Editorial

A mortality score for acute respiratory distress syndrome: predicting the future without a crystal ball

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Introduction

In a recent paper published in *Critical Care Medicine*, Villar *et al*. (1) proposed a scoring system that could be easily calculated at the bedside to predict mortality in patients with acute respiratory distress syndrome (ARDS) 24 hours after diagnosis. As in-hospital mortality ranges from 34.9% to 46.1% across the spectrum of mild to severe ARDS, respectively, the potential for improvement in management of patients with this syndrome remains high (2). Based on 62 recorded variables, age, oxygenation (PaO_2/FiO_2), and the plateau airway pressure score (APPS) were chosen to establish a 9-point stratification 24 hours after ARDS diagnosis, followed by categorization into low, intermediate, and high risk of death with predictive validity. The APPS classified ARDS into three severity subgroups (<5, 5–7, and >7 points), and significantly higher mortality was observed in those patients with an APPS greater than 7 (>80%) compared to those with an APPS of less than 5 (<14%).

To date, no validated scoring system has been available to predict mortality rates in ARDS. The strengths of the Villar *et al*. study include their standardization of mechanical ventilation parameters and the use of simple, low-cost variables that can be promptly gathered at the bedside (1). Among these variables, age is the only non-modifiable risk factor. Age is associated with increasing disease severity in patients admitted to intensive care units, and has also been used in general illness severity scores, such as APACHE, simplified acute physiology score (SAPS), and MPM (3). Conversely, oxygenation is potentially modifiable at the bedside. One previous study showed that, when positive end-expiratory pressure (PEEP) was adjusted to the standard low level (5 cm H_2O), patients were reclassified between ARDS categories (4). Even with the Berlin criteria stating that oxygenation can be evaluated with a PEEP level equal or higher than 5 cm H_2O, the reduction to PEEP =5 cm H_2O provided a clear cut-off for differentiation between the three categories of ARDS severity. Nevertheless, oxygenation has been used to predict therapeutic response after prone positioning (5), recruitment maneuvers (6), high levels of PEEP (7), and administration of neuromuscular blocking agents (8), which appeared to be more effective in severe ARDS patients. The 7-day oxygenation index change has limited utility in predicting mortality in individual patients with ARDS, but it discriminates between efficacious and non-efficacious ARDS therapies very well (9). Respiratory system mechanics parameters can add valuable information regarding patient severity at ICU admission, as well as for prognostic purposes, as these variables are monitored during the patient's ICU stay.

Prediction scores were developed to assess ARDS prognosis and risk of death (1,10-12). In 1988, Murray *et al*. proposed the lung injury score (LIS) (12), based on oxygenation, chest radiograph findings, PEEP, and static respiratory system compliance, to predict clinical therapies in ARDS trials (13,14). However, so far, the LIS has not been validated as an accurate predictor of ARDS severity (15). In the era of the Berlin definition, a large, multicenter study with 550 ARDS patients compared the predictive validity of LIS for mortality in mild, moderate, and severe stages of ARDS (15). Predictive validity to identify mortality according to ARDS severity was found to be limited [area under the receiver operating characteristic (ROC) curve =0.58 *vs*. 0.60, respectively; P=0.49]. A multicenter prospective cohort study in the ICU setting that included 646 patients with ARDS showed that death after hospital discharge was more related to underlying comorbidity and age than to ARDS severity, and that comorbidities could better predict long-term ARDS outcome (16). In 1998, Monchi *et al*. evaluated the ability of different severity scores-such as the SAPS and SAPS II, organ system failure (OSF), and LIS-to predict ARDS outcome, and concluded that the SAPS II was better to predict ARDS severity, while ARDS mortality was better related to the triggering risk factors of ARDS (direct or indirect lung injury associated with ARDS within the first 24 h) (11). In a sample of 1,999 patients with ARDS, Cooke *et al*. compared a score based on variables selected specifically for patients with lung injury, such as ventilator variables, arterial blood gases, severity of chest radiograph findings, and timing of acute lung injury onset, *versus* severity-of-illness scores (SAPS II, APACHE II, and APACHE III) (10). For a definition cohort, the area under the ROC curve for the multivariable model was superior to that of APACHE III (P<0.001); however, no difference was observed in the external validation cohort (P=0.64) (10). The lung injury prediction score (LIPS) seems to be a promising tool for ARDS outcome prediction. In a multicenter study, 5,584 patients met the criteria for ARDS after hospital admission and were screened for low or high risk according to presence of alcohol abuse, hypoalbuminemia, tachypnea, oxygen supplementation, chemotherapy, obesity, and diabetes mellitus. A LIPS score greater than 4 had 69% sensitivity and 78% specificity for identifying patients who would develop ARDS after admission (17). Conversely, Damluji *et al*. reported imprecise mortality prediction among patients with low, intermediate, and high risk of ARDS (18), probably due to an overly broad patient cohort. Based on these inconclusive data, a combination of the LIPS prediction score with a biomarker that reflects ARDS pathogenesis seems to be a promising alternative. In this context, the combination of LIPS score and angiopoietin-2, an endothelial growth factor that is a potent regulator of vascular permeability and a key mediator of mortality in ARDS patients, increased the area under the ROC curve to 0.84 (*vs*. 0.74, P=0.05). The early acute lung injury (EALI) score is another tool that has been proposed for identifying patients at risk for ARDS (19). An EALI score ≥2 had a sensitivity of 89%, specificity of 75%, and positive predictive value of 53% for this purpose; however, this tool still requires further validation in an external cohort or use in a clinical trial for ARDS prevention (*Table 1*).

