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# A universal definition of ARDS: the $PaO_2/FiO_2$ ratio under a standard ventilatory setting—a prospective, multicenter validation study

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**Abstract** *Purpose:* The $PaO_2/FiO_2$ is an integral part of the assessment of patients with acute respiratory distress syndrome (ARDS). The American-European Consensus Conference definition does not mandate any standardization procedure. We hypothesized that the use of $PaO_2/FiO_2$ calculated under a standard ventilatory setting within 24 h of ARDS diagnosis allows a more clinically relevant ARDS classification. *Methods:* We studied 452 ARDS patients enrolled prospectively in two independent, multicenter cohorts treated with protective mechanical ventilation. At the time of ARDS diagnosis, patients had a $PaO_2/FiO_2 \leq 200$. In the derivation cohort ($n = 170$), we measured $PaO_2/FiO_2$ with two levels of positive end-expiratory pressure (PEEP) ($\geq$5 and $\geq$10 $cmH_2O$) and two levels of $FiO_2$ ($\geq$0.5 and 1.0) at ARDS onset and 24 h later. Dependent upon $PaO_2$ response, patients were reclassified into three groups: mild ($PaO_2/FiO_2 > 200$), moderate ($PaO_2/FiO_2$ 101–200), and severe ($PaO_2/FiO_2 \leq 100$) ARDS. The primary outcome measure was ICU mortality. The standard ventilatory setting that reached the highest significance difference in mortality among these categories was tested in a separate cohort ($n = 282$). *Results:* The only standard ventilatory setting that identified the three $PaO_2/FiO_2$ risk categories in the derivation cohort was PEEP $\geq$ 10 $cmH_2O$ and $FiO_2 \geq 0.5$ at 24 h after ARDS onset ($p = 0.0001$). Using this ventilatory setting, patients in the validation

cohort were reclassified as having mild ARDS ($n = 47$, mortality 17 %), moderate ARDS ($n = 149$, mortality 40.9 %), and severe ARDS ($n = 86$, mortality 58.1 %) ($p = 0.00001$). *Conclusions:* Our method for assessing $PaO_2/FiO_2$ greatly improved risk stratification of ARDS and could be used for enrolling appropriate ARDS patients into therapeutic clinical trials.

**Keywords** Acute respiratory distress syndrome · Protective mechanical ventilation · Standard ventilatory settings · Lung injury severity · Phenotype classification · Definition · Prognosis

## Introduction

In 1967, Ashbaugh et al. [1] published the first clinical description of a syndrome they termed the acute respiratory distress syndrome (ARDS). Since that time, the hallmark of this syndrome has included: (1) a risk factor for the development of ARDS (i.e. sepsis, trauma, pneumonia, and aspiration), (2) severe hypoxemia with high $FiO_2$, (3) bilateral pulmonary infiltrates, and (4) no clinical evidence of cardiogenic pulmonary edema [2, 3].

Although there is a general agreement on the overall criteria on which to base a definition of ARDS, the specific values and conditions of measurement of the oxygenation defect vary greatly among clinicians and scientists. Thus, the original description of ARDS was incapable of identifying a uniform group of patients [4]. A more precise definition is necessary since the effects on outcome of certain ventilatory and adjunctive techniques could vary depending on the degree of lung injury at the time of enrollment into clinical trials [5, 6]. In 1994, an American-European Consensus Conference (AECC) [7] formalized the criteria for the clinical diagnosis of ARDS, although this definition has been challenged over the years [4, 8].

We designed this prospective, multicenter study to determine whether a standard ventilatory setting [specific level of positive end-expiratory pressure (PEEP) and $FiO_2$] applied within the first 24 h after patients first met AECC ARDS criteria would identify patients with mild, moderate, or severe degrees of lung injury. We hypothesized that the value of the $PaO_2/FiO_2$ calculated under a defined standard ventilatory setting within 24 h of ARDS onset will allow a better phenotypic classification and risk stratification of patients with ARDS during protective mechanical ventilation (MV), independent of the underlying disease or specific therapy applied.

## Methods

This study was approved by the Ethics Committees for Clinical Research at the coordinating center (Hospital Universitario Dr. Negrín, Las Palmas de Gran Canaria, Spain, CEIC-2008/1029) and the Hospital Virgen de La Luz, Cuenca, Spain (CEIC-2008/0715) [see electronic supplementary material (ESM) for details].

### Study populations

We analyzed data from 452 adult patients included prospectively in two independent, multicenter, longitudinal cohorts who met all AECC criteria for ARDS [7] (see ESM for details). All patients were mechanically ventilated with a lung protective MV strategy. The derivation cohort comprised 170 ARDS patients admitted in a network of 15 Spanish intensive care units (ICUs) from May 2004 to October 2005. Although these patients were assessed previously for identifying patients with persistent ARDS and those results were published elsewhere [8], none of the outcome data reported in the present study have been published. For the purpose of this study, we performed a secondary analysis of our prior database from these 170 patients using three different $PaO_2/FiO_2$ thresholds (>200, 101–200, and ≤100 mmHg).

