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The Association of Modifiable Postresuscitation Management and Annual Case Volume With Survival After Extracorporeal Cardiopulmonary Resuscitation

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IMPORTANCE: It is not know if hospital-level extracorporeal cardiopulmonary resuscitation (ECPR) case volume, or postcannulation clinical management associate with survival outcomes.

OBJECTIVES: To describe variation in postresuscitation management practices, and annual hospital-level case volume, for patients who receive ECPR and to determine associations between these management practices and hospital survival.

DESIGN: Observational cohort study using case-mix adjusted survival analysis.

SETTING AND PARTICIPANTS: Adult patients greater than or equal to 18 years old who received ECPR from the Extracorporeal Life Support Organization Registry from 2008 to 2019.

MAIN OUTCOMES AND MEASURES: Generalized estimating equation logistic regression was used to determine factors associated with hospital survival, accounting for clustering by center. Factors analyzed included specific clinical management interventions after starting extracorporeal membrane oxygenation (ECMO) including coronary angiography, mechanical unloading of the left ventricle on ECMO (with additional placement of a peripheral ventricular assist device, intra-aortic balloon pump, or surgical vent), placement of an arterial perfusion catheter distal to the arterial return cannula (to mitigate leg ischemia); potentially modifiable on-ECMO hemodynamics (arterial pulsatility, mean arterial pressure, ECMO flow); plus hospital-level annual case volume for adult ECPR.

RESULTS: Case-mix adjusted patient-level management practices varied widely across individual hospitals. We analyzed 7,488 adults (29% survival); median age 55 (interquartile range, 44–64), 68% of whom were male. Adjusted hospital survival on ECMO was associated with mechanical unloading of the left ventricle (odds ratio [OR], 1.3; 95% CI, 1.08–1.55; $p = 0.005$), performance of coronary angiography (OR, 1.34; 95% CI, 1.11– 1.61; $p = 0.002$), and placement of an arterial perfusion catheter distal to the return cannula (OR, 1.39; 95% CI, 1.05–1.84; $p = 0.022$). Survival varied by 44% across hospitals after case-mix adjustment and was higher at centers that perform more than 12 ECPR cases/yr (OR, 1.23; 95% CI, 1.04–1.45; $p = 0.015$) versus medium- and low-volume centers.

CONCLUSIONS AND RELEVANCE: Modifiable ECMO management strategies and annual case volume vary across hospitals, appear to be associated with survival and should be the focus of future research to test if these hypothesis-generating associations are causal in nature.

KEY WORDS: cardiac arrest; coronary angiography; critical care; extracorporeal cardiopulmonary resuscitation

The use of extracorporeal membrane oxygenation (ECMO) for refractory cardiac arrest—known as extracorporeal cardiopulmonary resuscitation (ECPR)—is increasing (1), but there is a lack of data to inform clinical

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management after ECMO cannulation in this high-risk population. For conventional cardiopulmonary resuscitation (CPR) treated patients, postresuscitation management is important because the period after reperfusion is of long duration in a vulnerable period relative to the cardiac arrest (2). Recent data have shown that overall hospital survival is more strongly correlated with the postresuscitation period than it is with immediate cardiac arrest survival, suggesting that clinical management in the postresuscitation period is a distinct skillset associated with outcome (3). Despite these data, there are few studies of the associations of postresuscitation management strategies for patients with cardiac arrest and survival (4–8), and none among ECPR patients. Identification of specific ECMO management practices associated with survival among ECPR patients will provide targets for studies using causal inference methods or clinical trials aimed at improving ECPR survival.

Modifiable management strategies of ECMO in the early postresuscitation period include performance of coronary angiography or percutaneous coronary interventions for patients with acute coronary ischemia, modulation of ECMO flow, the use of mechanical left ventricular (LV) unloading, the placement of arterial perfusion catheters distal to the arterial ECMO return cannula, and possibly management of patient hemodynamics such as controlled changes in blood pressure. Patients must survive long enough to receive these therapies, but among those who survive, the association between receipt of the therapy and survival is not known. Among these therapies, mechanical LV unloading during venoarterial ECMO for cardiogenic shock is associated with survival (9, 10), yet there are no data to support its use in ECPR-treated patients. Routine coronary angiography after cannulation is a component therapy of many ECPR programs (11–14), but comparative data are limited (15). How these management strategies vary across hospitals, their associations with hospital annual ECPR case volume, and their associations with survival are unknown.

In an effort to understand ECMO management among those successfully cannulated for ECPR after cardiac arrest, we examined associations of specific modifiable management practices and clinical variables on survival, the association of hospital-level annual ECPR case volume with survival, and how postresuscitation management practices and clinical variables differ according to hospital annual ECPR case volume.

