Title: Survival Outcomes of In-Hospital Cardiac Arrest in Pediatric Patients in the United States

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Abstract:

We report on in-hospital cardiac arrest outcomes in the United States. The data were obtained from the National (Nationwide) Inpatient Sample datasets for the years 2000–2017, which includes data from participating hospitals in 47 US states and the District of Columbia. We included pediatric patients (< 18 years of age) with cardiac arrest and we excluded patients with no cardiopulmonary resuscitation during the hospitalization. Primary outcome of the study was in-hospital mortality after cardiac arrest and the trend overtime. A multivariable logistic

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regression was performed to identify factors associated with survival. A total of 20,654 patients were identified, 8226 (39.82%) patients survived to discharge. The median length of stay and cost of hospitalization were significantly higher in the survivors vs. Non- survivors (LOS 18 days vs. 1 day, and cost $187,434 vs. $45,811, respectively, $p < 0.001$). In a multivariable model, patients admitted to teaching hospitals, elective admissions and those admitted on weekdays had higher survival (aOR=1.19, CI: 1.06–1.33, aOR=2.65, CI: 2.37–2.97 and aOR=1.17, CI: 1.07–1.27, respectively). Acute renal failure was associated with decrease in survival (aOR=0.66, CI: 0.60–0.73). There was no difference in mortality between patients with Extracorporeal CardioPulmonary Resuscitation (E-CPR) and those with conventional CardioPulmonary Resuscitation. E-CPR patients were likely to have congenital heart surgery (51.0% vs. 20.8%).

Key words: cardiac arrest; cardiopulmonary resuscitation; pediatric; survival; extracorporeal membrane oxygenation

List of Abbreviations:

ECPR: Extracorporeal CardioPulmonary Resuscitation.

ECMO: ExtraCorporeal Membrane Oxygenation.

HCUP: Healthcare Cost and Utilization Project.

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification.

ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification.

CPR: CardioPulmonary Resuscitation.

LOS: Length Of hospital Stay.

CHD: Congenital Heart Disease.

IQR: InterQuartile Range.

ELSO: Extracorporeal Life Support Organization

Introduction:

The average annual incidence of pediatric cardiac arrest in the United States is estimated to be 19,900 cases (1). Despite a half-century of pediatric-specific resuscitation guidelines being available and published regularly by the American Heart Association, the morbidity and mortality associated with these events and their burden on the hospital resources remain tremendous (2,3). Therefore, the need to analyze and gain knowledge from these events at institutional and national levels becomes paramount to improving pediatric cardiac arrest outcomes. A decade ago, the American Heart Association set an impact goal to increase survival by two-fold by 2020. Studies of pediatric in-hospital cardiac arrest (IHCA) were mainly based on retrospective single-institution studies, and very few large-scale multicenter studies reported the outcomes and predictors for survival in pediatric in-hospital cardiac arrest (2-6). Much remains unknown about the characteristics of survivors and non-survivors of IHCS and those who received Extracorporeal CardioPulmonary Resuscitation (ECPR). To help filling in the unknown, we utilized an extensive national database that spans over two decades and analyzed the data of more than twenty thousand patients with pediatric in-hospital cardiac arrest. Our objectives are to report on survival rates and trends in survival over two decades; correlate patient and hospital characteristics with IHCA outcomes; and report on ECPR utilization and its outcomes over time and compare ECPR and conventional CPR patients. We hypothesize that utilizing an extensive large national database with a wide range of practice variations would allow us to evaluate our objectives in-hospital cardiac arrests' national survival rates and trends in survival over time; correlate patient and hospital characteristics with IHCA outcomes; and determine the trends of extracorporeal membrane oxygenation (ECMO) utilization and its outcomes.

Methods:

The data were obtained from the National (Nationwide) Inpatient Sample, part of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality. This is the largest publicly available all-payer inpatient care database in the United States, containing data from more than seven million hospital stays each year (7). The National Inpatient Sample database randomly samples 20% of the discharges from participating hospitals in 47 US states and the District of Columbia. The sampling method provides a geographically distributed sample that represents all inpatient admissions in the nation. The use of data from approved public datasets is not considered human subject research; the study was granted exempt status from the Cleveland Clinic Institutional Review Board.