Definitions are an essential component of medical progress, and need to be continuously refined. In this line, any outcome score for ARDS requires that patients be: diagnosed on the basis of the Berlin definition, a more reliable definition that may facilitate case recognition and stratification, moving patients closer to individualized or ARDS-specific medicine (20); ventilated with low tidal volumes, a protective strategy associated with improved survival and the most important variable associated with reduction of ventilator-induce lung injury (VILI) (21); and included early (24 h after ARDS diagnosis) for outcome score calculation, which may facilitate interventions and treatments in the course of ARDS. In short, better identification of patients with ARDS is key for appropriate management and characterization of patient status.

The Villar *et al*. study presents some important limitations that must be addressed for better interpretation of their results. The authors did not take into account respiratory system compliance and driving pressure, since they share collinearity with tidal volume, plateau pressure, and PEEP (for the former) and plateau pressure and PEEP (for the latter). However, the variables included in their analysis can also present collinearity and thus must be carefully evaluated. The absolute value of plateau pressure, although easily measured at the bedside, also depends on tidal volume and PEEP level and thus shares collinearity with these parameters. Recent studies reported that driving pressure represents a good marker that can unify the forces that act in the ARDS-affected lung. Specifically, in one study, driving pressure >15 cm H_2O was associated with higher mortality rate in ARDS patients (22). Although driving pressure is indeed collinear with other variables, careful control of measurement technique may minimize this association.

The recently completed LUNG-SAFE study offers the most global assessment of ARDS prevalence and care patterns to date. Bellani *et al*. (2) showed, in 459 ICUs from 50 countries, that less than two-thirds of patients with ARDS received a tidal volume of 8 mL/kg predicted body weight or less, plateau pressure was measured in only 40.1% of patients, and 82.6% received a PEEP of <12 cm H_2O. Based on these findings, greater attention to individualized ARDS therapeutics, establishing when and for whom

Table 1 Prediction scores for acute respiratory distress syndrome used in clinical studies published in the peer-reviewed literature

