Respiration

Clinical Investigations

Respiration
DOI: 10.1159/000522275

Received: September 6, 2021
Accepted: January 11, 2022
Published online: March 15, 2022

# Early Variation of Respiratory Indexes to Predict Death or ICU Admission in Severe Acute Respiratory Syndrome Coronavirus-2-Related Respiratory Failure

Giorgio Maraziti  Cecilia Becattini

Internal and Cardiovascular Medicine – Stroke Unit, S. Maria della Misericordia Hospital, University of Perugia, Perugia, Italy

**Keywords**
COVID-19 · Respiratory distress syndrome · Respiratory insufficiency · Respiratory rate

**Abstract**
***Background:*** In severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-related respiratory failure, the prognostic value of clinically based or blood-gas-based respiratory indexes is unclear. ***Objectives:*** We aimed to assess the prognostic value of Respiratory Index (RI, oxygen saturation [SpO2]/respiratory rate [RR]), RR-oxygenation index (ROX, SpO2/fraction of inspired oxygen [FiO2]/RR), partial pressure of oxygen (PaO2)/FiO2 ratio (P/F), or standard PaO2/FiO2 ratio ($_{ST}$P/F) at admission and of their variation during hospitalization in SARS-CoV-2-related respiratory failure. ***Methods:*** In 100 consecutive patients hospitalized due to SARS-CoV-2-related respiratory failure, we assessed the association of RI, ROX, P/F and $_{ST}$P/F, and death; secondary outcome was the composite of 7-day death or intensive care unit (ICU) admission. ***Results:*** ROX <3.85 at admission (hazard ratio [HR] 2.95, 95% confidence interval [CI] 1.29–6.77) and decreasing RI or P/F during hospitalization (RI: HR 1.05, 95% CI: 1.00–1.09; P/F: HR 1.01, 95% CI: 1.00–1.02) were predictors of in-hospital death. RI ≤3.8, ROX <3.85, and P/F <100 at admission were predictors for death or ICU admission (RI: HR 3.77, 95% CI: 1.30–10.98; ROX: HR 4.56, 95% CI: 1.90–10.96; P/F: HR 7.37, 95% CI: 1.59–34.2). The decrease of RI (HR 1.14, 95% CI: 1.03–1.25), ROX (HR 1.45, 95% CI: 1.11–1.88), P/F (HR 1.08, 95% CI: 1.01–1.15), or $_{ST}$P/F (HR 1.05, 95% CI: 1.01–1.08) during hospitalization was associated with 7-day death or ICU admission. ***Conclusions:*** In patients with SARS-CoV-2-related respiratory failure, easy-to-calculate clinically based respiratory indexes at admission and their variation during hospital stay can be used to assess and monitor the risk for death or ICU admission.



## Introduction

Pneumonia resulting from infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has a high mortality, predominantly caused by deteriorating respiratory failure [1]. Early detection of patients with SARS-CoV-2-related pneumonia who are likely to deteriorate is of great importance and may aid in delivering personalized patient care and optimizing the use of limited resources.

The dominant respiratory feature of SARS-CoV-2-related pneumonia is arterial hypoxemia due to a combination of ventilation-perfusion mismatch and intrapulmonary shunt [2]. In this setting, the optimal respiratory measure to predict clinical outcome is uncertain [3, 4].

The ratio of arterial (partial pressure of oxygen [PaO2]) to inspired (FiO2) partial pressure of oxygen (P/F ratio)

Karger@karger.com
www.karger.com/res



Correspondence to:
Giorgio Maraziti, marazitigiorgio@gmail.com

Karger

is used to diagnose and assess the severity of patients with acute respiratory distress syndrome (ARDS) and guide clinical decisions [5, 6]. However, this index has no role in any biological process; rather, PaO2 and arterial oxygen saturation (SpO2) are directly related to oxygen delivery to the brain and the myocardium [2, 7]. Moreover, P/F does not reflect respiratory muscle effort [8, 9]. A correction of PaO2 by arterial carbon dioxide tension (PaCO2) – namely, standardized $PaO_2$ – was suggested to overcome this latter limit [10]. The role of standard P/F ($_{ST}$P/F) ratio was recently found to be accurate and superior to P/F in predicting in-hospital mortality in coronavirus disease 2019 (COVID-19) [11].

