ECMO Support for Influenza A: Retrospective Review of the ELSO Registry Comparing Seasonal and Pandemic Subtypes

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Abstract

Background: While there is substantial published experience of ECMO during the H1N1 pandemic, less is known about the use of ECMO in patients with seasonal influenza A virus. We hypothesized that the severity of illness and survival of patients supported with extracorporeal membrane oxygenation (ECMO) would differ for those with seasonal influenza A vs pandemic H1N1 (H1N1) influenza A.

Methods: Retrospective study of ECMO supported adults (>18 years) with influenza A viral infection reported to the Extracorporeal Life Support Organization (ELSO) Registry between 2009-2019. We describe the incidence and compare characteristics and factors associated with in-hospital survival using a least absolute shrinkage and selection operator regression.

Results: Of 2461 patients supported with ECMO for influenza A, 445 had H1N1 and 2004 had seasonal influenza A. H1N1 was the predominant subtype between 2009-2011. Pandemic H1N1 patients were younger, with more severe illness at ECMO cannulation and higher reported ECMO complications than those with seasonal influenza A. Patient characteristics including younger age and higher weight, and patient management including longer ventilation duration before ECMO were associated with worse survival. ECMO 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 ECMO for pandemic H1N1 were younger, with more severe illness than those supported for seasonal influenza A. Survival to hospital discharge, was associated with patient characteristics, management, and ECMO complications, but was not impacted by the specific influenza A subtype.

Trial registration: N/A

Background

In 2009, the H1N1 influenza A pandemic lead to a surge of extracorporeal membrane oxygenation (ECMO) use in critically ill patients with acute respiratory distress syndrome (ARDS) (1, 2, 3, 4). Prior to this, ECMO use in adults with ARDS was relatively rare because two early randomized clinical trials failed to demonstrate a survival benefit (4, 5). A large retrospective review of over 1400 adults with ARDS supported on ECMO before 2006 showed 50% survival (6). The conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR) 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 (EOLIA) 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 to 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%-90% (17–28). While there is substantial published experience of ECMO during the H1N1 pandemic, less is known about the use of ECMO in patients with seasonal influenza A virus.

We hypothesized that the severity of illness and survival of patients supported with ECMO would differ for those with seasonal influenza A vs pandemic H1N1. Against this background, our aims for this project were to 1) describe the incidence of ECMO use over time for H1N1 vs seasonal influenza A; 2) compare characteristics of patients supported on ECMO with H1N1 vs seasonal influenza A; and 3) identify and compare factors associated with survival to hospital discharge in adults with H1N1 vs seasonal influenza A supported with ECMO.

Methods

Study Design

We conducted a multicenter retrospective cohort study using the Extracorporeal Life Support Organization (ELSO) Registry. Adult patients (> 18 years) with influenza A during 2009–2019 were eligible for inclusion. Diagnosis of seasonal influenza A and H1N1 were defined by ELSO organism code (Influenza A 63) and/or documentation of International Classification of Diseases (ICD) 9 revision and 10 revision codes (**Online Supplement 1**).

Variable selection

Predictor variables were determined a priori, with the inclusion of previously identified factors associated with mortality (29, 30). Variables were identified by ICD codes (**Online Supplement 1**) including central nervous system (CNS) dysfunction, immunocompromised state, and shock (29, 30). Age, sex, race, weight, pre-ECMO variables including cardiopulmonary arrest or ECPR, duration of mechanical ventilation, renal dysfunction requiring renal replacement therapy, use of neuromuscular blockade agents or inhaled nitric oxide, metabolic buffer infusions, peak inspiratory ventilation pressure (PIP), mean airway pressure (MAP) and partial pressure of arterial carbon dioxide (paCO2) and any known non-pulmonary co-infections were included as covariates. Year of ECMO support, hours of ECMO support, mode of support, and primary indication for support were incorporated as explanatory variables.

Implausible blood gas values were assessed for possible entry in kilopascal instead of millimeters of mercury (mmHg) 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 mmHg by multiplying them by 7.5. Missing $paCO_2$ were replaced by calculated ones if pH and HCO3 were entered; missing pH values were calculated if paCO2 and HCO_3 were available. Variables with more than 15% missing data were excluded from the analysis.

Outcome

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**) (30).

