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Original paper

Duration of emergency medical services-initiated prehospital cardiopulmonary resuscitation efforts and survival for pediatric patients with out-of-hospital cardiac arrest

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Abstract

Background: While longer duration of cardiopulmonary resuscitation (CPR) is associated with unfavorable patient outcomes after pediatric out-of-hospital cardiac arrest (OHCA), it remains unclear how the probability of survival changes as a function of CPR duration.

Methods: We conducted a retrospective cohort study of the Resuscitation Outcomes Consortium Epidemiologic Registry, including consecutive patients with non-traumatic OHCA at ten regional coordinating sites in the US and Canada from 2011 to 2015. We included pediatric patients (age <18 years) with emergency medical services (EMS)-treated OHCA. The exposure was EMS-initiated prehospital CPR duration in minutes, defined as the interval between the start of chest compressions by EMS clinicians and prehospital return of spontaneous circulation (ROSC), prehospital termination of resuscitation (TOR), or hospital arrival. The outcome was survival to hospital discharge. Time-dependent probability of subsequently surviving to hospital discharge if patients with ongoing CPR at each minute received further CPR beyond that time point was estimated, assuming that all decisions on TOR prior to or at that time point were adequate.

Results: Among 1313 included patients (median [IQR] age, 1[0–9]), 236 (18.0%) achieved prehospital ROSC with a median CPR duration of 10 min (IQR 5.5–16.5 min); 1077 did not; and 136 (10.4%) survived to hospital discharge. The time-dependent probabilities of survival to hospital discharge for patients with ongoing CPR were 7.9% (95% CI: 6.4–9.3%) at 1 min and decreased to less than 1% at 14.8 min (95% CI: 11.1–22.0 min) of EMS-initiated prehospital CPR duration. The upper bound of 95% CI of the probabilities of survival decreased to less than 1% (0.86%, 95% CI: 0.34–0.94%) at 22.0 min.

Conclusion: In this North American retrospective cohort study of pediatric patients with OHCA, we quantified the time-dependent probability of survival to hospital discharge as a function of prehospital CPR duration. The findings provide EMS clinicians and patients' surrogates with objective insights into the likelihood of survival when CPR is continued beyond 15 min.

Keywords: Cardiac arrest, Out-of-hospital cardiac arrest, Pediatric cardiac arrest, Pediatric out-of-hospital cardiac arrest, Cardiopulmonary resuscitation, CPR, Duration of cardiopulmonary resuscitation, Duration of CPR, Resuscitation, Emergency medical services

Introduction

Out-of-hospital cardiac arrest (OHCA) is a major public health issue among infants, children, and adolescents, annually impacting 7000–23,000 individuals in the United States.[1,2] Among children with OHCA who undergo resuscitation attempts by emergency medical services (EMS) clinicians, a low proportion of children (7.4–18.5%) survive to hospital discharge.[1–4]

For patients with cardiac arrest, achieving prompt return of spontaneous circulation (ROSC) is the first step toward survival and functional recovery. When children do not respond to the initial

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cardiopulmonary resuscitation (CPR), one challenge lies with how long to continue CPR. The 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care report that a lack of clinical tools to help in the decision to terminate resuscitative efforts in children is a critical knowledge gap.[5] For children with cardiac arrest, previous studies have suggested that a longer duration of CPR before ROSC is associated with poor outcomes.[6–13] These prior studies were conducted in Asia,[6,8,9] or investigated pediatric patients with in-hospital cardiac arrest (IHCA).[7] Given the differences in EMS systems across nations and in characteristics between OHCA and IHCA,[6,8,9,14–17] these findings may not be generalizable to children with OHCA in North America. A dedicated North American study to quantify the probability of favorable outcomes based on the duration of CPR for pediatric OHCA is informative for EMS, in-hospital clinicians, and patients' surrogates.

We attempted to answer our research question: How does the probability of survival change as a function of EMS-initiated prehospital CPR duration? Our primary objective was to quantify the time-dependent probability of survival to hospital discharge as a function of each minute of EMS-initiated prehospital CPR duration among children with OHCA with ongoing CPR pending ROSC. Our secondary objective was to quantify the time-dependent probability of survival to hospital discharge among children who achieved ROSC prior to or at each minute.

Methods

Study design and setting

We conducted a retrospective cohort study of the Resuscitation Outcomes Consortium (ROC) Epidemiologic Registry. The ROC is a multicenter research network focusing on clinical trials in OHCA at ten regional coordinating sites in the United States and Canada.[18,19] The ROC Epidemiologic Registry-Cardiac Arrest contains information on consecutive patients with non-traumatic OHCA presenting to the study sites from 2011 to 2015. The dataset includes patient demographics, cardiac arrest characteristics, bystander and EMS interventions, and patient outcomes. Decisions for terminating resuscitation were made by treating EMS clinicians and/or online medical control, and there were not standardized criteria among the ROC EMS systems.[19,20] Additional details of the ROC data are provided in the Supplemental Methods. We used the publicly available, de-identified ROC dataset from the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center (https://biolincc.nhlbi.nih.gov/home/). The Institutional Review Board at the University of Pittsburgh deemed this study exempt from regulations related to human participant research because of the use of publicly available de-identified data. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study participants

We included pediatric patients (age <18 years) with EMS-treated OHCA, defined as resuscitation attempts with chest compressions by an EMS clinician and/or shock delivery with an external defibrillator by a bystander or EMS clinician.[19] We excluded patients who underwent termination of resuscitation (TOR) because of do-not-resuscitate orders, had missing data to classify the duration of CPR, or had missing data on survival to hospital discharge.

