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Ventilation/ARDS/VAP

Early prediction of extracorporeal membrane oxygenation eligibility for severe acute respiratory distress syndrome in adults☆

J. Kyle Bohman, MD [a,*], Joseph A. Hyder, MD, PhD [a], Vivek Iyer, MD, MPH [b], Sonal R. Pannu, MD, MS [c], Pablo Moreno Franco, MD [d], Troy G. Seelhammer, MD [a], Louis A. Schenck, MS [e], Gregory J. Schears, MD [a]

[a] Department of Anesthesiology, Division of Critical Care Medicine, Mayo Clinic, Rochester, MN
[b] Department of Medicine, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN
[c] Division of Pulmonary Care and Critical Medicine, Ohio State University, Wexner Medical Center, Columbus, OH
[d] Department of Medicine, Division of Transplant and Critical Care, Mayo Clinic, Jacksonville, FL
[e] Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN

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ABSTRACT

Purpose: Appropriately identifying and triaging patients with newly diagnosed acute respiratory distress syndrome (ARDS) who may progress to severe ARDS is a common clinical challenge without any existing tools for assistance.

Materials and methods: Using a retrospective cohort, a simple prediction score was developed to improve early identification of ARDS patients who were likely to progress to severe ARDS within 7 days. A broad array of comorbidities and physiologic variables were collected for the 12-hour period starting from intubation for ARDS. Extracorporeal membrane oxygenation (ECMO) eligibility was determined based on published criteria from recent ECMO guidelines and clinical trials. Separate data-driven and expert opinion approaches to prediction score creation were completed.

Results: The study included 767 patients with moderate or severe ARDS who were admitted to the intensive care unit between January 1, 2005, and December 31, 2010. In the data-driven approach, incorporating the ARDS index (a novel variable incorporating oxygenation index and estimated dead space), aspiration, and change of Pao_2/fraction of inspired oxygen ratio into a simple prediction model yielded a c-statistic (area under the receiver operating characteristic curve) of 0.71 in the validation cohort. The expert opinion–based prediction score (including oxygenation index, change of Pao_2/fraction of inspired oxygen ratio, obesity, aspiration, and immunocompromised state) yielded a c-statistic of 0.61 in the validation cohort.

Conclusions: The data-driven early prediction ECMO eligibility for severe ARDS score uses commonly measured variables of ARDS patients within 12 hours of intubation and could be used to identify those patients who may merit early transfer to an ECMO-capable medical center.

1. Introduction

An important theme emerging from recent acute respiratory distress syndrome (ARDS) studies is that delayed application of ARDS treatment modalities and specifically extracorporeal membrane oxygenation (ECMO) for severe ARDS may lead to worse outcomes. Recent ARDS research suggests that outcomes may be improved with transfer to ECMO-capable centers, early institution of adjunctive therapies (proning and paralysis), and prevention or early mitigation of ventilator-induced lung injury [1-5].

A key challenge for clinicians and researchers working with ARDS patients is being able to identify which newly diagnosed ARDS patients are most likely to experience significant worsening. Our current practice lacks the clinical indicators to recognize patients with ARDS who progress to refractory hypoxemia and time-sensitive markers for initiation of rescue strategies. If these patients could be identified early in their course of ARDS, then facilitation of transfer to an ECMO-capable center and/or initiation of ECMO could be accomplished earlier to maximize the presumed benefit of protective lung ventilation.

The objective of this study was to identify risk factors that were present during the first 12 hours after intubation for ARDS, which predict progression to ARDS severe enough to meet previously published ECMO eligibility criteria. The goal of such a prediction model was to identify ARDS patients, shortly after initiation of mechanical ventilation, who may merit consideration for transfer to an ECMO-capable center and/or initiation of ECMO. It should be stressed that "ECMO eligibility"

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* Corresponding author at: 200 First Street SW, Rochester, MN 55905. Fax: +1 507 255 2939.
E-mail address: bohman.john@mayo.edu (J.K. Bohman).

