Risk stratification of acute respiratory distress syndrome using a PaO2: Fio2 threshold of 150 mmHg: A retrospective analysis from an Indian intensive care unit

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ABSTRACT

Background: Whether a PaO2: FiO2 ratio of 150 mmHg could be used to classify patients with acute respiratory distress syndrome (ARDS) as severe or non-severe is unknown. Herein, we study whether PaO2: FiO2 <150 mmHg could be used as a risk stratification and prediction tool for mortality in patients with ARDS. Methods: Patients with ARDS (PaO2: FiO2 ratio ≤300 mmHg) were categorized as nonsevere ARDS (150≤PaO2: FiO2 ratio ≤300 mmHg) and severe ARDS (PaO2: FiO2 ratio <150 mmHg). We compared the physiological characteristics, ventilatory parameters, and mortality between the two groups. Further, we subcategorized those with severe ARDS as very severe (PaO2: FiO2 ratio ≤ 100 mmHg) or severe ARDS (100<PaO2: FiO2 ratio <150 mmHg). We also compared the performance of this cut off value with the Berlin criteria using the receiver operating characteristic curve. Results: Four hundred and sixty (256, non-severe ARDS; 204, severe ARDS) patients (mean standard deviation age, 40 (17) years, 55% males) with ARDS were included. Patients with severe ARDS had significantly lower baseline pH and higher PaCO2. Patients with severe ARDS also had higher plateau pressure, peak airway pressure, applied positive end-expiratory positive pressure. The odds ratio (95% confidence interval [CI]) of mortality in those with severe ARDS was 1.6 (95% CI, 1.1–2.4). Although the AUC for both the revised and Berlin models was low, on a multivariate logistic regression analysis, after adjusting for age, gender, sequential organ failure assessment score, driving pressure, and mechanical power, PaO2: FiO2 ratio of 150 mmHg remained an independent risk for mortality. Conclusions: The PaO2: FiO2 ratio threshold of 150 mmHg may be used to identify severe ARDS. However, used alone a PaO2: FiO2 threshold of 150 mmHg has poor sensitivity in predicting mortality. Due to the small sample, the results of our study should be confirmed in a larger multicentric study.

KEY WORDS: Acute hypoxic respiratory failure, acute lung injury, pneumonia, sepsis

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a clinical manifestation of injury to the alveolar epithelium or the endothelium of the pulmonary vasculature. It clinically presents with acute onset (within 7 days of insult) hypoxic respiratory failure along with bilateral opacities on chest radiograph. Based on the level of hypoxemia (estimated by ratio of arterial oxygen partial pressure (PaO2) to fraction of oxygen in inspired air (FiO2) [PaO2: FiO2 ratio]) assessed at a positive end expiratory pressure ≥5 cm H2O, ARDS is further categorized as mild (200 < PaO2: FiO2 ratio ≤300 mmHg), moderate (100 < PaO2: FiO2 ratio ≤200 mmHg) or severe (PaO2: FiO2 ratio ≤100 mmHg). This classification is primarily based on the difference in mortality rates across the three groups increasing from 27% in mild ARDS to as high as 45% in severe ARDS. The severity of ARDS also impacts other secondary outcomes such as ventilator-free days, intensive care unit (ICU), and hospital length of stay (LOS). However, some of the studies included in formulating the Berlin criteria were performed before the ARDSnet trial and used high tidal volumes.

Few clinical trials have considered a threshold PaO2: FiO2 ratio of 150 for classifying severe ARDS. However, few of these studies were performed using high tidal volumes. In a recent study of subjects with moderate ARDS, the authors could identify two different physiological and anatomical categories of ARDS using a threshold of 150 mmHg. The clinical outcomes such as mortality, the ICU, and the hospital LOS using this threshold remain unclear. Furthermore, many recent intervention studies (the use of prone position ventilation, neuromuscular blocking agents, and others) have used this cut off. We hypothesized that a PaO2: FiO2 ratio threshold of 150 would categorize ARDS as severe or nonsevere ARDS. Herein, we describe the clinical features and physiological characteristics, the lung mechanics, and the outcomes in patients with ARDS using a PaO2: FiO2 ratio threshold of 150 mmHg. We also compare the performance of the Berlin classification with PaO2:FiO2 ratio<150 mmHg in predicting mortality.

