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# Extracorporeal Membrane Oxygenation Support for Influenza A: Retrospective Review of the Extracorporeal Life Support Organization Registry Comparing H1N1 With Other Subtypes

**OBJECTIVES:** Although there is a substantial published experience of extracorporeal membrane oxygenation during the H1N1 pandemic, less is known about the use of extracorporeal membrane oxygenation in patients with other subtypes of the influenza A virus. We hypothesized that the severity of illness and survival of patients supported with extracorporeal membrane oxygenation would differ for those with H1N1 influenza A compared with other subtypes of influenza A.

**DESIGN, SETTING, PATIENTS:** Retrospective study of extracorporeal membrane oxygenation–supported adults (> 18 yr) with influenza A viral infection reported to the Extracorporeal Life Support Organization Registry between 2009 and 2019. We describe the frequency and compare characteristics and factors associated with in-hospital survival using a least absolute shrinkage and selection operator regression analysis.

**MAIN OUTCOMES AND MEASURES:** Of 2,461 patients supported with extracorporeal membrane oxygenation for influenza A, 445 had H1N1, and 2,004 had other subtypes of influenza A. H1N1 was the predominant subtype between 2009 and 2011. H1N1 patients were younger, with more severe illness at extracorporeal membrane oxygenation cannulation and higher reported extracorporeal membrane oxygenation complications than those with other influenza A subtypes. Patient characteristics including younger age and higher weight and patient management characteristics including longer ventilation duration before extracorporeal membrane oxygenation were associated with worse survival. Extracorporeal membrane oxygenation complications were associated with reduced survival. There was no difference in survival to hospital discharge according to influenza subtype after adjusting for other characteristics.

**CONCLUSIONS:** Patients supported with extracorporeal membrane oxygenation for H1N1 were younger, with more severe illness than those supported for other influenza A subtypes. Survival to hospital discharge was associated with patient characteristics, management characteristics, and extracorporeal membrane oxygenation complications but was not impacted by the specific influenza A subtype.

**KEY WORDS:** acute respiratory distress syndrome; extracorporeal membrane oxygenation; respiratory distress

In 2009, the H1N1 influenza A pandemic led to a surge of extracorporeal membrane oxygenation (ECMO) use in critically ill patients with acute respiratory distress syndrome (ARDS) (1–4). Prior to this, ECMO use in adults with ARDS was relatively rare due to logistics, expense, and two early randomized clinical trials that failed to demonstrate a survival benefit (4, 5). A large retrospective review of over 1,400 adults with ARDS supported on

Erika R. O'Neil, MD<sup>1</sup>Huiming Lin, MS<sup>2</sup>Meng Li, PhD<sup>2</sup>Lara Shekerdemian, MD<sup>1</sup>Joseph E. Tonna, MD, MS<sup>3</sup>Ryan P. Barbaro, MD<sup>4</sup>Jayvee R. Abella, PhD<sup>5</sup>Peter Rycus, MPH<sup>6</sup>Graeme MacLaren, MBBS, MSc<sup>7</sup>Marc M. Anders, MD<sup>1</sup>Peta M. A. Alexander, MBBS<sup>8,9</sup>

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ECMO before 2006 showed 50% survival (6). The conventional ventilatory support versus ECMO for severe adult respiratory failure trial in 2009 was the first to demonstrate the safety of ECMO utilization in patients with ARDS (7). More recently, the ECMO to Rescue Lung Injury in Severe ARDS trial supports a role for ECMO in adult ARDS management (8, 9).

The novel pandemic H1N1 influenza A (H1N1) virus was associated with increased mortality compared with seasonal influenza A (10–16). Clinical deterioration in young, otherwise well patients during the H1N1 pandemic despite maximal conventional intensive care therapies prompted increased utilization of ECMO, with reported survival rates between 35% and 90% (17–28). Although there is substantial published experience of ECMO during the H1N1 pandemic, less is known about the use of ECMO in patients with other influenza A virus subtypes.

