Perspective

# On the complexity of scoring acute respiratory distress syndrome: do not forget hemodynamics!

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**Abstract:** Acute respiratory distress syndrome (ARDS) remains associated with a poor outcome despite recent major therapeutic advances. Forecasting the outcome of patients suffering from such a syndrome is of a crucial interest and many scores have been proposed, all suffering from limits responsible for important discrepancies. Authors try to elaborate simple, routine and reliable scores but most of them do not consider hemodynamics yet acknowledged as a major determinant of outcome. This article aims at reminding the approach of scoring in ARDS and at deeply describing the most recently published one in order to highlight their main pitfall, which is to forget the hemodynamics.

**Keywords:** Acute respiratory distress syndrome (ARDS); hemodynamics; outcome; score

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## Introduction

Forecasting the outcome of patients is a daily concern. More than two thousand years ago, Hippocrates said that it is a most excellent thing for physicians to practice forecasting. Past decades have witnessed a growing interest in scores designed to predict outcome, particularly for the most critically ill patients. Scores have been developed for different goals. First, a score may help decide whether or not to perform some diagnostic procedures, as, for instance, a CT scan in suspected pulmonary embolism. Second, it should help physicians to conduct adequate randomized controlled trials in a more homogeneous population with the same risk of dying in order to test new drugs or types of management. Acute respiratory distress syndrome (ARDS), as a very heterogeneous syndrome, well illustrates that need in the light of the unlimited debates and discussions regarding the disappointing results of positive end-expiratory pressure (PEEP) trials or even prone positioning (PP) studies, until the "definitive" PROSEVA study (1). But above all, an appropriate score should allow in daily practice appropriate adjustment of therapeutic strategies in the hope of improving survival. Unfortunately, scoring systems are limited by their consubstantial link to the pattern and treatment of the development and validation cohorts. In other words, their external validity is difficult to approach.

In ARDS, a lot of studies have reported many predictors of prognosis (2-6). Very recently, Villar *et al.* proposed a new score called the "APPS" which is very simply based on age, $PaO_2/FiO_2$ and plateau pressure (Pplat) (7). This gives us the opportunity to reiterate how important it is to predict prognosis in ARDS, to briefly present the promising Villar *et al.* score, and finally to underline some forgotten parameters, focusing on hemodynamics and right ventricular (RV) function, which could help improve prognostic prediction and then management.

## Outcome prediction: why and how

ARDS is still associated with a poor outcome in the

**Table 1** Identified risk factors with a potential impact on outcome (ICU mortality, in-hospital mortality, 6-month mortality) in acute respiratory distress syndrome (non-exhaustive list)

| Factor | Commentary |
|---|---|
| Predisposing factor | |
| Age | Age >65 years is strongly associated with mortality |
| Severity of illness | Severity scores at admission (APACHE III and II, SAPS II) are powerful markers of outcome, but do not discriminate the weight of ARDS |
| BMI | Higher BMI has been identified as a possible protective factor during ARDS, but further study is needed |
| ARDS characteristics | |
| $PaO_2/FiO_2$ | The weight of $PaO_2/FiO_2$ is questionable since it may be altered by many factors, such as hemodynamics and intra-cardiac shunt. A ratio <150 mmHg after one day of ventilation, when shock is resolved, is probably a more relevant predictor |
| Pplat | Compliance alteration reflects the severity of the ARDS and a Pplat >27 $cmH_2O$ can be considered as accurately associated with mortality |
| Driving pressure | This parameter has been emerging for a decade and a driving pressure >14 $cmH_2O$ is a strong risk factor for mortality in ARDS |
| CT scan | Diffuse alveolar damage on CT-scan is worse than focused lesions, but its impact on prognosis has yet to be studied |
| Ventilatory strategy | |
| Tidal volume | Tidal volume higher than 10–12 mL/kg is associated with poor outcome, but there are no data to discriminate the effect of lower tidal volumes provided that Pplat is controlled |
| PEEP | There are no data on the beneficial effect of high PEEP |
| Neuromuscular blockade | Such therapeutics have been shown to be beneficial in the most severe cases of ARDS |
| Prone position | Prone positioning has a protective effect in patients with a $PaO_2/FiO_2$ <150 mmHg a few hours after ventilation |
| Extra-pulmonary failure | |
| SOFA score | SOFA score reflects the level of organ failure and each organ failure does not have the same impact on outcome |
| Circulatory failure | Shock is strongly associated with mortality. In one half of cases it is related to RV failure |
| RV failure | Severe ACP is clearly associated with mortality. There is no study of how a strategy limiting RV failure may improve prognosis |

