# A Clinical Classification of the Acute Respiratory Distress Syndrome for Predicting Outcome and Guiding Medical Therapy*

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Drs. Villar and Kacmarek designed the original study. Drs. Ambrós, Parra, Blanco, Domínguez-Berrot, Gutiérrez, Blanch, Añón, Martín, Prieto, Collado enrolled patients and collected the data. Dr. Villar obtained funding for the study. Dr. Villar, Dr. Pérez-Méndez, Ms. Fernández, and Drs. Kacmarek, Ambrós, Parra, Blanco, Domínguez-Berrot, Gutiérrez, Blanch, Añón, Martín, Prieto, and Collado have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and approved the final version to be published. Dr. Villar, Ms. Fernández, and Dr. Kacmarek wrote the first draft. Dr. Villar, Ms. Fernández, and Drs. Pérez-Méndez and Kacmarek performed and supervised data management and statistical analysis. Dr. Villar, Ms. Fernández, and Dr. Pérez-Méndez 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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**Objective:** Current in-hospital mortality of the acute respiratory distress syndrome (ARDS) is above 40%. ARDS outcome depends on the lung injury severity within the first 24 hours of ARDS onset. We investigated whether two widely accepted cutoff values of $Pao_2/Fio_2$ and positive end-expiratory pressure (PEEP) would identify subsets of patients with ARDS for predicting outcome and guiding therapy.

**Design:** A 16-month (September 2008 to January 2010) prospective, multicenter, observational study.

**Setting:** Seventeen multidisciplinary ICUs in Spain.

**Patients:** We studied 300 consecutive, mechanically ventilated patients meeting American-European Consensus Conference criteria for ARDS ($Pao_2/Fio_2 \leq 200$ mm Hg) on PEEP greater than or equal to 5 cm $H_2O$, and followed up until hospital discharge.

**Interventions:** None.

**Measurements and Main Results:** Based on threshold values for $Pao_2/Fio_2$ (150 mm Hg) and PEEP (10 cm $H_2O$) at ARDS onset and at 24 hours, we assigned patients to four categories: group I ($Pao_2/Fio_2 \geq 150$ on PEEP $< 10$), group II ($Pao_2/Fio_2 \geq 150$ on PEEP $\geq 10$), group III ($Pao_2/Fio_2 < 150$ on PEEP $< 10$), and group

IV ($Pao_2/Fio_2$ < 150 on PEEP ≥ 10). The primary outcome was all-cause in-hospital mortality. Overall hospital mortality was 46.3%. Although at study entry, patients with $Pao_2/Fio_2$ less than 150 had a higher mortality than patients with a $Pao_2/Fio_2$ greater than or equal to 150 ($p = 0.044$), there was minimal variability in mortality among the four groups ($p = 0.186$). However, classification of patients in each group changed markedly after 24 hours of usual care. Group categorization at 24 hours provided a strong association with in-hospital mortality ($p < 0.00001$): group I had the lowest mortality (23.1%), whereas group IV had the highest mortality (60.3%).

**Conclusions:** The degree of lung dysfunction established by a $Pao_2/Fio_2$ of 150 mm Hg and a PEEP of 10 cm $H_2O$ demonstrated that ARDS is not a homogeneous disorder. Rather, it is a series of four subsets that should be considered for enrollment in clinical trials and for guiding therapy. A major contribution of our study is the distinction between survival after 24 hours of care versus survival at the time of ARDS onset. (*Crit Care Med* 2015; 43:346–353)

**Key Words:** acute respiratory distress syndrome; classification; $Pao_2/Fio_2$ ratio; positive end-expiratory pressure; risk stratification; outcome.

The acute respiratory distress syndrome (ARDS) is caused by injury to the alveolar-capillary membrane that results in increased permeability and protein-rich alveolar edema. Diagnosis of ARDS is based on a constellation of clinical, radiographic, and physiologic abnormalities, including 1) a risk factor for the development of ARDS, 2) severe hypoxemia, 3) bilateral pulmonary infiltrates on chest x-ray, and 4) no clinical evidence of hydrostatic pulmonary edema or a pulmonary artery occlusion pressure less than or equal to 18 mm Hg when measured (1–4). These criteria allow the inclusion of a highly heterogeneous group of patients because various types of lung injury can lead to a similar pulmonary response. Although there is general agreement on the overall criteria on which to base a definition of ARDS, some investigators have questioned current definitions of ARDS because those definitions are not very helpful for enrolling patients with ARDS and homogeneous levels of lung injury into clinical studies evaluating the natural history, prevalence, treatment, and outcome of ARDS (5, 6). Current in-hospital mortality of patients with ARDS is above 40% (7) and lung injury severity within the first 24 hours of ARDS onset is a major determinant of outcome(5).