Statistical Analysis

Patient and ECMO characteristics were compared between pandemic H1N1 and seasonal influenza A cohorts using univariate analysis. Variables included demographics, comorbidities, pre-ECMO respiratory status, and complications. Categorical and dichotomous variables were expressed as exact numbers with percentages and analyzed with Fisher's exact or Pearson's chi-square. Continuous variables were expressed as median values with 25th – 75th interquartile ranges (IQR) and analyzed with the Wilcoxon-Mann-Whitney test. Univariate 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% confidence intervals (CI).

We describe the incidence and compare characteristics and factors associated with in-hospital survival by both unadjusted logistic regression and multivariate logistic regression with the least absolute shrinkage and selection operator (LASSO) regularization. We employ the LASSO method to achieve data-adaptive variable selection to build a parsimonious, interpretable model (31). Inference in LASSO is notoriously difficult; to this end, we adopt a recently proposed statistical method to mitigate the randomness in the selection of LASSO that supports principled comparison of mortality between influenza subtypes in the presence of LASSO. In particular, CIs and p-values for ORs in the multivariate analysis are derived by exact post-selection inference to ensure valid inference after variable selection by LASSO (32). We preselected the following variables for prediction of mortality: H1N1 and seasonal influenza A, sex, weight (stratified by interquartile ranges with the highest interquartile weight 110–361kg as reference variable), age by 18–49 years, 50–59 years, and ≥ 60 years, mechanical ventilation prior ECMO < 48 hours, 48 hours to 7 days or ≥ 7 days, CNS dysfunction, diagnosis of shock or immunocompromised state, neuromuscular blockade prior to ECMO, nitric oxide prior to ECMO, metabolic buffer infusions prior to ECMO, other non-respiratory co-infections, cardiac arrest prior to ECMO, and paCO2 ≥ 75 mmHg. For an explanatory model of survival, we added to our prediction model, the year of ECMO support (stratified by pandemic years 2009–2011, years after 2011), hours of ECMO support (stratified by interquartile ranges with variable reference < 146.5 hours), and complications while on ECMO support.

Statistical significance was defined as a p-value < 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 2528 patients and after exclusions, 2449 underwent univariate analysis, 2335 patients were included in the predictive analysis, and 2311 patients remained in the final

explanatory model (Fig. 1).

Patients supported on ECMO with H1N1 vs other influenza A subtypes

Patients with pandemic H1N1 were differentiated from seasonal influenza A and the incidence was determined (Fig. 2). The frequency of reported ECMO support increased during the years 2009–2011 with pandemic H1N1 as the predominant early subtype, but since 2012 other seasonal 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 seasonal influenza A (Table 1). Patients with H1N1 were younger (41.1 vs 48.0 years, $p < 0.0001$) and more commonly white (79.3% vs 64.0%, $p < 0.0001$). Patients with H1N1 were more frequently ventilated with higher PIP (36 vs 33 cmH2O, $p < 0.0001$) and MAP (28 vs 24 cmH2O, $p < 0.0001$), 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 hours, $p < 0.0001$) than in patients with seasonal influenza A. More patients with seasonal influenza A received renal replacement therapy prior to ECMO (8.9 vs 4.9%, $p = 0.005$).

Table 1
Patient demographics, characteristics, management, and features of ECMO run.

	Influenza A total (n = 2449)	Survived p*	H1N1 (n = 445)	Seasonal influenza A (n = 2004)	Difference among H1N1 / Seasonal influenza A p
	N (%) or Median [IQR]†		N (%) or Median [IQR]		
Survival	1613 (65.9)		289 (64.9)	1324 (66.1)	0.66
Age in years	47.2 [36.7–56.3]	< .0001 OR 0.97 [0.97–0.98]	41.1 [30.5–51.9]	48.0 [38.5–57.3]	< .0001
18–49	1443 (58.5)	< .0001 OR 2.56 [2.03;3.23]	318 (71.5)	1125 (55.8)	< .0001
50–59	633 (25.8)	0.12	99 (22.3)	534 (26.5)	0.06
> 60	383 (15.6)	reference	28 (6.3)	357 (17.7)	< .0001
Sex n=2421					
Male	1435 (59.3)	0.055	252 (56.9)	1183 (59.8)	0.26
Female	986 (40.7)	0.055	191 (43.1)	795 (40.2)	0.26
Weight in kg n=2349	90.0 [75.0-110.0]	0.002 OR 1.00 [1.00;1.01]	92.0 [79.7–114.0]	90.0 [74.6-109.5]	0.005

* If statistically significant association with survival the odds ratio with confidence intervals are listed.

