Annals of Intensive Care

RESEARCH

Risk stratification using SpO_2/FiO_2 and PEEP at initial ARDS diagnosis and after 24 h in patients with moderate or severe ARDS

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Abstract

Background: We assessed the potential of risk stratification of ARDS patients using SpO_2/FiO_2 and positive end-expiratory pressure (PEEP) at ARDS onset and after 24 h.

Methods: We used data from a prospective observational study in patients admitted to a mixed medical–surgical intensive care unit of a university hospital in the Netherlands. Risk stratification was by cutoffs for SpO_2/FiO_2 and PEEP. The primary outcome was in-hospital mortality. Patients with moderate or severe ARDS with a length of stay of > 24 h were included in this study. Patients were assigned to four predefined risk groups: group I ($SpO_2/FiO_2 \geq 190$ and PEEP < 10 cm H_2O), group II ($SpO_2/FiO_2 \geq 190$ and PEEP $\geq$ 10 cm), group III ($SpO_2/FiO_2 < 190$ and PEEP < 10 cm H_2O) and group IV ($SpO_2/FiO_2 < 190$ and PEEP $\geq$ 10 cm H_2O).

Results: The analysis included 456 patients. SpO_2/FiO_2 and PaO_2/FiO_2 had a strong relationship ($P < 0.001$, $R_2 = 0.676$) that could be described in a linear regression equation ($SpO_2/FiO_2 = 42.6 + 1.0 * PaO_2/FiO_2$). Risk stratification at initial ARDS diagnosis resulted in groups that had no differences in in-hospital mortality. Risk stratification at 24 h resulted in groups with increasing mortality rates. The association between group assignment at 24 h and outcome was confounded by several factors, including APACHE IV scores, arterial pH and plasma lactate levels, and vasopressor therapy.

Conclusions: In this cohort of patients with moderate or severe ARDS, SpO_2/FiO_2 and PaO_2/FiO_2 have a strong linear relationship. In contrast to risk stratification at initial ARDS diagnosis, risk stratification using SpO_2/FiO_2 and PEEP after 24 h resulted in groups with worsening outcomes. Risk stratification using SpO_2/FiO_2 and PEEP could be practical, especially in resource-limited settings.

Keywords: Acute respiratory distress syndrome (ARDS), Pulse oximetry, Blood gas analysis, Positive end-expiratory pressure (PEEP), Classification, Risk stratification, Outcome, Mortality

Introduction

In the Berlin definition for acute respiratory distress syndrome (ARDS), risk stratification was suggested by categorizing patients as having 'mild,' 'moderate' or 'severe' ARDS based on the ratio of the arterial oxygen tension (PaO_2)

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to the fraction of inspired oxygen (FiO_2) at initial diagnosis [1]. This approach knows several challenges. First, it requires invasive and expensive arterial blood sampling and analysis that is frequently not available, in particular in resource-limited settings. Second, the robustness of this way of classifying patients was not confirmed by external validation [2]. Most important, though, is that the level of positive end-expiratory pressure (PEEP) may affect the PaO_2/FiO_2 [3] and that PaO_2/FiO_2 and PEEP collected at later time points, for instance 24 h after the initial ARDS diagnosis, largely improve risk stratification [4, 5].

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Due to the sigmoidal nature of the oxyhemoglobin dissociation curve, the pulse oximetry saturation (SpO_2) may serve as a reliable alternative for the PaO_2 in patients with SpO_2 levels lower than 97% [6]. Indeed, patients with ARDS diagnosed by means of the SpO_2/FiO_2 have similar characteristics and outcomes as patients in whom ARDS is diagnosed using the PaO_2/FiO_2 [7], and persistence of a high oxygen saturation index at 24 h has been found to be associated with worse outcomes in cases of pediatric ARDS [8]. As pulse oximetry is noninvasive, inexpensive and widely available, SpO_2/FiO_2 could serve as an attractive alternative for PaO_2/FiO_2 in risk stratification of ARDS patients.

The overarching aim of the present investigation was to determine whether classification of patients using SpO_2/FiO_2 and PEEP at initial ARDS diagnosis and after 24 h could be used to stratify for risk of mortality. Specifically, we hypothesized that the SpO_2/FiO_2 could serve as an alternative for the PaO_2/FiO_2 in risk classification and that re-classification using SpO_2/FiO_2 and PEEP after 24 h improves risk stratification in a cohort of consecutive adult patients with moderate or severe ARDS in an intensive care unit (ICU) in the Netherlands.

Methods
Study design
We used data from a prospective observational conveniently sized cohort of well-defined critically ill patients admitted to the mixed surgical–medical intensive care unit of one university hospital in the Netherlands [9]. These data were matched with nurse-validated oxygenation data at baseline and after 24 h that was retrospectively collected from the patient data management system (Metavision®, iMDSoft, Tel Aviv, Israel). The Institutional Review Board of the Academic Medical Center approved the parent study protocol and use of an 'opt-out' consent method (IRB no. 10-056C).

Inclusion and exclusion criteria
A team of trained ICU researchers scored patients for the absence or presence of ARDS according to the criteria stated by the American–European Consensus Conference on ARDS [10]. Although this study started in 2011 (i.e., before publication of the Berlin definition for ARDS [1]), all patients diagnosed with ARDS fulfilled the criteria of the latest definition for ARDS. Patients with mild ARDS were excluded as were patients discharged or transferred to another ICU before 24 h after the initial ARDS diagnosis.