A cutoff $Pao_2/Fio_2$ of 150 mm Hg has been found to predict outcome within the first 24 hours of ARDS onset in several clinical studies (8–12). Most patients with ARDS are ventilated with PEEP levels between 10 and 16 cm $H_2O$. Arterial $Pao_2$ responses to PEEP have indicated that the evolution and prognosis of ARDS is related to changes of $Pao_2/Fio_2$ in response to levels of PEEP greater than or equal to 10 cm $H_2O$ (5, 6, 13). To this end, we investigated whether a threshold value of 150 mm Hg for $Pao_2/Fio_2$ and of 10 cm $H_2O$ for positive end-expiratory pressure (PEEP) would identify subsets of patients with ARDS for predicting outcome and guiding therapy, independent of the underlying disease or specific therapy. Our classification system predicts in-hospital mortality independent of the patients age and precipitating factor. We have found that each subset was associated with a concrete overall mortality, which increased with advancing lung dysfunction. We believe that this classification system could be helpful for better selecting patients with ARDS in future observational and clinical trials and potentially for guiding medical therapy.

## METHODS

This observational study was approved by the Ethics Committees at the coordinating centers (Hospital Universitario Dr. Negrin, Las Palmas de Gran Canaria, Spain [2008/1029] and the Hospital Virgen de La Luz, Cuenca, Spain [2008/0715]). The study was considered an audit.

### Patients

We studied 300 consecutive patients with ARDS from a multicenter, prospective, observational study performed in a network of 17 hospitals in Spain from September 15, 2008, to January 15, 2010. All patients were mechanically ventilated with PEEP greater than or equal to 5 cm $H_2O$ and met the American-European Consensus Conference (AECC) criteria (3) and the Berlin criteria (4) for moderate and severe ARDS ($Pao_2/Fio_2 \leq 200$ mm Hg). Patients younger than 18 years old, and patients with chronic pulmonary disease or cardiac failure or fluid overload as a primary cause of respiratory failure, were excluded. Also, because diagnostic confusion could occur with other diseases that cause hypoxemia and show bilateral pulmonary infiltrates on radiographs, physicians were asked to exclude lymphangitic carcinoma, acute eosinophilic pneumonia, hypersensitivity pneumonitis, and idiopathic pulmonary fibrosis carefully. For the purpose of this study and for appropriate identification of patients with ARDS, attending physicians were requested to consider only blood gas values while patients were clinically stable and not to consider blood gas values resulting from an acute event unrelated to the disease process (such as patient-ventilator asynchrony, obstruction of endotracheal tubes by secretions, suctioning, ventilator disconnection, sudden pneumothorax, and hemodynamic instability). Although most patients from this study were used for reporting the 1-year incidence of ARDS (14) and for validating a PEEP/$Fio_2$ trial (6), none of the outcome data reported in the present study have been published.

### Study Design and Data Collection

Onset of ARDS was defined as the day and time in which the patient first met ARDS criteria. Demographics, arterial blood gases, laboratory, radiographic, hemodynamic, and ventilator data were collected at study entry, at 24 hours, at days 3 and 7, and on the last day of mechanical ventilation (MV). Organ failure was documented daily. Although patient care was not strictly protocolized, attending physicians were asked to follow the current standards for the general management of critically ill patients, which included the following: 1) in case of sepsis, physicians were urged to ensure early identification of causative microorganism, administer IV antibiotics as soon as sepsis was suspected or recognized, and to optimize antibiotic selection

and their timely administration on the basis of the antibiogram; 2) fluid resuscitation and vasopressor administration were individualized with the goal of maintaining a systolic blood pressure greater than or equal to 90 mm Hg or a mean arterial pressure of greater than or equal to 65 mm Hg; 3) to maintain hemoglobin between 7 and 10 g/dL. None of the patients received activated protein C, or nitric oxide as an adjunctive treatment. Also, none of the participating centers used prone ventilation, high-frequency ventilation, or extracorporeal membrane oxygenation during the study period. For ventilatory management, clinicians were encouraged to apply lung protective MV with a tidal volume ($V_T$) of 5–8 mL/kg predicted body weight, a ventilatory rate that maintained $PaCO_2$ between 35 and 50 mm Hg, a plateau pressure less than 30 cm $H_2O$, and PEEP and $FIO_2$ combinations to maintain $PaO_2$ greater than 60 mm Hg or $SpO_2$ greater than 90%. We have no data to assess the degree of compliance with these recommendations. None of the patients studied were enrolled in any other clinical trial.

