

Impact of Extracorporeal Membrane Oxygenation on Mortality in Adults With Cardiac Arrest



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Previous studies regarding benefit of extracorporeal membrane oxygenation (ECMO) in adults with cardiac arrest have yielded conflicting results. We aimed to determine whether ECMO in adults hospitalized with cardiac arrest is associated with improved survival compared with conventional cardiopulmonary resuscitation in a nationally representative sample. The U.S. Healthcare Cost and Utilization Project's Nationwide Inpatient Sample (2006 to 2014) was utilized to identify a cohort of adults hospitalized with cardiac arrest at ECMO-capable facilities (defined by the presence of at least 1 ECMO procedure at the facility during the study period of 2006 to 2014). In-hospital mortality was compared between the ECMO and non-ECMO groups using generalized estimating equations with and without coarsened exact matching analysis. Of 273,690 hospitalizations for adults with cardiac arrest, 33,274 occurred at 363 ECMO-capable facilities, of which 775 (2.3%) involved the use of ECMO. There was no significant difference in in-hospital mortality between patients who received ECMO versus those who did not (60.1% vs 57.2%, $p = 0.106$). In the risk-adjusted analysis, the presence of ECMO was associated with higher rates of in-hospital mortality in the overall sample [odds ratio 1.59, 95% confidence interval 1.37 to 1.85] and the coarsened exact matching sample ($n = 1,068$ with 534 adults in each group; odds ratio 1.47, 95% confidence interval 1.14 to 1.88). In this cohort of hospitalizations for cardiac arrest at ECMO-capable centers in the U.S., adults who received ECMO had significantly higher mortality than those who did not receive ECMO. Large scale, adequately powered, randomized controlled trials are warranted to assess the benefit of ECMO in cardiac arrest. © 2019 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;124:1857–1861)

Cardiac arrest (CA) is a leading cause of mortality worldwide.¹ In the United States, CA claims an estimated 300,000 lives per year with an annual incidence of 350,000 out-of-hospital and 750,000 in-hospital-related events. Though survival has increased dramatically over the past few decades, overall survival in CA remains extremely low at 20% for in-hospital (IHCA) and 5% to 9% for out of hospital cardiac arrest (OHCA).^{1–5} Utilization of veno-arterial extracorporeal membrane oxygenation (ECMO) in CA is steadily increasing.^{6,7} While there are no randomized controlled trials that compare ECMO with conventional cardiopulmonary resuscitation (CPR) in patients with CA, data from small observational propensity-matched studies have yielded conflicting results.^{8–15} In the absence of a randomized controlled trial, propensity score or coarsened exact matching (CEM) is a useful alternative to minimize selection bias resulting from confounding. The purpose of this study was to determine whether ECMO, compared with conventional CPR, is associated with improved mortality in

a large nationwide cohort of CA hospitalizations using a CEM analysis.

Methods

We utilized data from the 2006 to 2014 Nationwide Inpatient Sample (NIS), collected by the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project, which is the largest all-payer inpatient publicly available database in the United States containing nationally representative information regarding up to 8 million hospitalizations annually. The NIS uses *International Classification of Diseases, 9th edition, Clinical Modification* (ICD-9-CM) codes to capture up to 15 procedures and 25 diagnoses associated with the index hospitalization. ICD-9-CM codes were utilized to identify a cohort of adults (≥ 18 years) hospitalized with a diagnosis of CA. CA was identified based on the presence of ICD-9-CM code 427.5. Among those who presented with cardiac arrests, Ventricular Tachycardia (VT) was identified by ICD-9-CM code 427.1, and ventricular fibrillation (VF) was identified based on the presence of ICD-9-CM code 427.4. We identified a cohort of 264,774 hospitalizations for CA during the study period. Since many hospitals are not ECMO-capable, we excluded any hospital with no reported ECMO procedure recorded during the study period. In addition, 1,297 hospitalizations from patients with human immunodeficiency virus or cancer were further excluded due to the lower likelihood of using ECMO. The remaining 33,274 hospitalizations from 363 hospitals were retained as the final analytic sample and were classified based upon the presence or absence of ECMO. Demographic

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and medical history data extracted included age, gender, race, socioeconomic status, and presence of medical comorbidities including coronary artery disease, previous myocardial infarction, previous CABG, previous percutaneous coronary intervention (PCI), diabetes mellitus, chronic kidney disease, cerebrovascular disease, hypertension, dyslipidemia, peripheral arterial disease, congestive heart failure, atrial fibrillation/flutter, chronic obstructive lung disease, obstructive sleep apnea, smoking history, obesity, metabolic syndrome, and human immunodeficiency virus and/or acquired immunodeficiency syndrome, and use of advanced therapies including coronary angiogram, PCI and therapeutic hypothermia. The primary outcome of interest was in-hospital all-cause mortality.