METHODS

Hypotheses

We hypothesized that the following nine on-ECMO management variables would be individually associated with hospital survival: 1) bilateral femoral cannulation versus unilateral femoral cannulation; 2) mechanical LV unloading versus no mechanical unloading; 3) distal perfusion catheter (DPC) placement in the femoral artery versus no DPC placement; 4) coronary angiography after cannulation versus no coronary angiography; 5) higher ECMO flow versus lower ECMO flow; 6) greater arterial (cardiac) pulse pressure on ECMO versus lower arterial pulse pressure; 7) higher mean arterial blood pressure versus lower mean arterial blood pressure; 8) no use of inotropes on ECMO versus use of inotropes; and 9) hospital-level adult ECPR-specific annual case volume. Factors with an adjusted association would then be candidate factors for causal analysis and randomized study. Further details on the physiologic rationale for each of these management factors being associated with hospital survival are listed in the **Supplement** (http://links.lww.com/CCX/B33).

Data Source and Study Population

This secondary analysis of de-identified data was approved by the Institutional Review Board at the University of Utah (Number 91962). Data came from the Extracorporeal Life Support Organization (ELSO) Registry and was approved by the ELSO Registry Scientific Oversight Committee. Extensive details on the ELSO Registry data source are listed in the Supplement (http://links.lww.com/CCX/B33).

Of note, no data on initial rhythm or other Utstein variables were available in the ELSO Registry data for this analysis. To this point, previous data and guidelines demonstrate that once patients have achieved return of spontaneous circulation (ROSC), no single intra-arrest factor is reliably predictive of outcome (16); thus, in this cohort of patients who survived to ECMO, it is reasonable to analyze the association of postresuscitation factors with survival, as has been previously done (3).

Patients were included in the analysis if they were greater than or equal to 18 years old and received ECMO during cardiopulmonary resuscitation (ECPR). We included patients with both in-hospital cardiac arrest treated with ECMO and out-of-hospital cardiac arrest who were brought to the emergency department and cannulated for ECMO. For patients with multiple ECMO runs per hospital admission, only the first ECMO run was analyzed. To overcome the bias that patients had to survive long enough to receive interventions and have values measured at 24 hours, and in order to minimize the risk of immortal time bias, we limited the multivariable analyses to subjects who survived to 24 hours.

Outcomes

The primary outcome was survival at hospital discharge, as coded in the ELSO Registry. Descriptive characteristics include the patient-level demographic, laboratory, and clinical variables after ECMO cannulation. We defined categories of center-level annual ECPR case volume as low (< 6 cases/yr), medium (6–12 cases/yr) and high (> 12 cases/yr). Hospital-level annual ECPR volume strata cutoffs were selected based on the prevalence of U.S. ECPR cases per hospital per year (14) and previous analysis of ECMO annual case volume (17). This method resulted in balanced patient distribution across strata.

Demographic and Clinical Variables

Data were analyzed for all patients from 2008 to 2019. Our predictive variables included on-ECMO therapeutic procedures, including: the performance of coronary angiography (including percutaneous coronary interventions), the placement of DPCs, laterality of ECMO cannulas placement (same side or contralateral sides), and placement of a mechanical ventricular unloading device (such as intra-aortic balloon pump, peripherally inserted ventricular assist device, etc.). Understanding that the use of vasoactive and inotropic medications, and changes in ECMO pump speed confer some modifiability to patient hemodynamics (blood pressure, arterial pulsatility), we examined on-ECMO mean arterial pressure, arterial pulse pressure (systolic blood pressure-diastolic blood pressure), and ECMO flow as candidate on-ECMO factors potentially associated with survival.

Due of complex relationships among these on-ECMO variables, and a desire to examine their independent relationships with survival, we separately modeled each individual on-ECMO variable with the survival outcome. We selected a case-mix approach for adjustment given that this is a national data set and patients differ regionally; this approach has been previously used for cardiac arrest analyses (18, 19). Case-mix adjustment is typically used among diverse populations of patients to risk stratify for center variation or patient severity of illness when covariates are not sufficiently complete for causal analysis (20, 21). For covariate selection, we a priori selected covariates with known survival associations within analyses of ECMO patients or cardiac arrest patients and which were fixed during this period of time and thus are relevant in estimating the survival association for all examined factors. These covariates included: year of ECMO (17, 22), age (17, 22, 23), sex, PaO_2/FIO_2 prior to ECMO, primary diagnosis (17, 22–26), comorbid conditions (22, 23), and a center identifier. Further details are listed in the Supplement (http://links.lww.com/CCX/B33).

Hospital ECPR-specific volume was included because of the known relationship between hospital total ECMO volume and survival (17). Due to ELSO policy regarding individual manufacturers, we coded mechanical ventricular unloading as an aggregate variable encompassing multiple devices/approaches, as discussed in the Supplement (http://links.lww.com/CCX/B33).

Missing Data

To ensure missing data (**eTable 1**, http://links.lww.com/CCX/B33) did not meaningfully influence our findings for the main models, we first compared subjects with complete data for key intervention variables to subjects with any missing data for those key intervention variables (**eTable 2**, http://links.lww.com/CCX/B33). We then quantified the differences in physiologic variables by reporting standardized mean differences between groups with or without missing data (**eTable 3**, http://links.lww.com/CCX/B33). Finally, to address whether the differences between groups had a qualitative influence on our findings, we performed multiple imputation with chained equations using 50 imputed datasets and examined the resultant models (**eTable 4**, http://links.lww.com/CCX/B33).

