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Impact of COVID-19 on the association between pulse oximetry and arterial oxygenation in patients with acute respiratory distress syndrome

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Managing patients with acute respiratory distress syndrome (ARDS) requires frequent changes in mechanical ventilator respiratory settings to optimize arterial oxygenation assessed by arterial oxygen partial pressure (PaO_2) and saturation (SaO_2). Pulse oxymetry (SpO_2) has been suggested as a non-invasive surrogate for arterial oxygenation however its accuracy in COVID-19 patients is unknown. In this study, we aimed to investigate the influence of COVID-19 status on the association between SpO_2 and arterial oxygenation. We prospectively included patients with ARDS and compared COVID-19 to non-COVID-19 patients, regarding SpO_2 and concomitant arterial oxygenation (SaO_2 and PaO_2) measurements, and their association. Bias was defined as mean difference between SpO_2 and SaO_2 measurements. Occult hypoxemia was defined as a $SpO_2 \geq 92\%$ while concomitant $SaO_2 < 88\%$. Multiple linear regression models were built to account for confounders. We also assessed concordance between positive end-expiratory pressure (PEEP) trial-induced changes in SpO_2 and in arterial oxygenation. We included 55 patients, among them 26 (47%) with COVID-19. Overall, SpO_2 and SaO_2 measurements were correlated ($r = 0.70$; $p < 0.0001$), however less so in COVID-19 than in non-COVID-19 patients ($r = 0.55$, $p < 0.0001$ *vs.* $r = 0.84$, $p < 0.0001$, $p = 0.002$ for intergroup comparison). Bias was $+1.1\%$, greater in COVID-19 than in non-COVID-19 patients (2.0 *vs.* 0.3%; $p = 0.02$). In multivariate analysis, bias was associated with COVID-19 status (unstandardized $\beta = 1.77$, $95\%CI = 0.38–3.15$, $p = 0.01$), ethnic group and ARDS severity. Occult hypoxemia occurred in 5.5% of measurements (7.7% in COVID-19 patients *vs.* 3.4% in non-COVID-19 patients, $p = 0.42$). Concordance rate between PEEP trial-induced changes in SpO_2 and SaO_2 was 84%, however less so in COVID-19 than in non-COVID-19 patients (69% *vs.* 97%, respectively). Similar results were observed for PaO_2 regarding correlations, bias, and concordance with SpO_2 changes. In patients with ARDS, SpO_2 was associated with arterial oxygenation, but COVID-19 status significantly altered this association.

From December 2019, a worldwide pandemic with an kk coronavirus SARS-CoV-2 is responsible for Coronavirus disease (COVID-19[1]. Up to two-thirds of hospitalized COVID-19 patients develop severe pneumonia leading to an acute respiratory distress syndrome (ARDS)[2,3]. ARDS is characterized by an impairment in arterial oxygenation, leading to profound hypoxemia. Hence, the ratio between arterial oxygen partial pressure (PaO_2) and inspired fraction in oxygen (FiO_2), delivered by the mechanical ventilator, is a crucial in ARDS management. Yet, PaO_2 requires arterial blood gas analyses and cannot be continuously monitored. It may be approximated

by arterial oxygen saturation (SaO$_2$), which in turn, may be estimated by pulse oximetry (SpO$_2$), a continuous non-invasive measurement[4]. The latter showed benefit in decreasing complications related to intraoperative hypoxemia incidents[5], rate of unplanned intensive care unit (ICU) admissions of surgical patients[6] and number arterial blood gas analysis[7–10].

Managing patients with ARDS requires frequent changes in mechanical ventilator respiratory settings. While arterial oxygenation is paramount towards guiding the fine-tuning of mechanical ventilators in ARDS, SpO$_2$ has been suggested as surrogate for arterial oxygenation[11–13]. Known caveats of SpO$_2$ mostly lie in its accuracy in ICU due to confounding factors : hypoxemia[14–18], vasoconstriction with microcirculatory disorders[19], vasopressor treatments[15,20] and racial bias[21].

Since some COVID-19 patients are black[22]22/11/2021 13:53:00, severely hypoxemic[23] and may also experience microcirculatory disorders[24], the main goal of the following study was to investigate the impact of COVID-19 status on the association between SpO$_2$ and arterial oxygenation (SaO$_2$ and PaO$_2$) in patients with ARDS. Furthermore, we assessed whether SpO$_2$ changes could track changes in arterial oxygenation (SaO$_2$ and PaO$_2$) during positive end-expiratory pressure (PEEP) trial.

Methods

This prospective and observational study was conducted in a 24-bed ICU of a French university hospital between March 2019 and July 2020 for non COVID-19 patients and in the first pandemic wave (March–April 2020) for COVID-19 patients, in accordance with relevant guidelines and regulations.

Patients and data collection. We included all consecutive patients admitted in our ICU department for acute respiratory failure and presented ARDS criteria, according to Berlin definition[26] at the initial phase of ventilatory management (within one hour after intubation). Exclusion criteria were those related to known causes of low-reliability of SpO$_2$ measurements: (i) low-quality SpO$_2$ signal assessed on the SpO$_2$ curve aspect and (ii), patients with nail varnish, methaemoglobinemia or carbon monoxide poisoning[4] and (iii), patients with marked movements leading to SpO$_2$ signal artefacts[27].

ARDS severity was categorized as mild for PaO$_2$/FiO$_2$ ratio between 200 and 300 mmHg, moderate between 100 and 200 mmHg, and severe, under 100 mmHg[26].

Data were prospectively collected using a clinical software allowing data management and extraction, Centricity Critical Care (General Electric Healthcare, Massachusetts, United States of America).

SpO$_2$ and SaO$_2$ measurements. SpO$_2$ was continuously measured using a finger or ear probe of a last generation pulse oximeter (Masimoset®, Masimo Corporation, Irvine, CA, USA). The location of SpO$_2$ probe was left at the discretion of nurses to obtain the best possible SpO$_2$ signal. The pulse oximeter was connected to patients' monitor (GE Healthcare, Chicago, Il, USA) and SpO$_2$ signal maximized on the monitor screen. SpO$_2$ measurement was recorded at the time the arterial blood gas was performed by the patient's nurse.

A blood sample was obtained from radial or femoral arterial catheter, not necessarily located on the same side as SpO$_2$ probe. SaO$_2$ was measured with the ICU blood gas analyser (ABL800, Radiometer®, Copenhagen, Denmark) and thus obtained within five minutes of blood sampling.

Occult hypoxemia was defined as SaO$_2 < 88\%$, while concomitant SpO$_2$ measure was $\geq 92\%$[21].

