

Prediction of PaO₂ from SpO₂ values in critically ill invasively ventilated patients: rationale and protocol for a patient-level analysis of ERICC, LUNG SAFE, PRoVENT and PRoVENT-iMiC (PRoPERLy II)

Simon Corrado Serafini¹, David M. P. van Meenen², Luigi Pisani³, Ary Serpa Neto⁴, Luciano César Pontes Azevedo⁵, Tai Pham⁶, Eya Sahraoui⁷, Giacomo Bellani⁸, John G. Laffey⁹, Marcus J. Schultz¹⁰, Guido Mazzinari¹¹, for the ERICC, LUNG SAFE, PRoVENT and PRoVENT-iMiC investigators

¹ Department of Surgical Sciences and Integrated Diagnostics, University of Genoa - Genova, Italy.

² Department of Anesthesiology, Amsterdam UMC, location 'AMC' - Amsterdam, The Netherlands.

³ Department of Precision-Regenerative Medicine and Ionic Area, Section of Anesthesiology and Intensive Care Medicine, University of Bari "Aldo Moro" - Bari, Italy.

⁴ Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University - Melbourne, Australia.

⁵ Department of Critical Care Medicine, Hospital Israelita Albert Einstein - São Paulo (SP), Brazil.

⁶ Service de Médecine Intensive-Réanimation, Université Paris-Saclay, AP-HP, Hôpital de Bicêtre, DMU CORREVE, FHU SEPSIS, Groupe de Recherche Clinique CARMAS - Le Kremlin - Bicêtre, France.

⁷ Equipe d'Epidémiologie Respiratoire Intégrative, Centre de Recherche en Epidémiologie et Santé des Populations, Université Paris-Saclay, UVSQ, Univ. Paris-Sud, Inserm U1018 - Villejuif, France.

⁸ Centre for Medical Sciences, University of Trento - Trento, Italy.

⁹ Department of Anaesthesia and Intensive Care Medicine, School of Medicine, University of Galway - Galway, Ireland.

¹⁰ Department of Intensive Care, Amsterdam UMC, location 'AMC' - Amsterdam, The Netherlands.

¹¹ Department of Anesthesiology, Hospital Universitario la Fe - Valencia, Spain.

ABSTRACT

Introduction: In patients with acute respiratory distress syndrome (ARDS), mortality risk is typically assessed using the arterial partial pressure of oxygen (PaO₂) divided by the fraction of inspired oxygen (FiO₂), known as the PaO₂/FiO₂ ratio. Recently, the SpO₂/FiO₂ ratio, which uses peripheral oxygen saturation (SpO₂) instead of PaO₂, has been suggested as a reasonable alternative when there is little access to arterial blood gas analyses. Additionally, equations that predict PaO₂ from SpO₂ values could offer another viable method for assessment.

Aim: To evaluate the accuracy of methods for predicting PaO₂ from SpO₂ values and compare risk stratification based on measured versus predicted PaO₂/FiO₂ ratios using a large database that harmonizes the individual data of patients included in four observational studies.

Methods and analysis: The individual data from four observational studies ('Epidemiology of Respiratory

Insufficiency in Critical Care study' [ERICA], 'Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure' [LUNG SAFE], 'Practice of VENTilation in critically ill patients without ARDS' [PRoVENT], and 'Practice of VENTilation in critically ill patients in Middle-income Countries' [PRoVENT-iMiC]) were harmonized and pooled into a database named 'PRoPERLy II'. The primary endpoint of this planned analysis will be the accuracy of currently available methods to predict PaO₂ from SpO₂ values. The secondary endpoint will be the accuracy of classification based on SpO₂/FiO₂ ratio and the predicted PaO₂/FiO₂ ratio.

Dissemination: Our planned analysis addresses a clinically important research question by comparing different equations for predicting PaO₂ from SpO₂ values.

Keywords: Critical illness; Critical care; Respiratory distress syndrome; Respiratory insufficiency; Respiration, artificial; Oxygen; Oxygen saturation; Partial pressure; Risk assessment

Registry: PRoPERLy II and the initial analysis described here (NCT06589427) and the original studies (ERICA, NCT01268410; LUNG SAFE, NCT02010073; PRoVENT, NCT01868321; and PRoVENT-iMiC, NCT03188770) are all registered at clinicaltrials.gov.

INTRODUCTION

For patients with acute respiratory distress syndrome (ARDS), mortality risk is commonly stratified by the ratio of the arterial partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2), referred to as the $\text{PaO}_2/\text{FiO}_2$ ratio.⁽¹⁾ In centers where access to repeated arterial sampling is limited or unavailable, such as in resource-limited settings, alternative methods must be considered. Moreover, during pandemic outbreaks with high patient volumes, alternative approaches to repeated sampling could be necessary. This has prompted consideration of $\text{SpO}_2/\text{FiO}_2$ as an alternative to the $\text{PaO}_2/\text{FiO}_2$ ratio, where peripheral oxygen saturation (SpO_2) is a substitute for PaO_2 .⁽²⁾ However, it remains uncertain whether risk stratification based on the $\text{SpO}_2/\text{FiO}_2$ ratio performs equivalently to that based on the $\text{PaO}_2/\text{FiO}_2$ ratio.