Outcomes
The primary outcome was all-cause in-hospital mortality. Secondary outcomes included ICU mortality,

30- and 90-day, and 1-year mortality, and the number of ventilator-free days and alive at day 28 (VFD-28), defined as the number of days from days 1 to 28 that the patient is alive and breathing without invasive assistance of the mechanical ventilator for at least 24 consecutive hours.

Data collection
At initial ARDS diagnosis and after 24 h, pulse oximetry results were retrospectively collected, and the corresponding SpO_2/FiO_2 was calculated. For this, we first collected ten successive nurse-validated SpO_2 and FiO_2 values over 10 min directly preceding, and at the time, an arterial blood sample was drawn for blood gas analysis. The median of these ten SpO_2 and FiO_2 values was used to calculate the SpO_2/FiO_2 to alleviate potential artifactual SpO_2 values. In all patients, pulse oximetry was measured by conventional two-wavelength finger pulse oximeters. The local protocol dictated a change in finger position every 3–4 h to avoid decubitus lesions and to use alternative probes, such as nose and forehead probes, only in patients in whom no adequate signal could be obtained with a conventional pulse oximeter on a finger. In addition to this, PaO_2 and $PaCO_2$ levels, pH levels and body temperature were collected, and it was determined whether or not patients received treatment with vasopressors at both time points.

Baseline data collected from the original database included demographic and ventilator data, comorbidities, admission type, patient category and cause of ARDS. The Acute Physiology and Chronic Health Evaluation (APACHE) IV score [11], the Lung Injury Prediction Score [12] and Charlson comorbidity score [13] were calculated.

Analysis plan
The correlation between SpO_2/FiO_2 and PaO_2/FiO_2 was studied only using SpO_2/FiO_2 and PaO_2/FiO_2 at initial ARDS diagnosis. SpO_2 values of > 97% were excluded from the correlation analysis as the oxyhemoglobin dissociation curve flattens above this level and large changes in the PaO_2 may result in little or no change in the SpO_2, in line with previous investigations that analyzed this relationship [6, 14, 15]. A nonlinear equation (the 'Ellis formula') was also used to estimate PaO_2/FiO_2 from SpO_2 and FiO_2 values [16, 17].

Next, we classified all patients at initial ARDS diagnosis and re-classified patients after 24 h, into four risk groups based on predefined SpO_2/FiO_2 and PEEP cutoffs. As two recent studies of risk stratification of ARDS patients used a cutoff for the PaO_2/FiO_2 of 150 mmHg [4, 5], which corresponds to a SpO_2/FiO_2 of 190 [6], we used this value as a cutoff for SpO_2/FiO_2 in the present analysis. We used the same

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cutoff for PEEP as in two previous studies [4, 5]. Accordingly, we created four groups: $SpO_2/FiO_2 \geq 190$ and PEEP < 10 cm H_2O (group I); $SpO_2/FiO_2 \geq 190$ and PEEP $\geq$ 10 cm (group II); $SpO_2/FiO_2 < 190$ and PEEP < 10 cm H_2O (group III); and $SpO_2/FiO_2 < 190$ and PEEP $\geq$ 10 cm H_2O (group IV). The comparison among groups included all pairwise comparisons across the four risk groups.

Statistical analysis

Data were expressed as mean $\pm$ standard deviation (SD), median with interquartile range (IQR) or number with percentage, where appropriate.

A two-way scatterplot and Pearson correlation analysis were used to characterize the relationship between SpO_2/FiO_2 (linear and nonlinear estimations) and PaO_2/FiO_2. Linear regression allowed quantification of the best regression line and derive a predictive equation for the relationship. Hence, based on the derived regression equation, we obtained the SpO_2/FiO_2 values that correspond to PaO_2/FiO_2 ratio values of 100, 150 and 200 mmHg. $PaCO_2$, arterial pH, body temperature, PEEP and use of vasopressors were tested as interaction terms in the model to evaluate moderation of the association between SpO_2/FiO_2 and PaO_2/FiO_2. The area under the receiver operating characteristic (ROC) curve evaluated the applicability of SpO_2/FiO_2 in discriminating moderate from severe ARDS.

Differences between risk groups were tested with the Pearson Chi-square or Fisher exact test for categorical variables and with one-way ANOVA or Kruskal–Wallis test for continuous variables. In-hospital mortality and other mortality endpoints were calculated for each of the four groups, and a *P* value for trend was calculated from a chi-squared test for trend in proportions (i.e., the Cochrane–Armitage test), testing the null hypothesis that the proportions in several groups are the same. A pairwise comparison at ARDS diagnosis and after 24 h was performed using a contrast matrix predictor approach in which odd ratios (ORs) and 95% confidence intervals are generated for each mutual comparison between groups.

Post hoc analyses

Several post hoc analyses were performed. First, we evaluated whether transforming the data to fractions (1/ PaO_2/FiO_2 and 1/SpO_2/FiO_2) improved the fit between SpO_2/FiO_2 and PaO_2/FiO_2, as previously reported [18].

Second, risk classification using the Berlin definition threshold for severe ARDS (i.e., 100 mm Hg) [6] was performed.

Third, in the last post hoc analysis we analyzed whether the association between risk stratification and in-hospital mortality was confounded by factors such as disease severity, and other readily available parameters in the database,

such as arterial pH and plasma lactate levels, blood pressure levels and vasopressor therapy. For this analysis, a multivariable logistic regression model was built to assess the confounding effect of these variables on the association between risk groups and the primary outcome.

