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ORIGINAL RESEARCH

Outcomes of Venoarterial Extracorporeal Membrane Oxygenation for Cardiac Arrest in Adult Patients in the United States

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BACKGROUND: Factors associated with poor prognosis following receipt of extracorporeal membrane oxygenation (ECMO) in adults with cardiac arrest remain unclear. We aimed to identify predictors of mortality in adults with cardiac arrest receiving ECMO in a nationally representative sample.

METHODS AND RESULTS: The US Healthcare Cost and Utilization Project's National Inpatient Sample was used to identify 782 adults hospitalized with cardiac arrest who received ECMO between 2006 and 2014. The primary outcome of interest was all-cause in-hospital mortality. Factors associated with mortality were analyzed using multivariable logistic regression. The overall in-hospital mortality rate was 60.4% (n=472). Patients who died were older and more often men, of non-White race, and with lower household income than those surviving to discharge. In the risk-adjusted analysis, independent predictors of mortality included older age, male sex, lower annual income, absence of ventricular arrhythmia, absence of percutaneous coronary intervention, and presence of therapeutic hypothermia.

CONCLUSIONS: Demographic and therapeutic factors are independently associated with mortality in patients with cardiac arrest receiving ECMO. Identification of which patients with cardiac arrest may receive the utmost benefit from ECMO may aid with decision-making regarding its implementation. Larger-scale studies are warranted to assess the appropriate candidates for ECMO in cardiac arrest.

Key Words: cardiac arrest ■ extracorporeal cardiopulmonary resuscitation ■ extracorporeal membrane oxygenation ■ mortality ■ outcomes ■ survival

The use of venoarterial extracorporeal membrane oxygenation (ECMO) for refractory cardiac arrest has significantly increased over the past decade,[1–5] yet extracorporeal cardiopulmonary resuscitation is limited to a Class 2b recommendation in the most recent American Heart Association guidelines[6] for select patients as rescue therapy when conventional efforts are failing and when it can be implemented expeditiously by skilled providers. The majority of contemporary data on the efficacy of ECMO in cardiac arrest is provided by single-center studies with differing selection criteria and conflicting results.[7–12] A recent national analysis has reported higher mortality in patients hospitalized with cardiac arrest who received ECMO compared with those who did not,[13] but the use of more stringent selection criteria has been shown to improve outcomes.[14] The identification of factors associated with a worse prognosis is important to enable the selection of patients with cardiac arrest who may benefit the most from ECMO. This study was therefore designed to identify the predictors of all-cause mortality in adults hospitalized with cardiac arrest receiving ECMO using the largest publicly available all-payer inpatient database in the United States.

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CLINICAL PERSPECTIVE

What Is New?

- The in-hospital survival rate in a nationally representative sample of adults hospitalized with cardiac arrest who received extracorporeal membrane oxygenation in the United States was 40%.
- A variety of patient, demographic, and procedural factors were identified as independent predictors of mortality in this study population.

What Are the Clinical Implications?

- The poor prognostic factors identified may aid clinical decision-making regarding the implementation of extracorporeal membrane oxygenation in patients with cardiac arrest and highlights the need for large clinical trials to determine the patients who may receive the utmost benefit from this intervention.

Nonstandard Abbreviations and Acronyms

NIS National Inpatient Sample

METHODS

Study Data and Population

The data set used for this study cannot be directly shared by the authors because of the sensitive nature of the data collected, but requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the Healthcare Cost and Utilization Project (HCUP) at hcup@ahrq.gov.