† Categorical variables expressed in numbers with percentages [n (%)] and continuous variables in medians with interquartile ranges (median, [IQR]).

CNS: central nervous system, ECMO: extracorporeal membrane oxygenation, ECPR: ECMO cardiopulmonary resuscitation, H1N1: pandemic influenza A H1N1 subtype, IQR: interquartile range, kg: kilograms, NaH2CO3: sodium bicarbonate, paCO2: partial pressure of arterial carbon dioxide, PIP: positive inspiratory pressure, THAM: tromethamine, VA; venoarterial, VV: venovenous, VVA: veno-venoarterial

	Influenza A total (n = 2449)	Survived p*	H1N1 (n = 445)	Seasonal influenza A (n = 2004)	Difference among H1N1 / Seasonal influenza A p
< 75kg	641 (26.2)	0.0005 OR 0.65 [0.51;0.83]	85 (19.1)	556 (27.7)	0.0004
75–90kg	610 (24.9)	0.015 OR 0.74 [0.57; 0.94]	116 (26.1)	494 (24.7)	0.54
90–110kg	547 (22.3)	0.74	108 (24.3)	439 (21.9)	0.29
>110kg	100 (22.5)	reference	108 (24.3)	443 (22.1)	0.35
Missing	100 (4.1)	0.81	28 (6.3)	72 (3.6)	0.02
Race / Ethnicity n=2352					
White	1569 (66.7)	reference	336 (79.3)	1233 (64.0)	< .0001
Asian	335 (14.2)	0.18	34 (8.0)	301 (15.6)	< .0001
Hispanic	189 (8.0)	0.12	20 (4.7)	169 (8.8)	0.004
Black	131 (5.6)	0.51	21 (5.0)	110 (5.7)	0.64
Multiple	105 (4.4)	0.75	13 (3.1)	92 (4.8)	0.15
Ventilation n=2069					

* If statistically significant association with survival the odds ratio with confidence intervals are listed.

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	Influenza A total (n = 2449)	Survived p*	H1N1 (n = 445)	Seasonal influenza A (n = 2004)	Difference among H1N1 / Seasonal influenza A p
PIP (cmH2O) n=1627	33 [30–38]	0.33	36 [31–42]	33 [29–37]	< .0001
PIP (cmH2O) > 42 n=1627	211 (13.0)	0.21	126 (9.8)	85 (25.8)	< .0001
Mean airway pressure (cmH2O) n=996	25 [20–29]	0.81	28 [23–33]	24 [20–28]	< .0001
Blood gas					
pH n=2104	7.26 [7.16–7.34]	< .0001 OR 1.02 [1.01;1.03]	7.27 [7.18–7.35]	7.25 [7.15–7.34]	0.005
paCO2 (mmHg) n=2112	57 [46–71]	0.09 OR 1.00 [1.00;100]	58 [47–73]	56 [46–71]	0.06
paCO2 (mmHg) ≥ 75 n=2097	443 (21.1)	0.02 OR 0.77 [0.62;0.96]	93 (23.5)	350 (20.6)	0.22
Pre-ECMO arrest	152 (6.2)	< .0001 OR 0.32 [0.23;0.45]	23 (5.2)	129 (6.4)	0.38
Comorbidities					
Non- respiratory co-infection	277 (11.3)	0.32	115 (25.8)	162 (8.1)	< .0001

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	Influenza A total (n = 2449)	Survived p*	H1N1 (n = 445)	Seasonal influenza A (n = 2004)	Difference among H1N1 / Seasonal influenza A p
CNS dysfunction	181 (7.4)	< .0001 OR 0.38 [0.28;0.52]	45 (10.1)	136 (6.8)	0.02
Immunocompromised state	138 (5.6)	< .0001 OR 0.42 [0.30;0.60]	19 (4.3)	119 (5.9)	0.21
Shock	399 (16.2)	< .0001 OR 0.51 [0.41;0.63]	54 (12.1)	345 (17.2)	0.009
Pre-ECMO support					
Neuro-muscular blockade	1216 (49.7)	0.39	246 (55.3)	970 (48.4)	0.009
Nitric oxide	300 (12.2)	1.00	88 (19.8)	212 (10.6)	< .0001
Renal replacement therapy	200 (8.2)	0.07	22 (4.9)	178 (8.9)	.005
Metabolic buffers (THAM or NaH2CO3)	215 (8.8)	< .0001 OR 0.45 [0.34;0.60]	41 (9.2)	174(8.7)	0.71
Intubation to time on ECMO (hrs) n=2212	39 [14–107]	0.01 OR 0.998 [0.998;0.999]	72 [24–152]	35 [12–97]	< .0001
< 48 hours	1212 (49.5)	reference	162 (39.2)	1050 (58.4)	< .0001

