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Correlation of SpO$_2$/FiO$_2$ and PaO$_2$/FiO$_2$ in patients with symptomatic COVID-19: An observational, retrospective study

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Abstract

Some patients affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) experience acute hypoxemic respiratory failure progressing toward atypical acute respiratory distress syndrome (ARDS). The aim of the study is to evaluate whether a correlation between ratio of peripheral saturation of oxygen (SpO$_2$) and fraction of inspired oxygen (S/F) and ratio of arterial partial pressure of oxygen and fraction of inspired oxygen (P/F) exists in COVID-19-related ARDS as already known in classical ARDS. In this multicenter, retrospective, observational study, consecutive, adult (≥ 18 years) patients with symptomatic coronavirus disease 2019 (COVID-19) admitted to different COVID-19 divisions in Italy between March and December 2020 were included. Patients with SpO$_2 > 97\%$ or missing information were excluded. We included 1,028 patients (median age 72 years, prevalence of males [62.2%]). A positive correlation was found between P/F and S/F ($r = 0.938$, $p < 0.0001$). A receiver operating characteristic (ROC) curve analysis showed that S/F accurately recognizes the presence of ARDS (P/F ≤ 300 mmHg) in COVID-19 patients, with a cut-off of $\leq 433\%$ showing good sensitivity and specificity. S/F was also tested against P/F values ≤ 200 and ≤ 100 mmHg (suggestive for moderate and severe ARDS, respectively), the latter showing great accuracy for S/F $\leq 178\%$. S/F was accurate in predicting ARDS for SpO$_2 \geq 92\%$. In conclusion, our findings support the routine use of S/F as a reliable surrogate of P/F in patients with COVID-19-related ARDS.

Keywords COVID-19 · SARS-CoV-2 · ARDS · Respiratory failure · Diagnosis · Cytokine storm

Abbreviations

ARDS	Acute respiratory distress syndrome
AUC	Area under the curve
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure
ICU	Intensive care unit
IQR	Interquartile range
LR	Likelihood ratio
NIV	Noninvasive ventilation
P/F	Ratio between arterial partial pressure of oxygen and fraction of inspired oxygen
PaO$_2$	Arterial partial pressure of oxygen
ROC	Receiver operating characteristic

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S/F	Ratio between peripheral oxygen saturation and fraction of inspired oxygen
SaO$_2$	Arterial blood saturation
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SpO$_2$	Peripheral oxygen saturation

Introduction

In a subset of patients, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for acute hypoxemic respiratory failure, that may progress toward acute respiratory distress syndrome (ARDS) [1, 2]. While most patients meet Berlin criteria for ARDS [3], a portion of them presents the so-called "happy" [4] or "silent hypoxemia" [5, 6] as they are not dyspnoic despite an abnormally low peripheral oxygen saturation. These patients display an atypical form of ARDS, characterized by a dissociation between a relatively preserved lung mechanics and severe hypoxemia, also referred to as early phenotype or L phenotype (lower elastance [high compliance], lower ventilation/perfusion ratio, lower lung weight, and lower recruitment) [7, 8]. Some of these patients may get worse and develop a phenotype closer to typical ARDS referred to as late phenotype or H phenotype, where high lung elastance [low compliance], high right-to-left shunt, high lung weight, and high recruitment are observed [7, 8].

Peripheral oxygen saturation (SpO$_2$) is routinely used to estimate arterial oxygen saturation (SaO$_2$) [9], but may be influenced by a number of factors, including peripheral perfusion [10]. A more precise estimation of arterial partial pressure of oxygen (PaO$_2$) is obtained through arterial blood gas analysis that, however, requires a blood draw and is not feasible for long-term monitoring outside the intensive care unit (ICU). Changes in PaO$_2$ present a good correlation with SpO$_2$ variation in the range of 80–100% in healthy individuals [10–12]. The ratio between SpO$_2$ and fraction of inspired oxygen (FiO$_2$) (S/F) was found to well correlate with PaO$_2$/FiO$_2$ (P/F) in defining ARDS in adults [13, 14] and children [15] and to independently indicate short-term development of ARDS [16] and as a measure of hypoxia in patients under general anesthesia [17]. A recent paper emphasized the importance of S/F in predicting progression to severe illness or death in COVID-19 patients [18].

