Stratification for Identification of Prognostic Categories In the Acute RESpiratory Distress Syndrome (SPIRES) Score

OBJECTIVES: To develop a scoring model for stratifying patients with acute respiratory distress syndrome into risk categories (Stratification for identification of Prognostic categories In the acute RESpiratory distress syndrome score) for early prediction of death in the ICU, independent of the underlying disease and cause of death.

DESIGN: A development and validation study using clinical data from four prospective, multicenter, observational cohorts.

SETTING: A network of multidisciplinary ICUs.

PATIENTS: One-thousand three-hundred one patients with moderate-to-severe acute respiratory distress syndrome managed with lung-protective ventilation.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: The study followed Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis guidelines for prediction models. We performed logistic regression analysis, bootstrapping, and internal-external validation of prediction models with variables collected within 24 hours of acute respiratory distress syndrome diagnosis in 1,000 patients for model development. Primary outcome was ICU death. The Stratification for identification of Prognostic categories In the acute RESpiratory distress syndrome score was based on patient's age, number of extrapulmonary organ failures, values of end-inspiratory plateau pressure, and ratio of Pao_2 to Fio_2 assessed at 24 hours of acute respiratory distress syndrome diagnosis. The pooled area under the receiver operating characteristic curve across internal-external validations was 0.860 (95% CI, 0.831–0.890). External validation in a new cohort of 301 acute respiratory distress syndrome patients confirmed the accuracy and robustness of the scoring model (area under the receiver operating characteristic curve = 0.870; 95% CI, 0.829–0.911). The Stratification for identification of Prognostic categories In the acute RESpiratory distress syndrome score stratified patients in three distinct prognostic classes and achieved better prediction of ICU death than ratio of Pao_2 to Fio_2 at acute respiratory distress syndrome onset or at 24 hours, Acute Physiology and Chronic Health Evaluation II score, or Sequential Organ Failure Assessment scale.

CONCLUSIONS: The Stratification for identification of Prognostic categories In the acute RESpiratory distress syndrome score represents a novel strategy for early stratification of acute respiratory distress syndrome patients into prognostic categories and for selecting patients for therapeutic trials.

KEY WORDS: acute respiratory distress syndrome; clinical trials; outcome; phenotypes; scoring system, stratification

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The acute respiratory distress syndrome (ARDS) represents an intense inflammatory process in the lungs that develops in the context of pulmonary and extrapulmonary insults (1, 2). The primary disease, patient's physiologic responses, and preexisting comorbid conditions are some of the factors contributing to development, progression, and prognosis of ARDS.

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Characterized by acute hypoxemic respiratory failure due to noncardiogenic pulmonary edema, ARDS is a syndrome that cannot be diagnosed by any laboratory test. Treatment remains supportive using mechanical ventilation (MV) with low tidal volumes (VTs) of 4–8 mL/kg predicted body weight (PBW), end-inspiratory plateau pressure (Pplat) below 30 cm H_2O, and sufficient positive end-expiratory pressure (PEEP), although the optimal ventilatory strategy for ARDS remains to be determined. About 40% of ARDS patients do not leave the hospital alive (3, 4).

There is not a scoring system to assess on how an ARDS patient is presenting or progressing. Scoring systems provide an average prediction value for ranking patients according to how well the score anticipate the true outcome. At present, patients are classified as mild, moderate, or severe ARDS based on the ratio of Pao_2 to Fio_2 (Pao_2/Fio_2) at ARDS onset (5, 6). If Pao_2 measurements are not standardized, the calculated Pao_2/Fio_2 may mask the severity of the underlying lung pathology in a substantial proportion of patients (7). It is well established that changes in PEEP and Fio_2 alter the Pao_2/Fio_2 in lung-injured patients (8). Therefore, attempting to predict outcomes based solely in Pao_2/Fio_2 on this basis is inherently flawed (8). Patients stratified according to baseline Pao_2/Fio_2 (as mandated by Berlin criteria) can change markedly within 24 hours of management in the ICU (9) and would move to a different category of severity, making the initial stratification useless for trial enrollment. Thus, clustering ARDS patients into risk categories based on clinical variables for assessment of heterogeneity and probability of outcome of interest has been suggested (10).