The study population was identified using the International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9&10-CM). Data were queried from the years 2000–2017. Pediatric patients (≤18 years of age) who had cardiac arrest during their in-hospital stay between January 1, 2000, and December 31, 2017, were included. Cardiac arrest was defined as a primary or secondary diagnosis of cardiac arrest (ICD codes 427.5, I46.2, I46.8, I46.9) or ventricular fibrillation (ICD codes 427.41, I49.01). To distinguish between in-hospital and out-of-hospital CA, we excluded patients with no cardiopulmonary resuscitation (CPR) procedure during the hospitalization. Patients were divided into two groups, survivors and non-survivors. We collected patient demographics, hospital-level data (location of the hospital, type of hospital, bed size of the hospital, the region of the hospital), type of admission (elective or non-elective), and day of admission (weekday versus weekend).

Outcomes measured were in-hospital mortality, length of hospital stay (LOS), and cost of hospitalization. Medical cardiac conditions compiled into one category included myocarditis, pulmonary heart disease, heart failure, acute myocardial infarction, hypertrophic cardiomyopathy, cardiogenic shock, cardiac tamponade, Marfan syndrome, and coronary artery anomalies. The arrhythmias group included heart block, sinus node dysfunction, long QT dysfunction, Wolff-Parkinson-White syndrome, and conduction disorders. To identify patients with congenital heart surgery, we used ICD-9 and ICD-10 procedural codes for congenital heart surgery operations, patients were included in the congenital heart disease (CHD) group if they received the procedure during the hospitalization. We also examined survival of inpatient cardiac arrest in the CHD group over the years of the study.

We also included secondary analysis of the use of ECMO at the time of CPR. For this analysis, patients were divided into two groups, CPR with ECMO (ECPR) and CPR without ECMO. For the multivariable regression analysis, we first compiled a list of clinically important potential predictors of in-hospital survival after cardiac arrest, which included both patient and hospital characteristics as demographics, clinical diagnoses, ECMO utilization and hospital teaching status. A univariate analysis was initially performed, followed by multivariable analysis incorporating variables with significance ($p < 0.2$) using a logistic regression model. Because of the limited information we can gather from this database, this study did not have details about the location and duration of cardiopulmonary resuscitation provided, medications administered during CPR and hemodynamic data.

Statistical Analysis

Continuous variables were described using median and interquartile range (IQR). Categorical variables were described using frequencies and percentages. Demographics, clinical characteristics, and outcomes were compared using Mann-Whitney U test for continuous variables and Chi-square or Fisher's exact tests for categorical variables. The non-parametric Jonckheere-Terpstra test was used to study the trends of in-hospital cardiac arrest survival, ECPR, and survival in congenital heart disease surgical patients with in-hospital cardiac arrest. Statistical significance was set at $p < 0.05$. The statistical analysis was performed utilizing SPSS software, version 25 (SPSS Inc., Chicago, IL).

Results

Characteristics of the study population (Supplemental Table 1):

A total of 20,654 pediatric cases with in-hospital cardiac arrest were identified. Of those, 8226 (39.82%) patients survived. Patients were mostly males (11,366, 55.1%) and white (7738, 42.7%). Infants (7861, 38.1%) were the most common age group in the study followed by toddlers (4891, 23.7%), adolescents (4862, 23.5%), and school age children (3040, 14.7%). Most of the cases were admitted non-electively (17,006, 87.2%) versus 2493 elective admissions (12.8%). Cases were mainly admitted to hospitals: with large bed sizes (10,941, 67.2%), that are mainly urban teaching hospitals (14,319, 88%) with a large percentage of these hospitals located in the southern region of the US (6350, 38.9%).

Characterestics of survivors versus non-survivors (Table 1):

The median LOS and the median cost of hospitalization were significantly higher in the survivor group compared to the non-survivor group (LOS 18 days vs. 1 day, and cost $187,434 vs. $45,811, respectively, p < 0.001). The following were present more frequently in the survivor group versus the non survivors, respiratory diagnoses including asthma (survivors 7.7% vs. non survivors 6%, OR = 1.32; 95% CI: 1.18–1.47; p < 0.001), pneumonia (survivors 29.6% vs. non survivors 14.6%, OR = 2.45; 95% CI: 2.29–2.63; p < 0.001), and respiratory failure (survivors 62.6% vs. non survivors 49.8%, OR = 1.69; 95% CI: 1.60–1.79; p < 0.001) as well as congenital heart diseases (survivors 30.6% vs. non survivors 18.4%, OR = 1.95; 95% CI: 1.83–2.08; p < 0.001). Anoxic brain damage was less likely to be found in the survivors group compared to non survivors (14.4% vs. 23.8%, OR = 0.54; 95% CI: 0.50–0.58; p < 0.001).