Statistical Analysis

We summarized baseline patient characteristics and clinical variables of interest using median and interquartile range for continuous variables; counts and percentages for categorical variables. We stratified our analysis by survival status at hospital discharge (alive or dead) or by center-level annual ECPR case volume. We separately compared each variable of interest with survival using a series of multivariable logistic generalized estimating equation (GEE) models adjusting for the a priori selected case-mix variables described above. GEE was used to account for correlation of survival outcomes by center as opposed to mixed-effects modeling (which was used to construct caterpillar plots described below) due to convergence issues for some variables when we used mixed-effects modeling. Similarly, we assessed factors related to hospital annual case volume using GEE logistic regression models, comparing the medium and high categories versus the low category. Again, each predictor variable was compared separately to the hospital volume-outcome, adjusting for the case-mix variables described above. As a sensitivity analysis to test the robustness of our findings, we also modeled hospital case volume continuously (27). Only patients with no missingness were included in the adjusted models. Adjusted odds ratios (aORs), 95% CIs, and *p* values were reported from all models. Caterpillar plots were constructed to show center-level variation in select interventions and survival as described in the Supplement (http://links.lww.com/CCX/B33).

Center-level variation in survival was summarized using the median odds ratio (MOR) from a case-mix adjusted mixed-effects model. The MOR is calculated by taking the median of all possible pairwise comparisons among the centers, thus giving an effect estimate for center-level variability (28). All statistical analyses were conducted in R v.3.4 (R.Studio, PBC, Boston, MA) (29). Statistical significance was assessed at the 0.05 level, and all tests were two-tailed.

RESULTS

Study Population

From 2008 to 2019, 7,702 patients were treated with ECPR for cardiac arrest and entered into the ELSO Registry. After filtering, there were 7,488 patients for analysis (Supplement, http://links.lww.com/CCX/B33). Twenty-nine percent of patients (2,175/7,488) survived to hospital discharge. Baseline patient characteristics, stratified by survival status, are reported in **Table 1** and in **eTable 5** (http://links.lww.com/CCX/B33). Adjusted *p* values come from separate multivariable models constructed for each variable, adjusting for case mix. A similar analysis format is used for all results tables.

Case-Mix Adjusted Survival

Case-mix adjusted analysis demonstrated that older age (aOR, 0.93 for every 10 yr; 95% CI, 0.9–0.97; $p < 0.001$) and increasing weight (aOR, 0.96 per 10 kg; 95% CI, 0.93–0.99; $p = 0.020$) were significantly associated with decreased odds of survival (**eTable 6**, http://links.lww.com/CCX/B33). The primary diagnosis for which the patient received ECPR was associated with survival for the following diagnoses only and not for the others: acute myocardial infarction, acute cardiogenic shock, chronic heart failure, and acute myocarditis (eTable 6, http://links.lww.com/CCX/B33). Comorbidity status by Charlson Comorbidity Index was not significantly associated with survival (aOR, 0.97 per point; 95% CI, 0.91–1.04; $p = 0.46$).

Postresuscitation Management and Survival

At 24 hours of ECMO support, factors associated with increased odds of survival included increasing mean blood pressure (aOR, 1.13 per 5 mm Hg increase; 95% CI, 1.11–1.16; $p < 0.001$), increased arterial pulsatility (systolic blood pressure–diastolic blood pressure) (aOR, 1.09 per 5 mm Hg increase; 95% CI, 1.07–1.11; $p < 0.001$), the placement of an arterial perfusion catheter distal to the return cannula (DPC) (aOR, 1.39; 95% CI, 1.05–1.84; $p = 0.022$), mechanical unloading of the LV (aOR, 1.3; 95% CI, 1.08–1.55; $p = 0.005$), and the performance of coronary angiography after ECMO cannulation (aOR, 1.34; 95% CI, 1.11–1.61; $p = 0.002$) (**Table 2**). The use of inotropes was not significantly associated with survival (aOR, 0.93; 95% CI, 0.78–1.11; $p = 0.45$). Unilateral versus bilateral cannulation was not associated with survival (aOR, 0.98; 95% CI, 0.84–1.15; $p = 0.76$). Sensitivity analysis using multiple imputation had qualitatively similar results for almost all variables, except for inotrope use, which became significantly associated with mortality (eTable 4, http://links.lww.com/CCX/B33).

