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Clinical paper

Epidemiology and outcomes of infants after cardiopulmonary resuscitation in the neonatal or pediatric intensive care unit from a national registry☆

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Abstract

Aim: Cardiopulmonary resuscitation (CPR) in hospitalized infants is a relatively uncommon but high-risk event associated with mortality. The study objective was to identify factors associated with mortality and survival among infants who receive CPR in the neonatal intensive care unit (NICU) or pediatric intensive care unit (PICU).

Methods: Retrospective observational study of infants with an index CPR event in the NICU or PICU between 1/1/06 and 12/31/18 in the American Heart Association's Get With The Guidelines-Resuscitation registry. Associations between patient, event, unit, and hospital factors and the primary outcome, mortality prior to discharge, were examined using multivariable logistic regression.

Results: Among 3521 infants who received CPR, 2080 (59%) died before discharge, with 25% mortality during CPR and 40% within 24 h. Mortality prior to discharge occurred in 65% and 47% of cases in the NICU and PICU, respectively. Factors most strongly independently associated with pre-discharge mortality were vasoactive agent before CPR (adjusted odds ratio (aOR): 2.77, 95% confidence interval (CI) 2.15–3.58), initial pulseless condition (aOR: 2.38, 95% CI 1.46–3.86) or development of pulselessness (aOR: 2.36, 95% CI 1.78–3.12), and NICU location compared with PICU (aOR: 3.85, 95% CI 2.86–5.19). Endotracheal intubation during CPR was associated with decreased odds of pre-discharge mortality (aOR: 0.40, 95% CI 0.33–0.49).

Conclusion: Infants who receive CPR in the intensive care unit experience high mortality rates; identifiable patient, event, and unit factors increase the odds of mortality. Further investigation should explore the association between unit type, resuscitation processes, and mortality.

Keywords: Infant resuscitation, Intensive care, Mortality, Event location

☆ Prior presentation: This work was presented as a webinar as part of the Pediatric Academic Societies Neonatology Summer Webinar Series in June 2020.

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https://doi.org/10.1016/j.resuscitation.2021.05.029
Received 24 March 2021; Received in revised form 12 May 2021; Accepted 28 May 2021

Introduction

Cardiopulmonary resuscitation (CPR) in hospitalized neonates and infants is relatively uncommon, with published rates of 0.25% −3%.[1−4] Reported in-hospital mortality rates after CPR range from 39% to 80%.[1−4] Much of the literature regarding infants and CPR focus on either very low birth weight infants or delivery room CPR.[5−7] Published reports of CPR among infants in the neonatal intensive care unit (NICU) are primarily single center studies with limited generalizability.[1,2,4] Available studies contain limited CPR event details and could not identify associations with resuscitation interventions and outcomes.[3] Furthermore, few studies have evaluated infants separately from older pediatric patients, despite data showing newborns and infants have better survival rates after CPR in the intensive care setting.[8]

Infants receive intensive care in a variety of hospital types and settings. These include perinatal hospitals, in which infants are often born, and children's hospitals, where both NICUs and pediatric intensive care units (PICUs) can provide infant intensive care. As an increasing number of extremely preterm infants with prematurity-associated comorbidities survive, surgical techniques evolve, and the scope of neonatal intensive care shifts, the case mix of infants in the NICU and hospitals is changing.[9] Additionally, infants represent 15−50% of all patients admitted to children's hospitals.[10] Hospital case mix, variation in the proportion of infants receiving care in a hospital, infant age, admission diagnosis, and intensive care unit census, may influence the admitting unit (NICU vs PICU) location for sick infants. To date, most studies of infants receiving CPR in the intensive care setting have focused exclusively on infants in either the NICU or PICU.[8] More generalizable studies in the infant population are needed to identify patient, event, unit, and hospital factors associated with CPR outcomes among infants receiving intensive care across units.

We obtained data from the American Heart Association's Get With The Guidelines-Resuscitation (GWTG-R) registry to address this topic. We designed this study using Donabedian's model, a foundational and widely used framework for evaluating the quality of medical care.[11] This model separates variables into the triad of structure (the setting where care takes place, e.g. unit and hospital), process (the components of care delivered, e.g. CPR event interventions), and outcome.[11] The study objective was to identify patient, event, unit, and hospital factors associated with the primary outcome of mortality prior to hospital discharge after in-unit CPR among non-cardiac infants.[11] Secondary study outcomes were CPR event mortality and mortality within 24 h of CPR.

Methods

Data source

The GWTG-R registry is a prospective, quality improvement registry of in-hospital cardiac arrest and resuscitation data from North American hospitals. Trained data abstractors identify all institutional cases and extract data from cardiac arrest flow sheets, hospital paging systems, routine code cart checks, pharmacy records, and hospital billing charges.[12] Data are checked via periodic reabstraction, by reexamining randomly selected event records and corresponding datasheets.[13] The registry employs Utstein-style templates for cardiac arrest with standardized reporting guidelines for patient variables and outcomes to facilitate consistent reporting across sites.[14,15] Hospitals submit data through an online, interactive case report form and Patient Management Tool™ (IQVIA, Parsippany, New Jersey), in accordance with the Health Insurance Portability and Accountability Act. Hospital-level data were obtained from the American Hospital Association Annual Hospital Survey administered in 2018, which were merged with the GWTG-R prior to receipt by the study team.[16]

Study design and population

This is a retrospective cohort study of infants ($\leq$365 days old) with CPR events between January 1st, 2006 and December 31st, 2018 captured in the GWTG-R registry. Infants were included if they had a CPR event $>$1 min in duration occurring in the NICU or PICU. For infants with multiple CPR events, only the index event was analyzed. Infants with congenital heart disease were excluded as their outcomes differ from those without congenital heart disease.[17] CPR occurring in the delivery room and infants without hospital-level data were excluded. The study period was chosen based on the availability of pediatric resuscitation data and ascertainment of the primary outcome, mortality prior to hospital discharge.