Regression analysis for characteristics of survival vs non-survivals (Table 2):

A univariate analysis followed by a multivariable regression analysis were performed to further analyze the dynamics between survival characteristics. The following patient characteristics were found to be associated with higher survival rates: age < 1 year (aOR=1.43), White race (aOR=1.14), asthma diagnosis (aOR=1.25), pneumonia (aOR=2.84), patients with congenital heart disease (aOR=1.59), cardiomyopathy (aOR=1.94) and arrhythmias (aOR=1.3). Post arrest acute renal failure was associated with decrease in survival (aOR=0.66). Patients admitted to teaching hospitals, elective admissions and those admitted on a weekday have better survival (aOR=1.19, aOR=2.65 and aOR=1.17, respectively)

Outcomes of CPR with ECMO (ECPR) versus CPR without ECMO (Table 3):

Despite having no statistically significant difference in mortality between patients with ECPR and those with CPR without ECMO (59.7% vs. 60.2%, OR = 0.98; 95% CI: 0.88–1.08; p < 0.681), patients with ECPR had longer median LOS (14 days vs. 4 days; p < 0.001) and a much higher median cost of hospitalization ($327,515 vs. $66,681, p < 0.001). ECPR patients were also likely to have congenital heart diseases (51.0% vs. 20.8%, OR = 3.96; 95% CI: 3.57–4.38; p < 0.001), cardiomyopathy (14.3% vs. 4.5%, OR = 3.54; 95% CI: 3.04–4.13; p < 0.001), stroke (Post ECPR diagnoses) (21.0% vs. 4.5%, OR = 5.67; 95% CI: 4.95–6.50; p < 0.001). Patient who underwent ECPR were more likely to have cardiac interventions like cardiac catheterization (20.2% vs. 4.9%, OR = 4.97; 95% CI: 4.33–5.69; $p < 0.681$) and heart transplantation (3.4% vs. 0.3%, OR = 13.14; 95% CI: 8.9–19.30; $p < 0.001$).

Throughout the years of the study, there were significant trends of increasing survival after in-hospital cardiac arrest and an increased trend of utilizing ECPR (Std. J-T Statistic = 3.184, and Std. J-T Statistic = 3.371, respectively, p = 0.001) (Figures 1 and 2). Additionally, the group with CHD had a sharp rise in survival rates throughout the years of the study (Figure 3).

Discussion:

In-hospital pediatric cardiac arrest occurs in 2-6% of pediatric intensive care admissions (8-10). Despite the improvement in resuscitation science and practice over the last two decades (11), cardiac arrests had an impact on hospital resources and a significantly high mortality rate. This study is one of the largest studies to date of pediatric IHCA survival outcomes and trend of survival over two decades. We report that survival to discharge in pediatric IHCA was 39.8% with a steady increase in patients' survival with in-hospital cardiac arrest between 2000 and 2017 (survival rate was 30% in 2000 and 44% in 2017). Our study results are consistent with Holmberg and colleagues' recent study examined the survival trends after pediatric in-hospital cardiac arrest in the United States between 2000 and 2018. The survival trend for pulseless cardiac arrest increased from 19% in 2000 to 38% in 2018. This improvement in survival in both studies is probably multifactorial and may be attributed to earlier recognition and management of at-risk patients, greater emphasis on quality of resuscitation (e.g., high-quality chest compressions with minimal interruptions), use of ECPR, post-resuscitation bundle care (e.g., multidisciplinary care) (12-16) and enhanced critical care staffing, with the majority of intensive care units implementing a 24-hour in-hospital pediatric critical care attending physician presence (14)