We prospectively evaluated these $PaO_2/FiO_2$ thresholds in an independent cohort for predictive validity. The validation cohort consisted of 282 consecutive patients who met the AECC definition and were admitted from September 2008 to December 2009 in a network of ICUs from 17 Spanish hospitals (see "Appendix"). Some patients from this cohort were used for reporting the 1-year ARDS incidence in Spain [9]. However, none of the outcome data reported in the present study has been published elsewhere.

### Patient classification

At the time of ARDS onset (baseline), we examined whether there were significant differences in the overall ICU mortality between patients with a $PaO_2/FiO_2 \leq 100$ mmHg and a $PaO_2/FiO_2 > 100$ mmHg, regardless of applied PEEP and $FiO_2$. Our goal was to determine a $PaO_2/FiO_2$ classification/prognosis system based on a usual care setting.

Then, we examined in the derivation cohort to see whether standard ventilatory settings applied on the day patients met ARDS AECC criteria or 24 h later identified groups of patients with different lung injury severity (as assessed by changes in $PaO_2/FiO_2$) and ICU outcome. Patients were examined under the following standard ventilatory settings: volume assist/control mode, tidal volume ($V_T$) 7 ml/kg PBW, inspiratory:expiratory time

ratio (I:E) < 1:1, ventilator rate to maintain $PaCO_2$ of 35–50 mmHg plus the following $FiO_2$ and PEEP settings applied in the following order: (1) $FiO_2 \geq 0.5$ with PEEP $\geq$ 5 $cmH_2O$, (2) $FiO_2 \geq 0.5$ with PEEP $\geq$ 10 $cmH_2O$, (3) $FiO_2 = 1.0$ with PEEP $\geq$ 5 $cmH_2O$, and (4) $FiO_2 = 1.0$ with PEEP $\geq$ 10 $cmH_2O$. Thus, a total of eight PEEP-$FiO_2$ settings were evaluated: four at the onset of ARDS and the same four 24 h later. The precise rules for adjusting $FiO_2$ and PEEP during the standard ventilator settings have been reported elsewhere [8] (see ESM).

Patients who had a $PaO_2/FiO_2 > 200$ mmHg were reclassified as having "mild" ARDS, a $PaO_2/FiO_2$ between 101 and 200 mmHg as "moderate" ARDS, and a $PaO_2/FiO_2 \leq 100$ mmHg as "severe" ARDS. The standard ventilatory setting that reached the highest statistical differences in ICU mortality among the three $PaO_2/FiO_2$ categories in the derivation cohort was chosen as the only setting for prospective evaluation in the validation cohort.

### Data collection and analysis

We recorded demographic, gas-exchange, MV, and hemodynamic data at the time of ARDS onset, on days 0, 1, 3, and 7, and the last day of MV (see ESM for details). Data are expressed as percentages, mean ± standard deviation (SD), or medians and interquartile ranges (IQR). Differences between ICU mortality rates among groups for different settings were analyzed by Pearson's $\chi^2$ or Fisher's exact tests. For continuous variables, the data were evaluated by analysis of variance and the Kruskal-Wallis test. We used the Mann-Whitney *U* rank test for variables with non-normal distribution. Probability of 28-day survival was analyzed for all three ARDS phenotypes in the validation cohort according to the Kaplan-Meier method, and the results were compared with the log-rank test. The 95 % confidence intervals (CI) for ICU mortality rate were computed using Jeffrey's interval for a binomial proportion. For all these comparisons, a two-sided $p$ value $< 0.05$ was considered statistically significant.

## Results

### Baseline data of patient populations

Main baseline characteristics of the 452 ARDS patients are displayed in Table 1. The overall ICU mortality was 38.9 %. The overall hospital mortality was 42 %. Mean $V_T$ and mean $PaO_2/FiO_2$ were significantly lower in the validation cohort. Sepsis, bacterial pneumonia, and multiple traumas were the most common causes of ARDS. The distribution of pulmonary and non-pulmonary causes of ARDS was similar in both cohorts.