Study variables and outcomes

As per the GWTG-R registry inclusion criteria, an eligible CPR event was defined as the receipt of chest compressions and/or defibrillation. Patient and event characteristics were obtained from the registry. As per standard resuscitation reporting guidelines[14,15], interventions in place prior to the event, termed 'pre-event', are those interventions in place when the need for chest compressions was first recognized. In the GWTG-R registry, birth weight is only collected if an infant is $<$30 days old at the time of admission and gestational age is only collected if the event occurred during an infant's birth hospitalization or if the infant was transferred to the current hospital from the birth hospital. Thus, both variables were missing for many patients. Birth weight was missing for 78% of patients in the full cohort, 68% in the NICU, and 98% in the PICU and gestational age was missing for 42% of patients in the full cohort, 13% in the NICU, and 93% in the PICU. These variables were not included in this analysis.

Event characteristics were event time of day (day versus night/weekend/holiday), the patient's initial condition when the need for chest compressions was identified (pulselessness, pulse prior to pulselessness, or pulse without pulselessness during the event), the initial cardiac arrest rhythm, event interventions, defibrillation for ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT), endotracheal intubation, adrenaline (epinephrine) administration, the number of adrenaline doses administered, delay in adrenaline administration, non-drug interventions, other drug interventions, and event duration.[14,15]

The event location, NICU or PICU, and total number of CPR events per site were obtained from the registry. All other unit and hospital characteristics were obtained from the American Hospital Association Annual Hospital Survey. Unit characteristics were the number of NICU and/or PICU beds. Hospital characteristics included the number of eligible CPR events per site in the cohort, children's hospital designation, available pediatric cardiology and pediatric surgery services, teaching hospital status, hospital location, and hospital administration type.

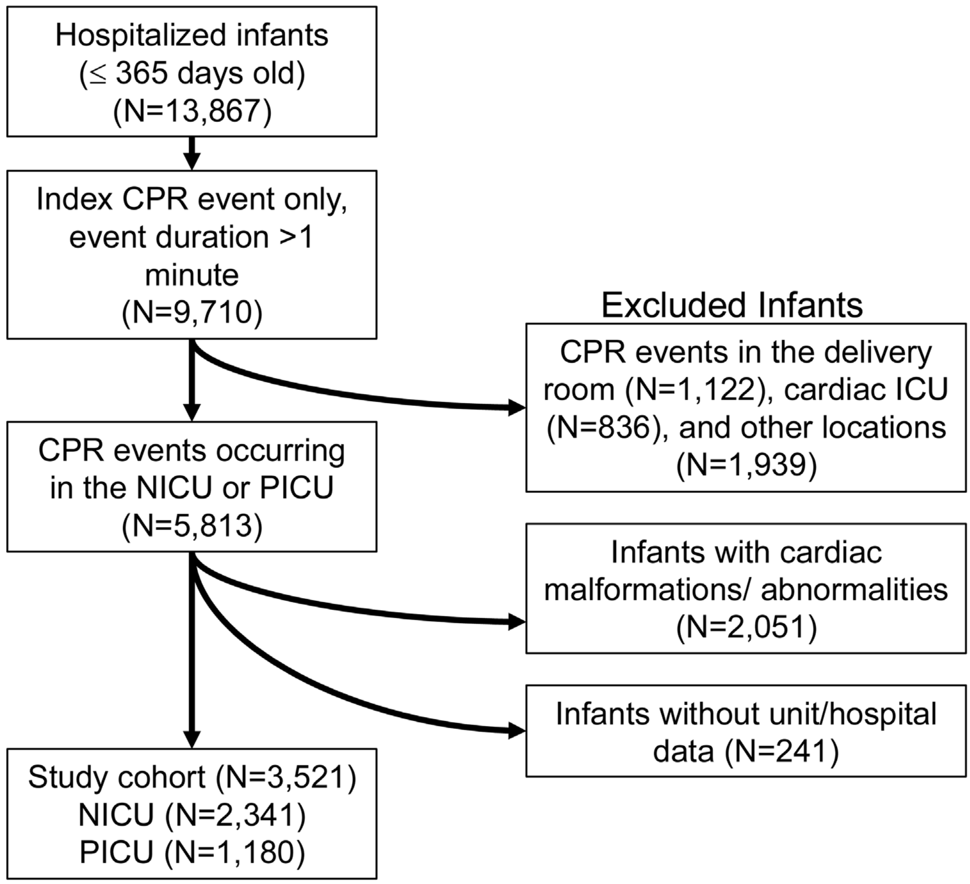

Fig. 1 – Cohort identification.