Two clinically based measures, both including respiratory rate (RR), may have a role in predicting clinical course of COVID-19 patients. RR-oxygenation index (ROX index) can predict the risk of intubation in patients with pneumonia/ARDS admitted to the intensive care unit (ICU) and treated with a high-flow nasal cannula (HFNC) [12–14]. Its prognostic role seems maintained in COVID-19 pneumonia [15, 16]. Respiratory index (RI, SpO2 to RR ratio) was validated in prognostic stratification of patients with acute pulmonary embolism, but its role in severity assessment of patients with ARDS is unknown [17]. The purpose of this study was to assess whether clinically based respiratory indexes including RR (RI and ROX) at admission and their variation during hospital stay can better predict death or ICU admission in comparison with blood-gas-based (P/F and $_{ST}$P/F) indexes in hospitalized patients with SARS-CoV-2-related pneumonia.

## Materials and Methods

*Study Design and Population*

Consecutive adult patients admitted to the acute care COVID Unit at the Internal and Cardiovascular Medicine department, Perugia, Italy, from March to May 2021 due to SARS-CoV-2 pneumonia and respiratory failure were included in the study. Exclusion criteria were as follows: admission from other departments than Emergency Room (ER), pregnancy, or absence of SpO2, RR, PaO2, PaCO2, or FiO2 assessment.

The primary study outcome was in-hospital death. The secondary study outcome was the composite of 7-day death or ICU admission.

The following general data were collected: age, gender, comorbidities (history of chronic obstructive pulmonary disease, cancer, systemic arterial hypertension, obesity), clinical parameters at admission and during hospital stay before admission to ICU (heart rate, SpO2, RR, PaO2, PaCO2, FiO2), use of supplemental oxygen therapy (conventional or HFNC), or noninvasive respiratory strategies (Noninvasive Mechanical Ventilation or Continuous Positive Airway Pressure).

SpO2 was assessed by standard pulse oximetry. RR was derived either from surface leads in case of patients with continuous monitoring or by health care personnel's direct assessment both in the presence or absence of respiratory support. FiO2 was derived either by FiO2 sensor (in ventilator or HFNC with this feature) or estimated through validated formulas considering administrated oxygen liters or manufacturer's instructions in conventional oxygen support devices (i.e., Venturi masks).

The following respiratory indexes were calculated: RI (SpO2/RR ratio), P/F ratio, $_{ST}$P/F ratio, ROX index (SpO2/FiO2/RR ratio). $_{ST}$PaO2 was calculated according to the formula: 1.66 × PaCO2 + PaO2 – 66.4 mm Hg [10, 11]. Continuous measures were then categorized according to validated cutoff values: RI ≤3.8, ROX <3.85, P/F ratio at four levels >300, 300–200, 200–100, <100, and $_{ST}$P/F ratio ≤170 [5, 11, 13, 17].

*Statistical Analysis*

Patients' characteristics and respiratory measures were described by descriptive statistics. Differences in continuous variables were tested by the independent *t* test if normally distributed or by the Mann-Whitney U test otherwise and presented as mean ± standard deviation or median and interquartile range, respectively. Differences in categorical characteristics were compared by Fisher exact test and/or the $\chi^2$ test, and values were presented as percentages.

We assessed the discriminatory ability for respiratory indexes at admission by calculating the area under the curve (AUC), with AUC = 0.5 for prediction no better than chance and AUC = 1.0 for perfect discriminatory ability. We evaluated calibration with the modified Hosmer-Lemeshow $\chi^2$ statistic. Respiratory indexes were used as continuous and dichotomized versions to assess their association with study outcome events by the Cox proportional-hazards model, including significant stratification factors as covariates.

To assess the effect of variation of respiratory indexes in the risk for study outcome events, we built a joint model [18, 19]. In particular, we modeled respiratory indexes and time to clinical outcome to understand the relationship between indexes and the risk for outcome events.

The two components of the joint model were as follows:

- A linear mixed model for the time-course of respiratory indexes;
- a proportional-hazards model for the time to clinical outcome with time-varying random effects.

The final set of covariates included in the multivariate analysis was selected among those with a *p* value ≤0.15 at univariate analyses. Respiratory indexes were treated as a time-varying, patient-specific random effect. All analyses were performed in R version 3.6.2 (R Foundation for Statistical Computing).