We hypothesized that an ARDS score could stratify and identify distinct prognostic classes of ARDS (termed the Stratification for identification of Prognostic categories In the acute RESpiratory distress syndrome [SPIRES] score) and could be helpful for selecting ARDS patients for randomized clinical trials (RCTs).

METHODS

Our studies were approved by the Ethics Committees for Clinical Research at Hospital Universitario Dr. Negrín (Las Palmas de Gran Canaria, Spain, number 2008-0915-EPI), Hospital Virgen de La Luz (Cuenca, Spain, number 2014/PI-1114), Hospital Clínico Universitario (Valladolid, Spain, number PI17-594), and institutional review boards of participating hospitals. Waivers of informed consent were granted.

Patient Population

The study was conducted in three steps (**Supplemental Data File**, http://links.lww.com/CCM/G487). We focused our analysis on clinically relevant variables collected within the first 24 h of ARDS diagnosis to estimate the probability of ICU death (**Fig. S1**, http://links.lww.com/CCM/G487). The study was conducted in three steps (**Fig S2**, http://links.lww.com/CCM/G487). For the first two steps (model development and internal-external validation), we performed a secondary analysis in an unrestricted set of pooled data from 1,000 adult patients included in three multicenter, observational cohorts enrolling consecutive patients meeting current criteria for moderate-to-severe ARDS (6) and managed with lung-protective MV in a network of ICUs from hospitals under the Spanish Initiative for Epidemiology, Stratification, and Therapies of ARDS Program (4, 8, 11) (Appendix).

In the third step, we tested the performance of our model in a new cohort of 301 consecutive patients with moderate-to-severe ARDS included in a multicenter, prospective, observational study (unpublished data) admitted in a network of 22 ICUs from May 2017 to March 2018. With this approach, we studied the temporal aspect of external validity since this new cohort contains recently treated ARDS patients. As recommended by recent guidelines (12), we avoided the retraining on the external dataset. This study conformed Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis guidelines (13).

Variables, Primary Outcome, and Predefined Rules

We recorded information from demographics, comorbidities, etiology of ARDS, Acute Physiology and Chronic Health Evaluation II (APACHE II) score (14), arterial blood gases, and MV data at ARDS onset and at 24 hours after ARDS diagnosis. We recorded occurrence of extrapulmonary organ failures (OFs) included in the Sequential OF Assessment (SOFA) scale (15) at ARDS onset and after 24 hours of treatment and cause of ICU death. Extrapulmonary OF was defined as an acute change in organ-specific SOFA score greater than or equal to 2 (16, 17). For the purpose of this study, the

values of Pao_2/Fio_2 and Pplat at 24 hours were measured under a standardized ventilatory setting (8, 11) (Supplemental Data File, http://links.lww.com/CCM/G487). Based on Pao_2/Fio_2 at study entry, patients were categorized as severe ($Pao_2/Fio_2 \leq 100$) or moderate ($100 < Pao_2/Fio_2 \leq 200$) ARDS. Based on standardized Pao_2/Fio_2 at 24 hours, patients were reclassified as severe, moderate, mild ($200 < Pao_2/Fio_2 \leq 300$) ARDS or Pao_2/Fio_2 greater than 300. Patients were followed until ICU and hospital discharge. Primary outcome was all-cause ICU mortality.

We listed in sequential order the values of variables in all 1,000 patients at ARDS onset and at 24 hours of ARDS diagnosis and the number of associated ICU deaths. Although the distribution of values identified patients with a wide range of ICU mortality, we narrowed the search to 28 variables (**Table S1**, http://links.lww.com/CCM/G487) as potential early predictors of outcome (8, 11, 18, 19): age, gender, and APACHE II, SOFA, number of extrapulmonary OF, gas-exchange variables (Pao_2, Fio_2, Pao_2/Fio_2, $Paco_2$, pH), MV variables (VT, respiratory rate, PEEP, Pplat, minute ventilation) at ARDS onset and at 24 hours. Although we calculated driving pressure (Pplat minus PEEP), we valued Pplat over driving pressure for prognosis based on our previous work (18). We specified in advance rules and expectations (20, 21) before final statistical analyses were conducted (Supplemental Data File, http://links.lww.com/CCM/G487).