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as the primary outcome of this study was chosen for ease of communication, but in its most accurate form would be stated as "ARDS severe enough to meet widely recognized, published ECMO eligibility criteria." In other words, this study attempted to predict ARDS progression and eventual ECMO eligibility (without concern for relative contraindications to ECMO) based on changes in physiological variables within the first 12 hours of intubation for respiratory failure.

2. Materials and methods

2.1. Study design and setting

This was a retrospective observational study using the electronic medical records of all intensive care unit (ICU) admissions at a single tertiary medical center between January 1, 2005, and December 31, 2010. Institutional review board approval was granted before study initiation.

2.2. Determining presence of ARDS

All adult ICU patients at the Mayo Clinic from 2005 to 2010 were identified by the Mayo Clinic ICU Data Mart. Steps of development of the database, data security, and validation of demographics have been published previously [6]. All patients younger than 18 years of age and those who refused the use of their medical records for research were excluded. Patients were then electronically screened using validated methods to identify all patients with moderate or severe ARDS according to the Berlin definition [7,8]. Every patient who electronically screened positive for ARDS was then manually reviewed by 3 independent critical care physicians to ensure compliance with the Berlin definition of ARDS and to also determine the most likely etiology of the ARDS.

2.3. Patient inclusion and exclusion

Patient inclusion and exclusion are outlined in Table 1. To better temporally match each individual patient's ARDS course, the time of intubation for ARDS was identified. It is difficult to precisely estimate time of onset of ARDS for patients intubated at other facilities before transfer to our hospital, and these patients were therefore excluded to preserve internal validity. Similarly, we excluded patients intubated initially for nonrespiratory reasons (eg, cardiac arrest or general anesthesia) as it was often difficult to accurately determine time of onset of ARDS. Following the data mining procedures, using a computerized random number generator, the complete set of patients was pseudorandomized into 2 groups: the derivation and validation cohorts.

2.4. Determining ECMO eligibility

Based on widely recognized published ECMO eligibility criteria, we created an amalgamated ECMO eligibility criterion (see Table 1) [5,9,10,12,13]. Each patient was manually reviewed by an ECMO physician to determine ECMO eligibility. Because of a high degree of variability in opinion in the ECMO literature, relative contraindications to ECMO were not considered when determining ECMO eligibility. In prior studies, successful respiratory ECMO has been reported in the context of the listed relative contraindications, including severely immunocompromised hosts, contraindications to anticoagulation (such as massive diffuse alveolar hemorrhage), and advanced age [14-20]. Based on previously published observational data and selection criteria used in recent major ECMO trials, pre-ECMO mechanical ventilation duration greater than or equal to 7 days was an absolute contraindication for the purposes of this study [5,9,10,21,22].

2.5. Expert opinion prediction model

Using the modified Delphi technique, serial surveys of several experienced, international ECMO physicians were conducted to create a list of physiologic variables that were present within 12 hours of intubation for ARDS that were felt to best predict eventual ECMO eligibility [23]. The participating ECMO physicians represent medical centers that collectively care for more than 200 respiratory ECMO patients annually. The 5 highest-ranked variables were then chosen for inclusion in the Expert Opinion ECMO Prediction Model. Continuous variables were categorized or dichotomized to produce a simple prediction score that could be easily calculated at the bedside. Dichotomization cutoffs for oxygenation index (OI) and Δ Pao_2/fraction of inspired oxygen (Fio_2) for the expert opinion score were based on the median value in the derivation cohort and then rounded to convenient integers.

3. Statistical analysis

3.1. Identification of risk factors associated with ECMO eligibility

The derivation cohort was used to assess each variable's association with a patient's ECMO eligibility (the outcome). Continuous data were assessed using Wilcoxon rank sum test. For categorical data, counts with percentages were reported and associated P values were estimated using χ^2 or Fisher exact test, as appropriate. Variables reaching a statistical significance level of $P \leq .1$ in univariate analysis were considered for inclusion in the data-driven prediction model. Data were analyzed using JMP 10.0 (SAS Institute, Inc, Cary, NC). Data imputation was performed using R 3.1.1 (R Core, Vienna, Austria) and random Forest SRC 1.6 package [24-27].

