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Technological advances in emergency medical services system, treatment, and prognostication for cardiac arrest

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Technological advances in emergency medical services system, treatment, and prognostication for cardiac arrest

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Editorial: Technological advances in emergency medical services system, treatment, and prognostication for cardiac arrest

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KEYWORDS

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Editorial on the Research Topic
Technological advances in emergency medical services system, treatment, and prognostication for cardiac arrest

This Research Topic on technological advances in cardiac arrest is divided into the following sections: emergency medical system, emergency room treatment to intensive care after ROSC, and prognosis (Figure 1).

Emergency medical system

A first-pass success rate of 85.7%, an adverse event rate of 19.8%, and a muscle relaxant use rate of 5.3% were reported in tertiary care institutions across China for tracheal intubation procedures (Dai et al.). The most common adverse events were hypoxia, hypotension, and aspiration, which were more common in patients with complications such as pulmonary disease and shock. Since only 25% of the patients in this study had cardiac arrest, it is necessary to examine the success rate of tracheal intubation and adverse events in patients with cardiac arrest only, as well as to evaluate outcomes.

The relationship between MAP or SAP from the femoral artery, and cerebral oxygen saturation rSO2 was examined to determine the effect of chest compressions, and it was reported that rSO2 showed a significant association with MAP and SAP (Kishihara et al.) It is possible that rSO2 can non-invasively assess the quality of chest compressions. The challenge is that this report does not provide the rSO2 values necessary for effective chest compressions because the values were evaluated using log transformation and only cases with poor outcome (92% died) were studied. High rSO2 values during CPR have been reported to be associated with cardiac resumption and good neurological outcome (1), and should be discussed with MAP or SAP in the future.

Intensive care after cardiac resumption from the emergency room

REBOA is used for trauma resuscitation in patients with life-threatening bleeding below the diaphragm (Aoki and Abe). REBOA is contraindicated in TCA patients with chest

trauma, i.e., major bleeding from the chest or cardiac tamponade. During cardiopulmonary resuscitation (CPR) in TCA, REBOA increases perfusion of the brain and coronary arteries. REBOA is less invasive than resuscitative thoracotomy with aortic cross-clamping (RT-ACC) and does not require interruption of chest compressions during the procedure. It is important to note that this study notes that REBOA can have serious complications and that future studies are needed to determine the aortic cutoff time of REBOA.

A study of oxygen status in OHCA patients undergoing ECPR found no significant association between hyperoxia in the first 24 h after admission and 30-day survival (Kobayashi et al.). In previous reports of hyperoxia after ECPR being associated with poor outcome, the site of blood gas collection was unknown. In this study, blood gases were drawn from the right radial or right brachial artery, which is significant in that the oxygen status reflects the oxygen status of the brain. Generally, retrograde blood flow from ECMO mixes with retrograde blood flow from the patient's own heart, creating a watershed condition known as Harlequin syndrome (North-South syndrome). Cardiac function was not assessed in this study and it is not known where the watershed is located, and that evaluation is needed in the future.

SpotOn^{TM} creates an isothermal tunnel under the measurement site by applying a probe to the forehead to insulate heat loss from the skin surface, and estimates central body temperature with a zero-heat-flux technology SpotOn^{TM} has been compared to an esophageal temperature probe in patients with cardiac arrest during TTM. Although its accuracy is slightly less than the predetermined 0.5°C, it is a potential method for non-invasively monitoring central body temperature (Fiorini et al.). Previous reports have examined this method over a 9-h monitoring period, but the evaluation of TTM over a 72-h period was obtained in this study, which increases its practicality.

A systematic review showed that the TTM strategy had no significant effect on mortality and neurological outcome in cardiac arrest survivors who presented with an initial non-shockable rhythm (Zhu et al.). However, the greatest weakness of the present study is that it did not distinguish between TTM, i.e., hypothermia, normothermia, fever prevention, and fever left untreated. In addition, although the title of this study indicates that it is an RCT, it is mainly an analysis of observational research articles, and in this sense, there is a lot of bias, which requires caution when interpreting the results.

Prediction of prognosis

The Survival After ROSC in Cardiac Arrest (SARICA) score (pre-hospital ROSC, age and initial heart rhythm) was shown to predict survival at 30 days with high accuracy in an external validation study using a multinational pan-Asian cohort (Rajendram et al.). The authors comment that the SARICA score is a routinely available and objective variable to evaluate. However, in Japan, serum lactate, pH, cause of arrest, and other factors can be rapidly assessed in the emergency department of a tertiary care hospital, and low-flow or no-flow time can be estimated, even with recall bias, allowing more complex score calculations to assess prognosis (2). On the other hand, a common thread in East Asia is the strong cultural influence regarding the withholding and stopping of life support, which can confound outcomes. This East Asian view differs from that of the West and requires caution when interpreting prognostic assessments.

In a report examining factors that predict the occurrence of IHCA, five factors were reported: SBP, HR, hypothermia,

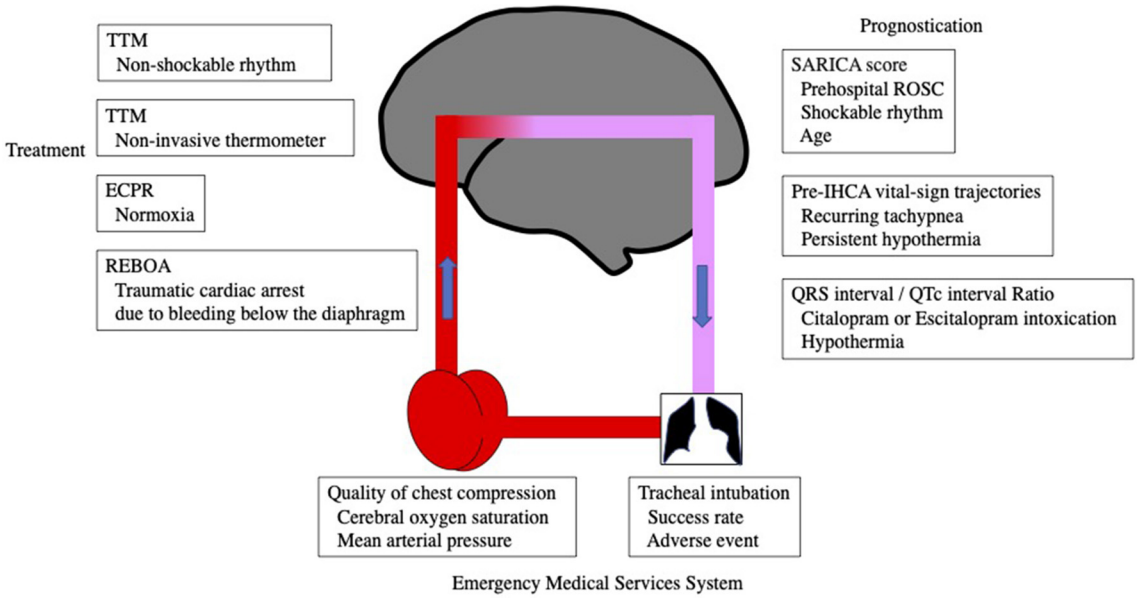

FIGURE 1
Research topics at the points of cerebral oxygen demand/supply balance.

tachypnea, and oxygen saturation. Furthermore, in a multivariate analysis, hypothermia and repetitive tachypnea were independently associated factors as predictors of IHCA (Tsai et al.), suggesting that a better understanding of vital sign changes before IHCA may lead to early detection of deteriorating patients and prevention of IHCA. IHCA is different from OHCA in its cause, and because it is in-hospital, a prompt response can be expected. In this sense, this score is useful.

The QRS interval/QTc interval-ratio has been reported as a predictor of ventricular arrhythmia and cardiac arrest in patients treated with hypothermia or accidental hypothermia. Citalopram and escitalopram, commonly used for depression, often have elevated blood levels, and the QRS/QTc ratio was reported to be predictive of ventricular arrhythmias in these patients (Dietrichs et al.) new score, but future studies are needed to determine how much better it is than the QTc itself.

In this Research Topic, therefore, I will focus on the use of REBOA for traumatic cardiac arrest, control of oxygenation status in ECPR, and factors that predict IHCA (sustained hypothermia, repeated tachypnea).

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Trajectories of Vital Signs and Risk of In-Hospital Cardiac Arrest

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Background: Little is known about the trajectories of vital signs prior to in-hospital cardiac arrest (IHCA), which could explain the heterogeneous processes preceding this event. We aimed to identify clinically relevant subphenotypes at high risk of IHCA in the emergency department (ED).

Methods: This retrospective cohort study used electronic clinical warehouse data from a tertiary medical center. We retrieved data from 733,398 ED visits over a 7-year period. We selected one ED visit per person and retrieved patient demographics, triage data, vital signs (systolic blood pressure [SBP], heart rate [HR], body temperature, respiratory rate, oxygen saturation), selected laboratory markers, and IHCA status. Group-based trajectory modeling was performed.

Results: There were 37,697 adult ED patients with a total of 1,507,121 data points across all vital-sign categories. Three to four trajectory groups per vital-sign category were identified, and the following five trajectory groups were associated with a higher rate of IHCA: low and fluctuating SBP, high and fluctuating HR, persistent hypothermia, recurring tachypnea, and low and fluctuating oxygen saturation. The IHCA-prone trajectory group was associated with a higher triage level and a higher mortality rate, compared to other trajectory groups. Except for the persistent hypothermia group, the other four trajectory groups were more likely to have higher levels of C-reactive protein, lactic acid, cardiac troponin I, and D-dimer. Multivariable analysis revealed that hypothermia (adjusted odds ratio [aOR], 2.20; 95% confidence interval [95%CI], 1.35–3.57) and recurring tachypnea (aOR 2.44; 95%CI, 1.24–4.79) were independently associated with IHCA.

Conclusions: We identified five novel vital-sign sub-phenotypes associated with a higher likelihood of IHCA, with distinct patterns in clinical course and laboratory markers. A better understanding of the pre-IHCA vital-sign trajectories may help with the early identification of deteriorating patients.