Statistical Analysis

The statistical analysis plan is provided in the Supplemental Data File (http://links.lww.com/CCM/G487). Quantitative variables are described using mean ± SD and median and 25–75% percentiles. We used the Shapiro-Wilk to test normal distribution of data. We calculated the frequency and percentage of qualitative variables and analyzed differences between categorical variables with the Fisher exact test. We performed a univariate analysis of candidate variables as predictors of outcome. We determined the overall significance for each independent association between the variable and the ICU outcome. Once we determined the ICU mortality associated with each subgroup, we identified the variables that could be included in the score based on our predefined rules, the area under the receiver operating characteristic curve (AUC), and the prespecified *p* values. Once risk variables were identified, we performed a multivariable logistic regression analysis. Internal validation was performed by bootstrapping (22–24) in 2,000 samplings. With the probabilities obtained on the logistic model, we evaluated the AUC and estimated 95% CIs. For the final SPIRES score, we considered the minimum number of variables that provided similar performance as the full 28-predictor model. We performed internal-external validation in independent parts of the data by leaving each of the three parent cohorts out once (22, 23). Each patient was given a score based on risk variables. We aggregated patients with similar scores into major prognostic categories and classes. We analyzed the probability of ICU survival for the prognostic classes using the Kaplan-Meier method with the log-rank test. We used the Hosmer-Lemeshow test for model calibration (12) and plotted the observed/expected probability of ICU mortality across deciles of prediction. We used R Core Team 2019 software (R version 3.6.1) for statistical computing (R Foundation for Statistical Computing, Vienna, Austria). For all comparisons, a two-sided *p* of value less than 0.005 was considered a real effect size (20).

RESULTS

From the pooled 1,000 patients used for model development and internal-external validation, 375 patients (37.5%) died in ICU (**Table 1**). Mean values for most selected variables changed after 24 hours of care. Ten variables closely related to other variables in the model (APACHE II, SOFA, Pao_2, Fio_2, and driving pressure—at baseline and at 24 hr) were not included as potential predictors in the final model (Supplemental Data File, http://links.lww.com/CCM/G487). From the remaining 20 variables, those with an AUC greater than or equal to 0.65 had the potential for being early predictors of ICU outcome (Table S1, http://links.lww.com/CCM/G487). Finally, we included four predictors in the SPIRES score: patient's age, extrapulmonary OFs at 24 hours of ARDS diagnosis, and Pao_2/Fio_2 and Pplat recorded at 24 hours under standardized ventilatory settings. Distribution of patients based on thresholds for those four variables had a distinctive ICU mortality and were grouped for building the final SPIRES model (**Table S2**, http://links.lww.com/CCM/G487) (**Table 2**). We rated thresholds for score description, such that the predicted interval separated patients into categories with distinct ICU mortality.

TABLE 1.

Characteristics of 1,301 Patients With Moderate-to-Severe Acute Respiratory Distress Syndrome at the Time of Acute Respiratory Distress Syndrome Diagnosis and at 24 Hours After Diagnosis and Outcome Data