Ventilatory settings and respiratory measurements. All patients were placed in 45-degree semi-recumbent position and mechanically ventilated (CARESCAPE R860, GE Healthcare, Chicago, Il, USA) in pressure regulated volume control mode. Tidal volume was set at 6 mL/kg of predicted body weight. Respiratory rate and inspiratory/expiratory times ratio were adjusted to prevent hypercapnia (pH goal: 7.30–7.45) and to avoid dynamic hyperinflation, without exceeding a respiratory rate of 35 breaths/min[12,28]. The fraction of inspired oxygen (FiO$_2$) was adjusted to obtain a SpO$_2 \geq 90\%$[29]. An airway humidification system was used in all patients.

The plateau pressure was calculated during a 5-s inspiratory hold and total PEEP during a 5-s expiratory hold. The driving pressure was calculated as the difference between plateau pressure and total PEEP. The static respiratory system compliance was calculated as tidal volume/(plateau pressure–total PEEP).

PEEP trial description. Since only patients with moderate to severe ARDS with a high potential for lung recruitment benefit from high PEEP strategies and since the amount of potentially recruitable lung vary widely in the population[30], we systematically performed a PEEP trial in all patients with ARDS to individualize at best the initial PEEP level[29]. According to local protocols, PEEP level was initially set at 5 cmH$_2$O[31] and a first set of measurements, including SpO$_2$, SaO$_2$ and PaO$_2$ was performed. Then, PEEP was increased to 15 cmH2O and a second set of measurements was performed. All measurements were recorded after a 10-min period of stabilization[32] and two couples of simultaneous SpO$_2$ and SaO$_2$ measurements were obtained per patient. Other ventilatory settings were unchanged during the study period.

COVID-19 diagnosis. All patients were confirmed with SARS-Cov-2 using routine RT-PCR methodology, with two sets: either Allplex® 2019-nCoV assay (Seegene, Seoul, South Korea) with Microlab NIMBUS® extractor (Hamilton Bonaduz AG, Rapperswil-Jona, Switzerland) and CFX96® thermocycler (Bio-Rad laboratories, Hercules, California, United States of America); or RealStar® SARS-CoV-2 RT-PCR Kit 1.0 assay (Altona Diagnostics, Hamburg, Germany) with QIAsymphony SP® extractor (QIAGEN, Hilden, Germany) and QuantStudio® thermocycler (Thermo Fisher Scientific, Waltham, Massachusetts, United States of America). RT-PCR was performed on nasopharyngeal swabs or on distal bronchial samples.

Statistical analysis. Normality distribution of continuous variables was tested using the Agostino-Pearson test. Continuous variables were expressed as mean (standard deviation) or median [interquartile] and categorical variables as counts (percentages). Continuous variables were compared using Wilcoxon or paired Student t-tests and Mann–Whitney U-test or Student t-tests. Categorical variables were compared using Chi-2 or Fisher-exact tests.

We used four different methods to assess the association between SaO_2 and SpO_2: correlations, agreement, multivariable regression models and concordance. Specifically, correlations were performed using Pearson or Spearman's correlation coefficients, according to data distribution. Agreement between SpO_2 and SaO_2 measurements was assessed with Bland–Altman analysis[33] and intraclass correlation coefficients (ICC), with ICC value > 0.7 and > 0.9 indicating satisfactory and excellent agreement respectively[34]. Accuracy of SpO_2 measurement was estimated by the bias, calculated as the mean difference between SpO_2 and SaO_2 measurements. Precision of SpO_2 measurement was estimated by the standard deviation of the bias and the 95% limits of agreement[33]. The concordance between relative changes in SpO_2 and SaO_2 was assessed (i) with a four-quadrant plot analysis[35], (ii) the clinical concordance method[36] and (iii) the inter-rater agreement kappa coefficient (κ), with κ-value < 0.20 and > 0.80 indicating poor and good strength of agreement respectively[37].

Multiple linear regressions were performed to identify variables associated with the dependent variable SpO_2. Separate models were built depending on the selected variable (SaO_2 or PaO_2) in regard to SpO_2. Moreover, multivariable models accounted for confounding variables (in regard to SpO_2), and their interactions: SaO_2 or PaO_2, COVID-19 status, ethnic group, PEEP level, FiO_2 setting, temperature, SpO_2 probe and arterial catheter side (ipsilateral or contralateral), ARDS severity (as defined above, with mild category used as reference) and norepinephrine administration (defined as a categorical binary variable)[14–21].

Assuming a correlation coefficient of 0.69 between SpO_2 and SaO_2[38] and an ICC > 0.9 with a 95% confidence interval (CI) (0.84–0.96), we planned to include at least 50 patients with at least 25 COVID-19 patients. A p value < 0.05 was considered statistically significant. Statistical analyses were performed using MedCalc 11.6.0 software (MedCalc®, Mariakerke, Belgium), and SPSS version 25.0 (IBM®, Armonk, USA).

Ethics approval and consent to participate. This study was approved by the Comité de Protection des Personnes Ile-de-France X (IDCRB2018-A00050-55, protocol 59–2018) and by the Ethics Committee of the Société de Réanimation de Langue Française (CE SRLF 20–72)[25], which waived the need for informed consent, following national regulation on standard-of-care data collection. Indeed, this study was performed on data collected in the course of a prospective data collection, without any additional blood sample, as compared to standard of care. As such, only refusal to participate was systematically sought.

Results

Patient characteristics. Among 55 included patients: 33(60%) were men, 17(31%) were black and no patient had sickle-cell anaemia history. The ICU mortality rate was 38%. All patients had pulmonary ARDS and 26(47%) had an ARDS related to COVID-19. COVID-19 patients were more frequently black, tended to have more diabetes mellitus and had a lower SAPS-3 than non-COVID-19 patients (Table 1). The other characteristics of patients are shown in Tables 1 and 2.

A SpO_2 finger probe was used in all patients but three and a radial arterial catheter was used in 39(71%) patients. SpO_2 probe and arterial catheter were located on the same side in 30(55%) patients (Table 1). SpO_2 values ranged from 83 to 100% and SaO_2 values from 80 to 100%. Carboxyhaemoglobin and methaemoglobin rates were < 2% in all patients.