Another approach could be to predict PaO_2 from SpO_2 values, for which several equations have been suggested.⁽³⁻⁸⁾ However, their use remains limited. Not all equations have been validated in invasively ventilated patients⁽⁷⁾ or in adult patients,⁽⁹⁾ and inaccuracies may occur, particularly at higher PaO_2 values.^(3-5,7) Newer equations for noninvasive respiratory support patients⁽⁷⁾ and critically ill pediatric patients⁽⁹⁾ have been suggested, but these equations also need validation in invasively ventilated patients and adult patients.

We have recently established a large database named PROPERLY II. This database consists of harmonized and pooled individual patient data from four prospective, observational studies named the Epidemiology of Respiratory Insufficiency in Critical Care study (ERICC),⁽¹⁰⁾ the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE),⁽¹¹⁾ the PRactice of VENTilation in critically ill patients without ARDS (PROVENT),⁽¹²⁾ and the PRactice of VENTilation in critically ill patients in Middle-income Countries (PROVENT-iMiC).⁽¹³⁾ Since these studies collected simultaneously obtained PaO_2 and SpO_2 values, along with the corresponding FiO_2 at the time of collection, this database is well suited for validating various equations for calculating PaO_2 from SpO_2 values.

Here, we outline the structure of the PROPERLY II database and present a detailed analysis plan for its initial analysis, focusing on the accuracy of several suggested methods for predicting PaO_2 . Our primary objective is

to assess the accuracy of these equations. The secondary objective is to determine whether classifications based on predicted $\text{PaO}_2/\text{FiO}_2$ ratios create comparable mortality risk groups to those based on measured $\text{PaO}_2/\text{FiO}_2$ ratios. We hypothesize that the accuracies of the various equations will differ; however, they will result in similar stratification of patients into severity groups based on $\text{PaO}_2/\text{FiO}_2$ ratios.

METHODS

Study design

PROPERLY II is a harmonized and pooled database comprising individual data of patients included in four large, prospective, observational studies focusing on ventilation management in critically ill patients, including 773 patients from Brazil in ERICC,⁽¹⁰⁾ 3,446 patients from 50 countries worldwide in LUNG SAFE,⁽¹¹⁾ 1,021 patients from 16 countries worldwide in PROVENT,⁽¹²⁾ and 1,315 patients from 10 Asian countries in PROVENT-iMiC⁽¹³⁾ (Figure 1). PROPERLY II thus contains data from a total of 6,555 invasively ventilated patients. Further information regarding the original studies can be found in the original publications. The creation of the pooled database, including the harmonization of collected data, required neither additional ethical approval nor individual patient informed consent. Each analysis of PROPERLY II will follow the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.⁽¹⁴⁾

The databases of the 4 original studies were standardized, using case report forms and data dictionaries, and thereafter merged into the pooled database. The original studies met the following inclusion criteria, as reported in table 1.

ERICC included patients aged 18 years or older who received ventilatory support for at least 24 hours during the first 48 hours of intensive care unit (ICU) admission at participating ICUs. They excluded patients who underwent tracheostomy, patients admitted for routine uncomplicated postoperative care, patients who were readmitted, and patients with terminal conditions. ERICC enrolled patients over a 2-month period.

LUNG SAFE included patients aged 16 years or older who received invasive or noninvasive ventilation. LUNG SAFE excluded patients who never received invasive ventilation, patients whose electronic case report forms were not fully complete, those who did not develop acute

