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Clinical paper

Percutaneous mechanical circulatory support and survival in patients resuscitated from Out of Hospital cardiac arrest: A study from the CARES surveillance group



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Abstract

Introduction: Maintenance of cardiac function is required for successful outcome after out-of-hospital cardiac arrest (OHCA). Cardiac function can be augmented using a mechanical circulatory support (MCS) device, most commonly an intra-aortic balloon pump (IABP) or Impella[®].

Objective: Our objective is to assess whether the use of a MCS is associated with improved survival in patients resuscitated from OHCA in Michigan.

Methods: We matched cardiac arrest cases during 2014–2017 from the Cardiac Arrest Registry to Enhance Survival (CARES) in Michigan and the Michigan Inpatient Database (MIDB) using probabilistic linkage. Multilevel logistic regression tested the association between MCS and the primary outcome of survival to hospital discharge.

Results: A total of 3790 CARES cases were matched with the MIDB and 1131 (29.8%) survived to hospital discharge. A small number were treated with MCS, an IABP (n = 183) or Impella[®] (n = 50). IABP use was associated with an improved outcome (unadjusted OR = 2.16, 95% CI [1.59, 2.93]), while use of Impella[®] approached significance (OR = 1.72, 95% CI [0.96, 3.06]). Use of MCS was associated with improved outcome (unadjusted OR = 2.07, 95% CI [1.55, 2.77]). In a multivariable model, MCS use was no longer independently associated with improved outcome (OR_{adj} = 0.95, 95% CI [0.69, 1.31]). In the subset of subjects with cardiogenic shock (N = 725), MCS was associated with improved survival in univariate (unadjusted OR = 1.84, 95% CI [1.24, 2.73]) but not multi-variable modeling (OR_{adj} = 1.14, 95% CI [0.74, 1.77]).

Conclusion: Use of MCS was infrequent in patients resuscitated from OHCA and was not independently associated with improvement in post arrest survival after adjusting for covariates.

Keywords: Mechanical circulatory support, Out-of-hospital cardiac arrest, Cardiogenic shock, Intra-Aortic balloon pump, Impella[®]

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Introduction

Approximately 70% of cardiac arrests occur out of hospital.¹ Patients resuscitated from out of hospital cardiac arrest (OHCA) have higher risk of complications and lower likelihood of a favorable outcome compared to patients who arrest in the hospital.^{2,3} Despite modest improvement in clinical outcomes from an enhanced focus on layperson educational campaigns to increased availability of automated external defibrillators, as well as improved prehospital care, overall survival in OHCA remains <10%. Of those surviving to hospital admission, only 30% survive to hospital discharge.⁴

Whether the etiology of cardiac arrest or a sequelae of post cardiac arrest syndrome, some degree of myocardial dysfunction complicates up to two thirds of cases resuscitated from OHCA.⁵ Many develop overt cardiogenic shock (CS). When cardiogenic shock accompanies acute ST-elevation myocardial infarction (STEMI), current American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend emergent invasive coronary angiography and revascularization as indicated.^{6,7} The role and timing of invasive coronary angiography after OHCA without STEMI is less clear. Other causes of cardiogenic shock in OHCA could include but are not limited to: acute valvular heart disease, pericardial tamponade, acute right ventricular failure in the setting of massive pulmonary embolism, and refractory primary ventricular dysrhythmia.

In addition to revascularization, the treatment of post-arrest cardiogenic shock centers around decreasing cardiac work while maintaining vital organ perfusion. Vasopressors increase systemic blood pressure and cardiac output, but may do so at the expense of increasing myocardial oxygen demand and peripheral vascular resistance, but may accelerate the development of tissue acidosis and multi-organ failure. The use of increasing numbers of vasopressors is associated with poor clinical outcomes in cardiogenic shock from acute myocardial infarction.⁸

Mechanical circulatory support (MCS) offers the opportunity to reduce cardiac work and maintain vital organ perfusion without the potential adverse effects of vasopressors. The intra-aortic balloon pump (IABP) and Impella[®] (Abiomed, Danvers, MA) are two commonly deployed MCS devices, particularly in the setting of acute myocardial infarction. IABP improves coronary artery perfusion and augments cardiac output (up to 0.5L/min) by inflating during ventricular diastole and deflating during systole, respectively. These hemodynamic effects may be important in post arrest patients, particularly those with obstructive coronary artery disease. Impella[®] is a percutaneous left ventricular assist device that actively unloads the left ventricle during systole and diastole by spanning the aortic valve with a miniature axial flow pump. In contrast to IABP, Impella[®] can increase cardiac output by 3–4L/min. Both devices are typically inserted percutaneously in the cardiac catheterization laboratory at the time of left heart catheterization.