In an attempt to help clinicians involved in the care of patients with coronavirus disease 2019 (COVID-19), we sought to evaluate whether the correlation between S/F and P/F established for typical ARDS is confirmed also in COVID-19 symptomatic patients, irrespective of ARDS.

Materials and methods

Study design

This is a multicenter, retrospective, observational study including consecutive adult patients (≥ 18 years) with symptomatic COVID-19 confirmed by real-time polymerase chain reaction and admitted to COVID-19 divisions between March 1st and December 31st 2020. Participating centers were located in different Italian regions severely hit by both first and second wave of COVID-19: Lombardy (Varese, Legnano, and Magenta), Tuscany (Florence, Empoli, and Cecina), and Campania (Ariano Irpino). Patients with SpO$_2 > 97\%$ were excluded from the analysis as the oxyhemoglobin dissociation curve plateaus above this level [19] (Fig. 1). As well, patients for whom data were missing were not considered for the analysis (Fig. 1). The exclusion of patients with SpO$_2 > 97\%$ is based on findings by Van de Louw et al., who found that patients with an SpO$_2 > 94\%$ had at least an SaO$_2 > 90\%$ [20], which is considered as a clinical target in ICU patients receiving invasive mechanical ventilation [19]. It is then reasonable to assume that SpO$_2 > 97\%$ depicts a sufficient oxygenation (in terms of SaO$_2$). As ours was a non-ICU setting and invasive assessments were not available, we relied on pulse oximetry and patient clinical status to establish respiratory failure. For this reason, we feel that findings by Van de Louw et al. are reassuring about our decision to not consider patients with an SpO$_2 > 97\%$.

The research has been conducted in accordance with the Declaration of Helsinki (revised version 2000) and after approval of the local Institutional Review Board (Valutazione dell'efficacia di parametri clinici, laboratoristici e radiologici nella predizione dell'efficacia delle terapie in uso per il trattamento della sindrome da distress respiratorio acuta secondaria ad infezione da SARS-CoV-2 [REgistro COvid-19 asST settE LAghi, RECOSTELA; number 150/2021).

