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Research Article

Factors Influencing Survival to Hospital Discharge in Children Following In-Hospital Cardiopulmonary Arrest

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Abstract

Aim: The incidence of pediatric in-hospital cardiac arrest (IHCA) is between 2-6%. There is significant morbidity and mortality associated with these events which leads to tremendous burden on the hospital resources. It is necessary to fully analyze these events. This study aimed at evaluating the survival predictors after in-hospital pediatric cardiac arrest. **Methods**: Patients aged <18 years who received cardiopulmonary resuscitation (CPR) for > 1 min during their hospital stay between June 1, 2015, and May 31, 2020, were included. We examined the pre arrest, intra arrest, and post arrest factors. Analysis of risk factors between survivors and non-survivors to discharge was performed on a complete-case basis and all tests were two-tailed and performed at a significance level of 0.05. **Results:** Of the 144 cardiac arrest events included in the study, the survival to hospital discharge was 58%. Pre-arrest factors associated with survival in the univariate model were median age < 1-year, female sex, and factors associated with lower survival were hematological/oncological disease, cyanotic congenital heart disease, and presence of central and arterial lines. In a multivariable regression model, the following factors were associated with mortality: CPR duration > 14 minutes (aOR 12.3, 95% CI-4.8-31.5, p<0.001), serum lactate > 8 mg/dl (aOR 10, 95% CI, 2.7-38.7; p<0.001), number of epinephrine doses (aOR 1.24, 95% CI-1.13-1.37, p<0.001), number of sodium bicarbonate doses (aOR 1.81, 95% CI-0.6- 2.7, p<0.001), and fluid administration (aOR 1.06, 95% CI-1.03-1.09, p<0.001), all with p-values <0.001. **Conclusion:** We identified modifiable factors in in-hospital cardiac arrest associated with survival: fewer doses of epinephrine, CPR duration <14 minutes, fluid boluses < 10 ml/kg, inciting event of arrest due to bradycardia or hypoxia from respiratory failure, post arrest serum lactate level <8 mg/dl, and fewer doses of sodium bicarbonate. Considering these factors during resuscitation could aid healthcare practitioners in predicting children at risk of poor prognosis, allowing appropriate treatment decisions, improving resuscitation methods, and counseling families.

Keywords: Cardiac arrest; Cardiopulmonary resuscitation; Pediatric intensive care; Outcomes

Abbreviations

CPR: Cardiopulmonary Resuscitation

ECMO: Extra Corporeal Membrane Oxygenation

$ETCO_2$: End tidal carbon dioxide

IHCA: In Hospital Cardiac Arrest

PEA: Pulseless Electrical Activity

VF: Ventricular Fibrillation

VT: Ventricular Tachycardia

Introduction

In the United States, approximately 15,200 children experience in-hospital cardiac arrest (IHCA) each year [1]. There has been a substantial improvement in pediatric IHCA, with a current survival of 28 – 30% [2]. This improvement in survival over the past 18 years is in part due to the improved quality of resuscitation practices, such as high-quality chest compressions with minimal interruptions, use of extracorporeal membrane oxygenation during resuscitation, and post-resuscitation care [1]. A detailed analysis of peri-arrest management is necessary, as it is associated with high mortality and morbidity and places a heavy burden on hospitals [3]. IHCA occurs more frequently in intensive care units despite being highly monitored because of the severity of illness. It is likely that advanced hemodynamic monitoring devices were already in place at the time of the arrest.

Intensivists can adjust their resuscitation efforts during the intra-arrest period based on the patient's underlying physiological data, such as diastolic blood pressure and end-tidal carbon dioxide ($ETCO_2$) [4-6]. There is little guidance [7-9] in terms of the utilization of these tools during resuscitation.

This study aimed to identify factors associated with survival to hospital discharge after an in-hospital cardiac arrest (IHCA), including pre-arrest, intra-arrest, and post-arrest factors.

Methods

Design and Setting

Following Institutional Review Board (IRB) approval (Study ID 21-062), this retrospective single-center study identified pediatric patients with cardiopulmonary arrest at the Cleveland Clinic Children's (Cleveland, OH) Pediatric Cardiac Resuscitation Review Committee records. We included patients (age 0 – 18 years) who received cardiopulmonary resuscitation for > 1 min (defined as requiring manual CPR and/or defibrillation) between June 1, 2015, and May 31, 2020, at our institution. Newborn resuscitation in the delivery room, patients with "do not attempt resuscitation" orders, and those with out-of-hospital resuscitation performed during transport by the emergency medical service or in the emergency room were excluded.