All analyses were performed in R via the R-studio interface (R version 3.0, www.r-project.org). A *P* value below 0.05 was considered significant.

Results

Patients

Of 554 patients with ARDS, 456 were classified as having moderate or severe ARDS according to the Berlin definition and had complete datasets. Of them, 382 could be used for the correlation analyses, and all patients for the classification and re-classification analyses (Fig. 1). Pneumonia, sepsis, major surgery and trauma were the most common causes of ARDS (Table 1). At baseline, there were no differences between survivors and non-survivors with regard to oxygenation parameters, tidal volume size, the Lung Injury Prediction Score and the etiology of ARDS. Also, there were no differences with regard to the comorbidity score. Overall all-cause in-hospital mortality rate was 39.7%. Non-survivors were older, had a lower arterial pH levels at ARDS diagnosis, were ventilated at higher respiratory rates and had higher disease severity scores. Berlin definition class distribution was not different between survivors and non-survivors.

Relationship between SpO_2/FiO_2 and PaO_2/FiO_2

The correlation between SpO_2/FiO_2 and PaO_2/FiO_2 was strong ($P < 0.001$, $R^2 = 0.676$; Fig. 2) and could be described in a linear regression equation:

Fig. 1 Study flowchart. SpO_2, pulse oximetry oxygen saturation; ARDS, acute respiratory distress syndrome

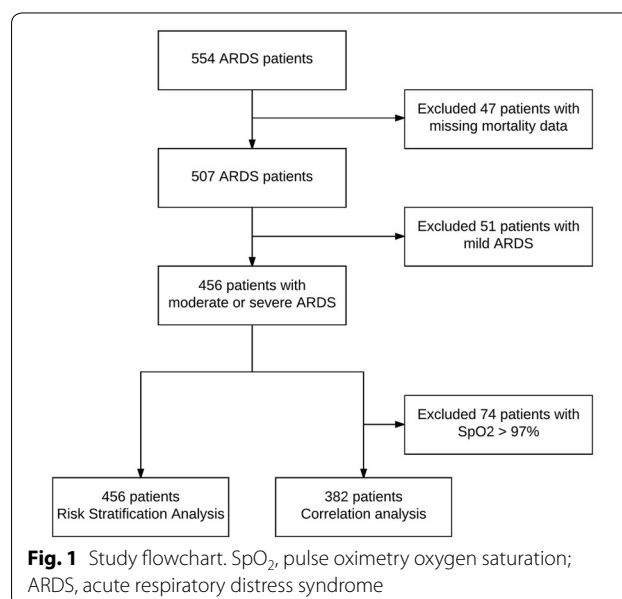Pisani *et al. Ann. Intensive Care* (2017) 7:108

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Table 1 Baseline characteristics of 456 survivors and non-survivors with moderate and severe ARDS

Variables	All patients	Survivors N = 275	Non-survivors N = 181	P value
Age, years	62 (51–72)	60 (48–70)	63 (55–72)	0.008
Female		113 (41.1)	59 (32.6)	0.075
Weight, kg	80 (70–90)	80 (70–90)	80 (68–87)	0.347
APACHE IV	68 (51–89)	72 (58–95)	90 (74–113)	< 0.001
Charlson comorbidity index 2	1 (0–3)	1 (0–2)	1 (0–3)	0.103
Lung Injury Prediction Score	8.5 (7–10)	8 (6.5–10)	9 (7–10)	0.074
Tidal volume, ml/kg	6.3 (5.3–7.6)	6.3 (5.3–7.8)	6.3 (5.4–7.3)	0.412
Respiratory rate	23 (17–29)	20 (16–27)	25 (19–30)	0.001
PEEP, cmH_2O	10 (8–12)	10 (8–12)	10 (8–13)	0.436
FiO_2, %	60 (50–75)	60 (50–70)	60 (50–80)	0.462
Arterial pH	7.34 (7.26–7.41)	7.35 (7.28–7.41)	7.31 (7.22–7.39)	0.001
PaCO2, kPa	5.8 (5.1–6.9)	5.7 (5–6.9)	6 (5.2–7.3)	0.072
PaO_2/FiO_2	120 (89–149)	123 (91–149)	115 (89–149)	0.353
SpO_2/FiO_2	160 (126–190)	163 (127–191)	157 (124–190)	0.344
Vasopressor use in first 24 h	293 (64.3)	164 (59.6)	129 (71.3)	0.015
ARDS class				
Moderate ARDS	300 (65.8)	181 (65.8)	119 (65.7)	1
Severe ARDS	156 (34.2)	94 (34.2)	62 (34.3)	1
Cause of ARDS				
Pulmonary origin	325 (71.3)	200 (72.7)	125 (69.1)	0.732
Non-pulmonary origin	185 (40.6)	104 (37.8)	81 (44.8)	0.382

Categorical variables: number (percentage); continuous variables: median (25–75 percentile)