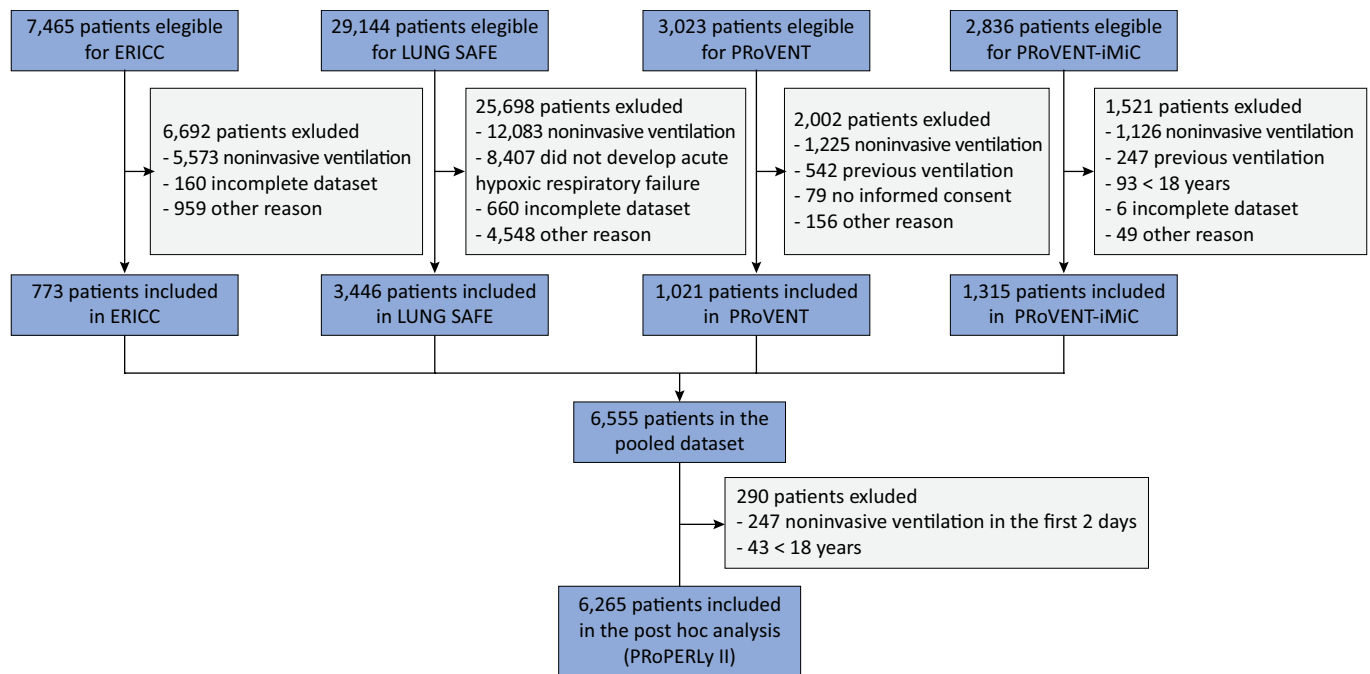


Figure 1 - Flow of patients.

ERICC - Epidemiology of Respiratory Insufficiency in Critical Care; LUNG SAFE - Large observational study to Understand the Global impact of Severe Acute respiratory Failure; PROVENT - Practice of VENTilation in critically ill patients without ARDS study; PROVENT-iMiC - Practice of VENTilation in critically ill patients in middle income countries study.

Table 1 - Summary table: inclusion and exclusion criteria across trials

| Study | Eligibility criteria | Exclusion criteria |
|--------------|---|---|
| ERICC | <ol style="list-style-type: none"> 1. Aged 18 years or older 2. Admitted to an ICU 3. Receiving invasive mechanical ventilation for a minimum of 24 hours within the initial 48 hours of admission, or NIV for at least 6 hours per day | <ul style="list-style-type: none"> — Tracheostomy patients — Patients admitted for uncomplicated postoperative care — Readmitted patients — Those with a terminal condition |
| LUNG SAFE | <ol style="list-style-type: none"> 1. Admitted to an ICU 2. Receiving invasive ventilation or NIV | <ul style="list-style-type: none"> — Patients under the age of 16 — Those who did not provide informed consent when deemed necessary |
| PROVENT | <ol style="list-style-type: none"> 1. Aged 18 years or older 2. Admitted to an ICU 3. Receiving invasive ventilation, even if initiated outside the hospital, in the emergency room, clinical ward, or operating room, or if it started in the ICU after admission | <ul style="list-style-type: none"> — Patients in whom ventilation started before the study recruitment week — Patients receiving only NIV — Those transferred from another hospital under mechanical ventilation |
| PROVENT-iMiC | <ol style="list-style-type: none"> 1. Admitted to an ICU 2. Receiving invasive ventilation, even if initiated outside the hospital, in the emergency room, clinical ward, or operating room | <ul style="list-style-type: none"> — Patients under 18 years of age — Patients receiving only NIV — Those transferred from another hospital under mechanical ventilation |

ERICC - Epidemiology of Respiratory Insufficiency in Critical Care; ICU - intensive care unit; NIV - noninvasive ventilation; LUNG SAFE - Large observational study—Understand the Global impact of Severe Acute respiratory Failure; PROVENT - Practice of VENTilation in critically ill patients without ARDS study; PROVENT-iMiC - Practice of VENTilation in critically ill patients in middle-income countries study.

hypoxic respiratory failure, and those without informed consent. LUNG SAFE enrolled patients during a 4-week period during the winter months.

PROVENT included patients aged 18 years or older who received invasive ventilation. They excluded patients in whom ventilation was started before the study recruitment

week, patients receiving only noninvasive ventilation, and patients who were transferred to the ICU from another hospital under mechanical ventilation. PROVENT enrolled patients during a predefined 1-week period.