ICU, intensive care unit; APACHE, acute physiology and chronic health evaluation; SAPS II, simplified acute physiology score II; ARDS, acute respiratory distress syndrome; BMI, body mass index; Pplat, plateau pressure; PEEP, positive end-expiratory pressure; SOFA, sequential organ failure assessment; RV, right ventricle; ACP, acute cor pulmonale.

intensive care unit (ICU). In the recent epidemiological cohort study from the European Society of Intensive Care Medicine in nearly 30,000 patients, ARDS accounted for 10% of ICU admissions and was associated with mortality ranging from 30% in mild cases to more than 46% in severe ones (8). After 40 years of studies seeking to understand the pathophysiology of ARDS, the 21st century started with three major therapeutic advances leading to a decrease of nearly 10% in crude mortality (1,9,10). Nevertheless, despite ventilation with a low tidal volume, the early and brief use of muscular blockade, and PP ventilation, one third to one half of patients still die (1,9,10). This is probably due in part to the disappointingly low rate of routine application of these procedures, even in the target population in which they are validated (8).

How ARDS is defined is frequently interlinked with its prognosis (*Table 1*). Twenty years after the landmark definition of ARDS (11), Murray *et al.* expanded the definition using the lung injury score (LIS) (12). A score of zero defined no lung injury, whereas a score between 0.1 and 2.5, and higher than 2.5 defined mild to moderate and severe lung injury, respectively (12). They recommended using the

 

term ARDS only for patients with the most severe lung injury, i.e., with a score >2.5 (12). However, this score was somewhat subjective in certain regards, such as the chest X-ray evaluation, and difficult to use routinely everywhere. Moreover, Doyle *et al.* and Zilberberg *et al.* later reported that it is actually not associated with prognosis (13,14), suggesting the existence of cofounding factors between lung injury and outcome. Interestingly, Cooke *et al.* identified predictors of mortality very similar to those of the general intensive care population and especially confirmed that "general" severity at admission is a big marker (2). They also proposed a score combining arterial pH (protective per 0.1 more alkalotic), minute ventilation (protective when <9 L/min), $PaCO_2$ (protective per 5 mmHg increase), and $PaO_2/FiO_2$ (associated with mortality when decreasing) (2). The overall in-hospital mortality in their study was 38.5% and the predictive value of the score was better than the acute physiology and chronic health evaluation (APACHE) III in their development cohort, although not different in their validation cohort (2). Later, the same group validated a simpler clinical predictive score (3). Age, bilirubin, fluid balance before enrollment and hematocrit were the four parameters used in the model (3). This 4-point score was elaborated in the low tidal volume group of patients included in the ARMA study (9). In the validation cohort, i.e., patients from the ALVEOLI study (15), in-hospital mortality increased from 12% for a score of zero to 67% for a score of 4. Nevertheless, this predictive score has not been validated in a nonclinical trial population and so may expose frontline intensivists to major bias.

For many years the definition of ARDS was based on the American-European consensus conference (16). In the case of bilateral infiltrates on chest X-ray without any evidence of left atrial hypertension, acute lung injury (ALI) was defined as an acute fall in $PaO_2/FiO_2$ to between 200 and 300 mmHg and as ARDS when $PaO_2/FiO_2$ is below 200 mmHg (16). Whether this definition was adapted to score the risk of death is questionable. Bersten *et al.* found no difference in 28-day mortality between ALI and ARDS, 32% and 34%, respectively in an Australian cohort (17). Others, as Brun-Buisson *et al.* in a European cohort, found a significant difference for in-hospital mortality, respectively 49.4% and 57.9% (18).

The Berlin definition has recently revisited ARDS, which is now defined as acute hypoxemia developing in a week or less, in patients with bilateral opacities on chest X-ray, having at least one risk factor for lung injury or no argument for hydrostatic edema (19). ARDS is also classified as mild, moderate or severe, according to $PaO_2/FiO_2$ following ventilation with a minimal PEEP of 5 $cmH_2O$ (19). Each stage has been demonstrated to be associated with different mortality rates, i.e., around 27–29% in mild, 32–35% in moderate and 42–45% in severe ARDS (8,19), and with different duration of mechanical ventilation in survivors (5, 7 and 9 days, respectively). However, this is still questionable, since Hernu *et al.* did not report that neither classification of ARDS as mild, moderate or severe nor $PaO_2/FiO_2$ is associated with mortality (20).