METHODS

The current study was a retrospective analysis of subjects with ARDS admitted to the respiratory ICU (RICU) of this Institute between January 1, 2004 and December 31, 2018. The Institute Ethics Committee approved the study protocol (INT/IEC/2018/000105) with a waiver of informed consent. The patient data were entered prospectively using specifically designed computer software, as previously described. Briefly, data were recorded at the time of RICU admission, and after that every 24 h. The worst value for each variable during the 24-h period was recorded. The time interval from RICU admission to 8:00 AM the next day was defined as day 0. Values on day 0 were used to calculate the baseline acute physiology and chronic health evaluation (APACHE II) scores. Subsequent days were calendar days timed from 8:00 AM to 8:00 AM of the next day.

All the study individuals received sedation and analgesia to facilitate mechanical ventilation. We used neuromuscular blocking agents for 48–72 h in those with patient-ventilator dyssynchrony despite adequate sedation and analgesia. They also received standard care for the management of the underlying disease along with stress ulcer and deep venous thrombosis prophylaxis. Patients were given enteral nutrition using a nasogastric tube.

All patient records were screened for study inclusion. Repeat ICU admissions were excluded from the analysis. The following information was retrieved on a data abstraction form: (a) demographic profile; (b) cause of ARDS; (c) baseline APACHE II scores and sequential organ failure assessment (SOFA) score; (d) worst values of the following physiologic and ventilator parameters recorded daily (PaO2: FiO2 ratio, positive end expiratory pressure [PEEP], plateau pressure [Pplat], driving pressure, and static compliance [Cstat]); (e) ICU and hospital LOS; and (f) the final outcome (death or discharge).

All individuals were mechanically ventilated using the volume targeted mode and low tidal volume strategy. The PEEP was set according to the ARDSnet protocol. We also calculated the ventilator power required to ventilate the individuals using the formula Power = 0.98 × respiratory rate × tidal volume × (Ppeak-[Pplat-PEEP])/2.

Definition

The diagnosis of ARDS at admission was made based on Berlin definition. Briefly, ARDS was diagnosed if all of the following were present (i) acute (<7 days) onset respiratory failure; (ii) bilateral infiltrates on chest radiograph; (iii) PaO2: FiO2 ratio ≤300 mmHg; and (iv) applied PEEP of at least 5 cm H2O. For this study, individuals were categorized as severe ARDS if they had PaO2: FiO2 ratio<150 mmHg or nonsevere ARDS, if they had 150 ≤ PaO2: FiO2 ratio≤300 mmHg.

We also stratified those with severe ARDS as very severe (PaO2: FiO2 ratio ≤100 mmHg) or severe ARDS (100 < PaO2: FiO2 ratio <150 mmHg).

We also used the Berlin criteria for the categorization of severity of ARDS as mild (200 < PaO2: FiO2 ratio ≤300 mmHg), moderate (100 < PaO2: FiO2 ratio ≤200 mmHg), or severe (PaO2: FiO2 ratio ≤100 mmHg).

Objective

The primary objective was to ascertain whether PaO2: FiO2 ratio<150 mmHg as a threshold could be used to categorize ARDS as nonsevere and severe ARDS. The secondary objective was to compare its performance with the Berlin criteria.
Primary objective: The overall mortality was 38.7% in the study cohort. The mortality was significantly higher ($P = 0.012$) in those with severe ARDS (45.1% vs. 33.6%) using the $P_{aO_2}$: $Fi_{O_2}$ ratio threshold of 150 mmHg. The OR (95% confidence interval) of mortality in those with severe ARDS was 1.6 (95% confidence interval [CI], 1.1–2.4). We did not find any significant difference between the ICU and hospital LOS between the two study groups [Table 2]. The time to mortality was shorter in those with severe ARDS [Figure 1]. Figure 2 shows the trends of oxygenation ($P_{aO_2}$,$Fi_{O_2}$ ratio) and lung mechanics (Pplat and peak airway pressure) for the hospital stay (day 0 to day 5). The $P_{aO_2}$,$Fi_{O_2}$ ratio, peak airway pressure, and Pplat were different between individuals at baseline and with-in individuals at days 1 through 5 when compared to baseline. The $P_{aO_2}$,$Fi_{O_2}$ ratio was also significantly different between subjects at baseline and day 1. The driving pressure reduced with time with-in subjects compared to baseline, however, driving pressure was significantly higher in those with severe ARDS day 4 onwards. We further stratified subjects with severe ARDS ($P_{aO_2}$,$Fi_{O_2}$ ratio $<150$) as very severe ($P_{aO_2}$,$Fi_{O_2}$ ratio $<100$ mmHg). Although there was a significant difference in the physiological (compliance, applied PEEP) and the ventilator parameters (Pplat, peak airway pressure), there was no difference in the mortality, the ICU and the hospital LOS [Supplemental Table 1].