Association between SpO_2, SaO_2 and PaO_2. In the whole population, SpO_2 and SaO_2 measurements were significantly correlated (r = 0.70, p < 0.0001). Correlation between SpO_2 and SaO_2 was lower in COVID-19 than in non-COVID-19 patients (r = 0.55, p < 0.0001 $vs.$ r = 0.84, p < 0.0001, p = 0.002 for intergroup comparison) (Fig. 1A). After adjusting for confounding covariables, variables independently associated with SpO_2 were: SaO_2 (unstandardized β = 0.46, 95%CI = 0.35–0.57, p < 0.0001), COVID-19 status (unstandardized β = 1.96, 95%CI = 1.03–2.88 l, p < 0.0001) and PEEP level (unstandardized β = 0.11, 95%CI = 0.01–0.21, p = 0.03).

For sensitivity, correlation between SpO_2 and PaO_2 was also assessed and found significant (r = 0.62, p < 0.0001). Similarly, correlation between SpO_2 and PaO_2 was lower in COVID-19 than in non-COVID-19 patients (r = 0.47, p = 0.001 $vs.$ r = 0.75, p < 0.0001, p = 0.002 for intergroup comparison) (Fig. 1B). After adjusting for confounding covariables, variables independently associated with SpO_2 were: PaO_2 (unstandardized β = 0.03, 95%CI = 0.02–0.05, p < 0.0001), COVID-19 status (unstandardized β = 2.04, 95%CI = 0.99–3.08, p < 0.0001) and PEEP level (unstandardized β = 0.17, 95%CI = 0.06–0.28, p = 0.002).

Agreement between SpO_2 and SaO_2. In the whole population, the bias between SpO_2 and SaO_2 measurements was 1.1%, the precision was 3.4% and the limits of agreement ranged from -5.6 to + 7.9% (Fig. 2A). Bias and SaO_2 measurements were significantly correlated (r = − 0.56, p < 0.0001). The bias was higher (2.0 $vs.$ 0.3%; p = 0.02) and the precision lower (4.1 $vs.$ 2.5%) in COVID-19 than in non-COVID-19 patients (Fig. 2B). ICC = 0.79 (95%CI = 0.69–0.86), 0.62 (95%CI = 0.34–0.78) and 0.90 (95%CI = 0.84–0.94) in the whole population, in COVID-19 and in non-COVID-19 patients respectively. After adjusting for confounding covariables, COVID-19 status (unstandardized β = 1.77, 95%CI = 0.38–3.15, p = 0.01), ethnic group (unstandardized β = − 1.58, 95%CI = − 2.99 to − 0.18, p = 0.03) and ARDS severity (unstandardized β = 1.09, 95%CI = 0.21–1.97, p = 0.02) were independently associated with the bias. Interaction analyses did not yield significant association between COVID-19 status, ethnic group and bias.

Variables	All patients (n = 55)	COVID-19 patients (n = 26)	Non COVID-19 patients (n = 29)
Age (years)	60 (17)	59 (15)	60 (18)
Male (n, %)	33 (60)	17 (65)	16 (55)
Body mass index (kg/m^2)	28 (5)	29 (5)	26 (5)
Black patients (n, %)	17 (31)	12 (46)	5 (17)*
Hypertension (n,%)	23 (42)	11 (42)	12 (41)
Diabetes mellitus (n,%)	14 (25)	10 (38)	4 (14)
Smokers (n,%)	18 (33)	7 (27)	11 (38)
SAPS-3	56 (15)	52 (11)	60 (17)*
ICU mortality (n, %)	21 (38)	7 (27)	14 (48)
Patients in sinus rhythm (n, %)	54 (98)	26 (100)	28 (97)
Patients receiving norepinephrine (n, %)	40 (73)	20 (77)	20 (69)
Neuromuscular blocking agents (n, %)	30 (55)	12 (46)	18 (62)
SpO$_2$ probe location			
Finger (n,%)	52 (95)	26 (100)	26 (90)
Ear (n,%)	3 (5)	0 (0)	3 (10)
Arterial catheter location			
Radial (n,%)	39 (71)	24 (92)	15 (52)*
Femoral (n,%)	16 (29)	2 (8)	14 (48)*

Table 1. Patient characteristics. Variables are expressed as mean (standard deviation) or counts (percentages). *ICU* Intensive Care Unit, *SAPS* Simplified Acute Physiology Score, *SpO$_2$* pulse oximetry. *$p < 0.05$ non-COVID-19 versus COVID-19 patients.

Occult hypoxemia, occurred in 6 (5.5%) pairs of measurements. There was no significant difference between COVID-19 and non-COVID-19 patients (7.7% vs. 3.4%, respectively, $p = 0.42$).

Effects of PEEP trial on SpO$_2$, SaO$_2$ and PaO$_2$. In the whole population, PEEP increase from 5 to 15 cmH2O significantly increased SpO$_2$, SaO$_2$ and PaO$_2$ by $3 \pm 4\%$, $4 \pm 5\%$ and $43 \pm 57\%$ respectively, (Table S1). SpO$_2$ changes were significantly correlated to that of SaO$_2$ ($r = 0.65$, $p < 0.0001$) and PaO$_2$ ($r = 0.47$, $p < 0.001$). The concordance rate between PEEP trial-induced changes in SpO$_2$ and SaO$_2$ was 84% (Fig. 3A) and the κ-coefficient was 0.60. The concordance rate between PEEP trial-induced changes in SpO$_2$ and PaO$_2$ was 85% and the κ-coefficient was 0.55 (Figure S1).

Concordance rate between PEEP trial-induced changes in SpO$_2$ and SaO$_2$ was lower in COVID-19 than in non-COVID-19 patients (69 *vs.* 97%), as was the κ-coefficient (0.35 *vs.* 1.00) (Fig. 3B). Similar results were found for PaO$_2$ (73 *vs.* 97% for concordance rate and 0.28 *vs.* 1.00 for the κ-coefficient) (Figure S1).

Discussion

A reliable SpO$_2$ measurement would be interesting in patients with ARDS, given the medico-economic impact of the decrease in arterial blood gas analysis overuse[10]. In this cohort of patients with ARDS monitored with last generation pulse oximeter, we found that (i) SpO$_2$ was overall well-correlated with arterial oxygenation (SaO$_2$ and PaO$_2$) and that SpO$_2$ slightly overestimated SaO$_2$, (ii) COVID-19 status significantly impacted the association between SpO$_2$ and arterial oxygenation (SaO$_2$ and PaO$_2$) and (iii), changes in SpO$_2$ could not reliably track changes in arterial oxygenation (SaO$_2$ and PaO$_2$) during PEEP trial in COVID-19 patients.