Hospital-Level Variation

After case-mix adjustment, the adjusted odds of hospital survival was 26% greater at centers performing greater than 12 cases/yr versus less than 6 cases/yr (aOR, 1.26; 95% CI, 1.06–1.49; $p = 0.07$). Modeled continuously,

TABLE 1.
Patient Characteristics Stratified by Survival Status at Hospital Discharge

Variable[a]	Alive (*n* = 2,175)	Dead (*n* = 5,313)	Adjusted *p*[b]
Baseline variables			
Age	55.1 (43.7–64.8)	57.3 (45.2–66.3)	< 0.001
Sex, male, *n* (%)	1,435 (67.7)	3,654 (70.2)	0.18
Weight (kg)	79.0 (68.0–93.0)	80.0 (69.0–97.0)	0.02
Charlson Comorbidity Index	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.95
Charlson Comorbidity Index, stratified, *n* (%)			
0	977 (50.8)	2,477 (51.1)	0.63
1–2	862 (44.8)	2,118 (43.7)	
3–4	78 (4.1)	218 (4.5)	
≥ 5	8 (0.4)	35 (0.7)	
Clinical variables prior to cardiac arrest			
Mean arterial pressure	60.0 (43.0–75.0)	54.0 (38.0–70.0)	< 0.001
Arterial pulse pressure	30.0 (18.0–44.0)	30.0 (18.0–45.0)	0.29
pH (per 0.1)	7.2 (7.0–7.3)	7.1 (7.0–7.3)	< 0.001
Clinical variables/therapies on ECMO after cardiac arrest			
Mean blood pressure[c]	75.0 (67.0–84.0)	71.0 (63.0–80.0)	< 0.001
Arterial pulse pressure[c]	33.0 (21.0–48.0)	24.0 (11.0–41.0)	< 0.001
pH[c]	7.4 (7.4–7.5)	7.4 (7.3–7.5)	< 0.001
Coronary angiography, *n* (%)	170 (7.8)	350 (6.6)	0.002
Mechanical left ventricular unloading, *n* (%)	265 (12.2)	555 (10.4)	0.005
Distal perfusion catheter, *n* (%)	96 (4.4)	191 (3.6)	0.022
Inotrope use, *n* (%)	522 (24)	1,382 (26)	0.45
Bilateral femoral cannulae, *n* (%)	705 (42.5)	1,539 (39)	0.79
ECMO flow (at 4 hr)	3.5 (2.8–4.1)	3.5 (2.9–4.2)	0.17
ECMO flow (at 24 hr)	3.5 (2.8–4.2)	3.7 (3.0–4.3)	0.29
Hospital annual extracorporeal cardiopulmonary resuscitation case volume, *n* (%)			
Low (< 6 cases/yr)	901 (41.4)	2,360 (44.4)	0.029
Medium (6–12 cases/yr)	552 (25.4)	1,527 (28.7)	
High (> 12 cases/yr)	722 (33.2)	1,426 (26.8)	

ECMO = extracorporeal membrane oxygenation.
[a]Median (interquartile range).
[b]Adjusted *p* from logistic generalized estimating equation model, including covariates: age, sex, year, Charlson Comorbidity Index score, and primary diagnosis. For example, age is modeled as: survival status ~ age + other case-mix variables excluding age, where we report the coefficient from age in this model.
[c]Measured at 24 hr.

hospitals performing fewer than 10 cases per year had decreased survival (aOR, 0.36; 95% CI, 0.32–0.39; $p < 0.001$); each additional 10 patients annually per center increased the odds of survival by 11% (aOR, 1.11; 95% CI, 1.07–1.16; $p < 0.001$). Hospital annual ECPR case volume varied across all centers, with 3,261 patients managed at centers performing less than 6 cases/yr (n = 307 centers), 2,079 patients managed at centers performing 6–12 cases/yr (n = 34 centers), and 2,148 patients managed at centers performing greater than

TABLE 2.
Adjusted Probability of Hospital Survival

Variable	Adjusted OR (95% CI)	p[b]	No. of Subjects
Therapies and characteristics on ECMO			
Mean blood pressure (per 5 mm Hg)[a]	1.13 (1.11–1.16)	< 0.001	4,784
Arterial pulse pressure (per 5 mm Hg)[a]	1.09 (1.07–1.11)	< 0.001	4,400
Coronary angiography	1.34 (1.11–1.61)	0.002	7,488
Mechanical left ventricular unloading	1.3 (1.08–1.55)	0.005	7,488
Distal perfusion catheter	1.39 (1.05–1.84)	0.022	7,488
Inotrope use[a]	0.93 (0.78–1.11)	0.45	7,488
Cannula laterality			
Bilateral	Reference	Reference	5,607
Unilateral	0.98 (0.84–1.15)	0.79	
ECMO flow (per L/min, at 4 hr)	1.06 (0.97–1.16)	0.17	6,065
ECMO flow (per L/min, at 24 hr)	0.96 (0.86–1.05)	0.29	5,104
Hospital annual ECPR case volume			
Low (< 6 cases/yr)	Reference	Reference	6,744
Medium (6–12 cases/yr)	0.98 (0.8–1.2)	0.86	
High (> 12 cases/yr)	1.26 (1.06–1.49)	0.007	
Hospital annual ECPR case volume[c]			
0–9 cases annually	0.36[d] (0.32–0.39)	< 0.001	6,744
Per each additional 10 cases annually	1.11 (1.07–1.16)	< 0.001	6,744

ECMO = extracorporeal membrane oxygenation, ECPR = extracorporeal cardiopulmonary resuscitation, OR = odds ratio.
[a]Measured at 24 hr.
[b]Adjusted p from separate logistic generalized estimating equation models, each including case-mix covariates: age, sex, year, Charlson Comorbidity Index score, Pao_2/Fio_2, and primary diagnosis.
[c]Plotted as a continuous variable.
[d]This adjusted OR (95% CI and p) is reported from the model without additional covariates to enable convergence.
The adjusted OR (95% CI and p) for each 10 cases annually was the same between the two models.
Number of subjects indicates the number of subjects analyzed per variable.