Data Collection

All data were collected from patients' electronic medical records and entered into the Cleveland Clinic's Research Electronic Data Capture (REDCap®). Pre-arrest characteristics included patient demographics, comorbid conditions present prior to resuscitation, admission diagnosis, presence of invasive lines or endotracheal tubes prior to cardiac arrest, and location of cardiac arrest. Intra-arrest details included inciting event to cardiac arrest, duration of CPR, number of defibrillation attempts, utilization of Extracorporeal Membrane Oxygenation (ECMO) in the resuscitation event, and hemodynamic parameters including systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, oxygen saturation, medications, blood products and fluid administered during resuscitation, placement of intravenous catheters, intraosseous lines, invasive lines, intubation, and chest tube during resuscitation. Post-resuscitative care details included the use of therapeutic hypothermia, treatment of status epilepticus, fluid balance for 48 hours, duration of ECMO, and utilization of continuous renal replacement therapy.

Definitions

Initial arrest rhythm was categorized as bradycardia, pulseless electrical activity (PEA), ventricular tachycardia/ fibrillation (VF/VT), asystole, or unknown. Medications administered included epinephrine dose per 5 min of cardiac arrest time, sodium bicarbonate dose per 5 min of cardiac arrest time, and calcium gluconate dose per 5 min of cardiac arrest time. The location of arrest was categorized as pediatric ICU, Floor, neonatal ICU, and Operation theater. Inciting events such as hypoxia due to lung disease and hypoxia due to airway issues categorized as respiratory-induced cardiac arrest, bradycardia, and hypotension were categorized as cardiac-induced cardiac arrest.

Statistical analysis

Clinical characteristics were described using medians with 25th and 75th percentiles for continuous variables, and absolute counts with percentages for categorical variables. Univariate associations between these characteristics and the outcomes were examined using the Wilcoxon rank-sum test for continuous or ordinal characteristics and Pearson's chi-square test or Fisher's exact test for categorical characteristics, as appropriate. Factors with low prevalence (< 5%) were excluded. Logistic regression models were used to estimate the odds ratios and 95% confidence intervals. For these models, the clinical characteristics that had a univariate p-value <0.1 were entered into the model using a backward selection approach, and only those with a p < 0.05 were retained in the final model. All tests were two-tailed and were performed at an overall significance level of 0.05. SAS software (version 9.4; SAS Institute, Cary, NC, USA) was used for all analyses and plots.

Results

In total, 144 cardiac arrest events were included in this study. The survival to hospital discharge rate was 58%. Patient characteristics and univariate comparisons of pre-arrest factors between survivors and non-survivors are shown in (Table 1a and 1b). Pre-arrest factors that were significantly higher in survivors and non-survivors were age < 1 year (69% *vs.* 56%; p=0.045) and female sex (61% *vs.* 42%; p=0.019). Lower survival rates among survivors as compared to non-survivors were noted among patients with hematological/oncological disorders [1 (1.2%) *vs.* 6 (9.8%), p= 0.042], cyanotic congenital cardiac disease [11 (14%) *vs.* 18 (32%), p= 0.011], and those with advanced monitoring, such as arterial line [30 (25%) *vs.* 13 (62%), p=0.001] and central line [31 (25%) *vs.* 38 (63%), p = 0.002].

