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Clinical paper

Verification of the termination of resuscitation rules in pediatric out-of-hospital cardiac arrest cases

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Abstract

Aim: Pediatric out-of-hospital cardiac arrest has an unfavorable prognosis; therefore, making accurate predictions of outcomes is crucial for tailoring treatment plans. The termination of resuscitation rules must accurately predict unfavorable outcomes. In this study, we aimed to assess if the current termination of resuscitation rules for adults can predict factors associated with unfavorable outcomes in pediatric out-of-hospital cardiac arrest and examine the relationship between these factors and unfavorable outcomes.

Methods: A retrospective nationwide cohort study of pediatric cases registered in the Japanese Association for Acute Medicine Multicenter Out-of-Hospital Cardiac Arrest Registry from June 1, 2014, to December 31, 2020, was conducted. The association between the current termination of resuscitation rules and outcomes, such as 30-day mortality and unfavorable 30-day neurological outcomes following out-of-hospital cardiac arrest, was evaluated.

Results: A total of 1,216 participants were included. The positive predictive value for predicting 30-day mortality for each termination of resuscitation rule exceeded 0.9. The specificity and positive predictive value for predicting unfavorable 30-day neurological outcomes were 1.00, indicating that no rules identified favorable outcomes. Factors such as no bystander witness, no return of spontaneous circulation before hospital arrival, no automated external defibrillator or defibrillator use, and no bystander cardiopulmonary resuscitation were associated with poor 30-day mortality and neurological outcomes.

Conclusion: Adult termination of resuscitation rules had a high positive predictive value for predicting pediatric out-of-hospital cardiac arrest. However, surviving cases make it challenging to use these rules for end-of-resuscitation decisions, indicating the need for identifying new rules to help predict neurological outcomes.

Keywords: Children, Out-of-hospital cardiac arrest, Termination of resuscitation, Positive predictive value, Neurological outcome, Life support

Introduction

Pediatric out-of-hospital cardiac arrest (pOHCA) has an unfavorable prognosis, with only 6–8% of patients being discharged from the hospital and only 1–2% experiencing favorable neurological outcomes among those who survive.[1–3] Pediatric patients typically survive longer, making decisions regarding the termination of resuscitation (TOR) ethically complex.[4] Therefore, accurate prognosis prediction is crucial for determining a treatment plan that aligns with the family's preferences.

The TOR rules for adults have been employed to assess the appropriateness of prehospital resuscitation termination.[5,6] Multiple

Abbreviations: pOHCA, Pediatric out-of-hospital cardiac arrest, TOR, termination of resuscitation, JAAM-OHCA Registry, Japanese Association for Acute Medicine Multicenter Out-of-Hospital Cardiac Arrest Registry, CPR, cardiopulmonary resuscitation, ROSC, return of spontaneous circulation, AED, automated external defibrillator, BLS, Basic Life Support, ALS, Advanced Life Support, SOS-KANTO, Survey of survivors after cardiac arrest conducted in the Kanto area of Japan, PCPC, Pediatric Cerebral Performance Category, ROC, receiver operating characteristic, AUC, area under the curve, PPV, positive predictive value, NPV, negative predictive value, CI, confidence intervals, OR, odds ratio

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studies have investigated the association between the TOR rules and mortality and neurological outcomes, demonstrating its high accuracy.[1,7,8]

This approach has also been considered in pediatric cases[8]; however, the evidence for the TOR rule suitable for pediatric patients is insufficient. Furthermore, current TOR rules developed for adults do not consider the characteristics of pOHCA.

In this study, we aimed to evaluate the accuracy of current TOR rules for adults in predicting mortality and unfavorable neurological outcomes in pOHCA patients. In addition to the TOR rules developed in Europe and the United States, this study expanded the scope by examining three additional TOR rules developed in Asia. Furthermore, we examined which variables within these rules are significantly associated with unfavorable neurological outcomes.