## Results

From March to May 2021, 107 patients with SARS-CoV-2-related respiratory failure were admitted to the acute care COVID Unit at the University Hospital in Perugia, Italy. After exclusion of 7 patients due to admission from departments other than ER (6 patients) and absence of pneumonia (1 patient), 100 patients were included in

**Table 1.** Characteristics of study patients

| Clinical feature | Total (*n* = 100) | Alive (*n* = 63) | Dead (*n* = 37) | *p* value |
|---|---|---|---|---|
| Age, in years | | | | |
| Range | 28–94 | 28–91 | 53–94 | **<0.001** |
| Mean ± SD | 65±15 | 59±13 | 76±9 | |
| Male sex, *n*/*N* (%) | 65/100 (65) | 40/63 (63) | 25/37 (68) | 0.680 |
| Cancer, *n*/*N* (%) | 4/100 (4) | 1/63 (2) | 3/37 (8) | 0.108 |
| SAH, *n*/*N* (%) | 58/100 (58) | 33/63 (52) | 25/37 (68) | 0.137 |
| CHF, *n*/*N* (%) | 4/100 (4) | 1/63 (2) | 3/37 (8) | 0.108 |
| COPD, *n*/*N* (%) | 8/100 (8) | 4/63 (6) | 4/37 (11) | 0.427 |
| Obesity, *n*/*N* (%) | 19/100 (19) | 18/63 (29) | 1/37 (3) | **0.001** |
| DNR, *n*/*N* (%) | 25/100 (25) | 5/63 (8) | 20/37 (54) | **<0.001** |
| Hospital stay, in days | | | | |
| Range | 1–44 | 2–25 | 1–44 | **<0.001** |
| Mean ± SD | 12±8 | 10±5 | 16±10 | |

SD, standard deviation; SAH, systemic arterial hypertension; CHF, congestive heart failure; COPD, chronic obstructive lung disease; DNR, do not reanimate. *p* value <0.05 for statistical significance.

the study. Table 1 shows the main patients' features according to clinical outcome during hospitalization. The mean age was 65 ± 15 years; the most prevalent comorbidity was systemic arterial hypertension (58%). Fifty-two patients required Noninvasive Mechanical Ventilation within 24 h from admission and 34 during the hospitalization.

Mean values of respiratory indexes at admission and during hospital stay are reported in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000522275). Thirty-seven patients (37%) died during hospital stay; 25 patients (25%) were admitted to ICU, 18 of which died during ICU stay. Respiratory indexes at admission and during the hospital stay significantly differed between patients experiencing and not experiencing death or ICU admission (online suppl. Table 1).

*Respiratory Indexes and In-Hospital Death*

Patients' characteristics associated with in-hospital death are reported in online supplementary Table 2. ROX <3.85 at admission was a predictor for in-hospital death, while RI <3.8, P/F <100, and $_{ST}$P/F <170 at admission were not (Table 2). RI and ROX at admission showed adequate calibration and good discriminatory power for in-hospital death (Fig. 1 and online suppl. Table 3).

Univariate analysis for determinants of mean respiratory indexes over time is reported in Table 3. Variation of RI and P/F during the hospital stay was independently associated with in-hospital death by the survival joint model, while variation of ROX and $_{ST}$P/F was not (Table 4).

**Table 2.** Respiratory indexes at admission and risk for in-hospital death according to Cox proportional-hazards model (multivariate analysis)

| Variable | HR | 95% CI | *p* value |
|---|---|---|---|
| RI <3.8 | 0.97 | 0.44–2.16 | 0.942 |
| Age | 1.08 | 1.04–1.12 | **<0.001** |
| P/F 200–300 | 1.35 | 0.74–4.20 | 0.603 |
| P/F 100–200 | 0.91 | 0.27–3.07 | 0.875 |
| P/F <100 | 1.77 | 0.54–5.78 | 0.343 |
| Age | 1.08 | 1.04–1.12 | **<0.001** |
| $_{ST}$P/F <170 | 0.837 | 0.41–1.72 | 0.629 |
| Age | 1.082 | 1.04–1.12 | **<0.001** |
| ROX <3.85 | 2.95 | 1.29–6.77 | **0.0106** |
| Age | 1.089 | 1.05–1.13 | **<0.001** |

HR, hazard ratio; CI, confidence interval; SE, standard error; RI, respiratory index; P/F, PaO2/FiO2 ratio; $_{ST}$P/F, standard P/F ratio; ROX, RR-oxygenation index.