The accuracy of SpO$_2$ measurement in ICU is still debated because of several confounding factors[14–20,39,40] with an unconstant and unpredictable bias between SpO$_2$ and SaO$_2$ measurements[14,15,18–20,39,41]. Overall, we found that SpO$_2$ and arterial oxygenation (SaO$_2$ and PaO$_2$) were well-correlated and that SpO$_2$ only slightly overestimated SaO$_2$ but with wide limits of agreement, suggesting the lack of precision of SpO$_2$ measurement. Our results are comparable to those from previous ICU studies, which found similar correlation[38] and a bias ranging from 0.2 to 3%[14,15,38,40,42] with a mean bias of 1.5%[43] but wide limits of agreement[14,15,38,40,42], highlighting the lack of improvement in the last generation pulse oximeter reliability. We also confirmed that that SpO$_2$ measurement was still less reliable in black[21] and in most hypoxemic[14–18] patients. It has been very recently shown that black patients had nearly three times the frequency of occult hypoxemia that was not detected by SpO$_2$ measurement as Caucasian patients[21]. Conversely to previous studies[14,39], we also found that changes in SpO$_2$ could track changes in arterial oxygenation (SaO$_2$ and PaO$_2$) during PEEP trial with a moderate to good strength of agreement. To our knowledge, this is one of the first studies analyzing not only the magnitude (correlation) but also the direction

Variables	COVID-19 patients (n = 26)		Non COVID-19 patients (n = 29)	
	PEEP + 5	PEEP + 15	PEEP + 5	PEEP + 15
Respiratory parameters				
Tidal volume (mL/kg of PBW)	5.9 [5.7–6.2]	5.9 [5.7–6.2]	5.9 [5.5–6.0]	5.9 [5.5–6.0]
Respiratory rate (cycles/min)	30 [26–33]	30 [26–33]	30 [25–30]	30 [25–30]
Total PEEP (cmH$_2$O)	6 [5–6]	16 [15–16]*	5 [5–6]£	15 [15–16]*
Plateau pressure (cmH$_2$O)	15 [14–17]	27 [24–28]*	18 [15–21]£	28 [26–29]*
Driving pressure (cmH$_2$O)	9 [8–11]	10 [8–12]	13 [10–15]£	12 [10–14]£
Respiratory system compliance (mL/cmH$_2$O)	44 [32–50]	38 [31–43]	28 [23–39]£	30 [28–37]
Haemodynamic parameters				
Heart rate (bpm)	80 [70–90]	78 [71–91]	93 [80–121]£	83 [75–117]£
Systolic arterial pressure (mmHg)	113 [102–131]	111 [103–120]	103 [92–122]	100 [93–127]
Diastolic arterial pressure (mmHg)	57 [50–61]	58 [50–62]	53 [51–57]	52 [49–57]£
Mean arterial pressure (mmHg)	75 [67–81]	74 [69–81]	71 [68–76]	69 [65–73]
Dosage of norepinephrine (µg/kg/min)	0.17 [0.10–0.28]	0.19 [0.12–0.39]£	0.50 [0.18–0.97]	0.50 [0.18–0.99]£
Lactate (mmol/L)	1.1 [0.8–1.2]	1.0 [0.8–1.2]£	1.8 [1.1–2.7]	1.7 [1.1–2.9]£
Biological parameters				
SpO$_2$ (%)	95 [93–96]	96 [95–98]	91 [89–94]£	96 [93–98]*
SaO$_2$ (%)	92 [89–95]	96 [94–98]*	90 [88–94]	96 [92–99]*
PaO$_2$/FiO$_2$ ratio	154 [99–225]	200 [152–250]*	101 [81–147]£	175 [110–211]*
PaO$_2$ (mmHg)	69 [59–85]	87 [68–118]*	62 [58–73]	82 [65–126]*
PaCO$_2$ (mmHg)	44 [41–50]	47 [42–51]	46 [41–50]	48 [41–52]*
Carboxyhaemoglobin (%)	0.8 [0.6–0.9]	0.7 [0.5–0.9]*	1.0 [0.8–1.5]£	0.9 [0.8–1.4]*£
Methaemoglobin (%)	0.7 [0.6–0.8]	0.7 [0.6–0.8]	0.6 [0.5–0.8]	0.6 [0.5–0.8]
Haemoglobin (g/dL)	11.8 [9.8–13.2]	11.9 [9.6–13.4]	9.7 [8.8–11.8]£	9.8 [8.5–11.6]£
Temperature (°C)	37.3 [36.8–38.0]	37.0 [37.0–37.8]	36.8 [36.4–37.5]£	36.8 [36.3–37.5]£
pH	7.38 [7.32–7.41]	7.36 [7.30–7.39]*	7.33 [7.30–7.38]	7.32 [7.29–7.35]*
Bicarbonates (mmol/L)	25.7 [22.8–28.0]	26.3 [22.4–28.4]	24.0 [21.7–27.1]	23.6 [21.7–27.2]
Fibrinogen (g/L)	6.8 [5.2–8.0]	NA	4.9 [3.6–6.5][1]£	NA
D-Dimer (ng/mL)	1524 [977–2389][9]	NA	4872 [NA][28]	NA

Table 2. Respiratory, haemodynamic and oxygenation effects of the PEEP trial according to patients' COVID-19 status. Variables are expressed as median [interquartile]. No missing values, except otherwise specified between {}. NA: non-available. *PaO$_2$* partial arterial pressure of oxygen, *PaCO$_2$* partial arterial pressure of carbon dioxide; PBW: predicted body weight, *PEEP* positive end-expiratory pressure, *SaO$_2$* arterial oxygen saturation, *SpO$_2$* pulse oximetry. *$p < 0.05$ PEEP + 15 *vs.* PEEP + 5 cmH2O. £ $p < 0.05$ non-COVID-19 versus COVID-19 patients. Formulas: driving pressure = plateau pressure-total PEEP; respiratory system compliance = tidal volume/(plateau pressure-total PEEP).

(concordance rate and κ-coefficient) of SpO$_2$ and SaO$_2$ changes. The discrepancy of our results to those of previous studies may be explained by the fact that rather than considering multiple therapeutic manoeuvres[15,40], we only considered a PEEP trial to ensure that the possible lack of agreement between changes in SpO$_2$ and SaO$_2$ could not be attributed to the multiple therapeutic manoeuvres used.