Materials and methods

Study design, settings, and population

This study employed a retrospective nationwide cohort study using the Japanese Association for Acute Medicine Multicenter Out-of-Hospital Cardiac Arrest Registry (JAAM-OHCA Registry), accessible at https://www.jaamohca-web.com. The JAAM-OHCA Registry is a nationwide, multicenter prospective registry that enrolls patients with OHCA transported to 153 participating medical institutions (as of October 2023). This registry is integrated by the JAAM-OHCA Registration Committee, and it collects both before and during hospitalization data. Prehospital data are obtained from the All-Japan Utstein Registry maintained by the Fire and Disaster Management Agency of the Ministry of Internal Affairs and Communications. Inhospital data are collected by physicians or medical staff at each facility using an internet-based system. The physicians or medical staff at each facility entered information obtained during the period from admission to discharge, including survival information.

The study participants included pediatric patients under the age of 18 years who were registered in the OHCA Registry between June 1, 2014, and December 31, 2020. The exclusion criteria were adults aged 18 years or older and cases with missing data. The data collected included age, sex, witnesses to cardiac arrest, bystander cardiopulmonary resuscitation (CPR), cause of cardiac arrest, initial rhythm, rhythm upon arrival at the hospital, presence and timing of the return of spontaneous circulation (ROSC), CPR duration by emergency medical services, automated external defibrillator (AED) or defibrillator usage, 30-day survival, and 30-day neurological outcome. Based on the clinical findings, the physician in charge determined the cause of the cardiac arrest.

The institutional Ethics Committees of Yokohama City University Medical Center approved this study (approval number 2022–008 of December 23, 2022). The Japanese Association for the Acute Medicine Multicenter was the authority to approve the study data access. The need for consent was waived by the Institutional Ethics Committees that approved our study due to the observational nature of the study design, per the Personal Information Protection Law and National Research Ethics Guideline in Japan.

Emergency medical services system in Japan

As of 2023, Japan's population was approximately 123 million, with around 18 million children under the age of 17 years.[9] In Japan, when an emergency call is received, at least three emergency personnel, including one certified paramedic, are dispatched to the scene in an ambulance. Emergency paramedics in Japan hold national qualifications and receive training in advanced airway management, intravenous line insertion, intravenous epinephrine administration, and defibrillation.[10] In Japan, emergency personnel are prohibited by law from terminating resuscitation efforts at the scene except when clear signs of irreversible death are present, such as decapitation, rigor mortis, charring, or decomposition. Emergency personnel in Japan follow the Japanese Cardiopulmonary Resuscitation Guidelines[11] and perform CPR while transporting the patient to a medical facility.

Pediatric life support in Japan

In Japan, consideration of extracorporeal cardiopulmonary resuscitation (ECPR) for children with congenital heart disease who suffer in-hospital cardiac arrest has been proposed, but there are no recommendations for ECPR for pOHCA.[12] Respiratory and circulatory management and temperature control are standard treatments after return of spontaneous circulation. Euthanasia is not legalized, and discontinuation of therapy is generally prohibited for both children and adults.

TOR rules

Based on previous literature, we used the current available five TOR rules: Basic Life Support (BLS),[3] Advanced Life Support (ALS),[5] modified Goto,[13] Lee's,[14] and Survey of survivors after cardiac arrest conducted in the Kanto area of Japan (SOS-KANTO) [15]. The BLS TOR and ALS TOR rules have a high predictive value for determining unfavorable neurologic outcomes and are recommended in the American Heart Association and European Resuscitation Council guidelines. The modified Goto's TOR rule was proposed in 2022 and is a novel rule that incorporates prehospital Emergency Medical Service (EMS) CPR time into the rule. The TOR rules of Lee and SOS-KANTO incorporate prehospital ECG rhythm to predict unfavorable neurologic outcomes. A summary of these rules is shown in Supplementary Table S1.

