

# Age, Pao<sub>2</sub>/Fio<sub>2</sub>, and Plateau Pressure Score: A Proposal for a Simple Outcome Score in Patients With the Acute Respiratory Distress Syndrome\*

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## \*See also p. 1437.

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A list of Stratification and Outcome of Acute Respiratory Distress Syndrome (STANDARDS) Network investigators are listed in Appendix 2.

This study has been registered with <http://www.clinicaltrials.gov> (NCT 00736892 and NCT02288949).

Drs. Villar, Pérez-Méndez, and Kacmarek designed the original study. Drs. Ambrós, Soler, Martínez, Ferrando, Solano, Mosteiro, Blanco, Copyright © 2016 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

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**Objectives:** Although there is general agreement on the characteristic features of the acute respiratory distress syndrome, we lack a scoring system that predicts acute respiratory distress syndrome outcome with high probability. Our objective was to develop an outcome score that clinicians could easily calculate at the bedside to predict the risk of death of acute respiratory distress syndrome patients 24 hours after diagnosis.

**Design:** A prospective, multicenter, observational, descriptive, and validation study.

**Setting:** A network of multidisciplinary ICUs.

**Patients:** Six-hundred patients meeting Berlin criteria for moderate and severe acute respiratory distress syndrome enrolled in two independent cohorts treated with lung-protective ventilation.

**Interventions:** None.

**Measurements and Main Results:** Using individual demographic, pulmonary, and systemic data at 24 hours after acute respiratory distress syndrome diagnosis, we derived our prediction score in 300 acute respiratory distress syndrome patients based on stratification of variable values into tertiles, and validated in an independent cohort of 300 acute respiratory distress syndrome patients. Primary outcome was in-hospital mortality. We found that a 9-point score based on patient's age,  $\text{PaO}_2/\text{FiO}_2$  ratio, and plateau pressure at 24 hours after acute respiratory distress syndrome diagnosis was associated with death. Patients with a score greater than 7 had a mortality of 83.3% (relative risk, 5.7; 95% CI, 3.0–11.0), whereas patients with scores less than 5 had a mortality of 14.5% ( $p < 0.0000001$ ). We confirmed the predictive validity of the score in a validation cohort.

**Conclusions:** A simple 9-point score based on the values of age,  $\text{PaO}_2/\text{FiO}_2$  ratio, and plateau pressure calculated at 24 hours on protective ventilation after acute respiratory distress syndrome diagnosis could be used in real time for rating prognosis of acute respiratory distress syndrome patients with high probability. (*Crit Care Med* 2016; 44:1361–1369)

**Key Words:** acute respiratory distress syndrome; age; arterial partial pressure of oxygen/fraction of inspired oxygen; plateau pressure; scoring system

Prognosis is a key factor for clinicians caring for critically ill patients. Although there is general agreement on the characteristic features of the acute respiratory distress syndrome (ARDS), we lack a scoring system that can predict ARDS outcome with a high probability similar to the Apgar score (1), Acute Physiology and Chronic Health Evaluation (APACHE) II score (2), and the Glasgow Coma Scale (3). Those scoring systems have been effective in evaluating the condition of newborns, critically ill patients, and head trauma patients, respectively, and help clinicians predict short- and long-term survival.

Scoring systems are increasingly being incorporated into clinical trial design (4). Murray et al (5) used a lung injury severity (LIS) score that takes into account various pathophysiologic features of the syndrome. However, although the LIS score has been used to screen ARDS patients, it is not specific for ARDS and has not been validated. The APACHE II score has been proposed as a clinical measure of patient condition, but it is not easily calculated at the bedside, requires numerous data elements, and relies on laboratory data that are not uniformly collected. They are a few prior studies attempting to characterize predictors of death in ARDS integrated into a prognostic index (6–9), but their predictive power remains controversial. In most of those studies, patients were treated with tidal volumes (VTs) above current practice, and in all of

them, the predictors of death were similar to those in the general population of critically ill patients.

Currently, there is no simple, routine, and reliable index of ARDS patient's condition that predicts hospital outcome. We designed this observational study to improve prognostic accuracy of hospital mortality in ARDS patients. Our goal was to develop a simple outcome score that incorporates variables known to be relevant to ARDS and that clinicians could routinely and easily calculate to predict risk of death at 24 hours after ARDS diagnosis. We postulated that such a scoring system for ARDS would be a useful screening tool for identifying individual patients at greater risk of death, independent of the underlying disease or specific therapy. We derived a simple outcome score (age,  $\text{PaO}_2/\text{FiO}_2$ , and plateau pressure score [APPS]) based on individual data from three variables routinely collected (age,  $\text{PaO}_2/\text{FiO}_2$ , and plateau pressure) at 24 hours after ARDS diagnosis while patients were on mechanical ventilation (MV). Because the APPS predicted patients at high risk of fatal outcome, it could be helpful for bedside decision making, for selection of ARDS patients in clinical studies, and for guiding ventilatory management that would prevent or reduce the associated fatality rate.