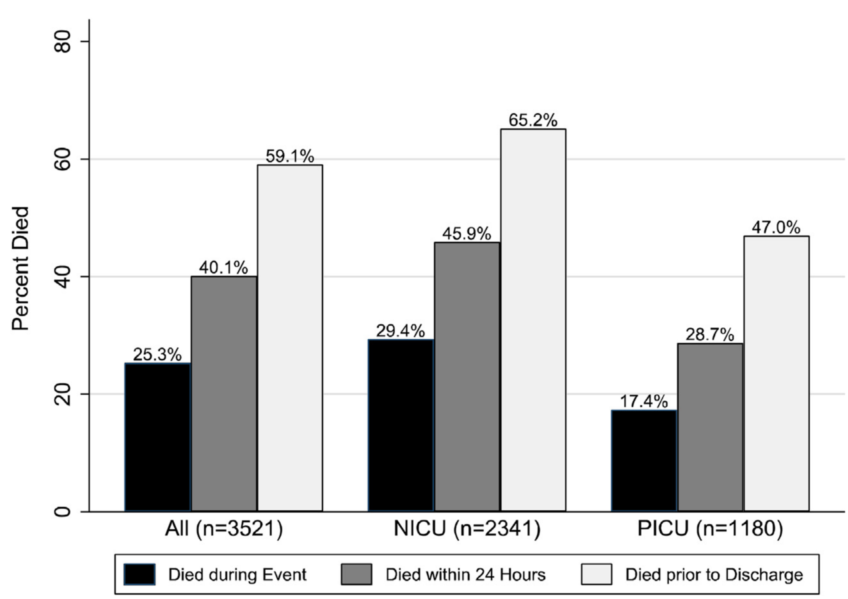

Fig. 2 – Unadjusted death during a CPR event, within 24 h of a CPR event, and prior to hospital discharge.
***Abbreviations*: NICU—neonatal intensive care unit, PICU—pediatric intensive care unit.**
“All” reflects the full cohort of infants in both the NICU and PICU.

Table 1 – Patient and event characteristics.

	Survived to discharge	Died prior to discharge	p-Value
	1441 (40.9%)	2080 (59.1%)	
Patient characteristics, n (%)			
Male	831 (57.7%)	1164 (56%)	0.32
Race/ethnicity			0.04
White	545 (37.8%)	705 (33.9%)	
Black	446 (31%)	669 (32.2%)	
Hispanic	237 (16.5%)	330 (15.9%)	
Other	48 (3.3%)	91 (4.4%)	
Unknown	165 (11.5%)	285 (13.7%)	
Congenital anomalies	298 (20.7%)	382 (18.4%)	0.09
Age at event (days), mean (SD)	91 (117)	58 (107)	<0.0001
Weight at event (grams), mean (SD)	3852 (2820)	2990 (3026)	<0.0001
Pre-existing condition count[a], median (IQR)	1 (1–2)	2 (1–3)	<0.0001
Interventions in place prior to the event			
Pre-event status			
Respiratory support			<0.0001
No pre-event respiratory support	390 (27.1%)	204 (9.8%)	
Pre-event non-invasive ventilation[b]	221 (15.3%)	213 (10.2%)	
Pre-event invasive ventilation[c]	830 (57.6%)	1663 (80%)	
Pre-event vascular access	1172 (81.3%)	1756 (84.4%)	0.02
Pre-event vasoactive agent	135 (9.4%)	805 (38.7%)	<0.0001
Event year (2006–2018)	NA	NA	0.012[d]
Event characteristics, n (%)			
Event during night/weekend/holiday[e]	721 (50%)	1096 (52.7%)	0.12
Condition best describing event			<0.0001
Pulseless when need for CC was identified	277 (19.2%)	550 (26.4%)	
Pulse requiring CC, prior to pulselessness	151 (10.5%)	623 (30%)	
Pulse requiring CC, never pulseless	1013 (70.3%)	907 (43.6%)	
Rhythm prior to chest compressions			0.001
Asystole	88 (6.1%)	185 (8.9%)	
Bradycardia	1122 (77.9%)	1493 (71.8%)	
PEA	118 (8.2%)	229 (11%)	
VF/pVT	18 (1.3%)	25 (1.2%)	
Other	11 (0.8%)	18 (0.9%)	
Unknown	84 (5.8%)	130 (6.3%)	
Event Interventions			
Defibrillation provided	14 (1%)	37 (1.8%)	0.05
Endotracheal intubation	683 (47.4%)	476 (22.9%)	<0.0001
Adrenaline administered	649 (45%)	1738 (83.6%)	<0.0001
Adrenaline doses, median (range)	2 (1–3)	3 (2–5)	<0.0001
Delay in adrenaline[f]	50 (8.2%)	148 (9.2%)	0.48
Other drug intervention[g]	552 (38.3%)	1446 (69.5%)	<0.0001
Non-drug intervention[h]	208 (14.4%)	606 (29.1%)	<0.0001
Event duration (minutes), median (IQR)	5 (2–10)	13 (5–28)	<0.0001

SD—standard deviation, IQR—interquartile range, CC—chest compressions, PEA—pulseless electrical activity, VT—ventricular tachycardia, VF—ventricular fibrillation.

[a] Pre-existing condition count is a cumulative count of the number of diagnoses present prior to the event. These include: acute central nervous system (CNS) non-stroke event, acute stroke, baseline depression in CNS function, congenital malformation non-cardiac, congestive heart failure (CHF) this admission, CHF prior admission, diabetes mellitus, hepatic insufficiency, hypotension/hypoperfusion, major trauma, metastatic/hematologic malignancy, metabolic/electrolyte abnormalities, myocardial ischemia/infarction (MI/I) this admission, MI/I prior to admit, pneumonia, renal insufficiency, respiratory insufficiency, septicemia.

[b] Non-invasive ventilation is defined by any of the following approaches to non-invasive ventilation: bag-valve-mask, mask and/or nasal continuous positive airway pressure (CPAP), mouth-to-barrier device, mouth-to-mouth, laryngeal mask airway (LMA), or other non-invasive ventilation.

[c] Invasive ventilation is defined by any of the following interventions: an endotracheal tube, tracheostomy tube, or mechanical ventilation.

[d] This p-value indicates differences between the years, not a linear trend with directionality.