Assessment of whether MCS improves survival in patients post cardiac arrest is important, since it has implications for regional prehospital triage of resuscitated OHCA subjects to specialized post-arrest centers that offer MCS.^{9–12} For this reason, the objective of our study is to test the association of percutaneous MCS on survival after resuscitation from OHCA using two statewide population-based registries. We also analyzed the subset of subjects with specific diagnostic codes for cardiogenic shock.

Methods

Data sources

We performed a secondary analysis of two prospectively created registries in the state of Michigan: Cardiac arrest Registry to Enhance Survival (CARES) database and the Michigan Inpatient Database (MIDB). CARES is a national OHCA registry that collects data on patients including demographic, clinical and treatment data, pre-hospital and limited hospital therapies, and hospital outcome data.⁴ During the study period, CARES data was submitted from EMS agencies from a catchment area of nearly 70% of the state population (approximately 7 million persons).¹³ Maintained by the Michigan Department of Community Health, The MIDB records diagnosis, procedure and outcome data on acute care admissions in the State of Michigan and was utilized to capture these data on post arrest patients.¹³

Study cohort

We initially included all subjects entered into CARES between 2014–2017 with a non-traumatic OHCA. Subjects under 18 years of age, traumatic cardiac arrests, those with do not resuscitate orders, and those who did not survive to hospital admission were excluded. Subjects who were transferred from the original receiving hospital or transported out of state were excluded because we could not link EMS and inpatient records. The IABP and Impella[®] devices along with cardiogenic shock cases were extracted and identified from the MIDB dataset using ICD-9 and ICD-10 codes.

We linked at the patient level, OHCA cardiac arrest cases between these two datasets using probabilistic linkage methodology as previously described.¹⁴ An honest broker was also used to blind hospital and patient identifiers from the two datasets. We matched CARES subjects with subjects in the MIDB who were admitted with a diagnosis of cardiac arrest (ICD-9=427.5 or ICD-10=I46.9) or ventricular fibrillation (ICD-9=427.41 or ICD-10=I49.01) using a probabilistic linkage process. Match scores were tabulated using a composite point score from points assigned to each of the match variables including age, sex, date of arrest/hospital admission, and receiving hospital.¹⁵ We assigned weighted scores based on the perceived ability of each variable that met the following match criteria: (1) gender (exact: 90 points); (2) age (exact: 80 points; +/- 1 year: 75 points; +/- 2 years: 65 points; +/- 3 years: 60 points; +/- 4 years: 50 points; +/- 5 years: 40 points); (3) date of arrest/hospital admission (+/- 1 day: 85 points; +/- 2 days 65 points; +/- 3 days 40 points; +/- 4 days 10 points); and (4) receiving hospital (exact: 80 points). The matching process was implemented using the SQL procedure in SAS (Cary, NC). We further determined the threshold from the distribution of match scores to identify the linkage of records from the same patient. The final study cohort included OHCA patients who were successfully linked to a MIDB record.

Patient characteristics

Patient age, sex, arrest location type (private residence, health facility, public), arrest witness status (unwitnessed, bystander witnessed, 911 responder witnessed), CPR (no bystander, bystander), and initial rhythm type (non-shockable, shockable) were obtained from CARES.

The MIDB database was used to extract information on diagnosis and procedure codes.

Study outcomes

The primary outcome was in-hospital mortality extracted from CARES. We defined MCS use as use of either an IABP or the Impella[®]. The use of IABP and Impella[®] devices along with cardiogenic shock was identified using ICD-9 and ICD-10 procedure and diagnosis codes.