Secondary objective: The use of $P_{aO_2}$,$Fi_{O_2}$ ratio of 150 as a threshold performed better than the Berlin criteria [Figure 3]. The area under the ROC curve (AUC) for $P_{aO_2}$,$Fi_{O_2}$ ratio of 150 mmHg for predicting the mortality was 0.56 (95% CI, 0.51–0.61). The AUC for the Berlin criteria to predict mortality was 0.43 (95% CI, 0.37–0.48). After adjusting for age, gender, driving pressure, mechanical power, and the baseline SOFA score, severe ARDS ($P_{aO_2}$,$Fi_{O_2}$ ratio $<150$ mmHg) remained an independent predictor of mortality [Table 3].

RESULTS

During the study, 460 (256, nonsevere ARDS; 204, severe ARDS) individuals were admitted to the RICU with ARDS [Table 1]. The mean (SD) age of the study population (55% males) was 40 (17) years. The common causes of ARDS were community-acquired pneumonia (44.1%), multiple organ dysfunction due to tropical illness (28.5%), and sepsis (16.1%). The baseline mean (SD) Apache II score of the study population was 20.1 (8.1), with a predicted mortality of 40% [Table 1]. The severity of illness as measured by the Apache II score was significantly worse in those with severe ARDS. The mean baseline pH and $P_{aCO_2}$ were worse in those with severe ARDS. There was a significant difference in the mean $C_{stat}$ (26.8 vs. 23.1 cm H$_2$O, nonsevere ARDS vs. severe ARDS, $P = 0.002$). There was a considerable difference between the Pplat, applied PEEP, and the peak airway pressure between the two study groups [Table 1]. Patient with severe ARDS required significantly ($P \leq 0.0001$) higher mechanical power to ventilate (27.2 $\pm$ 9.7 vs. 21.7 $\pm$ 8.2) compared to nonsevere ARDS. Lung recruitment maneuvers were not performed routinely.

Statistical analysis

The statistical analysis was performed using a commercial statistical software package (SPSS for MS-Windows, version 22.0; IBM SPSS Inc; Chicago IL, USA). Data are presented as mean (standard deviation [SD]) or number with percentages. Differences between the categorical and continuous variables were compared using the Chi-square test and the Kruskal–Wallis analysis of variance (ANOVA) tests, respectively.

We compared the baseline characteristics and outcomes (mortality, ICU, and hospital LOS) between the nonsevere ARDS and severe ARDS. Survival curves were constructed to study the effect of severity of ARDS on ICU mortality for the ICU stay using Kaplan–Meier curves. Differences between the survival curves were analyzed using the log-rank test. Trends in physiological ($P_{aO_2}$,$Fi_{O_2}$ ratio), and ventilatory parameters, (Pplat, driving pressure, and airway pressure) were analyzed using mixed model technique for repeated measures analysis of variance (autoregressive model); the within-groups factor was time (day 0 through day 5), and the between-groups factor was nonsevere ARDS and severe ARDS. We performed multivariate logistic regression analysis to identify factors predicting mortality. We used nonmodifiable variables (age, gender), the severity of illness (baseline (SOFA) score), ventilatory parameters (driving pressure and mechanical power), and severity of ARDS ($P_{aO_2}$,$Fi_{O_2}$ ratio $<150$) as variables in the multivariate analysis. In addition, we used the receiver operating characteristic (ROC) curve to determine the performance of $P_{aO_2}$,$Fi_{O_2}$ ratio threshold of 150 versus the existing Berlin criteria. A $P < 0.05$ was considered statistically significant.
The Berlin definition stratifies ARDS into three categories: mild-moderate ARDS, moderate ARDS (100 < Pa\textsubscript{O2}:Fi\textsubscript{O2} ratio <150 mmHg), and severe-moderate ARDS using Pa\textsubscript{O2}:Fi\textsubscript{O2} ratio <150 mmHg. Also, two recent studies categorized moderate ARDS (100 < Pa\textsubscript{O2}:Fi\textsubscript{O2} ratio ≤200 mmHg) as mild-moderate ARDS and severe-moderate ARDS using Pa\textsubscript{O2}:Fi\textsubscript{O2} ratio <150 mmHg. Patients with severe-moderate ARDS had more recruitable lungs, higher inhomogeneity, higher Pplat, and a higher proportion of dead space ventilation compared to mild-moderate ARDS.