PROVENT-iMiC included patients aged 18 years or older who started with invasive ventilation. They excluded patients who

received only noninvasive ventilation, patients whose invasive ventilation started before the inclusion phase of the study, and patients transferred from another hospital while under ventilation. PROVENT-iMiC enrolled patients during a 4-week period.

All patients included in PROPERLY II were eligible for participation in an analysis in which we determined the accuracy of various equations for the prediction of PaO₂ from SpO₂. For this specific analysis, we will apply additional exclusion criteria: patients without reported SpO₂ values and those whose SpO₂ values were recorded more than 2 hours after their corresponding PaO₂ values. Importantly, these exclusion criteria pertain only to this initial analysis and do not affect the overall dataset creation.

The dataset for PROPERLY II was constructed to include all eligible patients who received invasive mechanical ventilation, regardless of whether they had a diagnosis of ARDS. Therefore, the complete dataset encompasses both patients with ARDS and those without ARDS, allowing for a comprehensive evaluation of the relationship between SpO₂ and PaO₂ values across a diverse patient population. This approach ensures that the analysis is robust and representative of the various underlying conditions leading to acute respiratory failure.

Data collected in the original studies

In the ERICC, LUNGSAFE, PROVENT, and PROVENT-iMiC studies, the following data were collected. The baseline and demographic variables included age, sex,

actual body weight, height, body mass index (BMI), type of admission (medical, elective surgery, urgent surgery, or trauma), and comorbidities, including chronic obstructive pulmonary disease (COPD), diabetes mellitus, chronic kidney disease, neoplasia, neoplasia hematological, heart failure, and chronic liver failure.

The following disease severity score was collected: Sequential Organ Failure Assessment (SOFA). Additionally, for each patient, the main reason for invasive ventilation was reported.

For each patient, ventilation characteristics, including ventilation mode, positive end expiratory pressure (PEEP), tidal volume (V_T), respiratory rate (RR), peak pressure (P_{peak}) or plateau pressure (P_{plat}), inspired oxygen fraction (FiO₂), blood gas analysis data when available (arterial pH, partial pressure of arterial blood oxygen tension (PaO₂), and partial pressure of arterial blood carbon dioxide tension (PaCO₂)), were collected on Day 1 and Day 2, as captured in the original studies.

Harmonization and merging

The reasons for invasive ventilation were harmonized and merged into PROPERLY II, as shown in table 2. These included the predisposing condition according to the lung injury prediction score (LIPS) for several ARDS risk factors. The ventilation days were merged into 'Day 1' for the first day of ventilatory variables in patients receiving invasive mechanical ventilation in the ICU and 'Day 2' for the

Table 2 - Data collected across the studies

| Reason for intubation | | Data collection frequency |
|-----------------------|--|--|
| ERICC | <ul style="list-style-type: none"> – Pneumonia – Neurological – Nonpulmonary sepsis – Asthma/COPD – Cardiogenic pulmonary edema – Extracranial trauma – Hypovolemic/cardiogenic shock – Aspirative syndromes – Others | Data were recorded daily for the first 72 hours after ICU admission |
| LUNG SAFE | <ul style="list-style-type: none"> – Medical or surgical admission – Trauma – Neoplastic or immune or hematologic disease – Pneumonia – Pancreatitis – Heart failure | The case report forms automatically prompted investigators to provide an expanded dataset for Days 1, 2, 3, 5, 7, 10, 14, 21, and 28 or at ICU discharge or death. All data were recorded at the same time, normally as close as possible to 10 AM each day. Patient outcomes included date of liberation from mechanical ventilation and vital status at ICU discharge and at either hospital discharge or on Day 90, whichever occurred earlier. |
| PROVENT | <i>Cardiac arrest, Anesthesia for surgery (planned), Depressed consciousness, Respiratory failure</i> | <i>Investigators were prompted on the case report form to provide an expanded dataset until Day 7, at discharge from the ICU, and at 90 days after discharge, or after death in the ICU. We counted a ventilation day as any day that the patient received mechanical ventilation, irrespective of the duration of mechanical ventilation for that day and whether or not it was done through an orotracheal tube or tracheostomy.</i> |

Continue...