Statistical analyses

Descriptive analyses were used to summarize subject characteristics stratified by survival outcome with the *t*-test or Kruskal-Wallis test (continuous variables) and Chi-squared or Fisher's exact test (categorical data). Our data has a two-level structure with patients clustered within hospitals. To account for potential hospital variation, a multilevel logistic regression model was used to evaluate the effect of MCS association with survival to hospital discharge, adjusting for patient characteristics and the clustering of patients within hospitals. Patient characteristics were chosen based on prior demonstrated effects on survival outcome and included age, gender, arrest location type, arrest witness status, and initial rhythm type. The model was implemented using the GLIMMIX procedure in SAS. Moreover, in a

subgroup analysis, we studied patients with cardiogenic shock after their initial cardiac arrest event using ICD-9 and 10 codes. We presented unadjusted and adjusted odds ratios reported for survival to hospital discharge. All tests of statistical significance were two-sided with *p*-value < 0.05 considered to be statistically significant. Analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

This study was approved by William Beaumont Hospital Institutional Review Board.

Results

During the study period, 5486 CARES subjects survived to hospital admission of which 4943 subjects were selected after exclusion criteria was applied. Matches for the CARES patients were taken from the 35,109 patients with an admission diagnosis of either cardiac arrest or ventricular fibrillation etiology from the MIDB database. We identified a total of 3790 (76.7%) CARES cases who were linked with MIDB records (Fig. 1). On matching-index characteristics, prior to matching, age ($p < 0.001$) and gender ($p = 0.10$) were different from two databases. Post-matching, age ($p = 1.00$) were balanced, gender and receiving hospital were fully matched, and 99% of arrest/hospital admission were within 1 day.

Of all patients 1131 (29.8%) survived to hospital discharge. Characteristics of patients on admission with and without survival to