3.2. Collecting variables of interest

The electronic medical records of all confirmed ARDS patients were electronically mined for multiple variables, which were defined a priori, including baseline characteristics, comorbidities, physiologic variables, and ventilator data. Collecting variables beyond 12 hours of intubation, such as 24 hours after intubation, was considered but not pursued due to missing data and patient dropout. In addition, further delay of prediction would limit the clinical utility of the prediction score to some

Table 1
Extracorporeal membrane oxygenation eligibility criteria

Inclusion criteria [5,9,10]	Absolute exclusion criteria [5,9,10]	Relative exclusion criteria [5,9,10]
ARDS per Berlin definition, and ≥1 of the following: Pao_2/Fio_2 <80 for ≥3 h despite Vt 6 mL/kg + PEEP ≥5 pH <7.25 for ≥3 h with RR ≥30 while Pplat <32	Mechanical ventilation ≥7 d CNS catastrophe[b] Irreversible condition and not lung transplant candidate Death within 3 h of intubation ARDS not severe enough to meet inclusion criteria	Immunocompromised state[a] Age >70 y Chronic CNS deficit or CNS status unknown Contraindications to anticoagulation Multiple-organ dysfunction syndrome Weight >150 kg

The eligibility criteria listed here are an amalgamation of published criteria from recent large ECMO trials and guidelines.
CNS indicates central nervous system; PEEP, positive end-expiratory pressure; Pplat, plateau pressure; RR, respiratory rate.
[a] Solid organ or stem cell transplant, solid organ or hematologic malignancy, chronic immunosuppressive therapy, HIV/AIDS, and inherited immunodeficiency [8,11].
[b] Significant anoxic brain injury, diffuse axonal injury, massive intracranial hemorrhage, or herniation.

degree. Future prediction studies may consider alternative time points after intubation for ARDS.

3.3. Handling of missing data

In the derivation cohort, 18 (9%) of the patients were missing change in Pao_2/Fio_2 from intubation to 12 hours after intubation, 16 (8%) of the patients were missing ARDS index, and 3 (2%) were missing OI. In the validation cohort, 8 (4%) of the patients were missing change in Pao_2/Fio_2, 4 (4%) of the patients were missing ARDS index, and 4 (2%) were missing OI. After identification of potentially important predictor variables, a random forest was used to impute the missing data in the derivation and validation data sets for the predictor variables.

3.4. Data-driven ECMO prediction score creation

Only the derivation cohort was used for fitting the prediction model. An all-subsets method was used for selecting prediction score variables [28,29]. Performance of all combinations of candidate predictor variables was compared using the resulting whole model χ^2 and c-statistics. The combination of variables with the greatest χ^2 statistic and c-statistic was selected for the final prediction score. Continuous variables were categorized or dichotomized to produce a more simple prediction score that could be easily calculated at the bedside. Cutoffs for ARDS index and $\Delta\ \chi^2$ for the data-driven score were determined based on quartile distribution in the derivation cohort and then rounded to convenient integers.

3.5. Assessing model performance

The receiver operating characteristic curve was plotted for both the derivation and validation cohorts [30,31]. Calibration was assessed by the Hosmer-Lemeshow test and qualitatively by plotting expected vs observed results across the range of prediction scores [32]. Because positive predictive value and negative predictive value are heavily influenced by prevalence, positive likelihood ratios were also assessed and reported to increase external validity [33].

4. Results

4.1. Characteristics of the ARDS cohort

Of the 79846 mechanically ventilated patients admitted to the ICUs during the study period, 767 patients met Berlin criteria for at least moderate ARDS [7]. The baseline characteristics of the final derivation cohort of 198 patients and validation cohort of 192 patients and univariate analyses are summarized in Table 2.

4.2. Selection of expert opinion ECMO prediction model

The results of the Modified Delphi Technique of consensus building among the participating ARDS and ECMO experts are summarized in Table S1 in the supplemental material. In descending order, the 5 highest ranked candidate predictor variables chosen were OI at 12 hours, change in Pao_2/Fio_2 during the first 12 hours, immunocompromised state (protective), aspiration (protective), and obesity with body mass index (BMI) greater than 30 (protective). In this setting, "protective" means a factor that is associated with a lower risk of developing ECMO eligibility. The expert opinion ECMO eligibility prediction model is defined in Table 3.