* If statistically significant association with survival the odds ratio with confidence intervals are listed.

† Categorical variables expressed in numbers with percentages [n (%)] and continuous variables in medians with interquartile ranges (median, [IQR]).

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	Influenza A total (n = 2449)	Survived p*	H1N1 (n = 445)	Seasonal influenza A (n = 2004)	Difference among H1N1 / Seasonal influenza A p
≥ 48 hours and < 7 days	721 (29.4)	0.002 OR 0.74 [0.61;0.90]	167 (40.4)	554 (30.8)	0.0002
≥ 7 days	279 (11.4)	0.001 OR 0.63 [0.48;0.83]	84 (20.3)	195 (10.8)	< .0001
Missing	237 (9.7)	0.11	32 (7.2)	205 (10.2)	0.051
ECMO mode					
VV	2108 (86.1)	reference	377 (84.7)	1731 (86.4)	0.34
VA or VVA	207 (8.5)	< .0001 OR 0.32 [0.24;0.43]	31 (7.0)	176 (8.8)	0.26
Conversion	113 (4.6)	< .0001 OR 0.34 [0.23;0.49]	30 (6.7)	83 (4.1)	0.02
Other / Unknown	21 (0.9)	0.48	7 (1.6)	14 (0.7)	0.08
Support type					
Pulmonary	2290 (93.5)	reference	434 (97.5)	1856 (92.6)	< .0001
Cardiac	128 (5.2)	< .0001 OR 0.40 [0.28;0.57]	8 (1.8)	120 (6.0)	0.0004

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	Influenza A total (n = 2449)	Survived p*	H1N1 (n = 445)	Seasonal influenza A (n = 2004)	Difference among H1N1 / Seasonal influenza A p
ECPR	31 (1.3)	< .0001 OR 0.14 [0.06;0.33]	3 (0.7)	28 (1.4)	0.22
ECMO hours n=2425	257 [146–440]	0.42	264 [157–417]	255 [144–449]	0.73
< 146.5	607 (24.8)	reference	101 (23.1)	506 (25.5)	0.30
146.5–256.0	597 (24.3)	< .0001 OR 2.87 [2.24;3.68]	105 (24.0)	492 (24.8)	0.76
256.0–442.5	619 (25.3)	< .0001 OR 2.29 [1.81;2.91]	136 (31.1)	483 (24.3)	0.004
> 442.5	602 (24.6)	0.0004 OR 0.66 [0.52;0.83]	96 (21.9)	506 (25.5)	0.13
Missing	24 (1.0)	0.68	7 (1.6)	17 (0.9)	0.18
Any complication reported					
Cardiovascular	384 (15.7)	< .0001 OR 0.36 [0.29;0.46]	108 (24.3)	276 (13.8)	< .0001

* If statistically significant association with survival the odds ratio with confidence intervals are listed.

† Categorical variables expressed in numbers with percentages [n (%)] and continuous variables in medians with interquartile ranges (median, [IQR]).

CNS: central nervous system, ECMO: extracorporeal membrane oxygenation, ECPR: ECMO cardiopulmonary resuscitation, H1N1: pandemic influenza A H1N1 subtype, IQR: interquartile range, kg: kilograms, NaH2CO3: sodium bicarbonate, paCO2: partial pressure of arterial carbon dioxide, PIP: positive inspiratory pressure, THAM: tromethamine, VA; venoarterial, VV: venovenous, VVA: veno-venoarterial