...continuation

| | | |
|--------------|---|--|
| PRoVENT-iMiC | <i>Cardiac arrest, Anesthesia for surgery, Hemodynamic instability, Other, Depressed level of consciousness, Acute respiratory failure (Cause of acute respiratory failure: Community acquired pneumonia, Nosocomial pneumonia, Unplanned postoperative ventilation, Cardiogenic pulmonary edema, Sepsis (other than pneumonia), COPD exacerbation, Other).</i> | Baseline and demographic variables collected on the day of admission; Extended dataset collected daily until Day 7 and at discharge from the ICU |
| PRoPERLy II | Patients with ARDS risk factor for: <ul style="list-style-type: none"> – Aspiration – Pneumonia – Contusion – Trauma – Sepsis – Burns – Pancreatitis – Drug overdose – Unknown | The observations of ventilatory parameters occur on Day 1 and the subsequent evaluations take place the day after in the ICU (labeled as Day 2) |

ERICC - Epidemiology of Respiratory Insufficiency in Critical Care; COPD - chronic obstructive pulmonary disease; ICU - intensive care unit; LUNG SAFE - Large observational study–Understand the Global impact of Severe Acute respiratory Failure; PRoVENT - Practice of VENTilation in critically ill patients without ARDS study; PRoVENT-iMiC, Practice of VENTilation in critically ill patients in middle income countries study; ARDS - acute respiratory distress syndrome.

second day. Mortality was defined as any death, for all causes, occurring in the 'ICU or in the hospital (Table 3).

When one study collected a variable differently—for example, by categorizing patients on the Glasgow Coma Scale into groups such as < 7, between 8 and 12, and > 13—the same categorization method was adopted across all studies. During the polling operation, if a variable was not found in at least two datasets and data dictionaries, that variable was excluded.

Analysis plan

We will assess the accuracy of the following four proposed equations for correctly estimating PaO₂ and stratifying patient severity based on PaO₂/FiO₂ ratio: Rice et al.,⁽⁸⁾ Pandariphande et al.,⁽⁶⁾ Severinghaus et al.,⁽¹⁵⁾ Ellis⁽³⁾ and Gadrey et al.,⁽⁷⁾ and Sauthier et al. (Table 4).⁽⁹⁾

Table 3 - Outcomes across the studies

| | Risk of ARDS or ARDS at admission | Occurrence of ARDS | Length of stay in ICU | Length of stay in hospital | All-cause mortality | Tracheostomy |
|--------------|-----------------------------------|--------------------|-----------------------|----------------------------|---------------------|--------------|
| ERICC | X | X | X | X | X | X |
| LUNG SAFE | X | X | X | X | X | X |
| PRoVENT | X | X | X | X | X | X |
| PRoVENT-iMiC | X | X | X | X | X | X |
| PRoPERLy II | X | X | X | X | X | X |

ARDS - acute respiratory distress syndrome; ICU - intensive care unit; ERICC - Epidemiology of Respiratory Insufficiency in Critical Care; LUNG SAFE - Large observational study–Understand the Global impact of Severe Acute respiratory Failure; PRoVENT - Practice of VENTilation in critically ill patients without ARDS study; PRoVENT-iMiC - Practice of VENTilation in critically ill patients in middle income countries study.

Table 4 - Summary table of equations

| | |
|---|---|
| Pandariphande et al. ⁽⁶⁾ | $\log_{10} \left(\frac{PaO_2}{FiO_2} \right) = 0.48 + 78 \times \log_{10} \left(\frac{SpO_2}{FiO_2} \right)$ |
| Gadrey et al. ⁽⁷⁾ | $PaO_2 = \left(\frac{28.6025^3}{\frac{1}{SpO_2} - 0.99} \right)^{\frac{1}{3}}$ |
| Rice et al. ⁽⁸⁾ | $\frac{PaO_2}{FiO_2} = \frac{\frac{SpO_2}{FiO_2} - 64}{0.84}$ |
| Sauthier et al. ⁽⁹⁾ | $PaO_2 = \left(\frac{27.8^{2.8}}{\frac{1}{SpO_2} - 0.99} \right)^{\frac{1}{2.8}}$ |
| Severinghaus et al., ⁽¹⁵⁾ Ellis ⁽³⁾ | $PaO_2 = \left(\frac{11700}{SpO_2 - 1} + \sqrt{50^3 + \left(\frac{11700}{SpO_2 - 1} \right)^2} \right)^{\frac{1}{3}} + \left(\frac{11700}{SpO_2 - 1} + \sqrt{50^3 + \left(\frac{11700}{SpO_2 - 1} \right)^2} \right)^{\frac{1}{3}}$ |

PaO₂ - partial pressure of oxygen in arterial blood (mmHg); FiO₂ - fraction of inspired oxygen; SpO₂ - peripheral capillary oxygen saturation; log₁₀ - logarithm to the base 10.

Calculations and definitions

V_T is expressed in mL/kg predicted body weight (PBW), where PBW is calculated as follows:

$$\text{in males, PBW} = 50 + 0.91 * (\text{height (cm)} - 152.4 \text{ (cm)}) \quad [\text{Eq. 1}]$$

$$\text{in females, PBW} = 45.5 + 0.91 * (\text{height (cm)} - 152.4 \text{ (cm)}) \quad [\text{Eq. 2}].$$

For RR, expressed in breath/min, we use the total RR as reported in the original studies.