Pre-arrest Factor	**Total** (N=144)	**Survivors** (N=83)	**Non-survivors** (N=61)	**p-value**
Age (years)				***0.045*** [b]
< 1	91 (63)	57 (69)	34 (56)	
1-10	33 (23)	20 (24)	13 (21)	
11-18	20 (14)	6 (7.2)	14 (23)	
Gender				***0.019*** [c]
Female	76 (53)	51 (61)	25 (42)	
Male	67 (47)	32 (39)	35 (58)	
Weight (kilograms)	5.3 [3.0, 15]	5.3 [3.5, 10]	5.3 [2.6, 26]	0.80 [b]
Comorbidities prior to CPR				
Neurological	39 (27)	23(28)	16(26)	0.84 [c]
Respiratory	87 (60)	49 (59)	38 (62)	0.69 [c]
GI	12 (8.3)	7 (8.4)	5 (8.2)	0.96 [c]
Renal	5 (3.5)	1 (1.2)	4 (6.6)	0.16 [d]
Hematological	7 (4.9)	1 (1.2)	6 (9.8)	***0.042*** [d]
Infection	5 (3.5)	2 (2.4)	3 (4.9)	0.65 [d]
Cardiovascular	66 (46)	34 (41)	32 (52)	0.17 [c]
Cyanotic cardiac lesion	29 (21)	11 (14)	18 (32)	***0.011*** [c]
Access at the time of CPR				
Peripheral IV	133(95)	78(96)	55(93)	0.45 [d]
Arterial Line	44 (31)	17 (20)	27 (46)	***0.001*** [c]
Central line present at the initiation of CPR	69 (48)	31 (37)	38 (63)	***0.002*** [c]

Table 1: Pre-arrest factors and association with survival to hospital discharge; p-values: b = Wilcoxon Rank Sum test, c = Pearson's chi-square test, d = Fisher's Exact test.

(Table 2) shows the univariate comparison of intra-arrest factors between survivors and non-survivors. Systolic blood pressure >80 mmHg and diastolic blood pressure >40 mmHg was more frequent in survivors than in non-survivors [17/37 (46%) *vs.* 9/35 (26%), p=0.074 and 17/37 (46%) *vs.* 10/35 (29%), p=0.12, respectively]. End-tidal CO_2 was documented in 11/144 (7.6%) patients, and there was no significant difference between the end-tidal CO_2 measurements of survivors and non-survivors.

Intra arrest Factor	**Total (N=144)**	**Survivors (N=83)**	**Non-survivors (N=61)**	**p-value**
Inciting event to cardiac arrest				***0.002***[c]
Respiratory induced cardiac arrest				
hypoxia with lung disease	27 (19)	13 (16)	14 (23)	
hypoxia with airway problem	14 (9.8)	12 (14)	2 (3.3)	
Cardiac induced cardiac arrest				
bradycardia	62 (43)	41 (49)	21 (35)	
hypotension	29 (20)	9 (11)	20 (33)	
Other	11 (7.7)	8 (9.6)	3 (5.0)	
Duration of CPR (min)	8.0 [4.0, 30]	5.0 [4.0, 9.0]	30 [14, 50]	***<0.001***[b]
Duration of CPR (min) -- recreated based upon continuous CPR in REDCap				***<0.001***[b]
0-14	87 (61)	71 (86)	16 (27)	
15-29	17 (12)	4 (4.8)	13 (22)	
30-44	15 (10)	2 (2.4)	13 (22)	
≥45	24 (17)	6 (7.2)	18 (30)	
Median SBP				0.074[c]
>80	26 (36)	17 (46)	9 (26)	
≤80	46 (64)	20 (54)	26 (74)	
Median DBP				0.13[c]
>40	27 (38)	17 (46)	10 (29)	
≤40	45 (63)	20 (54)	25 (71)	
Median lactate				***<0.001***[b]
0-2	38 (33)	31 (48)	7 (14)	
2<-8	37 (32)	21 (32)	16 (31)	
>8	41 (35)	13 (20)	28 (55)	
Median endtidal CO2				0.56[d]
>20	7 (54)	3 (75)	4 (44)	
≤20	6 (46)	1 (25)	5 (56)	
Median O_2 saturation < 60				0.13[c]
>60	77 (62)	50 (68)	27 (54)	
≤60	47 (38)	24 (32)	23 (46)	
Location of CPR				***0.038***[d]
PICU	102 (71)	60 (73)	42 (69)	