## METHODS

This study was approved by the Ethics Committee for Clinical Research at the Hospital Clínico de Valencia (Valencia, Spain), Hospital Virgen de la Luz (Cuenca, Spain), Hospital Universitario Río Hortega (Valladolid, Spain), and the local institutional review boards of all participating hospitals.

### Study Design, Patient Selection, and Data Collection

We assessed and quantified risk of death based on tertile stratification of clinical variables at 24 hours after ARDS diagnosis, independent of the specific disease process or treatment. We developed and tested our score using data from ARDS patients enrolled in two independent prospective multicenter observational cohorts treated with lung-protective MV. All patients met the American-European Consensus Conference criteria for ARDS (10) on positive end-expiratory pressure (PEEP) greater than or equal to 5 cm  $\text{H}_2\text{O}$  and the Berlin criteria for moderate and severe ARDS (11).

The study was done in two steps. First, we derived our score from a cohort of 300 adult consecutive ARDS patients admitted in a network of ICUs from September 2008 to January 2010 (Appendix 1). Patients from this derivation cohort were previously used for reporting the 1-year ARDS incidence in Spain (12) and for reporting a new clinical classification of ARDS (13), but none of the data reported in the present study has been published. Second, we examined the predictive validity of the score in a separate cohort of 300 consecutive ARDS patients (validation cohort) admitted from January 2014 to June 2015 in a network of ICUs (Appendix 2).

We recorded information from 62 variables including age, gender, cause of ARDS, APACHE II score, hemodynamics, gas exchange, and MV data at ARDS onset, on days 1, 3, and 7 after ARDS diagnosis, and last day of MV. We considered the

lowest and highest values of respiratory physiology and MV at 24 hours after ARDS diagnosis. Based on our preliminary work (14), we analyzed the  $\text{PaO}_2/\text{FiO}_2$  value assessed under a standardized ventilatory setting ( $\text{FiO}_2 \geq 0.5$ ;  $\text{PEEP} \geq 10$  cm  $\text{H}_2\text{O}$ ) at 24 hours after ARDS onset. We also recorded LIS score (5), occurrence of shock, and the number of extrapulmonary organ failures included in the Sequential Organ Failure Assessment (SOFA) scale (15) at the time of ARDS diagnosis. Organ dysfunction was defined as scores 1 or 2, and organ failure as 3 or 4 in the SOFA scale. Although there was not a strict ventilatory protocol, it was recommended that patients be ventilated with a VT of 4–8 mL/kg predicted body weight (PBW), a ventilatory rate that maintained adequate  $\text{PaCO}_2$ , and PEEP and  $\text{FiO}_2$  combinations that maintained  $\text{PaO}_2$  60–90 mm Hg or  $\text{Spo}_2$  greater than 90%. None of the patients received nitric oxide, activated protein C, high-frequency ventilation, or extracorporeal assist.

### Statistical Analysis and Development of the Score

Primary outcome was all-cause death in the hospital. The population size of our derivation and validation cohorts satisfied various possible size scenarios for an absolute 15% mortality rate reduction between tertiles, an  $\alpha$  value equal to 0.05 and a power goal of greater than 0.80. Data are reported as mean  $\pm$  SD or percentages. We compared categorical variables with the chi-square and Fisher exact probability tests. We compared continuous variables with the Student *t* test. We used the Mann-Whitney *U* rank test for variables with nonnormal distribution.

Based on a preliminary exploratory study (16), we selected a series of 10 demographic and clinically relevant variables for the development of the score: age, VT, respiratory rate, PEEP, plateau pressure,  $\text{FiO}_2$ ,  $\text{PaO}_2/\text{FiO}_2$  ratio,  $\text{PaCO}_2$ , pH, and the number of extrapulmonary organ failures. We did not include respiratory compliance in the model because it shares colinearity with three independent variables needed for its calculation (VT, plateau pressure, and PEEP) nor driving pressure (plateau pressure – PEEP) for the same reason; they both suffer from redundancy in the descriptive model. The tertile ranges were based on the distribution of individual data from each variable in the derivation cohort (details are given in the **electronic supplementary material**, Supplemental Digital Content 1, <http://links.lww.com/CCM/B776>).