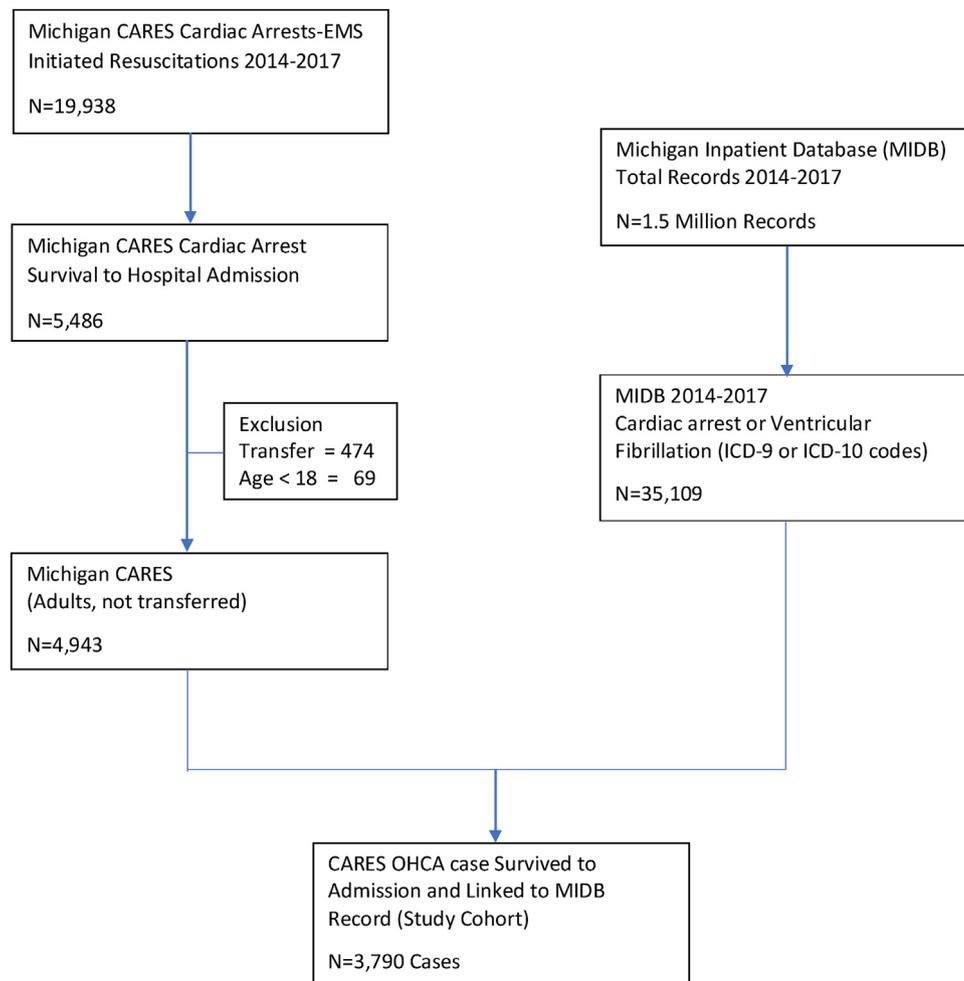


Fig. 1 – Flow Diagram for Case Ascertainment.

discharge are shown in Table 1. Overall, patients who were younger, males, bystander or 911 responder witnessed, arrested at public locations, and received bystander CPR were more likely to have a better survival outcome (Table 1).

We next explored survival to discharge by device use across 57 hospitals. IABPs were placed in 34 hospitals and Impella[®]s were placed in 13 hospitals. Table 2 shows that a small number of patients received therapy with IABP (n = 183) or an Impella[®] (n = 50). Hospitals infrequently (Median 5; IQR 2,9) placed MCS devices in patients, with only nine, placing either device more than twice annually. In the unadjusted analysis, use of MCS was associated with improved survival to discharge (OR = 2.07, 95% CI [1.55, 2.77]). IABP were used much more frequently and their use was associated with an improved outcome (OR = 2.16, 95% CI [1.59, 2.93]). Our findings also suggest that the likelihood of a survival outcome was increased with Impella[®] use, however this association was not statistically significant (OR = 1.72, 95% CI [0.96, 3.06]) (Table 2).

We identified 725 patients that also experienced cardiogenic shock after their initial cardiac arrest event. For this subset of patients in cardiogenic shock, MCS and IABP use, but not Impella[®] use were associated with improved survival to hospital discharge in the unadjusted analysis (Table 2).

Multivariable regression analyses examining the effect of MCS use on survival at discharge are displayed in Table 3. MCS use in the entire cohort did not demonstrate a significant survival benefit with device use. (adjusted odds ratio [aOR] 0.95, [95% CI: 0.69–1.31]). MCS use in the cardiogenic shock patients demonstrated a minimal, non-statistically significant survival benefit (aOR 1.14, [95% CI: 0.74, 1.77]).

Discussion

Our adjusted analysis did not demonstrate an independent effect of MCS on survival in patients resuscitated out of hospital cardiac arrest in Michigan. Prior to adjusting for prehospital variables, a higher percentage of survival to discharge was found in both IABP and Impella[®] use compared to no device use. After adjusting for prehospital variables, however, the association between MCS use and improved outcome was no longer observed. This finding was also observed in the subset of patients in cardiogenic shock. These findings may be explained by the small sample size due to infrequent use of these devices.

Although OHCA accounts for most cardiac arrest events in the US, little data is available on the effectiveness of MCS use on this specific population. Our findings are important and unique as we have used a large population based statewide dataset, which is the largest study to date to assess MCS use in OHCA patients. We identify a need for further work regarding this therapy. Few OHCA patients received MCS in this study, and treating hospitals infrequently provide it, identifying systemic barriers to MCS.

While the majority of existing literature on MCS focuses on their use in CS associated with acute myocardial infarction, very few are focused on cases with a cardiac arrest etiology.¹⁶ A recent review of published and registered trials studying post-cardiac arrest interventions found only 65 manuscripts reporting randomized clinical trials (RCTs) on post-arrest interventions and 48 registered trials online.¹⁷ Although 79% and 71% of participants were OHCA in the RCTs and registered trials respectively, the median number of participants were low with only 90 and 100 participants respectively.¹⁷ Furthermore, more than one-third of the manuscripts and one-fifth of the registered trials centered on targeted temperature therapy and almost none were focused on MCS interventions.¹⁷