Exposure

The main exposure was the EMS-initiated prehospital CPR duration, defined as the interval (in minutes) between the start of chest compressions by EMS clinicians and prehospital ROSC, prehospital TOR, or hospital arrival. This encompassed any CPR performed by EMS clinicians, including CPR at the scene and during transport.

Definition and measurement of the start of chest compressions by EMS clinicians

The start of chest compressions by EMS clinicians was defined as the time when the first chest compression was applied by a responding EMS clinician who was associated with the ROC or non-ROC EMS agency.[21] When a non-ROC EMS clinician-initiated chest compressions and the start time was unknown, the start of chest compressions was recorded as unknown.[21] As this data element is a challenge to acquire, the ROC employed several methods to accurately capture the start of chest compressions by EMS clinicians.[21] The ROC sites cooperated with participating EMS agencies to standardize practices that provide accurate time documentation or surrogates for the time of the start of chest compressions by EMS clinicians, including training them to power on the defibrillator when they arrive at the patient's side and begin chest compressions.[21] The preferred source for this data element was a voice recording to capture their verbalization of the initiation of chest compressions in relation to defibrillator power on.[21] For example, "Chest compressions were started XX seconds before the defibrillator was turned on."[21] The second preferred source was the continuous electrocardiogram monitor when the arrest was witnessed by EMS.[21] The third preferred source was inferred time from the time point when the defibrillator was turned on.[21]

Outcomes

Our outcome measurement was survival to hospital discharge. A functional outcome at hospital discharge was not included as the outcome because of low reporting of this variable in the ROC dataset.

Statistical analyses

We stratified patients based on the presence or absence of prehospital ROSC and reported patient demographics, cardiac arrest characteristics, and bystander and EMS interventions.

Cumulative proportion of patients achieving prehospital ROSC over time, stratified by patients who survived to hospital discharge and did not

Among patients who achieved prehospital ROSC, using the Kaplan-Meier estimate, we visualized curves of the cumulative proportion of patients achieving prehospital ROSC over time, stratified by patients who survived to hospital discharge and patients who had prehospital ROSC and subsequently died before hospital discharge. We also reported the estimates of the 95th and 99th percentiles of CPR duration for each stratified curve.

Time-dependent probability of survival to hospital discharge among patients with ongoing CPR pending prehospital ROSC at each minute of EMS-initiated prehospital CPR duration (Supplemental Methods)

As our primary objective, we calculated the time-dependent probability of survival to hospital discharge as a function of the EMS-initiated prehospital CPR duration, using a similar method that we previously used for adults with IHCA.[22] We calculated the time-dependent probability of survival to hospital discharge among those with ongoing CPR pending prehospital ROSC at each minute of the CPR duration. The numerator was the number of patients with ongoing CPR with pending prehospital ROSC at each minute and subsequently survived to hospital discharge. The denominator was the number of patients with ongoing CPR with pending prehospital ROSC at each minute. When patients arrived at hospitals without ROSC, the patients were excluded from the denominator and numerator as a censoring event after the hospital arrival, since our exposure was the EMS-initiated prehospital CPR duration, and the ROC registry primarily captured prehospital time course variables. This time-dependent probability represented the probability of subsequently surviving to hospital discharge if the patient with ongoing CPR with pending prehospital ROSC at that time point received further CPR beyond that time point. This time-dependent probability at time t is denoted as "conditional probability (survival = yes|CPR duration provided by EMS clinicians > t)".

We calculated two time-dependent probabilities of survival to hospital discharge among those with ongoing CPR pending prehospital ROSC at each minute. We defined two denominators, one including and one excluding patients with prehospital TOR prior to or at each time point. For our primary analysis, we included patients who had prehospital TOR prior to or at each minute of CPR duration in the denominator. This denominator assumes that all decisions on TOR prior to or at that time point where appropriate, and thus that patients with TOR never survived to hospital discharge, even if they had a longer CPR duration beyond the time point of TOR. The use of this denominator provides the probability of surviving to hospital discharge among the overall study population if patients with ongoing CPR at each minute underwent further CPR beyond that time point. We reported the EMS-initiated prehospital CPR duration when this probability became less than 1%, the traditional and reported metric for medical futility in the resuscitation guidelines, and 0%.[23,24] We obtained 95% confidence intervals (CIs) for the CPR duration via bootstrapping with 2000 resamples.[25] We also reported CPR duration when the upper bound of 95% CI of the time-dependent probabilities decreased to less than 1%.

As a sensitivity analysis, another denominator included only patients with ongoing CPR at each minute pending prehospital ROSC. In this denominator, patients who had TOR prior to or at each minute were excluded from the denominator. This denominator treated TOR as a censoring event that is not informative on subsequent time-dependent probabilities. Therefore, as the CPR duration increased, this denominator included only patients with ongoing CPR and represented a selected population.