Figure 1 represents the flow diagram of the study. All patients at study entry had a $PaO_2/FiO_2 \leq 200$ mmHg: 21.2 % of patients ($n = 36$) from the derivation cohort and 46.4 % of patients ($n = 131$) from the validation cohort had a $PaO_2/FiO_2 \leq 100$ mmHg (Fig. 2). Overall ICU mortality was significantly higher in patients with a baseline $PaO_2/FiO_2 \leq 100$ mmHg than in patients with a baseline $PaO_2/FiO_2 > 100$ mmHg (50 vs. 29.1 %, $p = 0.028$ for the derivation cohort; 51.9 vs. 33.8 %, $p = 0.002$ for the validation cohort). However, ICU mortality was non-significantly different in both cohorts for the same baseline $PaO_2/FiO_2$ category (50 vs. 51.9 %, $p = 0.853$ for patients with $PaO_2/FiO_2 \leq 100$ mmHg;

**Table 1** Main demographics, physiology, and clinical parameters at study entry of 452 patients with the acute respiratory distress syndrome (ARDS)

| Variables | Derivation cohort ($n = 170$) | Validation cohort ($n = 282$) | $p$ value |
|---|---|---|---|
| Median age (years) ($P_{25}$–$P_{75}$) | 54 (35–66) | 56 (40–73) | 0.560 |
| APACHE II score | 20 ± 8 | 21 ± 6 | 0.160 |
| Lung injury score | 2.74 ± 0.72 | 2.86 ± 0.62 | 0.072 |
| $V_T$ (ml/kg), PBW | 7.7 ± 1.6 | 7.2 ± 1.2 | <0.001 |
| Plateau pressure ($cmH_2O$) | 26 ± 6 | 26 ± 5 | 1 |
| PEEP ($cmH_2O$) | 9.0 ± 3.3 | 9.3 ± 2.5 | 0.308 |
| Respiratory rate (breaths/min) | 20 ± 6 | 21 ± 6 | 0.087 |
| $PaO_2/FiO_2$ (mmHg) | 128 ± 33 | 112 ± 39 | <0.001 |
| $PaCO_2$ (mmHg) | 43.9 ± 12.1 | 43.8 ± 10.1 | 0.928 |
| No. organ failures | 1.1 ± 1 | 1.3 ± 1.3 | 0.081 |
| Main causes of ARDS, *n* (%) | | | |
| Pulmonary | 93 (54.7) | 143 (50.7) | 0.437 |
| Nonpulmonary | 77 (45.3) | 139 (49.3) | 0.437 |
| Sepsis | 49 (28.8) | 91 (32.3) | 0.464 |
| Bacterial pneumonia | 46 (27) | 95 (33.7) | 0.144 |
| Multiple trauma | 30 (17.6) | 33 (11.7) | 0.067 |
| Aspiration pneumonia | 28 (16.5) | 29 (10.3) | 0.060 |
| Others | 17 (10) | 34 (12.0) | – |

*PBW* predicted body weight, *PEEP* positive end-expiratory pressure, $V_T$ tidal volume