The Institutional Review Board of Stony Brook University Medical Center deemed this study exempt because the NIS is a publicly available database containing de-identified patient information.

Univariate analyses were used to compare demographics, medical history, and clinical outcomes of patients in patients who received or did not receive ECMO. Categorical variables are presented as percentages and were compared with the chi-squared test. Continuous variables are presented as means \pm standard deviation and are compared using student's *t* test. STATA 15 (StataCorp LP, College Station, TX) was used for data analysis, and a 2-tailed *p* value of less than or equal to 0.05 was regarded as statistically significant.

To reduce selection bias related to the decision to use ECMO, we used CEM, a nonparametric matching technique aimed at balancing the multidimensional distribution of covariates that may be associated with the outcome (in-hospital death).^{16,17} There are 3 steps in CEM. First, a list of covariates that may be associated with either the treatment (ECMO) or the outcome (in-hospital death) is generated using clinical judgment and previous research. Second, the original dataset is then stratified by these matching variables and only patients with strata containing at least 1 receiving ECMO were kept. Third, for every patient who received ECMO, a patient who did not receive ECMO but otherwise matched on all other matching variables were identified and kept. A major advantage of CEM over the traditional logit/probit model-based propensity score-matching algorithms is its robustness due to the 2-step approach (as compared with regression adjustment alone) and its insensitivity to the specification of the selection model used to generate propensity scores.^{17–19}

Multivariable generalized estimating equation (GEE) models were estimated to examine whether in-hospital mortality rates differ between patients receiving ECMO versus those who did not. GEE takes into consideration the clustering of patients who were treated at the same hospital. To assess and account for residential imbalances from the CEM-matching process, we estimated GEE models with and without other clinically relevant covariates (besides ECMO status) To gauge possible selection effect due to CEM matching, all models were stratified by CEM-matching status, we repeated the analysis using the unmatched sample.

Results

During the study period, of the 33,274 hospitalizations for CA in 363 ECMO-capable hospitals, 775 (2.3%)

involved the use of ECMO. The demographics, medical history, and clinical presentation of this study population are summarized in Table 1. Patients who received ECMO were younger, more often man, and with higher household income. They had higher rates of coronary artery disease, cerebrovascular disease, and congestive heart failure, and lower rates of diabetes mellitus, chronic kidney disease, atrial fibrillation/flutter, hypertension, dyslipidemia, and chronic obstructive lung disease. Patients who received ECMO also had significantly higher rates of ventricular fibrillation and ventricular tachycardia compared with those who did not receive ECMO. Patients receiving ECMO were also more likely to receive postarrest adjunctive therapies including coronary angiogram, percutaneous coronary intervention, and therapeutic hypothermia. There was no significant difference in unadjusted rates of in-hospital mortality between patients who received ECMO versus those who did not (Figure 1).

In the risk-adjusted analysis, the presence of ECMO was associated with higher rates of in-hospital mortality in the overall population [odds ratio (OR) 1.59, 95% confidence interval (CI) 1.37 to 1.85] and the matched population (*n* = 1,068 with 534 adults in each group; OR 1.47, 95% CI 1.14 to 1.88). Two covariate-adjusted GEE models were estimated to examine the association between ECMO and in-hospital mortality while accounting for the hospital level patient clustering. The first model with the full analytic sample demonstrated that ECMO was associated with significantly higher in-hospital mortality (OR 1.59, 95% CI 1.37 to 1.85). The same analysis using the CEM-matched sample again demonstrated significantly higher in-hospital mortality with ECMO versus no ECMO (OR = 1.47, 95% CI 1.14 to 1.88; Table 2).

Discussion

In this cross-sectional, nationally representative study of adults hospitalized with CA, several findings are noteworthy. First, patients who receive ECMO are more likely to be younger, men, and have ventricular tachyarrhythmias. Second, patients receiving ECMO are more likely to receive advanced therapies including coronary angiogram, PCI, and therapeutic hypothermia. Third, risk-adjusted mortality was significantly higher in the ECMO group in both the overall population and the matched population. To our knowledge, this is the largest study to date to utilize CEM to study the impact of ECMO in adults with cardiac arrest.