We found that COVID-19 significantly impacted the association between SpO$_2$ and arterial oxygenation (SaO$_2$ and PaO$_2$). First, SpO$_2$ measurement was less reliable, as illustrated be weaker correlation, higher bias, wider limits of agreement, lower precision and lower ICC with an ICC < 0.7. Second, changes in SpO$_2$ could not reliably track changes in arterial oxygenation (SaO$_2$ and PaO$_2$) during PEEP trial, with a concordance rate of 69% and a κ-coefficient of 0.35 for changes in SaO$_2$ and a concordance rate of 73% and a κ-coefficient of 0.28 for changes in PaO$_2$ in COVID-19 patients, but a concordance rate of 97% and a κ-coefficient of 1.00 both for SaO$_2$ and PaO$_2$ in non-COVID-19 patients. To our knowledge, this is the first study investigating the reliability of SpO$_2$ measurement in COVID-19 patients, despite it has been suggested to use SpO$_2$ monitoring in these patients to detect "silent hypoxemia"[44,45]. Importantly, the impact of COVID-19 on the association between SpO$_2$ and arterial oxygenation cannot be explained solely by the fact that COVID-19 patients were predominantly black[22]. Moreover, the proportion of occult hypoxemia that we observed was that expected of our population, although
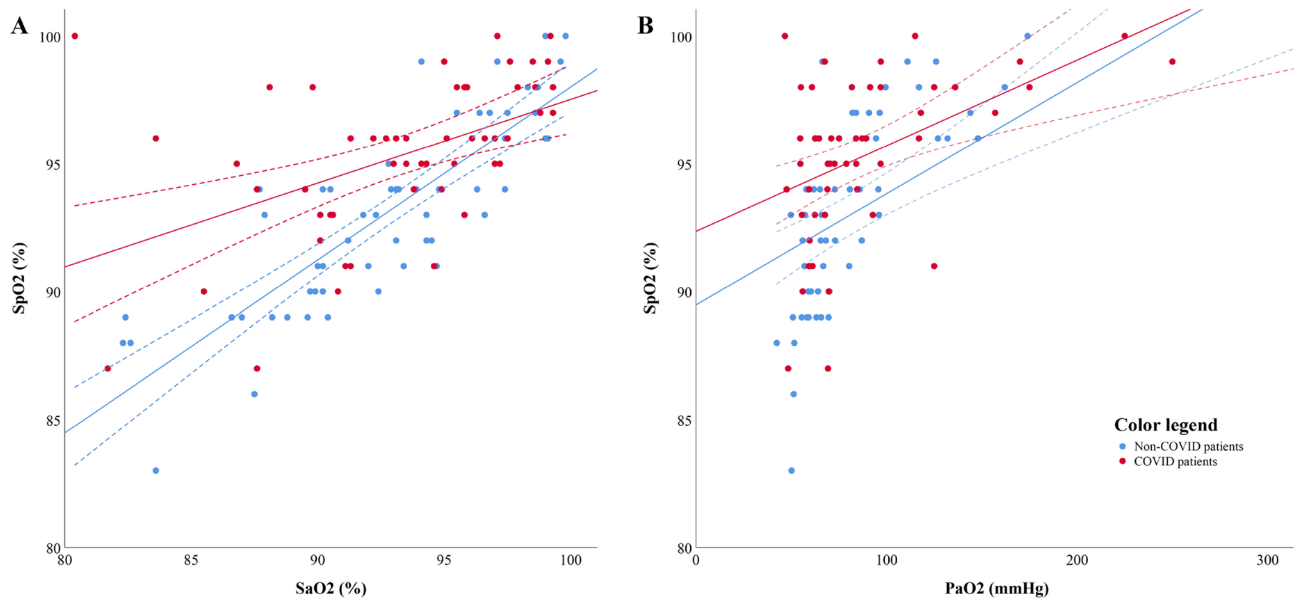
Figure 1. *Panel A*: correlation between pulse oximetry (SpO_2) and arterial oxygen saturation (SaO_2) in COVID-19 patients (red points, n = 52 measurements) and non-COVID-19 patients (blue points, n = 58 measurements). The solid line represents the correlation line. The dotted lines represent the 95% confidence interval of each correlation. *Panel B*: correlation between pulse oximetry (SpO_2) and arterial oxygen partial pressure (PaO_2) in COVID-19 patients (red points, n = 52 measurements) and non-COVID-19 patients (blue points, n = 58 measurements). The dotted lines represent the 95% confidence interval of each correlation.

no thorough analysis could be performed on this criterion due to its low prevalence. Indeed, although lack of power may have been involved, interaction analyses did not yield significant association between COVID-19 status, ethnic group and SpO_2. With caution, this may suggest that COVID-19 per se may alter the accuracy of SpO_2 measurement and the agreement between SpO_2 and arterial oxygenation. This could be explained by the fact that COVID-19 patients may experience systemic microvascular alterations that appear to be common and linked to coagulopathy[24] and/or endothelial dysfunction and endotheliitis[46]. Indeed, it has been shown that SARS-CoV-2 infection may facilitate the induction of endotheliitis with viral elements within endothelial cells and accumulation of inflammatory cells leading to apoptosis found in in several organs[46]. Further studies are needed to address the potential impact of COVID-19 on SpO_2 measurement.

The clinical implications of our results are two-fold. In non COVID-19 patients, our results suggest that SpO_2 measurements with latest generation pulse oximeter may be sufficient to monitor and track changes in arterial oxygenation in the most critically-ill patients. Thus, arterial blood gazes may not be necessarily mandatory after every ventilatory setting modification during the weaning process in patients with ARDS. Moreover, our results confirm those published by Martínez-Balzano who showed that there was an overuse of arterial blood gazes in critically ill patients and that their number could be reduced without negatively impacting patient care but with clear medico-economic impact[10]. Meanwhile, in COVID-19 patients, SpO_2 measurement may not be as reliable, and iterative arterial blood gazes' analyses to measure SaO_2 may still be mandatory.