Time-dependent probability of survival to hospital discharge among patients who had prehospital ROSC prior to or at each minute of EMS-initiated prehospital CPR duration (Supplemental Methods)

As our secondary objective, we calculated the time-dependent probabilities of survival to hospital discharge among those who had prehospital ROSC prior to or at each time point. The numerator was the number of patients with prehospital ROSC prior to or at each minute and subsequently survived to hospital discharge. The denominator was the number of patients with prehospital ROSC prior to or at each minute. This time-dependent probability quantified the probability of surviving to hospital discharge once the patient achieved prehospital ROSC prior to or at each time point. This time-dependent probability at time t is denoted as "conditional probability (survival = yes|time to prehospital ROSC ≤ t)". We carried out a pointwise estimation of a 95% CI for each time-dependent probability based on the variance of the binomial distribution.

Stratified analyses of time-dependent probabilities

In addition, we stratified the time-dependent probability curves based on age group (<1 year or ≥1 year), bystander witnessed status (bystander witnessed or unwitnessed), and presence or absence of bystander CPR to evaluate whether the time-dependent probabilities differ across each subset of patients. All statistical analyses were performed with R software, version 4.1.1 (R Foundation of Statistical Computing, Vienna. Austria: www.r-project.org).

Results

We identified 1541 pediatric patients with EMS-treated OHCA. After excluding those who met the exclusion criteria, we evaluated 1313 patients (Supplemental Fig. 1).

We report patient demographics, cardiac arrest characteristics, and bystander and EMS interventions (Table 1). Among 1313 evaluated patients, 236 (18.0%) achieved prehospital ROSC and 1077 (82.0%) did not. Among all patients evaluated, 136 (10.4%) survived to hospital discharge. Among 1077 patients without prehospital ROSC, 284 (26.4%) had prehospital TOR (Supplemental Table 1). The median interval between the initiation of chest compressions and prehospital ROSC was 10.0 min (IQR 5.5–16.5 min) among those who had ROSC. The median interval between the initiation of chest compressions and prehospital TOR was 21.3 min (IQR 9.8–29.0 min).

Cumulative proportion of patients achieving prehospital ROSC over time, stratified by patients who survived to hospital discharge and did not

Fig. 1 demonstrates the cumulative proportion of patients achieving prehospital ROSC, stratified by survival to hospital discharge. 99% of patients who survived to hospital discharge had prehospital ROSC within 24 min of the EMS-initiated prehospital CPR duration, and 95% of patients who survived to hospital discharge had prehospital ROSC within 18 min of the EMS-initiated prehospital CPR duration. Among the children who had ROSC after 24 and 18 min of prehospital CPR, 8.3% (2/24) and 9.3% (5/54) survived to hospital discharge. In contrast, 99% of patients who achieved prehospital ROSC and did not survive to hospital discharge had prehospital ROSC within 43 min of the EMS-initiated prehospital CPR duration, and 95% of patients who achieved prehospital ROSC and did not survive to hospital discharge had prehospital ROSC within 35 min of CPR duration.

Time-dependent probability of survival to hospital discharge among those with ongoing CPR pending prehospital ROSC at each minute of EMS-initiated prehospital CPR duration

We present time-dependent probability of survival to hospital discharge among those with ongoing CPR pending prehospital ROSC at each minute of the EMS-initiated prehospital CPR duration for all patients (Fig. 2A) and for patients by age group (<1 year or ≥1 year) (Fig. 2B), bystander-witnessed status (bystander witnessed or unwitnessed) (Fig. 2C), and presence or absence of bystander

Table 1 – Patient demographics, cardiac arrest characteristics, and bystander and emergency medical services interventions.

	All patients (*n* = 1313)	Patients without prehospital ROSC (*n* = 1077)	Patients with prehospital ROSC (*n* = 236)
Patient demographics			
Age, median (IQR), y	1 (0–9)	1 (0–6)	10 (1–14.25)
Sex, *n* (%)			
Male	773 (58.9)	639 (59.3)	134 (56.8)
Female	538 (41.0)	436 (40.5)	102 (43.2)
Unknown	2 (0.2)	2 (0.2)	0 (0)
Arrest characteristics			
Location, *n* (%)			
Private location	1167 (88.9)	984 (91.4)	183 (77.5)
Public location	143 (10.9)	91 (8.4)	52 (22.0)
Unknown	3 (0.2)	2 (0.2)	1 (0.4)
Witness status, *n* (%)			
Bystander witnessed	280 (21.3)	189 (17.5)	91 (38.6)
EMS witnessed	60 (4.6)	42 (3.9)	18 (7.6)
Unwitnessed	921 (70.1)	800 (74.3)	121 (51.3)
Unknown	52 (4.0)	46 (4.3)	6 (2.5)
Initial rhythm, *n* (%)			
Shockable	80 (6.1)	35 (3.2)	45 (19.1)
Nonshockable	1113 (84.8)	955 (88.7)	158 (66.9)
Unknown	120 (9.1)	87 (8.1)	33 (14.0)
Bystander intervention			
Bystander CPR, *n* (%)			
Presence	579 (44.1)	469 (43.5)	110 (46.6)
Absence	734 (55.9)	608 (56.5)	126 (53.4)

Table 1 (continued)

	All patients (n = 1313)	Patients without prehospital ROSC (n = 1077)	Patients with prehospital ROSC (n = 236)
EMS intervention			
Epinephrine administration, *n* (%)			
Presence	888 (67.6)	739 (68.6)	149 (63.1)
Absence	424 (32.3)	338 (31.4)	86 (36.4)
Unknown	1 (0.1)	0 (0)	1 (0.4)
Interval from dispatch to EMS clinician arrival, median (IQR), minutes	5.0 (3.9–6.4)	5.0 (3.9–6.3)	5.0 (3.8–6.7)