12 cases/yr (n = 10 centers) (**Table 3**; and **eTable 7**, http://links.lww.com/CCX/B33).

Hospital Variation in Postresuscitation Management

High-volume centers were more likely to perform coronary angiography after ECPR cannulation than medium- and low-volume centers, after adjustment for the primary diagnosis (11% vs 5%; p = 0.033) (Table 3 and **Fig. 1**). As seen in the figures, other on-ECMO therapies varied widely across individual hospital centers, but were not statistically significantly associated with categorized center volume after adjustment, including ECMO flow (p = 0.33) (Table 3; and **eFigs. 1** and **2**, http://links.lww.com/CCX/B33), mean blood pressure (p = 0.6) (Table 3; and **eFig. 3**, http://links.lww.com/CCX/B33), cannula laterality (p = 0.58), mechanical LV unloading (p = 0.67) (Table 3; and **eFig. 4**, http://links.lww.com/CCX/B33), DPC placement (p = 0.17), and the use of inotropes on ECMO (p = 0.37) (Table 3). After adjustment, the MOR of survival between individual centers was 1.44 (95% CI, 1.40–1.48), which suggests that the adjusted odds of survival for an ECPR patient could vary by as much as 44% across centers (**Fig. 2**).

DISCUSSION

We demonstrate that for adult cardiac arrest patients treated with ECMO (ECPR), modifiable postresuscitation management practices appear to be associated

TABLE 3.
Characteristics by Hospital Extracorporeal Cardiopulmonary Resuscitation Case Volume

Variable[a]	Low (< 6 Cases/yr), *n* = 3,261	Medium (6–12 Cases/yr), *n* = 2,079	High (> 12 Cases/yr), *n* = 2,148	Adjusted *p*[b]
Age[c]	54 (41–64)	58 (46–67)	60 (49–67)	< 0.001
Sex				
Female	1,032 (46%)	610 (27%)	592 (26%)	< 0.001
Male	2,194 (43%)	1,438 (28%)	1,457 (29%)	
Weight[c] (kg)	80 (68–96)	80 (68–97)	80 (69–94)	0.91
Charlson Comorbidity Index[c]	0 (0–1)	0 (0–1)	1 (0–1)	0.96
Charlson Comorbidity Index, stratified				
0	1,628 (47%)	1,087 (31%)	739 (21%)	0.14
1–2	1,371 (46%)	791 (27%)	818 (27%)	
3–4	122 (41%)	71 (24%)	103 (35%)	
≥ 5	26 (60%)	9 (21%)	8 (19%)	
Clinical variables prior to cardiac arrest				
Mean blood pressure[c]	54 (38–70)	58 (40–74.5)	55 (40–73)	0.019
Arterial pulse pressure[c]	29 (17–43)	30 (18–44.2)	33 (20–51)	0.003
pH (unit: 0.1)[c]	7.1 (7–7.3)	7.2 (7–7.3)	7.2 (7–7.3)	0.03
Therapies and characteristics on ECMO				
Mean blood pressure[c,d]	73 (65–82)	74 (66–84)	70 (62–79)	0.60
Arterial pulse pressure[c,d]	28 (14–43)	28 (14–42)	32 (16–49)	0.23
pH[c,d]	7.4 (7.3–7.5)	7.4 (7.3–7.5)	7.4 (7.3–7.5)	0.21
Coronary angiography[e]	168 (5%)	106 (5%)	246 (11%)	0.033
Mechanical left ventricular unloading[e]	350 (11%)	193 (9%)	277 (13%)	0.67
Distal perfusion catheter[e]	109 (8%)	110 (5%)	68 (3%)	0.17
Inotrope use[e]	827 (25%)	514 (25%)	563 (26%)	0.37
Cannula laterality[e]				
Bilateral	880 (38%)	642 (42%)	722 (40%)	0.58
Unilateral	1,416 (62%)	885 (58%)	1,062 (60%)	
ECMO flow (at 4 hr)[c]	3.7 (3–4.2)	3.5 (2.9–4.2)	3.2 (2.6–3.9)	0.16
ECMO flow (at 24 hr)[c]	3.8 (3.1–4.4)	3.7 (3–4.4)	3.3 (2.5–4)	0.33

ECMO = extracorporeal membrane oxygenation.
[a]*n*, row percent (%).
[b]*p* from adjusted generalized estimating equation model, including covariates: age, sex, year, Charlson Comorbidity Index score, primary diagnosis, and center.
[c]Median (interquartile range).
[d]Measured at 24 hr.
[e]*n*, column percent (%).