Notably, our dataset only included patients who arrested outside the hospital, thereby adding to the existing literature, which includes multiple studies that do not distinguish between in-hospital and out of hospital cardiac arrest. Patients who arrest outside of the hospital are more likely to suffer from cardiogenic shock and have a higher mortality rate than those who initially arrested or developed subsequent shock in the hospital.^{3,18}

A similar study that also analyzed data obtained from the MIDB during a three-year time span identified only 197 (4.5%) out of 4393 cardiac arrest cases that were assisted with devices.¹ It utilized a dataset from ICD-9 codes and included patients with an admission diagnosis of cardiac arrest or ventricular fibrillation. Impella devices were also not used in this time period. This study concluded that MCS use was positively associated with survival to discharge in cardiac arrest in both a univariate and multilevel multivariable analysis.¹ The findings of this study also showed that this positive association was more prominent in cardiac arrest cases that were complicated by cardiogenic shock.¹ However, this study differs from ours in that it did not use the additional CARES dataset that provided data on prehospital variables and may have include in-hospital cardiac arrests; factors known to be associated with increased survival.¹⁹

Table 1 – Demographic and clinical patient characteristics on admission in the entire cohort (n = 3790) and cardiogenic shock subgroup (n = 725).

Device Use, n (%)	Entire Cohort			Cardiogenic Shock Subgroup			
	Total	Survivors, n (%)	Unadjusted OR ^a (95% CI)	Total	Survivors, n (%)	Unadjusted OR ^a (95% CI)	
IABP	Yes	183	87 (47.5)	2.16 (1.59–2.93)	127	55 (43.3)	1.98 (1.32–2.98)
	No	3607	1044 (28.9)		598	167 (27.9)	
Impella	Yes	50	22 (44.0)	1.72 (0.96–3.06)	32	11 (34.4)	1.17 (0.54–2.54)
	No	3740	1109 (29.6)		693	211 (30.4)	
MCS	Yes	205	95 (46.3)	2.07 (1.55–2.77)	142	59 (41.5)	1.84 (1.24–2.73)
	No	3585	1036 (28.9)		583	163 (28.0)	

Abbreviations: IABP = intra-aortic balloon pump; MCS = intra-aortic balloon pump (IABP) or percutaneous left ventricular device (Impella); OR = odds ratio; CI = confidence interval.

^a The unadjusted multilevel logistic regression controlling for the clustering of patients within hospitals was employed.

Table 2 – Device use associated with survival to discharge in the entire cohort (n = 3790) and cardiogenic shock subgroup (n = 725).

Variables ^a	Entire Cohort				p-value	Cardiogenic Shock Subgroup				p-value
	Total	Survival to Discharge				Total	Survival to Discharge			
		Deaths	Survivors			Deaths	Survivors			
n	3790	2659	1131		725	503	222			
Age, years, mean ± SD, median (IQR)	62.5 ± 16.0	63.5 ± 16.4	60.1 ± 14.9	< 0.001	62.7 ± 15.4	63.4 ± 16.0	61.2 ± 13.7	0.03 ^b		
	63.0 (53.0, 74.0)	65.0 (54.0, 75.0)	61.0 (52.0, 70.0)		64.0 (54.0, 73.0)	65.0 (54.0, 75.0)	62.0 (54.0, 69.0)			
Gender, n (%)										
Male	2248 (59.3)	1486 (55.9)	762 (67.4)	< 0.001	488 (67.3)	324 (64.4)	164 (73.9)	0.01		
Female	1542 (40.7)	1173 (44.1)	369 (32.6)		237 (32.7)	179 (35.6)	58 (26.1)			
Arrest Location Type, n (%)										
Private Residence	2540 (67.0)	1883 (70.8)	657 (58.1)	< 0.001	497 (68.6)	365 (72.6)	132 (59.5)	< 0.001		
Public	653 (17.2)	334 (12.6)	319 (28.2)		166 (22.9)	92 (18.3)	74 (33.3)			
Health Facility	597 (15.8)	442 (16.6)	155 (13.7)		62 (8.5)	46 (9.1)	16 (7.2)			
Witness Status, n (%)										
Unwitnessed	1401 (37.0)	1111 (41.8)	290 (25.6)	< 0.001	252 (34.8)	192 (38.2)	60 (27.0)	0.01		
Bystander	1745 (46.0)	1139 (42.8)	606 (53.6)		356 (49.1)	235 (46.7)	121 (54.5)			
911 Responder	644 (17.0)	409 (15.4)	235 (20.8)		117 (16.1)	76 (15.1)	41 (18.5)			
CPR, n (%)										
No Bystander	2535 (66.9)	1828 (68.8)	707 (62.5)	< 0.001	477 (65.8)	337 (67.0)	140 (63.1)	0.30		
Bystander	1255 (33.1)	831 (31.3)	424 (37.5)		248 (34.2)	166 (33.0)	82 (36.9)			
Initial Rhythm Type, n (%)										
Non-Shockable	2626 (69.3)	2139 (80.4)	487 (43.1)	< 0.001	387 (53.4)	323 (64.2)	64 (28.8)	< 0.001		
Shockable	1164 (30.7)	520 (19.6)	644 (56.9)		338 (46.6)	180 (35.8)	158 (71.2)			