In particular, every 0.1-unit decrease in RI was associated with a 5% increase in the risk of in-hospital death and every 1-unit decrease in P/F with a 1% increase. Only increasing age and congestive heart failure were found to be associated with the risk of in-hospital death.

*Respiratory Indexes and Death or ICU Admission at 7 Days*

None of the patients' characteristics was independently associated with death or ICU admission at 7 days (on-

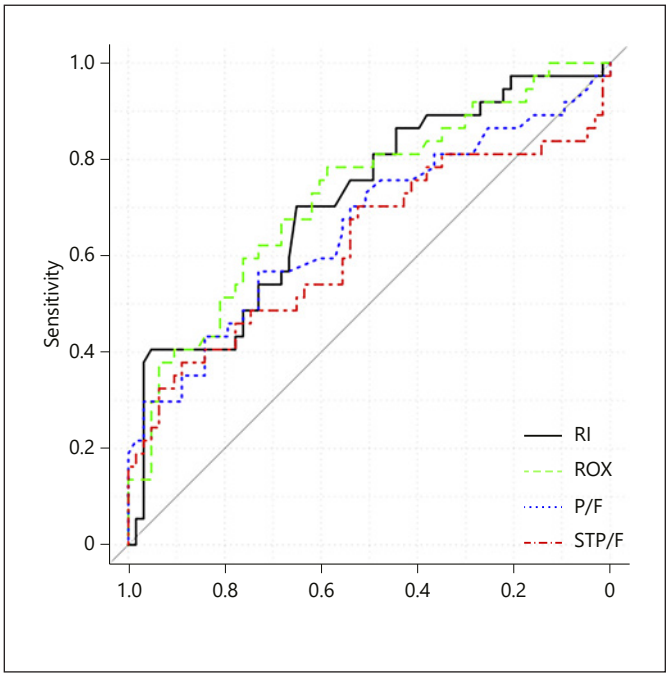


**Fig. 1.** Receiver operating characteristic for respiratory indexes at admission and in-hospital death. RI, respiratory index; P/F, PaO2/FiO2 ratio; $_{ST}$P/F, standard P/F ratio; ROX, RR-oxygenation index.

line suppl. Table 4). RI ≤3.8, ROX <3.85, and P/F <100 at admission were predictors for in-hospital death and ICU admission at 7 days by Cox regression models, while $_{ST}$P/F ≤170 was not (online suppl. Table 5). RI and ROX showed adequate calibration and good discriminatory power for death or ICU admission at 7 days (online suppl. Table 3).

Univariate analysis for determinants of mean respiratory indexes over time is reported in online supplementary Table 6. Decreasing RI, ROX, P/F, and $_{ST}$P/F were found to be independent predictors of death or ICU admission at 7 days by the survival joint model (online suppl. Table 7). In particular, every 0.1-unit decrease in RI was associated with a 14% increase in the risk of death or ICU admission at 7 days. Every 1-unit decrease in ROX, P/F, or $_{ST}$P/F was associated with a 45%, 8%, or 5% increase in the risk of death or ICU admission at 7 days, respectively.