Variables	Derivation Cohort (n = 1,000)		Validation Cohort (n = 301)	
Age, yr, mean ± SD	56.8 ± 16.0		58.2 ± 14.6	
Gender, *n* (%)				
Male	680 (68.0)		221 (73.4)	
Female	320 (32.0)		80 (26.6)	
Etiology, *n* (%)				
Pneumonia	480 (48.0)		114 (37.9)	
Sepsis	286 (28.6)		76 (25.3)	
Aspiration	94 (9.4)		43 (14.3)	
Trauma	74 (7.4)		38 (12.6)	
Acute pancreatitis	32 (3.2)		13 (4.3)	
Multiple transfusions	10 (1.0)		3 (1.0)	
Others	24 (2.4)		14 (4.6)	
	At ARDS Onset	**At 24 hr**	**At ARDS Onset**	**At 24 hr**
Degree of ARDS severity, *n* (%)				
Severe	410 (41.0)	218 (21.8)	107 (35.5)	55 (18.3)
Moderate	590 (59.0)	611 (61.1)	194 (64.5)	167 (55.5)
Mild	–	152 (15.2)	–	67 (22.3)
$Pao_2/Fio_2 > 300$	–	19 (1.9)	–	12 (4.0)
Acute Physiology And Chronic Health Evaluation II score, mean ± SD	20.8 ± 6.7	19.1 ± 7.2	21.5 ± 8.0	19.7 ± 8.8
Sequential Organ Failure Assessment score, mean ± SD	9.1 ± 3.5	9.1 ± 3.7	9.9 ± 3.6	9.8 ± 4.0
Pao_2/Fio_2, mm Hg, mean ± SD	114.3 ± 38.4	148.2 ± 59.0	120.1 ± 41.0	163.7 ± 67.6
Fio_2, mean ± SD	0.79 ± 0.19	0.66 ± 0.18	0.76 ± 0.20	0.63 ± 0.17
Pao_2, mm Hg, mean ± SD	85.9 ± 26.3	91.2 ± 27.2	86.1 ± 24.8	95.1 ± 30.5
$Paco_2$, mm Hg, mean ± SD	49.0 ±12.5	46.9 ± 10.4	50.5 ± 13.8	47.3 ± 10.6
pH, mean ± SD	7.30 ± 0.11	7.34 ± 0.10	7.29 ± 0.11	7.33 ± 0.10
Tidal volume, mL/kg predicted body weight, mean ± SD	6.76 ± 1.05	6.64 ± 0.89	6.7 ± 1.1	6.5 ± 1.1
Respiratory rate, breaths/min, mean ± SD	21.3 ± 4.9	23.3 ± 5.1	22.3 ± 4.5	23.5 ± 4.8
Minute ventilation, L/min, mean ± SD	9.1 ± 2.2	9.8 ± 2.2	9.5 ± 2.0	9.8 ± 2.4
Positive end-expiratory pressure, cm H_2O, mean ± SD	12.1 ± 3.3	12.5 ± 3.0	11.1 ± 3.1	11.6 ± 2.9
Plateau pressure, cm H_2O, mean ± SD	26.4 ± 4.9	26.8 ± 4.6	25.2 ± 4.8	25.0 ± 4.7
Number of extrapulmonary organ failure, mean ± SD	1.7 ± 1.1	1.7 ± 1.1	1.9 ± 1.1	2.0 ± 1.2
Length of ICU stay, d, median (IQR)	19 (11–31)		16 (9–27)	
Duration of mechanical ventilation, d, median (IQR)	14 (8–25)		10 (5–20)	
Days from ICU admission to ARDS onset, median (IQR)	1 (0–3)		1 (0–3)	
Days from ARDS onset to ICU discharge, median (IQR)	16 (9–29)		14 (7–22)	

(*Continued*)

TABLE 1. (*Continued*).

Characteristics of 1,301 Patients With Moderate-to-Severe Acute Respiratory Distress Syndrome at the Time of Acute Respiratory Distress Syndrome Diagnosis and at 24 Hours After Diagnosis and Outcome Data

Variables	Derivation Cohort (*n* = 1,000)	Validation Cohort (*n* = 301)
Days from ARDS diagnosis to ICU death, median (IQR)	12 (4–21)	6 (2–14)
All-cause ICU mortality, *n* (%)	375 (37.5)	111 (36.9)
All-cause hospital mortality, *n* (%)	415 (41.5)	122 (40.5)
Deaths within first 24 hr after ARDS onset, *n* (%)	1 (0.1)	1 (0.33)
Deaths within first 3 d after ARDS onset, *n* (%)	41 (4.1)	36 (12.0)

ARDS = acute respiratory distress syndrome, IQR = interquartile range, Pao_2/Fio_2 = ratio of Pao_2 to Fio_2.
Dashes represents 0 patients.

TABLE 2.