We calculated the mortality, relative risk (RR) of death, and the 95% CIs associated with each tertile. Then, we identified the variables that could be used as regressors, based on their *p* values and their potential for use in an outcome score, striving for simplicity and predictive power. We stratified the values into low-, middle-, and high-risk tertiles. We tested for linear trends using the tertile with the lowest mortality as the reference group and considered the tertile as an ordinal variable. After identifying the variables for inclusion into the score, we used the cutoff of each tertile for each point level so that a 1-point increase in the score for each variable would produce an equivalent increase in the odds of death.

We confirmed the predictive validity of the score by applying our model to individual data from an independent population

of 300 ARDS patients (validation cohort), and tested with the maximum-likelihood chi-square test. We evaluated the model's discrimination of both cohorts with the area under the receiver operating characteristic (ROC) curve and compared the overall performance of our model to that of the APACHE II score. Probability of 60-day survival was analyzed for the entire population of 600 patients according to the total score in each patient using the Kaplan-Meier method with the log-rank test. Data from patients who were discharged home before day 60 were censored at day 60, with the patients considered to be alive at day 60. For all comparisons, a two-sided *p* value of less than 0.05 was considered significant.

## RESULTS

There were no significant differences between the overall hospital mortality in both cohorts (46.3% vs 42.3%; *p* = 0.366). Characteristics of patients at the time of ARDS diagnosis are listed in **Table 1**. At study entry, patients in the validation cohort were ventilated with a slightly lower mean VT and a higher mean PEEP than patients in the derivation cohort. However, in the derivation cohort, mean VT at day 3 dropped to  $6.8 \pm 1.0$  mL/kg PBW (data not shown). There were no significant differences in mean VT between the two cohorts beyond day 1 (data not shown).

### Derivation Cohort

After stratifying patients based on the cutoff values of its tertiles, the values of PEEP,  $\text{FiO}_2$ , and the number of extrapulmonary organ failures at 24 hours after ARDS onset could not be distributed with a comparable number of cases in each tertile (**Table E1**, Supplemental Digital Content 1, <http://links.lww.com/CCM/B776>). Comparisons among the best possible distribution of patients in each tertile did not reach statistical significance with mortality. The tertile distribution for the other variables identified ARDS patients with a wide range of in-hospital mortality risk although only the tertile distribution for age,  $\text{PaO}_2/\text{FiO}_2$  ratio, and plateau pressure reached statistical significance (**Table 2**). An age more than 66 years old, a  $\text{PaO}_2/\text{FiO}_2$  ratio less than 105 mm Hg calculated under standardized ventilatory settings at 24 hours after ARDS diagnosis, and a plateau pressure greater than 30 cm  $\text{H}_2\text{O}$  at 24 hours after ARDS diagnosis were associated with the highest risk of death. Each of these tertiles correlated independently with ARDS outcome. The cutoff values of these three variables were used as the components for our ARDS prediction score, APPS (**Table 3**). The lowest total APPS was 3 points, and the maximum was 9 points.

We found that as APPS increased, in-hospital mortality increased monotonically (**Fig. E1A**, Supplemental Digital Content 1, <http://links.lww.com/CCM/B776>). Among 54 patients (18%) with an APPS greater than 7, death occurred in 45 (83.3%) (RR, 5.7; 95% CI, 3.0–11.0). In contrast, among the 55 patients (18.3%) with an APPS less than 5, only eight (14.5%) died (*p* < 0.0000001) (**Table E2**, Supplemental Digital Content 1, <http://links.lww.com/CCM/B776>). Only one patient with an APPS of 3 points died in the hospital (although

**TABLE 1. Patient Characteristics at Study Entry and Outcomes**

Variables	Derivation Cohort (n = 300)	Validation Cohort (n = 300)	p
Gender, male/female (n)	211/89	201/99	0.428
Age, yr (mean ± sd)	56 ± 17	57 ± 16	0.458
Main diagnosis, n (%)			
Pneumonia	129 (43.0)	136 (45.3)	0.622
Sepsis	92 (30.7)	97 (32.3)	0.725
Aspiration	29 (9.7)	28 (9.3)	1
Trauma	30 (10.0)	17 (5.7)	0.067
Disease severity (mean ± sd)			
Acute Physiology and Chronic Health Evaluation II	22 ± 6	21 ± 7	0.061
Lung injury severity score	2.9 ± 0.6	2.9 ± 0.6	1
Physiologic variables (mean ± sd)			
pH	7.31 ± 0.11	7.31 ± 0.11	1
Paco <sub>2</sub> , mm Hg	47 ± 11	48 ± 12	0.288
Pao <sub>2</sub> /Fio <sub>2</sub> , mm Hg	111 ± 40	117 ± 39	0.063
Respiratory system compliance, mL/cm H <sub>2</sub> O	32 ± 14	32 ± 15	1
Ventilation variables (mean ± sd)			
Tidal volume, mL/kg predicted body weight	7.2 ± 1.2	6.7 ± 1.0	< 0.001
Fio <sub>2</sub>	0.80 ± 0.20	0.80 ± 0.20	1
Respiratory rate, breaths/min	21 ± 6	21 ± 5	1
Positive end-expiratory pressure, cm H <sub>2</sub> O	9.2 ± 3.2	10.4 ± 3.2	< 0.001
Plateau pressure, cm H <sub>2</sub> O	26 ± 6	26 ± 5	1
No. of organ failures (mean ± sd)	1.4 ± 1.1	1.3 ± 1.1	0.266
Mortality, n (%)			
ICU	126 (42.0)	116 (38.7)	0.454
In-hospital	139 (46.3)	127 (42.3)	0.366