Outcomes

The primary outcomes of the study included 30-day mortality and 30-day unfavorable neurological outcome. The neurological outcome was assessed using the Pediatric Cerebral Performance Category (PCPC) scale,[16] which consists of several categories: Category 1 (normal), Category 2 (mild disabilities), Category 3 (moderate disabilities), Category 4 (severe disabilities), Category 5 (coma or vegetative state), and Category 6 (death or brain death). An unfavorable neurological outcome was determined based on the assessment of the attending physician 1 month after successful resuscitation using the PCPC scale, where Category 3 or higher was considered indicative of such an outcome.

Furthermore, we examined the association between each TOR and variable and unfavorable neurological outcomes. Synonymous variables were grouped as identical.

Statistical analyses

First, descriptive statistics were obtained for all variables. In the primary analysis, the predictive accuracy for 30-day mortality and unfavorable neurological outcomes were evaluated among pOHCA patients in Japan by the five TOR rules, using receiver operating characteristic (ROC) curve analysis. We calculated the area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and 95% confidence intervals (CI). In the secondary analysis, the mortality and unfavorable neurological outcome risks were analyzed using the multivariable logistic regression analysis. The odds ratio (OR) with a 95% CI for mortality and unfavorable neurological outcome was used to compare the relative risks. The predictive variables of five TOR rules were included in the multivariable logistic regression analysis to assess the risk of unfavorable neurological outcomes. A p-value of < 0.05 was considered statistically significant. The statistical analysis was conducted using the R statistical software (R Foundation for Statistical Computing, Vienna, Austria) with the RcmdrPlugin.EZR package.

Results

A total of 60,349 patients were included in the OHCA registry. After excluding adult patients and cases with missing data, 1,216 pediatric cases were eligible for the study. Among these, 307 cases (25.2%) had ROSC (Fig. 1).

Males represented 753 (61.9%) cases, with a median age of 6.5 years, and the majority being younger than 1 year (33.8%) or between 12–17 years (34.4%). Bystander-witnessed cases accounted for 30.6%, while cases with bystander CPR were 58.4%. The initial electrocardiography waveform revealed asystole in 75.5% of cases, and cardiogenic cases accounted for 5.3% of the total cases. Among the cases with ROSC, 23.7% (6.0% of the total) had achieved ROSC before hospital arrival. Of the cases admitted after ROSC, 30-day survival was 10.2% of the total, and only 4.0% had a favorable neurological outcome (Table 1).

Table 2 shows the predictive accuracy for the 30-day mortality of each TOR rule. The specificity of the BLS TOR rule was lowest (0.581), whereas the PPV for all rules remained above 0.9.

Table 3 shows the predictive accuracy for the 30-day unfavorable neurological outcome of each TOR rule. In all rules, both the specificity and PPV were 1.00. Notably, no cases with a favorable neurological outcome were identified among the patients.

The results of the secondary analysis revealed an association between 30-day mortality and the absence of a bystander witness (OR, 1.97; 95% CI, 1.17–3.32), no ROSC before hospital arrival (OR, 4.49; 95% CI, 2.33–8.67), asystole at hospital arrival (OR, 11.7; 95% CI, 6.47–21.1), no AED or defibrillator use (OR, 4.24; 95% CI, 2.13–8.46), and no bystander CPR (OR, 1.93; 95% CI, 1.16–3.22) (Table 4). Similarly, factors associated with unfavorable neurological outcomes included initial asystole (OR, 17.3; 95% CI, 1.5–200), the absence of a bystander witness (OR, 6.43; 95% CI, 1.81–22.8), no ROSC before hospital arrival (OR, 16.5; 95% CI, 5.86–46.3), no AED or defibrillator use (OR, 11.6; 95% CI 4.10–33.1), and no bystander CPR (OR, 3.44; 95% CI 1.11–10.7) (Table 5).

