00%	60,00%
	0.742	180 *	59%	83%	85%	48,00%
	0.742	150	76%	40%	80%	54,00%
Deaths						
standard P/F	0.710	170	47%	19%	93%	23%
	0.710	125 *	75%	66%	92%	33%
P/F	0.688	180	53%	26%	91,00%	24,00%
	0.688	150 *	70%	66%	91%	30%

* best cut-off

Table 3
Differences in terms of PaO_2, $PaCO_2$, standard PaO_2 ($_{ST}PaO_2$), P/F and $_{ST}$P/F by outcome failure and deaths in the study population (ANOVA).

Outcome failure		n	Mean	SD	Min	Max	p value
PaO2 (mmHg)	no	236	87,3	26,3	50	240	
	yes	113	82,6	23,1	51	200	
	tot	349	85,7	25,4	50	240	.105
PaCO2 (mmHg)	no	236	35,6	4,9	20	61	
	yes	113	34,8	5,0	23	55	
	tot	349	35,5	5,0	20	61	.057
$_{ST}$PaO2 (mmHg)	no	236	80,4	27,8	30	225	
	yes	113	73,9	24,2	31	183	
	tot	349	78,3	26,8	30	225	.034
P/F	no	236	209,1	84,3	60	629	
	yes	113	148,4	61,9	60	357	
	tot	349	189,4	82,7	60	629	.000
$_{ST}$P/F	no	236	192,2	83,1	41	623	
	yes	113	131,1	55,7	49	340	
	tot	349	172,4	80,1	41	623	.000
Deaths							
PaO2 (mmHg)	no	291	86,7	25,4	50,0	240,0	
	yes	58	80,1	24,8	51,0	200,0	
	tot	349	85,7	25,4	50,0	240,0	0.112
PaCO2 (mmHg)	no	291	35,8	4,9	20,0	61,0	
	yes	58	34,3	5,3	26,0	55,0	
	tot	349	35,5	5,0	20,0	61,0	.037
$_{ST}$PaO2 (mmHg)	no	291	79,6	26,9	30,0	225,0	
	yes	58	71,4	25,4	31,0	183,0	
	tot	349	78,3	26,8	30,0	225,0	.032
P/F	no	291	197,3	83,3	60,0	629,0	
	yes	58	149,9	67,5	60,0	357,0	
	tot	349	189,4	82,7	60,0	629,0	.000
$_{ST}$P/F	no	291	181,0	81,7	41,0	623,0	
	yes	58	129,8	58,4	49,0	306,0	
	tot	349	172,4	80,5	41,0	623,0	.000

died showed lower values of $PaCO_2$ and STPaO2 compared to the survivor subgroup ($p < 0.05$ - Table 3). Similar results were observed by outcome failure (need of IMV and/or deaths) with the exception of PaCO2 (Table 3). Duration of ARF (Table 4) was inversely associated with P/F and STP/F ($p = 0.000$ and $p = 0.000$), but not with paO2, STPaO2 and paCO2. Age and Respiratory Rate at the time of admission were positively related with duration of ARF ($p < 0.05$).

4. Discussion

The main finding of the current investigation is that accuracy of STP/F to predict death was higher than conventional P/F (0.710; 95% CI 0.638-0.782 vs. 0.688; 95% CI 0.650-0.846, $p = 0.012$), Fig. 1 and Table 2. Interestingly, STP/F is accurate and superior to P/F in predicting in-hospital mortality, but not outcome failure (defined as deaths or need of IMV), as if the need of IMV is not affected by STP/F or P/F

Table 4
Association between age, respiratory rate, PaO_2, $PaCO_2$, standard PaO_2 ($_{ST}PaO_2$), P/F, $_{ST}$P/F and ARF duration in days (Spearman's correlation)

		Duration of ARF
Age Respiratory	Correlation coefficient sig. n	0.136 0.061 191
Rate PaO_2 (mmHg)	Correlation coefficient sig n	0.286 0.000 172
	Correlation coefficient	-.022
	sig.	.764
	n	191
$PaCO_2$ (mmHg)	Correlation coefficient	-.066
	sig.	.362
	n	191
$_{ST}PaO_2$ (mmHg)	Correlation coefficient	-.040
	sig.	.583
	n	191
P/F	Correlation coefficient	-.385
	sig.	.000
	n	191
$_{ST}$P/F	Correlation coefficient	-.396
	sig.	.000
	n	191

values. STP/F can predict mortality in all patients of our study population.

Mean $PaCO_2$ of the study population was inferior to 40 mmHg, and mean respiratory rate was 22 ± 5 breaths per minute (Table 1B). This confirms the hypocapnic compensation of hypoxemia in Covid-19, mainly obtained by increase of tidal volume. Moreover, mean value of $PaCO_2$ of the subgroup died for ARF due to Covid-19 was inferior to the one of the survivors subgroup (Table 3), $p = 0.037$, as if low $PaCO_2$ might suggest risk of further ARF worsening, even if AUROC curve of paCO2 is not enough accurate to predict outcome failure.

Prevalence of never smokers in our study population was 85%; this reflects data emerged from literature about Covid-19 [[33,34],]. Smoking can modulate immunity reducing its effectiveness. Thus could result in a less reactive inflammatory response during Covid-19, preventing the cytokine storm responsible of the progression of the disease in ARF due to Covid-19 and explain the lower prevalence of current or former smokers in Covid-19 reported studies. [[33,34],]. We can speculate, in addition, that usually a fraction of current smokers or former smokers may be affected by chronic obstructive pulmonary disease (COPD). Having a respiratory chronic disease, COPD patient might have a more preventive social behavior strategy and respect strictly rules such as wearing masks and to respect physical distances. Moreover COPD patients could probably early recognize Covid-19 related respiratory symptoms and signs, leading them to have an early access to medical consultation and/or ER.