The Stratification for Identification of Prognostic Categories In the Acute Respiratory Distress Syndrome Scoring System

Variables	Thresholds	Score
Patient's age (yr)	< 50	1
	50–70	2
	> 70	3
Number of extrapulmonary organ failures at 24 hr of acute respiratory distress syndrome diagnosis	< 2	1
	2	2
	> 2	3
Ratio of Pao_2 to Fio_2 at 24 hr (mm Hg) measured under standardized ventilator settings	> 200	1
	101–200	2
	≤ 100	3
Plateau pressure at 24 hr (cm H_2O)	< 29	1
	29–30	2
	> 30	3
Total score		4–12

Minimum score is 4 points, and maximum score is 12 points.

Internal validation of the full 28-predictor model suggested minor statistical optimism in the score (**Tables S3** and **S4**, http://links.lww.com/CCM/G487). The four-variable model accomplished a similar performance as the larger model (AUC, 0.860; 95% CI, 0.836–0.884). Internal-external validation by leaving each of the three parent cohorts out once provided an average AUC of 0.860 (95% CI, 0.831–0.890) (**Table S5**, http://links.lww.com/CCM/G487). Individual SPIRES scores achieved better prediction than predictions by Pao_2/Fio_2 at baseline or at 24 hours of ARDS diagnosis, APACHE II, or SOFA (**Fig. 1**) (**Table S6**, http://links.lww.com/CCM/G487).

When we aggregated patients with the same total score (ranging from 4 to 12 points), the model divided the 1,000 patients into nine subgroups (**Table 3**). ICU mortality increased with each increment of total score. Predicted ICU outcome in each group suggested that it was appropriate to merge groups with an ICU mortality less than 30% and to merge groups with a mortality greater than 70%. Thus, we identified three prognostic classes of ARDS with significantly different ICU outcome ($p < 0.0001$): Class 1 (score < 8 points), Class 2 (score 8 points), Class 3 (score > 8 points) (**Fig. 2**).

The external validation cohort of 301 patients had baseline characteristics and an overall ICU mortality (111 deaths, 36.9%) similar to 1,000 patients for model development (Table 1) (**Tables S7** and **S8**, http://links.lww.com/CCM/G487) and provided a very good performance of the SPIRES score (AUC, 0.870; 95% CI, 0.829–0.911) (**Table S9**, http://links.lww.com/CCM/G487).

The observed/predicted probability of all-cause ICU mortality across deciles of prediction showed that the SPIRES model fits the data ($p = 0.87$) (**Fig. S3**, http://links.lww.com/CCM/G487).

DISCUSSION

The SPIRES score represents the combined thresholds for patient's age, Pao_2/Fio_2, Pplat, and extrapulmonary OF. The SPIRES score confirmed that age, degree of

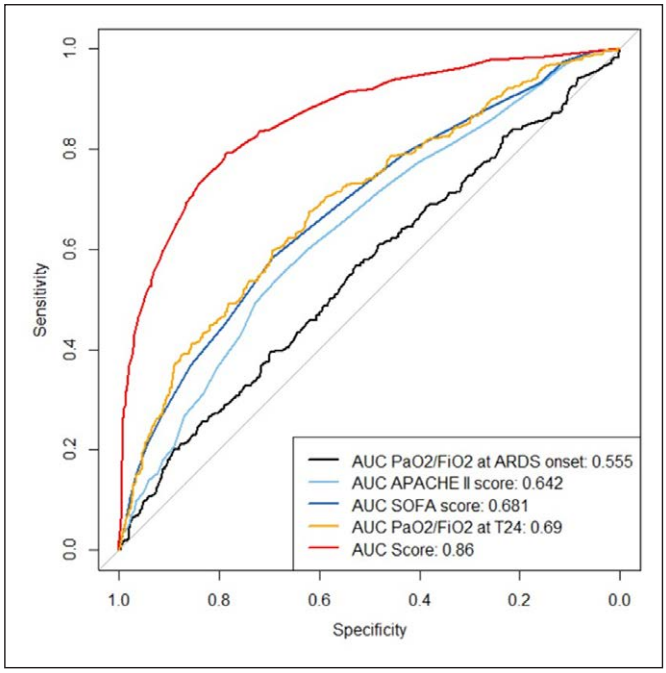

Figure 1. Receiver operating characteristic plots in 1,000 patients with moderate-to-severe acute respiratory distress syndrome (ARDS) comparing the performance for predicting death in the ICU using five prognostic models: the baseline values of ratio of Pao_2 to Fio_2 ($Pao_2/Fio_{2)}$ at ARDS onset—as mandated by current ARDS definition criteria—Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Sequential Organ Failure Assessment (SOFA) score at the day of ARDS diagnosis, the values of Pao_2/Fio_2 at 24 hr of ARDS diagnosis, and the Stratification for identification of Prognostic categories In the acute RESpiratory distress syndrome scoring model. AUC = area under the receiver operating characteristic curve.