We hypothesized that the severity of illness and survival of patients supported with ECMO would differ for those with H1N1 to other influenza A subtypes. Against this background, our aims for this project were to 1) describe the frequency of ECMO use overtime for H1N1 versus other influenza A subtypes, 2) compare characteristics of patients supported on ECMO with H1N1 versus other influenza A subtypes, and 3) identify and compare factors associated with survival to hospital discharge in adults with H1N1 versus other influenza A subtypes supported with ECMO.

## METHODS

### Study Design

We conducted a multicenter retrospective cohort study using the Extracorporeal Life Support Organization (ELSO) Registry, representing 463 ECMO centers from around the world. The ELSO Registry collects deidentified data from its member institutions via a standard registry form with logic-limited data entry to improve the quality of care to patients (29). Use of data for research may be requested and granted approval by the ELSO Registry Scientific Oversight Committee.

For this study, adult patients (> 18 yr) with influenza A-associated respiratory failure during 2009–2019 were eligible for inclusion. Diagnosis of H1N1 and other influenza A subtypes were defined by ELSO organism code (Influenza A 63) and/or documentation of *International Classification of Diseases* (ICD), 9th

revision and 10th revision codes (**Online Supplement 1**, <http://links.lww.com/CCX/A874>). This study was approved by the ELSO Registry Scientific Oversight Committee, and per the Institutional Review Board of the Baylor College of Medicine, no approval was needed given the use of deidentified data.

### Outcomes

The primary outcome of interest was survival to discharge from the ECMO center. The secondary outcomes were complications, which were selected by review of the ELSO International Summary Report 2020, where variables showed a proportional survival of less than 50% in adult patients with respiratory ECMO (**Online Supplement 2**, <http://links.lww.com/CCX/A874>) (30).

### Variable Selection

Explanatory variables (**Table 1**) were based on previously identified factors associated with mortality reported by ELSO and those used in the Respiratory ECMO Survival Prediction (RESP) score, a validated prediction score used to predict in-hospital survival in patients receiving ECMO for acute respiratory failure (30, 31). Comorbidity variables of immunocompromised state, CNS dysfunction, and shock were identified by ICD codes (Online Supplement 1, <http://links.lww.com/CCX/A874>). Variables with more than 15% missing data were excluded from the analysis.

Implausible blood gas values were assessed for possible entry in kilopascal instead of millimeters of mercury (mm Hg) using an algorithm to calculate the pH according to the Henderson-Hasselbalch equation. If the calculated pH corresponded to the pH of the source, arterial blood gas values were converted to mm Hg by multiplying them by 7.5. Missing  $\text{Paco}_2$  was replaced by calculated ones if pH and  $\text{Hco}_3$  were entered; missing pH values were calculated if  $\text{Paco}_2$  and  $\text{Hco}_3$  were available.

### Statistical Analysis

Patient and ECMO characteristics were compared between H1N1 and other influenza A subtypes using univariable analysis. Categorical and dichotomous variables were expressed as exact numbers with percentages and analyzed with Fisher exact or Pearson's chi-square. Continuous variables were expressed as median values with 25–75th interquartile ranges and