On the basis of threshold values for $PaO_2/FIO_2$ (150 mm Hg) and applied PEEP (10 cm $H_2O$) at ARDS onset and 24 hours later, we classified patients into four categories: group I, patients with a $PaO_2/FIO_2$ greater than or equal to 150 and PEEP less than 10; group II, patients with a $PaO_2/FIO_2$ greater than or equal to 150 and PEEP greater than or equal to 10; group III, patients with a $PaO_2/FIO_2$ less than 150 and PEEP less than 10; and group IV, patients with a $PaO_2/FIO_2$ less than 150 and PEEP greater than or equal to 10. A $PaO_2/FIO_2$ ratio of 150 mm Hg has been previously used as a surrogate for hypoxemia in patients with pulmonary dysfunction (8–10, 15, 16). We collected and analyzed the value of $PaO_2/FIO_2$ and PEEP based on the individualized target for $PaO_2$, PEEP, and $FIO_2$ that were chosen by the patient's physicians for each individual patient, following the recommendations for ventilatory support of patients with ARDS. Patients were followed up until hospital discharge. Primary outcome measure was all-cause in-hospital mortality for each subgroup.

### Data Analysis

Data are expressed as percentages, mean ± SD, or medians and interquartile ranges (IQR). Differences between distributions of categorical variables were analyzed by Pearson chi-square or Fisher exact tests. For continuous variables, data were analyzed using the *t* test, analysis of variance, Mann–Whitney, or the Kruskal–Wallis tests, depending on their distribution and number of variables. We also calculated the relative risk (RR) of death and the 95% CI associated with each group, and tested for linear trend. A two-sided value of *p* less than 0.05 was considered significant.

## RESULTS

The overall all-cause in-hospital mortality was 46.3%. Median age was 56 years (IQR = 40–73) years. Pneumonia, sepsis, and trauma were the most common disease processes associated with the development of ARDS. At baseline (ARDS onset), patients had a mean $PaO_2/FIO_2$ of 111 ± 40 mm Hg, with a mean $FIO_2$ of 0.82 ± 0.20 and a mean PEEP of 9.2 ± 3.2 cm $H_2O$. When comparing mean baseline values of survivors and nonsurvivors, no significant differences were found in ventilation and oxygenation parameters although nonsurvivors were older, had a higher Acute Physiology and Chronic Health Evaluation (APACHE) II score and higher organ dysfunctions (**Table 1**). In our cohort, 169

**TABLE 1. Baseline Characteristics of 300 Survivors and Nonsurvivors With the Acute Respiratory Distress Syndrome**

| Variables | Values | | |
|---|---|---|---|
| | Survivors *n* = 161 | Nonsurvivors *n* = 139 | *p* |
| Acute Physiology and Chronic Health Evaluation II | 20.2 ± 5.8 | 23.2 ± 5.8 | 0.0001 |
| Age, median, interquartile range | 49 (36–65) | 66 (51–75) | 0.0001 |
| Gender, number men/women | 111/50 | 100/39 | 0.613 |
| Tidal volume, mL/kg predicted body weight, mean ± SD | 7.1 ± 1 | 7.3 ± 1 | 0.388 |
| Plateau pressure, cm $H_2O$, mean ± SD | 26 ± 6.1 | 27 ± 6 | 0.151 |
| Positive end-expiratory pressure, cm $H_2O$, mean ± SD | 9.3 ± 3.1 | 9.2 ± 3.4 | 0.790 |
| $FIO_2$, mean ± SD | 0.80 ± 0.20 | 0.84 ± 0.19 | 0.078 |
| $PaO_2/FIO_2$, mean ± SD | 115 ± 41 | 106 ± 39 | 0.054 |
| No. of organ failure, mean ± SD | 1.3 ± 1.1 | 1.7 ± 1.3 | 0.004 |
| Main causes of acute respiratory distress syndrome | | | |
| Pneumonia | 75 | 54 | 0.199 |
| Sepsis | 44 | 48 | 0.209 |
| Trauma | 23 | 7 | 0.011 |
| Aspiration | 14 | 15 | 0.562 |

patients had ARDS from pulmonary sources and 131 from nonpulmonary origins (hospital mortality 42% vs 51.9%; $p = 0.112$).