Our study has some limitations. First, we assessed only one type of last generation pulse oximeter. Second, we only considered the same two PEEP levels in all patients and we cannot exclude that considering other PEEP levels might influence the association between SpO_2 and SaO_2 as well as the concordance between PEEP trial-induced SpO_2 and SaO_2 changes. Third, we did not study, as previous studies[18,40,41], the influence of carboxyhae-moglobin and methaemoglobin on the accuracy of SpO_2 measurement. Indeed, pulse oximeters cannot differenti-ate between these two forms of haemoglobin and oxyhaemoglobin, leading to SaO_2 overestimation in patients with high carboxyhaemoglobin and/or methaemoglobin rates[47,48]. Yet, we systematically excluded patients with methaemoglobinemia or carbon monoxide poisoning (all had carboxyhaemoglobin and methaemoglobin rates < 2%). Interestingly, Kerget and colleagues very recently showed that endogenous carboxyhaemoglobin may be an easily accessible biomarker of clinical course and prognosis in COVID-19 patients[49]. Fourth, we did not perform multiple arterial blood gas analyses, which may have allowed the estimation of the metrological preci-sion feature of the pulse oximeter device. Indeed, random error variability of replicate measurements, defined as
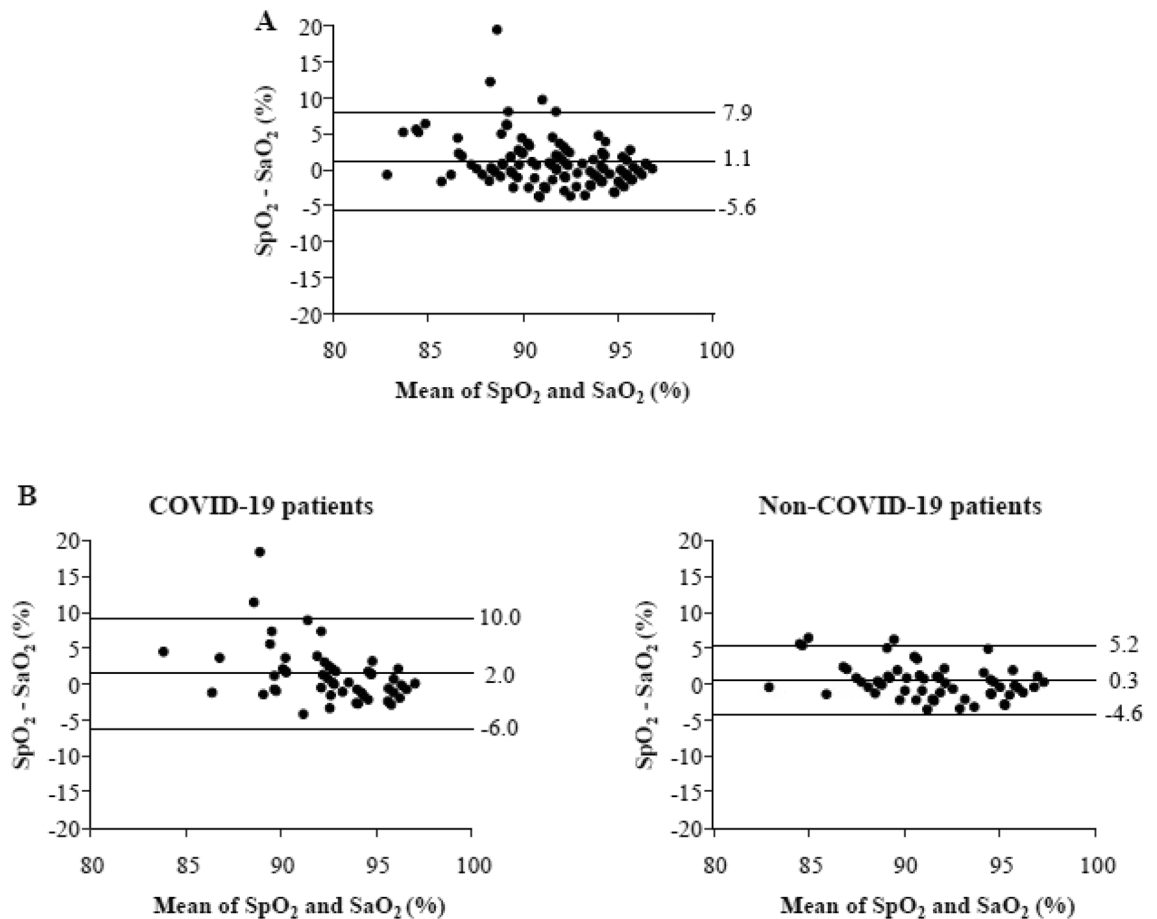
Figure 2. Comparison of pulse oximetry (SpO$_2$) and arterial oxygen saturation (SaO$_2$) measurements using the Bland–Altman method. The solid line represents the bias and the dotted lines represent the 95% limits of agreement (mean ± 1.96 standard deviation). *Panel A*: in the whole population (n = 110 measurements). *Panel B*: in COVID-19 patients (n = 52 measurements) and non-COVID-19 patients (n = 58 measurements).

precision, usually requires to perform multiple measurements for a given timepoint[50]. In our study, we did not deem ethical to sample arterial blood gases several times for each datapoint. We pragmatically assumed that precision remained constant and random error measurements were reproducible, following the device specifications[51].