Keywords: cardiac arrest, vital sign, group-based trajectory modeling, in-hospital cardiac arrest, longitudinal modeling, emergency department (ED)

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INTRODUCTION

In-hospital cardiac arrest (IHCA) is a major problem in the hospital and is associated with high morbidity and mortality worldwide (1). In the United States, the incidence of adult treated IHCA was about 10 per 1,000 hospital admissions (∼290,000 patients per year), about 10% of which occurred in the emergency department (ED) (2, 3). Only about 25% of the IHCA patients survived to hospital discharge, and among them, 85% were discharged with a favorable neurological outcome (1).

Despite the catastrophic nature of IHCA, little is known about the trajectories of vital signs prior to IHCA. Early recognition and prevention have been added as the first link in the Chain of Survival for IHCA (4). Understanding the pre-IHCA physiological derangements, particularly longitudinal dynamic changes, would help clinicians recognize the patterns and the heterogeneous processes preceding the devastating event. Previous studies have utilized a snapshot of vital-sign data to predict IHCA (5, 6). In clinical practice, intermittently measured snapshot vital-sign data sometimes cause confusion as to appropriate responses, especially when no prior data are compared or are too late for interventions (7). Other studies have created summary measures for longitudinal vital-sign data (8), or have monitored early warning summary scores over time (9). As such, information is somewhat lost in terms of the dynamic changes of each vital sign over time, which may be more intuitive and clinically useful in phenotyping and prognosticating patients with IHCA. Group-based trajectory modeling (GBTM) is an unsupervised modeling technique to identify hidden subpopulations comprising similar individuals (10). To the best of our knowledge, no previous study has examined the latent trajectories of vital signs in patients with IHCA. Understanding the vital-sign change patterns prior to IHCA may gain lead time for appropriate interventions.

In this study, we aimed to identify clinically relevant sub-phenotypes at high risk of IHCA in the ED using longitudinal vital-sign data. We hypothesized that certain trajectory groups would have a higher likelihood of IHCA, with distinct patterns in clinical course and laboratory findings.

METHODS

Study Design and Setting

We conducted a retrospective cohort study using data from the integrated Medical Database (iMD) of the National Taiwan University Hospital (NTUH). This database serves as a central clinical data warehouse for all electronic health records in the healthcare system (the main hospital and six branch hospitals), including inpatient, outpatient, and ED records. The electronic database houses a variety of information, including demographics, diagnosis, treatment, imaging, laboratory, prescription, nursing, billing, and administrative data. The database is maintained and updated by dedicated research personnel and has been used for clinical research studies (11, 12).

For the current study, we retrieved 7 years of de-identified iMD data from the NTUH main hospital between January 1, 2009 and December 31, 2015. The NTUH main hospital is a tertiary academic medical center with approximately 2,400 beds and 100,000 ED visits per year. The ED also manages an observation unit (EDOU), which is staffed by ED physicians. This study was approved by the NTUH Institutional Review Board, which waived the requirement for patient informed consent.

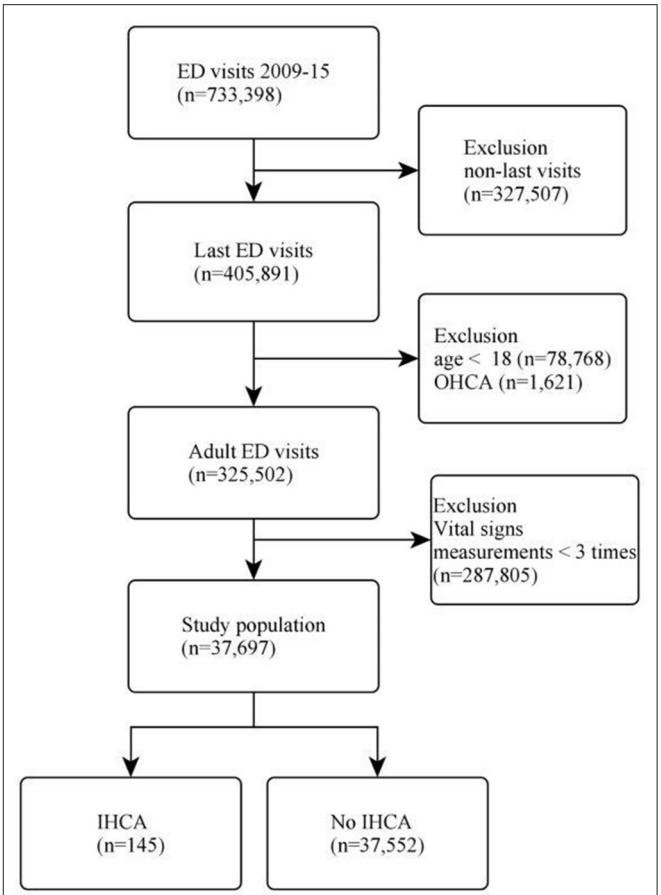

FIGURE 1 | Flow diagram of the patient selection process. ED, emergency department; OHCA, out-of-hospital cardiac arrest; IHCA, in-hospital cardiac arrest.

Study Population

We electronically extracted data from 733,398 ED visits over the 7-year period. For repeat visits, we selected the last visit per patient to maximize statistical power for the cardiac arrest analysis. If a patient had subsequent visits, it was much less likely that he/she suffered a cardiac arrest on a prior visit. We further excluded out-of-hospital cardiac arrests (OHCAs), patients aged less than 18 years, or those who had less than three vital-sign measurements. At least three measurements would ensure the stability of longitudinal analysis, and therefore many EDOU patients were included. The subject selection process is shown in **Figure 1**.

Variables

Patient demographics and time-stamped clinical information in the ED were extracted, including chief complaint on ED

presentation, mode of arrival, transfer status, serial vital sign measurements (systolic blood pressure [SBP], heart rate [HR], body temperature [BT], respiratory rate [RR], and oxygen saturation [SpO_2]). The vital-sign measurements were from hour 0 (at ED triage) to the last measurement available or hour 191 (the timing of the last IHCA event), whichever occurred earlier. The vital-sign data were split into 1-h blocks, and if multiple measurements occurred in the 1-h block, the average value was used. The quick Sepsis-related Organ Failure Assessment (qSOFA) score at ED triage was calculated (13). Selected laboratory test results were also retrieved, including C-reactive protein (CRP), lactic acid, cardiac Troponin I (cTnI), and D-dimer. The ED-based IHCA was identified via a cardiopulmonary resuscitation (CPR) code (i.e., treated cardiac arrest). All laboratory results were the earliest available data in the ED. For IHCA patients, laboratory data were restricted to those obtained prior to CPR.

We also electronically extracted the five-level computerized Taiwan triage and acuity scale (TTAS) that contains information on a total of 179 structured chief complaints. The chief complaints included OHCA, which was used to identify the OHCA population. Based on the computerized algorithms, the TTAS classifies patients in the following order of acuity: level 1, resuscitation; level 2, emergent; level 3, urgent; level 4, less urgent; and level 5, non-urgent. The TTAS was adapted from the Canadian Triage and Acuity Scale and has been validated against hospitalization, length of ED stay, and resource utilization (14). To study the possible causes of IHCA, the primary fields of ED discharge diagnosis codes were grouped into clinically meaningful categories using the Clinical Classification Software (CCS) (15).

The data extractors were hospital information technology engineers who were blinded to the study hypothesis. The data underwent electronic cleaning, and invalid data were set to missing values after periodic investigator meetings.

Outcome Measures

The primary outcome measure, ED-based IHCA, was identified via a cardiopulmonary resuscitation (CPR) procedure code (i.e., treated cardiac arrest). Patients with do-not-resuscitate (DNR) status were not counted as treated cardiac arrests, according to consensus guidelines on reporting IHCA (16). The secondary outcome measure was mortality in the ED.

Statistical Analysis

Summary statistics are presented as proportions (with 95% confidence intervals [CIs]), means (with standard deviations [SDs]), or medians (with interquartile ranges [IQRs]). Bivariate associations were examined using Student *t*-tests, Mann-Whitney tests, and chi-square tests, as appropriate. Patient characteristics, laboratory findings, mortality, and IHCA status were compared between the identified trajectory groups. We used available-case analysis for the laboratory analysis as not all patients had test results available.

Group-based trajectory modeling (GBTM) was performed to identify trajectory groups in each of the five vital-sign categories. GBTM is an explanatory modeling technique to identify hidden groups of individuals with similar trajectories for a particular variable of interest (17). This technique uses finite mixture modeling to identify clusters of longitudinal data (18). We tested models of two to six groups with the inclusion of constant, linear, quadratic, or cubic terms. The Bayesian information criterion was used to choose the optimal number and form of trajectories. GBTM was performed using the traj package in Stata software (StataCorp, College Station, TX, USA).

TABLE 1 | Baseline clinical characteristics of emergency department patients.