Abbreviations: CPR, cardiopulmonary resuscitation; EMS, emergency medical services; IQR, interquartile range; ROSC, return of spontaneous circulation

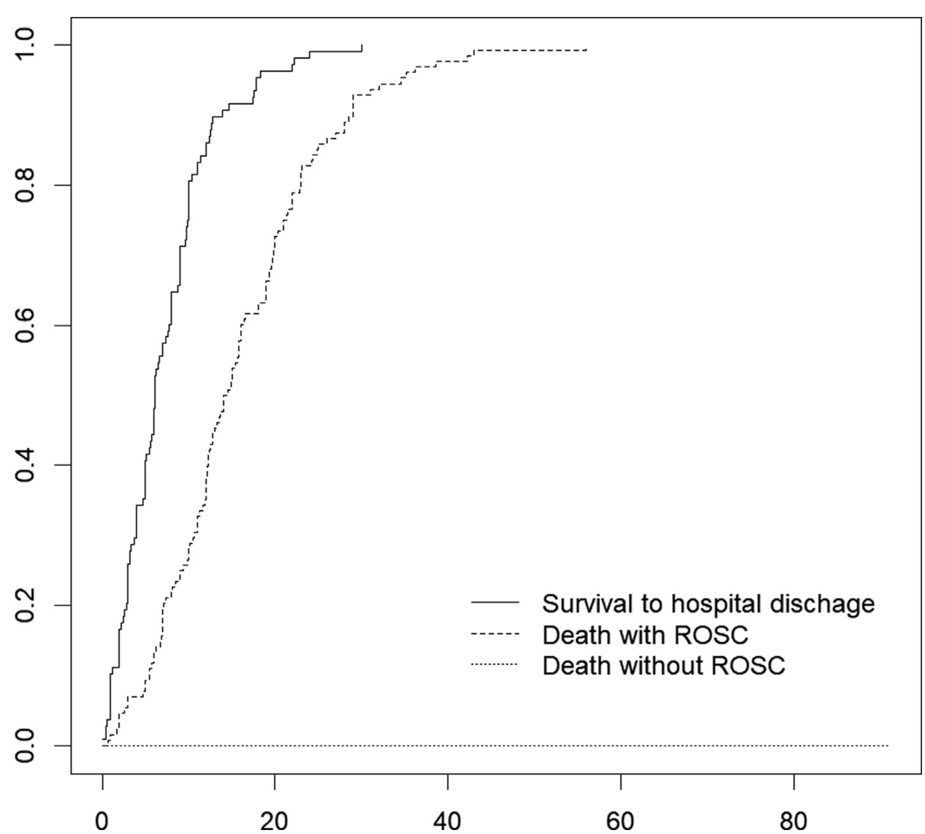

Fig. 1 – Cumulative proportion of patients achieving prehospital return of spontaneous circulation, stratified by survival to hospital discharge and death before hospital discharge with return of spontaneous circulation.
CPR indicates cardiopulmonary resuscitation; EMS, emergency medical services; ROSC, return of spontaneous circulation.

CPR (Fig. 2D), using the denominator including patients who had prehospital TOR prior to or at each time point (primary analysis). Among all patients, the probability of survival to hospital discharge for those with ongoing CPR pending prehospital ROSC at 1 min of the prehospital CPR duration was 7.9% (95% CI: 6.4–9.3%) (Fig. 2A). As the CPR duration increased, the probability of survival among all patients decreased to less than 1% at 14.8 min (95% CI: 11.1–22.0 min) of the CPR duration (Table 2), and the upper bound of 95% CI of the probabilities of survival decreased to less than 1% (0.86%, 95% CI: 0.34–0.94%) at 22.0 min (Supplemental Table 2). Patients in the age group of ≥1 year, of bystander-witnessed arrest, and with bystander CPR demonstrated higher estimates of the time-dependent probabilities of survival to hospital discharge.

As the sensitivity analysis, we report the time-dependent probabilities of survival to hospital discharge among those with ongoing CPR pending prehospital ROSC at each minute of the prehospital