In addition, 55 cases were identified that met at least one of the TOR rules but survived (Supplementary Table S2). All cases had ROSC after arrival at the hospital, and all had unfavorable neurological outcomes.

Discussion

The study evaluated the predictive accuracy of five TOR rules for pOHCA in Japan using data from the JAAM-OHCA Registry.

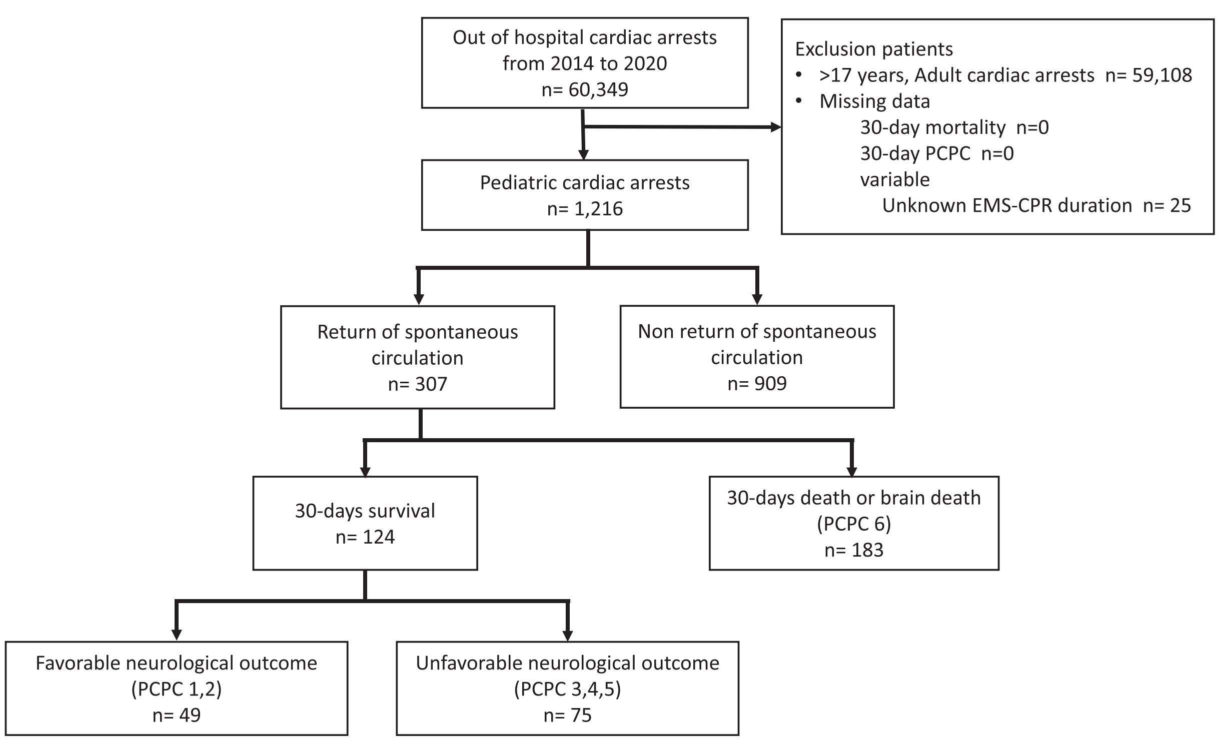

Fig. 1 – Study flowchart. PCPC, pediatric cerebral performance category. EMS-CPR, emergency medical services-cardiopulmonary resuscitation.

Table 1 – Characteristics and outcomes among eligible pediatric out-of-hospital cardiac arrest patients.