[e] Night events are those occurring between 10:59pm and 7am, weekend events occur between Friday at 10:59pm and Monday at 7am and holiday events occur on New Year's Day, Martin Luther King Day, Easter, Mother's Day, Memorial Day, Father's Day, July 4th, Labor Day, Halloween, Thanksgiving, Christmas.

[f] Delayed adrenaline administration defined as >5 min after the beginning of the event.

[g] Other drug interventions: adenosine, amiodarone, atropine, sodium bicarbonate, calcium chloride/calcium gluconate, dextrose bolus, dobutamine, dopamine, continuous adrenaline, lidocaine, magnesium sulfate, noradrenaline, phenylephrine, procainamide, reversal agent, vasopressin, 'other' antiarrhythmic, and 'other' vasopressor.

[h] Non-drug interventions: cardiopulmonary bypass, pericardiocentesis, needle thoracostomy, chest tube insertion, paracentesis, transcutaneous pacemaker, and epicardial transvenous pacemaker.

Table 2 – Unit and hospital characteristics.

	Survived to discharge	Died prior to discharge	p-Value
	1441 (40.9%)	2080 (59.1%)	
Unit characteristics			
Event location			<0.0001
NICU	815 (34.8%)	1526 (65.2%)	
PICU	626 (53.1%)	554 (46.9%)	
Number of NICU beds (for NICU events)			0.006
0	2 (0.1%)	1 (0.05%)	
1–20	122 (8.5%)	199 (9.6%)	
21–30	308 (21.4%)	458 (22%)	
31–40	227 (15.8%)	378 (18.2%)	
41–50	340 (23.6%)	384 (18.5%)	
51+	442 (30.7%)	660 (31.7%)	
Number of PICU beds (for PICU events)			<0.0001
0	72 (5%)	179 (8.6%)	
1–10	132 (9.2%)	293 (14.1%)	
11–20	348 (24.2%)	554 (26.6%)	
21–30	236 (16.4%)	289 (13.9%)	
31–40	362 (25.1%)	428 (20.6%)	
41+	291 (20.2%)	337 (16.2%)	
Hospital characteristics			
Hospital volume of infant CPR events in the study cohort			<0.0001
1–9	81 (5.6%)	121 (5.8%)	
10–49	272 (18.9%)	479 (23%)	
50–99	322 (22.4%)	393 (18.9%)	
100–149	189 (13.1%)	374 (18%)	
150–199	463 (32.1%)	591 (28.4%)	
>200	114 (7.9%)	122 (5.9%)	
Children's hospital	696 (48.3%)	780 (37.5%)	<0.0001
Pediatric cardiology services	1317 (91.4%)	1689 (81.2%)	<0.0001
Pediatric surgery services	1218 (84.5%)	1528 (73.5%)	<0.0001
Teaching hospital			0.07
No teaching services	9 (0.6%)	30 (1.4%)	
Minor teaching[a]	1110 (77%)	1580 (76%)	
Major teaching[b]	322 (22.4%)	470 (22.6%)	
Hospital location			0.46
Metropolitan	1436 (99.6%)	2069 (99.4%)	
Micropolitan	5 (0.4%)	9 (0.4%)	
Unknown	0 (0%)	2 (0.1%)	
Hospital administration			<0.0001
Nonprofit	1261 (87.5%)	1675 (80.5%)	
Other[c]	180(12.5%)	405 (19.5%)	

Abbreviations: NICU—neonatal intensive care unit, PICU—pediatric intensive care unit, CPR—cardiopulmonary resuscitation.

[a] Per the American Hospital Association, minor teaching hospitals are those that meet any one or more of the following designations (1) one or more Accreditation Council for Graduate Medical Education accredited programs, (2) a medical school affiliation reported to the American Medical Association, (3) an internship approved by the American Osteopathic Association, or (4) a residency approved by the American Osteopathic Association.

[b] Per the American Hospital Association, major teaching hospitals are members of the Council of Teaching Hospitals (COTH) of the Association of American Medical Colleges.

[c] Other = government, private, or missing administration status.

The primary study outcome was mortality prior to hospital discharge. Secondary outcomes included mortality during the CPR event and mortality within 24 h of the event.

Data analysis

Using SAS version 9.4 (Cary, NC) and Stata version 15 (College Station, TX), baseline characteristics of infants who did and did not die prior to hospital discharge were compared using Chi-Square and Wilcoxon Rank Sum tests. For analytic purposes, an unknown category for race/ethnicity and the initial cardiac arrest rhythm were used to facilitate complete case analysis. Multivariable logistic regression models examined factors associated with death prior to discharge. Model covariates included those identified a priori based on previously reported associations with adverse outcomes (sex,[18] congenital anomalies,[19] and time of event)[20,21] and those that were statistically imbalanced in univariate analysis ($p < 0.05$). The treatment hospital was included as a random effect (intercept) to account for unmeasured hospital factors. The same model was used to evaluate associations with secondary outcomes.

The univariate and multivariate analyses were completed for the entire cohort and pre-specified, subgroup analyses by event location, NICU or PICU. This analysis was completed given the potential for unit-level variation in the approach to CPR (e.g., neonatal resuscitation program (NRP) and/or pediatric advanced life support (PALS) algorithms). To explore if the presence of either a NICU or PICU or both a NICU and PICU in the treatment hospital contributes to associations between unit type and outcomes, we conducted a sensitivity analysis including only hospitals reporting events in both unit types.