hypoxemia, ventilating pressures, and systemic organ dysfunction are very important variables for the prognosis of ARDS patients (4, 11, 18, 25, 26). Some combinations of thresholds for patient's age, extrapulmonary OF at 24 hours, and Pao_2/Fio_2 and Pplat assessed at 24 hours after ARDS diagnosis (especially those with a SPIRES score of 7–9 points) provided very good prognostic accuracy for stratifying ARDS patients by risk of ICU death and could be considered for enrollment into RCTs.

ARDS stratification in prognostic risk categories and classes requires timely diagnosis and targeted treatments. Those classes define a distinct trajectory of outcome without any implication of a mechanism, especially in a syndrome with no single etiology and without a specific biomarker. Developing a scoring system based on individual values of variables entailed three issues: 1) rating the selected cut offs in ordinal range categories, akin to how clinicians routinely categorize patients into risk groups; 2) aggregating patients by the same total score; and 3) determining whether putative classes made by such aggregation reflect true structure in the data rather than simple aggregation. Restricting ARDS severity to the level of hypoxemia leads to inconsistencies (6, 7, 9). The original and current definitions of ARDS proved to be incapable of identifying similar groups of patients in terms of severity and/or outcome, because none of those definitions considered the sensitivity of oxygenation and general status to ventilator settings and management during the first 24 hours. Since baseline Pao_2/Fio_2 values are linked to multiple outcomes (8–10), standardized ventilatory settings for assessing Pao_2/Fio_2 at 24 hours should be incorporated into future ARDS trials for patient enrollment (8–11, 27). On the other hand, critical care physicians must contend with no less than 200 variables when caring for an ARDS patient (28). However, human working memory is limited to 4 ± 1 constructs (29). Clinical decision-making generally becomes degraded once this limit of four constructs is exceeded. The SPIRES score uses only four variables and outperformed other prediction tools because of its multifaceted nature, which considers patient's age, extrapulmonary OF, and response to standardized ventilatory settings plus some extra information connecting those constructs. We acknowledge that the number of extrapulmonary OF is based on a composite scale that requires five additional variables to properly calculate the SOFA score.

SPIRES classes seem real and reproducible. We tested the external validation of the score in an independent, recently treated cohort of ARDS patients with an appropriate sample size and an adequate number of events (30, 31). Having a contemporary external validation cohort strengthened the validity of the SPIRES model. The SPIRES score provides a wide range of ICU mortality for ARDS. Patients with a score less than 8 points (Class 1) represented almost 60% of our patient population and had an average all-cause ICU mortality of 15%. Our data suggest that it is questionable whether patients with a total score of 4–6 points (average ICU mortality < 9%) could benefit from a therapeutic RCT. Patients with scores of 8 points were the most important class among our ARDS patients, both in terms of underlying lung/systemic injury (and probably, biology) and need for treatment or enrollment into innovative RCTs. The

TABLE 3.

Overall All-Cause Mortality in the ICU in Relation to the Total Stratification for Identification of Prognostic Categories In the acute RESpiratory Distress Syndrome Score in 1,000 Patients With Moderate-to-Severe Acute Respiratory Distress Syndrome

Total Score	No. of Patients	ICU Deaths	ICU Mortality (%)	Classes	ICU Mortality, *n/N* (%, 95% CI)
4	28	1	4	Class 1	87/585 (15, 12–18)
5	142	7	5		
6	200	24	12		
7	215	55	26		
8	174	87	50	Class 2	87/174 (50, 42–58)
9	126	93	74	Class 3	201/241 (83, 78–88)
10	67	63	94		
11	41	38	93		
12	7	7	100		
	1,000	375	38		

Nine scoring groups were clustered in three classes of acute respiratory distress syndrome. Percentages have been rounded to zero decimals.

observation that a score above 8 points (Class 3) at 24 hours of ARDS onset is associated with an ICU mortality greater than 80% could indicate presumably extensive lung and systemic damage and may provide an opportunity for using techniques for pulmonary and extrapulmonary organ support that target oxygenation and multiple organ recovery.