		Pediatric out of hospital cardiac arrests (n = 1216)	
Male, n (%)		753	(61.9%)
Age			
	<1 year, n (%)	411	(33.8%)
	1–5 years, n (%)	258	(21.2%)
	6–11 years, n (%)	129	(10.6%)
	12–17 years, n (%)	418	(34.4%)
Bystander witness, n (%)		372	(30.6%)
Bystander CPR, n (%)		710	(58.4%)
Cardiogenic cardiac arrest, n (%)		64	(5.3%)
Initial rhythm			
	VF, n (%)	35	(2.9%)
	VT, n (%)	3	(0.2%)
	PEA, n (%)	202	(16.6%)
	Asystole, n (%)	918	(75.5%)
	Other, n (%)	58	(4.8%)
Initial rhythm in the hospital			
	VF, n (%)	10	(0.8%)
	VT, n (%)	4	(0.3%)
	PEA, n (%)	192	(15.8%)
	Asystole, n (%)	962	(79.1%)
	Other, n (%)	73	(6.0%)
EMS-CPR duration > 20 min		549	(45.1%)
Public-access AED use or shock by EMS		77	(6.3%)
Return of spontaneous circulation, n (%)		307	(25.2%)
	before hospital arrival, n (%)	73	(6.0%)
30 days survival, n (%)		124	(10.2%)
	with favorable neurological (PCPC 1,2), n (%)	49	(4.0%)

CPR, cardiopulmonary resuscitation; PCPC, pediatric cerebral performance category; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; EMS, emergency medical services; AED, automated external defibrillator.

All current TOR rules demonstrated a high PPV for predicting mortality and unfavorable outcomes. However, some cases survived despite the application of these rules, indicating that mortality prediction was not entirely accurate. Additionally, by analyzing the variables of each rule, several factors associated with unfavorable outcomes were identified, including the absence of a bystander witness, no ROSC before hospital arrival, no AED or defibrillator use, and no bystander CPR.

All TOR rules in this study showed highly accurate PPVs and specificity for unfavorable neurological outcomes, similar to studies in adults.[1,7,14,15] Studies of pOHCA are limited, and the ALS and BLS TOR rules, which have been evaluated in the past, have shown high accuracy in predicting unfavorable neuroprognosis,[8] similar to this study.

In this study, the diagnostic accuracy of the TOR rule for predicting 30-day survival was poor. Achieving extremely high specificity, ideally close to 100%, is crucial when using the TOR rule to discontinue resuscitation efforts to avoid prematurely terminating potentially reversible cases. Consequently, the utility of the TOR rule as a criterion for discontinuing pediatric resuscitation may be challenging. Furthermore, various non-medical considerations, including parental emotional distress and moral distress among the medical staff, may influence the decision to terminate resuscitation in children.[4] Additionally, family and cultural values may strongly influence the perception that survival with poor neurological outcomes is acceptable. Therefore, despite its high accuracy, the adaptation of the TOR rule is limited to adults.[5,6]

However, none of the patients who met the TOR rule and survived had a favorable neurological outcome. A common factor observed among these patients was the absence of prehospital ROSC, which may have contributed to prolonged cerebral hypoperfusion. Previous studies involving adults have reported that less than 1% of patients meeting the TOR rule achieve favorable neurological outcomes.[17] This suggests that patients meeting the TOR rule are likely to have an unfavorable neurological outcome. Another study suggests using the TOR rule as a decision-support tool for medical professionals and patient families.[18] The TOR rule could serve as a tool to predict unfavorable neurological outcomes, facilitating shared decision-making between clinicians and families regarding the withdrawal of resuscitative measures.

This study showed that the risk ratios associated with death or unfavorable neurological outcomes varied among the predictive factors used in the current TOR rule. Previous studies have reported that blood neuron-specific enolase, blood lactate levels, and light reflex within 24 h after ROSC are factors predicting neurological prognosis in children.[19–21] These factors are typically evaluated in the posthospitalization period, making it challenging to assess neurological outcomes in the early postresuscitation phase. Therefore, identifying the factors that can predict outcomes in the early phase after resuscitation is essential, and the predictive factors used in the TOR rule may be useful in this regard.