the patient was alive at ICU discharge), whereas all patients but one with an APPS of 9 points died ( $p < 0.00000001$ ).

### Validation Cohort

The differences in outcome among patients with different APPS were statistically significant ( $p < 0.0000001$ ) (Fig. E1B, Supplemental Digital Content 1, <http://links.lww.com/CCM/B776>). Among 44 patients (14.7%) with an APPS greater than 7, in-hospital death occurred in 40 (90.1%) (RR, 12.0; 95% CI, 4.7–31.0). In contrast, among the 53 patients (17.7%) with an APPS less than 5, only four (7.5%) died ( $p < 0.0000001$ ) (Table E2, Supplemental Digital Content 1, <http://links.lww.com/CCM/B776>).

When we compared the ROC curve for the model in the derivation and validation cohorts to the APACHE II scores, APPS outperformed APACHE II (Fig. 1). The area under the curve for APPS in the derivation cohort was 0.755 (95% CI,

0.699–0.811), compared with 0.633 (95% CI, 0.567–0.699) for APACHE II ( $p < 0.000001$ ). For the validation cohort, the area under the curve for APPS was 0.800 (95% CI, 0.750–0.850), whereas the area under the curve for APACHE II was 0.660 (95% CI, 0.598–0.722) ( $p < 0.000001$ ).

When both cohorts were combined, the 60-day probability of survival clearly separated ARDS patients into three phenotypes defined by three groups of total APPS (< 5, 5–7, and > 7 points) (Fig. 2). The risk of death increased as a function of progressive APPS in the combined population ( $p < 0.0000001$ ).

### DISCUSSION

We have described and validated a simple outcome score for assessing and evaluating ARDS mortality prediction based on tertiles of individual data from three routinely available demographic, oxygenation, and ventilatory variables at 24 hours after ARDS diagnosis. Our model applies only to patients with

**TABLE 2. Tertile Association With In-Hospital Mortality in 300 Acute Respiratory Distress Syndrome Patients From the Derivation Cohort**

Variables	Tertiles	Mortality, %	Relative Risk	95% CI of Relative Risk	p for Trend
Age, yr					
< 47	1	27.5	1.0	NA	< 0.000001
47–66	2	44.4	1.6	1.1–2.4	
> 66	3	66.0	2.4	1.7–3.4	
Tidal volume, mL/kg predicted body weight					
< 6.7	1	41.8	1.0	NA	0.135
6.7–7.8	2	42.6	1.0	0.7–1.4	
> 7.8	3	54.5	1.3	1.0–1.7	
Respiratory rate, breaths/min					
> 26	1	38.2	1.0	NA	0.103
21–26	2	47.9	1.2	0.9–1.7	
< 21	3	52.9	1.4	1.0–1.9	
Positive end-expiratory pressure, cm H <sub>2</sub> O					
< 10	1	54.5	1.4	1.0–1.9	0.072
10–12	2	39.1	1.0	NA	
> 12	3	48.8	1.2	0.9–1.7	
Plateau pressure, cm H <sub>2</sub> O					
< 27	1	28.7	1.0	NA	< 0.00001
27–30	2	46.5	1.6	1.1–2.3	
> 30	3	64.0	2.2	1.6–3.1	
Fi <sub>o</sub> <sub>2</sub>					
< 0.7	1	38.8	1.0	NA	0.244
0.7–0.9	2	47.4	1.2	0.9–1.7	
> 0.9	3	50.3	1.3	0.9–1.8	
Pao <sub>2</sub> /Fi <sub>o</sub> <sub>2</sub> , mm Hg					
> 158	1	32.3	1.0	NA	0.0001
105–158	2	45.0	1.4	1.0–2.0	
< 105	3	61.4	1.9	1.4–2.6	
Paco <sub>2</sub> , mm Hg					
< 44	1	40.0	1.0	NA	0.339
44–52	2	49.5	1.2	0.9–1.7	
> 52	3	49.0	1.2	0.9–1.7	
pH					
> 7.33	1	43.0	1.0	NA	0.658
7.26–7.33	2	46.4	1.1	0.8–1.5	
< 7.26	3	49.5	1.2	0.9–1.6	
No. of organ failures, at acute respiratory distress syndrome onset (in addition to the lung)					
0	1	37.7	1.0	NA	0.082
1	2	44.0	1.2	0.8–1.7	
> 1	3	53.9	1.4	1.0–2.0	

NA = not applicable.