PEEP positive end-expiratory pressure, *FiO2* fraction of inspired oxygen, *PaCO$_2$* arterial carbon dioxide tension, *PaO$_2$* arterial oxygen tension, *SpO$_2$* pulse oximetry saturation, *ARDS* acute respiratory distress syndrome, *APACHE IV* acute physiology and chronic evaluation IV
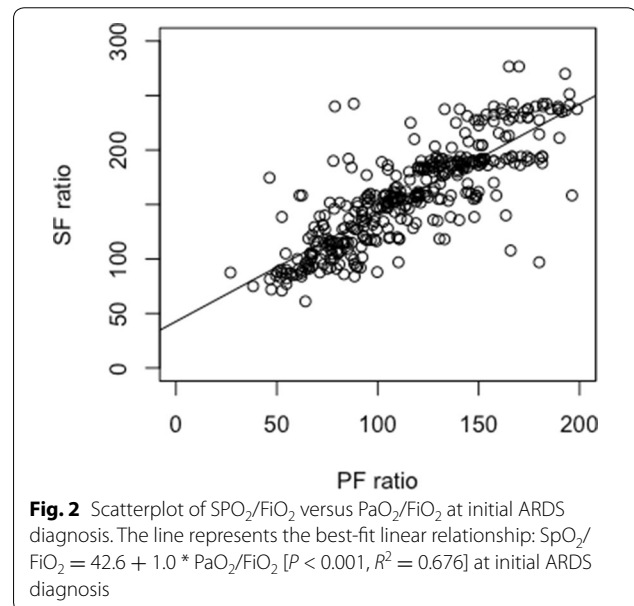
$$SpO_2/FiO_2 = 42.6 + 1.00 * PaO_2/FiO_2$$

This relationship was neither moderated by arterial $PaCO_2$ and PEEP, nor by body temperature and vasopressor therapy. There was a moderation effect by arterial pH and FiO_2, as the steepness of the slope between PaO_2/FiO_2 and SpO_2/FiO_2 was inclined by arterial pH (1.4, $P < 0.001$) and declined by FiO_2 (-0.01, $P < 0.001$).

Based on the found equation, a PaO_2/FiO_2 of 200 mm Hg corresponded to a SpO_2/FiO_2 of 243 [95% CI 220–265], a PaO_2/FiO_2 of 150 mm Hg to a SpO_2/FiO_2 of 193 [95% CI 174–211] and a PaO_2/FiO_2 of 100 mm Hg to a SpO_2/FiO_2 of 143 [95% CI 127–158].

The SpO_2/FiO_2 had an excellent ability to discriminate moderate from severe ARDS, with a ROC area under the curve of 0.928 (Fig. 3). The nonlinear formula (Ellis formula) to estimate the PaO_2/FiO_2 from the SpO_2 and FiO_2 was not superior to the linear model when $SpO_2 \leq 97\%$ ($N = 382$, $R^2 = 0.656$).

The use of fractions ($1/SpO_2/FiO_2$ and $1/PaO_2/FiO_2$) did not result in a stronger linear relationship ($R^2 = 0.629$). The regression equation, though, was very similar to one previously reported in pediatric patients ($1/SpO_2/FiO_2 = 0.0024 + 0.46/PaO_2/FiO_2$) [18].

Fig. 2 Scatterplot of SPO$_2$/FiO$_2$ versus PaO$_2$/FiO$_2$ at initial ARDS diagnosis. The line represents the best-fit linear relationship: SpO$_2$/FiO$_2$ = 42.6 + 1.0 * PaO$_2$/FiO$_2$ [P < 0.001, R^2 = 0.676] at initial ARDS diagnosis

Risk stratification

The distribution and outcome data for the four risk groups are presented in Table 2. There was no trend for

increasing in-hospital mortality rate among the four risk groups at baseline (*P* value for trend = 0.90). A pairwise comparison also showed no significant differences in hospital mortality between groups at ARDS diagnosis. In contrast, the same categorization after 24 h resulted in risk groups with increasing rates of in-hospital mortality (*P* value for trend < 0.001). A pairwise comparison showed that the differences in in-hospital mortality

Fig. 3 ROC curve for SpO_2/FiO_2 versus PaO_2/FiO_2 < 100. Dotted lines represent 95% confident intervals, AUC = 0.928. AUC, area under the curve

between group IV and group II (OR 2.40 [1.15–4.82]; *P* value = 0.012), and between group IV and group I were significant (OR 2.47 [1.26–4.85]; *P* value = 0.003) (Table 3).

Findings were comparable for the secondary outcomes. While classification using cutoffs for SpO_2/FiO_2 and PEEP at initial ARDS diagnosis were not related to any of these outcomes, risk stratification at 24 h resulted in significant positive trends across groups, and significantly worse secondary outcomes in group IV compared to group I and to group II (Additional file 1: Table E1).

Distribution of patients in each subset noticeably changed at 24 h. Less than a quarter of patients maintained to have SpO_2/FiO_2 < 190; their in-hospital mortality was much higher than that of patients with a $SpO_2/FiO_2 \geq 190$ (56.1 vs. 35.2%, *P* = 0.001). Half of the patients were ventilated at PEEP < 10 cm H_2O; their in-hospital mortality was similar to that of patients who were kept at PEEP $\geq$ 10 cm H_2O (36.1 vs. 43.4 *P* = 0.107). When considering the characteristics of the four risk groups at 24 h, we found statistical differences in the APACHE IV score, arterial pH and FiO_2 at 24 h, maximum plasma lactate levels and vasopressor use, which could explain the significant differences in outcome (Table 3).