4.3. Predictive characteristics of the data-driven and expert opinion ECMO eligibility prediction models

Following the variable selection techniques described in the "Materials and methods" section above, the final data-driven ECMO eligibility prediction model was created and is presented in Table 3. In the validation cohort, the c-statistic was 0.71 ($P < .001$) for the data-driven prediction model and 0.61 ($P = .02$) for the expert opinion prediction model. An alternative data-driven model using the OI in place of the ARDS index was tested and found to have a c-statistic of only 0.67 in the validation cohort. Therefore, the ARDS index was chosen for inclusion in the data-driven prediction model instead of the OI. Expanded predictive statistics for both ECMO eligibility prediction models are summarized in Table 4, along with practical interpretations in Table 5. The Hosmer-Lemeshow test for the data-driven model indicated no evidence of

Table 2
Baseline and clinical characteristics

	Derivation cohort (n = 198)			Validation cohort (n = 192)		
	ECMO eligible (n = 47)	Not ECMO eligible (n = 151)	P[a]	ECMO eligible (n = 33)	Not ECMO eligible (n = 159)	P[a]
Demographics						
Age, median (IQR)	60 (51-67)	56 (47-69)	.44	54 (46-67)	60 (50-73)	.104
Male, n (%)	27 (57.5)	85 (56.3)	.89	24 (72.3)	93 (58.5)	.170
BMI, median (IQR)	27.2 (22-33)	27.9 (23-33)	.60	27.5 (24-34)	28.6 (24-33)	.968
Immunocompromised, n (%)	27 (57.5)	75 (49.7)	.35	19 (57.6)	63 (39.6)	.081
SOFA day 1, median (IQR)	9 (6-15)	9 (6-11)	.27	11 (6-13)	9 (6-12)	.132
APACHE III, median (IQR)	97 (75-130)	88 (70-112)	.11	98 (74-111)	91 (73-111)	.776
ARDS triggers						
Aspiration, n (%)	2 (4.3)	30 (19.9)	.01	1 (3.0)	17 (10.7)	.32
Pneumonia, n (%)	43 (91.5)	129 (85.4)	.33	32 (97.0)	146 (91.8)	.47
Sepsis (nonpneumonia), n (%)	23 (48.9)	91 (60.3)	.17	26 (78.8)	98 (61.6)	.07
Trauma, n (%)	1 (10.0)	46 (24.5)	.46	0 (0.0)	1 (0.63)	1.0
Pancreatitis, n (%)	5 (10.6)	31 (20.5)	.14	4 (12.1)	22 (13.8)	1.0
Clinical variables						
Pao_2/Fio_2 12 h, median (IQR)	122 (87-164)	150 (118-205)	<.001	122 (90-160)	163 (126-201)	.002
OI 12 h, median (IQR)	12.7 (9.1-18.8)	10.5 (7.8-14)	.003	13.7 (8.2-23.1)	9.9 (7.2-13.2)	<.001
ARDS index 12 h,[b] median (IQR)	148 (121-292)	117 (82-168)	.001	156 (87-317)	104 (70-162)	<.001
Δ Pao_2/Fio_2 0-12 h,[c] median (IQR)	−2.5 (−32 to +30)	+25 (−14 to +77)	.007	+19 (−42 to +66)	+36 (0 to +81)	.30
Static compliance 12 h, median (IQR)	33 (23-49)	36 (27-45)	.56	40 (27-57)	34 (26-47)	.13
pH 12 h, median (IQR)	7.33 (7.24-7.37)	7.37 (7.31-7.41)	.048	7.32 (7.22-7.43)	7.35 (7.28-7.41)	.72

12 h indicates 12 hours after intubation for ARDS; APACHE III, Acute Physiology and Chronic Health Evaluation III; SOFA, Sequential Organ Failure Assessment.