	Influenza A total (n = 2449)	Survived p*	H1N1 (n = 445)	Seasonal influenza A (n = 2004)	Difference among H1N1 / Seasonal influenza A p
Hemorrhagic	229 (9.3)	< .0001 OR 0.51 [0.38;0.66]	50 (11.2)	179 (8.9)	0.15
Infectious	42 (1.7)	0.001 OR 0.23 [0.12;0.44]	12 (2.7)	30 (1.5)	0.10
Mechanical	76 (3.1)	0.0008 OR 0.45 [0.29;0.72]	25 (5.6)	51 (2.5)	0.002
Metabolic	277 (11.3)	< .0001 OR 0.32 [0.25;0.41]	90 (20.2)	187 (9.3)	< .0001
Neurological	196 (8.0)	< .0001 OR 0.16 [0.11;0.22]	51 (11.5)	145 (7.2)	0.005
Pulmonary	322 (13.1)	< .0001 OR 0.43 [0.34;0.55]	101 (22.7)	221 (11.0)	< .0001
Renal	1023 (41.7)	< .0001 OR 0.60 [0.50;0.70]	240 (54.0)	783 (39.1)	< .0001

* If statistically significant association with survival the odds ratio with confidence intervals are listed.

† Categorical variables expressed in numbers with percentages [n (%)] and continuous variables in medians with interquartile ranges (median, [IQR]).

CNS: central nervous system, ECMO: extracorporeal membrane oxygenation, ECPR: ECMO cardiopulmonary resuscitation, H1N1: pandemic influenza A H1N1 subtype, IQR: interquartile range, kg: kilograms, $NaH2CO3$: sodium bicarbonate, $paCO2$: partial pressure of arterial carbon dioxide, PIP: positive inspiratory pressure, THAM: tromethamine, VA; venoarterial, VV: venovenous, VVA: veno-venoarterial

There was no difference in the proportion of patients supported with veno-arterial (VA) vs veno-venous (VV) ECMO between groups, but more patients with H1N1 received ECMO for primary pulmonary indication than for seasonal influenza A (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 influenza A vs H1N1 respectively. Patients with H1N1 were reported to experience more complications while on ECMO (74.2% vs 56.4%, p < 0.0001, Table 1).

Factors associated with survival to hospital discharge

Univariate analyses are presented in Table 1. A priori selected variables from the univariate analysis were incorporated into a multivariate regression analysis with LASSO to associate with survival to hospital discharge in a predictive model (AUC 0.708, Table 2). Influenza A subtype was not associated with the primary outcome. Patient characteristics, including younger age (18–49 years vs others OR 2.57 (1.65–3.30)) and higher weight (OR 0.67 (0.53–0.86)) were associated with increased survival. Longer ventilation duration before ECMO (OR 0.53 (0.40–0.72)) and the use of metabolic buffer agents (OR 0.49 (0.35–0.67)) were associated with lower survival. Immunocompromised state (OR 0.54 (0.37–0.81)) and severity of illness at ECMO cannulation were also associated with lower survival, including pre-ECMO CNS dysfunction (OR 0.43 (0.31–0.61)), shock (OR 0.66 (0.52–0.86)) and cardiac arrest before ECMO (OR 0.39 (0.27–0.56)).

Table 2

Predictive Model. Patient characteristics and pre-ECMO management associated with survival to hospital discharge by multivariable logistic regression with the least absolute shrinkage and selection operator (LASSO) predictive model.

	OR [IQR]	P value
Influenza A vs. H1N1	0.83 [0.63–1.23]	0.1553
Male	0.89 [0.74–1.33]	0.2896
Pre-ECMO arrest or ECPR	0.39 [0.27–0.56]	< 0.0001
Neuromuscular blockade	0.25 [1.00-1.50]	0.0258
Metabolic buffer agents	0.49 [0.35–0.67]	< 0.0001
Non-respiratory co-infections	0.91 [0.70–3.09]	0.6242
CNS dysfunction	0.43 [0.31–0.61]	< 0.0001
Immunocompromised state	0.54 [0.37–0.81]	0.0021
Shock	0.66 [0.52–0.86]	0.0013
$PaCO_2$ ≥ 75mmHg	0.84 [0.66–1.23]	0.1660
$PaCO_2$ unknown	0.91 [0.71–2.88]	0.5947
Age 18–49 years	2.57 [1.65–3.30]	0.0003
Age 50–59 years	1.18 [0.60–1.54]	0.3409
Intubation to time on ECMO ≥ 7 days	0.53 [0.40–0.72]	< 0.0001
Intubation to time on ECMO ≥ 48 hours < 7 days	0.66 [0.53–0.83]	0.0003
Intubation to time on ECMO unknown	0.68 [0.49-1.00]	0.0241
Weight ≤ 75 kg	0.67 [0.53–0.86]	0.0010
Weight 75–90 kg	0.82 [0.66–1.14]	0.1060