Color version available online

**Table 3.** Univariate analysis for determinants of mean respiratory indexes over time

| Variable | Estimate | SE | *p* value |
|---|---|---|---|
| *RI* | | | |
| Age | −0.11 | 0.05 | **0.0219** |
| Sex (female) | −3.96 | 1.41 | **0.0061** |
| Cancer | −1.31 | 3.61 | 0.7167 |
| SAH | −0.47 | 1.44 | 0.7458 |
| Heart failure | 2.38 | 3.71 | 0.5224 |
| COPD | −0.67 | 2.57 | 0.7951 |
| Obesity | 1.86 | 1.76 | 0.2944 |
| DNR | −2.80 | 1.61 | 0.0862 |
| *P/F* | | | |
| Age | −1.59 | 0.32 | **<0.001** |
| Sex (female) | −3.77 | 10.63 | 0.7238 |
| Cancer | 14.57 | 27.18 | 0.5930 |
| SAH | −10.83 | 10.22 | 0.2920 |
| Heart failure | −31.62 | 26.17 | 0.2298 |
| COPD | −0.28 | 19.18 | 0.9883 |
| Obesity | 6.36 | 12.74 | 0.6188 |
| DNR | −39.35 | 11.30 | **<0.001** |
| *$_{ST}$P/F* | | | |
| Age | −1.45 | 0.32 | **<0.001** |
| Sex (female) | 5.67 | 10.48 | 0.5901 |
| Cancer | −1.90 | 26.16 | 0.9424 |
| SAH | −8.01 | 10.06 | 0.4279 |
| Heart failure | 10.83 | 26.65 | 0.6854 |
| COPD | 7.42 | 18.56 | 0.6902 |
| Obesity | 7.72 | 12.61 | 0.5416 |
| DNR | −30.62 | 11.30 | **0.0080** |
| *ROX* | | | |
| Age | −0.07 | 0.02 | **<0.001** |
| Sex (female) | −0.41 | 0.57 | 0.4743 |
| Cancer | −0.28 | 1.37 | 0.8408 |
| SAH | −0.54 | 0.55 | 0.3302 |
| Heart failure | −2.00 | 1.41 | 0.1583 |
| COPD | −0.91 | 0.99 | 0.3617 |
| Obesity | 0.64 | 0.68 | 0.3497 |
| DNR | −1.71 | 0.60 | **0.0055** |

HR, hazard ratio; SE, standard error; RI, respiratory index; P/F, PaO2/FiO2 ratio; $_{ST}$P/F, standard P/F ratio; ROX, RR-oxygenation index; SAH, systemic arterial hypertension; CHF, congestive heart failure; COPD, chronic obstructive lung disease; DNR, do not reanimate.

## Discussion/Conclusions

Our study shows that, in patients with SARS-CoV-2-related respiratory failure, decreasing RI or P/F during hospital stay are independent predictors of in-hospital death. RI, ROX, and P/F at admission are independent predictors for death or ICU admission at 7 days, while $_{ST}$P/F is not. The decrease of RI, ROX, P/F, and $_{ST}$P/F during hospital stay is independently associated with in-hospital death or ICU admission at 7 days.

COVID-19 pandemic led clinicians to provide medical care to a huge number of patients suffering from a single

**Table 4.** Risk factors for in-hospital death according to the survival joint model

| Variable | HR | 95% CI | *p* value |
|---|---|---|---|
| RI | 1.05 | 1.00–1.09 | **0.0322** |
| Age | 0.92 | 0.88–0.96 | **<0.001** |
| CHF | 0.23 | 0.06–0.88 | **0.0324** |
| P/F | 1.01 | 1.00–1.02 | **0.0046** |
| Age | 0.92 | 0.87–0.98 | **0.0057** |
| CHF | 0.29 | 0.07–1.28 | 0.1023 |
| $_{ST}$P/F | 1.01 | 0.99–1.03 | 0.4412 |
| Age | 0.94 | 0.90–0.95 | **0.0086** |
| CHF | 1.01 | 0.99–1.03 | **0.0417** |
| ROX | 1.05 | 1.0–1.11 | 0.0556 |
| Age | 0.93 | 0.90–0.97 | **<0.001** |
| CHF | 0.24 | 0.06–0.92 | **0.0373** |

HR, hazard ratio; CI, confidence interval; SE, standard error; RI, respiratory index; P/F, PaO2/FiO2 ratio; STP/F, standard P/F ratio; ROX, RR-oxygenation index.

disease. This was severe respiratory failure for the majority of hospitalized COVID-19 patients [1]. In this view, although dramatic, COVID-19 was a tremendous experience for clinicians dealing with respiratory medicine and rose several questions on the individual prognostic value of different respiratory parameters.