**TABLE 1.**  
**Explanatory Model**

Variables	OR (CI)	<i>p</i>
Influenza A H1N1 subtype vs other influenza A subtypes	1.25 (0.38–1.73)	0.4577
Male	0.91 (0.74–1.66)	0.4456
Pre-ECMO arrest or ECMO cardiopulmonary resuscitation	0.52 (0.35–0.86)	0.0075
Neuromuscular blockade	1.27 (0.80–1.65)	0.1369
Nitric oxide	1.07 (0.02–1.70)	0.8235
Metabolic buffer agents	0.60 (0.41–0.91)	0.0101
Cardiovascular complication	0.70 (0.39–0.88)	0.0020
Hemorrhagic complication	0.96 [0.03–41.80]	0.8889
Mechanical complication	0.78 (0.57–1.05)	0.0452
Metabolic complication	0.56 (0.30–0.92)	0.0137
Neurologic complication	0.17 (0.11–0.24)	<0.0001
Pulmonary complication	0.42 (0.27–0.57)	< 0.0001
Renal complication	0.67 (0.52–0.85)	0.0012
Nonrespiratory coinfections	0.93 (0.81–5,553.48)	0.9301
CNS dysfunction	0.80 (0.54–1.93)	0.3199
Immunocompromised	0.53 (0.35–0.83)	0.0038
Shock	0.78 (0.56–1.10)	0.0695
Paco <sub>2</sub> ≥ 75 mm Hg	0.89 (0.68–1.84)	0.4546
Age 18–49 yr	3.15 (2.17–4.15)	< 0.0001
Age 50–59 yr	1.39 (0.94–1.87)	0.0445
Intubation to time on ECMO ≥ 7 d	0.58 (0.31–0.81)	0.0015
Intubation to time on ECMO ≥ 48 hr < 7 d	0.72 (0.53–0.94)	0.0097
Intubation to time on ECMO unknown	0.66 (0.47–1.01)	0.0265
Weight ≤ 75 kg	0.67 (0.31–1.02)	0.0296
Weight 75–90 kg	0.87 (0.47–1.81)	0.3524
Weight 90–110 kg	1.09 (0.33–1.60)	0.6092
Hours ECMO > 442.5	2.50 (1.26–3.67)	0.0070
Hours ECMO 256.0–442.5	2.73 (1.65–3.76)	0.0005
Hours ECMO 146.5–256.0	3.09 (2.25–4.10)	< 0.0001

ECMO = extracorporeal membrane oxygenation, OR = odds ratio.

Patient characteristics, pre-ECMO management, and ECMO run factors associated with survival to hospital discharge by multivariable logistic regression with the least absolute shrinkage and selection operator explanatory model with exact postselection interference.

analyzed with the Wilcoxon-Mann-Whitney *U* test. Univariable unadjusted logistic regression was used to explore the association of patient characteristics against the primary outcome of survival to hospital discharge and reported as odds ratio (OR) with 95% CIs.

We described the incidence and compared characteristics and factors associated with in-hospital survival by both unadjusted logistic regression and multivariable logistic regression with the least absolute shrinkage

and selection operator (LASSO) regularization. We employed the LASSO method to achieve data-adaptive variable selection to build a parsimonious, interpretable explanatory model (32). Inference in LASSO is notoriously difficult; to this end, we adopted a recently proposed statistical method to mitigate the randomness in the selection of LASSO that supports principled comparison of mortality between influenza subtypes. In particular, CIs and *p* values for ORs in the multivariable

analysis are derived by exact postselection inference to ensure valid inference after variable selection by LASSO. Exact postselection inference characterizes the distribution of LASSO estimators conditional on the selection event and derives confidence regions that are exact for finite sample size instead of being asymptotic. This leads to statistically valid CIs after the LASSO selection procedure without bootstrap sampling.

Statistical significance was defined as a *p* value of less than 0.05. Statistical analyses were carried out using R software (Version 3.6.1, R foundation for Statistical Computing).