**TABLE 3. A 9-Point Acute Respiratory Distress Syndrome Outcome Score (Age, Pao<sub>2</sub>/Fio<sub>2</sub>, and Plateau Pressure Score)**

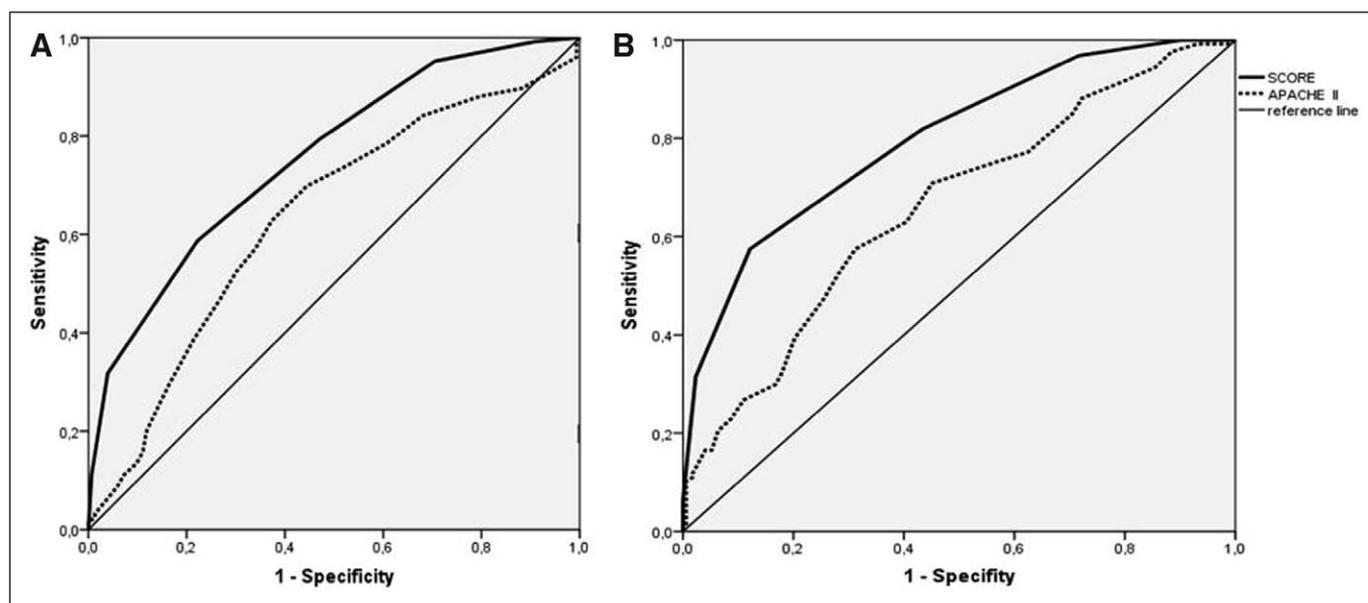
Variables	Range of Values	Score
Age, yr	< 47	1
	47–66	2
	> 66	3
Pao <sub>2</sub> /Fio <sub>2</sub> , mm Hg	> 158	1
	105–158	2
	< 105	3
Plateau pressure, cm H <sub>2</sub> O	< 27	1
	27–30	2
	> 30	3
Total score		3–9

Total score is equal to the sum of the points for each category of high-risk tertiles, based on the values at 24 hr after acute respiratory distress syndrome diagnosis.