Given the absence of randomized controlled trials to study the potential benefit of ECMO in adults with CA, multiple studies have performed small observational propensity-matched analyses which have demonstrated a benefit with respect to IHCA but have yielded conflicting results in the OHCA population.^{8–15} A retrospective study of 406 adults with IHCA, of which 21% received ECMO, demonstrated that in the matched population (*n* = 120), survival with minimal neurologic impairment at hospital discharge and 6 months was significantly higher in the matched ECMO group.¹⁰ Survival with minimal neurologic impairment at 2 years was fourfold higher in the ECMO group than in those receiving conventional CPR.¹¹ The prognostic benefit for ECMO in OHCA patients is less

Table 1
Demographics, medical history, and cardiac arrest rhythm

Variable	Unmatched ECMO		p Value	Coarsened exact-matched ECMO		p Value
	No	Yes		No	Yes	
Sample size	32,499	775		534	534	
Age group (years)			<0.001			
18-44	11.9%	32.8%		32.4%	32.4%	1
45-64	34.2%	44.4%		46.8%	46.8%	1
65-74	22.6%	16.1%		14.4%	14.4%	1
75-84	20.2%	5.9%		6.0%	6.0%	1
85+	11.0%	0.8%		0.4%	0.4%	1
Gender			0.001			
Male	42.6%	36.5%		36.7%	36.7%	1
Female	57.4%	63.5%		63.3%	63.3%	1
Race/ethnicity			0.001			
White	55.6%	56.8%		63.1%	63.1%	1
Black	17.2%	12.6%		13.3%	13.3%	1
Hispanic	8.0%	7.2%		5.8%	5.8%	1
Other	6.1%	8.6%		6.4%	6.4%	1
Missing	13.1%	14.7%		11.4%	11.4%	1
Median household income (quartile)			<0.001			
1	31.6%	24.0%		24.5%	24.7%	1
2	23.0%	22.8%		23.8%	23.8%	1
3	22.6%	26.1%		26.4%	26.4%	1
4	20.2%	24.5%		23.8%	23.8%	1
Missing	2.5%	2.6%		1.3%	1.3%	1
<i>Medical History</i>						
Coronary artery disease	28.0%	38.1%	<0.001	28.5%	28.5%	1
Prior myocardial infarction	5.8%	4.6%	0.185	1.9%	1.9%	1
Prior coronary artery bypass surgery	5.9%	5.9%	0.939	1.9%	1.9%	1
Prior percutaneous coronary intervention	3.8%	4.3%	0.509	1.9%	2.6%	0.537
Diabetes mellitus	28.4%	22.8%	0.001	21.3%	21.3%	1
Chronic Kidney disease	21.8%	11.2%	<0.001	9.7%	9.7%	1
Cerebrovascular disease	7.5%	10.6%	0.002	6.0%	6.0%	1
Hypertension	31.4%	23.4%	<0.001	20.6%	20.6%	1
Dyslipidemia*	22.5%	17.2%	<0.001	14.4%	15.0%	0.863
Peripheral arterial disease	7.4%	6.6%	0.444	5.8%	6.9%	0.531
Congestive heart failure	16.1%	32.1%	<0.001	19.9%	19.9%	1
Atrial fibrillation/flutter	22%	19.4%	0.079	15.7%	15.7%	1
Chronic obstructive lung disease	14.9%	5.4%	<0.001	3.0%	3.0%	1
Obstructive sleep apnea	4.3%	3.4%	0.241	3.4%	3.2%	1
Smoking history	16.1%	14.2%	0.166	10.1%	10.1%	1
Obesity*	7.5%	10.1%	0.009	10.5%	8.1%	0.205
Metabolic syndrome	0.1%	0.5%	0.018	0%	0.7%	0.124
Ventricular fibrillation	16.9%	29.0%	<0.001	24.3%	24.3%	1
Ventricular tachycardia	15.3%	22.6%	<0.001	17.6%	19.9%	0.388
Coronary angiogram	15.9%	21.2%	<0.001	19.9%	18.2%	0.533
Percutaneous coronary intervention	8.7%	16.3%	<0.001	11.8%	12.4%	0.851
Therapeutic hypothermia	2.8%	3.6%	0.187	2.6%	2.8%	1

* Dyslipidemia and obesity were captured using *International Classification of Diseases, 9th edition, Clinical Modification (ICD-9-CM)* codes 272.4 and 278.00, respectively.

clear. A retrospective study of 499 adults with OHCA, of which 11% received ECMO, demonstrated that the matched ECMO group had a more favorable neurologic outcome than the conventional CPR group at 3 months postarrest.⁸ In a Japanese study of 162 adults with OHCA, of which 1/3 received ECMO, the matched ECMO group (n = 24) had significantly higher survival (29% vs 8%, p = 0.018).⁹ However, a Korean study of 36,547 adults with OHCA, of which 320 adults received ECMO, demonstrated no significant difference in neurologically favorable survival to discharge

in both the unmatched and matched populations.¹⁴ A recent meta-analysis of ECMO use in CA which included 9 mixed studies of both OHCA and IHCA (n = 3,098) demonstrated that the use of ECMO was associated with an absolute increase of 13% with respect to 30-day survival and a higher rate of 30-day favorable neurologic outcome.²⁰ Propensity-matched analysis involving 5 studies (n = 438 patients, 219 in both groups) demonstrated similar results.²⁰

This study has several limitations. First, the NIS is an administrative database and hence may contain coding errors.