Patients sharing the ARDS "label" differ in regard to severity of lung injury and response to ventilator strategies. However, incomplete or ambiguous evidence for identifying less heterogeneous ARDS subgroups or specific patient populations for enrollment into RCTs has come to the cost of an unreasonable number of negative trials (21, 32, 33). Our scoring model is in line with recent recommendations (34) stating that a better identification of patient populations is key for appropriate characterization of patient status. Interest in identifying distinct subgroups of ARDS and ICU patients is a growing field, not only for predicting the outcome of interest but also for knowing their shared needs and similar clinical trajectories (35). There is a possibility of using measurable biomarkers in plasma for determining whether this approach could identify ARDS patients with different risks who will benefit from various therapies.

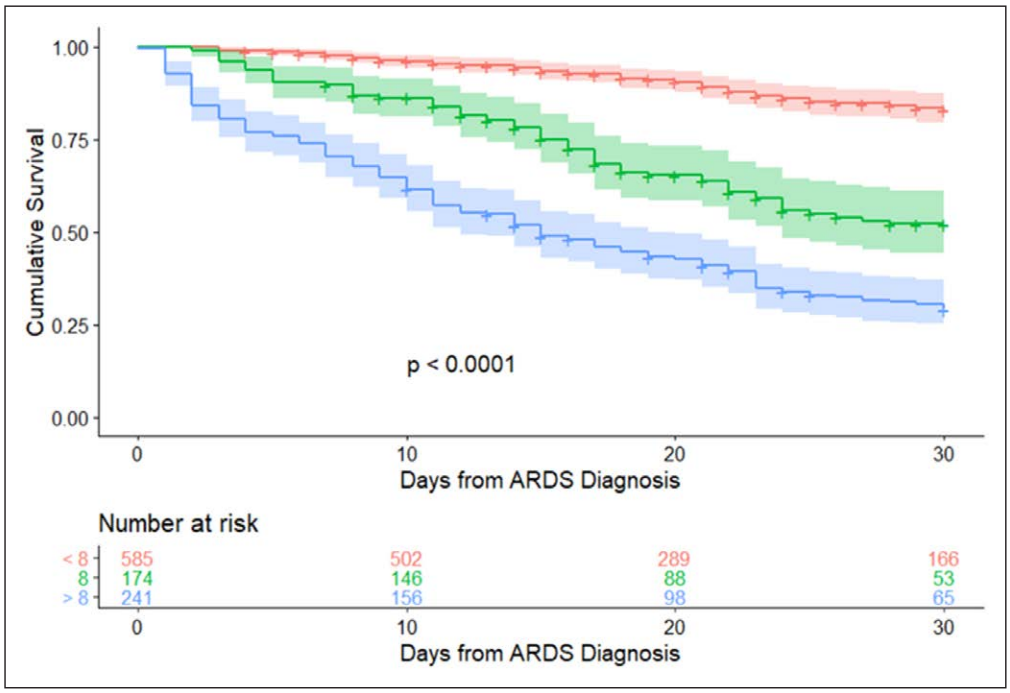

Figure 2. Kaplan-Meier probability of ICU survival curves (± 95% CI) in 1,000 patients with moderate-to-severe acute respiratory distress syndrome (ARDS) when categorized from Class 1 to Class 3.

Some authors have proposed two different ARDS phenotypes (hyperinflammatory and hypoinflammatory) for optimizing therapy and allow patient selection for future trials using retrospective analyses of RCTs (36). However, that classification based on numerous clinical variables and biomarkers that are not specific for ARDS is not feasible at the bedside. Those phenotypes were also retrospectively (37, 38) and prospectively (39) identified using a parsimonious model with three biomarkers. Despite the pathobiological relevance of identifying biomarkers for targeting treatment and predicting outcome in future trials, there are serious limitations to the two-class inflammatory model (**Supplementary Discussion**, http://links.lww.com/CCM/G487). We are patiently waiting further data from prospective RCTs before adopting those phenotypes to alter management of ARDS.