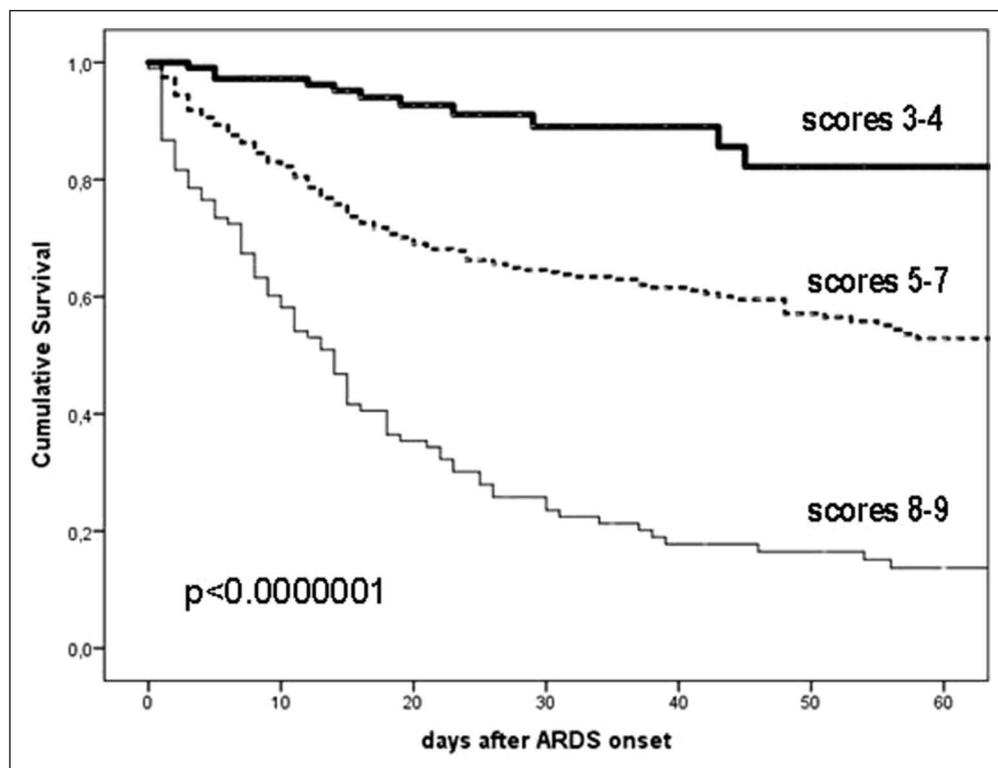
moderate/severe ARDS while they are ventilated with protective MV. We believe that APPS could serve several important purposes. First, it would allow clinicians working in the ICU environment to identify ARDS patients who are at the highest risk of death. Second, we speculate that APPS could facilitate the rapid implementation of clinical decisions that could alter ARDS management although future research using comparative studies is needed to quantify whether the daily use of the model improves decision making and patient outcomes. Third, the APPS might identify patients in whom benefit from treatment may be limited or disproportional to the resources used.

On the other hand, some interventions may have greater benefit in patients with moderate risk severity (scores of 5–7 points). Finally, APPS could be used to select and stratify patients for enrollment into clinical trials moving us closer to “individualized” or “precision” ARDS medicine (17). In that sense, our model is in line with a recent recommendation suggesting that a better identification of the ARDS patient population is the key for appropriate management and characterization of patient status (18).

Our findings are consistent with our previous exploratory findings (16) and with other reports (8, 14, 19, 20). Our results are in agreement with our previously published report on tertile distribution in ARDS patients (16). In that report, we demonstrated in 170 patients with moderate to severe ARDS that the three variables able to predict mortality in ARDS were the same as in the current article. Although the tertile ranges were not exactly the same, the difference between that data and our current data is less than 10%. What had not been recognized is the collective importance of the individual tertiles within each variable. As we enter the era of “big data,” we can be assured that such tools will be encountered with increasing frequency. Although useful as a risk stratification tool, our approach may provide a better understanding of pathophysiology and potentially a better methodology for reduction of clinical heterogeneity, given the history of failed clinical trials in ARDS. Our findings illustrate that ARDS cannot be viewed as a homogeneous disorder. On the contrary, when scoring patients after 24 hours of usual care, patients were grouped more uniformly in three categories of increasing mortality that were also associated with increasing lung dysfunction. In this sense, ARDS trials may have failed simply because of an overly broad range of mortality because there are multiple subsets of patients within the syndrome of ARDS.



**Figure 1.** Receiving operating characteristic curves for age, Pao<sub>2</sub>/Fio<sub>2</sub>, and plateau pressure score (APPS) versus Acute Physiology and Chronic Health Evaluation (APACHE) II score. **A.** Derivation cohort: area under the curve was 0.755 (95% CI, 0.699–0.811) for APPS versus 0.633 (95% CI, 0.567–0.699) for APACHE II (*p* < 0.00001). **B.** Validation cohort: area under the curve was 0.800 (95% CI, 0.750–0.850) for APPS versus 0.660 (95% CI, 0.598–0.722) for APACHE II (*p* < 0.000001).



**Figure 2.** Kaplan-Meier 60-day probability of survival curves for the combined population of 600 acute respiratory distress syndrome (ARDS) patients. Patients were classified in three phenotypes according to their age,  $\text{PaO}_2/\text{FiO}_2$ , and plateau pressure score ( $< 5$ ,  $5-7$ , and  $> 7$  points). Most deaths occurred within the first 15 d of inclusion into the study.