## RESULTS

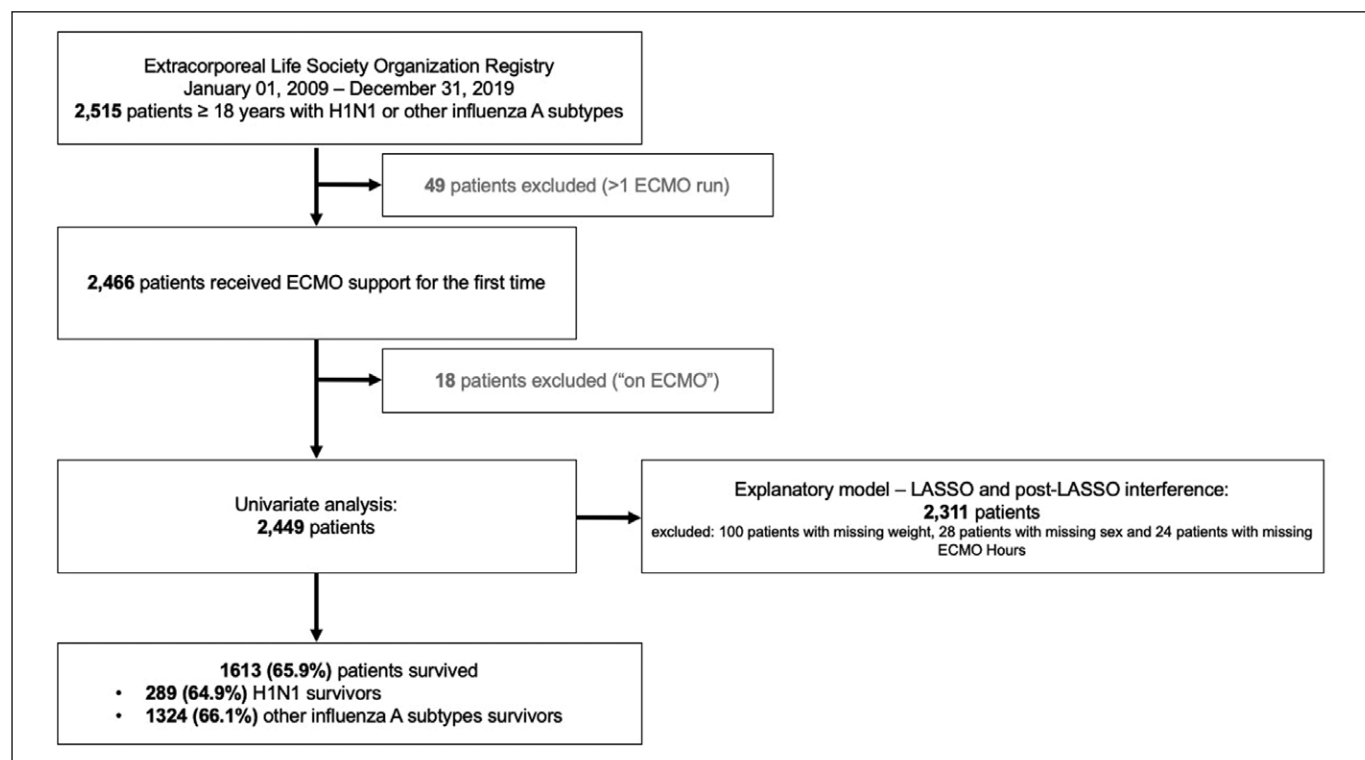
Inclusion criteria were met for 2,528 patients and after exclusions, 2,449 underwent univariable analysis (**Supplemental Table 1**, <http://links.lww.com/CCX/A875>) and 2,311 patients remained in the final explanatory model (**Fig. 1**).