Results

There were 3521 infants from 128 sites reporting events in both the NICU and PICU (n = 68), NICU only (n = 37), or PICU only (n = 23). Among the study cohort, 66% (n = 2341) of infants had a CPR event in the NICU and 34% (n = 1180) of infants were in the PICU (Fig. 1). Of these, 59% (n = 2080) died prior to discharge, with 65% of infants in the

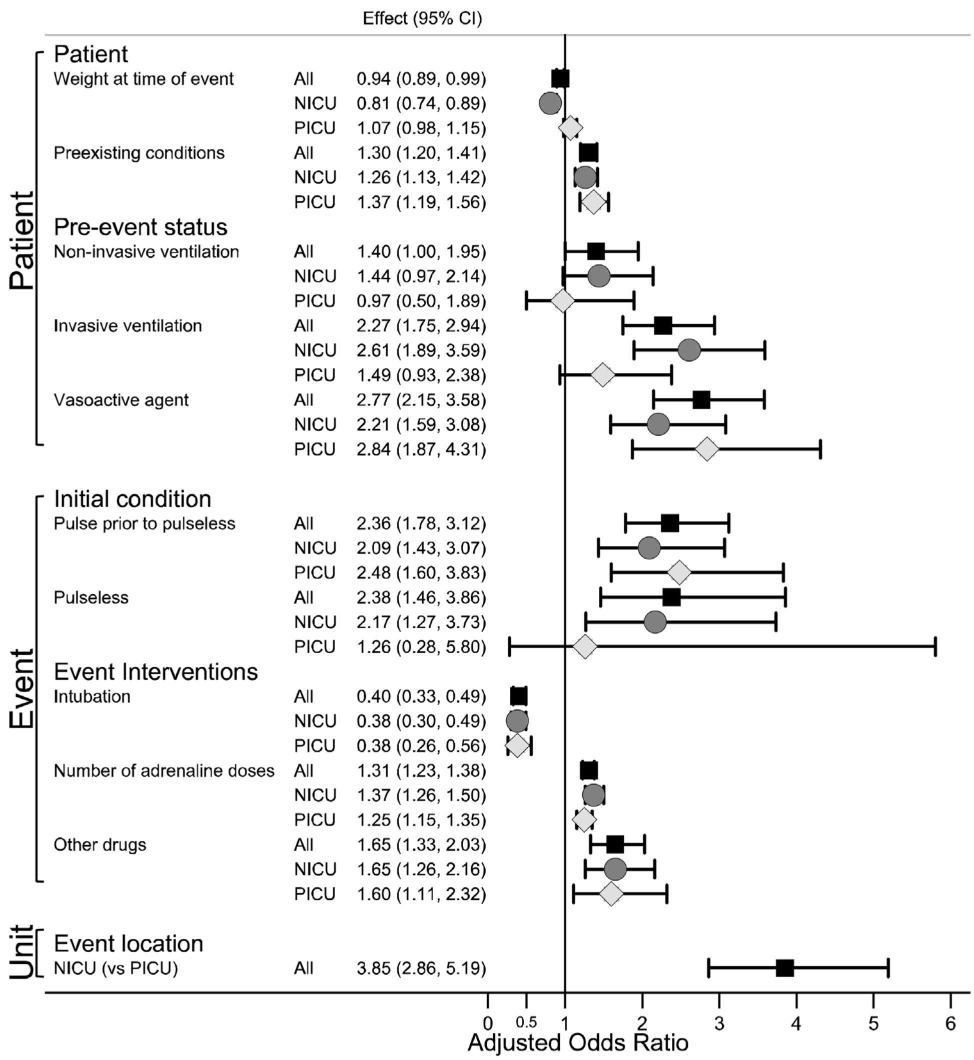

Fig. 3 – Significant patient, event, and unit factors associated with mortality prior to hospital discharge.
***Abbreviations*: NICU—neonatal intensive care unit, PICU—pediatric intensive care unit.**
"All" reflects the full cohort of infants in both the NICU and PICU.
Event duration (in minutes) was associated with mortality prior to hospital discharge, though figure scale did not adequately represent the difference. All: adjusted odds ratio (aOR) 1.01, 95% confidence interval (CI) 1.002–1.017; NICU: aOR 1.014, 95% CI 1.004–1.024; PICU aOR 1.009, 95% CI 0.998, 1.02.
Multivariate model variables: Patient variables: Event year, sex#, race/ethnicity, congenital anomalies#, age at time of event, weight at time of event, pre-event invasive ventilation, pre-event vascular access, pre-event vasoactive agent; Event variables: Event occurred during the night/weekend/holiday#, condition best describing event, rhythm prior to chest compressions, endotracheal intubation/tracheotomy during the event, the number of adrenaline doses administered during the event, non-drug interventions during the event, other drug (non-adrenaline boluses) during the event, event duration; Unit/Hospital variables: event location, number of NICU beds, number of PICU beds, number of events per year, children's hospital, presence of pediatric cardiology services, presence of pediatric surgery services, teaching hospital, hospital administration. #Variables included based on previous literature that were not significant in the univariate analysis.

NICU and 47% of infants in the PICU dying prior to discharge. Unadjusted mortality rates during the CPR event, within 24 h of the event, and prior to discharge were higher in the NICU than the PICU (Fig. 2).

In univariate analysis, patient and event characteristics differed between infants who did and did not die prior to discharge (Table 1). For example, infants who survived to discharge were older and weighed more at the time of the CPR event, had an initial bradycardic rhythm prior to compressions, and a shorter event duration. When stratified by unit, statistical differences in race/ethnicity, age and weight at time of the event persisted in the NICU, but not the PICU (Supplemental Tables 1 and 2). Unit and hospital characteristics associated with death before discharge also differed (Table 2). Hospital characteristics including available pediatric cardiology and pediatric surgery services, children's hospital designation, and hospital administration type differed between infants who did and did not die prior to discharge in the NICU (Supplemental Table 3), while only the presence of pediatric cardiology services differed in the PICU (Supplemental Table 4).