According to our findings, $_{ST}$P/F better describes ARF due to Covid-19 in its hypocapnic nature. Using $_{ST}PaO_2$ instead of PaO_2 (*standard P/F* versus P/F) better describes this phenomenon and could better relate to prognosis, in particular in-hospital mortality.

Defining all mechanisms responsible for ARF during SARS-CoV-2 pneumonia with one parameter is not simple, since pathophysiology of lung injury due to Covid-19 is multifactorial and the impact of every single compensatory mechanism varies between subjects and through the course of the disease. [35–37] In Covid-19, inflammation and oedema in alveoli are the main responsible of hypoxemia in the early phases of disease, so that P/F reasonably relate to severity of diffusing impairment here. With the progression of disease (consolidation phase), V/Q mismatch and shunt mechanism become prevalent, so that hypoxemic ARF becomes less responder to implementation of FiO_2 due to incapacity to improve PaO_2 in non-ventilated alveoli. In lung regions where shunt is prevalent, P/F could be not so representative of severity of the disease. [[38,39],] Reducing partial pressure of carbon dioxide (PaCO2) represents a protective mechanism: low values of PaO2 increase minute ventilation in response to chemoreceptor stimulation. Hyperventilation is a feedback mechanism to correct hypoxia at the

expense of $PaCO_2$ reduction and left shift of the HbO_2 dissociation curve. In this way, tachypnea and hyperpnoea, generated by a rise of minute ventilation through increasing respiratory rate and tidal volume, compensate both hypoxemia and prevent blood acidosis [40].

Notably, the presence of microvascular thrombosis in subjects with Covid-19 ARF, highlighted by the increase of D-dimer and alveolar dead space; may contribute to the severity and progression of hypoxia observed in Covid-19 [41]. Several data showed that outcome is related to dead space through measurement of ventilatory ratio in typical ARDS and in Covid-19 [3]. These measurements in subjects in spontaneous breathing are not obtainable, so that $_{ST}$PF could represent a surrogate of the ventilatory ratio.

There is an urgent need to identify patients at higher risk of intubation and death, since de novo ARF plays a central role in Covid-19, being responsible for morbidity and mortality [4,42,43]. In addition, defining the best setting where to allocate patients affected by SARS-CoV-2 pneumonia could play a central role in this emergency era for health care resources worldwide. Finding a parameter which could help clinicians to detect early which patient will need more resources, in particular the need of respiratory support and so Pulmonology Unit hospitalization, may optimize Covid-19 outcomes and improve costs-benefits ratio.

This is the first study assessing the role of standard paO2 in relationship to prognosis in acute respiratory failure: this pilot study identifies $_{ST}$PF as a better predictor of mortality than PF in Covid-19 ARF. We propose the use of STP/F because, from a pathophysiological point of view, it better describes the compensatory mechanism present in hypoxemic ARF typical of Covid-19 and our study showed that is more accurate in discriminating prognosis. STPaO2 is a parameter obtainable simply in standard practice using a formula validated since years [17].

Limits of this study are its observational nature and the short enrollment phase due to its pilot nature. Moreover it does not take into account patients with ARF due to Covid-19 admitted directly from ER to ICU; this could explain the relatively low outcome failure and mortality ratio seen in our study (respectively 32.4% and 16.6%). However, outcome failure, as defined by need for invasive mechanical ventilation and/or death, was online with previous literature describing patients outside ICU setting [[29–32],]. Outcome failure results could be affected to the decision to start IMV according to PF value of the patient (for example a rapid decline of P/F), so that this could represent a bias of this study, while mortality is independent. To avoid selection bias we enrolled all consecutive patients with ARF due to Covid-19, all admitted at our Units managed by pulmonologists due to a worsening of their clinical condition. Maybe differences emerged from our pilot study are not enough to change the clinical practice, but it may be helpful in considering the pathophysiological features leading to the calculation of this index (P/F).

Clinical use of $_{ST}$P/F as a predictor of in-hospital mortality could be used to allocate patients in the right setting. Enlarging sample size in an extension future study, and, if properly uniformed, considering uniformed ABGs at the time of ER admission, could better define the impact of using STP/F in hypoxemic Covid-19 ARF and its management. In addition, the prognostic significance of STP/F could be compared in future with other Covid-19 prognostic indices such as C-reactive protein, blood leukocyte count and D-dimer, simpler to obtain in clinical practice.

More prospective studies are needed to validate the value of STP/F as a marker of outcome in Covid-19 and to define its severity cut-offs. In future, STP/F could also be studied in other ARF settings such as acute exacerbation of chronic obstructive pulmonary disease, interstitial lung diseases and pneumonia due to other infectious agents than Covid-19.

Author's contribution

IP study design, study coordination, data collection and analysis, draft manuscript. LDA study design, data integrity and accuracy. PC, FD, RD, RF, AMGP, LP, CT, MLV data collection. VMR manuscript revision. SN study design, supervision, manuscript revision. PP study design, data analysis, manuscript revision, final approval of the version submitted for publication. IP conceptualization, data curation, formal analysis.

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Declaration of Competing Interest

All Authors declare no conflict of interests.

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