The role of hypoxemia as a driver for mortality was well-known before COVID-19 [7]. However, this may be influenced by oxygen therapy and requires blood-gas analysis to monitor patient status. Whether blood-gas-based indexes are better than clinically based ones for prognostic assessment of patients with COVID-19 is undefined. In our study, easy-to-calculate and promptly available respiratory indexes either at admission or during hospital stay (RI and ROX) have similar prognostic values as blood-gas-based measures. In particular, as variation of RI and ROX during hospital stay was associated with death or ICU admission, a periodic assessment of these indexes could represent a signal of need for closer observation and clinical deterioration. Moreover, clinically based indexes make prognostic evaluation rapidly available and could reduce the need for repeated blood-gas analysis.

The pathway of breathing control is frequently impaired in COVID-19 patients with abnormal relationships between respiratory drive and oxygenation; in this setting, breathing efforts can amplify the severity of lung injury [20]. RR is probably the most under-reported and under-regarded vital parameter [21]. Since clinically based respiratory indexes include RR in their formulas, our results renew the need for improving physicians' awareness on RR evaluation in COVID-19 patients as a common surrogate of respiratory muscle effort and, probably, as a determinant of lung injury in nonintubated patients. This concept is similar to that of ventilator-induced lung injury [22].

Upgrading from non-invasive to invasive mechanical ventilation is often based on physician judgment and may be physician-dependent [2]. P/F can be used to drive decisions on upgrading to invasive mechanical ventilation. In this view, our choice to consider in-hospital death as the primary outcome is aimed at avoiding bias regarding physician-dependent decision on ICU admission. On the other side, death in ICU can be caused by emergent non-COVID-related complications [2]. Thus, considering death or ICU admission at 7 days as the secondary outcome may reduce the background noise of hospital-acquired infection and ventilator-induced lung injury.

The high in-hospital mortality observed in our study is consistent with previous findings in COVID-19 patients with severe respiratory failure [23]. Almost all patients in our study had severe respiratory failure and qualified for ARDS criteria at admission (83%). Notably, about one-fourth of patients were not candidates for ICU admission because of important comorbidities. Whether our results also apply to patients with less severe respiratory failure remains to be defined.

Our study has some limits. As with many other studies in COVID-19 patients, this is a retrospective analysis. Second, despite the not negligible amount of longitudinal data and considerable event rate, some analyses may need a larger number of patients and parameters assessments to compare the relative value of individual respiratory indexes.

Third, we used previously validated cutoff levels at admission for individual respiratory indexes in a context different from COVID-19, except for $_{ST}$P/F ratio; thus, further studies in future may identify different and more accurate cutoff values in this kind of patient. Lastly, interpretation of the association between increased mortality and unit variation of the singular respiratory measure during hospitalization must take into account the difference in scaling, with the subsequent inappropriateness of direct comparison.

Our study has also some strengths. First, we validate the easy-to-calculate RI as a useful and prompt index for risk stratification in SARS-CoV-2 pneumonia either at admission and during hospitalization. Second, our study is by far

the first one to assess longitudinal variations of respiratory measures over time as predictors of unfavourable outcomes in patients with SARS-CoV-2 pneumonia, providing an adequate sample size for the credibility of the results. In conclusion, our study shows that simple, clinically based respiratory indexes (RI and ROX) at admission and their variation during hospital stay are useful to predict unfavourable outcomes in patients with SARS-CoV-2-related respiratory failure.

## Statement of Ethics

The study protocol was reviewed and approved by the local Ethics Committee (Comitato Etico Regionale dell'Umbria, approval number CRU Unipg 20-05 SARS-CoV-2). Written informed consent was not required (Comitato Etico Regionale dell'Umbria).

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


## Funding Sources

No funding was received.


## Author Contributions

G.M. and C.B. were involved in primary study design, statistical analyses, results interpretation, drafting of the manuscript, and are responsible for the integrity of the work as a whole.

## Data Availability Statement

All data generated or analyzed during this study are included in this article or its online supplementary material files. Further inquiries can be directed to the corresponding author.