Conclusion
In patients with ARDS, SpO$_2$ was associated with arterial oxygenation (SaO$_2$ and PaO$_2$) and could track changes in arterial oxygenation with good reliability. Nevertheless, COVID-19 status significantly impacted the association between SpO$_2$ and arterial oxygenation.
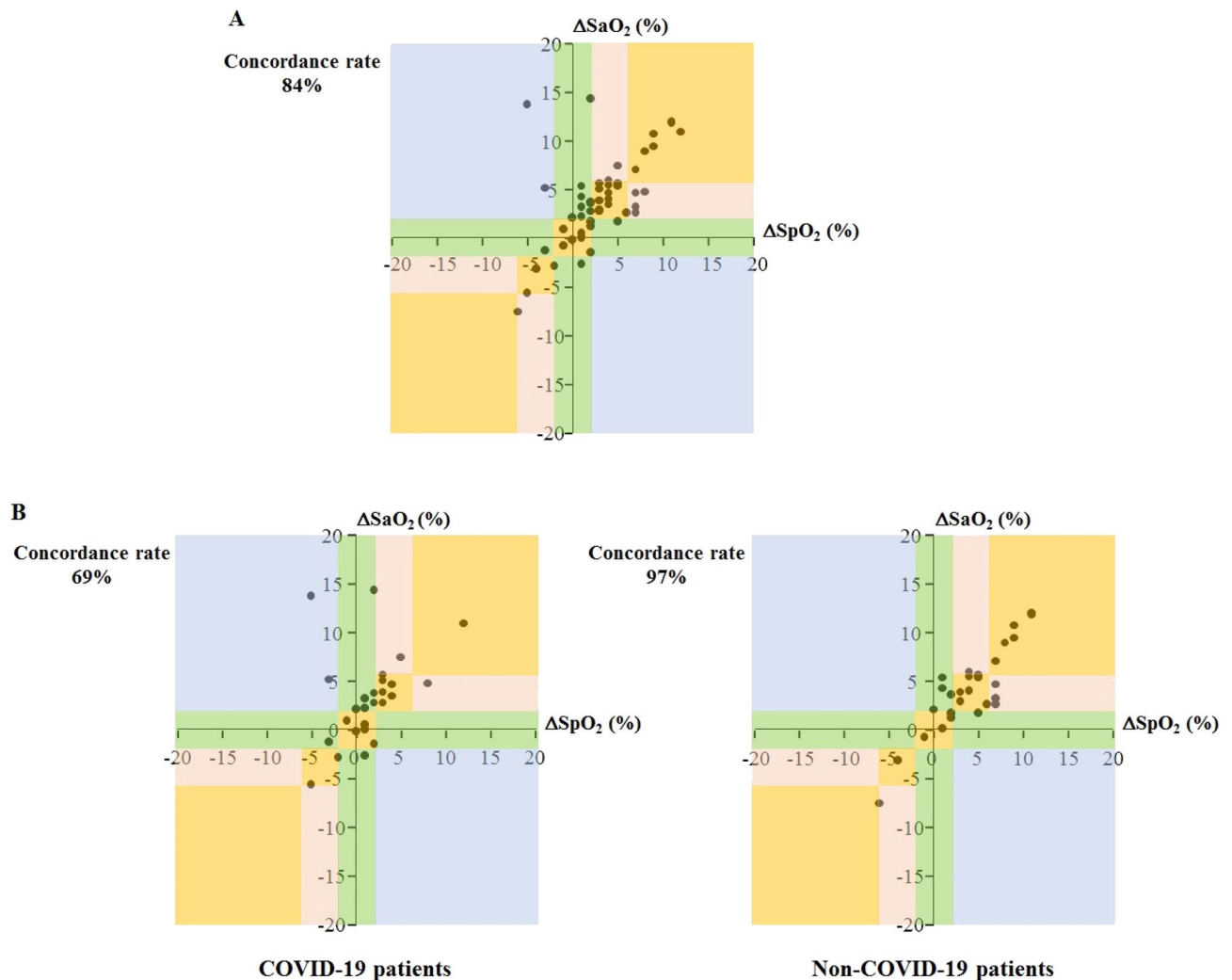
Figure 3. Trending ability of pulse oximetry (SpO$_2$) against arterial oxygen saturation (SaO$_2$) measurements during a positive end-expiratory pressure trial based on four-quadrant concordance analysis. The error grid reflects the therapeutic consequences in specific zones in the concordance plot. *Orange zone*: ΔSpO$_2$ and ΔSaO$_2$ change in the same direction and to the same extent. *Pink zone*: ΔSpO$_2$ and ΔSaO$_2$ change in the same direction but not to the same extent. *Green zone*: ΔSpO$_2$ changes while ΔSaO$_2$ is constant or vice versa. *Blue zone*: ΔSpO$_2$ and ΔSaO$_2$ change in opposite directions. *Panel A*: in the whole population (n = 55). *Panel B*: in COVID-19 (n = 26) and non-COVID-19 (n = 29) patients.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Guan, W. J. Clinical characteristics of coronavirus disease 2019 in China. *N. Engl. J. Med.* **382**, 1708–1720 (2020).
2. Wang, Y. Clinical course and outcomes of 344 intensive care patients with COVID-19. *Am. J. Respir. Crit. Care Med.* **201**, 1430–1434 (2020).
3. Grasselli, G. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the lombardy region, Italy. *JAMA* https://doi.org/10.1001/jama.2020.5394 (2020).
4. Jubran, A. Pulse oximetry. *Crit. Care* **19**, 272 (2015).
5. Moller, J. T. Randomized evaluation of pulse oximetry in 20,802 patients: II. Perioperative events and postoperative complications. *Anesthesiology* **78**, 445–453 (1993).
6. Ochroch, E. A. The impact of continuous pulse oximetry monitoring on intensive care unit admissions from a postsurgical care floor. *Anesth. Analg.* **102**, 868–875 (2006).
7. Solsona, J. F. Effect of pulse oximetry on clinical practice in the intensive care unit. *Lancet* **342**, 311–312 (1993).
8. Le Bourdelles, G., Estagnasie, P., Lenoir, F., Brun, P. & Dreyfuss, D. Use of a pulse oximeter in an adult emergency department: impact on the number of arterial blood gas analyses ordered. *Chest* **113**, 1042–1047 (1998).

9. Durbin, C. G. Jr. & Rostow, S. K. More reliable oximetry reduces the frequency of arterial blood gas analyses and hastens oxygen weaning after cardiac surgery: a prospective, randomized trial of the clinical impact of a new technology. *Crit. Care Med.* **30**, 1735–1740 (2002).

10. Martinez-Balzano, C. D. An educational intervention optimizes the use of arterial blood gas determinations across ICUs from different specialties: a quality-improvement study. *Chest* **151**, 579–585 (2017).

11. Rice, T. W. Comparison of the SpO_2/FIO_2 ratio and the PaO_2/FIO_2 ratio in patients with acute lung injury or ARDS. *Chest* **132**, 410–417 (2007).

12. Beitler, J. R. Effect of titrating positive end-expiratory pressure (PEEP) with an esophageal pressure-guided strategy vs an empirical high PEEP-Fio_2 strategy on death and days free from mechanical ventilation among patients with acute respiratory distress syndrome: a randomized clinical trial. *JAMA* **321**, 846–857 (2019).

13. Barrot, L. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. *N. Engl. J. Med.* **382**, 999–1008 (2020).

14. Wilson, B. J., Cowan, H. J., Lord, J. A., Zuege, D. J. & Zygun, D. A. The accuracy of pulse oximetry in emergency department patients with severe sepsis and septic shock: a retrospective cohort study. *BMC Emerg. Med.* **10**, 9 (2010).

15. Louw, A. Accuracy of pulse oximetry in the intensive care unit. *Intensive Care Med.* **27**, 1606–1613 (2001).

16. Severinghaus, J. W. & Naifeh, K. H. Accuracy of response of six pulse oximeters to profound hypoxia. *Anesthesiology* **67**, 551–558 (1987).

17. Severinghaus, J. W., Naifeh, K. H. & Koh, S. O. Errors in 14 pulse oximeters during profound hypoxia. *J. Clin. Monit.* **5**, 72–81 (1989).

18. Jubran, A. & Tobin, M. J. Reliability of pulse oximetry in titrating supplemental oxygen therapy in ventilator-dependent patients. *Chest* **97**, 1420–1425 (1990).

19. Secker, C. & Spiers, P. Accuracy of pulse oximetry in patients with low systemic vascular resistance. *Anaesthesia* **52**, 127–130 (1997).