The dynamic driving pressure (ΔP) is expressed in cm H₂O and is calculated as follows:

$$\Delta P = P_{\text{plat}} (\text{cmH}_2\text{O}) - \text{PEEP} (\text{cmH}_2\text{O}) \quad (\text{in volume-controlled ventilation}) \quad [\text{Eq. 3}]$$

$$\Delta P = P_{\text{peak}} (\text{cmH}_2\text{O}) - \text{PEEP} (\text{cmH}_2\text{O}) \quad (\text{in pressure-controlled ventilation}) \quad [\text{Eq. 4}]$$

The dynamic compliance respiratory system (C_{RS}), expressed in mL/cm H₂O, is calculated as follows:

$$C_{\text{RS}} = V_T (\text{mL}) / \Delta P (\text{cmH}_2\text{O}) \quad [\text{Eq. 5}].$$

The dynamic mechanical power (MP) is expressed in J/min and is calculated as follows:

$$\text{MP} = 0.098 * V_T * \text{RR} * (P_{\text{max}} - 0.5 * \Delta P) \quad [\text{Eq. 6}].$$

Endpoints

The primary endpoint is the accuracy of currently available methods to predict PaO₂ from SpO₂ values. The secondary endpoint is the accuracy of classification based on SpO₂/FiO₂ ratio and the predicted PaO₂/FiO₂ ratio.

Sample size

No formal sample size calculation was performed. The sample size for this initial analysis of PRoPERLy II was based on the number of available patients in the pooled database. In anticipation of a 60% dropout rate due to the application of exclusion criteria for this analysis, we expect to include at least 2,500 patients. The number of missing data points will be reported in a specific table in the supplement, and no imputation will be used.

Statistical analysis plan

We will use simultaneously obtained PaO₂ and SpO₂ values, along with the corresponding FiO₂, if the timeframe does not exceed 2 hours. We will fit each estimation method to the data to obtain a predicted PaO₂ and predicted PaO₂/FiO₂ ratios using these estimated values. All the models will be validated with 500 bootstrap repetitions to improve the robustness of the effect estimates and control for overfitting. PaO₂ will be measured via arterial blood gas (ABG) analysis. The accuracy of the predicted PaO₂ will be assessed via the root mean squared error (RMSE), mean absolute error (MAE)

and mean absolute percentage of error (MAPE) of the derived models. ARDS severity will be classified according to the Berlin criteria cutoff (ordinal score) by Somers' Dxy rank correlation. The accuracy of the predictions will be further evaluated with the Diebold–Mariano t-test. Moreover, calibration plots and intraclass correlation coefficient will be reports as recommended.⁽¹⁶⁾

Additionally, precision error, bias, and limits of agreement will be assessed with Bland–Altman analysis, where the reference method is the measured PaO₂. The threshold of acceptable bias and precision (defined as the difference between the upper and lower LoAs) was preestablished at 19 to account for the variability of ABG measurements.⁽¹⁷⁾ The precision error will be calculated as follows: $1.96 \times \text{standard deviation (SD) of the bias of the methods} \times 100\%$.⁽¹⁸⁾ The normality distribution of the differences will be checked with quantile–quantile (QQ) plots and histograms. If the normality assumption is not fulfilled, logarithmic data transformation will be performed. Proportional bias will be assessed by fitting an ordinary linear regression in Bland–Altman plots.⁽¹⁹⁾ If repeated measures are obtained from patients, confidence intervals for LoA will be adjusted as recommended.⁽²⁰⁾ Trending ability will be assessed in addition to accuracy analysis. We use the four-quadrant plot, polar plot, and clinical concordance plot methods to test the magnitude and directionality of the change.⁽²¹⁾

The amount of fixed and proportional bias will also be assessed with orthogonal (Deming) regression. Orthogonal regression is a variant of least products regression analysis and allows for both the y and the x values to be attended by random errors. It depends on minimizing the sum of the products of the deviations of both the x and y values from the estimated regression line. Orthogonal regression requires no judgment on whether the y or x variables provide 'true' or 'benchmark' values. If the scatter increases with the level of y (and x), then weighted least products (WLP) Passing–Bablok regression analysis will be used.⁽²²⁾

After obtaining the best method of predicting PaO₂ among those tested, we will plot a table of predicted PaO₂ values according to the administered FiO₂ and measured SpO₂ to provide a rapid and easy assessment method.

The accuracy of each estimation in stratifying ARDS severity as defined by the Berlin criteria⁽¹⁾ with respect to the measured PaO₂/FiO₂ ratio by Somers' Dxy rank correlation, a generalization of the receiver operating characteristic area for ordinal variables. Dxy will be calculated after correction for overfitting by cross-validation.