Post hoc analyses

The post hoc analysis with the adapted SpO_2/FiO_2 cutoff of 150, in line with the Berlin definition cutoff of PaO_2/FiO_2 of 100 mm Hg, showed similar results to the primary analysis, albeit group sizes changed. No trends in risk were observed other than for ICU mortality when
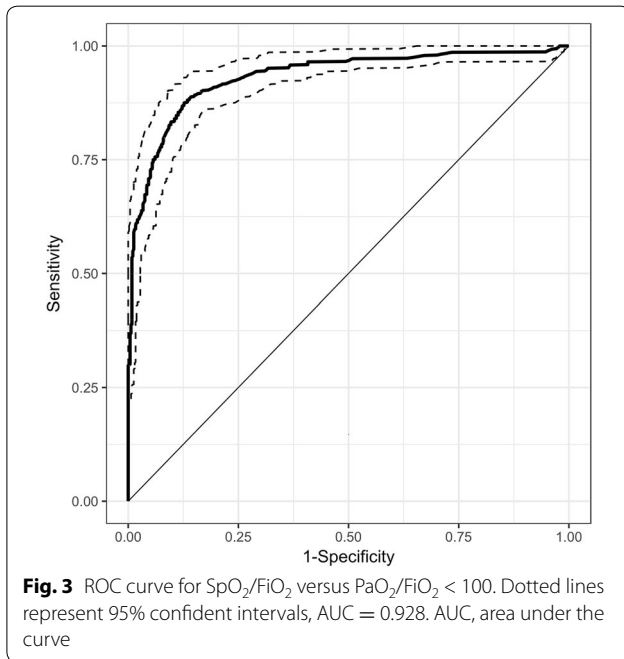
Table 2 Distribution and outcomes of each subset of patients with ARDS at initial diagnosis and after 24 h

Outcome	Group I	Group II	Group III	Group IV	*P* value
	$SpO_2/FiO_2 \geq 190$ and PEEP < 10	$SpO_2/FiO_2 \geq 190$ and PEEP $\geq$ 10	SpO_2/FiO_2 < 190 and PEEP < 10	SpO_2/FiO_2 < 190 and PEEP $\geq$ 10	
At onset of ARDS (N)	87	43	100	226	
ICU mortality (%)	19.5	23.3	18.0	30.1	0.042
In-hospital mortality (%)	44.8	30.2	36.0	41.2	0.897
30-day mortality (%)	27.6	27.9	24.0	33.2	0.276
90-day mortality (%)	47.1	34.9	41.0	42.0	0.636
1-year mortality (%)	60.9	41.9	47.0	49.6	0.182
VFD (days) (IQR)	19 (7–24)	22 (6.5–25)	20.5 (6–25)	18 (0–23)	0.070
After 24 h (N)	213	145	17	81	
ICU mortality (%)	15.5	24.1	35.3	48.2	< 0.001
In-hospital mortality (%)	34.7	35.9	52.9	56.8	< 0.001
30-day mortality (%)	23.9	26.9	47.1	45.7	< 0.001
90-day mortality (%)	38.0	38.6	52.9	56.8	0.003
1-year mortality (%)	47.4	45.5	58.8	65.4	0.006
VFD 28 (days) (IQR)	23 (15–26)	18 (0–23)	6 (0–17)	0 (0–17)	< 0.001

VFD-28 ventilator-free days and alive at day 28, *IQR* interquartile range, *CI* confidence interval

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Table 3 Intergroup comparisons at ARDS diagnosis and after 24 h for in-hospital mortality

Comparison	At ARDS diagnosis		After 24 h	
	OR (95% CI)	P value	OR (95% CI)	P value
Group II versus I	0.53 (0.19–1.46)	0.376	1.05 (0.59–1.86)	0.996
Group III versus I	0.69 (0.32–1.49)	0.600	2.11 (0.59–7.62)	0.433
Group IV versus I	0.86 (0.45–1.65)	0.933	2.47 (1.26–4.85)	0.003
Group III versus II	1.30 (0.48–3.53)	0.907	2.01 (0.55–7.43)	0.509
Group IV versus II	1.61 (0.65–4.03)	0.531	2.40 (1.15–4.82)	0.012
Group IV versus III	1.24 (0.66–2.34)	0.811	1.17 (0.30–4.53)	0.991

ARDS acute respiratory distress syndrome, *OR* odd ratio, *CI* confidence interval

using this cutoff at onset of ARDS, while a significant trend across the four risk groups was noted using this cutoff after 24 h (Additional file 1: Table E2). The intergroup comparisons also mirrored the primary analysis, with no significant contrasts at ARDS diagnosis, but clear contrast after 24 h (group IV vs. group I and II) (Additional file 1: Table E3).

The multivariable model showed that APACHE IV scores, plasma lactate levels and arterial pH significantly confounded the relationship between the group stratification and in-hospital mortality (Additional file 1: Table E4). The same applied when restricting this analysis to the extreme risk groups (i.e., groups I and IV), in which even vasopressor therapy was a significant confounder (Additional file 1: Table E5).

Discussion

To our best knowledge, this is the first study in which ARDS patients were classified using predefined cutoff values for SpO_2/FiO_2 and PEEP. The most relevant findings of this study are: (1) SpO_2/FiO_2 confirms to be a valid surrogate for PaO_2/FiO_2 in patients with moderate or severe ARDS; (2) re-classification after 24 h using predefined cutoffs for SpO_2/FiO_2 and PEEP improves risk stratification compared to the same cutoffs at baseline; and (3) the association between risk group and outcome, however, is confounded by disease severity, arterial pH and lactate levels, and vasopressor therapy. We believe that the approach of using SpO_2/FiO_2 and PEEP to classify patients could be useful for the implementation of an individualized approach for appropriate diagnosis and therapy in ARDS patients, in particular in settings where it is difficult, if not impossible, to perform (repeated) blood gas analyses (Table 4).

Our study has several strengths. The prospective design of the collection of data, the completeness of follow-up and the fact that the ARDS diagnosis was scored by a team of trained ICU researchers prevented against bias.