Very recently, following a preliminary study (4), Villar's group proposed a simpler score for all ARDS patients, called "APPS" (7). The authors highlighted the importance of a simple, routine and reliable index of the ARDS patient's condition that can quickly predict outcome, such as the Apgar score for newborns (21) or the Glasgow coma score for head trauma (22). This score was appropriately elaborated since it was built in a development cohort and validated in a different validation cohort. This new score is based on age, $PaO_2/FiO_2$ and Pplat separated in tertiles, 24 hours following admission (7). The minimum score is 3 and the maximum 9, corresponding respectively to 60-day survival of more than 80% and less than 20% (7).

## APPS for stratifying ARDS patients

### *Age*

Most cohort studies designed to identify mortality risk factors demonstrate a major role of age (3,5,7). Among the 414 medical patients of the low tidal volume group of the ARMA study (9), patients who died were more than 10 years older than patients who survived [60 (range, 45–72) *vs.* 48 (range, 37–61) years old, respectively] (3). The same result was initially reported by Villar *et al.* (5). Overall, age above 65 appears to be a strong predictor of mortality in ARDS. Age is linearly associated with severity in the APACHE (23,24) and also in the simplified acute physiology score II (SAPS II) (25). Based on these results, Villar *et al.* elaborated their score in tertiles. Patients <47 years old were attributed one point, whereas patients aged 47 to 66 and >66 were attributed two and three points, respectively (7).

### *Oxygenation*

$PaO_2/FiO_2$ is used as a reflection of lung injury, yet many factors that have nothing to do with the severity of lung injury may affect blood gas analysis. Hemodynamic failure,

 

which will be discussed further below, may especially contribute to $PaO_2/FiO_2$ by two mechanisms that have opposite effects. The first, called low $PvO_2$ effect, leads to a decrease in oxygenation and then to an overestimation of lung injury. Lemaire *et al.* demonstrated that, for a given shunt fraction, $PaO_2/FiO_2$ dramatically decreases in patients with an elevated arteriovenous oxygen content difference (due to an increase in oxygen extraction) compared with the others (26). The second mechanism regards alterations of shunt fraction according to cardiac output changes. A low cardiac output decreases the shunt, increases $PaO_2/FiO_2$ and so may lead to underestimation of lung injury (27). Another mechanism may also limit interpretation of $PaO_2/FiO_2$ as a marker of lung injury. This is intra-cardiac shunt through a patent foramen ovale because the right ventricle is overloaded. Mekontso Dessap *et al.* reported that it occurs in close to 20% of ARDS patients submitted to protective ventilation and is associated with a significant increase in duration of ventilation (28). Pulmonary imaging as well as respiratory mechanics may reflect lung injury more efficiently. Rouby *et al.* reported that differences in lung morphology evaluated by CT-scan and in respiratory mechanics help identify ARDS with a high mortality, since mortality was 75% in patients with diffuse attenuations and 42% in patients with lobar attenuations (29). Finally, $PaO_2/FiO_2$ is strongly related to respiratory settings. In the ARMA study, patients ventilated with 12 mL/kg had better $PaO_2/FiO_2$ ratios than patients ventilated with low tidal volume, but a poorer outcome (9). In the Berlin consensus conference, experts proposed standardizing ventilation with a PEEP of 5 $cmH_2O$ and a tidal volume of 6 mL/kg to so as to interpret $PaO_2/FiO_2$ correctly (9). However, as shown by the recent ESICM trial, many intensivists still do not ventilate patients with such a low tidal volume (8). In the preliminary study by Villar's group, $PaO_2/FiO_2$ did not differ significantly between survivors and non-survivors (115±41 *vs.* 106±39, respectively, P=0.054), but the overall population actually had severe ARDS (4). Hernu *et al.* also reported no difference in mortality according to the $PaO_2/FiO_2$ ratio (20). Nevertheless, Cooke *et al.* demonstrated an association between death and the lowest $PaO_2/FiO_2$ ratio (3). In their APPS, Villar *et al.* constructed tertiles, in which patients with a $PaO_2/FiO_2$ <158 mmHg were given two points and those with a ratio <105 mmHg were given three points (7). These tertiles appear to be in accordance with studies demonstrating the beneficial effects of neuromuscular blockade and PP for patients with a $PaO_2/FiO_2$ below 150 mmHg (1,10).

### *Pplat*

The third parameter of the APPS focuses on respiratory mechanics. Pplat is the consequence of tidal volume and compliance of the respiratory system and may be understood as a surrogate of lung stress/transpulmonary pressure at end-inspiration. It is now widely established that ARDS is characterized by diffuse alveolar damage (30), which can be dramatically worsened by ventilator-induced lung injury (VILI) (31-33). Since the beginning of the 1990s, authors have demonstrated the value of limiting tidal volume and Pplat in reducing mortality (9,34). More recently, Amato *et al.* as well as Bellani *et al.* provided some clarification by showing that the deleterious effects of tidal ventilation are actually more related to the driving pressure (Pplat minus total PEEP), reflecting the lung stress induced by inspiration (8,35,36). For "APPS", Pplat is separated in tertiles: <27 $cmH_2O$ (one point), 27–30 $cmH_2O$ (two points) and >30 $cmH_2O$ (three points) (7).