CNS: central nervous system, ECMO: extracorporeal membrane oxygenation, ECPR: ECMO cardiopulmonary resuscitation, H1N1: pandemic influenza A H1N1 subtype, IQR: interquartile range, kg: kilograms, OR: odds ratio, paCO2: partial pressure of arterial carbon dioxide

For further assessment of explanatory factors during ECMO support associated with survival to hospital discharge, additional variables were incorporated into an explanatory multivariable model, including duration of ECMO run and complications sustained during ECMO (Table 3, AUC 0.785). There was no difference in survival according to Influenza A subtype across the study period. Patient characteristics, including younger age (18–49 years vs others OR 3.15 (2.17–4.15)) and higher weight (OR 0.67 (0.31–1.02)) were associated with higher survival.

Table 3

Explanatory Model. 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 (LASSO) explanatory model with exact post-selection interference.

	OR	P value
Influenza A vs. H1N1	1.25 [0.38–1.73]	0.4577
Male	0.91 [0.74–1.66]	0.4456
Pre-ECMO arrest or ECPR	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
Neurological 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
Non-respiratory co-infections	0.93 [0.81-5553.48]	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
$PaCO_2$ ≥ 75mmHg	0.89 [0.68–1.84]	0.4546
Age 18–49 years	3.15 [2.17–4.15]	< 0.0001
Age 50–59 years	1.39 [0.94–1.87]	0.0445
Intubation to time on ECMO ≥ 7 days	0.58 [0.31–0.81]	0.0015
Intubation to time on ECMO ≥ 48 hours < 7 days	0.72 [0.53–0.94]	0.0097
Intubation to time on ECMO unknown	0.66 [0.47–1.01]	0.0265

CNS: central nervous system, ECMO: extracorporeal membrane oxygenation, ECPR: ECMO cardiopulmonary resuscitation, H1N1: pandemic influenza A H1N1 subtype, IQR: interquartile range, kg: kilograms, OR: odds ratio, paCO2: partial pressure of arterial carbon dioxide

	OR	P value
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
CNS: central nervous system, ECMO: extracorporeal membrane oxygenation, ECPR: ECMO cardiopulmonary resuscitation, H1N1: pandemic influenza A H1N1 subtype, IQR: interquartile range, kg: kilograms, OR: odds ratio, paCO2: partial pressure of arterial carbon dioxide		

Patient management, including longer ventilation duration before ECMO (OR 0.58 (0.31-0.0.81)) 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 hours) 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 pandemic 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 seasonal influenza A. These findings support increased virulence associated with novel virus triggering the pandemic, but may additionally reflect 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 pandemic H1N1 compared with patients subsequently managed on ECMO with seasonal influenza A. 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 success of ECMO during the H1N1 pandemic (2, 3, 17–25). Our study demonstrates continued ECMO use after the 2009 pandemic, more for seasonal 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 COVID-19 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 to the 2009 pandemic, which likely reflects improvements in their patient selection and management (40, 41). Our study found that, overall, there was no difference in survival in the pandemic H1N1 subtype patients supported on ECMO during the 2009 pandemic year compared to 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, 29, 42, 43). However, the majority of our patients had seasonal influenza and not specifically H1N1, and thus factors associated with mortality in our predictive and explanatory models 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, who had not progressed to cardiac arrest prior to ECMO cannulation were found to have improved survival, supporting early initiation of ECMO for viral ARDS (3, 6, 18, 29, 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).

Study limitations

Our study has the expected limitations inherent in a retrospective observational study. ELSO Registry data is entered voluntarily, without external validation of data in the represented era, however, the institution of a data dictionary, data entry exam, and logic-limited data entry has resulted in improved data quality in the ELSO registry over the duration of this study (45). Our data may be 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 adjusting for predefined comorbidities used in the RESP score is a strength of our analysis; however, we did not specifically include other potential comorbidities (29, 46). 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 pandemic H1N1 were younger, with more severe illness than those supported for seasonal influenza A. Survival to hospital discharge was associated with patient characteristics, management, 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 limitation.