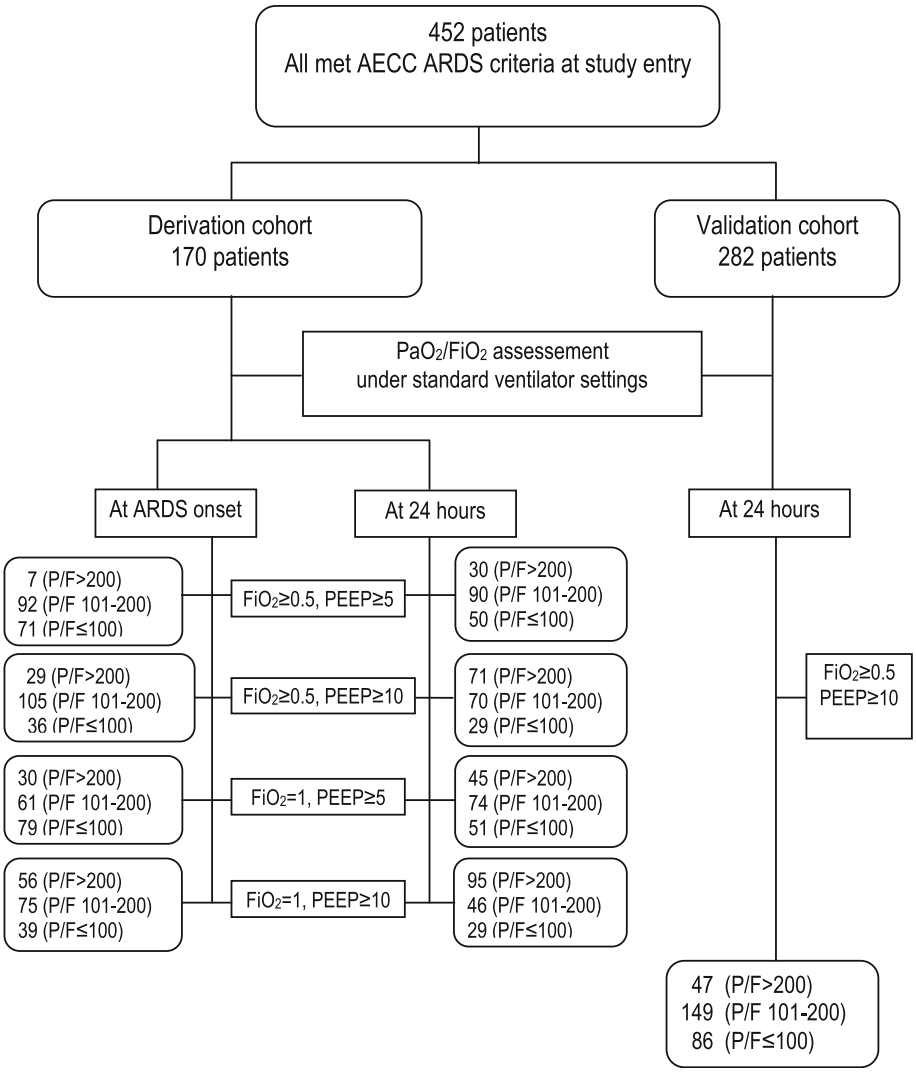


**Fig. 1** Flow diagram of the study. *AECC* American-European Consensus Conference, *ARDS* acute respiratory distress syndrome, *PEEP* positive end-expiratory pressure, *P/F* $PaO_2/FiO_2$ ratio

29.1 vs. 33.8 %, $p = 0.444$ for patients with $PaO_2/FiO_2 > 100$ mmHg) (Fig. 2).

## Phenotype ARDS classification based on standard ventilatory settings

### *Derivation cohort*

The responses to the four standard ventilatory settings at ARDS onset and at 24 h in the 170 patients from the derivation cohort are displayed in Table 2 (see ESM for details). We found that many patients did not continue to meet the AECC ARDS definition ($PaO_2/FiO_2$ increased to >200 mmHg in 56 cases after ARDS onset and 95 cases at 24 h). At ARDS onset, none of the four ventilatory settings were capable of separating patients into subgroups with significantly different ICU mortalities.

At 24 h after ARDS onset, the only ventilatory setting that significantly correlated the ranges of $PaO_2/FiO_2$ ratios with ICU mortality was $FiO_2 \geq 0.5$ with PEEP $\geq$ 10 $cmH_2O$. More than half of the patients (66.7 %, $n = 24$) with a baseline $PaO_2/FiO_2 \leq 100$ mmHg progressed to a $PaO_2/FiO_2 > 100$ at 24 h under this standard ventilator setting, while only 12.7 % of patients ($n = 17$) with a $PaO_2/FiO_2 > 100$ progressed to a $PaO_2/FiO_2 \leq 100$. Under this ventilator setting, and regardless of the $PaO_2/FiO_2$ at ARDS onset, 71 patients (41.8 %) were classified as having mild ARDS ($PaO_2/FiO_2 > 200$ mmHg, ICU mortality 16.9 %), 70 patients (41.2 %) were classified as having moderate ARDS ($PaO_2/FiO_2$ 101–200 mmHg, ICU mortality 41.4 %), and 29 patients (17 %) were classified as having severe ARDS ($PaO_2/FiO_2 \leq 100$ mmHg, ICU mortality 55.2 %) ($p < 0.0001$) (Table 2). This was the standard ventilator setting tested in the validation cohort.

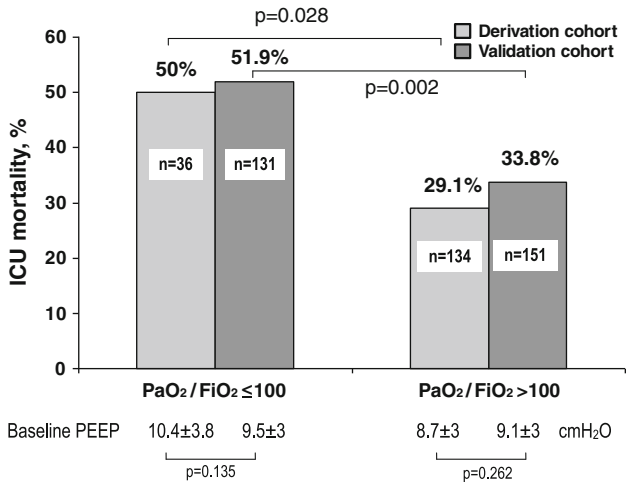


**Fig. 2** Classification of 452 patients from two cohorts of patients with the acute respiratory distress syndrome (ARDS) according to the baseline value of the $PaO_2/FiO_2$ ratio measured at the time of meeting American-European Consensus Conference criteria for ARDS. Mean baseline PEEP levels for each subgroup at the time at ARDS onset are displayed *below each bar*