Abbreviations: SD = standard deviation; IQR = interquartile ranges.

^a For continuous variables, means ± standard deviations and medians (interquartile ranges) were presented. For categorical variables, frequencies and percentages were presented.

^b Significance was based on the Kruskal-Wallis test.

We showed that in Michigan, from 2014 and 2017, only a small proportion of OHCA survivors were treated with MCS, which is consistent with prior studies.^{20–28} This is despite the hemodynamic benefits and several published series demonstrating feasibility of this strategy.^{16,29–31} Furthermore, Impella[®] was used much less frequently than IABP. Indications for these devices may also limit their use. While Impella[®] provides a more robust cardiac output than IABP, unless an RV specific device is used, it does not support RV dysfunction. IABP also does not provide support of RV dysfunction. The infrequent use of these devices, may be due to the invasive nature of larger-bore catheter insertion (for Impella[®], 13 or 14 French; for IABP, 8 French), and higher complication rates of Impella[®] compared to IABP.^{21,32–35} Patients with OHCA may be at particularly high risk of vascular access site complications in general, and specifically with larger bore cannulation.^{3,18}

Until recently, the mortality rate for cardiogenic shock associated with acute myocardial infarction has been a disappointing 50%, despite aggressive emergency care including primary percutaneous coronary intervention.^{33,34} Use of MCS in cardiogenic shock has been the subject of numerous clinical trials of various devices. The randomized IABP-SHOCK II trial demonstrated no improvement in survival in patients with acute myocardial infarction complicated by cardiogenic shock who were treated with IABP versus medical therapy.³⁶ The Impella[®] device has demonstrated the ability to generate greater augmentation of cardiac output and cardiac power output than IABP.³⁷ However, randomized controlled trials comparing the two devices have failed to show improved survival with Impella[®] versus IABP.^{21,22} More recently, the National Cardiogenic Shock Initiative, a multi-center registry study employing an algorithm

emphasizing invasive hemodynamic monitoring in patients with acute myocardial infarction and cardiogenic shock and early use of Impella demonstrated a survival benefit of 72%. This represents a considerable improvement relative to historic data.⁸ Given the inherent limitations of registry studies, randomized trials are needed to further explore this potential benefit.

Limitations

Despite our use of one of the largest datasets on this topic in the literature which included four years of data from a moderately large state, we were still limited by the low frequency of MCS use in our patient population. This finding is striking, given the high incidence of post-arrest myocardial dysfunction, and raises questions regarding the barriers to MCS use in this population. IABP was used more frequently than the Impella[®] but IABP use was only used in 4.8% of cases and Impella[®] use was only used in 1.3% of cases. Our analysis did not capture specific reason for MCS use or lack thereof, including whether or not the patient was in cardiogenic shock (beyond ICD 9 or 10 coding), or may not have been used (i.e. patient deemed irrecoverable or having a contraindication to device placement). We also cannot exclude the impact of selection bias regarding perceived pre-arrest quality of life or potential patient outcome on device utilization. In addition, CARES and MIDB did not include data on whether MCS devices were inserted in the setting of refractory cardiac arrest (salvage cases), or whether all patients had spontaneous circulation prior to proceeding with device implant. We believe use during refractory cardiac arrest would be unusual.