Data assessment

Arterial blood gas measurement was performed using RAPIDPoint® 500e Blood Gas System (Siemens Healthcare Srl, Milan, Italy) in Varese, Florence, and Ariano Irpino; GEM® 3500 PREMIER (Werfen, Instrumentation Laboratory S.p.A., Milan, Italy) in Cecina; ABL800 FLEX (A. De Mori S.p.A., Milan, Italy) in Magenta and Legnano; and ABL90 FLEX (Radiometer Medical ApS, Brønshøj, Copenhagen, Denmark) in Empoli. SpO$_2$ was measured using the Pulse CO-Oximeter® Radical-7® (Masimo, Irvine, California, USA) in Varese, Florence,
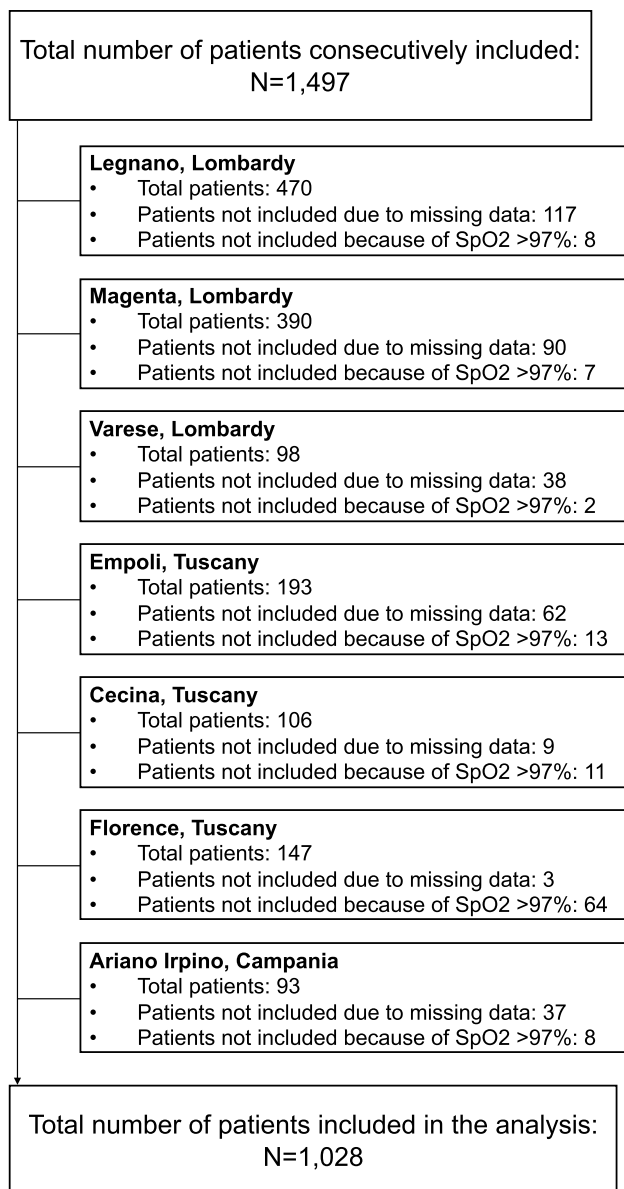
Total number of patients consecutively included:
N=1,497

Legnano, Lombardy
- Total patients: 470
- Patients not included due to missing data: 117
- Patients not included because of SpO2 >97%: 8

Magenta, Lombardy
- Total patients: 390
- Patients not included due to missing data: 90
- Patients not included because of SpO2 >97%: 7

Varese, Lombardy
- Total patients: 98
- Patients not included due to missing data: 38
- Patients not included because of SpO2 >97%: 2

Empoli, Tuscany
- Total patients: 193
- Patients not included due to missing data: 62
- Patients not included because of SpO2 >97%: 13

Cecina, Tuscany
- Total patients: 106
- Patients not included due to missing data: 9
- Patients not included because of SpO2 >97%: 11

Florence, Tuscany
- Total patients: 147
- Patients not included due to missing data: 3
- Patients not included because of SpO2 >97%: 64

Ariano Irpino, Campania
- Total patients: 93
- Patients not included due to missing data: 37
- Patients not included because of SpO2 >97%: 8

Total number of patients included in the analysis:
N=1,028

Fig. 1 CONSORT diagram. The study flow including patients initially included and those excluded from the analysis is shown

and Ariano Irpino; Nellcor™ Portable SpO$_2$ Patient Monitoring System, PM10N (Medtronic, Minneapolis, MN, USA) in Cecina and Empoli; and OXY-100 Pulsiossimeter (GIMA S.p.A., Gessate, Italy) in Magenta and Legnano. All measurements of SpO$_2$, PaO$_2$ and FiO$_2$ were documented in patient medical records. Previously trained personnel, including nurses and doctors, assessed SpO$_2$ values at the time of arterial blood gas sampling. When not feasible, the PaO$_2$ assessment closest to the SpO$_2$ value was recorded. To ensure accuracy of SpO$_2$ assessments, the following considerations were followed: (1) no position changes 5 min prior to the measurement; (2) checking for the accurate position and cleanliness of the sensor;

and (3) evaluation of satisfactory waveforms on the monitor. After 1 min of steady SpO$_2$ measurement, the value was recorded along with the oxygen setting, i.e., room air or supplemental inspired oxygen (nasal cannula, Venturi mask, nonrebreather mask, continuous positive airway pressure [CPAP] or noninvasive ventilation [NIV]). FiO$_2$ was estimated using a conversion table when oxygen was delivered via low-flow nasal cannula [21] and following manufacturer's specifications when delivered via Venturi mask (Supplementary Table 1). For patients on non-rebreather mask, FiO$_2$ was estimated using a 3%-formula (21% + oxygen flow rate in L/min × 3) [22, 23], that was found to have the best agreement and highest accuracy when compared with measured FiO$_2$ [24]. Patients breathing on CPAP or noninvasive ventilation NIV had FiO$_2$ recorded based on settings provided by the attending physician.