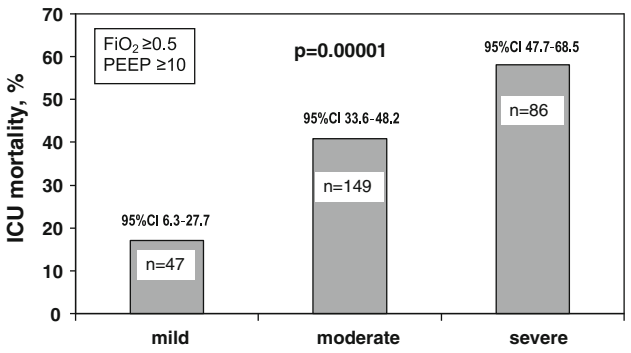


**Fig. 3** Classification of 282 patients from the validation cohort into severe, moderate, and mild acute respiratory distress syndrome (ARDS) at 24 h after ARDS onset, based on the only standard ventilatory setting that best categorized patients in the derivation cohort (PEEP $\geq$ 10 $cmH_2O$ on $FiO_2 \geq 0.5$). *P* value refers to statistical differences in mortality rates among the three new categories of ARDS. *CI* confidence interval

*Validation cohort*

Using the $FiO_2 \geq 0.5$ with PEEP $\geq$ 10 $cmH_2O$ ventilatory setting at 24 h after ARDS onset in the 282 patients from the validation cohort, 16.7 % of patients ($n = 47$) were reclassified as having mild ARDS [ICU mortality 17 % (95 %CI 6.3–27.7 %)], 52.8 % of patients ($n = 149$) were reclassified as having moderate ARDS [ICU mortality 40.9 % (95 %CI 33.6–48.2 %)], and less than a third of patients (30.5 %, $n = 86$) were reclassified as having severe ARDS [ICU mortality 58.1 % (95 %CI 47.7–68.5 %)] ($p = 0.00001$) (Fig. 3). More than half of patients (52.7 %, $n = 69$) with a baseline $PaO_2/FiO_2 \leq 100$ mmHg at ARDS onset progressed to a $PaO_2/FiO_2 > 100$ at 24 h, while only 15.9 % ($n = 24$) with a $PaO_2/FiO_2 > 100$ mmHg progressed to a $PaO_2/FiO_2 \leq 100$. Five patients (out of 47 patients with "mild" ARDS) had a $PaO_2/FiO_2 > 300$ mmHg at 24 h, and their ICU mortality was 0 %.

The 28-day probability of survival for patients included in the validation cohort after ARDS onset clearly separated ARDS patients into three phenotypes defined by a standard ventilatory setting at 24 h ($p < 0.0001$) (Fig. 4).

When these three ARDS phenotypes (mild, moderate, severe) were analyzed separately, we found significant differences in mean plateau pressures among the three categories (Table 3). In general, maximum $FiO_2$, maximum PEEP, maximum plateau pressure, and number of organ dysfunctions developed during the ICU stay were higher in patients with "severe" ARDS (Table 4).

**Table 2** Classification of 170 ARDS patients from the derivation cohort into three phenotypic categories based on the $PaO_2$ response to four ventilatory settings at the time of ARDS diagnosis (ARDS onset) and at 24 h

| | $PaO_2/FiO_2 > 200$ No. patients (% mortality) | $PaO_2/FiO_2$ 101–200 No. patients (% mortality) | $PaO_2/FiO_2 \leq 100$ No. patients (% mortality) | *p* value |
|---|---|---|---|---|
| At ARDS onset | | | | |
| $FiO_2 \geq 0.5$, PEEP $\geq 5$ | 7 (14.3) | 92 (33.7) | 71 (46.5) | 0.114 |
| $FiO_2 \geq 0.5$, PEEP $\geq 10$ | 29 (17.2) | 105 (38.1) | 36 (33.3) | 0.100 |
| $FiO_2 = 1$, PEEP $\geq 5$ | 30 (40.0) | 61 (29.5) | 79 (34.2) | 0.586 |
| $FiO_2 = 1$, PEEP $\geq 10$ | 56 (30.3) | 75 (34.7) | 39 (35.9) | 0.833 |
| 24 h after ARDS onset | | | | |
| $FiO_2 \geq 0.5$, PEEP $\geq 5$ | 30 (23.3) | 90 (31.1) | 50 (44.0) | 0.139 |
| $FiO_2 \geq 0.5$, PEEP $\geq 10$ | 71 (16.9) | 70 (41.4) | 29 (55.2) | 0.0001 |
| $FiO_2 = 1$, PEEP $\geq 5$ | 45 (33.3) | 74 (27.0) | 51 (43.1) | 0.174 |
| $FiO_2 = 1$, PEEP $\geq 10$ | 95 (30.5) | 46 (28.3) | 29 (51.7) | 0.081 |

*p* values refer to statistical differences in mortality rates among the three categories in each ventilatory setting

*ARDS* acute respiratory distress syndrome, *$FiO_2$* fraction of inspiratory oxygen concentration, *$PaO_2$* partial pressure of oxygen in arterial blood, *PEEP* positive end-expiratory pressure