The Agency for Healthcare Research and Quality HCUP's National Inpatient Sample (NIS) was used to identify 782 hospitalized adults aged ≥18 years with cardiac arrest who received ECMO between 2006 and 2014. The NIS provides a nationally representative sample of information from nonfederal short-term hospitals across the United States, with data on more than 7 million hospital stays annually. The database comprises billing data submitted by hospitals for the index hospitalization, including *International Classification of Diseases, Ninth Revision* (*ICD-9*) clinical modulation codes, as well as patient characteristics such as age, sex, race, and median household income by zip code. Patients with cardiac arrest who received ECMO during their admission were identified from the database by the presence of the *ICD-9* diagnosis code for cardiac arrest (427.5) and the procedural code for ECMO (39.65) in the same inpatient episode. A similar methodology was used in a previous study assessing the impact of ECMO in patients with cardiac arrest.[13] The primary outcome of the study was in-hospital all-cause mortality. This study was deemed exempt by the institutional review board of Stony Brook University, given the retrospective nature of the study and the use of a public database that contains deidentified information.

Statistical Analysis

Continuous variables were normally distributed and are presented as means and SDs; categorical variables are presented as proportions. Baseline demographics, medical history, and postresuscitative management were compared in patients who died and in those who survived to hospital discharge. Student *t* test and chi-square test were used to compare continuous and categorical variables, respectively. Multivariable logistic regression was performed to identify independent predictors of mortality in adults with cardiac arrest who received ECMO. Variables associated with mortality with a $P<0.1$ on univariate analysis were included in the model as covariates. STATA 15 (StataCorp LLC) was used for data analysis. All analyses were 2-tailed and a P value of ≤0.05 was regarded as statistically significant.

RESULTS

The overall in-hospital mortality rate of patients with cardiac arrest who received ECMO was 60.4% (n=472). The demographics, comorbidities, and clinical presentation of the study population are summarized in Table 1. Patients who died were older than those who survived to discharge (mean age, 52.2±16.2 versus 49.1±17.0; $P<0.01$) and more likely to be men (66.9% [n=316] versus 59% [n=183]; $P=0.03$). Patients who died were also more often of non-White race ($P=0.04$) and more likely to have a lower household income ($P<0.01$). The rates of comorbidities assessed were similar between the 2 study groups. Patients who died had lower rates of ventricular tachycardia (26.8% versus 19.7%, $P=0.02$) than those who survived, but the difference in rates of ventricular fibrillation did not reach statistical significance (32.6% versus 26.7%, $P=0.08$). Patients who died were also less likely to receive percutaneous coronary intervention (13.8% versus 19.7%, $P=0.03$).

Table 2 summarizes the results of the multivariable logistic regression model for predictors of mortality in this population. In the risk-adjusted analysis, factors independently associated with mortality included older age (odds ratio [OR], 4.1; 95% CI, 1.9–8.9 [$P<0.01$]), male sex (OR, 1.61; 95% CI, 1.16–2.22 [$P<0.01$]), higher annual income (OR, 0.62; 95% CI, 0.39–0.96 [$P=0.04$]), presence of ventricular arrhythmia (OR, 0.7; 95% CI, 0.5–1.0 [$P=0.05$]), occurrence of