P/F < 300 mmHg was considered as a cut-off suggestive for ARDS, although not all patients were accurately screened for all Berlin criteria (bilateral opacities on chest imaging and respiratory failure not fully explained by cardiac failure or fluid overload) [3].

Study endpoints

The primary endpoint of the study was to evaluate whether a correlation between S/F and P/F exists in symptomatic COVID-19 patients admitted to Internal Medicine divisions, irrespective of ARDS occurrence.

The secondary endpoint was the evaluation of S/F as a reliable surrogate of P/F in defining ARDS based on P/F values defined by Berlin criteria [3].

Statistical analysis

Continuous variables that followed a non-normal distribution are presented as median and interquartile range [IQR]. Categorical variables are expressed as numbers and percentages (%). Ranked Spearman's correlation coefficients were used to establish correlations between P/F and S/F. Plot calibration of the models assessing the goodness-of-fit of S/F to predict mild, moderate and severe ARDS was performed using the Hosmer–Lemeshow test. Receiver operating characteristic (ROC) curve analyses were performed to evaluate the accuracy of S/F to predict ARDS. The area under the curve (AUC) was given with 95% confidence interval (CI) and a cut-off point of S/F was also provided maximizing sensitivity and specificity in accordance with the Youden index. Positive and negative likelihood ratios (LRs) as well as positive and negative predictive values were also computed. Multiple ROC curve analyses were used to check for accuracy of S/F according to SpO$_2$ strata and P/F cutoffs. A ROC curve analysis was finally run to test the prognostic

Table 1 Baseline characteristics

Variables	
Age, years	72 [61–82]
Sex—female/male (%)	389/639 (37.8/62.2)
SpO$_2$, %	93.0 [90.0–95.0]
PaO$_2$/FiO$_2$, mmHg	196.43 [115.57–285.71]
SpO$_2$/FiO$_2$	277.14 [178.0–433.33]

PaO$_2$/FiO$_2$ ratio between arterial partial pressure of oxygen and fraction of inspired oxygen, *SpO$_2$* peripheral oxygen saturation, *SpO$_2$/FiO$_2$* ratio between peripheral oxygen saturation and fraction of inspired oxygen
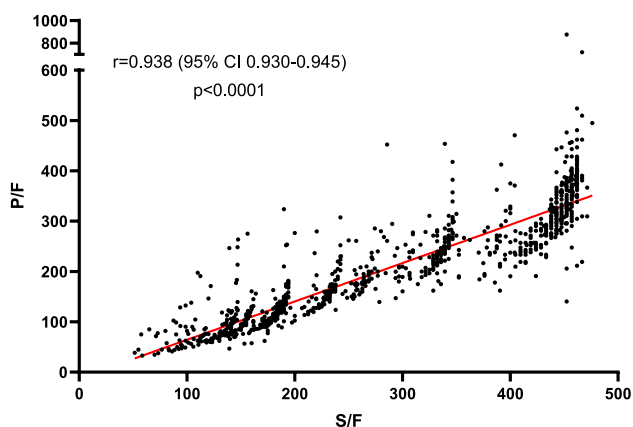
Fig. 2 Correlation between P/F and S/F. Correlation between S/F and P/F is provided (values shown with 95% confidence interval)

accuracy of S/F in identifying ARDS according to the cut-off described by Rice et al. (i.e., < 315 mmHg) [13]. Plot calibration of the three ROC curves was performed using the Hosmer–Lemeshow test. A two-sided $p < 0.05$ value was considered as statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Mac version 26.0 (IBM Co., Armonk, NY, USA), MedCalc 12.5 (MedCalc Software, Ostend, Belgium), and GraphPad Prism version 8.0.2 for Windows (GraphPad Software, San Diego, California USA, http://www.graphpad.com).