Variable	*N* = 37,697
Age, mean (SD), yr	62.9 (18.3)
Female sex, *n* (%)	17,258 (45.8)
Season, *n* (%)	
Spring (Mar. – May)	8,410 (22.3)
Summer (Jun. – Aug.)	10,430 (27.7)
Fall (Sep. – Nov.)	9,721 (25.8)
Winter (Dec. – Feb.)	9,136 (24.2)
Presenting time, *n* (%)	
7:00 am to 2:59 pm	17,071 (45.3)
3:00 pm to 10:59 pm	15,692 (41.6)
11:00 pm to 6:59 am	4,934 (13.1)
Most common chief complaint, *n* (%)	
Fever	5,703 (15.3)
Dyspnea	5,409 (14.5)
Abdominal pain	4,993 (13.4)
Triage level, *n* (%)	
1	2,013 (5.3)
2	13,022 (34.5)
3	21,765 (57.7)
4	827 (2.2)
5	70 (0.2)
qSOFA at triage, median (IQR)	0 (0–1)
Vital sign at triage	
Systolic blood pressure, mean (SD), mmHg	136.3 (31.1)
Heart rate, mean (SD), beats per min	96.5 (22.1)
Body temperature, mean (SD), °C	37.2 (1.1)
Respiratory rate, mean (SD), breaths per min	19.3 (2.9)
Oxygen saturation, median (IQR), %	97 (95–98)
IHCA, *n* (%)	145 (0.4)
Time to IHCA, median (IQR), hr	39.6 (9.2–83.4)
Hospital admission, *n* (%)	23,614 (62.6)
ED mortality, *n* (%)	805 (2.1)
ED/EDOU length of stay, median (IQR), hr	46.6 (22.4–81.6)
Selected laboratory results	
WBC count (K/μL) (<10 K/μL)[a]	9.4 (6.7–13.2)
C–reactive protein (mg/dL) (<1 mg/dL)[b]	5.0 (1.3–12.0)
Lactic acid (mmole/L) (<2 mmole/L)[c]	2.0 (1.3–3.2)
Cardiac troponin I (ng/mL) (<0.05 ng/mL)[d]	0.0 (0.0–0.1)
D–dimer (mg/L) (<0.5 mg/L)[e]	1.8 (0.6–5.0)

[a]*Available in 29,007 patients.* [b]*Available in 5,884 patients.* [c]*Available in 8,556 patients.* [d]*Available in 11,602 patients.* [e]*Available in 2,776 patients. SD, standard deviation; qSOFA, quick Sepsis- related Organ Failure Assessment; IQR, interquartile range; IHCA, in-hospital cardiac arrest; ED, emergency department; EDOU, emergency department observation unit; WBC, white blood cell.*

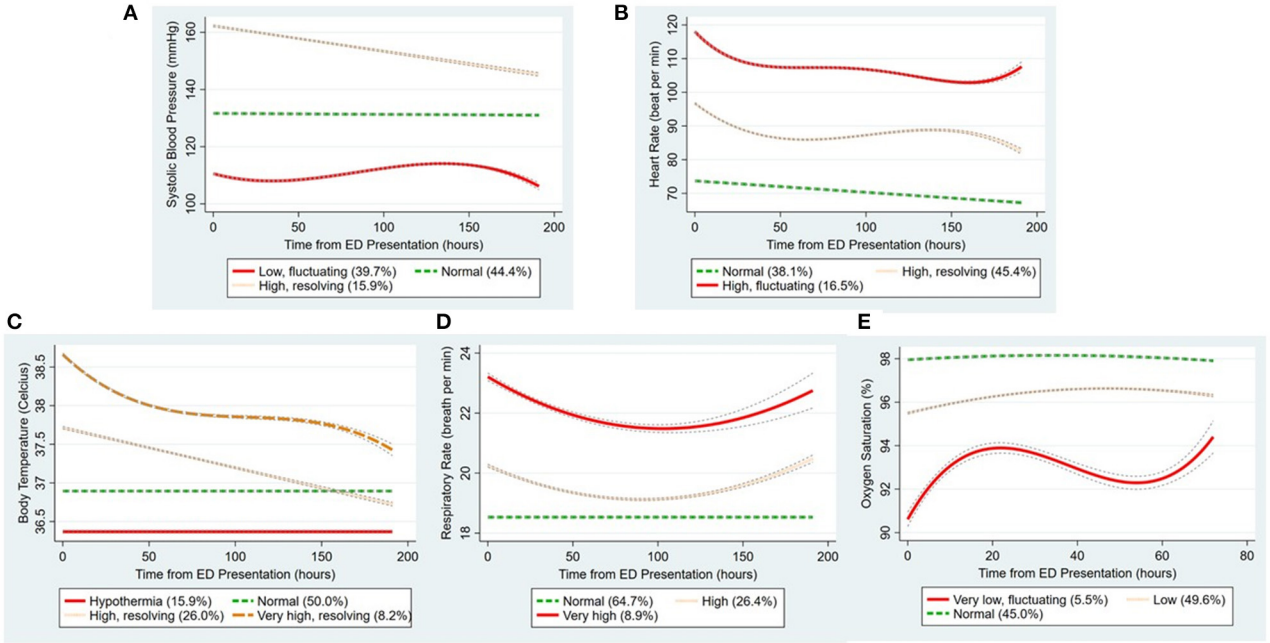

FIGURE 2 | The trajectory groups identified by group-based trajectory modeling in each vital-sign category. **(A-E)** Indicate systolic blood pressure, heart rate, body temperature, respiratory rate, and oxygen saturation, respectively. The percentage in parenthesis denotes the proportion of patients in that trajectory group. The lines around the trajectory show the confidence intervals. ED, emergency department.

After the unsupervised identification of longitudinal trajectories, we used supervised multivariable logistic regression to examine the independent association between the trajectory group memberships and ED-based IHCA, controlling for age, sex, and triage levels. To internally validate the identified trajectory groups, we bootstrapped the model 100 times to obtain the bias-corrected confidence intervals. All odds ratios (ORs) and beta-coefficients are presented with 95% CIs. To test if the trajectory groups using the early data could also relate to the occurrence of IHCA, we conducted a sensitivity analysis by restricting vital-sign measurements from 0 to 24h.

All analyses were performed using Stata 16.0 software. All P values are two-sided, with $P < 0.05$ considered statistically significant.

RESULTS

Of 733,398 ED visits during the 7-year study period, 405,891 unique patient visits were included. After excluding patients aged less than 18 years or patients with out-of-hospital cardiac arrest, 325,502 adult visits were included in the analysis. We further excluded those who had vital signs measurements less than three times, leaving 37,697 patients in the analysis. The patient selection process is shown in **Figure 1**. There were 145 (0.4%) patients who developed IHCA in the ED.

Overall, the mean age of these patients was 63 years, and 46% were women (**Table 1**). Most patients arrived in the ED during the daytime or in the evening, and patients were evenly distributed across seasons. Most patients presented with fever, followed by dyspnea and abdominal pain, were triaged to level 3, and had a median qSOFA score of 0 (IQR, 0–1). The initial vital signs were generally acceptable, except for slightly faster HR and lower SpO_2. The overall incidence of ED-based IHCA was 0.4%, with a median time to IHCA of 40 h. About 63% were admitted to the hospital, and 2% died in the ED. The median ED/EDOU length of stay was about 47 h. Among patients in whom laboratory tests were ordered, some laboratory abnormalities were observed (e.g., leukocytosis and elevated levels of CRP, lactic acid, cTnI, and D-dimer). The baseline clinical characteristics of the 145 IHCA patients are shown in the **Supplementary Table 1**. The most common discharge diagnoses/symptoms for ED/EDOU patients with IHCA were pneumonia, gastrointestinal hemorrhage, and fever (**Supplementary Table 2**). Of the IHCA patients, 122 (84%) were intubated and mechanically ventilated.

The 37,697 patients contributed to a total of 1,507,121 data points across all vital-sign categories. Each patient was measured multiple times, with a median measurement of 7 times (IQR, 4–13 times). **Figure 2** depicts the trajectory groups in each vital-sign category. Three to four trajectory groups per vital sign were identified by the trajectory modeling. For example, in the SBP category, three distinct trajectory groups were identified, representing "normal" (44% of patients), "high, resolving" (16%), and "low, fluctuating" (40%) SBP over time. Similarly, three trajectory groups were identified for the longitudinal HR data. Notably, four trajectory groups were identified in the body temperature category, representing "hypothermia" (16%), "normal" (50%), "high, resolving" (26%), "very high, resolving" (8%) groups. For the longitudinal RR and SpO_2 data, three

TABLE 2 | Patient characteristics and clinical outcomes by the trajectory group (systolic blood pressure and heart rate).

Variable	SBP group			*P* value	HR group			*P* value
	Low, fluctuating (*n* = 14,974)	**Normal (*n* = 16,822)**	**High, resolving (*n* = 5,901)**		**Normal (*n* = 14,344)**	**High, resolving (*n* = 17,246)**	**Very high, fluctuating (*n* = 6,107)**	
Age, mean (SD), yr	57.7 (19.1)	65.4 (17.3)	69.0 (15.1)	<0.001	63.7 (18.2)	62.4 (18.5)	62.2 (17.8)	<0.001
Female sex, *n* (%)	7,223 (48.2)	7,263 (43.2)	2,772 (47.0)	<0.001	6,743 (47.0)	7,914 (45.9)	2,601 (42.6)	<0.001
Triage, *n* (%)				<0.001				<0.001
1	1,055 (7.0)	717 (4.3)	241 (4.1)		479 (3.3)	874 (5.1)	660 (10.8)	
2	4,860 (32.5)	5,330 (31.7)	2,832 (48.0)		4,793 (33.4)	5,708 (33.1)	2,521 (41.3)	
3	8,609 (57.5)	10,364 (61.6)	2,792 (47.3)		8,665 (60.4)	10,257 (59.5)	2,843 (46.6)	
4	417 (2.8)	377 (2.2)	33 (0.6)		377 (2.6)	371 (2.2)	79 (1.3)	
5	33 (0.2)	34 (0.2)	3 (0.1)		30 (0.2)	36 (0.2)	4 (0.1)	
Most common chief complaint, *n* (%)		Fever				Fever		
	2751 (18.6)	2526 (15.2)	426 (7.3)	<0.001	1244 (8.8)	3257 (19.1)	1202 (20.0)	<0.001
qSOFA, median (IQR)	0 (0–1)	0 (0–1)	0 (0–0)	<0.001	0 (0–0)	0 (0–1)	1 (0–1)	<0.001
CRP, median (IQR), mg/dL[a] (<1 mg/dL)	5.7 (1.7–12.5)	4.9 (1.3–11.8)	2.9 (0.7–9.1)	<0.001	2.1 (0.5–7.1)	5.6 (1.8–12.2)	9.1 (3.7–16.3)	<0.001
Lactic acid, median (IQR), mmole/L[b] (<2 mmole/L)	2.2 (1.4–3.7)	1.9 (1.3–2.9)	1.6 (1.1–2.5)	<0.001	1.6 (1.1–2.4)	1.9 (1.3–3.1)	2.6 (1.6–4.6)	<0.001
cTnI, median (IQR), ng/mL[c] (<0.05ng/mL)	0.03 (0.01–0.08)	0.02 (0.01–0.06)	0.03 (0.01–0.07)	<0.001	0.02 (0.01–0.05)	0.03 (0.01–0.07)	0.04 (0.01–0.09)	<0.001
D–dimer, median (IQR), mg/L[d] (<0.5 mg/L)	2.2 (0.8–5.9)	1.8 (0.6–4.9)	1.2 (0.5–3.5)	<0.001	0.9 (0.3–2.4)	2.1 (0.8–5.4)	3.4 (1.6–8.9)	<0.001
IHCA, *n* (%)	81 (0.5)	45 (0.3)	19 (0.3)	<0.001	36 (0.3)	59 (0.3)	50 (0.8)	<0.001
ED mortality, *n* (%)	543 (3.6)	218 (1.3)	44 (0.7)	<0.001	100 (0.7)	274 (1.6)	431 (7.1)	<0.001

[a]Available in 5,884 patients. [b]Available in 8,556 patients. [c]Available in 11,602 patients. [d]Available in 2,776 patients. SBP, systolic blood pressure; HR, heart rate; SD, standard deviation; qSOFA, quick Sepsis–related Organ Failure Assessment; IQR, interquartile range; CRP, C–reactive protein; cTnI, cardiac troponin I; IHCA, in–hospital cardiac arrest; ED, emergency department.