In addition, we could re-categorize patients from the criteria stated by the American–European Consensus Conference on ARDS [10] to the newer Berlin definition for ARDS [1], after we could select patients with moderate or severe ARDS. Finally, the number of participants was large, patients were homogeneous regarding their clinical characteristics as well as type of ARDS and the overall in-hospital mortality rate of our cohort was comparable to the pooled mortality for moderate and severe ARDS patients in the recently published LUNG SAFE study [19].

SpO_2/FiO_2 is an increasingly appreciated parameter in the diagnosis and management of patients with ARDS [6, 15, 17, 20, 21]. The current pediatric ARDS definition includes oximetry-based measures in preference of the PaO_2/FiO_2, captured in the oxygenation saturation index [22]. Unfortunately, mean airway pressures, necessary for calculation of the oxygenation saturation index, were not reliably captured in our cohort preventing us from comparing our results to those from previous studies in children [8, 18, 23]. We used a previously reported equation $(SpO_2/FiO_2 = 64 + (0.84 * PaO_2/FiO_2)$ [6] to convert a previously used cutoff for PaO_2/FiO_2 (i.e., 150 mm Hg) to a cutoff for SpO_2/FiO_2 of 190. Using the equation that came from our own data a very similar cutoff for SpO_2/FiO_2 would have been chosen. Due to its increased feasibility, the SpO_2/FiO_2 was actually considered for inclusion during the Berlin criteria definition process [24], but was successively excluded on the possibility that it may misclassify mild into severe ARDS patients. A cutoff for PaO_2/FiO_2 of 150 mm Hg has frequently been shown to accurately stratify for in-hospital mortality [4, 5, 25] and was also used in two of the largest, and ultimately positive, randomized controlled trials in ARDS patients [26, 27].

The present findings on the relationship between SpO_2/FiO_2 and PaO_2/FiO_2 mirror results from previous investigations in adult [6, 15] and pediatric patients [14, 18, 23, 28], albeit that a marginally different regression equation was found. One investigation did not find a strong relationship between SpO_2/FiO_2 and PaO_2/FiO_2, but in that study the data were collected from automated anesthesia information system with a very high portion of the data excluded due to high SpO_2 values [29]. Recently, the linear relation between SpO_2/FiO_2 and PaO_2/FiO_2 was re-challenged and both a fractional transformation [14] and a nonlinear imputation method [17, 30] were proposed to improve the model fit or better represent the sigmoidal shape of the oxyhemoglobin dissociation curve. Despite the clear physiological rationale, these approaches did not improve the relationship in the present dataset.

It has been described before that FiO_2 at levels > 70% alters the PaO_2/FiO_2: an increase in FiO_2 > 70% gradually

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Table 4 Main characteristics of 456 patients with ARDS—classification 24 h after initial ARDS diagnosis based on SpO_2/ FiO_2 cutoff of 190 and PEEP cutoff of 10 cm H_2O

Variables	Group I (*N* = 213) SpO_2/$FiO_2 \geq$ 190 and PEEP < 10	Group II (*N* = 145) SpO_2/$FiO_2 \geq$ 190 and PEEP $\geq$ 10	Group III (*N* = 17) SpO_2/$FiO_2 <$ 190 and PEEP < 10	Group IV (*N* = 81) SpO_2/$FiO_2 <$ 190 and PEEP $\geq$ 10	P value
APACHE IV score	75 (60–93)	84 (65–108)	78 (65–112)	86 (68–110)	0.001
Age, years	63 (53–73)	60 (49–69)	57 (42–70)	59 (49–69)	0.018
Female	80 (37.6)	61 (42.1)	5 (29.4)	26 (32.1)	0.436
CCI 2	1 (0–3)	1 (0–2)	2 (0–3)	1 (0–2)	0.423
LIPS	8 (6.5–9.5)	9 (7.5–10.5)	7 (6.5–8)	9.5 (7.5–11.5)	< 0.001
Tidal volume, ml/kg	6.4 (5.3–7.7)	6.2 (5.2–7.5)	7.2 (6.5–8.2)	6.4 (5.6–7.4)	0.166
FiO_2, %	40 (36–40)	40 (40–50)	60 (55–60)	60 (55–65)	< 0.001
PEEP, cm H_2O	5 (5–8)	12 (10–13)	7 (5–8)	14 (12–15)	< 0.001
Arterial pH	7.4 (7.4–7.5)	7.4 (7.3–7.4)	7.4 (7.3–7.5)	7.3 (7.3–7.4)	< 0.001
$PaCO_2$, kPa	5.3 (4.7–6.2)	5.6 (4.9–6.2)	5.6 (5–7)	5.8 (5.1–6.6)	0.018
Plasma lactate level, mmol/l	2.4 (1.4–4.1)	3.1 (1.7–6.2)	1.6 (1.4–3.9)	5.4 (2.6–10.9)	< 0.001
Respiratory rate	22 (17–27)	24 (17.2–30)	22 (18–28)	24 (16–34)	0.183
PaO_2/FiO_2	207 (175–252)	193 (167–226)	128 (120–149)	133 (105–153)	< 0.001
SpO_2/FiO_2	243 (231–265)	232 (200–245)	165 (154–170)	158 (136–176)	< 0.001
Vasopressor use in first 24 h	100 (47.0)	102 (70.3)	6 (35.3)	67 (82.72)	< 0.001
ARDS class after 24 h					
Mild ARDS	122 (57.3)	61 (42.1)	0 0	5 (6.2)	< 0.001
Moderate ARDS	91 (42.7)	84 (57.9)	15 (88.2)	59 (72.8)	< 0.001
Severe ARDS	0 0	0 0	2 (11.8)	17 (21)	< 0.001
Cause of ARDS					
Pulmonary	156 (73.2)	99 (68.3)	12 (70.6)	58 (71.6)	0.509
Non-pulmonary	67 (31.5)	78 (53.8)	5 (29.4)	40 (49.4)	0.426