Table 1. Demographics and Medical History

	Alive	Dead	
	(n=310)	(n=472)	*P* value
Age, mean±SD, y	49.1±16.2	52.2±17.0	0.009
Age group, y			0.041
18–44	114 (36.8)	143 (30.3)	
45–64	137 (44.2)	211 (44.7)	
65–74	48 (15.5)	77 (16.3)	
75+	11 (3.5)	41 (8.7)	
Sex			0.027
Male	183 (59)	316 (66.9)	
Female	127 (41)	156 (33.1)	
Race/ethnicity			0.041
White	189 (61.1)	254 (53.8)	
Black	37 (11.9)	63 (13.3)	
Hispanic	18 (5.8)	38 (8.1)	
Other*	24 (7.7)	44 (9.3)	
Missing	42 (13.5)	73 (15.5)	
Median household income, quartile			0.004
1	59 (19.0)	130 (27.5)	
2	62 (20.0)	116 (24.6)	
3	99 (31.9)	104 (22.0)	
4	83 (26.8)	109 (23.1)	
Missing	7 (2.3)	13 (2.8)	
Coronary artery disease	119 (38.4)	176 (37.3)	0.763
Prior myocardial infarction	16 (5.2)	20 (4.2)	0.602
Prior coronary artery bypass surgery	13 (4.2)	33 (7.0)	0.121
Prior percutaneous coronary intervention	12 (3.9)	21 (4.4)	0.856
Diabetes	60 (19.4)	118 (25.0)	0.068
Chronic kidney disease	28 (9.0)	59 (12.5)	0.163
Cerebrovascular disease	38 (12.3)	46 (9.7)	0.289
Hypertension	64 (20.6)	118 (25.0)	0.167
Dyslipidemia	45 (14.5)	89 (18.9)	0.121
Peripheral arterial disease	17 (5.5)	34 (7.2)	0.377
Congestive heart failure	102 (32.9)	148 (31.4)	0.695
Atrial fibrillation/flutter	64 (20.6)	86 (18.2)	0.405
Chronic obstructive lung disease	17 (5.5)	26 (5.5)	1.000
Obstructive sleep apnea	12 (3.9)	14 (3.0)	0.543
Smoking history	45 (14.5)	65 (13.8)	0.834
Obesity	27 (8.7)	51 (10.8)	0.394
Metabolic syndrome	3 (1.0)	1 (0.2)	0.307
HIV/AIDS	1 (0.3)	2 (0.4)	1.000

Values are expressed as number (percentage) unless otherwise indicated.
*Other includes the following races/ethnicities reported in the NIS database: Asian or Pacific Islander, Native American and Other.

percutaneous coronary intervention (OR, 0.6; 95% CI, 0.4–1.0 [*P*=0.03]), and presence of therapeutic hypothermia (OR, 3.0; 95% CI, 1.1–7.6 [*P*=0.03]).

Table 2. Multivariable Logistic Regression for Risk-Adjusted Mortality

Variable	Odds ratio	95% CI	*P* value
Age ≥75 y (vs age 18–44 y)	4.06	1.85–8.88	<0.001
Female sex	0.62	0.45–0.86	0.004
Income quartile 3 (vs quartile 1)	0.48	0.30–0.75	0.001
Income quartile 4 (vs quartile 1)	0.62	0.39–0.97	0.038
Ventricular arrhythmia	0.72	0.52–1.00	0.047
Percutaneous coronary intervention	0.58	0.36–0.96	0.033
Therapeutic hypothermia	2.94	1.13–7.60	0.027

Model included age group, sex, race, income quartile, coronary artery disease, prior myocardial infarction, prior coronary artery bypass graft surgery, prior percutaneous coronary intervention, diabetes, chronic kidney disease, cerebrovascular disease, hypertension, dyslipidemia, peripheral arterial disease, congestive heart failure, atrial fibrillation, chronic obstructive lung disease, obstructive sleep apnea, smoking, obesity, metabolic syndrome, HIV/AIDS, ventricular arrhythmia (ventricular tachycardia or ventricular fibrillation), coronary angiogram, percutaneous coronary intervention, therapeutic hypothermia, and hospital discharge year.

DISCUSSION

This is the largest cohort study to date focused on adults with cardiac arrest receiving ECMO in the United States. Our analysis of a nationally representative sample has several significant findings. First, ≈40% of adults hospitalized with cardiac arrest who received ECMO survived to hospital discharge. Second, patients who died were older, male, and with lower annual income. Finally, absence of ventricular arrhythmia, lack of percutaneous coronary intervention, and presence of therapeutic hypothermia were independently associated with worse outcomes in this patient population.

Survival rates of patients with cardiac arrest receiving venoarterial ECMO have widely varied in previous studies from 8% to 75%.[5,7–19] The majority of data on the efficacy of venoarterial ECMO in patients with cardiac arrest is confined to single-center series. These small studies have differing criteria for the implementation of venoarterial ECMO in cardiac arrest, including cardiac arrests occurring in different settings, and hence—unsurprisingly—report conflicting outcomes. The largest study assessing the use of ECMO in adults hospitalized with cardiac arrest has reported a higher risk-adjusted likelihood of mortality in patients receiving ECMO.[13] Given that decisions to implement ECMO in patients with cardiac arrest are largely made on a case-by-case basis and that ECMO is reserved for rescue therapy, the overall mortality rate reported in this nationally representative sample suggests that a survival rate of 40% can be achieved with evidence-based implementation criteria in patients who are not otherwise responding to standard therapy.