TABLE 3 | Patient characteristics and clinical outcomes by the trajectory group (body temperature, respiratory rate, and oxygen saturation).

Variable	BT group					RR group				SpO_2 group			
	Hypothermia (*n* = 4,771)	Normal (*n* = 18,932)	High, resolving (*n* = 8,998)	Very high, resolving (*n* = 2,810)	*P* value	Normal (*n* = 15,642)	High (*n* = 5,526)	Very high (*n* = 1,954)	*P* value	Very low, fluctuating (*n* = 1,190)	Low (*n* = 11,205)	Normal (*n* = 10,673)	*P* value
Age, mean (SD), yr	67.3 (17.3)	62.9 (18.3)	61.9 (18.5)	57.5 (18.9)	<0.001	63.8 (17.7)	69.7 (16.5)	71.2 (16.0)	<0.001	72.2 (15.9)	68.7 (15.8)	62.0 (18.6)	<0.001
Female sex, *n* (%)	1,608 (33.7)	8,908 (47.1)	4,476 (49.7)	1,325 (47.2)	<0.001	6,899 (44.1)	2,290 (41.4)	792 (40.5)	<0.001	457 (38.4)	4,661 (42.6)	4,840 (45.4)	<0.001
Triage, *n* (%)					<0.001				<0.001				<0.001
1	329 (6.9)	762 (4.0)	368 (4.1)	136 (4.8)		600 (3.8)	684 (12.4)	618 (31.6)		557 (46.8)	648 (5.8)	676 (6.3)	
2	1,741 (36.5)	6,361 (33.6)	2,700 (30.0)	812 (28.9)		5,558 (35.5)	2,659 (48.1)	919 (47.0)		419 (35.2)	4,645 (41.5)	4,040 (37.9)	
3	2,553 (53.5)	11,238 (59.4)	5,785 (64.3)	1,836 (65.3)		8,969 (57.3)	2,129 (38.5)	409 (20.9)		208 (17.5)	5,690 (50.8)	5,606 (52.5)	
4	134 (2.8)	528 (2.8)	132 (1.5)	25 (0.9)		480 (3.1)	49 (0.9)	7 (0.4)		5 (0.4)	207 (1.9)	326 (3.1)	
5	14 (0.3)	43 (0.2)	13 (0.1)	1 (0.0)		35 (0.2)	5 (0.1)	1 (0.1)		1 (0.1)	15 (0.1)	25 (0.2)	
Most common chief complaint, n (%)		Fever					Dyspnea				Dyspnea		
	122 (2.6)	1,399 (7.5)	2,980 (33.4)	1,433 (51.7)	<0.001	1,612 (10.4)	2,170 (39.9)	1,140 (59.4)	<0.001	663 (55.2)	2,611 (23.3)	1,770 (16.4)	<0.001
qSOFA, median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	<0.001	0 (0–1)	1 (0–1)	1 (1–2)	<0.001	1 (1–2)	0 (0–1)	0 (0–1)	<0.001
CRP, median (IQR), mg/dL[a] (<1 mg/dL)	2.6 (0.5–7.5)	3.6 (0.8–9.1)	7.1 (2.4–14.2)	8.4 (3.3–16.7)	<0.001	5.4 (1.5–12.3)	7.0 (2.1–15.0)	8.9 (4.1–16.0)	<0.001	8.5 (4.4–15.6)	7.1 (2.2–14.4)	4.6 (1.2–11.7)	<0.001
Lactic acid, median (IQR), mmole/L[b] (<2 mmole/L)	2.1 (1.4–3.8)	1.9 (1.2–3.0)	1.9 (1.3–3.0)	2.1 (1.4–3.4)	<0.001	1.9 (1.3–3.0)	2.2 (1.4–4.0)	2.8 (1.7–4.9)	<0.001	3.1 (1.8–5.5)	2.0 (1.5–3.3)	2.0 (1.3–3.3)	<0.001
cTnI, median (IQR), ng/mL[c] (<0.05ng/mL)	0.03 (0.01–0.08)	0.03 (0.01–0.06)	0.03 (0.01–0.07)	0.03 (0.01–0.08)	<0.001	0.02 (0.01–0.06)	0.04 (0.02–0.10)	0.05 (0.02–0.13)	<0.001	0.05 (0.02–0.13)	0.03 (0.01–0.08)	0.03 (0.01–0.07)	<0.001
D–dimer, median (IQR), mg/L[d] (<0.5 mg/L)	1.8 (0.6–5.8)	1.6 (0.6–4.3)	2.8 (1.1–6.6)	3.0 (1.4–7.8)	<0.001	1.7 (0.6–4.6)	3.0 (1.1–7.5)	3.2 (1.6–8.7)	<0.001	4.1 (1.8–10.5)	2.3 (0.9–6.5)	1.8 (0.6–5.0)	<0.001
IHCA, n (%)	38 (0.8)	48 (0.3)	23 (0.3)	17 (0.6)	<0.001	48 (0.3)	53 (1.0)	23 (1.2)	<0.001	18 (1.5)	63 (0.6)	41 (0.4)	<0.001
ED mortality, n (%)	231 (4.8)	254 (1.3)	160 (1.8)	118 (4.2)	<0.001	105 (0.7)	235 (4.3)	435 (22.3)	<0.001	344 (28.9)	272 (2.4)	147 (1.4)	<0.001

[a]Available in 5,884 patients. [b]Available in 8,556 patients. [c]Available in 11,602 patients. [d]Available in 2,776 patients. BT, body temperature; RR, respiratory rate; SpO_2, oxygen saturation; SD, standard deviation; qSOFA, quick Sepsis-related Organ Failure Assessment; IQR, interquartile range; CRP, C-reactive protein; cTnI, cardiac troponin I; IHCA, in-hospital cardiac arrest; ED, emergency department.

TABLE 4 | Bootstrapped multivariable model of trajectory groups associated with emergency department in-hospital cardiac arrest.

Variable	Adjusted odds ratio	95% confidence interval	*P* value
BT trajectory group			
Hypothermia	**2.20**	1.35–3.57	0.001
Normothermia (reference)	1.00		
High, resolving	0.95	0.50–1.80	0.880
Very high, resolving	1.60	0.85–2.99	0.142
RR trajectory group			
Normal (reference)	1.00		
High, recurring	**2.51**	1.54–4.09	<0.001
Very high, recurring	**2.44**	1.24–4.79	0.010

Significant odds ratios are highlighted in bold. BT, body temperature; RR, respiratory rate. Model adjusted for age, sex, triage level, and all five trajectory groups (systolic blood pressure, heart rate, body temperature, respiratory rate, and oxygen saturation). Statistically non-significant predictors are not shown.

trajectory groups were identified for each vital-sign category. The detailed summary measurements (initial value, mean, minimum, maximum, and standard deviation) for each vital-sign category is shown in **Supplementary Tables 3, 4**.

Tables 2, **3** show the clinical characteristics and outcomes of the trajectory groups in each vital-sign category. Across all vital-sign categories, the following five trajectory groups were associated with a higher rate of IHCA: low and fluctuating SBP, high and fluctuating HR, persistent hypothermia, initially-resolving but recurring tachypnea, and low and fluctuating oxygen saturation. Within each vital-sign category, the IHCA-prone trajectory group was associated with a higher triage level and a higher mortality rate, compared to other trajectory groups. Except for the persistent hypothermia group, the other four IHCA-prone trajectory groups were more likely to have a higher qSOFA score and higher levels of CRP, lactic acid, cTnI, and D-dimer, compared with other trajectory groups in their corresponding vital-sign category.

The bootstrapped multivariable analysis showed that hypothermia (vs. normothermia) and higher RR groups (high/very high, recurring tachypnea vs. normal RR group) were independently associated with IHCA, adjusting for age, sex, triage levels, and other trajectory groups (**Table 4**). For example, hypothermia was independently associated with a 2.2-fold increased risk of IHCA (95% CI, 1.35–3.57).

In the sensitivity analysis by restricting the GBTM analysis to hours 0–24, the early trajectories were quite similar to the entire trajectories, except that some fever trajectories had not fully resolved to the normal level and that recurring tachypnea had not fully appeared (**Supplementary Figure 1**). The aforementioned five trajectories using early data were still associated with IHCA ($P \leq 0.001$), expect for the high RR groups.

DISCUSSION

In this study of 37,697 patients comprising >1 million longitudinal data points, we discovered five distinct vital-sign trajectory groups associated with a higher rate of IHCA. In contrast to other four trajectory groups, the hypothermia group appeared to have a unique pattern of suppressed laboratory markers findings. The internally validated multivariable analysis suggested hypothermia and recurring tachypnea were independently associated with IHCA.