Categorical variables: number (percentage); continuous variables: median (25–75 percentile)

CCI Charlson Comorbidity Index, *LIPS* Lung Injury Prediction Score, *APACHE* acute physiology and chronic health evaluation, *PEEP* positive end-expiratory pressure, *FiO_2* fraction of inspired oxygen, *$PaCO_2$* arterial carbon dioxide tension, *PaO_2* arterial oxygen tension, *SpO_2* pulse oximetry oxygen saturation, *ARDS* acute respiratory distress syndrome

increases the PaO_2/FiO_2 [31], particularly at low levels of shunt fraction [32]. The effect of FiO_2 on SpO_2/ FiO_2, however, could be opposite as pulse oximetry has an intrinsic upper limit much tighter than PaO_2. An increase in FiO_2 will gradually decrease the SpO_2/FiO_2. This intrinsic mathematical limitation of the SpO_2/FiO_2 can possibly lead to misclassification of individual ARDS cases. Of note, $FiO_2 > 70\%$ was used in 25% of patients at ARDS diagnosis, and only in 3% after 24 h.

The level of PEEP is known to be particularly relevant as the evolution and prognosis of ARDS are related to changes in PaO_2/FiO_2 in response to changes in PEEP greater than or equal to 10 cm H_2O [3, 33, 34]. While PEEP does not affect the oxyhemoglobin curve and may not significantly alter the relationship between SpO_2 and PaO_2 [15], it may impact the SpO_2/FiO_2 ratio by improving ventilation–perfusion matching and thus was considered in our analysis. Of note, the approach of using PaO_2/ FiO_2, or SpO_2/FiO_2, and PEEP is not new. Indeed, risk

classification in the Berlin definition uses PaO_2/FiO_2 and PEEP levels [1], though only at onset of ARDS and not after 24 h of standard care. The empathic aim of the present investigation was to see whether two easy to collect and almost always-available ventilator parameters, even in resource-limited settings, i.e., SpO_2/FiO_2 and PEEP, would alter risk groups.

Despite several classification and prediction systems for ARDS patients [1, 3, 25, 33, 35–37], we still lack a proper classification system for clinical management and research purposes that can serve as a practical model for setting individual therapeutic targets. Several investigations have shown that the PaO_2/FiO_2 measured at onset of ARDS cannot be used for risk stratification in patients with moderate or severe ARDS [35, 38–41]. Recently, it was shown that standardization of ventilator settings at the moment of collecting PaO_2/FiO_2 data [33] as well as re-categorization based on both PaO_2/FiO_2 and PEEP level cutoffs, measured 24 h after the initial ARDS

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diagnosis, largely improves risk stratification for hospital mortality [4, 5]. The findings of the present study are in agreement with and extend these findings showing for the first time that pulse oximetry after 24 h perform better than at the initial ARDS diagnosis in short- and long-term outcome stratification in adult patients with moderate or severe ARDS. Similar findings derive from the pediatric population, where oximetry derived indexes after 24 h reliably stratified outcome while initial values were not helpful in prognostication [8].

In the studied cohort of patients with moderate or severe ARDS, improvement or worsening of the SpO_2/FiO_2 in the first 24 h was strongly associated with outcome. Group I represents the less complicated patients with ARDS and a great portion of our patients fit in this group after 24 h (46.7 vs. 19.1% at baseline), underlining the ample clinical change that characterizes the initial hours of care. Few patients (17, 3.7%) were classified after 24 h as having a $SpO_2/FiO_2 < 190$ and $PEEP < 10$ cm H_2O (group III), in accordance with previous observations in which only few patients with a worsening oxygenation are managed with low levels of PEEP [4]. The use of a different SpO_2/FiO_2 cutoff (150, corresponding with 100 mm Hg as used in the Berlin definition for ARDS to classify severe ARDS) did not essentially change the results. This underlines the rationale of the 24 h re-classification.

The comparisons between risk groups emphasize the improvement in risk stratification after 24 h but also suggest that the proposed classification by SpO_2/FiO_2 and PEEP in four risk groups is dependent on other factors. The fact that differences between group III and the other groups did not reach significance could be explained in part by the small number of patients in this group after 24 h. Also interestingly, differences in outcomes between groups separated by PEEP were not significant (group I vs. II and group III vs. IV). This does not weaken the improvement in risk stratification after 24 h, but probably suggests that our findings are driven more by SpO_2/FiO_2 than by PEEP. Hence, although PEEP is an attractive stratification tool due to its ubiquity, alternative variables might result in a better classification when combined to the SpO_2/FiO_2 ratio.