## The "forgotten" hemodynamics

ARDS is very frequently associated with hemodynamic failure, since more than 60% of patients have shock (37) and 65% require infusion of catecholamines (38,39). As discussed above, hemodynamic failure limits the accuracy of $PaO_2/FiO_2$ in evaluating the severity of lung injury. In most of the predictors previously discussed, hemodynamics *per se* is not evaluated. Yet, Doyle *et al.* reported that in-hospital mortality is very similar (56% *vs.* 59%) in patients with a $PaO_2/FiO_2$ < or >150 mmHg, whereas nonpulmonary organ system dysfunction is a strong predictor of mortality (13). Vieillard-Baron *et al.* reported in 98 patients with moderate to severe ARDS that septic shock or the need for epinephrine/norepinephrine infusion is strongly associated with mortality, although the level of hypoxemia is not, suggesting that hemodynamic failure is key among nonpulmonary organ dysfunctions (40). Later, Page *et al.* reported parameters associated with mortality in 150 patients with moderate to severe ARDS (41). The overall hospital mortality was 38%. The only two parameters independently associated with mortality were $PaO_2/FiO_2$, with an odds ratio (OR) of 1.01 (1.00–1.02), and the severity of circulatory failure, with an OR of 10.17 (3.43–30.32), whereas LIS was not (41). In a cohort of more than 752 patients with moderate to severe ARDS submitted to protective ventilation, Mekontso Dessap *et al.* recently re-emphasized that shock is one of the factors independently associated with mortality and has

 

the highest OR [3.25 (2.32–4.56)] among age, SAPS II, and a $PaO_2/FiO_2$ <100 mmHg during the first 2 days following mechanical ventilation [OR 1.45 (1.02–2.08)] (37). In these two last studies, $PaO_2/FiO_2$ was slightly but significantly associated with mortality. However, it was recorded a few hours or days following mechanical ventilation in a period when hemodynamics is stabilized and may therefore reflect severity more accurately. This is the position of Villar *et al.*, who record $PaO_2/FiO_2$ 24 hours after ventilation.

Apart from sepsis, which is frequently associated and responsible for shock in half of ARDS patients (18), one of the main causes of hemodynamic failure is RV failure. The reasons for such RV failure are many, and all lead to acute pulmonary hypertension and increased RV afterload: lung inflammation induces pulmonary vascular injury (42), hypoxemia and respiratory acidosis induce pulmonary vasoconstriction and mechanical ventilation may induce a vascular waterfall at the level of the pulmonary capillaries (43). In this situation, RV failure is detected by echocardiography as a pattern of acute cor pulmonale (ACP), which associates RV dilatation and paradoxical septal motion, without significant RV hypertrophy (44). Risk factors for ACP are pneumonia-related ARDS, $PaO_2/FiO_2$ <150 mmHg, driving pressure ≥18 $cmH_2O$ and $PaCO_2$ ≥48 mmHg, with an incidence of ACP less than 10% in the absence of risk factors, but of 60% when four risk factors are present (37). Severe ACP (the right ventricle is bigger than the left) has been reported as independently associated with mortality with an OR of 1.89 (1.08–3.30) (37). Interestingly, it has been reported that PP may normalize RV function (45) and also improve hemodynamics (46). On the other hand, the beneficial effect of PP on survival is not related to blood gas analysis changes (47), whereas PP increases the number of cardiovascular failure-free days up to 28 days after randomization and decreases the incidence of cardiac arrest (1). In the development and validation cohorts of the APPS, it seems that patients did not benefit from PP (at least it is not reported), which could result in a major bias (7).

## Conclusions

Scoring the outcome of patients suffering from ARDS is one of the most difficult evaluations that intensivists have to face, because the "salad" of ARDS mixes cabbages and carrots. Heterogeneity regards patients, lung injury and histologic lesions, but also treatments, some of which are proven to change the prognosis. This could explain the huge variability among studies. However, it is clear that potential circulatory and RV failures play a great role and should be taken into account so as to classify patients well, since ARDS is most certainly not a single-organ failure. The "geocentric" vision of ARDS focused on the lung and gas exchange must be replaced by a more post-Copernican and "heliocentric" vision including hemodynamics and especially the RV, on the one hand, and genetic variants on the other.

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