Journal of Critical Care 33 (2016) 125–131

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Ventilation/ARDS/VAP

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

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ARTICLE INFO

Keywords:
Adult
Extracorporeal membrane oxygenation
Acute respiratory distress syndrome
Patient selection
Clinical prediction

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"

☆ Conflicts of interest and source of funding: The authors have no conflicts of interest to declare. The study was funded in part by the Mayo Clinic Critical Care Research Committee.
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http://dx.doi.org/10.1016/j.jcrc.2016.01.021
0883-9441/

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.