### Patients Supported on ECMO With H1N1 Versus Other Influenza A Subtypes

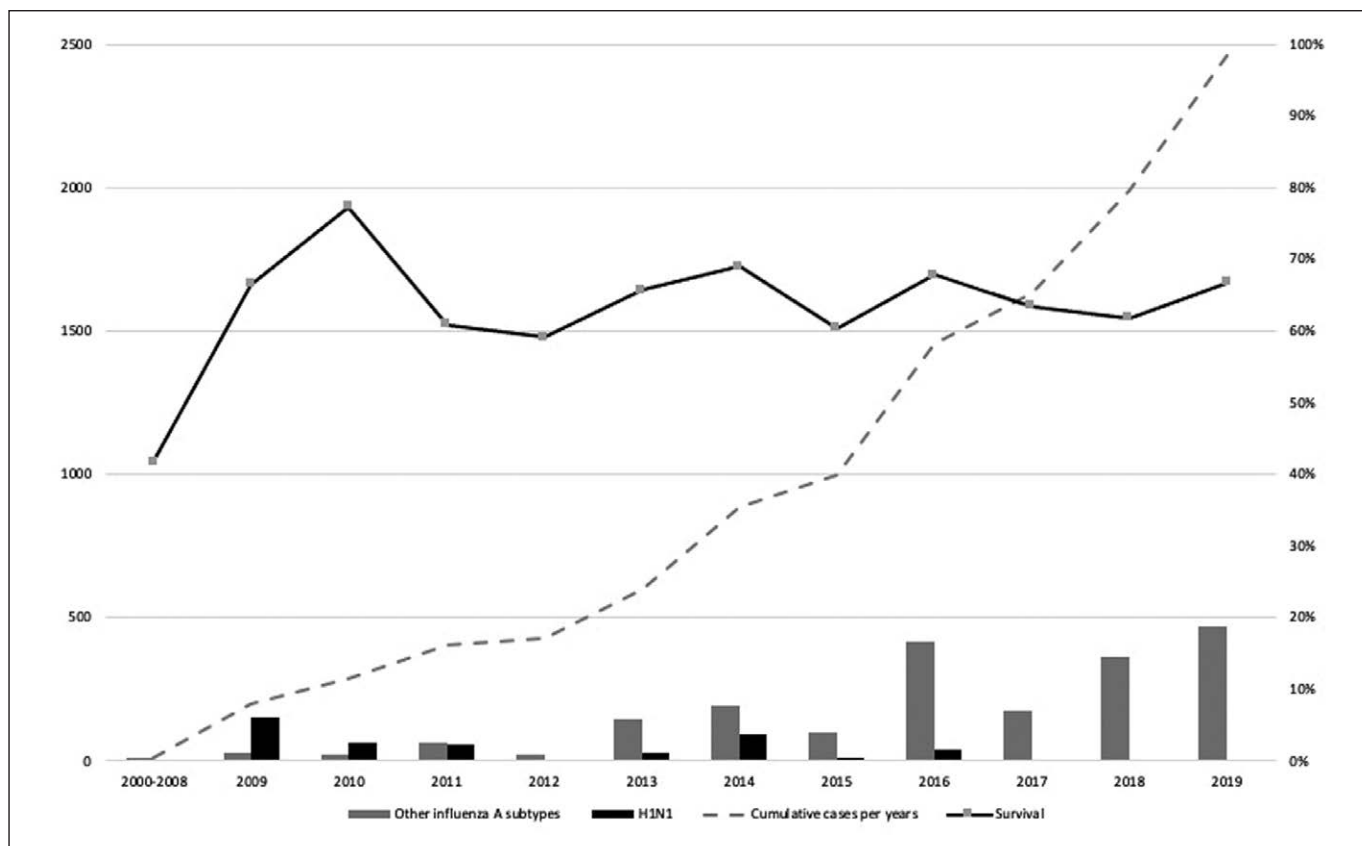
Patients with H1N1 were differentiated from other influenza A subtypes, and the yearly incidence was

determined (**Fig. 2**). The frequency of reported ECMO support increased during the years 2009–2011 with H1N1 as the predominant early subtype, but since 2012, other influenza A subtypes became the leading viral etiology associated with ECMO support. The number of ECMO centers contributing data to the ELSO registry increased from 164 to 463 during the study period (30). ECMO was provided for 445 patients with H1N1 and 2004 patients with other influenza A subtypes (**Supplemental Table 2**, <http://links.lww.com/CCX/A875>). Patients with H1N1 were younger (41.1 vs 48.0 yr;  $p < 0.0001$ ) and more commonly White (79.3% vs 64.0%;  $p < 0.0001$ ). Patients with H1N1 were more frequently ventilated with higher peak inspiratory pressure (36 vs 33 cm H<sub>2</sub>O;  $p < 0.0001$ ) and mean arterial pressure (28 vs 24 cm H<sub>2</sub>O;  $p < 0.0001$ ), with more frequent use of inhaled nitric oxide (19.8 vs 10.6%;  $p < 0.001$ ) and neuromuscular blockade (55.3 vs 48.6%;  $p = 0.01$ ). Intubation-to-ECMO time in patients with H1N1 was longer (72 vs 35 hr;  $p < 0.0001$ ). More patients with other influenza A subtypes received renal replacement therapy prior to ECMO (8.9 vs 4.9%;  $p = 0.005$ ).