We will perform a sensitivity analysis of the accuracy by analyzing only values below an SpO₂ of 98%. As a secondary sensitivity analysis, we will reanalyze the data with SpO₂

values $\leq 96\%$ excluded, recalculating correlations with PaO₂ to examine the effect of removing these higher saturation levels. In addition, we will perform the following subgroup analysis to assess the effects of the following parameters on the accuracy of the different methods:

- 1) pH, i.e., < 7.35 , 7.35 to 7.45 , or > 7.45 ;
- 2) PEEP, i.e., < 10 cmH₂O and high PEEP, i.e., > 10 cmH₂O

DISCUSSION

This will be the first analysis of PRoPERLy II, a pooled database that harmonizes and merges individual patient data from critically ill patients included in four previously conducted global studies of invasive ventilation. The primary objective of this initial analysis was to assess the accuracy of the currently available methods for predicting PaO₂ from SpO₂ values. The secondary objective of this study was to assess the accuracy of the classification of ARDS severity by using predicted PaO₂/FiO₂ ratios compared with measured PaO₂/FiO₂ ratios in various patient categories.

This analysis addresses a clinically important research question by comparing different equations for predicting PaO₂ from SpO₂ values. This investigation is crucial, as accurate prediction of PaO₂ from SpO₂ can inform clinical decisions, such as oxygen therapy management and even respiratory support strategies. By evaluating various prediction equations, this study aims to identify the most reliable method for noninvasively estimating arterial oxygenation status, particularly in settings where direct arterial blood gas measurements may be limited or impractical.

The initial analysis of PRoPERLy II may confirm whether the SpO₂/FiO₂ ratios constitute a reasonable alternative in settings with little access to arterial blood gas analyses, potentially aiding inclusion in observational studies, facilitating risk stratification, and enabling timely enrollment in randomized clinical trials.

This study is based on data from the PRoPERLy II dataset, which has certain limitations. The four parent studies were conducted independently and in different years, potentially introducing variability in data collection methods, patient populations, and clinical practices. Additionally, we lacked access to variables such as shock status (i.e., use of vasopressors), skin color, and distal perfusion quality, as these variables were not collected in the original studies; this limits our ability to assess certain factors that may influence SpO₂ measurement accuracy. This specific analysis has additional limitations. Indeed, while previous findings show⁽⁷⁾ acceptable SpO₂ and PaO₂ pairing with measures taken up to 30 minutes apart, reducing the timeframe to under 30 minutes was not feasible

with the data available from the original studies. As a post hoc analysis of previously collected observational data, the findings can be interpreted only as hypothesis-generating and need to be confirmed through prospective studies to establish causality. Despite these limitations, this analysis provides valuable insights that could guide future research and clinical practice. The application of robust statistical methods, including multivariable models, ensures the reliability and validity of the results. By strictly adhering to a predefined statistical analysis plan, the study minimizes the risk of deviations from the initial research hypotheses, thereby maintaining the integrity and credibility of the analysis. The strengths of the analysis derive partially from the extensive PROPERLy II database, which enables sophisticated and comprehensive analyses, enhancing the statistical power and reliability of the findings. Additionally, the inclusion of global participation, encompassing data from various types of hospitals in both resource-rich and resource-limited settings, increases the generalizability of the results.

Notably, after this initial analysis of PROPERLy II, the database will be available for additional analysis. For this purpose, interested investigators will have to provide a detailed analysis plan, containing a testable hypothesis, clearly described endpoints and an analysis plan. After approval, investigators will be provided with a mock database that will allow them to write an analysis script in R. PROVE network investigators will then run the script on the PROPERLy II database and provide the investigators with the results. Any publication from an additional analysis must follow the rules for publication denoted by the PROVE network.⁽²³⁾

Publisher's note

Conflicts of interest: None.

Submitted on August 31, 2024
Accepted on December 23, 2024

Corresponding author:

Simon Corrado Serafini
Department of Surgical Sciences and Integrated Diagnostics
University of Genoa
Viale Benedetto XV, 6, 16132
Genoa, Italy
E-mail: simonserafini@gmail.com