In general, outcome of ARDS patients is worse with increasing age (19). Patients with more severe lung disease tend to have lower  $\text{PaO}_2/\text{FiO}_2$  ratios (12–14). In our model, a  $\text{PaO}_2/\text{FiO}_2$  less than 105 mm Hg calculated under a standardized ventilatory setting at 24 hours after ARDS diagnosis identified a subgroup of patients with an absolute mortality that was almost double that of those with a  $\text{PaO}_2/\text{FiO}_2$  ratio greater than 158 mm Hg ( $p < 0.0001$ ). Also, it is well established that there is a direct relationship between plateau pressure and mortality (20). In many epidemiologic studies that have used the American-European Consensus Conference definition (21) or the Berlin criteria (22, 23), the impact of plateau pressure on outcome was not evaluated. In our series, patients with a plateau pressure greater than 30 cm  $\text{H}_2\text{O}$  at 24 hours after ARDS diagnosis had a risk of dying that was more than double that of those with a plateau pressure less than 27 cm  $\text{H}_2\text{O}$ .

As a general rule, all prediction models can only at their best predict the behavior of a group of patients that exactly match the patients in the development population. All medical decisions are ambiguous and cannot be both 100% sensitive and 100% specific. Since APPS functioned well in both the derivation and validation cohorts, we expect that APPS will function equally as well when applied to all patients with moderate or severe ARDS ventilated in a lung-protective manner, regardless of etiology or comorbidities.

Risk stratification using tertiles is a common practice in other fields of medicine (24–27). By evaluating physiologic variables and biomarkers, studies have revealed that tertile

stratification can predict a profile associated with the greatest or the lowest risk for a selected outcome of a specific disease, as we found in our model. The APPS allows the expression of clinical values in ordinal range categories, akin to how clinicians routinely categorize patients into risk groups, and detects useful information about the overall population that may not be as evident when evaluating the mean values of those variables.

The present study has several strengths. First, it included all consecutive patients who meet criteria for moderate and severe ARDS. Second, APPS was described and tested on patients in a multidisciplinary network of teaching hospitals, not just one single health center. Third, we validated our model with a large independent cohort of patients with moderate and severe ARDS. Fourth, our prediction model

is simple and stable and combines variables of potentially modifiable severity (plateau pressure and  $\text{PaO}_2/\text{FiO}_2$ ) and a non-modifiable risk factor (age) that are readily quantified at the bedside. Finally, APPS outperformed APACHE II in predicting hospital mortality. However, despite the strengths of our study, we acknowledge potential limitations of our findings. First, it is plausible that additional variables that improve the prediction of hospital outcome may be identified in future studies and need to be added to APPS. Second, the actual ranges of each of the APPS tertiles may vary as more patient data are analyzed, as noted when our earlier tertile stratification data are compared with our current data. In spite of this, APPS represents a framework upon which to build a highly robust prediction model. Third, we cannot expect that our approach for risk stratification to hold for patients ventilated in a non-lung-protective manner since it is clear that MV with large VT and high plateau pressures causes ventilator-induced lung injury on top of the preexisting ARDS (28), and we do not expect our approach to predict outcomes in that setting.

In conclusion, a simple 9-point score based on age, oxygenation, and ventilatory data calculated at 24 hours after ARDS diagnosis, while patients were on lung-protective MV, discriminates well between groups of patients at high or low risk of in-hospital mortality. Whether APPS will prove to be as useful in real time as other scores (29, 30) for predicting prognosis with high probability, for quality improvement, and for research in ARDS patients remains to be seen.