The etiology of cardiac arrest in children differs from that in adults, with respiratory problems being reported as a more common cause in pediatric cardiac arrest; moreover, the causes and risks of

Table 2 – Diagnostic accuracy of 5 TOR rules (pediatric out-of-hospital cardiac arrest patients 30-days survival).

	Death	Survival	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Modified GOTO's TOR rule			0.53 (0.491–0.569)	0.277 (0.251–0.305)	0.782 (0.699–0.851)	0.918 (0.883–0.945)	0.109 (0.090–0.132)
Met 4/4 criteria, n	303	27					
Did not meet criteria, n	789	97					
Lee's TOR rule			0.774 (0.743–0.804)	0.652 (0.623–0.680)	0.895 (0.827–0.943)	0.982 (0.970–0.990)	0.226 (0.190–0.266)
Met 3/3 criteria, n	712	13					
Did not meet criteria, n	380	111					
SOS-KANTO's TOR rule			0.775 (0.744–0.805)	0.654 (0.625–0.682)	0.895 (0.827–0.943)	0.982 (0.970–0.990)	0.227 (0.191–0.267)
Met 3/3 criteria, n	714	13					
Did not meet criteria, n	378	111					
BLS TOR rule			0.742 (0.698–0.787)	0.904 (0.885–0.921)	0.581 (0.489–0.669)	0.95 (0.950–0.962)	0.407 (0.334–0.483)
Met 3/3 criteria, n	987	52					
Did not meet criteria, n	105	72					
ALS TOR rule			0.599 (0.574–0.624)	0.263 (0.237–0.290)	0.935 (0.877–0.972)	0.973 (0.947–0.988)	0.126 (0.105–0.149)
Met 5/5 criteria, n	287	8					
Did not meet criteria, n	805	116					

TOR, termination of resuscitation; AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Table 3 – Diagnostic accuracy of 5 TOR rules (pediatric out-of-hospital cardiac arrest patients unfavorable neurological outcome).

	PCPC≧3	PCPC1/2	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Modified GOTO's TOR rule			0.641 (0.628–0.654)	0.283 (0.257–0.310)	1 (0.894–1.000)	1 (0.983–1.000)	0.055 (0.041–0.072)
Met 4/4 criteria, n	330	0					
Did not meet criteria, n	837	49					
Lee's TOR rule			0.811 (0.797–0.825)	0.621 (0.593 0.649)	1 (0.894–1.000)	1 (0.992–1.000)	0.1 (0.075–0.130)
Met 3/3 criteria, n	725	0					
Did not meet criteria, n	442	49					
SOS-KANTO's TOR rule			0.811 (0.798–0.825)	0.623 (0.594–0.651)	1 (0.894–1.000)	1 (0.992–1.000)	0.1 (0.075–0.130)
Met 3/3 criteria, n	727	0					
Did not meet criteria, n	440	49					
BLS TOR rule			0.945 (0.936–0.954)	0.89 (0.871–0.908)	1 (0.894–1.000)	1 (0.995–1.000)	0.277 (0.212–0.349)
Met 3/3 criteria, n	1039	0					
Did not meet criteria, n	128	49					
ALS TOR rule			0.626 (0.614–0.639)	0.253 (0.228–0.279)	1 (0.894–1.000)	1 (0.981–1.000)	0.053 (0.040–0.070)
Met 5/5 criteria, n	295	0					
Did not meet criteria, n	872	49					

PCPC, pediatric cerebral performance category; TOR, termination of resuscitation; AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

cardiac arrest differ by age group.[22,23] In this study, only 3.1% of patients exhibited a shockable rhythm, which is considerably lower than those observed in adults (15–30%).[24,25] Nevertheless, "no use of AED/defibrillator" has been identified as an independent risk factor for unfavorable neurological outcomes despite its small prevalence. Previous reports have indicated that shockable rhythms are associated with favorable outcomes in children.[26,18] By excluding the shockable rhythm group, it may be possible to perform a more accurate analysis. Additionally, given that several components of the current TOR rule have a cardiac origin, it is important to consider non-cardiac factors as well.