A common theme across the five IHCA-prone vital-sign trajectory groups was the initial deviation from the norm, followed by a persistent deviation without resolution. In general, within each vital-sign category, those whose vital signs resolved to near normal (e.g., initially high but resolving SBP or HR) tended to have better outcomes, compared with those with persistently deviating vital signs. The degree to which the vitals deviated and fluctuated also differed by the vital-sign category. For instance, the fluctuation of SBP and HR seemed smaller, compared to that of RR and SpO_2. This smaller longitudinal variation might also implicate that hypotension and tachycardia in the early phase of ED stay could predict worse outcomes. Indeed, studies have shown the "shock index" at triage, defined as HR divided by SBP, predicted hospital admission and inpatient mortality among ED patients (19). The higher levels of lactic acid, cTnI, and D-dimer may reflect the combination of various forms of shock (e.g., septic or cardiogenic) in the groups of low/fluctuating SBP and high/fluctuating HR. On the other hand, high blood pressure in the ED is common but does not seem to be associated with subsequent adverse events (20).

The hypothermia trajectory group appeared to have a relatively flat temperature course and relatively low levels of inflammatory markers. Consistent with previous studies (21–23), we found that hypothermia was associated with a higher rate of mortality and extended this association to include IHCA. Hypothermia is known to be arrhythmogenic and could be related to sepsis, both of which may have contributed to IHCA in our study. The hypothermia group demonstrated a "hypoinflammatory" state as evidenced by a low qSOFA score and a lower level of CRP. These patients were older and were probably immunosuppressed, and therefore their immune response was insufficient to generate fever. A previous study also showed that hypothermia in sepsis patients was associated with persistent lymphopenia, a sepsis-induced immunosuppression (24). Our study further demonstrated that the hypoinflammatory state usually persisted, at least in the ED, and predicted worse outcomes. On the other hand, a study has reported that hyperthermic patients in the ED received more antibiotic therapy, and thus had lower mortality compared with normothermic patients (25).

Multivariable analysis suggested that, besides hypothermia, an initially resolving but recurring tachypnea was independently associated with IHCA. Many IHCA events are caused by respiratory failure, such as acidosis and pneumonia, and cardiac causes (26). Prior to IHCA, tachypnea is often present as a compensatory response to shock-induced metabolic acidosis. A previous ward study also reported RR was the most important vital sign in predicting critical events (8). In our study, the degree of fluctuation of RR and SpO_2 over time was quite large, indicating dynamic changes between treatment response and failure and a strong terminal deviation from the norm. Among various diseases, pneumonia may particularly alter the longitudinal patterns of RR and SpO_2. A previous study has shown that deteriorating pneumonia demonstrated

rapidly-worsening respiratory failure, with high RR and low SpO_2, but only minor changes in other vital signs (27). Our study also suggested that, unlike the evolution of SBP and HR, the changes in RR and SpO_2 could be drastic just prior to IHCA. As shown in the sensitivity analysis, the early RR trajectory was not reliable to detect imminent IHCAs. Recognizing these late changing respiratory trajectories, along with various important clinical and social factors, might prompt an early discussion of the risks and benefits of airway interventions or do-not-resuscitate orders if not already available.

This study has some potential limitations. First, this was a single-center study at a tertiary medical center, and our findings may not be generalizable to hospitals of different settings. Second, our study population was restricted to those who underwent at least three measurements of vital signs to ensure the stability of statistical analysis. As such, less ill patients were excluded, and the findings may not be applied to them. At the other end, our study population included EDOU patients potentially awaiting an inpatient bed, and our results may be potentially useful for EDOU and hospitalized patients. Third, we did not control for the medication effects (e.g., inotropes and antipyretics), which may have altered the trajectories. However, this rendered our results more reflective of a real-world situation. Finally, although we performed bootstrapping to internally validate our results, the identified trajectories and their relationships with IHCA still need to be externally validated in future large studies.

CONCLUSIONS

In summary, in this large study of 37,697 patients with about 1.5 million longitudinal data points, we identified five novel vital-sign sub-phenotypes associated with a higher likelihood of IHCA, with distinct patterns in clinical course and laboratory markers. A better understanding of the pre-IHCA vital-sign trajectories may help with the early identification of deteriorating patients and has potential implications for personalized prevention of IHCA.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by NTUH Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

C-LT and T-CL: study concept and design, acquisition of data, and statistical analysis. C-LT: first drafting of the manuscript, had access to all the data in the study, takes responsibility for the integrity of the data, and the accuracy of the data analysis. C-LT and C-HH: obtained funding and study supervision. All authors: analysis and interpretation of data, critical revision of the manuscript for important intellectual content, administrative, technical, and material support.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.800943/full#supplementary-material

Supplementary Figure 1 | The trajectory groups identified by group-based trajectory modeling in each vital-sign category within 24 hours. **(A-E)** Indicate systolic blood pressure, heart rate, body temperature, respiratory rate, and oxygen saturation, respectively.

Supplementary Table 1 | Baseline clinical characteristics of emergency department patients with in-hospital cardiac arrest.

Supplementary Table 2 | Most common discharge diagnoses of emergency department patients with in-hospital cardiac arrest.

Supplementary Table 3 | The detailed summary measurements (initial value, mean, minimum, maximum, and standard deviation) for each vital-sign category.

Supplementary Table 4 | The detailed summary measurements (initial value, mean, minimum, maximum, and standard deviation) for each vital-sign category.

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Can Cerebral Regional Oxygen Saturation (rSO_2) Be Used as an Indicator of the Quality of Chest Compressions in Patients With Cardiopulmonary Arrest? A Study Evaluating the Association Between rSO_2 and Mean Arterial Pressure: The PRESS Study

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Introduction: Sudden cardiac arrest causes numerous deaths worldwide. High-quality chest compressions are important for good neurological recovery. Arterial pressure is considered useful to monitor the quality of chest compressions by the American Heart Association. However, arterial pressure catheter might be inconvenient during resuscitation. Conversely, cerebral regional oxygen saturation (rSO_2) during resuscitation may be associated with a good neurological prognosis. Therefore, we aimed to evaluate the correlation between mean arterial pressure and rSO_2 during resuscitation to evaluate rSO_2 as an indicator of the quality of chest compressions.

Materials and Methods: This study was a single-center, prospective, observational study. Patients with out-of-hospital cardiac arrest who were transported to a tertiary care emergency center in Japan between October 2014 and March 2015 were included. The primary outcome was the regression coefficient between mean arterial pressure (MAP) and rSO_2. MAP and rSO_2 were measured during resuscitation (at hospital arrival [0 min], 3, 6, 9, 12, and 15 min), and MAP was measured by using an arterial catheter inserted into the femoral artery. For analysis, we used the higher value of rSO_2 obtained from the left and right forehead of the patient measured using a near-infrared spectrometer. Regression coefficients were calculated using the generalized estimating equation with MAP and systolic arterial pressure as response variables and rSO_2 as an explanatory variable since MAP and rSO_2 were repeatedly measured in the same patient. Since the confounding factors between MAP or systolic arterial pressure and rSO_2 were not clear clinically or from previous studies, the generalized estimating equation was analyzed using a univariate analysis.

Results: In this study, 37 patients were analyzed. The rSO_2 and MAP during resuscitation from hospital arrival to 15 min later were expressed as follows: (median [interquartile range, IQR]): rSO_2, 29.5 (24.3–38.8)%, and MAP, 36.5 (26–46) mmHg. The regression coefficient (95% *CI*) of log-rSO_2 and log-MAP was 0.42 (0.03–0.81) ($p = 0.035$).

Conclusion: The values of rSO_2 and MAP showed a mild but statistically significant association. rSO_2 could be used to assess the quality of chest compressions during resuscitation as a non-invasive and simple method.

Keywords: arterial pressure, cardiopulmonary resuscitation, cerebral regional oxygen saturation, cerebrovascular circulation, prognosis

INTRODUCTION

Despite the advancements in medical technology, a good neurological recovery from sudden cardiac arrest remains low, and sudden cardiac arrest is responsible for numerous deaths worldwide (1, 2). Although specific data are not yet available, it has been hypothesized that the social cost of these deaths is estimated to be enormous. To increase good neurological recovery after cardiopulmonary arrest, resuscitation procedures for sudden cardiac arrest have been studied, and high-quality chest compressions have been considered the most important factor for return of spontaneous circulation (ROSC) (3). Moreover, we hypothesized that an improved rate of ROSC is associated with improved neurological outcomes; however, no previous study has examined this association.

The American Heart Association 2020 guidelines have considered the use of arterial pressure to monitor the quality of chest compressions (4). Arterial pressure, especially mean arterial pressure (MAP), is often used to monitor the organ perfusion in critically ill patients (5). Previous studies have shown that the high MAP during resuscitation might correlate with a good neurological prognosis in patients with cardiopulmonary arrest (6). Therefore, the use of arterial pressure to monitor organ perfusion in patients with cardiopulmonary arrest may be reasonable. However, arterial pressure measurement requires an arterial pressure catheter, which cannot be inserted during emergency medical transportation to the hospital and requires a certain level of skill for insertion during resuscitation in hospitals. Therefore, it may not be considered as a convenient device. In addition, the American Heart Association 2020 guidelines refer to end-tidal carbon dioxide as a non-invasive means of assessing the quality of chest compressions (4). However, the measurement of end-tidal carbon dioxide requires tracheal intubation, especially in pre-hospital situations, which might be difficult to use.