NICU	25 (17)	9 (11)	16 (26)	
OR	6 (4.2)	5 (6.1)	1 (1.6)	
Other	10 (7.0)	8 (9.8)	2 (3.3)	
ECMO- CPR	21 (15)	8 (10)	13 (22)	0.056[c]
Duration of ECMO (Hrs)	96 [72, 144]	72 [72, 96]	144 [96, 144]	0.25[b]
Standardized epinephrine doses (doses/5 min)	1.2 [0.71, 1.7]	1.3 [0.57, 1.7]	1.1 [0.87, 1.7]	0.29[b]
Standardized sodium bicarbonate doses (doses/5 min)	0 [0, 0.22]	0 [0, 0]	0.18 [0, 0.31]	***<0.001[b]***
Total no. of doses of epinephrine administered during entire CPR	2.0 [1.0, 8.0]	1.0 [1.0, 2.0]	7.5 [2.5, 12]	***<0.001[b]***
Total amount of fluids administered during CPR (ml/kg)	0 [0, 17]	0 [0, 0]	10 [0, 30]	***<0.001[b]***
Total no. of sodium bicarbonate administered in CPR	0 [0, 1.0]	0 [0, 0]	1.0 [0, 3.0]	***<0.001[b]***

Table 2: Intra-arrest factors and associations with survival to hospital discharge; Standardized epinephrine doses (doses/5 min) = 1; Standardized sodium bicarbonate doses (doses/5 min) = 3; Total no. of doses of epinephrine administered during entire CPR = 1; Total amount of fluids administered during CPR (ml/kg) = 2; Total no. of sodium bicarbonate administered in cpr = 3; Statistics presented as Median [P25, P75], N (column %); p-values: b=Wilcoxon Rank Sum test, c=Pearson's chi-square test, d=Fisher's Exact test.

(Table 3) shows the logistic regression analysis, after adjusting for gender, cardiac history, arterial line presence and ECMO we found that CPR duration > 14 minutes (aOR 12.3, 95% CI-4.8-31.5, p<0.001), serum lactate > 8 mg/dl (aOR 10,95% CI-2.7-38.7, p<0.001), number of epinephrine doses (aOR1.24,95% CI-1.13-1.37,p<0.001), number of sodium bicarbonate (aOR1.81, 95%CI-0.6-2.7, p<0.001), fluid administration (aOR 1.06, 95% CI-1.03-1.09, p<0.001) were independently associated with in-hospital mortality. The clinical model developed to predict survival to hospital discharge had good discrimination with an AUC for significant factors namely CPR duration 0.84 (CI- 0.768-0.906), epinephrine doses 0.818 (CI-0.748-0.889), sodium bicarbonate doses 0.715 (CI-0.640-0.790), and fluid boluses 0.722 (CI=0.644-0.800) (Figure 1).

Risk factors	**OR**	**95% CI**		**p-Value**
CPR duration > 14 min *vs* 0-14 min	12.37	4.84	31.59	< 0.001
Number of epinephrine doses during CPR	1.24	1.13	1.37	< 0.001
Epinehrine doses (dose/5 min)	1.03	0.81	1.31	0.80
Sodium bicarbonate doses during CPR	1.81	1.29	2.55	< 0.001
Sodium bicarbonate doses (No. of doses/5min)	1.30	0.62	2.70	0.49
Amount of Fluid given during CPR	1.06	1.03	1.09	< 0.001
Median lactate 2mg/dl < 8mg/dl *vs* 0-2mg/dl	2.82	0.82	9.73	0.10
Median lactate >8mg/dl *vs* 0-2mg/dl	10.32	2.75	38.78	< 0.001
Median oxygen saturation <60 %	1.37	0.57	3.33	0.48
Median systolic blood pressure <80 mm of Hg	1.99	0.63	6.27	0.24
Median diastolic blood pressure <40mm of Hg	2.01	0.66	6.18	0.22

Table 3: Adjusted association between mortality before discharge and each of the following factors after adjusting for gender, cardiac history, arterial line presence and ECMO during CPR; CPR: cardiopulmonary resuscitation.