There was no difference in the proportion of patients supported with venoarterial versus venovenous ECMO between groups, but more patients with



**Figure 1.** Study flowchart. ECMO = extracorporeal membrane oxygenation, H1N1 = influenza A H1N1 subtype, LASSO = least absolute shrinkage and selection operator.



**Figure 2.** Survival and number of H1N1 patients and other influenza A subtype patients over the study period. H1N1 = influenza A H1N1 subtype.

H1N1 received ECMO for primary pulmonary indication (97.5% vs 92.6%;  $p < 0.0001$ ), where the additional diagnosis of shock was also more common (17.2 vs 12.1%;  $p = 0.009$ ) for other influenza A subtypes. Patients with H1N1 were reported to experience more complications while on ECMO (74.2% vs 56.4%;  $p < 0.0001$ ) (Supplemental Table 2, <http://links.lww.com/CCX/A875>).

### Factors Associated With Survival to Hospital Discharge

A priori selected variables from the univariable analysis were incorporated into a multivariable regression analysis with LASSO to associate with survival to hospital discharge in an explanatory model (Table 1). Influenza A subtype was not associated with survival. Patient characteristics, including younger age (18–49 yr vs others OR 3.15 [2.17–4.15]) and higher weight (OR 0.67 [0.31–10.2]), were associated with increased survival. Longer ventilation duration before ECMO (OR 0.58 [0.31–0.81]) and the use of metabolic buffer agents (OR 0.60 [0.41–0.91]) were associated with

lower survival. Immunocompromised state (OR 0.53 [0.35–0.85]) and severity of illness at ECMO cannulation were also associated with lower survival, including cardiac arrest before ECMO (OR 0.52 [0.35–0.86]). Patients with the shortest ECMO runs (< 146.5 hr) were more likely to be associated with lower survival than those with longer ECMO runs (OR 3.09 [2.25–4.10]). ECMO complications except bleeding were associated with reduced survival ( $p < 0.001$ ).

### DISCUSSION

This study demonstrates that patients supported on ECMO for H1N1 had more severe features of critical illness, despite being younger, with higher weight and having fewer comorbidities than those subsequently managed on ECMO for other subtypes of influenza A. These findings may reflect increased virulence associated with this novel virus triggering the pandemic but may additionally indicate resource limitation of this invasive support during the associated abrupt increase in critical care utilization. Importantly, despite differences in severity of illness, there was no difference in



survival to hospital discharge for those patients with H1N1 compared with patients subsequently managed on ECMO with other influenza A subtypes. We did identify patient characteristics, aspects of patient management before ECMO, and ECMO complications that were associated with survival to hospital discharge.

Igniting the surge in ECMO use for adults with ARDS was the application of ECMO during the H1N1 pandemic (2, 3, 17–25). Our study demonstrates continued ECMO use after the 2009 pandemic, more for other influenza A subtypes than H1N1. Despite the higher severity of illness in the H1N1 patients, we did not find a difference in survival according to viral subtype. Studies evaluating the use of ECMO for other viral etiologies of ARDS continue to emerge (33–38). Since the novel coronavirus disease 2019 pandemic, investigators have reported successful ECMO support with similar survival to hospital discharge, even when directly compared with influenza cohorts (36, 37).

ECMO support for ARDS continued to evolve after the H1N1 pandemic. A single-center study reported up to 80% survival for H1N1 patients supported on ECMO during 2013–2014 (39). Studies from Japan and Korea demonstrated improved outcomes during a resurgence of H1N1 in 2016 when compared with the 2009 pandemic, which likely reflects improvements in their patient selection and management and improvements in equipment (40, 41). Our study found that, overall, there was no difference in survival in the H1N1 subtype patients supported on ECMO during the 2009 pandemic year compared with years thereafter. The abrupt increase in hospitalizations and ECMO use during the 2009 pandemic reflected intensified virulence and amplification of the novel H1N1 virus in the community, which highlights the capacity to surge and allocate resources appropriately to support ECMO patients when needed (10).