Results

Out the 1,497 patients consecutively considered, 1,028 were included in the present analysis (Fig. 1). Median age was 72 [61–82] years, with a prevalence of males ($n = 639$, 62.2%). At baseline, median P/F was 196.43 [115.57–285.71] mmHg, while median S/F was 277.14 [178.0–433.33] % (Table 1). A positive correlation was found between P/F and S/F in the overall cohort ($r = 0.938$, $p < 0.0001$; Fig. 2).

A ROC curve analysis showed that S/F accurately recognizes the presence of ARDS (as defined by P/F ≤ 300 mmHg

[3]) in COVID-19 patients (AUC 0.958, $p < 0.0001$; Fig. 3A and Supplementary Table 2). The cut-off of S/F ≤ 433% was found to have the best sensitivity and specificity (94.6 and 86.2%, respectively; positive LR 6.85, negative LR 0.14). S/F was also tested against lower P/F values, i.e., ≤ 200 and ≤ 100 mmHg, suggesting moderate and severe ARDS, respectively. S/F highlighted moderate ARDS (as defined by P/F ≤ 200 mmHg [3]) with lower accuracy (AUC 0.713, 95% CI 0.944–0.969, $p < 0.0001$; Fig. 3B and Supplementary Table 2). Accordingly, the S/F cut-off ≤ 336% presented poor sensitivity and specificity as well as poor positive and negative LRs (Fig. 3B and Supplementary Table 2). Finally, a S/F cut-off ≤ 178% showed great accuracy in recognizing patients with severe ARDS (as defined by P/F ≤ 100 mmHg [3]), with good specificity and sensitivity (98.4% and 90.8%, respectively) and good positive and negative LRs (Fig. 3C and Supplementary Table 2). Calibration plots are provided in Supplementary Fig. 1.

We then observed that S/F was accurate in predicting ARDS for SpO$_2$ ≥ 92% (AUC > 0.900, $p < 0.0001$), while it failed for lower SpO$_2$ values (Table 2).

Finally, we confirmed that the S/F cut-off of < 315 mmHg, as found by Rice et al. [13], was accurate in diagnosing ARDS in patients with COVID-19 (AUC 0.826, 95% CI 0.802–0.849, $p < 0.0001$).

Discussion

In this study, we reported that S/F was very accurate in suggesting the occurrence of ARDS (P/F ≤ 300 mmHg, as defined by Berlin criteria [3]) for SpO$_2$ values ≥ 92%. This held true also when considering lower P/F values. In addition, we confirmed that S/F presented an excellent correlation with P/F also in COVID-19 patients.

COVID-19-related ARDS has some peculiar features [6], as previously mentioned. In the initial phase, a large portion of patients have a relatively good compliance in spite of a low oxygenation [8]. A subgroup of individuals progresses to a more aggressive disease with typical features of ARDS and usually referred to as having an H phenotype [8]. S/F was demonstrated to have a good correlation with P/F to detect patients with typical ARDS, either among adults [13, 14] and children [15]. S/F was also found to independently predict short-term development of ARDS [16]. S/F was found to be lower in non-survivor patients with ARDS compared with survivors and to be independently associated with death in the ICU [14] as well as with need for admission to the ICU [25].