The multivariable regression analysis revealed patient, event, and unit factors independently associated with mortality prior to discharge (Fig. 3). The factor most strongly associated with mortality prior to discharge was event location; infants who received CPR in the NICU had nearly four-fold higher odds of death (adjusted odds ratio (aOR): 3.85, 95% confidence interval (CI) 2.86–5.19) compared to infants in the PICU. The patient variable most strongly associated with in-hospital mortality was the presence of a vasoactive agent prior to CPR (aOR: 2.77, 95% CI 2.15–3.58), and the most strongly associated event variable was a patient whose initial event condition was pulselessness (aOR: 2.38, 95% CI 1.46–3.86). The factor most strongly associated with a decreased odds of in-hospital mortality was endotracheal intubation (insertion or reinsertion) during CPR (aOR: 0.40, 95% CI 0.33–0.49).

The multivariate analysis of CPR event mortality and mortality within 24 h of the event revealed similar patterns. Factors suggesting increased illness acuity and CPR events with administration of multiple doses of adrenaline or other agents were independently associated with higher odds of event mortality (Fig. 4). The relative magnitude of the association between event location, NICU versus PICU, and event and 24-h mortality remained. Supplemental Tables 5 and 6 show unit stratified analyses of secondary outcomes.

The sensitivity analysis results were similar to the primary analysis demonstrating increased odds of mortality before discharge following CPR in the NICU compared to the PICU (aOR: 3.92, 95% CI 2.9–5.3).

Discussion

This study illustrates high mortality rates among infants who receive CPR in the NICU or PICU and identifies patient, event, and unit factors associated with in-hospital mortality. Factors indicating higher patient acuity, events with pulselessness, and more drug administration were associated with increased mortality. Our analysis revealed strong associations between the event location, NICU versus PICU, and all mortality outcomes. To our knowledge, this is the first multisite study to identify differences in CPR risk factors and mortality by event location among infants.

Following the Donabedian framework, we identified factors at the patient, event (process) and unit (structure) level associated with in-hospital mortality.[11] Patient variables which reflect higher acuity illness and administration of more adrenaline or other medications were associated with in-hospital mortality, regardless of event

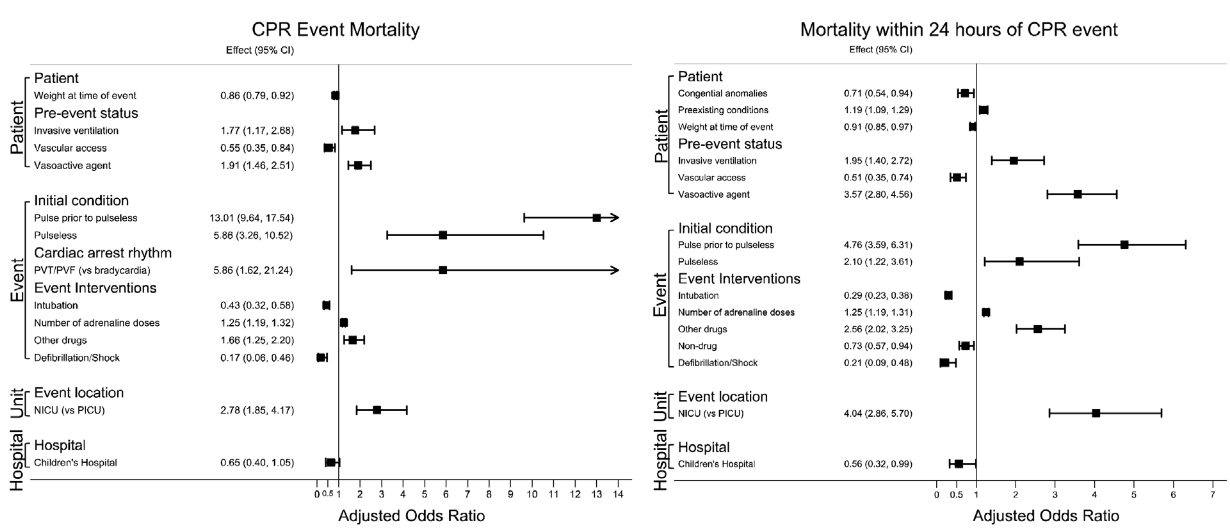

Fig. 4 – Significant patient, event, and unit factors associated with CPR event mortality and mortality within 24 h of the CPR event.

***Abbreviations*: CPR-cardiopulmonary resuscitation, NICU—neonatal intensive care unit, PICU—pediatric intensive care unit, PVT—ventricular tachycardia, PVF—ventricular fibrillation.**

Event duration (in minutes) was associated with event mortality (adjusted odds ratio (aOR) 1.03, 95% confidence interval (CI) 1.02–1.04) and mortality with 24 h of a CPR event adjusted odds ratio ((aOR) 1.016, 95% confidence interval (CI) 1.009–1.023), though figure scale did not adequately represent the difference.

The hospital variable, registry event volume was significant. Compared to 200–300 events in the registry lower volume, aside from 10 to 49 events was associated with a lower odds of event mortality. Though this is not necessarily reflective of hospital volume and thus was not included in the figure.

location. The patient variable of weight at time of the event and associations with mortality differed by unit. In the NICU, infants who survived weighed more at the time of the event and in the multivariable models increased weight was associated with decreased odds of mortality at all time points. Conversely, in the PICU, infants who survived to discharge weighed more at the time of the event and there were no associations between weight and mortality. Although age at the time of the event was not associated with any outcomes, it is plausible the association detected in the NICU reflects infants who are smaller and physiologically immature.