### ARDS Subsets at Baseline

At study entry, 79.7% of patients ($n = 239$) had a $Pao_2/Fio_2$ less than 150 mm Hg, and their overall hospital mortality was higher than in patients with a $Pao_2/Fio_2$ greater than or equal to 150 (49.4% vs 34.4%, $p = 0.044$). Also, at baseline, almost half of patients (48.7%) ($n = 146$) were on PEEP less than 10 cm $H_2O$, and their mortality rate was not statistically significantly different than those patients on PEEP greater than or equal to 10 cm $H_2O$ (47.3% vs 45.5%; $p = 0.817$). There was a nonsignificant variability in the overall hospital mortality rate among the four clinical subsets of patients (RR, 1.16; 95% CI, 1.01–1.33; p for trend = 0.186) at the time of ARDS diagnosis (**Fig. 1*A*** and **Table 2**). No significant differences in hospital mortality rates were found at the time of ARDS diagnosis when any combination of comparison between two groups was analyzed.

### ARDS Subsets at 24 Hours After ARDS Onset

The distribution of patients in each subset changed dramatically after 24 hours (**Fig. 1*B*** and Table 2). A total of 169 patients (56.3%) still maintained a $Pao_2/Fio_2$ less than 150 mm Hg, and their hospital mortality was almost double that of 131 patients with a $Pao_2/Fio_2$ greater than or equal to 150 (58.6% vs 30.5%, $p = 0.000001$). Most patients ($n = 290$, 96.7%) were on $Fio_2$ greater than or equal to 0.5. Only 14.7% of patients ($n = 44$) were on PEEP less than 10 cm $H_2O$, and their mortality was lower than those requiring a PEEP greater than or equal to 10 cm $H_2O$ (31.8% vs 48.8%; $p = 0.048$). There were no differences in outcome or in the response to PEEP between patients with pulmonary versus nonpulmonary ARDS (data not shown). Group categorization after 24 hours of ARDS onset demonstrated strong association with in-hospital mortality (RR, 1.80; 95% CI, 1.51–2.14; $p$ for trend < 0.00001) (Fig. 1*B* and Table 2).

When considering the characteristics of these four subsets of patients with ARDS at 24 hours, we found statistical differences in the APACHE II, number of organ failures, plateau pressures, $Fio_2$, and days on MV, which could explain the significant differences in hospital outcome among groups (**Table 3**). Only six patients died in group I: one died several days after being discharged from the ICU from a cause unrelated to ARDS, and five died while in the ICU. Those five patients were more than 72 years old, their $Pao_2/$