The SPIRES scoring model could be implemented into an artificial learning and teaching machine for improving healthcare (40, 41). However, standardized data collection is a necessary step—as we did in our study—to improve ARDS outcome.

We acknowledge some limitations to this study. First, we cannot expect that our model to hold for patients ventilated in a nonlung-protective manner since MV with large VTs and high Pplat causes ventilator-induced lung injury, and we do not expect our approach to predict outcomes in that setting. Second, we cannot exclude some uncertainty in our scoring model because the initial candidate variables were 28. However, since it would be impractical to include all 28 predictors in a prognostic model, some form of selection was required. Third, the SPIRES score deserves further prospective validation in ARDS patients from other countries before it could be accepted into clinical practice. However, our study has several strengths. First, our study population is large enough to fairly reflect the population to which ARDS stratification takes place in clinical practice. Second, validation increases when studies include patients from different hospitals, as in our study. Third, in our ARDS population, a high proportion of patients did not meet oxygenation criteria for moderate/severe ARDS after 24 hours of routine care, suggesting that misdiagnosis can occur if clinicians only consider qualifying Pao_2 at the time of ARDS diagnosis for trial enrollment. Fourth, since better outcome predictions can be applied to disrupt existing processes, by knowing the SPIRES score, clinicians could have the advantage for interrupting the possible sequence of events associated with a predicted outcome. Although this hypothesis requires further testing in an RCT, it is plausible that modest reductions in either Pplat and/or SOFA score could reduce the risk of death.

In summary, we developed and validated an easy-to-use risk stratification score for ARDS based on commonly available variables within the first 24 hours of ARDS presentation. The SPIRES score can be used to stratify patients into different prognostic (probably, management) categories. This score should be further validated to determine its applicability in other countries.

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Members of the Spanish Initiative for Epidemiology, Stratification and Therapies of ARDS (SIESTA) Network are listed in the Appendix.

Study Registered with www.clinicaltrials.gov (NCT00736892, NCT02288949, NCT02836444, NCT03145974).

All data needed to evaluate the conclusions in the article are present and tabulated in the main text and/or the supplementary digital content (http://links.lww.com/CCM/G487). This article is the result of an original analysis of data from patients with moderate-to-severe acute respiratory distress syndrome enrolled in four observational, multicenter, prospective cohorts.

Drs. Steyerberg amd Kacmarek are senior authors contributed equally. Drs. Villar, Kacmarek, and Steyerberg designed and supervised the study. Drs. R. L. Fernández and C. Fernández were the project managers and supervised data collection and storage. Drs. Ambrós, Mosteiro, Martínez, L. Fernández, Soler, Parra, Solano, Soro, del Campo, González-Luengo, Civantos, Montiel, Pita-García, Vidal, Añón, Ferrando, Diaz-Dominguez, Mora-Ordóñez, and Fernández enrolled patients and collected the data. Drs. Villar and Rodríguez-Suárez obtained funding for the study. Drs. Villar, González-Martín, C. Fernández, R. L. Fernández, Steyerberg, and Kacmarek wrote the first draft. Drs. Villar, González-Martín, C. Fernández, R. L. Fernández, and Steyerberg performed and/or supervised data management and statistical analysis. All authors made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; drafting the article or revising it for important intellectual content; and approved the final version of the article. Drs. Villar, R. L. Fernández, and Kacmarek were involved in all stages of study development and delivery. Drs. Villar, C. Fernández, R. L. Fernández, and González-Martín 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. Dr. Villar has full access to all the data in the study and has final responsibility for the decision to submit for publication.

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APPENDIX: LIST OF INVESTIGATORS OF THE "SPANISH INITIATIVE FOR EPIDEMIOLOGY, STRATIFICATION AND THERAPIES OF ARDS (SIESTA)" NETWORK

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