The high mortality rates, especially in the lower risk groups, are high, but confirm those from previous investigations [4, 5]. Re-classification after 24 h lead to lower mortality rates in the lowest risk group, but still the proportion of patients that died was high. This too is in line with findings from the earlier studies [4, 5]. Noticeable differences were seen in APACHE IV, arterial pH, plasma lactate levels in the first 24 h, and vasopressor use between the risk groups, and all could, at least in part be associated with the significant differences in mortality rates. In fact, the post hoc multivariate analysis showed

that stratification based on SpO_2/FiO_2 and PEEP looses it predictive capability when controlled for APACHE IV scores, plasma lactate levels, arterial pH, blood pressure levels and vasopressor therapy. This at least suggests that persistence of hypoxemia after 24 h could be a surrogate, e.g., overall disease severity but also underlines the weakness of a simplified classification system. Nevertheless, we think that the proposed risk stratification may still be useful in settings where only pulse oximetry is available for monitoring and where laboratory examinations to compute disease severity scores are lacking.

The results of this study suggest that the SpO_2/FiO_2 can accurately surrogate the PaO_2/FiO_2 in stratifying for mortality of adult patients with established ARDS in resource-rich settings. This simple approach may in particular be useful in settings where repeated blood gas analyses are difficult to obtain or unavailable, such as in pediatric patients [23] and resource-limited settings [42]. However, it must be acknowledged that oximetry may never fully replace arterial blood gas analyses completely. Indeed, acid–base status and $PaCO_2$ levels are clinically important. However, we stress that pulse oximetry is consistently present in low-resource settings while blood gas analyzers are scarce, if not completely absent. Moreover, several point-of-care devices allow to measure capillary or venous acid–base, potentially alleviating the need for an arterial blood sample and expensive blood gas analysis devices.

The SpO_2/FiO_2 may also turn useful in identifying patients at risk for ARDS. It has already been shown to be a useful independent indicator of ARDS in the Kigali criteria for ARDS, in which SpO_2/FiO_2 and lung ultrasound were used instead of PaO_2/FiO_2 and chest radiography [42]. Further studies in resource-rich and resource-poor settings are still needed to assess the utility of these adapted criteria in patients at risk for ARDS.

Limitations of our analysis include its single-center design and the lack of standardization of the SpO_2 measurements, due to their retrospective collection. Indeed, standardization of ventilatory settings at baseline and after 24 h, and thus calculation of the PaO_2/FiO_2, may be crucial for appropriate stratification and patient selection bias minimization [43], and the same may apply for SpO_2-based markers. While we tried to minimize potential errors by increasing the number of SpO_2 values collected, we are aware that potential artifactual SpO_2 values or ones resulting from acute events unrelated to the disease process may have been included (such as patient–ventilator asynchrony, obstruction of endotracheal tubes, suctioning and hemodynamic instability). We also did not collect information on skin pigmentation, motion artifacts, skin perfusion, ambient light, methemoglobinemia and carboxyhemoglobinemia levels—factors that

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all may be associated with the accuracy of SpO_2 measurements. Its retrospective design allowed us neither to determine the type of pulse oximeter used nor to capture the positions of the probes used in individual patients. The minor but not quantifiable amount of measurements from a different probe or location other than the conventional finger oximeter represents a methodological weakness, but we do not believe affects the outcome or correlation analysis in an important way. We focused on only two time points, i.e., the time of initial ARDS diagnosis and after 24 h. It may be possible that SpO_2/FiO_2 and PEEP at other time points add to risk stratification. Finally, re-classification after 24 h means that patients who died in the first 24 h are missed. The same happens with the small proportion of patients who are extubated or transferred before 24 h. We also excluded patients with a PaO_2/FiO_2 > 200 mm Hg; however, we do not believe this weakens our results. We did this for the two following reasons. Patients classified as having mild ARDS [1] are very 'heterogeneous' with respect to outcomes. Moreover, the milder degree of oxygenation impairments in these patients increases the number of patients with SpO_2 values > 97%, above which the relationship between PaO_2 and SpO_2 becomes weak.

Conclusions
SpO_2/FiO_2 and PaO_2/FiO_2 have a strong linear relationship. In contrast to risk stratification at initial ARDS diagnosis, risk stratification using SpO_2/FiO_2 and PEEP at 24 h leads to risk groups with worsening outcomes. Despite the fact that the association between risk group assignment and outcome is confounded by several factors, risk stratification using SpO_2/FiO_2 and PEEP could be useful and practical, especially in settings where repeated blood analyses are difficult or impossible.

Additional file

Additional file 1. SF and PEEP in ARDS_Electronic Supplementary Material.

Abbreviations
SpO_2: peripheral capillary oxygen saturation; FiO_2: fraction of inspired oxygen; PaO_2: arterial oxygen partial pressure; PEEP: positive end-expiratory pressure; ARDS: acute respiratory distress syndrome; ICU: intensive care unit; VFD: ventilator-free days; APACHE: acute physiology and chronic health evaluation; LIPS: Lung Injury Prediction Score; ROC: receiver operating characteristic; AUC: area under the curve; AECC: American–European Consensus Conference on ARDS.

Authors' contributions
LP, FDS and MJS designed the study. LP, JPR, FDS, LRS and LDB performed the analyses. JPR and AG and members of the MARS consortium collected the data. LP, JPR, FDS, LDB, ASN and MJS drafted the manuscript. SMvdH, JH, ASN, EF, AMD, SG, MJS critically reviewed the manuscript. All authors read and approved the final version of this manuscript. LP, JPR, FDS and MJS had full

access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests
On behalf of all authors, the corresponding author states that there is no conflict of interest.

Availability of data and materials
Original data can be requested upon specific approval by MARS consortium and Academic Medical Center.

Consent for publication
Not applicable.

Ethics approval and consent to participate
The Institutional Review Board of the Academic Medical Center approved the protocol and opt-out consent method of the parent study (IRB No. 10-056C).

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Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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