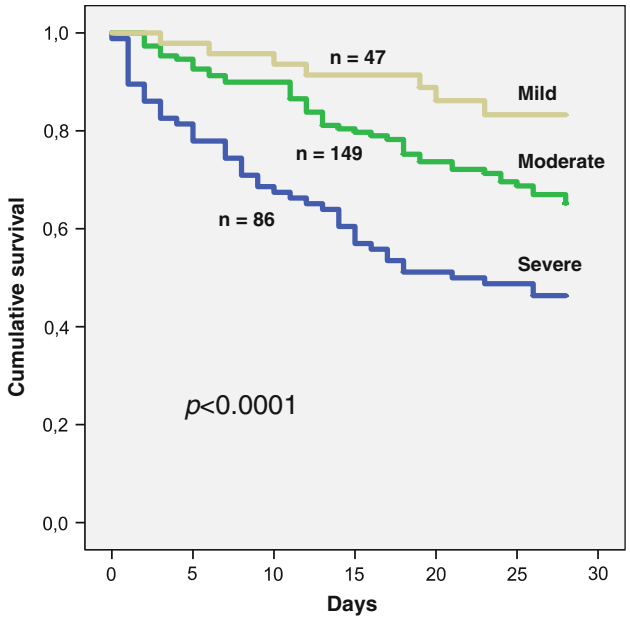


**Fig. 4** Kaplan-Meier 28-day probability of survival curves for the three phenotypes of 282 patients with the acute respiratory distress syndrome (ARDS) from the validation cohort classified by their response to $FiO_2 \geq 0.5$ plus PEEP $\geq 10$ $cmH_2O$ at 24 h of ARDS onset (see text for details). More than half of deaths (55.3 %) occurred within the first 15 days of inclusion into the study: 38 of 53 deaths (71.7 %) in the severe ARDS subgroup, 31 of 68 deaths (45.6 % in the moderate ARDS subgroup, and 4 of 11 deaths (36.4 %) in the mild ARDS subgroup

## Discussion

This is the first prospective report demonstrating that phenotypic classification of ARDS patients, treated under current MV practices, can be separated into three distinct categories. The findings of this study have two major implications: (1) we cannot rely on the AECC ARDS definition for selecting a population of ARDS patients with a similar level of lung injury, and (2) it establishes a standardized method for assessing the severity of lung injury for enrolling appropriate ARDS patients into therapeutic clinical trials.

The idea of using standard ventilatory settings for ARDS diagnosis has been explored previously [4, 8, 10], but its use has not been advocated worldwide. We were the first to report that after evaluating the $PaO_2/FiO_2$ response under a specific standard ventilator setting, patients meeting the AECC ARDS criteria had variable levels of lung injury and outcome [4, 8]. It is well established that changes in PEEP and $FiO_2$ alter the $PaO_2/FiO_2$ values in lung-injured patients [11–13]. The $FiO_2$ level at which the $PaO_2/FiO_2$ ratio is measured should be carefully defined when specifying diagnostic criteria for ARDS. It is also well known that the use of PEEP can improve oxygenation sufficiently to change the physiology in the lung such that the patient does not meet the criteria for ARDS [12]. Therefore, a patient could fit the ARDS criteria when the $PaO_2$ is measured with zero PEEP but not when measured at a PEEP of 5 or 10 $cmH_2O$ or when measured on $FiO_2 = 0.35$ but not when measured on $FiO_2 = 0.5$ [4, 10] (see ESM for further discussion).

At the time of preparing this manuscript for submission, a proposal for an update of the AECC ARDS definition was published by a task force panel of experts using similar terminology [14]. Using a teleconference and in-person discussion approach and retrospective data, they proposed an ARDS classification in three severity categories (mild, moderate, and severe) for empirical evaluation. The panel used seven data sets: four muticenter studies (enrolling 4,188 patients with a $PaO_2/FiO_2 \leq 300$ mmHg) and three-single-center studies

**Table 3** Demographics, physiology, and clinical parameters at ARDS onset in 282 ARDS patients from the validation cohort classified by categories based on the response at 24 h to PEEP $\geq 10$ $cmH_2O$ and $FiO_2 \geq 0.5$