Declarations

Ethics approval and consent to participate: Permission to analyze the data was granted by the Extracorporeal Life Support Organization Scholarly Oversite Committee and consent was exempted by the Institutional Review Board of Baylor College of Medicine, Houston, Texas, USA.

Consent for publication: Exempted by the Institutional Review Board of Baylor College of Medicine, Houston, Texas, USA.

Availability of data and materials: The data that support the findings of this study are available from the Extracorporeal Life Support Organization Scholarly Oversite Committee with submission of the written request form.

Competing interests: PA reports grants from the National Institutes of Health (NIH) to support research activities not specific to this study (1R13HD104432-01 Pediatric ECMO Anticoagulation CollaborativE – PEACE). JET is supported by a Career Development Award from the National Institutes of Health/National Heart, Lung, And Blood Institute (K23 HL141596). JET received speaker fees and travel compensation from LivaNova and Philips Healthcare, unrelated to this work. RPB reports grants from National Institutes of Health (R01 HL153519-ASCEND; K12 HL138039-TACTICAL; R01 HD01543-Pediatric Implantable Artificial Lung) outside the submitted work; RPB also discloses that he is the Extracorporeal Life Support Organization (ELSO) Registry Chair. All other authors have no conflicts of interest to disclose (EO, MA, ML, HL,JL, PR, GL, and LS).

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Authors' contributions: Study conception, design, material preparation, data collection and analysis were performed by MA, EO, and PA. ML conceived and supervised the statistical analysis. HL, JA, and ML performed the statistical analysis. The first draft of the manuscript was written by EO, and all authors revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Figures

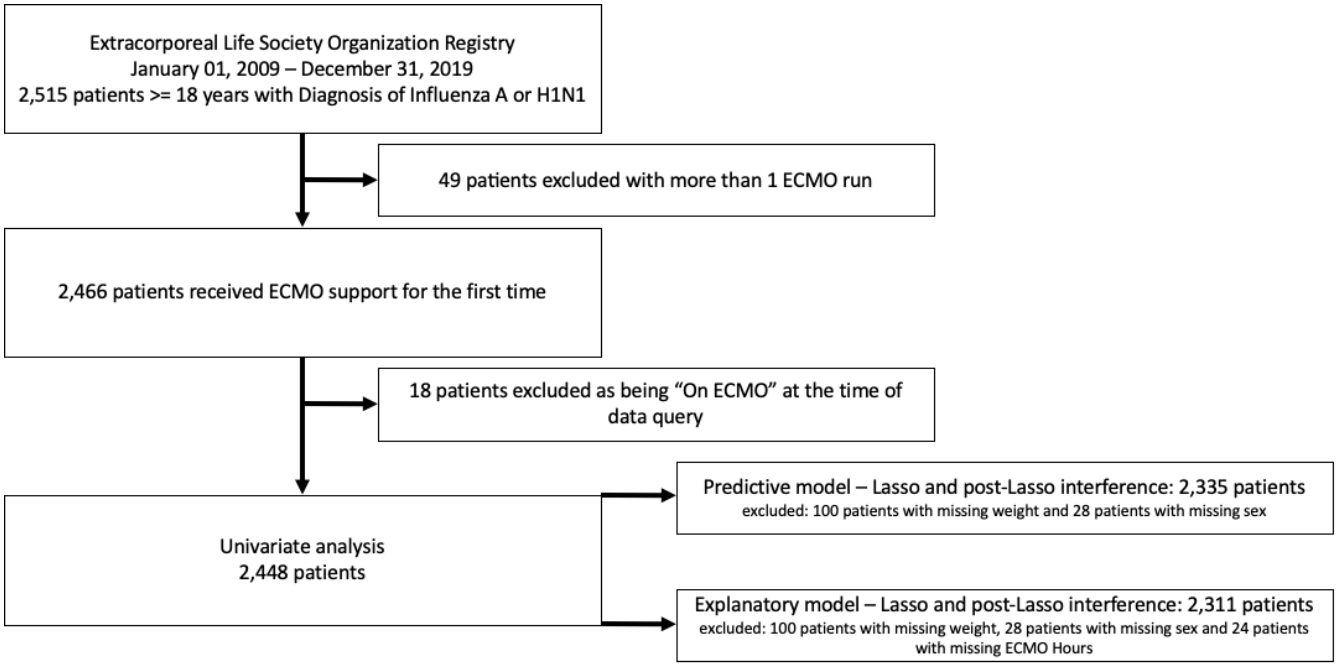

Figure 1

Study Flowchart ECMO: extracorporeal membrane oxygenation, H1N1: pandemic influenza A H1N1 subtype, LASSO: least absolute shrinkage and selection operator