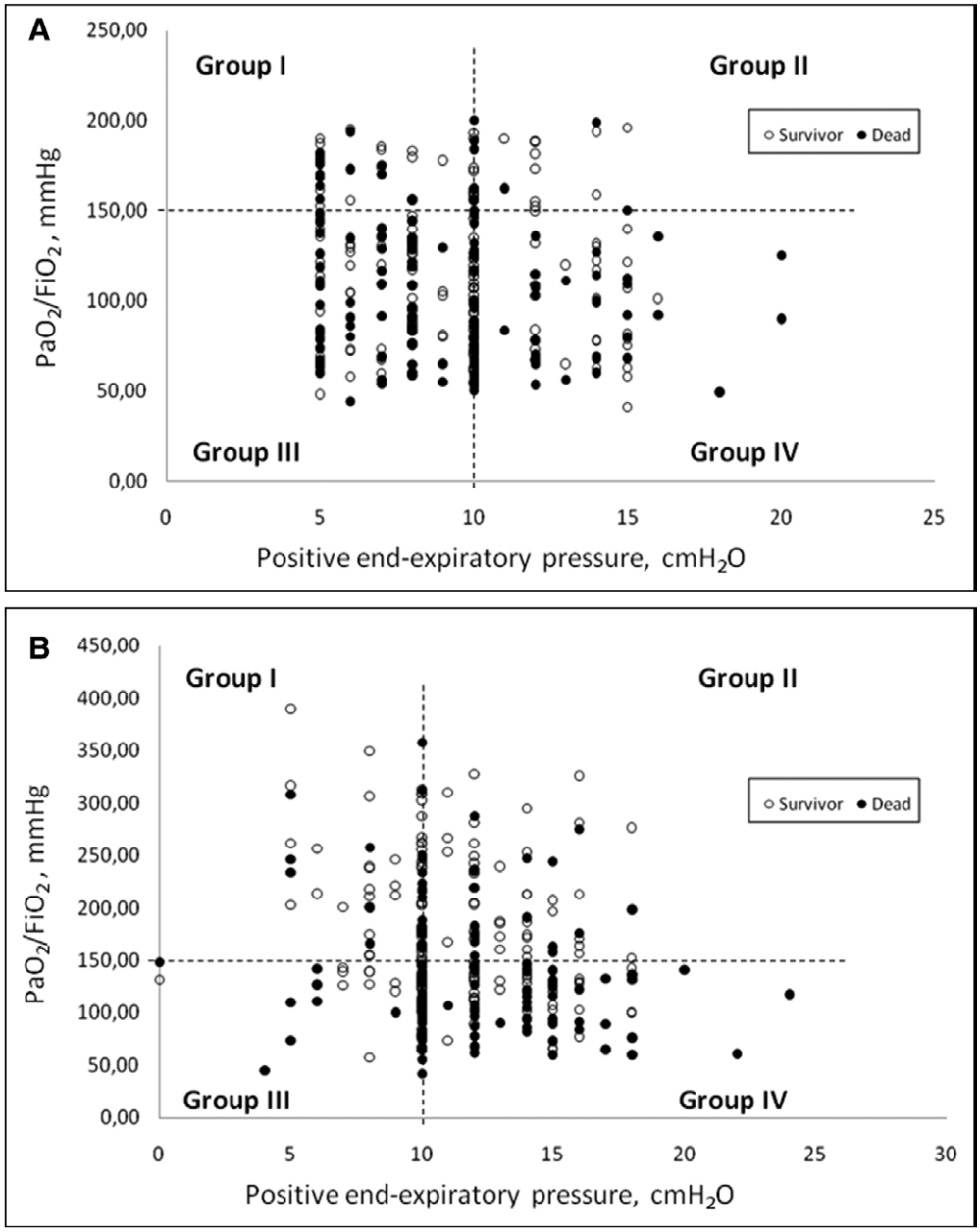


**Figure 1.** Distribution of 300 patients with the acute respiratory distress syndrome (ARDS) based on cutoff values for $Pao_2/Fio_2$ ratio (150 mm Hg) and positive end-expiratory pressure level (10 cm $H_2O$) for each individual patient. **A**, At the time of ARDS diagnosis (baseline). **B**, After 24 hours of usual critical care with protective mechanical ventilation. The dotted lines are placed at the levels of 150 mm Hg for $Pao_2/Fio_2$ ratio and 10 cm $H_2O$ for positive end-expiratory pressure. There was a wider degree of variability of lung injury at ARDS onset than at 24 hours, and mortality increases as lung function deteriorates at 24 hours.

**TABLE 2. Distribution and Mortality of Each Subset of Patients With the Acute Respiratory Distress Syndrome**

| | Group I | Group II | Group III | Group IV | |
|---|---|---|---|---|---|
| | $Pao_2/FIO_2 \geq 150$ and PEEP < 10 | $Pao_2/FIO_2 \geq 150$ and PEEP ≥ 10 | $Pao_2/FIO_2 < 150$ and PEEP < 10 | $Pao_2/FIO_2 < 150$ and PEEP ≥ 10 | *p* for Trend |
| At acute respiratory distress syndrome onset, n | 31 | 30 | 115 | 124 | 0.186 |
| Hospital mortality, % | 38.7 | 30 | 49.6 | 49.2 | |
| At 24 hr after onset, n | 26 | 105 | 18 | 151 | < 0.00001 |
| Hospital mortality, % | 23.1 | 32.4 | 44.4 | 60.3 | |

PEEP = positive end-expiratory pressure.