with case-mix adjusted hospital survival. These findings should be considered hypothesis generating due to residual confounding in these exposure-outcome relationships. These management practices vary widely across individual hospitals and include the performance of coronary angiography, mechanical LV unloading, and the placement of a DPC. Less easily modifiable clinical factors including increasing arterial pulsatility and mean blood pressure were associated with improved adjusted survival. Across

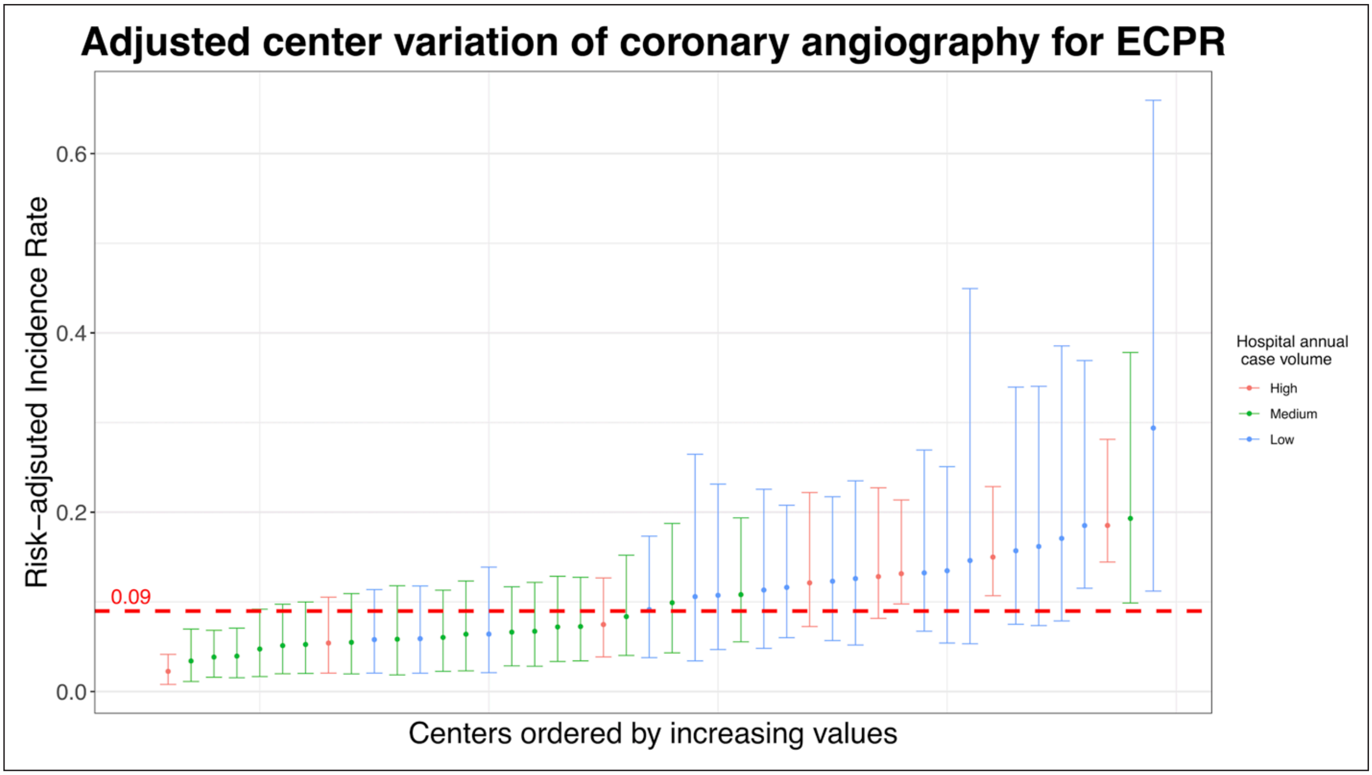

Figure 1. Adjusted center variation in the probably of coronary angiography for extracorporeal cardiopulmonary resuscitation (ECPR). Standardized case-mix adjusted incidence (0 to 1), by center, of coronary angiography for adults receiving ECPR. *Dashed red line*: Average value across centers. *Center dot*: Standardized case-mix adjusted estimate for each center. *Bars*: 95% CI by center. Centers are ordered by increasing values and colored by average annual adult ECPR case volume. No centers performing coronary angiography for fewer than three patients were included.

hospitals, higher annual case volume was associated with improved odds of success with wide variability in the adjusted odds of survival by center. The use of coronary angiography after ECPR cannulation was more common at high-volume centers, but other practices were not significantly associated with hospital average annual case volume.