Conversely, the high cerebral regional oxygen saturation (rSO_2), which is a measure of cerebral perfusion obtained non-invasively *via* near-infrared spectroscopy (7), during resuscitation of patients with cardiopulmonary arrest may be associated with a good neurological prognosis (8–10). We hypothesized that the higher MAP increases rSO_2 and, accordingly, improves neurological prognosis when considering the association between MAP and neurological prognosis. However, no previous study has examined the association between MAP and rSO_2. If the association between MAP and rSO_2 could be demonstrated, it would be possible to evaluate the quality of chest compressions in any situation during resuscitation using rSO_2, which is a non-invasive and easy method, and it might help to improve the neurological prognosis of patients with cardiopulmonary arrest. The current study, also known as The Presumption of Resuscitation for Sustaining cerebral oxidation (PRESS) study, aimed to evaluate the association between MAP and rSO_2 during the resuscitation of patients with cardiopulmonary arrest.

MATERIALS AND METHODS

Design and Patients

This was a single-center, prospective, observational study. Patients transported to the Japanese Red Cross Musashino Hospital, a tertiary care emergency center in Japan, between October 2014 and March 2015 were enrolled. This study was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN000015479) and approved by the ethics committee of the Japanese Red Cross Musashino Hospital (ethical review no. 642). In addition, this study was based on the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement (11). Informed consent was not needed because the data could be collected during normal resuscitation care, and the information was revealed by opt-outs.

Patients with out-of-hospital cardiac arrest who were transported to the Japanese Red Cross Musashino Hospital were included in this study. However, the following patients were excluded from this study: patients 1) aged less than 18 years, 2) with trauma, 3) introduced with extracorporeal membrane oxygenation, 4) with a maximum measured rSO_2 value of 15%, 5) with a do-not-resuscitate order, or 6) not eligible to participate in the study based on the discretion of an attending physician. Since the lower limit of rSO_2 measurement of the measurement device was 15%, if the maximum value of rSO_2 measured was 15%, it was not possible to distinguish whether the measured value was 15% or less than 15%. In such a case, the use of the measured value of 15% would cause measurement bias and was therefore excluded.

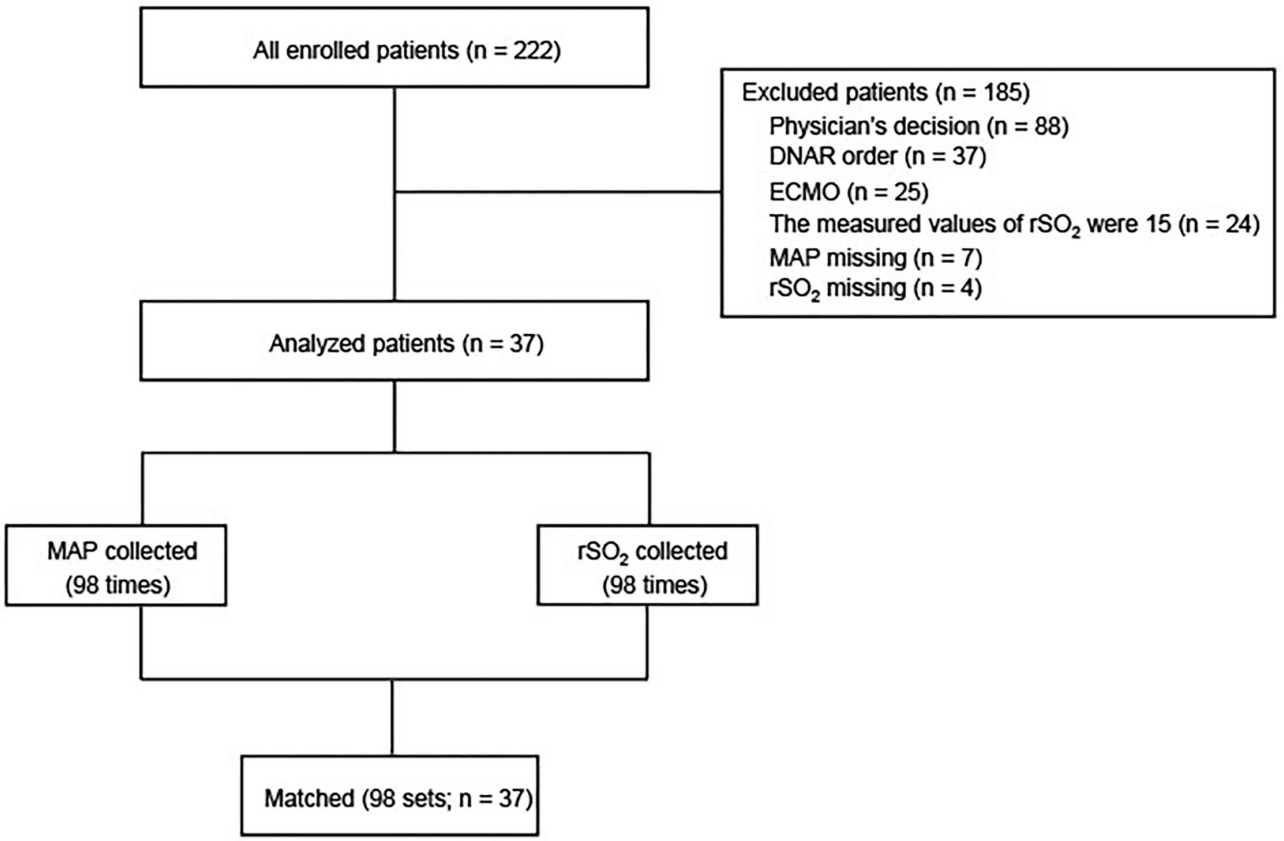


FIGURE 1 | Flowchart of screening and enrollment of patients in this study. DNAR, do not attempt resuscitation; ECMO, extracorporeal membrane oxygenation; MAP, mean arterial pressure; rSO_2, regional saturation of oxygen; SAP, systolic arterial pressure.

Data Collection

The following data were collected, such as age, sex, whether or not the cardiac arrest was witnessed, whether or not bystander-initiated cardiopulmonary resuscitation was performed, cause of cardiac arrest (cardiogenic, non-cardiogenic), initial rhythm at the time of emergency medical services contact (ventricular fibrillation/pulseless ventricular tachycardia, pulseless electrical activity, and cardiac arrest), time from EMS call to hospital arrival, rSO_2 and arterial pressure (systolic arterial pressure [SAP], MAP) during resuscitation (at hospital arrival [0 min], 3, 6, 9, 12, and 15 min), and with or without return of spontaneous circulation (ROSC) of patients. Arterial pressure was measured by the arterial catheter in the femoral artery since arterial catheter insertion into the radial artery during resuscitation is difficult with a high probability of complications and requires a long time. Chest compressions were performed by selecting the site where the arterial pressure measured by the arterial catheter was highest. The rSO_2 values were collected from the left and right forehead of the patient using a near-infrared spectrometer (INVOSTM5100C; Medtronic, Boulder, CO, USA), and the higher value of rSO_2 between the left and right value was used for the analysis. Data follow-up was terminated when the patient was discharged, died, or was transferred to another hospital.

The data collection was unmasked because the physicians in charge collected the data individually, and the outcome assessors were unblinded. Missing data were not completed, and patients with missing MAP or rSO_2 data were excluded.

Outcome

The primary outcome was the regression coefficient between MAP and rSO_2. The secondary outcome was the regression coefficient between SAP and rSO_2.

Statistical Analyses

Continuous variables are described using the median and interquartile range, and categorical variables are described using absolute values and percentages (%). Initially, rSO_2 and arterial pressures (MAP, SAP) were log-transformed, and the Kolmogorov–Smirnov test was used to confirm that each factor was normally distributed. Since rSO_2 and arterial pressures (MAP, SAP) were repeated-measured data, we hypothesized that the data measured at different points within the same patient were correlated. Therefore, we calculated regression coefficients using the generalized estimating equation, with MAP and SAP as response variables and rSO_2 as an explanatory variable. Since the confounding factors between MAP or SAP and rSO_2 were

not clear clinically or from previous studies, the generalized estimating equation was analyzed using a univariate analysis. EZR version 1.38, R version 3.5.2.tar.gz, and SAS version 9.4 (SAS Institute, Cary, NC, USA) were used for the analysis, and $p < 0.05$ was considered statistically significant by the two-sided test.

RESULTS

A total of 222 patients were included, and 37 patients were analyzed (**Figure 1**). The reasons for exclusion were as follows: 88 for the decision of physicians, 37 for do-not-resuscitate order, 25 for extracorporeal membrane oxygenation, 24 for maximum rSO_2 measured at 15%, 7 for missed MAP, and 4 for missed rSO_2. MAP and rSO_2 were measured 98 times.

The backgrounds of patients are shown in **Table 1**. The median age (interquartile range, IQR) was 75 (69–82) years; 26 patients (70.3%) had witnessed cardiac arrest; 12 patients (32.4%) had bystander-initiated cardiopulmonary resuscitation; 5 patients (13.5%) had ventricular fibrillation/pulseless ventricular tachycardia; 15 patients (40.5%) had pulseless electrical activity; and 17 patients (46.0%) had asystole. The time taken to hospital arrival was 36 (range, 30–44) min. The maximum rSO_2 value during resuscitation was 29.5% (24.3–38.8%), MAP was 36.5 (26–46) mmHg, and there were 34 (91.9%) deaths during resuscitation.

The trends of rSO_2, MAP, and SAP during resuscitation from hospital arrival to 15 min later are shown in **Figure 2**. Although statistical tests were not performed, rSO_2, MAP, and SAP remained generally unchanged from 0 to 15 min after resuscitation, and all factors showed similar trends.

Mean arterial pressure, SAP, and rSO_2 were log-transformed and tested for normality distribution using the Kolmogorov–Smirnov test for each factor. The results of the Kolmogorov–Smirnov test were as follows: log-MAP, $p = 0.14$; log-SAP, $p = 0.98$; and log-rSO_2, $p = 0.25$. Therefore, each factor was considered normally distributed. Next, the association between MAP or SAP and rSO_2 at each time point from 0 to 15 min later is shown in a scatterplot, and a scatterplot summarizing these repeated measurement data was created (**Figures 3A,B** and **Supplementary Figures 1A,B**).