We consider that new rules are needed to predict the prognostic value of therapeutic interventions for pOHCA. Furthermore, to instill confidence in medical professionals, instruments that more accu-

Table 4 – Results of multivariable logistic regression analysis of risk factors for 30-days survival.

	Odds ratio	95% CI	p-value
Initial asystole	0.86	(0.48-1.56)	0.626
Not witnessed by bystanders	1.97	(1.17-3.32)	0.011
EMS-CPR duration > 20 min	1.12	(0.69-1.82)	0.637
No prehospital ROSC	4.49	(2.33–8.67)	<0.001
Asystole on arrival to the hospital	11.7	(6.47-21.1)	<0.001
No public-access AED use or shock by EMS	4.24	(2.13-8.46)	<0.001
No bystander-initiated CPR	1.93	(1.16-3.22)	0.011

CI, confidence interval; EMS, emergency medical service; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; AED, automated external defibrillator.

Table 5 – Results of multivariable logistic regression analysis of risk factors for unfavorable neurological outcome.

	Odds ratio	95% CI	p-value
Initial asystole	17.3	(1.50-200)	0.022
Not witnessed by bystanders	6.43	(1.81-22.8)	0.004
EMS-CPR duration > 20 min	0.87	(0.32–2.40)	0.788
No prehospital ROSC	16.5	(5.86-46.3)	<0.001
Asystole on arrival to the hospital	51,000,000	(0.00-Inf)	0.989
No public-access AED use or shock by EMS	11.6	(4.10-33.1)	<0.001
No bystander-initiated CPR	3.44	(1.11-10.7)	0.032

CI, confidence interval; EMS, emergency medical service; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; AED, automated external defibrillator.

rately estimate the number of neurological consequences and the medical resources required, quantitatively rather than qualitatively, must be developed. Integration of key factors identified through multivariable analysis, along with the vital signs and the data collected upon hospital arrival, may facilitate the development of rules capable of accurately identifying unfavorable neurological outcomes in pOHCA.

Limitations

This study has several limitations. First, like all epidemiological observational studies, the present study has potential limitations related to data completeness, validity, and confirmation bias. Additionally, being an open-label study, clinicians' awareness of the TOR criteria might have inadvertently influenced decisions regarding withdrawing life-sustaining therapy, potentially impacting outcomes. Second, the dataset lacks information about the quality of prehospital care. While prehospital TOR is not common in Japan, application of consistent resuscitation measures to all patients following OHCA is not guaranteed. Third, due to the limited number of patients with favorable neurological outcomes, the statistical power to detect significant differences may not be sufficient.

Conclusion

Each TOR rule in adults exhibited a high PPV for predicting unfavorable neurological outcomes in children at one month. However, end-of-life decision-making is highly complex, and relying solely on TOR criteria may not comprehensively account for all the relevant factors that need to be considered in such decisions. These findings suggest the necessity to construct more precise rules that can provide a more comprehensive and accurate prognosis.

Ethical approval

The institutional Ethics Committees of Yokohama City University Medical Center approved this study (approval number 2022-008 of December 23, 2022).

Availability of data and materials

The dataset and/or analysis results of this study have not been made publicly available because they were not permitted by the Ethics Committee.

Consent for publication

The need for consent was waived by the Institutional Ethics Committees that approved our study due to the observational nature of the study design, per the Personal Information Protection Law and National Research Ethics Guideline in Japan.

CRediT authorship contribution statement

Sakura Minami: Writing – original draft. **Chiaki Toida:** Writing – review & editing. **Mafumi Shinohara:** Writing – review & editing, Conceptualization. **Takeru Abe:** Writing – review & editing. **Ichiro Takeuchi:** Supervision.

Declaration of competing interest

The 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 data

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