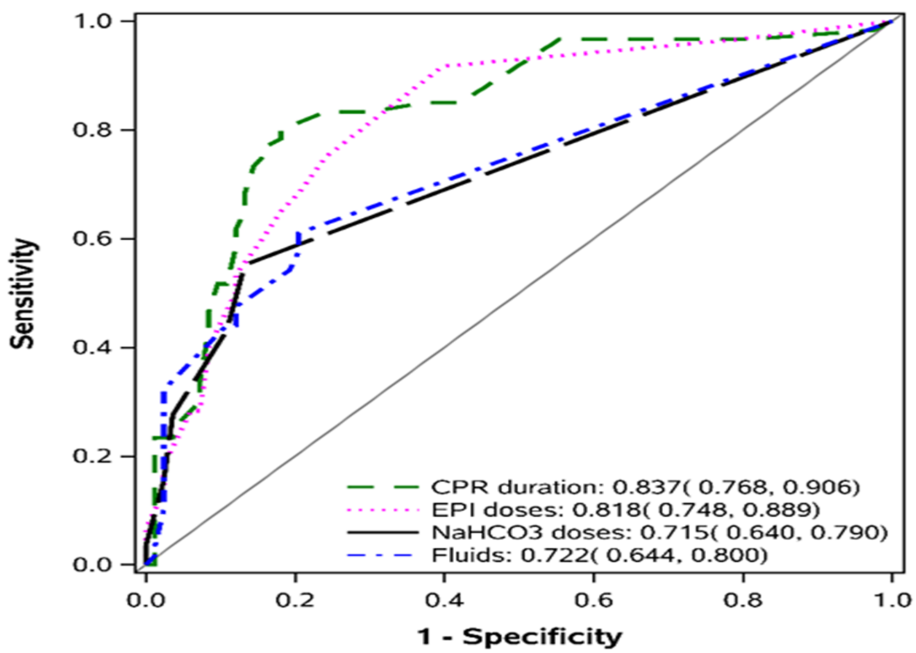

Figure 1: Validity of CPR characteristics to distinguish survivors from non-survivors: ROC Analysis (the numbers in the legend were AUC and its 95% CI)

(Supplemental Table 1) (STI) shows univariate survival associations in those with CPR duration 0-14 minutes and those with CPR duration ≥14 minutes.

Discussion

This retrospective study reports the association of pre-arrest, intra-arrest, and post-arrest factors with survival after IHCA. Pre-arrest survival factors were age < 1-year, female sex, absence of a premorbid condition associated with hematology and oncology, or cyanotic congenital heart disease. These factors are typically patient-specific and non-modifiable and are important associations that could guide clinicians in determining the expected prognosis and risk stratification.

In our study, a higher number of fluid boluses administered during intra- arrest event was associated with increased mortality. Fluids increase cardiac output during CPR by increasing coronary perfusion pressure [10,13]. The coronary perfusion pressure is the difference between aortic diastolic pressure and right ventricular end diastolic pressures [18]. It is only appropriate to administer intravenous fluid loading during CPR if therapy could increase aortic diastolic pressure rather than outflow pressure, such as right ventricular end-diastolic pressures [11,12]. An increase in outflow pressure is detrimental to tissue perfusion, as it results in a decrease in coronary perfusion pressure. Fluids are generally administered during CPR. Fluid resuscitation strategies are highly variable, given that there is little evidence and guidance for fluid therapy during resuscitation [10]. A thorough understanding of pre-arrest events would help determine an appropriate intravenous fluid strategy during resuscitation. It should be reserved only for patients with suspected or confirmed hypovolemia, hemorrhagic shock, or distributive shock.

A higher epinephrine dose administered during intra arrest event was associated with increased mortality in our study. Epinephrine increases coronary perfusion pressure, which increases the likelihood of the return of spontaneous circulation. Using further doses of epinephrine increases beta-adrenergic activity and oxygen demand, impairing myocardial function and causing ventricular tachycardia and ventricular fibrillation [16]. Pediatric resuscitation has used epinephrine for over 50 years, but there is insufficient evidence on dosing intervals or efficacy [14]. Hoyme et al [14], reports lesser doses of epinephrine and average intervals longer than 3–5 minutes were associated with improved survival to hospital discharge. Meert et al [15], noted higher dose of epinephrine was associated with mortality.