In term of patient characteristics and outcome, patient who were < 1 year of age or white race had higher survival rates. Patient diagnoses that were associated with the highest survival rates were pneumonia, congenital heart disease, and cardiomyopathy. Post-arrest acute renal failure was associated with a significant negative impact on survival. While total reported survival to hospital discharge for pediatric in-hospital cardiac arrest over the 18 years of the study is 39.8%, this rate is inversely related to age groups; the younger the age group, the better the survival rate. Infants had a survival rate of 47.5% versus the adolescent age group, who had a survival rate of 26.89%. This almost two-fold difference in survival is likely multifactorial, the underlying difference in disease process, the higher prevalence of congenital heart diseases in infants that comprised one-quarter of the study population that has a higher survival rate. Large proportion of the infant with congenital heart surgery needed ECPR compared to adolescents. Additionally, many of the infant age group had a respiratory- induced cardiac arrest that could quickly resolve with the prompt initiation of CPR and assisted ventilation. (17). A study by Bernes and colleagues found that respiratory induced cardiac arrest had a higher probability of survival if a return of spontaneous circulation occurred in the first few minutes of CPR (18). Studies have shown that the probability of survival depends mostly on the etiology of cardiac arrest in pediatric patients (19), and that respiratory induced cardiac arrest had a higher probability of survival if a return of spontaneous circulation occurred in the first few minutes of CPR (18). While our study does not differentiate between bradycardia with pulseless bradycardia versus bradycardia with poor perfusion, studies reported that among hospitalized children in whom CPR is initiated; half have bradycardia with poor perfusion at the initiation of chest compressions **(PMID: 31006260).** And that children with bradycardia and poor perfusion were younger more likely to survive to hospital discharge **(PMID: 32301844).**

Regarding hospital characteristics and outcome, patients admitted to teaching hospitals, elective admissions, and weekday admissions (Monday to Friday) were also associated with higher survival rates. Similar to previous reports, we found that in-hospital cardiac arrest occurring during weekends were associated with worse outcomes (20-22). This can be attributed to the implementation of early warning systems on the pediatric floors leading to early transfer of hemodynamically unstable patients to intensive care units, and decrease in in-hospital cardiac arrest frequency outside of the intensive care unit (16).

In this study, we reported that the use of rescue extracorporeal cardiopulmonary resuscitation in refractory cardiac arrest has increased by three folds, where more than 50% of the ECPR event were performed in patients with CHD. Previous studies showed that the use of ECPR is associated with improved survival and neurological outcomes in in-hospital pediatric cardiac arrest (13). In the most recent years of our study, ECPR was utilized in 12% of the patients. In total, 1670 patients with in-hospital cardiac arrest had received ECMO support. In our study, mortality in patients receiving ECPR was still high (59.7%). There were 673 patients (3.26%) whose survival was salvaged with utilization of ECPR; this could be a contributing factor to the improved overall survival we see over the years of the study. A study by Barbaro evaluated the use of ECPR in infants and children between 2009 and 2015 using the Extracorporeal Life Support Organization (ELSO) registry (12); there was a 63.8% increase in the number of ECPR throughout the study period. Another study by Bambea using Get With The Guidelines®-Resuscitation registry evaluated 593 ECPR cases linked to the ELSO registry (23). Mortality in the ECPR group in Bambea's study was 59.4%; these results are very similar to the mortality we reported in our study's ECPR group (59.7%). We reported an ECPR rate of 17.7% in patients with congenital heart surgery, other had reported similar rates (24).

Limitations: This study's findings should be interpreted with some caution as some limitations are inherent to studies using administrative databases. We used ICD-9 and ICD-10 codes to identify diagnoses and procedures which likely led to under identification of cardiac arrest cases. The database does not include details about the location and duration of cardiopulmonary resuscitation provided (initial rhythm, medications administered, duration of CPR, hemodynamic data, the success of reperfusion therapy). While this study advantage is the sample size, major limitation is lack ability to identify patients with co-existent conditions and differentiate pre-arrest patient characteristics and post arrest findings. The study also could not identify patients with a single cardiac arrest event versus multiple events during the same hospitalization. This study lacks data on the neurological function and cerebral performance category at discharge, and the results were limited to inpatient outcomes and lacked longer-term follow-up information.

Conclusion: We reported national survival outcomes and trends over two decades of in-hospital pediatric cardiac arrest, and we highlighted patient and hospital characteristics of survivors and non-survivorsThe results of this study can guide developing future studies aimed at improving outcomes in pediatric cardiac arrest.

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Figure legends:

Figure 1. Trend of survival after in-hospital cardiac arrest over the years.

Figure 2. Trend of Extracorporeal CardioPulmonary Resuscitation (ECMO-CPR) over the years.

Figure 3. Trend of survival after in-hospital cardiac arrest in pediatric patients with congenital heart disease