Table 3 – Multivariable multilevel models estimating the odds of survival to discharge as a function of MCS in the entire cohort (n = 3790) and cardiogenic shock subgroup (n = 725).

Variables	Entire Cohort ^a		Cardiogenic Shock Subgroup ^a	
	Adjusted OR	95% CI	Adjusted OR	95% CI
MCS				
No	Ref		Ref	
Yes	0.95	(0.69–1.31)	1.14	(0.74–1.77)
Age, years	0.98	(0.98 – 0.99)	0.99	(0.98–1.00)
Gender				
Male	Ref		Ref	
Female	0.82	(0.70 – 0.97)	0.90	(0.60–1.34)
Arrest Location Type				
Private Residence	Ref		Ref	
Public	1.92	(1.57–2.34)	1.81	(1.20–2.74)
Health Facility	1.42	(1.12–1.80)	1.68	(0.85–3.34)
Arrest Witness Status				
Unwitnessed	Ref		Ref	
Bystander	1.56	(1.30–1.88)	1.40	(0.92–2.12)
911 Responder	2.66	(2.11–3.37)	2.30	(1.32–3.99)
CPR				
No Bystander	Ref		Ref	
Bystander	1.27	(1.05–1.52)	1.12	(0.75–1.68)
Initial Rhythm Type				
Non-Shockable	Ref		Ref	
Shockable	4.86	(4.11–5.75)	4.27	(2.91–6.27)
Adjusted R ²	0.20		0.19	
Concordance Correlation	0.33		0.30	

Abbreviations: MCS = intra-aortic balloon pump (IABP) or percutaneous left ventricular device (Impella); CPR = cardiopulmonary resuscitation; OR = odds ratio; CI = confidence interval; Ref = reference value.

^a Multivariable multilevel analyses were controlling for the clustering of patients within hospitals. The corresponding R² and concordance correlation coefficient were calculated to assess goodness-of-fit used in generalized linear mixed-effects models.³⁸

The low rate of MCS device use limited our ability to use a more meaningful outcome such as discharge with good neurologic outcome. The infrequent use of MCS could have also negatively impacted our findings as less experience with implementation of these devices could have led to increased risk of complications and poor patient outcomes. The limitation that we encountered with sparse data despite use of a large dataset reinforces the need for prospective randomized controlled trials. Further work should also assess systemic barriers to MCS placement.

Another limitation of this study is that we used databases, which are limited in their ability to parse out clinical decision making. Other limitations with using databases are that our datasets used only ICD 9 and 10 codes which suffer from the typical limits of coding of diagnostic entities and may underrepresent new procedures such as Impella[®]. We would also assume that retrospective ICD coding may have misclassified some patients that were in cardiogenic shock yet not identified as such. Our study design did not allow for capture of in hospital hemodynamic and other clinical variables such as patient selection criteria for MCS use. If critically ill patients were more likely to be treated with MCS, the selection bias would have likely negatively skewed our findings. Information on time from arrest and time to MCS intervention was also not possible to obtain as time to therapy may have impacted outcomes.

Conclusion

Use of MCS either IABP or Impella[®] was infrequent in this large sample of OHCA patients. After adjusting for relevant covariates, MCS

use was not associated with an independent improvement in post-arrest survival in either the entire cohort or the subset of patients in cardiogenic shock. This study supports the need for further research to evaluate the benefits of these devices in patients successfully resuscitated from OHCA.

Author credit statement

J. Tram: Conceptualization, writing-original draft, Writing, reviewing, editing R. Swor: Conceptualization, Methodology, Writing reviewing editing; Funding acquisition; D. Berger, Funding acquisition; N. Chen, methodology, statistical analysis; A. Pressman, D. Berger, R. Welch, J. Reynolds, I. Hanson, J. Miller, J. Pribble. Writing- reviewing and editing.

Conflict of interest statement

The authors attest that they have no financial or other conflicts of interest with this work.

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