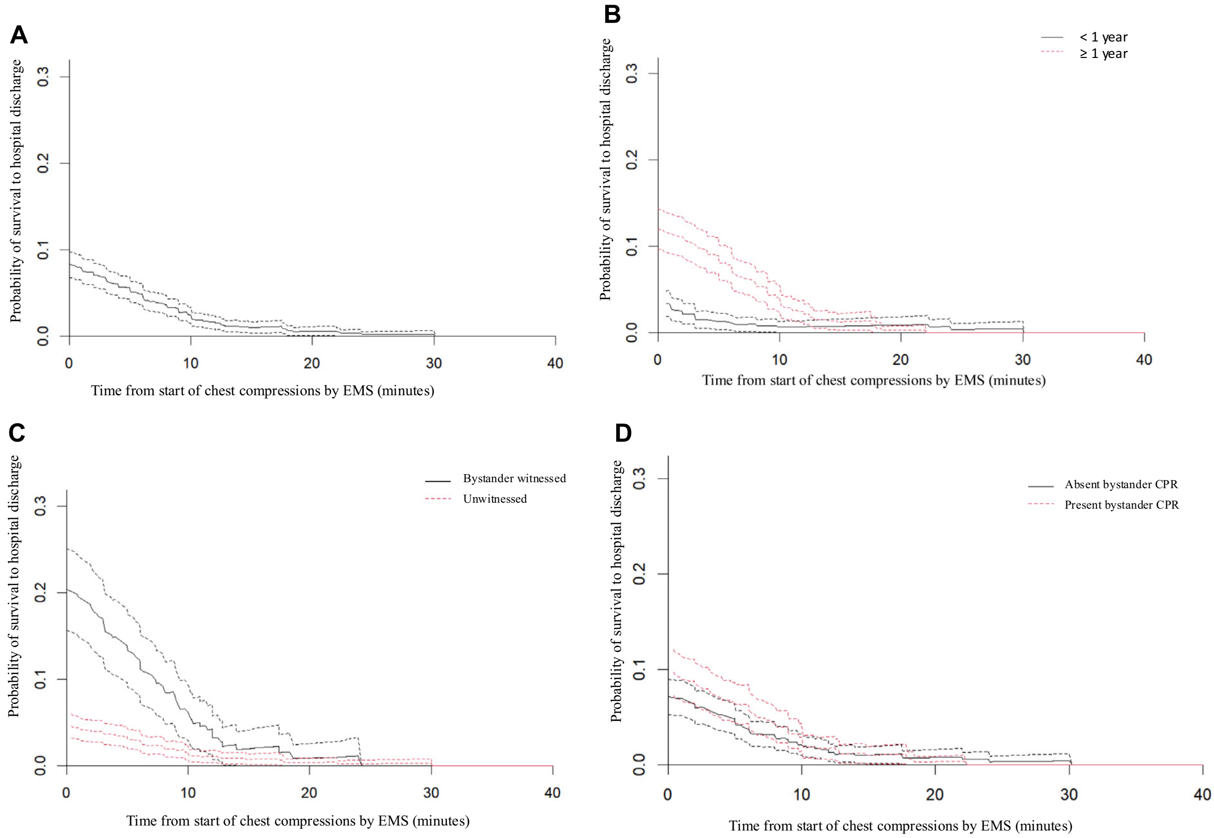

Fig. 2 – Time-dependent probability of survival to hospital discharge with 95% confidence intervals among those with ongoing cardiopulmonary resuscitation pending prehospital return of spontaneous circulation at each time point. All patients (A). Stratification by age group (B), witnessed status (C), and presence or absence of bystander cardiopulmonary resuscitation (D). The denominator included patients with ongoing cardiopulmonary resuscitation pending prehospital return of spontaneous circulation and patients who had termination of resuscitation prior to or at each time point. The numerator was the number of patients with ongoing cardiopulmonary resuscitation pending prehospital return of spontaneous circulation at each minute and subsequently survived to hospital discharge.

CPR indicates cardiopulmonary resuscitation; EMS, emergency medical services.

CPR duration for all patients (Supplemental Fig. 2A) and for patients in each age group (<1 year or ≥1 year: Supplemental Fig. 2B), bystander-witnessed status (bystander witnessed or unwitnessed: Supplemental Fig. 2C), and presence or absence of bystander CPR (Supplemental Fig. 2D), using the denominator excluding patients who had prehospital TOR prior to or at each time point. These probabilities were similar to those in the primary analysis.

Time-dependent probability of survival to hospital discharge among those with prehospital ROSC prior to or at each minute of EMS-initiated prehospital CPR duration

We present time-dependent probabilities of survival to hospital discharge among those who had prehospital ROSC prior to or at each minute of the EMS-initiated prehospital CPR duration for overall patients (Fig. 3A) and patients in each age group (<1 year or ≥1 year: Fig. 3B), bystander-witnessed status (bystander witnessed or unwitnessed: Fig. 3C), and presence or absence of bystander CPR (Fig. 3D). Patients in the age group of ≥1 year, of bystander-witnessed arrest, and with bystander CPR demonstrated higher estimates of the time-dependent probabilities of survival to hospital discharge.

Discussion

In this analysis of a large multicenter OHCA registry in the United States and Canada from 2011 through 2015, we quantified the time-dependent probability of survival to hospital discharge among pediatric patients as a function of the EMS-initiated prehospital CPR duration. Among those who eventually survived to hospital discharge, 99% and 95% of patients achieved prehospital ROSC within 24 min and 18 min after the start of chest compressions by EMS clinicians, respectively. Among the children who had ROSC after 24 and 18 min of prehospital CPR, 8.3% (2/24) and 9.3% (5/54) survived to hospital discharge. Time-dependent probabilities with 95% CIs of survival to hospital discharge among those with ongoing CPR pending prehospital ROSC, using the denominator including patients who had prehospital TOR prior to or at each time point, became less than 1% beyond 14.8 (11.1–22.0) minutes and 0% at 30.1 (22.0–30.2) minutes of the EMS-initiated prehospital CPR duration. The time points when the time-dependent probabilities became less than 1% differed across patients' age groups, witness status, and presence or absence of bystander CPR.

Table 2 – Emergency medical services-initiated prehospital cardiopulmonary resuscitation durations with 95% confidence intervals when point estimates of time-dependent probabilities of survival to hospital discharge among those with ongoing cardiopulmonary resuscitation pending prehospital return of spontaneous circulation decreased to less than 1% and 0%.