The regression coefficients were calculated using a generalized estimating equation with log-MAP and log-SAP as the response variables and log-rSO_2 as the explanatory variable. The regression coefficients (95% *CI*) between log-MAP and log-rSO_2 and log-SAP and log-rSO_2 were 0.43 (0.029–0.83) ($p = 0.035$) and 0.42 (0.03–0.81) ($p = 0.037$), respectively (**Tables 2A**,**B**).

TABLE 1 | Baseline characteristics of all the analyzed patients.

Variables	Patients ($n = 37$)
Age, years (median [IQR])	75 (69–82)
Male sex, no. (%)	31 (83.8)
Bystander witness, no. (%)	26 (70.3)
Bystander-initiated CPR, no. (%)	12 (32.4)
Origin of cardiac arrest, no. (%)	
Cardiac	21 (56.8)
Noncardiac	16 (43.2)
Initially documented rhythms on the scene of the cardiac arrest, no. (%)	
VF/pulseless VT	5 (13.5)
PEA	15 (40.5)
Asystole	17 (46.0)
Emergency call to arrival at the hospital in min, (median [IQR])	36 (30–44)
rSO_2 during resuscitation†, (median [IQR])	29.5 (24.3–38.8)
MAP during resuscitation, (median [IQR])	36.5 (26–46)
SAP during resuscitation, (median [IQR])	69 (47–105)
Death in the emergency room, no. (%)	34 (91.9)

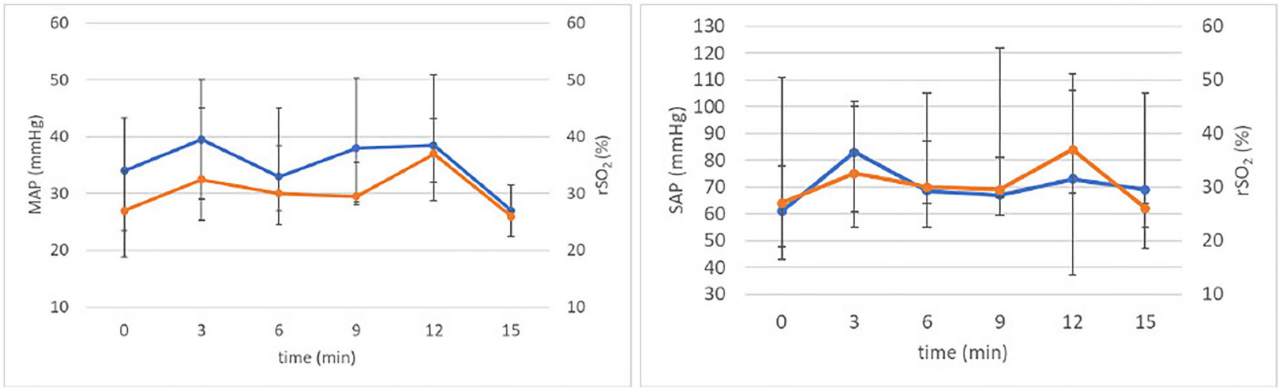
†*The highest value during resuscitation.*

CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; IQR, interquartile range; MAP, mean arterial pressure; PEA, pulseless electrical activity; OHCA, out-of-hospital cardiac arrest; rSO_2, regional saturation of oxygen; VF, ventricular fibrillation; VT, ventricular tachycardia.

DISCUSSION

In this study, MAP and SAP during resuscitation of patients with cardiopulmonary arrest showed a mild but statistically significant association with rSO_2.

It is considered that rSO_2 increased as MAP and SAP increased since rSO_2 might reflect the increased cerebral blood flow (CBF) caused by chest compressions during resuscitation. In general, MAP was considered to be related to organ perfusion including CBF (5). Previous studies in patients with sepsis have shown that both the lower MAP and SAP were likely to correlate with the poor prognosis (5). MAP and SAP were associated with organ perfusion, and it was considered that the prognosis was exacerbated by organ failure as a result of decreased organ perfusion (5). In contrast, rSO_2 was considered to reflect regional local tissue perfusion and might reflect CBF. The value of rSO_2 was expressed as the oxygen saturation (%) of local tissue and considered to be strongly influenced by the venous blood oxygen saturation because the local vascular area was larger in veins than that in arteries (7). Jugular venous oxygen saturation (SjO_2) was an example of venous blood saturation and expressed by an equation that includes CBF. Therefore, it has been considered that SjO_2 was associated with CBF (11). In fact, previous studies have shown that SjO_2 decreased in the following situations where CBF seems to have decreased: intracranial hypertension, hypocarbia, systemic hypotension, and cerebral vasospasm (12). Therefore, although no previous study has examined the association between rSO_2 and SjO_2, rSO_2 might be associated with CBF and SjO_2, which was venous



	0 min	3 min	6 min	9 min	12 min	15 min	All times
MAP (mmHg) (median [IQR]), n	34 (23.5—45.3), 28	39.5 (29—50), 30	33 (24.5—45), 23	38 (28.5—50.3), 10	38.5 (32—43.2), 4	27 (22.5—31.5), 3	36.5 (26—46), 98
SAP (mmHg) (median [IQR]), n	61 (43—111), 27	83 (55—102), 29	68.5 (55—105), 20	67 (59.5—122), 10	73 (37.3—106), 4	43 (36.5—53.5), 3	69 (47—105), 93
rSO_2 (%) (median [IQR]), n	27 (18.8—34) ,28	32.5 (25.3—45) ,30	30 (27—38.5) ,23	29.5 (28—35.5) ,10	37 (28.8—51) ,4	26 (22.5—27) ,3	29.5 (24.3—38.8) ,98

FIGURE 2 | Changes in MAP, SAP, and rSO_2 over 15 min. IQR, interquartile range; MAP, mean arterial pressure; rSO_2, regional saturation of oxygen; SAP, systolic arterial pressure.

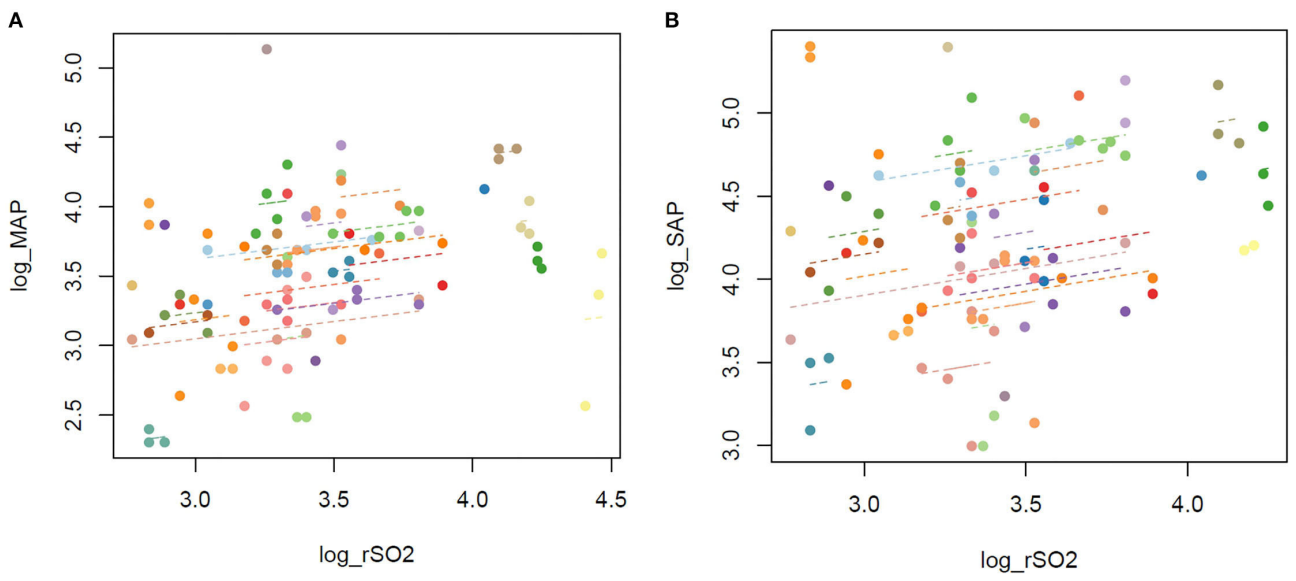


FIGURE 3 | (A) Scatterplot of MAP and rSO_2 in repeated measurements. **(B)** Scatterplot of SAP and rSO_2 in repeated measurements. MAP, mean arterial pressure; rSO_2, regional oxygen saturation; SAP, systolic arterial pressure. The repeated measurements of MAP and rSO_2 from 0 to 15 min are plotted.

oxygen saturation. In summary, chest compressions might have increased CBF, which was reflected in the increase in MAP, SAP, and rSO_2. Therefore, MAP and SAP showed a mild but statistically significant association with rSO_2.

To the best of our knowledge, this is the first study to demonstrate the significant association between MAP or SAP and rSO_2 during resuscitation in patients with cardiopulmonary arrest. In other words, as MAP or SAP increases, so does rSO_2;

TABLE 2A | Regression coefficients with MAP and rSO_2.

Log-MAP	Regression coefficient	95% CI (lower)	95% CI (upper)	*p*-value
Log-$rSO_2^{\dagger}$	0.43	0.029	0.83	0.035

†*The highest value during resuscitation.*
CI, confidence interval; rSO_2, regional saturation of oxygen; MAP, mean arterial pressure. MAP and rSO_2 were log-transformed, and we have used a univariate generalized estimating equation.

TABLE 2B | Regression coefficients with SAP and rSO_2.

Log-SAP	Regression coefficient	95% CI (lower)	95% CI (upper)	*p*-value
Log-$rSO_2^{\dagger}$	0.42	0.03	0.81	0.037

†*The highest value during resuscitation.*
CI, confidence interval; rSO_2, regional saturation of oxygen; SAP, systolic arterial pressure. SAP and rSO_2 were log-transformed, and we have used a univariate generalized estimating equation.

therefore, rSO_2 can be used to evaluate the quality of chest compressions during resuscitation as a non-invasive and simple method instead of measuring arterial pressure, which might help to improve the neurological prognosis.