Pulselessness at any point was associated with mortality in the whole cohort and NICU, but not in the PICU. Although an adjusted analysis, this finding may be influenced by the larger percentage of infants who were never pulseless and survived to discharge in the NICU (81%) versus the PICU (56%) as well as differences in underlying disease processes. This finding is similar to a pediatric study, which included infants, showing children who presented with or progressed to pulselessness had significantly higher rates of in-hospital mortality than those who maintain a pulse during CPR.[22] There are published differences between cardiac arrest rhythms, including asystole, PEA, pVT/VF, and outcomes.[13,23] Although there were detectable associations between cardiac arrest rhythms and event mortality in our analysis, they did not persist to discharge. Consistent with prior work, lack of or loss of a pulse despite CPR interventions is a key prognostic factor among infants after a CPR event.

Endotracheal intubation during CPR was associated with decreased odds of mortality at all time points in both units. This reflects initial insertion or reinsertion of an endotracheal airway after adjusting for receipt of invasive ventilation prior to the event. This finding differs from previous pediatric studies, which reported either no association with mortality among patients in the intensive care unit or an increased risk of mortality in hospitalized patients intubated during CPR.[24,25] Rates of respiratory insufficiency among neonates (<1 month) and infants (1 month to <1 year) who arrest in the PICU are 50% and 71%, respectively.[8] Our data suggest that infants who are intubated during CPR, which may indicate an underlying respiratory aetiology, have a lower risk of mortality than arrests that are not preceded by respiratory compromise, though this relationship remains unclear. Alternatively, patients who were intubated during CPR may primarily represent infants who were not previously receiving invasive ventilation, though we adjusted for this in our analysis.

We found marked differences in outcomes following CPR in the NICU versus the PICU. This association was present for all mortality outcomes and persisted in our sensitivity analysis. There are many potential explanations for this finding. Although we adjusted for age and weight at time of the event, which may reflect prematurity, we were unable to account for gestational age and birth weight in our models as they are not collected for all infants in the GWTG-R registry. Resuscitation processes, such as the approach to CPR and use of NRP and/or PALS algorithms, likely differ between units and may contribute to outcome differences between units. Another potential contribution is variation within unit type. The American Academy of Pediatrics classifies four levels of NICU care, ranging from basic (level I), to complex subspecialty care (level IV) and two levels of PICU care, with the most comprehensive care provided in level I PICUs.[26,27] The wider spectrum of NICU levels of care may result in greater variation in patient case mix that was not accounted for in our models. In this study, infants who received CPR in a NICU with a children's hospital designation (typically higher level NICUs) experienced lower odds of death during the event or within 24 h. Additionally, in hospitals with a NICU and PICU there may be variation in practices and policies for admitting infants who require intensive care. Furthermore, the approach to end-of-life decisions in the NICU and PICU may influence in-hospital mortality. Experiencing a CPR event may alter a patient's course and a shift towards palliation. A single center study comparing end-of-life decisions in pediatric deaths, including those in the NICU and PICU, found that withdrawal of life-sustaining treatment in stable patients was more frequent in the NICU (56%) compared to the PICU (16%).[28] Differences in underlying disease processes in these two units, such as prematurity versus a terminal illness, or philosophies surrounding end-of-life care may contribute to mortality differences.

Findings from this study have a variety of potential implications and associated hypotheses for clinicians and resuscitation scientists to consider. This study illustrates heterogeneity in the infant population and suggests that infancy is not a linear continuum for infants receiving intensive care. These data also highlight the need to further explore, in clinical care and research, differences in unit-level processes and approaches to resuscitation management. For example, future work examining the application of NRP and/or PALS for hospitalized infants may be valuable to clinicians and resuscitation councils.

Limitations and strengths

One important study limitation was the inability to adjust for gestational age and birthweight. While these variables are routinely collected in NICU-centric registries, they are less standard in pediatric datasets including the GWTG-R registry. Our analyses adjusted for hospital factors using a random effect to account for unmeasured hospital-level factors, though this may have blunted our ability to detect variation in measured hospital factors. The conditions prompting initiation of CPR varied, for example, maintaining a pulse in the setting of bradycardia versus initial pulselessness. Although we adjusted for the initial condition and rhythm in our analysis, the wide variation in these patient characteristics suggests other unmeasured confounders may have influenced outcomes. The secondary outcome analysis was hypothesis-generating as we did not adjust for multiple comparisons. Finally, because this study utilized a registry, we could not determine the incidence of CPR or identify variables that differentiate infants who are more likely to experience a CPR event.

Study strengths include the large, contemporary, multicenter cohort of CPR events captured in hospitalized infants, a population that has not been studied as a whole. Additionally, the granular data regarding the patient, event, unit, and hospital factors are a strength and highlight associations with the patient's pre-event status, event interventions, and event location on outcomes. These findings provide new insights for future studies surrounding the optimization of CPR management.

Conclusion

Infants who receive in-unit CPR are at high risk of in-hospital mortality; this risk is strongly associated with indicators of illness acuity and event medication administration. Mortality outcomes following CPR differ between the NICU and PICU at all timepoints assessed. Further study is needed to clarify how unit level differences between patients, CPR management, and processes contribute to these findings.

Funding source

This work was supported by the National Institutes of Health (T32HD007440 [to SCH] and K23HD084727 [to EEF]).

Disclosures

The authors have no disclosures.