At baseline (acute respiratory distress syndrome [ARDS] onset). Overall hospital mortalities among groups were not significantly different. At 24 hours after ARDS onset, in-hospital mortality increased as lung function deteriorates from groups I to IV.

**TABLE 3. Main Characteristics of 300 Patients With the Acute Respiratory Distress Syndrome (Classification Was Made at 24 hours After Acute Respiratory Distress Syndrome Onset as Groups I, II, III, and IV Based on Cutoff Values of 150 mm Hg for $Pao_2/FIO_2$ and 10 cm $H_2O$ for PEEP)**

| | Values | | | | |
|---|---|---|---|---|---|
| Variables | Group I *n* = 26 | Group II *n* = 105 | Group III *n* = 18 | Group IV *n* = 151 | *p* |
| Acute Physiology and Chronic Health Evaluation II | 16.6 ± 4.7 | 18.8 ± 7 | 17.2 ± 7.1 | 20.2 ± 5.9 | 0.016 |
| Age, median, interquartile ranges | 61 (44–75) | 52 (36–71) | 57 (49–73) | 58 (44–73) | 0.240 |
| Gender, number men/women | 16/10 | 70/35 | 12/6 | 113/38 | 0.359 |
| Tidal volume, mL/kg predicted body weight | 7.2 ± 1.1 | 6.7 ± 1.8 | 6.7 ± 1.3 | 6.2 ± 2.3 | 0.053 |
| Plateau pressure, mean ± SD | 22 ± 7 | 23 ± 6 | 26 ± 5 | 26 ± 5 | 0.0001 |
| PEEP, cm $H_2O$, mean ± SD | 7.1 ± 1.5 | 12 ± 2.3 | 6.2 ± 2.7 | 13 ± 3 | 0.0001 |
| $FIO_2$, mean ± SD | 0.53 ± 0.10 | 0.58 ± 0.14 | 0.81 ± 0.16 | 0.82 ± 0.18 | 0.0001 |
| $Pao_2/FIO_2$, mean ± SD | 238 ± 58 | 215 ± 50 | 118 ± 30 | 108 ± 26 | 0.0001 |
| Organ failures (total-baseline) | 0.0 ± 0.4 | 0.2 ± 0.1 | 0.5 ± 0.5 | 0.8 ± 0.3 | 0.0001 |
| Days on mechanical ventilation | 17 ± 14 | 17 ± 12 | 26 ± 18 | 23 ± 22 | 0.027 |
| Causes of death, *n* (%) | | | | | |
| Pulmonary | 1 (16.7) | 7 (20.6) | 2 (25.0) | 23 (25.3) | 0.503 |
| Nonpulmonary | 5 (83.3) | 27 (79.4) | 6 (75.0) | 68 (74.7) | |

PEEP = positive end-expiratory pressure.

$FIO_2$ increased above 250 within 72 hours, four of them died from extrapulmonary organ dysfunction associated with the underlying disease (cancer, acquired immunodeficiency syndrome, stroke, and pancreatitis), and one patient died with hypoxemic respiratory failure caused by ventilator-associated pneumonia developed after several weeks on MV. Only eight patients died from group III: two died several weeks after being discharged from the ICU, two died from multisystem organ dysfunction, one died from cancer, one died with acute pancreatitis, and only two died from hypoxemic respiratory failure because of severe chest trauma.

## DISCUSSION

To our knowledge, this is the first report in which patients with ARDS have been classified using a cutoff value of 150 mm Hg for $Pao_2/FIO_2$ and 10 cm $H_2O$ for PEEP. The most clinically relevant findings in our study are 1) ARDS is not a homogeneous disorder that can be simply categorized at onset and 2) this classification (at 24 hr after ARDS onset) comprises four clinical subsets of ARDS with different outcomes, independent of the patient's age, gender, the precipitating underlying disease (pulmonary vs nonpulmonary), and the specific treatment. We believe that this approach to classification of ARDS will be

useful for the implementation of an individualized approach for appropriate diagnosis and therapy in patients with ARDS.