[a] *P* values for comparison of patients who became ECMO eligible vs those who did not become ECMO eligible and were calculated by Wilcoxon rank sum, χ^2, or Fisher exact test, as appropriate.

[b] ARDS index = OI * (minute ventilation * $Paco_2/40$).

[c] Pao_2/Fio_2 ratio 12 hours after intubation − Pao_2/Fio_2 ratio at time of intubation.

Table 3
Data-driven and expert opinion–based ECMO eligibility prediction scores

	Variable	Value	Points
Data-driven early prediction of ECMO eligibility for severe ARDS score	Δ Pao_2/Fio_2 in first 12 h[a]	Less than −100	3
		−100 to 0	2
		0.1 to +100	1
		>+100	0
	ARDS index[b] at 12 h	>300	3
		200.1-300	2
		100-200	1
		<100	0
	Aspiration[c]	Not present	1
Expert Opinion Prediction Score	OI at 12 h	≥15	1
	Δ Pao_2/Fio_2 in first 12 h[a]	<0	1
	Body mass index	<30	1
	Immunocompromised state	Not present	1
	Aspiration[c]	Not present	1

Oxygenation index = Fio_2 * mean airway pressure/Pao_2.
[a] Pao_2/Fio_2 ratio 12 hours after intubation − Pao_2/Fio_2 ratio at time of intubation.
[b] OI * (minute ventilation * $Paco_2$/40).
[c] Aspiration was primary trigger for patient's ARDS.

poor fit ($P = .41$). The time between prediction scoring (12 hours after intubation for ARDS) until the onset of ECMO eligibility was a median of 46 hours (interquartile range [IQR], 16-84).

5. Discussion

This study found fair discrimination (c-statistic, 0.71) with a simple, clinical prediction tool using the ARDS index, aspiration, and the trend of Pao_2/Fio_2 ratios over the first 12 hours after intubation to predict ECMO eligibility. The authors suggest the most useful applications of the prediction tools presented in this study are (1) the early identification of ARDS patients who may benefit from transfer to an ECMO-capable medical center and (2) improving the efficiency of severe ARDS and ECMO research enrollment. However, neither of these suggested potential uses of the prediction scores was formally tested in this study.

There is a growing support for a hub-and-spoke model, which transfers the highest risk respiratory failure patients to high-volume ECMO centers for specialized cares [5,34]. There is also evidence to suggest that adjunctive ARDS therapies (including proning, paralysis, and perhaps ECMO) are likely more effective if applied early (<72 hours after onset) in the course of ARDS [1,2,35,36]. Furthermore, transfer (or remote cannulation for ECMO) of ARDS patients is often more challenging and resource intensive when the underlying ARDS has become significantly advanced in severity [37,38]. For these reasons, early identification of this subgroup of ARDS patients before inception of permanent lung damage and debility will be crucial in improving outcomes.

To increase external validity and recognizing that local referral patterns and hospital networks may have unique preferences, the diagnostic statistics of a range of prediction score cutoffs were reported in the "Results" section (see Table 4), and practical examples of these statistics are provided in Table 5. This information could be used to trigger electronic alerts (sniffers) and provide support for triage decisions. In the authors' opinion, for the purposes of facilitating early transfer of patients to ECMO-capable centers, we would recommend using an early prediction ECMO eligibility for severe ARDS score cutoff of greater than or equal to 6. At this score threshold, there is a robust positive likelihood ratio (33.7) suggesting a high likelihood of becoming ECMO eligible. Other hospital systems may choose another cutoff based on availability of ECMO resources, patient transfer logistics, or evolving evidence regarding the efficacy of ECMO for ARDS.

To give a frame of reference for the performance of this study's prediction score, one could compare it to other widely cited prediction scores. Discrimination by the data-driven ECMO prediction score presented here (c-statistic, 0.71) compares favorably to many notable, published prediction tools, including the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score, Early Warning Scores for Rapid Response Teams (RRT), and pediatric ARDS mortality. Reported c-statistics were 0.74 for the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score, 0.67 for the modified Early Warning Score, and 0.69 for pediatric ARDS mortality prediction [11,39-41].