CRediT authorship contribution statement

Sara C. Handley: Conceptualization, Methodology, Writing - original draft, Visualization. **Molly Passarella:** Methodology, Software, Formal analysis, Data curation, Visualization. **Tia T. Raymond:** Conceptualization, Writing - review & editing. **Scott A. Lorch:** Conceptualization, Methodology, Resources, Writing - review & editing. **Anne Ades:** Conceptualization, Writing - review & editing. **Elizabeth E. Foglia:** Conceptualization, Methodology, Supervision, Writing - review & editing.

Acknowledgements

The authors would like to acknowledge the infants, their families, and providers who are impacted by challenging events and outcomes.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2021.05.029.

REFERENCES

1. Barr P, Courtman SP. Cardiopulmonary resuscitation in the newborn intensive care unit. J Paediatr Child Heal 1998;34:503–7.
2. Chamnanvanakij S, Perlman JM. Outcome following cardiopulmonary resuscitation in the neonate requiring ventilatory assistance. Resuscitation 2000;45(3):173–80.
3. Hornik CP, Graham EM, Hill K, et al. Cardiopulmonary resuscitation in hospitalized infants. Early Hum Dev 2016;101:17–22.
4. Foglia EE, Langeveld R, Heimall L, et al. Incidence, characteristics, and survival following cardiopulmonary resuscitation in the quaternary neonatal intensive care unit. Resuscitation 2017;110:32–6.
5. Shah PS. Extensive cardiopulmonary resuscitation for VLBW and ELBW infants: a systematic review and meta-analyses. J Perinatol 2009;29:655–61.
6. Foglia EE, Jensen EA, Wyckoff MH, Sawyer T, Topjian A, Ratcliffe SJ. Survival after delivery room cardiopulmonary resuscitation: a national registry study. Resuscitation 2020;152:177–83.
7. Halling C, Raymond T, Brown LS, et al. Neonatal delivery room CPR: an analysis of the Get with the Guidelines®—Resuscitation Registry. Resuscitation 2021;158:236–42.
8. Meaney PA, Nadkarni VM, Cook EF, et al. Higher survival rates among younger patients after pediatric intensive care unit cardiac arrests. Pediatrics 2006;118:2424–33.
9. Murthy K, Dykes Fd, Padula Ma, et al. The Children's Hospitals Neonatal Database: an overview of patient complexity, outcomes and variation in care. J Perinatol 2014;34:582–6.
10. Auger KA, Teufel RJ, Harris JM, et al. Children's hospital characteristics and readmission metrics. Pediatrics 2017139:.
11. Donabedian A. Evaluating the quality of medical care. 1966. Milbank Q 2005;83:691–729.
12. Peberdy MA, Kaye W, Ornato JP, et al. Cardiopulmonary resuscitation of adults in the hospital: a report of 14 720 cardiac arrests from the National Registry of Cardiopulmonary. Resuscitation. Resuscitation 2003;58:297–308.
13. Nadkarni VM, Larkin GL, Peberdy MA, et al. First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. JAMA 2006;295:50–7.
14. Cummins RO, Chamberlain D, Hazinski MF, et al. Recommended guidelines for reviewing, reporting, and conducting research on in-hospital resuscitation: the in-hospital "Utstein style". Circulation 1997;95:2213–39.
15. Jacobs I, Nadkarni V, Bahr J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: Update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council. Circulation 2004;110:3385–97.
16. The American Hospital Association. AHA Annual Survey Data Fiscal Year. 2018 (Accessed 1 December 2019, https://www.ahadata.com/).
17. Steurer MA, Baer RJ, Keller RL, et al. Gestational age and outcomes in critical congenital heart disease. Pediatrics 2017140:.
18. Tyson JE, Parikh NA, Langer J, Green C, Higgins RD. Intensive care for extreme prematurity–moving beyond gestational age. N Engl J Med 2008;358:1672–81.
19. Tennant PWG, Pearce MS, Bythell M, Rankin J. 20-year survival of children born with congenital anomalies: a population-based study. Lancet 2010;375:649–56.
20. Peberdy MA, Ornato JP, Larkin GL, et al. Survival from in-hospital cardiac arrest during nights and weekends. JAMA 2008;299:785–92.
21. Jensen EA, Lorch SA. Association between off-peak hour birth and neonatal morbidity and mortality among very low birth weight infants HHS public access. J Pediatr 2017;186:41–8.
22. Khera R, Tang Y, Girotra S, et al. Pulselessness After initiation of cardiopulmonary resuscitation for bradycardia in hospitalized children. Circulation 2019;140:370–8.
23. Atkins DL, Everson-Stewart S, Sears GK, et al. Epidemiology and outcomes from out-of-hospital cardiac arrest in children: The resuscitation outcomes consortium epistry-cardiac arrest. Circulation 2009;119:1484–91.
24. Gupta P, Rettiganti M, Gossett JM, et al. Association of presence and timing of invasive airway placement with outcomes after pediatric in-hospital cardiac arrest. Resuscitation 2015;92:53–8.
25. Andersen LW, Raymond TT, Berg RA, et al. Association between tracheal intubation during pediatric in-hospital cardiac arrest and survival. JAMA 2016;316:1786–97.
26. Papile LA, Baley JE, Benitz W, et al. Levels of neonatal care. Pediatrics 2012;130:587–97.
27. Rosenberg DI, Moss MM. Guidelines and levels of care for pediatric intensive care units. Pediatrics 2004;114:1114–25.
28. Fontana MS, Farrell C, Gauvin F, Lacroix J, Janvier A. Modes of death in pediatrics: Differences in the ethical approach in neonatal and pediatric patients. J Pediatr 2013;162:1107–11.