Our observational finding of a survival association with percutaneous coronary intervention (PCI) among ECPR patients is consistent with previous data showing a benefit to urgent coronary angiography after cardiac arrest (30). Angiography is advocated for initial shockable rhythms by the American Heart Association as shockable rhythms are associated with coronary ischemia (12). It is possible that the improved survival seen with angiography was a correlate for patients with ventricular fibrillation; however, we could not identify subgroups by rhythm. The significance of the survival association for PCI among all patients—irrespective of initial rhythm—is highly important and suggests an urgent need to further characterize the ECPR patients in whom there may be greatest benefit. In the setting of ECPR, ECMO is used to support the patient allowing angiographic correction of the underlying lesion in a more stable setting. While coronary angiography is a component of established ECPR programs (11, 13, 31), no previous studies examined whether there is a survival benefit in relation to coronary angiography after ECPR. Our findings suggest future trials should test the hypothesis that coronary angiography is a therapy to improve survival after ECPR.

Mechanical unloading of the LV is associated with survival in patients on venoarterial ECMO for cardiogenic shock (10, 32). The use of ventricular unloading during myocardial infarction has been shown to decrease infarct size prior to reperfusion and is being studied (33, 34) but has not been previously associated with survival in patients with myocardial infarction, cardiac arrest, or ECPR. Our findings add to this literature, building upon previous demonstrations of myocardial dysfunction observed after cardiac arrest (16, 35) and ECPR (36). While the mechanism has not been elucidated, potential mechanisms include decreased wall stress and infarct size (37, 38) and are a critical area of further investigation.

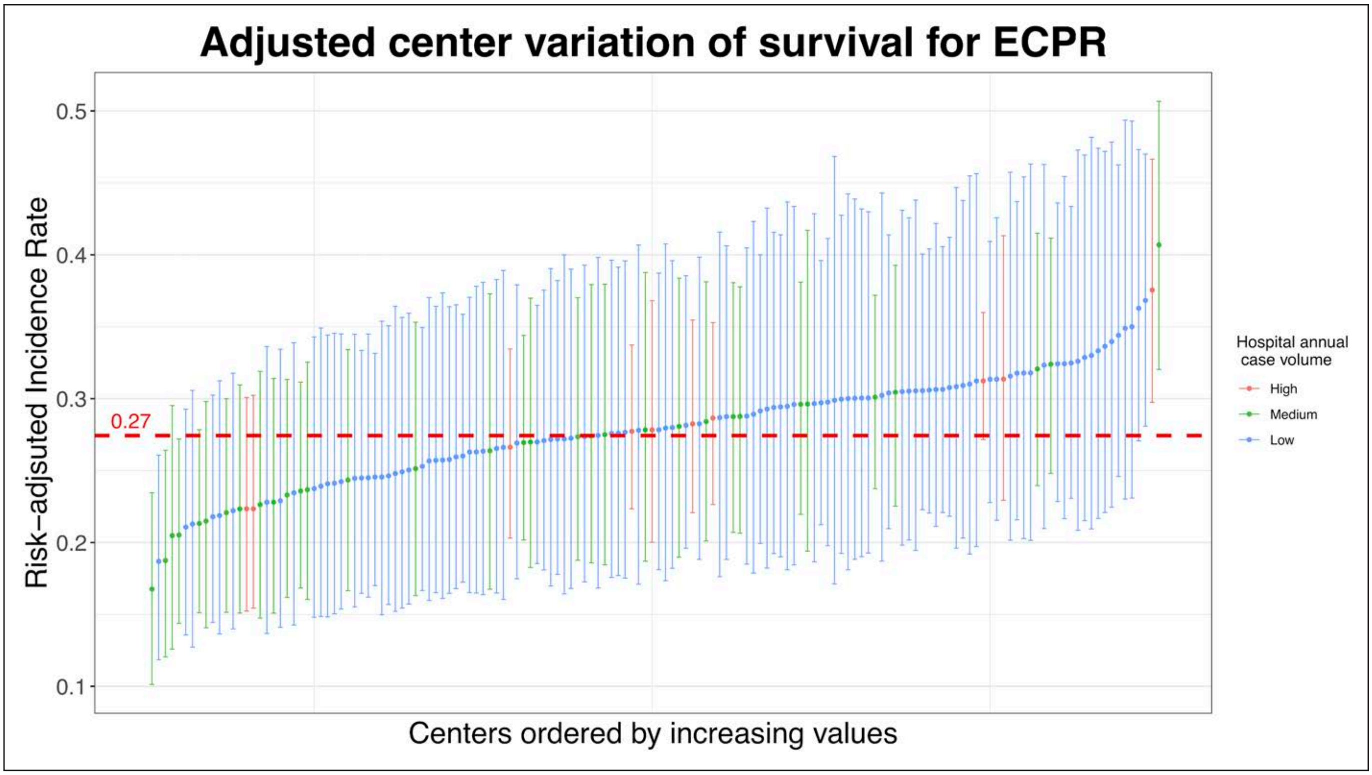

Figure 2. Adjusted center variation in the probability of hospital survival after extracorporeal cardiopulmonary resuscitation (ECPR). Standardized case-mix adjusted probability (0 to 1), by center, of hospital survival for adults receiving ECPR. *Dashed red line*: Average value across centers. *Center dot*: Standardized case-mix adjusted estimate for each center. *Bars*: 95% CI by center. Centers are ordered by increasing values and colored by average annual adult ECPR case volume. No centers performing outcomes for fewer than three patients were included.