Determining a patient's prognosis is an important responsibility of the bedside clinician (17). It is increasingly recognized that our understanding of ARDS outcome has been limited by the failure to accept the idea that ARDS is a syndrome with different phenotypes that are independent of each other (7). The need for developing an ARDS-specific model for mortality prediction and guiding therapy is particularly relevant because this syndrome is highly complex, evolves rapidly, and commonly results in poor hospital outcome. Attempts to simplify the categorization of patients with ARDS have been relatively easy to adopt (3, 4) but have not proved particularly useful for identifying specific therapeutic interventions that benefit certain subgroups of patients, especially when deaths are unrelated to lung dysfunction and cannot be prevented by MV. Despite considerable disappointment with other classification and prediction systems for patients with ARDS (4–6, 8–10, 18, 19), we still need a classification system for clinical management and research that can serve as a universal prototype for setting individual therapeutic targets in ARDS, as has been done in other critical conditions.

Our classification system uses two variables, $Pao_2/Fio_2$ and PEEP, known to be particularly relevant to the diagnosis and management of patients with ARDS. This study clearly demonstrated that classifying patients with ARDS shortly after ARDS onset is useless for assessing lung injury severity and predicting in-hospital mortality. Thus, we believe that by "lumping" all patients with ARDS at disease onset using any current ARDS definition without assessing the oxygenation response to current MV practices with low $V_T$ and moderate to high levels of PEEP within a 24-hour period, will lessen our ability to understand the contribution of each subset of patients to the overall picture of ARDS, and ultimately will hinder our efforts to recommend and to develop effective preventive and therapeutic interventions (20). The European Collaborative Study (9) performed from 1985 to 1987 in 38 European hospitals analyzed 583 patients with ARDS defined by a known risk factor for ARDS, diffuse bilateral pulmonary infiltrates, a pulmonary artery occlusion pressure less than 18 mm Hg, and severe hypoxemia defined by a $Pao_2$ less than 75 mm Hg with $Fio_2$ greater than or equal to 0.5 on PEEP greater than or equal to 5 cm $H_2O$ for at least 24 hours. In that study, the overall mortality of patients with a $Pao_2/Fio_2$ less than 150 at 24 hours was 69% compared with 38% for those with a $Pao_2/Fio_2$ greater than 150. In a similar study, Villar et al (10) found that $Pao_2$ response to PEEP after 24 hours of meeting ARDS criteria allowed the separation of 56 patients with ARDS into two different groups: 68% of patients with a $Pao_2/Fio_2$ less than or equal to 150 mm Hg died in the ICU, whereas only 22.6% of patients with a $Pao_2/Fio_2$ greater than 150 died. When the AECC criteria established a value of 200 mm Hg for ARDS, the use of the threshold value of 150 mm Hg for $Pao_2/Fio_2$ was abandoned until Papazian et al (11) and Guérin et al(12) used it as a threshold for defining patients with persistent ARDS and for enrollment into their trials. Of note, these trials are the only positive randomized controlled trials in patients with ARDS since the publication of the ARDSnet trial (21). In both trials, only patients with a $Pao_2/Fio_2$ less than 150 mm Hg under a specific level of PEEP and $Fio_2$ that persisted 12–48 hours were enrolled. In those trials, patients were screened using the AECC definition but randomized after assessment at 24 hours if they still met $Pao_2/Fio_2$ criteria for severity.

The overall in-hospital mortality rate of our cohort is in the range of recent reports in which the pooled mortality for ARDS in observational studies ranged between 44% and 55% (22, 23). The improvement or worsening of the $Pao_2/Fio_2$ over 24 hours was strongly associated with outcome. Group I represents the less complicated patient with ARDS, and specific lung-oriented therapy is not required at 24 hours after ARDS onset to improve lung function further. If the logical goal of therapy for the ARDS lung is to recruit consolidated and atelectatic alveoli by opening the lung and maintaining it open, ideally most patients are expected to be in group II at 24 hours. However, only 35% of patients from our cohort achieved a $Pao_2/Fio_2$ greater than or equal to 150 with a PEEP greater than or equal to 10 cm $H_2O$ at 24 hours although most of them increased their $Pao_2/Fio_2$ to greater than or equal to 150 mm Hg within the first 72 hours of ARDS, and 67.6% of patients from this subset were discharged home alive from the hospital. According to our classification, no patients should ideally be in group III after ARDS diagnosis, except when PEEP greater than or equal to 10 cm $H_2O$ is contraindicated for medical or surgical reasons. A patient with a trauma-associated ARDS was on 4 cm $H_2O$ of PEEP at 24 hours because of a severe bronchial rupture and a tension pneumothorax. Two patients were on zero PEEP at 24 hours: one with a combined severe head and chest trauma and the other one with several rib fractures and persistent bronchopleural fistula. However, both patients were managed at 48 hours with PEEP greater than or equal to 10 cm $H_2O$ and discharged alive from the ICU several days later without ventilatory support. Patients that at 24 hours after ARDS onset have a $Pao_2/Fio_2$ less than 150 mm Hg despite the use of PEEP greater than or equal to 10 cm $H_2O$ and $Fio_2$ greater than or equal to 0.5 (group IV) were in the most critical condition and very resistant to empirical therapy, likely suggesting the presence of a maladaptive lung repair process with early fibroproliferative changes (24). These patients should be the target for innovative or aggressive treatments, such as pharmacological therapies (11, 25), recruitment maneuvers (26, 27), prone ventilation (12, 28), or extracorporeal lung assist (29) for decreasing the extent of the intense lung inflammation and facilitating lung repair over time.