The ARDS index presented here is a novel variable proposed a priori using commonly available data to measure both oxygen exchange and an approximation of dead space. In addition to the information provided by the OI (Fio_2 and the mean airway pressure required to attain a specific Pao_2), the ARDS index also incorporates a derivative of VE_{40} to approximate dead space ventilation based on easily available clinical data [42-44]. Data-driven prediction scores including OI vs the ARDS index were compared, and the prediction score including the ARDS index had a higher c-statistic (0.71 vs 0.67).

Two approaches to prediction, each with their own inherent advantages and disadvantages, were planned a priori—a data-driven approach and an expert opinion–based approach. The primary advantage of the

Table 4
Extracorporeal membrane oxygenation prediction score diagnostic characteristics

In the validation cohort	c-statistic (95% CI)	Sensitivity (95% CI)	PPV (95% CI)	+LR (95% CI)
Data-driven score	0.71 (0.61-0.81)			
Cutoff ≥6		0.21 (0.09-0.39)	0.88 (0.47-1.00)	33.7 (4.29-265.01)
Cutoff ≥5		0.33 (0.18-0.52)	0.52 (0.30-0.74)	5.30 (2.45-11.45)
Cutoff ≥4		0.52 (0.34-0.69)	0.33 (0.21-0.48)	2.41 (1.54-3.76)
Cutoff ≥3		0.82 (0.65-0.93)	0.23 (0.15-0.31)	1.4 (1.14-1.72)
Cutoff ≥2		0.97 (0.84-1.00)	0.19 (0.13-0.26)	1.12 (1.03-1.22)
Expert opinion score	0.61 (0.51-0.71)			
Cutoff ≥5		0.09 (0.02-0.24)	0.60 (0.15-0.95)	7.21 (1.26-41.57)
Cutoff ≥4		0.21 (0.09-0.39)	0.26 (0.11-0.46)	1.69 (0.78-3.66)
Cutoff ≥3		0.67 (0.48-0.82)	0.22 (0.14-0.32)	1.38 (1.03-1.84)

CI indicates confidence interval; +LR, positive likelihood ratio; PPV, positive predictive value.

Table 5
Data-driven ECMO prediction score examples

Cutoff	For every 100 patients who will actually develop ARDS severe enough for consideration of ECMO, how many patients would this test miss?	If consulted for 100 consecutive ARDS patient with a positive ECMO prediction score, how many of these patients would actually go on to develop ARDS severe enough for ECMO?
≥6	79	88
≥5	67	55
≥4	48	34
≥3	18	23
≥2	3	19

data-driven approach is its ability to identify potentially important prediction variables from a large pool of candidate variables. The key disadvantage of the data-driven approach is its susceptibility to overfitting, which was partially addressed by assessing its performance in a validation cohort. The expert opinion–based approach using the modified Delphi technique has the advantage of using clinical factors suggested by multiple experienced ECMO physicians from several different medical systems and countries. Therefore, the expert opinion–based score may be more resistant to "overfitting" of the score and improved external validity. The primary disadvantage of the expert opinion–based score is that only the small subset of candidate predictor variables that are agreed upon by the experts were statistically analyzed and included in the score.

Strengths of this study overall include the use of a robust and comprehensive ICU database with electronic data mining techniques for ARDS and other ICU outcomes, which have been previously validated. An additional strength of this study is the focus on early detection