Based on the abovementioned pathophysiological premises, we evaluated whether S/F held its accuracy in detecting patients with ARDS driven by SARS-CoV-2. The hypothesis stems from the easiness of using a non-invasive parameter

Fig. 3 Receiver operator characteristic (ROC) curve analyses for S/F ▶ toward the diagnosis of ARDS. **A** The predictive role of S/F toward the occurrence of mild ARDS (P/F ≤ 300 mmHg) in hospitalized patients has been tested. **B** The predictive role of S/F toward the occurrence of moderate ARDS (P/F ≤ 200 mmHg) in hospitalized patients is provided. **C** The predictive role of S/F toward the occurrence of severe ARDS (P/F ≤ 100 mmHg) in hospitalized patients is shown

to assess the degree of respiratory failure in patients with SARS-CoV-2-related pneumonia. This was an unmet clinical need in our medical divisions (i.e. Internal Medicine divisions) that coped with a large number of patients not needing ICU admission, whose patient management is different and not comparable. Indeed, we found that S/F has a positive, strong correlation with P/F in COVID-19 patients. We noticed that S/F is reliable in diagnosis ARDS for SpO_2 values ≥ 92%, while it is not as accurate as for lower SpO_2 values. From a practical standpoint, this information appears of great importance for those clinicians working outside the ICU setting. The reliability of SpO_2 is known to be reduced for $SpO_2 < 90\%$ [9]. When SpO_2 falls below 90–92%, it is mandatory to have a blood gas analysis to carefully check for gas exchanges and modify therapeutic strategies accordingly. However, a simple tool like S/F may be a good surrogate of P/F to follow patients with respiratory failure due to SARS-CoV-2 pneumonia. This appears extremely important as P/F still represents an independent predictor of poor outcomes in COVID-19 patients [26, 27]. Differently from P/F, S/F does not need any blood draw and can be immediately available using a pulse oximeter both for outpatients and inpatients. The latter may represent an added value as S/F may be used as an accurate parameter to monitor patients with COVID-19 treated outside the hospital setting, who represented the majority of individuals affected by SARS-CoV-2 infection. As a further proof of this, we showed that S/F maintained a good accuracy in detecting patients with findings suggestive for different degrees of ARDS. By looking in more detail to our results, it looks like S/F may be used as a reliable surrogate for mild or severe ARDS (as per P/F values between 300 and 200 or ≤ 100 mmHg). On the contrary, for moderate ARDS, doubts still exist and blood gas analysis along with clinical evaluation appear the best tools for an escalating, therapeutic approach. This is in line with controversies recently arisen in the scientific community about this topic that certainly needs additional research in future [27, 28]. However, a recent study in COVID-19 patients strongly supports the reliability of S/F in predicting poor outcomes [18].