A longer CPR duration was associated with higher mortality rates in our study. Prolonged cardiac arrest results in a longer low-flow state, hypoperfusion, poor oxygen delivery, and tissue hypoxia, resulting in multi-organ dysfunction. A CPR duration >14 min was associated with a 75% mortality rate. Of the patients, 22% had respiratory-induced cardiac arrest and 70% had cardiac-induced cardiac arrest. (SI table 1). Cardiac-induced cardiac arrest is associated with a higher mortality rate. Similar findings were noted in a study by Bernes et al [18]. These differences, in part, may be related to the importance of CPR duration and its association with etiology. In contrast, Goldberg et al [17] reported patients at hospitals with longer attempts had a higher likelihood of ROSC and survival to discharge, particularly when the arrest was due to asystole and pulseless electrical activity. Matos et al [2] reported, CPR for >20 min is not futile in some patient illness categories, and CPR duration was independently associated with survival to hospital discharge. Despite the significant results of our study, we were unable to provide specific cut-off data for the termination of CPR. Some patients may require longer resuscitation than others do. Accurate identification of these patients is important to prevent the early termination of resuscitation in those who would otherwise have survived.

Limitations

This study had several limitations. This is constrained by the characteristics of retrospective chart reviews, data collection, and analysis. We considered that high-quality CPR was provided during the event with regard to compression quality and appropriate response time. There was limited statistical power owing to the small sample size. Perhaps a larger study would have provided different results regarding event survival, the association between hemodynamics and survival, or other characteristics during CPR.

Conclusions

A thorough understanding of peri-arrest factors would aid healthcare practitioners in predicting patient prognosis, making appropriate treatment decisions, improving resuscitation methods, and counseling families. Pre-arrest factors guide prognostication and risk stratification, as they are patient-specific and non-modifiable. During the intra-arrest period, a deeper understanding of the patient's physiology, cardiopulmonary interactions, appropriate medication use, and fluid resuscitation can significantly increase survival. Future research endeavors should focus on the efficacy of medications during intra arrest period, fluid resuscitation guidelines, incorporating physiological parameters into the arrest algorithm, and providing patient-centric care.

Statements

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Financial Disclosure

All authors have no financial relationships relevant to this article to disclose.

Conflict of Interest

All authors have no conflicts of interest to disclose.

Ethics approval

This is an observational study. The Research Ethics Committee of Cleveland Clinic Children's has confirmed that no ethical approval is required.

Author Contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Rashmitha Dachepally and Wei Liu. The first draft of the manuscript was written by Rashmitha Dachepally and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Consent to publish

Consent to publish has been received from all participants should appear in the manuscript.

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Factor	**> 14 min CPR** **(N non survivors = 56)**	**0-14 min CPR** **(N survival = 87)**	**p-value**
ECMO- CPR*			***<0.001[c]***
No	39 (70)	80 (95)	
Yes	17 (30)	4 (4.8)	
Congenital Heart Disease			0.14[c]
Yes	29 (52)	34 (39)	
No	27 (48)	53 (61)	
Central venous line placed during CPR			0.74[d]
Yes	4 (7.1)	5 (5.7)	
No	52 (93)	82 (94)	
Arterial Line*			***<0.001[c]***
Yes	26 (47)	18 (21)	
No	29 (53)	69 (79)	
Gender*			0.060[c]
Female	24 (44)	52 (60)	
Male	31 (56)	35 (40)	
Type of Cardiac History*(n%)			0.057[c]
Cyanotic	17 (31)	12 (15)	
Acyanotic	13 (24)	29 (35)	
Central line present at the initiation of CPR (n%)			***<0.001[c]***
Yes	40 (71)	29 (33)	
No	16 (29)	58 (67)	
Inciting event to cardiac arrest (n%)			0.003[c]

hypoxia with lung disease	11 (20)	16 (18)	
bradycardia	20 (36)	42 (48)	
hypoxia with airway problem	1 (1.8)	13 (15)	
hypotension	19 (34)	10 (11)	
Other	5 (8.9)	6 (6.9)	
Median lactate*(n%)			***<0.001*** [b]
0-2	6 (12)	32 (49)	
2<-8(n%)	15 (29)	22 (34)	
>8	30 (59)	11 (17)	
Median O_2 saturation*(n%)			0.026 [b]
0-9	1 (2.3)	3 (3.8)	
10-20	2 (4.5)	5 (6.3)	
20-40	5 (11)	3 (3.8)	
40-60	15 (34)	13 (16)	
60-80	13 (30)	28 (35)	
>80	8 (18)	28 (35)	

Supplemental Table 1: Univariate association between CPR duration and other factors univariate associated with mortality before discharge; p-values: b=Wilcoxon Rank Sum test, c=Pearson's chi-square test, d=Fisher's Exact test.