## References


1 Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 May;8(5):475–81.
2 Tobin MJ. Basing respiratory management of COVID-19 on physiological principles. Am J Respir Crit Care Med. 2020;201(11):1319–20.
3 Chen JH, Chang SS, Liu JJ, Chan RC, Wu JY, Wang WC, et al. Comparison of clinical characteristics and performance of pneumonia severity score and CURB-65 among younger adults, elderly and very old subjects. Thorax. 2010;65:971–7.
4 Gupta RK, Marks M, Samuels THA, Luintel A, Rampling T, Chowdhury H, et al. UCLH COVID-19 Reporting Group. Systematic evaluation and external validation of 22 prognostic models among hospitalised adults with COVID-19: an observational cohort study. Eur Respir J. 2020 Dec 24;56(6):2003498.
5 ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012; 307(23):2526–33.
6 Villar J, Blanco J, del Campo R, Andaluz-Ojeda D, Díaz-Domínguez FJ, Muriel A, et al. Spanish initiative for epidemiology, stratification & therapies for ARDS (SIESTA) network. Assessment of PaO2/FiO2 for stratification of patients with moderate and severe acute respiratory distress syndrome. BMJ Open. 2015 Mar 27;5(3):e006812.
7 Tobin MJ, Jubran A, Laghi F. PaO2/FIO2 ratio: the mismeasure of oxygenation in COVID-19. Eur Respir J. 2021;57(3):2100274.
8 Aboab J, Louis B, Jonson B, Brochard L. Relation between PaO2/FIO2 ratio and FIO2: a mathematical description. Intensive Care Med. 2006;32(10):1494–7.
9 Gowda MS, Klocke RA. Variability of indices of hypoxemia in adult respiratory distress syndrome. Crit Care Med. 1997;25(1):41–5.
10 Mays EE. An arterial blood gas diagram for clinical use. Chest. 1973;63(5):793–800.
11 Prediletto I, D'Antoni L, Carbonara P, Daniele F, Dongilli R, Flore R, et al. Standardizing PaO2 for PaCO2 in P/F ratio predicts in-hospital mortality in acute respiratory failure due to Covid-19: a pilot prospective study. Eur J Intern Med. 2021 Oct;92:48–54.
12 Roca O, Messika J, Caralt B, García-de-Acilu M, Sztrymf B, Ricard JD, et al. Predicting success of high-flow nasal cannula in pneumonia patients with hypoxemic respiratory failure: the utility of the ROX index. J Crit Care. 2016 Oct;35:200–5.
13 Roca O, Caralt B, Messika J, Samper M, Sztrymf B, Hernández G, et al. An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. Am J Respir Crit Care Med. 2019 Jun 1; 199(11):1368–76.
14 Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015 Jun 4; 372(23):2185–96.
15 Gianstefani A, Farina G, Salvatore V, Alvau F, Artesiani ML, Bonfatti S, et al. Role of ROX index in the first assessment of COVID-19 patients in the emergency department. Intern Emerg Med. 2021 Oct;16(7):1959–65.
16 Vega ML, Dongilli R, Olaizola G, Colaianni N, Sayat MC, Pisani L, et al. COVID-19 pneumonia and ROX index: time to set a new threshold for patients admitted outside the ICU. Pulmonology. 2021;27(5):475–6.
17 Vedovati MC, Cimini LA, Pierpaoli L, Vanni S, Cotugno M, Pruszczyk P, et al. Prognostic value of respiratory index in haemodynamically stable patients with acute pulmonary embolism: the Respiratory Index model study. Eur Heart J Acute Cardiovasc Care. 2020 Jun;9(4):286–92.
18 Asar Ö, Ritchie J, Kalra PA, Diggle PJ. Joint modelling of repeated measurement and time-to-event data: an introductory tutorial. Int J Epidemiol. 2015 Feb;44(1):334–44.
19 Rizopoulos D. JM: an R Package for the joint modelling of longitudinal and time-to-event data. J Stat Soft. 2010;35(9):1–33.
20 Gattinoni L, Marini JJ, Camporota L. The respiratory drive: an overlooked tile of COVID-19 pathophysiology. Am J Respir Crit Care Med. 2020;202(8):1079–80.
21 Cretikos MA, Bellomo R, Hillman K, Chen J, Finfer S, Flabouris A. Respiratory rate: the neglected vital sign. Med J Aust. 2008;188(11): 657–9.
22 Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. Am J Respir Crit Care Med. 2017;195(4):438–42.
23 Vaschetto R, Barone-Adesi F, Racca F, Pissaia C, Maestrone C, Colombo D, et al. Outcomes of COVID-19 patients treated with continuous positive airway pressure outside the intensive care unit. ERJ Open Res. 2021 Jan 25; 7(1):00541–2020.