	Time-dependent probability of survival to hospital discharge	
	<1%	0%
Primary analysis[a]		
All patients	14.8 min (11.1–22.0 min)	30.1 min (22.0–30.2 min)
Subgroup		
Age group, <1 year	6.4 min (3.1–30.1 min)	30.1 min (9.9–30.5 min)
Age group, ≥1 year	17.6 min (12.5–18.5 min)	22.0 min (18.0–22.1 min)
Witnessed	18.6 min (12.7–24.8 min)	24.3 min (14.0–24.9 min)
Unwitnessed	12.5 min (9.0–18.0 min)	30.1 min (18.0–30.3 min)
Present bystander CPR	14.9 min (10.1–18.9 min)	22.4 min (18.0–22.6 min)
Absent bystander CPR	14.0 min (9.9–24.1 min)	30.2 min (17.6–30.6 min)
Sensitivity analysis[b]		
All patients	17.8 min (11.5–22.4 min)	30.1 min (22.0–30.2 min)
Subgroup		
Age group, <1 year	6.2 min (3.1–30.1 min)	30.1 min (9.9–30.3 min)
Age group, ≥1 year	17.8 min (12.5–18.6 min)	22.0 min (17.9–22.1 min)
Witnessed	18.6 min (12.5–24.8 min)	24.3 min (14.0–24.8 min)
Unwitnessed	12.8 min (9.3–22.2 min)	30.1 min (9.9–30.3 min)
Present bystander CPR	17.8 min (10.1–22.4 min)	22.4 min (18.0–22.6 min)
Absent bystander CPR	17.6 min (10.2–30.1 min)	30.1 min (17.6–30.5 min)

[a] The denominator included patients with prehospital termination of resuscitation prior to or at each minute of emergency medical services-initiated prehospital cardiopulmonary resuscitation duration.

[b] The denominator excluded patients with prehospital termination of resuscitation prior to or at each minute of emergency medical services-initiated prehospital cardiopulmonary resuscitation duration.