The results of this study suggest that using a Pa\textsubscript{O2}:Fi\textsubscript{O2} ratio threshold of 150 mmHg, subjects with ARDS could be categorized as nonsevere and severe ARDS. Patients with severe ARDS had not only worse oxygenation and lung mechanics but also higher mortality. We did not find any difference in mortality on stratifying severe ARDS using a Pa\textsubscript{O2}:Fi\textsubscript{O2} ratio threshold of 100 mmHg.

The Berlin definition stratifies ARDS into three categories of severity using the Pa\textsubscript{O2}:Fi\textsubscript{O2} ratio.\[7,13\] This categorization was arbitrarily based on the recommendation of the expert panel using the face validity criteria and to ensure compatibility with the previous definition.\[8,11\] However, the use of Pa\textsubscript{O2}:Fi\textsubscript{O2} ratio does not correlate with pulmonary edema, predicted by computed tomography of the thorax. In a previous study, it was seen that the inflammatory edema (recruitable lung) increased significantly at a Pa\textsubscript{O2}:Fi\textsubscript{O2} ratio <150 mmHg.\[12\] Two recent studies categorized moderate ARDS (100 < Pa\textsubscript{O2}:Fi\textsubscript{O2} ratio ≤200 mmHg) as mild-moderate ARDS and severe-moderate ARDS using Pa\textsubscript{O2}:Fi\textsubscript{O2} ratio <150 mmHg.\[13\] Patients with severe-moderate ARDS had more recruitable lungs, higher inhomogeneity, higher Pplat, and a higher proportion of dead space ventilation compared to mild-moderate ARDS of moderate ARDS, similar to the current study.\[7,13\] There was also a difference in the clinical outcomes (ICU and hospital LOS, ventilator-free days but not mortality).\[13\] The physiological and the ventilatory parameters were also different in the current study. Thus, splitting ARDS to nonsevere and severe with a threshold of Pa\textsubscript{O2}:Fi\textsubscript{O2} ratio of 150 mmHg would seem logical. Unlike the previous studies,\[7,13\] we could also demonstrate a significant difference in mortality. Both the previous studies included only individual with moderate ARDS (100 < Pa\textsubscript{O2}:Fi\textsubscript{O2} ratio ≤200 mmHg) as mild-moderate ARDS.
ratio ≤200 mmHg) and not the entire gamut of ARDS; this might be the reason why they could not demonstrate a difference in mortality. In addition, the previous study had a small sample size and might not have been powered to demonstrate a difference in mortality.\[^7\]\ The other study was a secondary analysis of a randomized trial performed under controlled conditions.\[^{13}\]\ The difference in outcomes between the current and the previous studies could also be due to the different geographic locale, underlying cause of ARDS, and demographic profile.\[^{13}\]\ Furthermore, individuals in the previous studies were enrolled in clinical trials and had lower mortality (22%), which is lower than those with moderate ARDS in a real-world scenario.\[^1\]\

What are the clinical implications of current study? Our study supports the concept of stratifying ARDS into two categories using a $P_{aO_2}:F_{iO_2}$ ratio threshold of 150 mmHg.\[^{6,7,13}\]\ The suggested modification of threshold for the severity of ARDS in our study is in accordance with the criteria for modifying the existing definition of ARDS.\[^{14}\]\ In the current study, we did not find any difference in clinical outcomes (mortality, ICU, and hospital LOS) between very-severe and severe ARDS using threshold $P_{aO_2}:F_{iO_2}$ ratio of 100 mmHg, similar to previous studies.\[^{15,16}\]\ This suggests that $P_{aO_2}:F_{iO_2}$ ratio < 150 mmHg may identify a severe form of ARDS. Importantly, a $P_{aO_2}:F_{iO_2}$ ratio of 150 after 1-h of NIV could also predict worse outcomes in ARDS.\[^{17,18}\]\ Thus, using this threshold may allow the selection of a homogenous cohort, maintain uniformity for conducting future trials, and employ early aggressive management strategy (prone position ventilation, higher PEEP, and the use of neuromuscular blocker) in these individuals.\[^{11,4}\]\