20. Ibanez, J., Velasco, J. & Raurich, J. M. The accuracy of the Biox 3700 pulse oximeter in patients receiving vasoactive therapy. *Intensive Care Med.* **17**, 484–486 (1991).

21. Sjoding, M. W., Dickson, R. P., Iwashyna, T. J., Gay, S. E. & Valley, T. S. Racial bias in pulse oximetry measurement. *N. Engl. J. Med.* **383**, 2477–2478 (2020).

22. Price-Haywood, E. G., Burton, J., Fort, D. & Seoane, L. Hospitalization and mortality among black patients and white patients with Covid-19. *N. Engl. J. Med.* **382**, 2534–2543 (2020).

23. Network, C.-I. G. o b o t R. & the, C.-I. C. U. I. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. *Intensive Care Med.* **47**, 60–73, (2021).

24. Damiani, E. Microvascular alterations in patients with SARS-COV-2 severe pneumonia. *Ann. Intensive Care* **10**, 60 (2020).

25. Jozwiak, M. Use of venovenous extracorporeal membrane oxygenation in critically-Ill patients with COVID-19. *Front. Med. Lausanne* **7**, 614569 (2020).

26. Force, A. D. T. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* **307**, 2526–2533 (2012).

27. Louie, A. Four types of pulse oximeters accurately detect hypoxia during low perfusion and motion. *Anesthesiology* **128**, 520–530 (2018).

28. Mercat, A. *et al.* Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* **299**, 646–655 (2008).

29. Papazian, L. Formal guidelines: management of acute respiratory distress syndrome. *Ann. Intensive Care* **9**, 69 (2019).

30. Gattinoni, L. Lung recruitment in patients with the acute respiratory distress syndrome. *N. Engl. J. Med.* **354**, 1775–1786 (2006).

31. Caironi, P. Lung recruitability is better estimated according to the Berlin definition of acute respiratory distress syndrome at standard 5 cm H2O rather than higher positive end-expiratory pressure: a retrospective cohort study. *Crit. Care Med.* **43**, 781–790 (2015).

32. Young, D. Response time of pulse oximeters assessed using acute decompression. *Anesth Analg* **74**, 189–195 (1992).

33. Bland, J. M. & Altman, D. G. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* **1**, 307–310 (1986).

34. Shrout, P. E. & Fleiss, J. L. Intraclass correlations: uses in assessing rater reliability. *Psychol. Bull.* **86**, 420–428 (1979).

35. Critchley, L. A., Lee, A. & Ho, A. M. A critical review of the ability of continuous cardiac output monitors to measure trends in cardiac output. *Anesth. Analg.* **111**, 1180–1192 (2010).

36. Montenij, L. J., Buhre, W. F., Jansen, J. R., Kruitwagen, C. L. & Waal, E. E. Methodology of method comparison studies evaluating the validity of cardiac output monitors: a stepwise approach and checklist. *Br. J. Anaesth.* **116**, 750–758 (2016).

37. Chmura Kraemer, H., Periyakoil, V. S. & Noda, A. Kappa coefficients in medical research. *Stat. Med.* **21**, 2109–2129 (2002).

38. Thijssen, M., Janssen, L., Noble, J. & Foudraine, N. Facing SpO_2 and SaO_2 discrepancies in ICU patients: is the perfusion index helpful?. *J. Clin. Monit. Comput.* **34**, 693–698 (2020).

39. Vicenzi, M. N., Gombotz, H., Krenn, H., Dorn, C. & Rehak, P. Transesophageal versus surface pulse oximetry in intensive care unit patients. *Crit. Care Med.* **28**, 2268–2270 (2000).

40. Perkins, G. D., McAuley, D. F., Giles, S., Routledge, H. & Gao, F. Do changes in pulse oximeter oxygen saturation predict equivalent changes in arterial oxygen saturation?. *Crit. Care* **7**, R67 (2003).

41. Seguin, P. Evidence for the need of bedside accuracy of pulse oximetry in an intensive care unit. *Crit. Care Med.* **28**, 703–706 (2000).

42. Nickerson, B. G., Sarkisian, C. & Tremper, K. Bias and precision of pulse oximeters and arterial oximeters. *Chest* **93**, 515–517 (1988).

43. Singh, A. K., Sahi, M. S., Mahawar, B. & Rajpurohit, S. Comparative evaluation of accuracy of pulse oximeters and factors affecting their performance in a tertiary intensive care unit. *J. Clin. Diagn. Res.* **11**, 05–08 (2017).

44. Shenoy, N., Luchtel, R. & Gulani, P. Considerations for target oxygen saturation in COVID-19 patients: are we under-shooting?. *BMC Med.* **18**, 260 (2020).

45. Luks, A. M. & Swenson, E. R. Pulse oximetry for monitoring patients with COVID-19 at home. Potential pitfalls and practical guidance. *Ann. Am. Thorac. Soc.* **17**, 1040–1046 (2020).

46. Varga, Z. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* **395**, 1417–1418 (2020).

47. Watcha, M. F., Connor, M. T. & Hing, A. V. Pulse oximetry in methemoglobinemia. *Am. J. Child* **143**, 845–847 (1989).

48. Bozeman, W. P., Myers, R. A. & Barish, R. A. Confirmation of the pulse oximetry gap in carbon monoxide poisoning. *Ann. Emerg. Med.* **30**, 608–611 (1997).

49. Kerget, B. *et al.* Is endogenous carboxyhaemoglobin level a useful biomarker of clinical course and prognosis in COVID-19 patients?. *Int. J. Clin. Pract.* https://doi.org/10.1111/ijcp.14680 (2021).

50. Squara, P. Metrology part 1: definition of quality criteria. *J. Clin. Monit. Comput.* **35**, 17–25 (2021).

51. Asadian, S., Khatony, A., Moradi, G., Abdi, A. & Rezaei, M. Accuracy and precision of four common peripheral temperature measurement methods in intensive care patients. *Med. Devices Auckl.* **9**, 301–308 (2016).

Author contributions

M.J. and J.D.C. conceived and designed the study. L.S.N., M.H., L.R., E.N., P.J., S.B., Z.A.H., P.D. and M.J. recruited patients and collected data. L.S.N., M.H., L.R., E.N., P.J., S.B., Z.A.H., P.D., J.C., F.P., A.C., J.P.M., J.D.C.

and M.J. analyzed and interpreted the data. L.S.N., M.H. and M.J. drafted the report. All authors contributed to the final version. All authors approved the final version.

Competing interests

The authors declare no competing interests.

Additional information

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