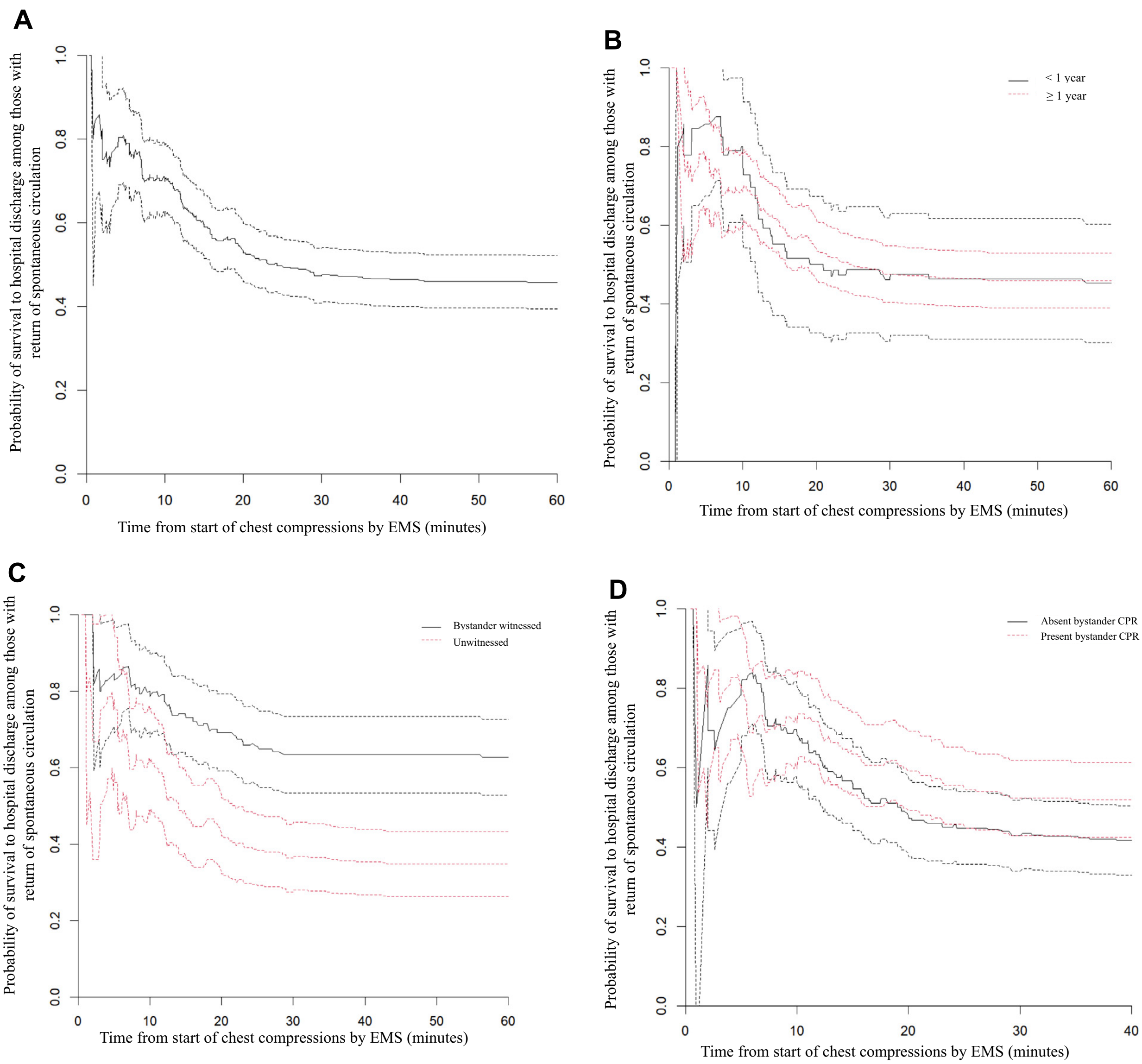

Fig. 3 – Time-dependent probability of survival to hospital discharge with 95% confidence interval among those with prehospital return of spontaneous circulation prior to or at each time point. All patients (A). Stratification by age group (B), witnessed status (C), and presence or absence of bystander cardiopulmonary resuscitation (D). The numerator was the number of patients with prehospital return of spontaneous circulation prior to or at each minute and subsequently survived to hospital discharge. The denominator was the number of patients with prehospital return of spontaneous circulation prior to or at each minute.
CPR indicates cardiopulmonary resuscitation; EMS, emergency medical services; ROSC, return of spontaneous circulation.

Relation to previous studies

An observational study using the nationwide, population-based OHCA registry in Japan (All-Japan Utstein Registry) evaluated the relationship between the prehospital CPR duration and patient outcomes (30-day survival and favorable functional outcome at 30 days, defined as Cerebral Performance Category scale 1 or 2) among 12,877 children (age <18 years) with EMS-treated traumatic and non-traumatic OHCA.[6] The proportions of children having 30-day survival and a favorable functional outcome at 30 days were 9.1% and 2.5%, respectively.[6] The probabilities of 30-day survival and favorable functional outcome at 30 days were reduced to 2.4% and 0.4% at 20 min of the prehospital CPR duration and became 0.7% and 0.1% at 30 min of the EMS-initiated prehospital CPR duration, respectively.[6]

Another observational study using the multi-center OHCA registry in Japan (JAAM-OHCA registry) examined the association of the total of EMS-initiated prehospital and in-hospital CPR duration with patient outcomes (1-month survival and favorable functional outcome at 1 month, defined as the Pediatric Cerebral Performance Category (PCPC) scales 1–3) among 1007 children (age <18 years) with EMS-treated traumatic and non-traumatic OHCA.[8] In the study cohort, the rates of 1-month survival and favorable functional outcome at 1 month were 10.2% and 5.3%, respectively. The probabilities of favorable functional outcome at 1 month became less than 1% after 63 min of the total of EMS-initiated prehospital and in-hospital CPR duration.[8]

The rate of survival to hospital (10.4%) identified in our North American pediatric OHCA study is similar to rates of 30-day survival

(9.1%) and 1-month survival (10.2%) in the prior two studies, both from Japan. Yet, the probability of survival to hospital discharge among those without prehospital ROSC became less than 1% at 14.8 min of CPR duration in our study, compared with the probability of 30-day survival less than 1% at 20–30 min in the All-Japan Utstein Registry study and the probability of favorable functional outcome at 1 month less than 1% at 63 min in the JAAM-OHCA registry study. There are several potential reasons for the differences in our findings and those of prior studies. First, TOR is not legally permitted in prehospital settings in Japan. Thus, all patients with EMS-treated OHCA were transported to receiving hospitals in both Japanese studies.[6,8] In contrast, 26.4% in our study cohort underwent prehospital TOR with a median interval from EMS-initiated chest compressions to prehospital TOR of 21.3 min. Our time-dependent probabilities of survival to hospital discharge assumed that the decision of TOR was adequate and that patients who had TOR would have never survived to hospital discharge, even if the patients had longer CPR duration beyond the time point of TOR. It is not possible to prove this assumption. Presumably, the differences in these prehospital practices and assumptions might have contributed to the observed substantial differences in the time of CPR durations when the probabilities of the favorable outcomes were less than 1%. Second, in the two prior studies in Japan, few patients received advanced life support interventions (e.g. epinephrine administration) in the prehospital setting: 2.0–4.3% of included patients received prehospital epinephrine in the two studies,[6,8] whereas 67.6% in our study population received prehospital epinephrine. These data suggest that epinephrine was administered after hospital arrival for most patients in these two studies, and the in-hospital advanced life support interventions might have improved the outcomes despite the longer CPR duration. Finally, the longer durations of CPR with favorable outcomes in the Japanese studies could be attributed to superior CPR performance; however, the similarity in overall survival at hospital discharge in North America and the 30-day survival rate in the Japanese studies suggests that the overall quality of CPR was likely comparable.

Studies of pediatric IHCA have demonstrated that the probabilities of survival to hospital discharge were 12% after 35 min of CPR in a large IHCA dataset, the Get With The Guidelines-Resuscitation registry,[7] and 28% after 30 min in a prospective observational study of large academic children's hospitals in the US.[26] Although the lower survival rate with long CPR duration in our study is not necessarily due to the biological inevitability of poor outcomes after more prolonged CPR, our findings are an acknowledgement that outcomes after prolonged CPR are worse in the resource-limited out-of-hospital setting. Favorable outcomes are less likely due to practical prehospital limitations, including the recognition of cardiac arrest by bystanders, the prompt initiation of bystander CPR, the prompt call to EMS, the quality of bystander and EMS CPR, and the performance of ALS interventions. Outcomes from prolonged CPR may improve with future solutions to some of these problems. Nevertheless, our findings quantify the recent time-dependent probabilities of survival to hospital discharge among pediatric patients as a function of the CPR duration in North America.