The adjusted survival association with DPC placement builds upon previous observations of a high prevalence of limb ischemia during ECMO (39). DPC placement can mitigate ischemia by augmenting arterial perfusion distal to the ECMO return cannula. Among previous studies of less than 200 patients with femoral cannulation for venoarterial ECMO (of which ECPR patients are a subset), DPC placement is associated with reduced limb complications (40, 41). Some of this previous work has also shown that fewer complications are then associated with decreased mortality after femoral cannulation for venoarterial ECMO (40). While a survival benefit has not been previously demonstrated, our observational findings support a future study of DPC placement on outcomes. The association of these practices with survival and the variation across hospitals suggests that this hypothesis could be tested in comparative trials.

The international use of ECPR has increased exponentially (1), with more than 2,000 adult cases reported in 2019 alone to the ELSO Registry. The recently published advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation trial demonstrated improved survival with ECPR compared with conventional CPR (42). With multiple additional ongoing trials (NCT03065647, NCT03101787, NCT03658759), we expect the increasing use of ECPR to continue. These make our finding of a relationship between higher hospital annual case volume and case-mix adjusted survival critical as new programs are started. Our results showing a survival advantage at higher volume programs supports consideration of a regionalized "hub-and-spoke" model for new programs, which has been previously demonstrated to improve outcomes in combination with expeditious coronary angiography for out of hospital cardiac arrest (43). Future work should examine how to balance expeditious arrest-to-cannulation times with regionalization to support higher volumes. Our study demonstrated three potentially modifiable postresuscitation interventions that should be considered hypotheses and candidate interventions in future studies of survival for ECPR patients. Clinical trials of angiography, ventricular unloading DPC placement, among other associated factors we identified, are needed to establish best practice guidelines for low- to high-volume hospitals performing ECPR.

Despite our study's strengths, we acknowledge a number of potential limitations. First, our analysis did not include arrest information, such as the Utstein variables, which were not available for this analysis. Interestingly, postcardiac arrest guidelines state that once patients achieve ROSC, no single intra-arrest factor (e.g., rhythm) is reliably predictive of outcome (16). While rhythm certainly influence the probability of ROSC and survival, once patients achieve ROSC on ECMO, their eventual hospital survival is more strongly influenced by postresuscitation care, at least among non-ECPR patients (3), and was thus the focus of our analysis. To account for this lack, we adjusted for all available variables previously associated with survival in this population. This revealed that select on-ECMO factors retain a significant association with survival among patients who survived at least 24 hours post cannulation. We acknowledge that these results should be considered exploratory and warrant prospective study. We fully acknowledge that there is a possibility of residual uncontrolled confounding. Further, we note that coronary angiography, DPC placement and mechanical LV unloading were infrequently used in both survivors and nonsurvivors, within only a small difference (< 2%) in use between these groups. We also demonstrated that each of these therapies was associated with greater than or equal to 30% increase in the adjusted odds of survival. This large magnitude association from such a small absolute difference could be due to 1) residual confounding or 2) subgroups in which these interventions matter more, rather than 3) a strong causal effect from these interventions. Our findings should be interpreted in this light. Future analyses could answer this question with more variables, a causal analysis, or prospective randomization.

Second, on-ECMO hemodynamic data were limited to a single assessment at 24 hours. As vital sign variability has previously been associated with mortality (44), we would expect that more granular management data would improve outcome discrimination. Third, this was an observational analysis that did not show causality, for example, the elevated blood pressure and arterial pulsatility likely reflect improved cardiovascular function and may not reflect clinical management as much. This is further supported by the observation that inotropes, which increase arterial pulsatility, were not associated with survival. In contrast, coronary angiography, mechanical ventricular unloading, and placement of a DPC are intentional. We acknowledge that residual confounding could skew the relationships. Our finding of improved survival at high-volume centers is reflective of improved process of care, such as faster time to ECMO, which has been strongly correlated with survival (45, 46). These limitations notwithstanding, in the largest case series to date of ECPR cases, we have demonstrated that the postresuscitation phase of care appears to be associated with hospital survival, as is case volume, and we have identified several modifiable factors as candidate interventions for future study.

CONCLUSIONS

Across an international registry of adult cardiac arrest patients treated with ECMO, we demonstrated that case-mix adjusted survival appears to be associated with modifiable postresuscitation management practices that vary across hospitals and center volume, although these results do not imply causality. Acknowledging an exponentially increasing use of adult ECMO, our data represent a foundational study identifying potential interventions that could be tested within clinical trials of ECPR.

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Drs. Tonna and Keenan were involved in study design, study conduct, and drafting the article. Dr. Keenan were involved in data acquisition and analysis. Dr. Tonna had full access to the study data and takes responsibility for the data integrity, accuracy, and integrity of the submission as a whole. All authors revised the *article for important intellectual content and approved the final article for publication.*

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