Clearly, the selection of therapy for an individual patient with ARDS involves both assessment of the degree of lung dysfunction, as measured by $Pao_2/Fio_2$, and evaluating the response to PEEP therapy. ARDS categorization could be simple and quickly assessed at the bedside by calculating the $Pao_2/Fio_2$ ratio as a modifier of treatment effect in clinical trials of therapies thought to have greater impact in sicker patients with ARDS (30). As suggested by our findings, considering the $Pao_2/Fio_2$ at ARDS onset could be harmful for influencing therapeutic decisions. In our study, the predominant ARDS subset after

24 hours of usual care was group IV (patients with $Pao_2/Fio_2$ < 150 and PEEP ≥ 10) followed by group II (patients with $Pao_2/Fio_2$ ≥ 150 and PEEP ≥ 10). However, until this classification system is used in other ICUs, we will not know for certain which ARDS groups predominate.

We acknowledge limitations and strengths of this study. We did not enroll patients with a $Pao_2/Fio_2$ greater than 200 at baseline. However, we do not believe that the exclusion of these patients weakens our results. Patients meeting baseline criteria for acute lung injury under the AECC definition or mild ARDS under the Berlin criteria (200 < $Pao_2/Fio_2$ ≤ 300) constitutes a heterogeneous group of patients who are usually underdiagnosed, representing a case-mix in which many do not require endotracheal intubation and invasive MV. Also, a number of concerns could exist regarding this classification. First, the $Pao_2/Fio_2$ was not determined under standardized ventilator settings although at 24 hours the majority of these patients were managed with $Fio_2$ greater than or equal to 0.5 and PEEP greater than or equal to 10 cm $H_2O$. Second, although a major finding of our study is that changes in $Fio_2$ and PEEP altered the $Pao_2/Fio_2$ in patients with ARDS, and depending on the clinician's selection of PEEP, a patient with ARDS may be moved from one group of severity to another within 24 hours of usual care, we acknowledge that the generalizability of our observations remains unclear because of the lack of details on how patients were managed during their hospital stay. However, therapy should be focused on moving patients into a classification with a better survival by applying increasingly aggressive therapy. As a result, no patient with ARDS should remain in group III ($Pao_2/Fio_2$ < 150 mm Hg with PEEP < 10 cm $H_2O$). Therapy should always be directed toward moving patients into the group with the lowest predicted mortality.

## CONCLUSIONS

In summary, the degree of lung dysfunction established by a $Pao_2/Fio_2$ of 150 mm Hg and a PEEP of 10 cm $H_2O$, 24 hours after ARDS onset, illustrates that ARDS is not a homogeneous disorder. A series of four subsets should be considered for enrollment in clinical trials and for guiding therapy. A major contribution of our study is the distinction between survival of different categories at the time of ARDS diagnosis versus survival after 24 hours of care when each subset demonstrated a mortality rate, which increased with advancing lung dysfunction. Because the use of these subsets for establishing prognosis or selecting therapy represents a synthesis of clinical presentation, future research should quantify whether the use of this classification in daily practice improves decision making and patient outcome. Additional multicenter observational studies are needed to validate whether this simple classification tool is truly capable of identifying four distinct clinical subsets of patients with ARDS, independent of age, gender, and precipitating factors.

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## APPENDIX 1: Acute Lung Injury: Epidemiology and Natural history (ALIEN) Network Investigators

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