While systematic reviews have attempted to perform meta-analyses on the outcomes of patients receiving venoarterial ECMO in cardiac arrest and its associated prognostic variables using single-center data, these analyses report a low quality of evidence and are uniformly limited by heterogeneity and significant bias—often precluding meaningful analysis.[20–23] The identification of which patients with cardiac arrest will receive the utmost benefit from ECMO initiation has therefore remained unclear. The size of this study provides sufficient power for a reasonable number of covariates to be included in the risk-adjusted regression model, enabling the identification of a variety of demographic and therapeutic factors associated with mortality in hospitalized adults with cardiac arrest who received ECMO. The presence of percutaneous coronary intervention and shockable rhythms as significant predictors of survival in our model is consistent with the ability of venoarterial ECMO to provide end-organ perfusion while reversible causes are being treated. The American Heart Association guidelines available during the study period recommended therapeutic hypothermia for unconscious patients with spontaneous circulation after out-of-hospital cardiac arrests with shockable rhythms,[24] therefore this variable may well serve as a surrogate for this subset of patients in our study. Therapeutic hypothermia is often used for patients with hypoxic encephalopathy following return of spontaneous circulation, so the variable may represent an indication of severity. Other variables that could not be captured from the NIS database and were found to be independently associated with survival in single-center studies may be used with discretion to supplement the mortality predictors we have identified (high lactate, low arterial pH, shorter cardiopulmonary resuscitation duration, time to venoarterial ECMO, and presence of return of spontaneous circulation before venoarterial ECMO initiation).[25–27] The poor prognosticators identified may be used to aid clinicians who are called to the bedside to decide whether a patient with cardiac arrest is an appropriate candidate for venoarterial ECMO and may be used in the design of randomized controlled trials to assess the suitability of this intervention.

Social determinants of health contribute to pervasive disparities that continue to exist in health care.[28,29] The association of household income and non-White race with worse outcomes in this study suggests that socioeconomic disparities similarly exist among the study population. Further research assessing disparities in venoarterial ECMO practice is needed to explore the mechanisms contributing to and perpetuating these disparities that may be targeted by interventions and inform ethical clinical decision-making in the field.

Limitations

Given that the NIS collects billing-related data, the use of this administrative database may be subject to coding errors. This analysis is also subject to confounding bias: despite the number of variables included in our multivariable model, several clinical variables such as medications, laboratory data, hemodynamics, duration of cardiopulmonary resuscitation and other interventions were not available and therefore could not be assessed. The granularity of the NIS enabled the capture of hospitalized patients who experienced a cardiac arrest and received ECMO during their hospitalization; the study population is therefore not limited to patients receiving extracorporeal cardiopulmonary resuscitation and may include some patients who received ECMO at other points in their hospitalization. There are also limited data available on the use of venoarterial ECMO, eg, the duration of therapy and timing of initiation. This study was limited to in-patient mortality, and important secondary outcomes such as neurological function and longer-term outcomes could not be assessed. Finally, data are only available up to 2014 in this study. Outcomes of extracorporeal cardiopulmonary resuscitation will have likely improved since this time period given the greater experience and improved extracorporeal life support technology available, but the predictors of mortality are unlikely to have changed.

CONCLUSIONS

In this nationally representative sample of adults with cardiac arrest receiving ECMO, demographic and therapeutic factors are independently associated with mortality. Identification of which patients with cardiac arrest may receive the utmost benefit from ECMO may aid with decision-making regarding its implementation and support the design of future large randomized controlled trials required to assess the optimal patient population to receive ECMO in cardiac arrest.

ARTICLE INFORMATION

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Disclosures

None.

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