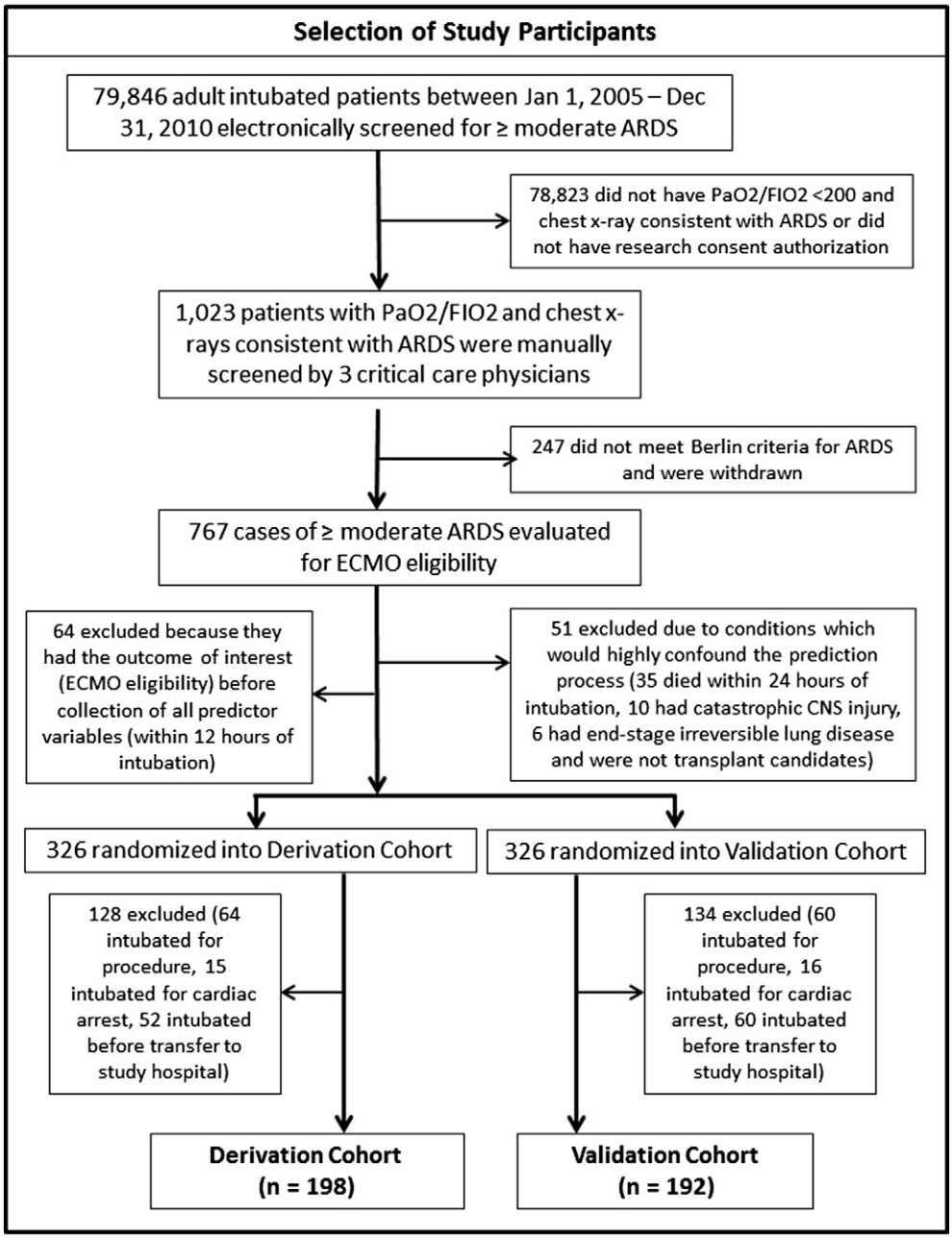

Fig. 1. Inclusion and exclusion flow chart of patients included in this study.

(within 12 hours of intubation) of progression to severe ARDS and eventual ECMO eligibility. Weaknesses of this study include its single-center nature and limitations inherent to a retrospective study (missing data, selection bias, and lack of randomization). The choice of ECMO contraindications (Table 1) and exclusion of patients initially intubated for reasons other than ARDS and intubation before transfer to our facility (Fig. 1) could negatively impact external validity. Finally, although a validation cohort was used, the validation cohort includes patients from the same database and institution as the derivation cohort, so this may be another potential limitation.

In conclusion, we present a simple ECMO prediction score that can be calculated using commonly available ventilator and oxygenation variables within the first 12 hours of intubation for ARDS. The score provided fair discriminatory power to detect ARDS progression to a severity sufficient for consideration of ECMO.

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Appendix A. Supplementary data

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