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**Figure 2:** Trends of driving pressure, plateau pressure, peak airway pressure, and $P_{aO_2}:F_{iO_2}$ ratio from baseline to day 5 in subjects with acute respiratory distress syndrome. There was a significant difference between severe acute respiratory distress syndrome (white circles) and nonsevere acute respiratory distress syndrome (black circles) at baseline. Circles = mean values; error bar = standard deviation. *significantly different within subjects; #significantly different between subjects (mixed model technique of repeated measure analysis)
Finally, our study has several limitations. It is limited by its retrospective nature, small sample, and single-center experience. Although both PaO2: FiO2 ratio of 150 as a threshold and Berlin criteria had a small AUC, PaO2: FiO2 ratio of 150 performed better than the Berlin criteria using the ROC curve analysis. This is because apart from oxygenation other components such as underlying etiology, the extent of disease on radiology, presence of co-morbid illness, and others would also affect the outcomes in ARDS. The study was conducted at a tertiary care center; thus, there could be a patient selection bias. We did not study the anatomical characteristics using the CT thorax. The bulk of ARDS in our study was caused by pneumonia, sepsis, and tropical illness-related multi-organ dysfunction. Thus, these results may not apply to other causes of ARDS. The management of ARDS has changed over the past few years (use of prone ventilation), and this might have affected the results. In addition, we did not use a standardized ventilator setting to determine PaO2: FiO2 ratio. However, 70% of our study population in both the non-severe and severe ARDS had a FiO2 and PEEP of 0.5 and 5 cm H2O at RICU admission. Future trials could use a FiO2 of 0.5 and PEEP of 5–10 cm H2O to determine this ratio as proposed previously [15,19]. We used the PaO2: FiO2 ratio at the time of admission to the RICU. It is possible that the time to onset of ARDS might be variable in the study population. For example, some patients might have been admitted to RICU within 6–12 h, while others might have been admitted after more than 24 h. However, this could also reflect a real-world scenario. Finally, the mortality in very severe ARDS (PaO2: FiO2 ratio < 100 mmHg) was higher (48%) compared to those with severe ARDS (43%); lack of statistical significance is probably due to small sample size. The strength of the study is the inclusion of all subjects with ARDS rather than only those with moderate ARDS.

CONCLUSION

Stratifying ARDS using a PaO2: FiO2 threshold of 150 mmHg identifies two different categories of ARDS with a different physiological profile and clinical outcomes. However, used alone a PaO2: FiO2 threshold of 150 mmHg has poor sensitivity in predicting mortality. Due to the small sample, the results of our study should be confirmed in a larger multicenter study.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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Supplemental Table 1: Comparison of clinical, physiological, ventilator and outcome parameters using a Pa$_{O2}$:Fi$_{O2}$ ratio threshold of 100

| Parameter                        | Severe ARDS (n=115) | Very-severe ARDS (n=89) | P  |
|---------------------------------|---------------------|-------------------------|----|
| Age, in years                   | 38.9±15.6           | 39.1±16.5               | 0.921 |
| Male gender, n (%)              | 60 (52.2)           | 51 (57.3)               | 0.482 |
| Baseline APACHE II score        | 20.5±8.7            | 23.1±8.7                | 0.038 |
| Ventilator and physiological parameters |                     |                         |    |
| Static compliance, mL/cm H$_2$O | 23.1±9.7            | 23.1±9.6                | 0.998 |
| pH                              | 7.34±0.12           | 7.27±0.14               | <0.0001 |
| Pa$_{CO2}$, mmHg                | 42.3±15.9           | 48.2±17.7               | <0.013 |
| Pa$_{O2}$:Fi$_{O2}$ ratio, mmHg | 123.6±13.4          | 72.7±19                 | <0.0001 |
| Plateau pressure, cm H$_2$O     | 25.3±5.9            | 27.8±5.2                | <0.002 |
| PEEP, cm H$_2$O                 | 8.5±2.9             | 11.5±4.7                | <0.0001 |
| Peak airway pressure, cm H$_2$O | 29.1±7.9            | 33.1±6.5                | <0.0001 |
| Mechanical power, Joules/min    | 25.8±9.8            | 28.6±9.4                | 0.088 |
| Outcome                         |                     |                         |    |
| ICU LOS, days                   | 10±9.4              | 10.8±10.5               | 0.572 |
| Hospital LOS, days              | 16±14.2             | 13.9±13                 | 0.286 |
| Death                           | 49 (42.6)           | 43 (48.3)               | 0.479 |

All values are described as mean±SD or n (%). APACHE II score: Acute physiology and chronic health evaluation score; ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit; LOS: Length of stay; Pa$_{CO2}$: Partial pressure of carbon dioxide in arterial blood; Pa$_{O2}$:Fi$_{O2}$ ratio: Ratio of partial pressure of oxygen in arterial blood and fraction of oxygen in inspired air; PEEP: Positive end expiratory pressure, SD: Standard deviation