Our study has, however, some limitations that should be acknowledged. First, the retrospective design of the study conducted in a limited number of centers in Italy may limit the generalization of the results due to selection bias. However, patients were consecutively included in the study and recruited in regions hardly hit by SARS-CoV-2 pandemic,
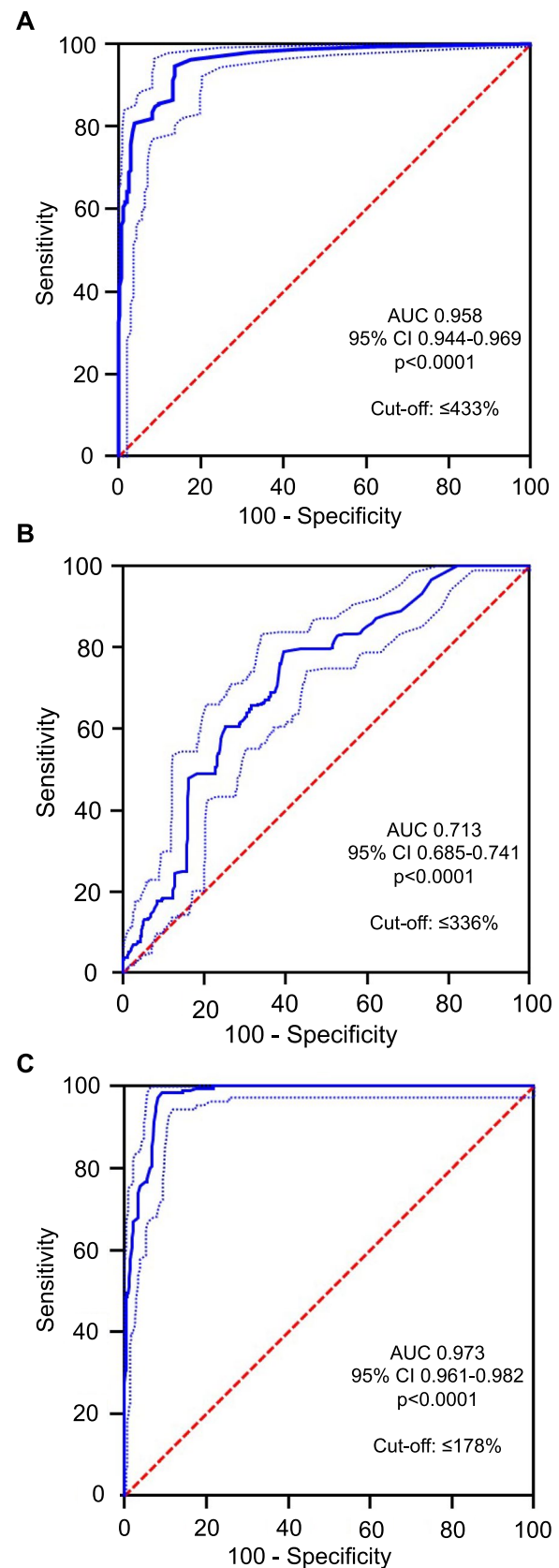
Table 2 ROC curve analyses for ARDS detection (P/F ≤ 300 mmHg) according to SpO_2 strata

SpO_2 (%)	# of patients per group	AUC	95% CI	p
97	126	0.958	0.924–0.993	< 0.0001
96	102	0.953	0.909–0.957	< 0.0001
95	133	0.939	0.892–0.986	< 0.0001
94	104	0.958	0.919–0.998	< 0.0001
93	137	0.951	0.918–0.985	< 0.0001
92	87	0.902	0.838–0.965	< 0.0001
91	45	0.534	0.382–0.686	0.908
90	46	0.642	0.276–1.000	0.501
< 90	248	0.764	0.679–0.849	0.198

AUC area under the curve, *CI* confidence interval, SpO_2 peripheral oxygen saturation

thus giving a real picture of the disease severity. In addition, the sample is sufficiently large to ensure consistent results. Second, the large majority of patients were first admitted to the emergency department and then to a medical ward, so limited data are herein available about critically ill patients, who were mostly admitted to the ICU. Third, patients with $SpO_2 > 97\%$ were excluded from analyses as for these values the slope of the relationship between SpO_2 and PaO_2 greatly plateaus. However, we do believe that this limitation may be acceptable as routine practice is based on FiO_2 titration to reach and maintain SpO_2 between 95 and 97% [29–31]. Fourth, we were not able to measure FiO_2, except for Venturi mask (provided by manufacturer), NIV and CPAP. For other oxygen supports, FiO_2 was estimated using the 3%-formula (21% + oxygen flow rate in L/min × 3), that was already tested in large trials [22, 23] and recognized to obtain the best agreement and highest accuracy compared with measured FiO_2 [24]. Finally, although most of SpO_2 and PaO_2 measurements were assessed at the same time, separation by a few hours was tolerated and might have contributed to minimal differences between measurements. However, correlation between S/F and P/F remained very high.

In conclusion, our results support the routine use of S/F as a reliable surrogate of P/F in patients with COVID-19-related ARDS. This noninvasive and continuously available tool is helpful for an earlier diagnosis of ARDS and monitoring of respiratory function over time. S/F may also contribute to evaluating whether a step-up or step-down therapy is needed. From a patient's perspective, routine use of S/F means less painful blood draws, that is important especially when hospital stay is prolonged. Future studies are warranted to evaluate whether this relationship between S/F and P/F holds true in the ICU setting.

Declarations

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