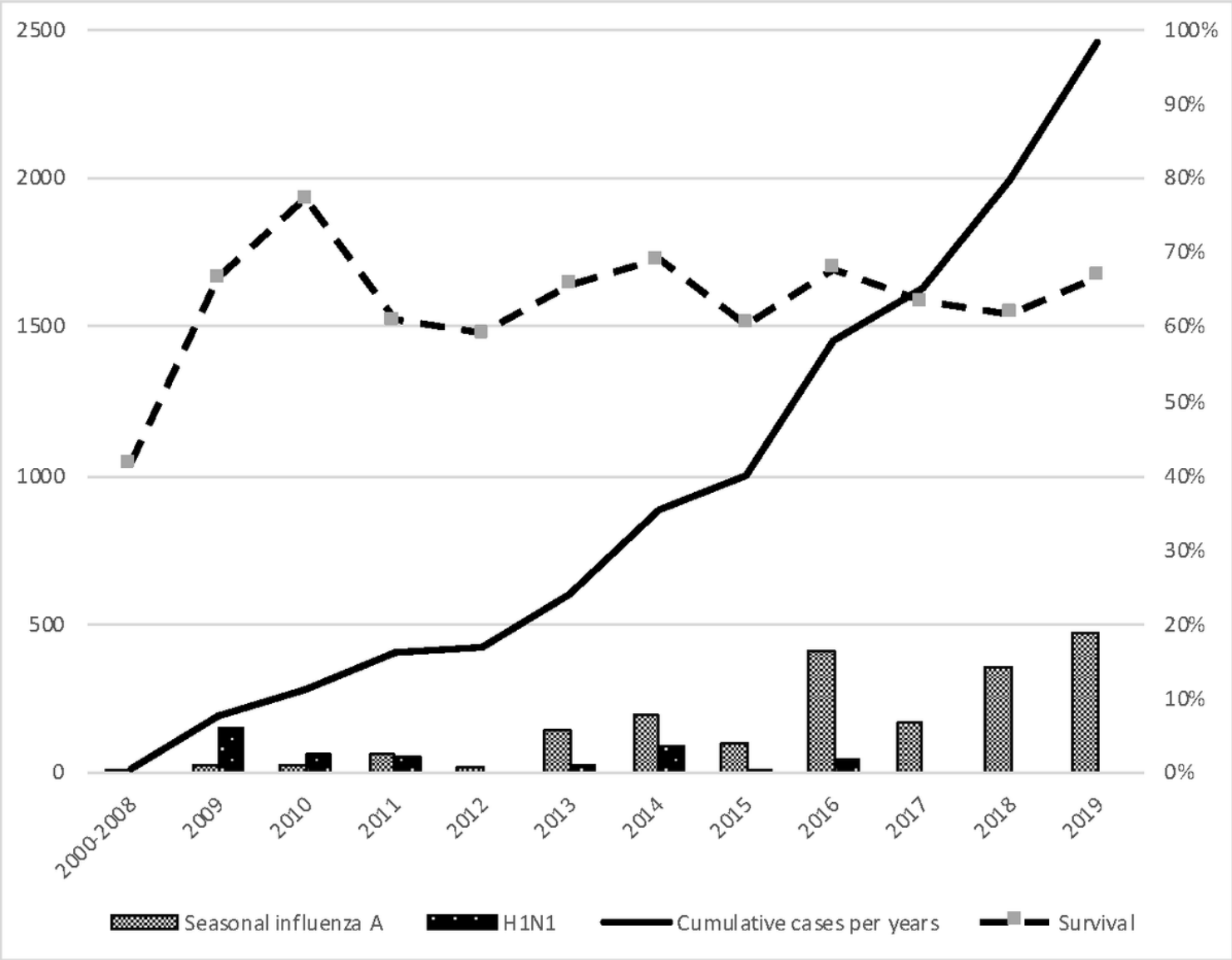

Figure 2

Survival and number of seasonal influenza A patients and H1N1 patients over the study period. H1N1: pandemic influenza A H1N1 subtype

Supplementary Files

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