## REFERENCES

1. Appgar V: A proposal for a new method of evaluation of the newborn infant. *Curr Res Anesth Analg* 1953; 32:260–267
2. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13:818–829
3. Teasdale G, Jennett B: Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974; 2:81–84
4. Vincent JL, Moreno R: Clinical review: Scoring systems in the critically ill. *Crit Care* 2010; 14:207
5. Murray JF, Matthay MA, Luce JM, et al: An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; 138:720–723
6. Heffner JE, Brown LK, Barbieri CA, et al: Prospective validation of an acute respiratory distress syndrome predictive score. *Am J Respir Crit Care Med* 1995; 152:1518–1526
7. Monchi M, Bellenfant F, Cariou A, et al: Early predictive factors of survival in the acute respiratory distress syndrome. A multivariate analysis. *Am J Respir Crit Care Med* 1998; 158:1076–1081
8. Cooke CR, Kahn JM, Caldwell E, et al: Predictors of hospital mortality in a population-based cohort of patients with acute lung injury. *Crit Care Med* 2008; 36:1412–1420
9. Cooke CR, Shah CV, Gallop R, et al: National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network: A simple clinical predictive index for objective estimates of mortality in acute lung injury. *Crit Care Med* 2009; 37:1913–1920
10. Bernard GR, Artigas A, Brigham KL, et al: The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149:818–824
11. Ranieri VM, Rubenfeld GD, Thompson BT, et al: The ARDS Definition Task Force: Acute respiratory distress syndrome. The Berlin definition. *JAMA* 2012; 307:2526–2533
12. Villar J, Blanco J, Añón JM, et al: ALIEN Network: The ALIEN study: Incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation. *Intensive Care Med* 2011; 37:1932–1941
13. Villar J, Fernández RL, Ambrós A, et al: Acute Lung Injury Epidemiology and Natural history Network: A clinical classification of the acute respiratory distress syndrome for predicting outcome and guiding medical therapy. *Crit Care Med* 2015; 43:346–353
14. Villar J, Pérez-Méndez L, Blanco J, et al: Spanish Initiative for Epidemiology, Stratification, and Therapies for ARDS (SIESTA) Network: A universal definition of ARDS: The Pao<sub>2</sub>/Fio<sub>2</sub> ratio under a standard ventilatory setting—A prospective, multicenter validation study. *Intensive Care Med* 2013; 39:583–592
15. Vincent JL, de Mendonça A, Cantraine F, et al: Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter, prospective study. Working group on “sepsis-related problems” of the European Society of Intensive Care Medicine. *Crit Care Med* 1998; 26:1793–1800
16. Villar J, Pérez-Méndez L, Basaldúa S, et al; Hospitales Españoles Para el Estudio de la Lesión Pulmonar (HELP) Network: A risk tertiles model for predicting mortality in patients with acute respiratory distress syndrome: Age, plateau pressure, and P(aO<sub>2</sub>)/F(IO<sub>2</sub>) at ARDS onset can predict mortality. *Respir Care* 2011; 56:420–428
17. Collins FS, Varmus H: A new initiative on precision medicine. *N Engl J Med* 2015; 372:793–795
18. Vincent JL, Hall JB, Slutsky AS: Ten big mistakes in intensive care medicine. *Intensive Care Med* 2015; 41:505–507
19. Gee MH, Gottlieb JE, Albertine KH, et al: Physiology of aging related to outcome in the adult respiratory distress syndrome. *J Appl Physiol* (1985) 1990; 69:822–829
20. Shiu KK, Rosen MJ: Is there a safe plateau pressure threshold for patients with acute lung injury and acute respiratory distress syndrome? *Am J Respir Crit Care Med* 2006; 173:686; author reply 687
21. Villar J, Sulemanji D, Kacmarek RM: The acute respiratory distress syndrome: Incidence and mortality, has it changed? *Curr Opin Crit Care* 2014; 20:3–9
22. Hernu R, Wallet F, Thiollère F, et al: An attempt to validate the modification of the American-European consensus definition of acute lung injury/acute respiratory distress syndrome by the Berlin definition in a university hospital. *Intensive Care Med* 2013; 39:2161–2170
23. Caser EB, Zandonade E, Pereira E, et al: Impact of distinct definitions of acute lung injury on its incidence and outcomes in Brazilian ICUs: Prospective evaluation of 7,133 patients. *Crit Care Med* 2014; 42:574–582
24. Nam BH, Kannel WB, D’Agostino RB: Search for an optimal atherogenic lipid risk profile: From the Framingham Study. *Am J Cardiol* 2006; 97:372–375
25. Störk S, Feelders RA, van den Beld AW, et al: Prediction of mortality risk in the elderly. *Am J Med* 2006; 119:519–525
26. Onat A, Can G, Hergenç G, et al: Serum apolipoprotein B predicts dyslipidemia, metabolic syndrome and, in women, hypertension and diabetes, independent of markers of central obesity and inflammation. *Int J Obes (Lond)* 2007; 31:1119–1125
27. Bishu K, Suri RM, Nkomo VT, et al: Prognostic impact of pulmonary artery systolic pressure in patients undergoing transcatheter aortic valve replacement for aortic stenosis. *Am J Cardiol* 2014; 114:1562–1567
28. Cabrera-Benitez NE, Laffey JG, Parotto M, et al: Mechanical ventilation-associated lung fibrosis in acute respiratory distress syndrome: A significant contributor to poor outcome. *Anesthesiology* 2014; 121:189–198
29. Finster M, Wood M: The Apgar score has survived the test of time. *Anesthesiology* 2005; 102:855–857
30. Lecky F, Woodford M, Edwards A, et al: Trauma scoring systems and databases. *Br J Anaesth* 2014; 113:286–294

## APPENDIX 1: Investigators of the Acute Lung Injury: Epidemiology and Natural History Network

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