| Variables | Mild ARDS $PaO_2/FiO_2 > 200$ ($n = 47$) | Moderate ARDS $PaO_2/FiO_2$ 101–200 ($n = 149$) | Severe ARDS $PaO_2/FiO_2 \leq 100$ ($n = 86$) | $p$ value |
|---|---|---|---|---|
| Age (years), mean ± SD | 53 ± 18 | 56 ± 18 | 55 ± 17 | 0.594 |
| APACHE II | 20.5 ± 5.5 | 21 ± 6 | 22 ± 6 | 0.505 |
| SOFA | 9.0 ± 3.3 | 8.8 ± 3.4 | 9.6 ± 3.5 | 0.221 |
| Lung injury score | 2.8 ± 0.6 | 2.9 ± 0.6 | 3.0 ± 0.6 | 0.172 |
| $V_T$ (ml/kg), PBW | 7.2 ± 1.0 | 7.2 ± 1.1 | 7.3 ± 0.9 | 0.753 |
| PEEP ($cmH_2O$) | 8.5 ± 2.9 | 9.2 ± 3.3 | 9.6 ± 3.8 | 0.205 |
| Plateau pressure ($cmH_2O$) | 25 ± 5.7 | 25.7 ± 6.0 | 28 ± 5.6 | 0.003 |
| Respiratory rate (breaths/min) | 21.2 ± 6.2 | 21.3 ± 5.8 | 21.5 ± 6 | 0.951 |
| $PaO_2/FiO_2$ (mmHg) | 130 ± 41 | 117 ± 39.5 | 86.6 ± 26.9 | 0.00001 |
| $PaCO_2$ (mmHg) | 44.7 ± 11.7 | 46 ± 10.2 | 46.8 ± 11.3 | 0.558 |
| No. organ failures | 1.4 ± 1.1 | 1.4 ± 1.1 | 1.6 ± 1.3 | 0.646 |
| Minute ventilation $\geq 10$ (l/min), $n$ (%) | 17 (36.2) | 67 (45) | 42 (48.8) | 0.371 |
| Main causes of ARDS, $n$ (%) | | | | |
| Sepsis | 16 (34) | 46 (30.9) | 29 (33.7) | 0.868 |
| Bacterial pneumonia | 21 (44.7) | 49 (32.9) | 25 (29.1) | 0.187 |

**Table 4** General data during intensive care unit stay of 282 ARDS patients of the validation cohort reclassified by categories based on the response at 24 h of ARDS onset to PEEP $\geq$ 10 $cmH_2O$ and $FiO_2 \geq 0.5$

| Variables | Mild ARDS ($n = 47$) | Moderate ARDS ($n = 149$) | Severe ARDS ($n = 86$) | $p$ value |
|---|---|---|---|---|
| Days on mechanical ventilation, $P_{50}$ ($P_{25}$–$P_{75}$) | 11 (8–24) | 17 (9–27) | 15 (8–30) | 0.148 |
| Maximum $FiO_2$ (>1 h), mean ± SD | 0.89 ± 0.18 | 0.95 ± 0.12 | 0.99 ± 0.05 | 0.0001 |
| Maximum PEEP, mean ± SD ($cmH_2O$) | 11 ± 2.9 | 12.9 ± 3.2 | 14.3 ± 3.4 | 0.0001 |
| Maximum plateau pressure, mean ± SD ($cmH_2O$) | 28 ± 5 | 30 ± 4 | 31 ± 4 | 0.0001 |
| Barotrauma, % ($n$) | 6.4 (3) | 8.7 (13) | 12.8 (11) | 0.472 |
| No. organ failures, mean ± SD | 1.5 ± 1.2 | 1.9 ± 1.4 | 2.5 ± 1.6 | <0.001 |
| ICU mortality, % ($n$) | 17.0 (8) | 40.9 (61) | 58.1 (50) | 0.00001 |

(enrolling 269 patients). By categorizing patients from the multicenter studies according to three cutoff $PaO_2/FiO_2$ values (>200/≤300, >100/≤200, and ≤100 mmHg) on PEEP $\geq$ 5 $cmH_2O$, they found that hospital mortality increased with every stage of severity (27, 32, and 45 %, respectively). In the database from the 3 small, single-center studies comprising 269 patients, the hospital mortality increased as well with every stage of ARDS (20, 41, 52 %). Although encouraging, those results may not be generalizable and are difficult to compare with our study for several methodological reasons.