Study	Patient/ARDS definition	Study design	Score parameters	Outcome
Murray *et al*., 1988 (12)	AECC	Observational cohort study	Chest imaging, hypoxemia, PEEP, and respiratory system compliance. Patients were also categorized according of ARDS onset, severity, and cause of disease	LIS has been widely used to predict clinical therapies in ARDS trials. However, it did not emerge as a predictor of mortality in ARDS
Monchi *et al*., 1998 (11)	117 patients in developmental sample and 82 for validation, according to AECC definition	Observational cohort study	Demographic, hemodynamic and respiratory variables; underlying diseases; and several severity scores (SAPS, SAPS-II, OSF, and LIS)	SAPS-II, severity of underlying diseases, oxygenation index, duration of mechanical ventilation, mechanism of lung injury, cirrhosis, and right ventricular dysfunction were associated with high risk of death
Cooke *et al*., 2008 (10)	1,113 patients with ARDS	Second-analysis, multicenter, prospective study	Comparison of a composite of variables selected specifically for ARDS patients, ventilator parameters, arterial blood gases, chest radiography, and timing of ARDS onset *vs*. established illness severity scores (SAPS II, APACHE II, and APACHE III)	In the definition cohort, the area under the ROC curve was higher than for APACHE III ($P<0.01$); however, no difference was achieved in the external validation cohort
Gajic *et al*., 2011 (17)	5,584 ARDS patients selected according to AECC definition	Multicenter observational cohort study	LIPS including high-risk trauma, high-risk surgery, aspiration, sepsis, shock, pneumonia, pancreatitis, alcohol abuse, hypoalbuminemia, acidosis, tachypnea, oxygen supplementation, obesity, chemotherapy, and diabetes mellitus	LIPS identifies patients at high risk of ARDS early in the course of illness (AUC of 0.80). LIPS outperformed the APACHE II score calculated at the time of hospital admission
Levitt *et al*., 2013 (19)	62 patients who met AECC criteria	Prospective observational cohort study	EALI criteria, based on respiratory rate and oxygen requirement, *vs*. LIPS and APACHE II	EALI score accurately identified patients who progressed to ARDS requiring positive pressure ventilation (AUC 0.86), similarly to LIPS and outperforming APACHE II. EALI still requires external validation
Damluj *et al*., 2011 (18)	508 patients with non-trauma ARDS	Observational cohort study	ARDS Net model (includes demographics, severity of illness, primary ARDS risk factor, and laboratory and physiology data at the time of ALI diagnosis) compared to APACHE II, Charlson comorbidity index, and SOFA score	Ability to predict in-hospital survival was similar for APACHE II and ARDS Net. However, the observed mortality among intermediate-risk patients was higher than that predicted by the model
Kangelaris *et al*., 2014 (15)	550 patients who met Berlin definition of ARDS	Multicenter prospective cohort study	ARDS severity according to LIS and Berlin stages of ARDS (mild, moderate, or severe)	Neither LIS nor Berlin definition of severity were designed to prognosticate outcomes
Wang *et al*., 2014 (16)	646 ARDS patients stratified according to AECC and compared with Berlin definition	Multicenter prospective cohort study	Berlin stages of severity, LIS, Brussels organ failure to compare in-hospital and 1-year ARDS mortality	LIS, APACHE II, organ failure, and PaO_2/FiO_2 did not emerge as predictors of mortality in survivors. Long-term mortality substantially higher than short-term mortality in patients with ARDS
Go *et al*., 2016 (9)	2,369 ARDS patients	Retrospective cohort study	Oxygenation index calculated from inspired oxygen concentration, arterial oxygen partial pressure, and airway pressures	Limited utility in predicting mortality in ARDS patients. However, discriminates between efficacious and non-efficacious ARDS therapies very well
Villar *et al*., 2016 (1)	300 patients in developmental sample and 300 for validation, according to AECC and Berlin definition	Prospective multicenter observational cohorts	Age, PaO_2/FiO_2, APPS	APPS score >7 resulted in higher mortality compared to APPS <5 (>80% *vs*. <14%, $P<0.0000001$). The area under the curve for APPS in the validation cohort was 0.80, *vs*. 0.66 for APACHE II ($P<0.000001$)

Summarize of clinical studies that described and compared different predictive scores for acute respiratory distress syndrome outcome. AECC, American European Consensus Conference; APACHE, Acute Physiology and Chronic Health Evaluation; APPS, and plateau pressure score; ARDS, acute respiratory distress syndrome; AUC, area under the receiver operator characteristic curve; LIS, lung injury score; LIPS, lung injury prediction score; ROC, receiver operating characteristic; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; EALI, early acute lung injury; OSF, organ system failure.

treatment may be selected and which specific subgroups may respond differently to interventions, is needed urgently. Future clinical trials will need to consider enrichment strategies and incorporate long-term functional outcomes.

Conclusions

Prognostic scores, such as APACHE III, SAPS 3 and MPM III_0, can provide estimates of the probability of death for individual patients in the ICU. However, there are controversies regarding the use of these scores for predicting outcome in patients with ARDS. Some studies have developed scores to predict mortality at bedside in this patient population (10,11,23,24); however, all had limitations such as the use of non-protective mechanical ventilation strategies and small sample sizes. Villar *et al*. designed an outcome score (APPS) that combines variables that are readily and routinely obtained at bedside 24 h after ARDS diagnosis (age, PaO_2/FiO_2, and plateau pressure). They reported that the APPS can be useful for predicting patients at high risk of fatal outcome, selecting patients with ARDS in clinical studies, and guiding ventilator management. Certainly, further multicenter studies should be performed for external validation of this score in other clinical management settings and countries.

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