Allocation of scarce resources or complex resource-intensive therapies during a pandemic can, however, become problematic. Identification of patient factors, as well as patient management strategies prior to ECMO which may be associated with improved outcomes, can inform prioritization during times of limited resource availability. Many of the mortality prediction scores created to help determine ECMO candidacy were developed using patients during the H1N1 pandemic, and thus, it is not surprising that we have identified similar clinical characteristics as associated with survival to hospital discharge (24, 31, 42, 43). However,

the majority of our patients had other influenza A subtypes and not specifically H1N1, and thus factors associated with mortality in our explanatory model may be more applicable to other viral subtypes causing ARDS. As in previous studies, younger age, higher weight, and lack of reported comorbidities were associated with survival (2, 6, 19, 22, 32, 34, 42). Additionally, those patients who were managed with a shorter duration of mechanical ventilation and who had not progressed to cardiac arrest before ECMO cannulation were found to have improved survival, supporting early initiation of ECMO for viral ARDS (3, 6, 18, 31, 42). Established ECMO programs with integrated systems to prevent and mitigate complications may be best placed to offer this invasive support, even during times of pandemic-associated resource limitation (37, 44).

Our study has the expected limitations inherent in a retrospective observational study. ELSO Registry data were entered voluntarily, without external validation of data in the represented era. The institution of a data dictionary, data entry examination, and logic-limited data entry have resulted in improved data quality in the ELSO registry throughout this study (29). Our data may be confounded by the improvements in ELSO registry data or subject to era effect. Some unidentified confounding covariates, such as the older population's prior exposure to H1N1, may impact our results. Our application of LASSO regression based on comorbidities used in the RESP score is a strength of our analysis; however, we did not specifically include other potential comorbidities (31, 45). Additionally, clinically relevant covariates that had more than 15% missing data were excluded from the analysis.

## CONCLUSIONS

Over the last decade, the utilization of ECMO for viral ARDS has become well established. In this study of patients with influenza A supported with ECMO, those with H1N1 were younger, with more severe illness than those supported for other influenza A subtypes. Survival to hospital discharge was associated with patient characteristics, management characteristics, and ECMO complications but was not impacted by the specific influenza A subtype. Identification of these factors may inform patient selection and pre-ECMO management, which is especially important in the setting of resource limitations. In the setting of

increased utilization of this resource-intensive therapy, further research to clarify optimal patient candidacy for ECMO, the timing of cannulation, and the impact of etiological viral agent/s on the outcome of adults with viral ARDS is required.

- 1 Department of Pediatrics, Baylor College of Medicine, Houston, TX.
- 2 Department of Statistics, Rice University, Houston, TX.
- 3 Division of Emergency Medicine, Division of Cardiothoracic Surgery, University of Utah Health, Salt Lake City, UT.
- 4 Department of Pediatrics, University of Michigan, Ann Arbor, MI.
- 5 Medical Informatics Corporation, Houston, TX.
- 6 Extracorporeal Life Support Organization, Ann Arbor, MI.
- 7 Cardiothoracic Intensive Care Unit, National University Health System, Singapore
- 8 Department of Cardiology, Boston Children's Hospital, Boston, MA.
- 9 Department of Pediatrics, Harvard Medical School, Boston, MA.

Drs. Anders and Alexander shared senior authorship.

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Study conception, design, material preparation, data collection, and analysis were performed by Drs. Anders, O'Neil, and Alexander. Dr. Li conceived and supervised the statistical analysis. Drs. Lin, Abella, and Li performed the statistical analysis. The first draft of the article was written by Dr. O'Neil, and all authors revised the article for important intellectual content. All authors read and approved the final article.

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For information regarding this article, E-mail: [erika.oneil.md@gmail.com](mailto:erika.oneil.md@gmail.com)

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