First, none of the patients included in the empirical analysis were prospectively enrolled for the purpose of revising the ARDS definition and/or evaluating risk stratification. Second, the categorization of patients was done based on the $PaO_2/FiO_2$ value at the time of inclusion into their respective observational study or randomized clinical trial. There is no information on whether those baseline values of $PaO_2/FiO_2$ were calculated at the time of ARDS onset or whether the $PaO_2$ was measured under a specific $FiO_2$ and PEEP level. In our study, $PaO_2/FiO_2$ was always calculated from the $PaO_2$ values measured 30 min after each standard ventilator setting under a specified $FiO_2$ and PEEP level after meeting the AECC ARDS criteria. Third, 24 % of patients included in the empirical analysis had a $PaO_2/FiO_2 > 200$ at the time of enrollment. We did not include those patients in our study because in many centers these patients do not require endotracheal intubation and invasive MV. Fourth, the empirical definition does not consider the level of $FiO_2$ for $PaO_2/FiO_2$ categorization despite the fact that changes in the applied $FiO_2$ results in changes in $PaO_2/FiO_2$ [8, 13]. In addition, since it is likely that a significant proportion of patients included in those multicenter studies were on $FiO_2 < 0.5$ at the time of study enrollment, there is no information on how many patients could not meet ARDS criteria if evaluated at a minimum level of $FiO_2 = 0.5$. Fifth, 518 patients were eliminated from the empirical analysis because PEEP was missing or <5 $cmH_2O$. In our prospective study, we did not exclude any patients based on baseline PEEP or $FiO_2$. Sixth, since there was no standardization of ventilator settings at the time $PaO_2$ was measured, and since more than 50 % of patients were on PEEP < 10 $cmH_2O$ at baseline, the basis for selecting 5 $cmH_2O$ PEEP is not well supported. In the derivation cohort of our study, we found that 5 $cmH_2O$ PEEP did not reach statistical significance when comparing $PaO_2/FiO_2$ categories and ICU mortality. Seventh, the four multicenter studies were a case mix of observational studies and clinical trials performed from 1996 to 2000 where patients were ventilated with a mean $V_T \geq 10$ ml/kg predicted body weight and low levels of PEEP and studies performed after 2000 when patients were ventilated with a lower $V_T$. In our series, all patients were ventilated with a lung protective strategy (low $V_T$ and moderate to high levels of PEEP). In summary, we think that the use of the Berlin empirical definition for ARDS to enroll patients into clinical trials may result in the inclusion of patients with highly variable severity of lung injury and mortalities. For example, in our study, if patients were classified as having severe ARDS by the Berlin criteria, more than half of them would not have severe ARDS by 24 h. Consequently, it can be argued that the Berlin proposal for modifying the AECC ARDS definition fails to provide a true risk assessment of ARDS patients.

Our study suggests that the $PaO_2/FiO_2$ ratio can be used to differentiate groups of patients at highest risk for adverse clinical outcomes, as has been suggested by others [15]. Measuring $PaO_2/FiO_2$ under a universal, standard ventilatory setting at 24 h after ARDS onset could help to identify and select patients with different risks of deaths for clinical trials. Our proposed classification based on the assessment of the $PaO_2/FiO_2$ values under a standard ventilator setting at 24 h after ARDS onset meets most of the criteria proposed by Shehabi and Seppelt [16] when seeking an ideal biomarker: "a SMART biomarker is Sensitive, Measurable (with a high degree of precision), Available (Affordable and safely Attainable), and Responsive (and Reproducible) in a Timely fashion to expedite clinical decision making". A persistently low $PaO_2/FiO_2$ is associated with the worst outcome and may be a marker of failure to respond to conventional therapy [17]. Thus, patients in the severe ARDS category may require additional treatments to improve outcome [6] and benefits from current supportive measures in patients

categorized as having "mild" ARDS ($PaO_2/FiO_2 > 200$), may be limited, deleterious, or disproportional to the resources used (see ESM for further discussion).

The present study has some limitations and strengths. First, in the validation cohort we have only evaluated one out of eight possible choices of ventilatory settings that were examined in the derivation cohort. Second, we cannot fully confirm that the highly significant predictive validity of changes in $PaO_2/FiO_2$ within the first 24 h under a specific standard ventilatory setting combines the effects of disease progression with the phenotypic reclassification. However, our findings suggest that a given standard ventilatory setting is needed to adjust for confounding by disease progression: it seems that patients who are getting better early in the course do better, and those who decline over the first 24 h do worse. Third, regarding the potential concerns for waiting 24 h for enrolling patients into therapeutic trials (if patients must be assessed by a PEEP-$FiO_2$ trial at 24 h after ARDS onset), it is important to emphasize that almost all published randomized controlled trials in ARDS enrolled patients $\geq$24 h after ARDS diagnosis [10, 18–30]. Although in future therapeutic clinical trials the goal may be to enroll severe ARDS patients within the first few hours after ARDS onset, our study suggests that to guarantee that enrolled patients are representative of the target population, randomization should not occur until patients qualify as severe ARDS at 24 h. If patients are not qualified at 24 h, it is plausible that an imbalance in the distribution of patients with severe ARDS may occur and, consequently, a potential failure of a useful intervention or the demonstration that a useless intervention is beneficial (see ESM for further discussion).

In conclusion, our findings suggest that calculating the $PaO_2/FiO_2$ under a specific, standard ventilatory setting ($FiO_2 \geq 0.5$ with PEEP $\geq$ 10 $cmH_2O$) no later than 24 h after ARDS onset helped to stratify patients into mild, moderate, and severe phenotypic categories of acute lung injury. Therefore, a standard method for assessing the severity of lung injury should be part of usual care for classifying patients' outcomes and enrolling appropriate ARDS patients into therapeutic clinical trials.

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**Conflicts of interest** We have the following competing interests: RMK has received research grants from Hamilton, honorarium for lecturing from Maquet and Hamilton, and is a consultant for Newport, KCL, and Bayer. JV has received research grants from Maquet. The rest of the authors declared that no competing interests exist in relation to the content of this study and manuscript.

## Appendix

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