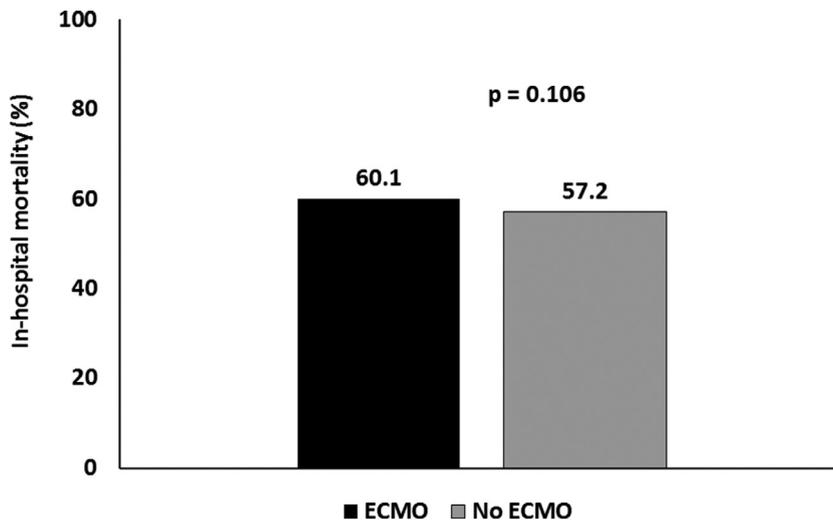


Figure 1. Unadjusted in-hospital mortality rates by ECMO versus no ECMO for the analytic sample.

Second, several confounding variables were not available in this database including etiology of CA, characteristics regarding CPR provided (i.e., duration, medications administered, and so on), hemodynamic data, success of reperfusion therapy, optimal maintenance of therapeutic hypothermia, use of additional mechanical support, and detailed information regarding ECMO, that is, timing of ECMO and location of ECMO insertion (i.e., cardiac catheterization laboratory, and institutional ECMO volume). Third, using an administrative database makes it difficult to accurately distinguish between OHCA and IHCA. Fourth, data on ROSC and cerebral performance category at discharge were not available in this database. Fifth, this study was limited to inpatient outcomes and hence, longer term follow-up data were not available. Finally, unlike randomization, propensity score or CEM can only balance measured confounders and therefore, residual confounding from unmeasured covariates may persist. In our CEM-matched cohort, both of the groups showed a well-balanced distribution of demographics and confounders.

Table 2

Generalized estimating equation models for risk-adjusted mortality for the full analytic sample and CEM-matched sample, adjusted for by covariates

Variable	Odds ratio	95% confidence interval	p Value
Full analytic sample (n = 33,274)*			
ECMO vs No ECMO	1.59	1.37-1.85	<0.001
Matched sample (n = 1,068) [†]			
ECMO vs No ECMO	1.47	1.14-1.88	0.003

* Full analytic sample: all admissions eligible to be included, regardless of CEM-matching status.

[†] Coarsened exact matching (CEM) criteria: age group, gender, race, income, hypertension, cerebrovascular disease, coronary artery disease, prior CABG, prior MI, congestive heart failure, atrial fibrillation, ventricular fibrillation, chronic obstructive lung disease, smoking, chronic kidney disease.

Covariates used in both models: age, gender, minority status, hypertension, cerebrovascular disease, coronary artery disease, prior CABG, Prior MI, CHF, atrial fibrillation, ventricular fibrillation, chronic lung disease, smoking status, and chronic kidney disease.

Because the nonparametric CEM approach typically uses fewer variables as compared with the logit/probit model-based propensity score-matching approach, it may be more restrictive in identifying which cases are considered “exact” match based on the prespecified criteria.¹⁶ As a result, findings from CEM-matched sample may not be generalizable beyond the matched sample. In contrast, CEM eliminates the need to test multiple alternative model specifications in the parametric logit/probit model employed by propensity score matching. However, based on our present knowledge, this study is the largest study comparing the effect of ECMO in CA patients in a nationally representative inpatient sample, which could help inform clinical decision making.

Conclusions

In this CEM cohort using a nationwide database of CA hospitalizations at ECMO-capable centers, patients who received ECMO had significantly higher mortality than those who did not receive ECMO. Ultimately, large-scale, adequately powered, randomized controlled trials are warranted to assess the benefit of ECMO in CA.

Disclosures

The authors have no conflicts of interest to disclose.

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