Responsible editor: Alexandre Biasi Cavalcanti 

REFERENCES

1. 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.
2. Matthay MA, Arabi Y, Arroliga AC, Bernard G, Bersten AD, Brochard LJ, et al. A New Global Definition of Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med*. 2024;209(1):37-47.
3. Ellis RK. Determination of PO₂ from saturation. *J Appl Physiol*. 1989;67(2):902.
4. Brown SM, Grissom CK, Moss M, Rice TW, Schoenfeld D, Hou PC, Thompson BT, Brower RG; NIH/NHLBI PETAL Network Collaborators. Nonlinear imputation of Pao₂/Fio₂ from SpO₂/Fio₂ among patients with acute respiratory distress syndrome. *Chest*. 2016;150(2):307-13.
5. Bilan N, Dastranji A, Ghalehgholab Behbahani A. Comparison of the SpO₂/Fio₂ ratio and the pao₂/fio₂ ratio in patients with acute lung injury or acute respiratory distress syndrome. *J Cardiovasc Thorac Res*. 2015;7(1):28-31.
6. Pandharipande PP, Shintani AK, Hagerman HE, St Jacques PJ, Rice TW, Sanders NW, et al. Derivation and validation of SpO₂/Fio₂ ratio to impute for PaO₂/Fio₂ ratio in the respiratory component of the Sequential Organ Failure Assessment score. *Crit Care Med*. 2009;37(4):1317-21.
7. Gadrey SM, Lau CE, Clay R, Rhodes GT, Lake DE, Moore CC, et al. Imputation of partial pressures of arterial oxygen using oximetry and its impact on sepsis diagnosis. *Physiol Meas*. 2019;40(11):115008.
8. Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB; National Institutes of Health, National Heart, Lung, and Blood Institute ARDS Network. Comparison of the SpO₂/Fio₂ ratio and the PaO₂/Fio₂ ratio in patients with acute lung injury or ARDS. *Chest*. 2007;132(2):410-7.
9. Sauthier M, Tuli G, Juvet PA, Brownstein JS, Randolph AG. Estimated PaO₂: a continuous and noninvasive method to estimate PaO₂ and oxygenation index. *Crit Care Explor*. 2021;3(10):e0546.
10. The ERICC (Epidemiology of Respiratory Insufficiency in Critical Care) investigators, Azevedo LC, Park M, Salluh JI, Rea-Neto A, Souza-Dantas VC, et al. Clinical outcomes of patients requiring ventilatory support in Brazilian intensive care units: a multicenter, prospective, cohort study. *Crit Care*. 2013;17(2):R63.
11. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*. 2016;315(8):788-800.
12. Neto AS, Barbas CS, Simonis FD, Artigas-Raventós A, Canet J, Determann RM, Anstey J, Hedenstierna G, Hemmes SNT, Hermans G, Hiesmayr M, Hollmann MW, Jaber S, Martin-Loeches I, Mills GH, Pearce RM, Putensen C, Schmid W, Severgnini P, Smith R, Treschan TA, Tschernko EM, Melo MFV, Wrigge H, de Abreu MG, Pelosi P, Schultz MJ; PROVENT; PROVE Network investigators. Epidemiological characteristics, practice of ventilation, and clinical outcome in patients at risk of acute respiratory distress syndrome in intensive care units from 16 countries (PROVENT): an international, multicentre, prospective study. *Lancet Respir Med*. 2016;4(11):882-93.
13. Pisani L, Algera AG, Serpa Neto A, Ahsan A, Beane A, Chittawatanarat K, Faiz A, Haniffa R, Hashemian SM, Hashmi M, Imad HA, Indraratna K, Iyer S, Kayastha G, Krishna B, Ling TL, Moosa H, Nadjm B, Pattnaik R, Sampath S, Thwaites L, Tun NN, Mohd Yunus N, Grasso S, Paulus F, Gama de Abreu M, Pelosi P, Day N, White NJ, Dondorp AM, Schultz MJ; PROVENT-iMiC Investigators, MORU, and the PROVE Network. Epidemiological characteristics, ventilator management, and clinical outcome in patients receiving invasive ventilation in intensive care units from 10 Asian middle-income countries (PROVENT-iMiC): an international, multicenter, prospective study. *Am J Trop Med Hyg*. 2021;104(3):1022-33.
14. Cuschieri S. The STROBE guidelines. *Saudi J Anaesth*. 2019;13(Suppl 1):S31-4.
15. Severinghaus JW. Simple, accurate equations for human blood O₂ dissociation computations. *J Appl Physiol*. 1979;46(3):599-602.
16. Liljequist D, Elfving B, Skavberg Roaldsen K. Intraclass correlation - A discussion and demonstration of basic features. *PLoS One*. 2019;14(7):e0219854.
17. Sasse SA, Chen PA, Mahutte CK. Variability of arterial blood gas values over time in stable medical ICU patients. *Chest*. 1994;106(1):187-93.

18. Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. *J Clin Monit Comput.* 1999;15(2):85-91.
19. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet.* 1986;1(8476):307-10.
20. Carstensen B, Simpson J, Gurrin LC. Statistical models for assessing agreement in method comparison studies with replicate measurements. *Int J Biostat.* 2008;4(1):16.
21. Montenij LJ, Buhre WF, Jansen JR, Kruitwagen CL, de Waal EE. Methodology of method comparison studies evaluating the validity of cardiac output monitors: a stepwise approach and checklist. *Br J Anaesth.* 2016;116(6):750-8.
22. Ludbrook J. Comparing methods of measurements. *Clin Exp Pharmacol Physiol.* 1997;24(2):193-203.
23. Network. PROVE Network: PROtective VEntilation network. Available from: <https://www.provenetwork.org>