Meaning of study: implications

The quantified time-dependent probabilities of survival among patients pending prehospital ROSC at each minute of CPR duration provide EMS clinicians and patients' surrogates with objective insights into the likelihood of survival if the patients have continued to receive CPR beyond that time point, which could be a part of a multi-factorial decision-making process to continue or discontinue resuscitation when ROSC cannot be achieved. The 95% CIs of EMS-initiated prehospital CPR durations when the time-dependent probabilities of survival to hospital discharge decreased to less than 1% (Table 2) and the CPR duration when the upper bound of 95% CIs of the time-dependent probabilities decreased to less than 1% (Supplemental Table 2) demonstrate objective data on the range of CPR duration when the resuscitation could be futile.

The time points when the time-dependent probabilities of survival to hospital discharge among those with ongoing CPR pending prehospital ROSC became less than 1% differed across patients' subgroups (age groups and witnessed status), suggesting that, in this study setting, the patients' subgroups were factors to affect the probability of subsequently surviving to hospital discharge when the patients did not achieve prehospital ROSC at that time point.

The probabilities of survival among those who had ROSC prior to or at each time point inform EMS clinicians, in-hospital resuscitation team, and patients' surrogates of the likelihood of survival to hospital discharge once the patients have achieved ROSC prior to or at the time point. This information is clinically relevant to predict outcomes.

Unanswered questions and future research

It remains unclear whether patients who had prehospital TOR had an optimal CPR duration without premature TOR in this data since it is not possible to predict counterfactual outcome: i.e., the potential outcome if patients with TOR had a longer CPR duration. The decision to continue or terminate CPR is multifactorial and complicated. As we observed, the CPR duration is highly correlated with mortality, and treating clinicians use the CPR duration as a part of the information to terminate (self-fulfilling prophecy), whereas treating clinicians provide prolonged CPR if they believe the patients benefit from prolonged CPR, based on clinical judgement (confounding by indication) or for non-medical factors.[27–29] Although these complexities on the decision to continue or discontinue CPR exist, the ideal duration of CPR for each individual, avoiding premature TOR and futile resuscitation, warrants further research.

Limitations

Our analysis has important limitations. First, as discussed, we used two definitions for the denominator of time-dependent probability of survival among those with ongoing CPR pending prehospital ROSC at each time point. The denominator included patients with ongoing CPR, and patients who had TOR depended on the assumption that all TOR was completely appropriate. However, it is not possible to prove this assumption. Second, our time-dependent probabilities are descriptively calculated using the denominators and numerators, defined in the Methods section. As a limitation of this methodology, we alternatively conducted multiple stratified analyses to account for the differences in the baseline characteristics.[22] Third, collection of time course variables during CPR (e.g., the start of chest compressions by EMS clinicians) is challenging, and the precision of the collected time variables is an important limitation. Although the use of the large OHCA registry with standardized data definitions and data-collecting systems was intended to minimize this limitation, misclassification of time course variables is possible. Fourth, we only included EMS-initiated prehospital CPR duration and could not take into account bystander CPR duration and in-hospital CPR duration for patients who received bystander CPR or arrived at hospitals with ongoing CPR, based on the data availability. The onset of cardiac arrest was also not available in the dataset, and we were unable to explore the relationship between the duration of cardiac arrest and survival. Alternatively, we conducted stratified analyses by witnessed status and by receipt of bystander CPR, as a proxy for downtime and low-flow time. Fifth, we were unable to account for post-resuscitation care after hospital arrival. Finally, the results may not be generalizable to other EMS systems since selected EMS systems were included in the ROC based on their adherence to performance metrics, ability to conduct trials, and interest in participating in research. However, the geographically diverse EMS systems in the United States and Canada may enhance the generalizability. Additionally, the data collection period from 2011 to 2015 limits the generalizability of the results into current practice.

Conclusion

In this retrospective pediatric cohort study of the large OHCA registry in the United States and Canada, the time-dependent probability of survival to hospital discharge decreased sharply with increasing EMS-initiated prehospital CPR duration from 7.9% at one minute of ongoing CPR to <1% by 15 min (11.1–22.0 min) and 0% by 30 min (22.0–30.2 min) of the EMS-initiated prehospital CPR duration. The findings provide EMS clinicians and patients' surrogates with objective insights into the likelihood of survival when CPR is continued beyond 15 min and may support more informed discussion with families and surrogates.

Ethical approval

The institutional review boards at the University of Pittsburgh deemed the study exempt from regulations related to human participant research because publicly available de-identified data were used.

Data sharing

The de-identified Resuscitation Outcomes Consortium Epidemiologic Registry dataset is publicly available at the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center (https://biolincc.nhlbi.nih.gov/home/).

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CRediT authorship contribution statement

Masashi Okubo: Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Sho Komukai:** Writing – review & editing, Visualization, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Junichi Izawa:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Shunsuke Amagasa:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Sriram Ramgopal:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Clifton W. Callaway:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Robert A. Berg:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: All authors have completed the ICMJE uniform disclosure form at https://www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work. Dr. Berg and Dr. Callaway are members of the Editorial Board of Resuscitation. Other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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