However, this study has several limitations. First, the clinical use of rSO_2 to assess the quality of chest compressions might be difficult because the association between MAP or SAP and rSO_2 was mild. It is possible that MAP, SAP, and rSO_2 were not increased; therefore, there was a weak association since we included only patients with a poor prognosis. If patients with good neurological prognosis are included, MAP, SAP, and rSO_2 will be higher, and it is possible that stronger associations can be shown. Therefore, further studies are required in patient groups with good neurological outcome that are more likely to have higher MAP, SAP, and rSO_2 during resuscitation, such as those with an initial rhythm other than asystole, shorter time to hospital arrival, and higher percentage of undergoing bystander-initiated cardiopulmonary resuscitation. Second, since the analysis in this study was performed by logarithmic transformation, it might be difficult to consider the quantitative significance of rSO_2 and MAP increase. For example, although the regression coefficient between log-MAP and log-rSO_2 was 0.43 (0.029–0.83) in this study, it was not easy to calculate how much MAP was increased when rSO_2 was increased by 1%. Since a positive correlation has been shown in this study, it was possible to evaluate the quality of chest compressions using increased values as an index, but quantitative assessment might be difficult in clinical settings. Third, the tissue oxygenation index measured by a different near-infrared spectroscopy mechanism than rSO_2 might be more accurate in assessing the CBF. Therefore, the regression coefficients evaluated by rSO_2 might not be correct. Although there were no studies comparing rSO_2 with tissue oxygenation index as a measure of CBF, using tissue oxygenation index other than rSO_2 might have stronger association with MAP and SAP. Fourth, the results of the regression coefficients might be underestimated because the number of patients analyzed were small. In this study, there were only 37 patients who were analyzed. This might have led to a lack of statistical power. Fifth, in this study, the generalized estimating equation was performed in univariate analysis, but if the analysis is performed in multivariate analysis using CaO_2, SaO_2, or PaO_2 as explanatory variables, different results might be obtained. CaO_2, SaO_2, or PaO_2 might affect rSO_2 pathophysiologically; however, there is no evidence of this in the literature, and we did not treat these factors as confounding factors in this study. Sixth, the clinical use of rSO_2 may be difficult since the target value of rSO_2 has not been considered in this study. Despite not showing the data of cerebral performance category (CPC) in the tables, the CPC value at 90 days of all patients was 5. Therefore, statistical analysis regarding the target value of rSO_2 was difficult, and we could not consider the target value of rSO_2.

In this study, MAP and SAP during resuscitation of patients with cardiopulmonary arrest and rSO_2 showed a mild but statistically significant association. rSO_2 could be used to assess the quality of chest compressions during resuscitation as a non-invasive and simple method, which might help to improve the neurological prognosis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Japanese Red Cross Musashino Hospital (ethical review no. 642). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HY conceived the study. YK and HY undertook the data collection and performed the statistical analysis of the data . YK interpreted the data and drafted the manuscript. All authors contributed substantially to the study design and revision of

the manuscript with supervision from HY. All authors have approved the manuscript and agree to be accountable for the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.810449/full#supplementary-material

Supplementary Figure 1 | (A) Scatterplot of MAP and rSO_2 of each time point. **(B)** Scatterplot of SAP and rSO_2 of each time point. MAP, mean arterial pressure; rSO_2, regional oxygen saturation; SAP, systolic arterial pressure.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Tracheal Intubation in Emergency Departments in China: A National Cross-Sectional Survey

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Background: Tracheal intubation is a necessary but risky procedure performed in emergency departments (EDs) around the world. Relatively high morbidity has been encountered in Chinese EDs, which has raised concerns about peri-intubation ED management. This study aimed to investigate intubation procedures and identify any areas for improvement in Chinese EDs.

Methods: This was a questionnaire-based survey lasting 1 month (March 2021) in 41 tertiary-care hospital EDs in mainland China. The primary outcome was complications associated with intubation. Secondary outcomes were the first-pass success rate and blood pressure variations during intubation. Univariate and binary logistic regression analyses were used to find possible risk factors for first-pass intubation failure.

Results: In total, 1,020 replies were analyzed out of 1,080 surveys submitted (94.4% response rate). Most patients were elderly men with severe medical conditions like cardiac arrest (24.8%). In total, 97.2% of patients were given preoxygenation, and 48.1% received some form of pretreatment. Induction drugs (e.g., etomidate and ketamine) were less often used: 39.9% of intubations used sedatives, 5.5% used analgesics, and only 5.3% used muscle relaxants. The overall first-pass intubation success rate was 85.7% and was accompanied by a 19.8% adverse event rate. A marked decrease in blood pressure after intubation was also identified.

Conclusion: This survey found an 85.7% tracheal intubation first-pass success rate (which is relatively high compared to other countries) and a 19.8% adverse event rate (which is also relatively high). Given the very low rate of using induction medications (5.3% used muscle relaxants), future education should focus on induction drugs and traditional intubation techniques.

Keywords: China, cross-sectional studies, emergency department, tracheal intubation, rapid sequence intubation

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INTRODUCTION

Tracheal intubation is an essential and frequently used skill in the emergency department (ED). Most patients presenting to the ED with cardiac arrest, respiratory failure, or other serious clinical situations require intubation. Statistically, ED physicians handle up to 81% of intubations by themselves (1). Intubation is, therefore, a key skill for any ED physician.

Emergency department intubation is also a potentially risky procedure, carrying a morbidity rate of 12% according to a recent study in the USA (2). Morbidity from intubation in EDs in the UK was greater than in operating rooms (ORs) according to two recent studies (3, 4). This may be because many ED patients requiring intubation are complicated, with severe cardiopulmonary and infectious diseases, which may increase the incidence of hypotension or hypoxia during intubation in the ED. Given the emergent nature of these cases, there is often insufficient time to ensure proper patient fasting, to thoroughly screen patients' past medical records, or to thoroughly prepare all tools for intubation.

Recognizing the status of intubation management in a country is vital to identify deficiencies and correct any shortcomings. However, few national-scale investigations in China have attempted to explore the characteristics of ED intubations. This study aimed to illuminate the existing circumstances of ED-based tracheal intubations in China. By elucidating the common peri-intubation ED management choices, we hope to identify any problems and provide potential corrective recommendations to reduce future rates of ED intubation adverse events in Chinese EDs.

METHODS

Study Design and Setting

This was a national cross-sectional survey. We selected tertiary-care hospitals according to China's geographical distribution. The Chinese mainland, according to current government statistical reporting, is divided into seven regions. At least one province in each region was chosen to participate in the study. Ultimately, 41 "Class A-III" hospitals (the highest grade of Chinese hospitals, which are urban, tertiary, and teaching hospitals) from 19 provinces participated in this trial. This study was registered in China (ChiCTR2100043745) and received ethics approval on December 22, 2020.

Selection of Participants

Adult patients who had a tracheal intubation procedure attempted in an enrolled Chinese ED met inclusion criteria. Other cases of intubation, such as being intubated in the field or in a non-ED part of the hospital, or those patients with data missing were excluded. Patients underwent routine treatment as per the local hospital's protocol and each patient's attending physician's orders. No additional interventions were recommended or required in this study protocol.

This study lasted for a month, from March 1, 2021, to March 31, 2021. March was chosen as it avoids both spring and summer temperature extremes and is free of major national holidays. During the study period, investigators in each enrolled ED entered study data on an internet-based survey form. This form included patient characteristics, intubation conditions, and peri-intubation management decisions (e.g., any pretreatment or preoxygenation methods, induction medication, and intubation devices used). Investigators filled out the survey either on a paper printout or through a web page linked to a centralized Research Electronic Data Capture (REDCap) database. REDCap is a secure web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources (5). Every hospital appointed a physician to oversee all data entries. There were random checks every 2 weeks to ensure data accuracy. Before analyzing study data, each questionnaire entry was rechecked for repetition, errors, or incomplete areas.

The primary outcome measure was the presence of any adverse events. Adverse events could include desaturation (defined as a SpO2 <90%), hypotension [defined as systolic blood pressure (SBP) <90 mmHg], aspiration, airway trauma, cardiac arrest, or death during the intubation procedure in the ED. Secondary outcomes included the rate of first-pass intubation success and blood pressure variations during intubation.

According to existing research data, the incidence of adverse events during ED intubation has been documented to be about 12%. With an allowable error of 2%, $\alpha = 0.05$, $1-\beta = 0.8$, and a CI of 95%, the target sample size for this study was calculated by Power Analysis & Sample Size (PASS) software (NCSS Incorporation, Kaysville, Utah, USA) to be 1063.

We downloaded the raw data from the REDCap database and analyzed it utilizing Statistical Product and Service Solutions (SPSS) version 22 (IBM Incorporation, Armonk, New York, USA), GraphPad Prism 8 (GraphPad Software Incorporation, San Diego, California, USA), and Python 3 (Python Software Foundation, Beaverton, Oregon, USA). Continuous variables were presented as medians with quartiles, and categorical variables as frequencies with percentages. Wilcoxon signed-rank tests were used to compare blood pressure changes before and after intubation. Chi-square tests were used to compare categorical variables. Univariate and binary logistic regression analyses were conducted to find possible factors influencing the success of first-pass intubation. First-pass intubation success was defined as the dependent variable, and patients' underlying disease, sex, age group, intubator experience, intubator professional rank, presence of an emergent condition, intubation devices, or induction drugs were screened for the possible association. Items with a $p < 0.1$ in the univariate analysis or significant clinical significance were entered into multivariate analysis.

RESULTS

This study collected a total of 1,080 questionnaires. After screening, 14 incomplete, 25 beyond the study period, eight pediatric, seven duplicate, and six questionnaires submitted in error were excluded, leaving a total of 1,020 questionnaires for statistical analysis (shown in **Supplementary Figure 1**).

There were 41 enrolled hospitals in this study. At least one representative hospital from more than half the provinces (19 out of 34, 55.9%) in China was enrolled in this trial. More enrolled hospitals were in the more populous eastern coastal

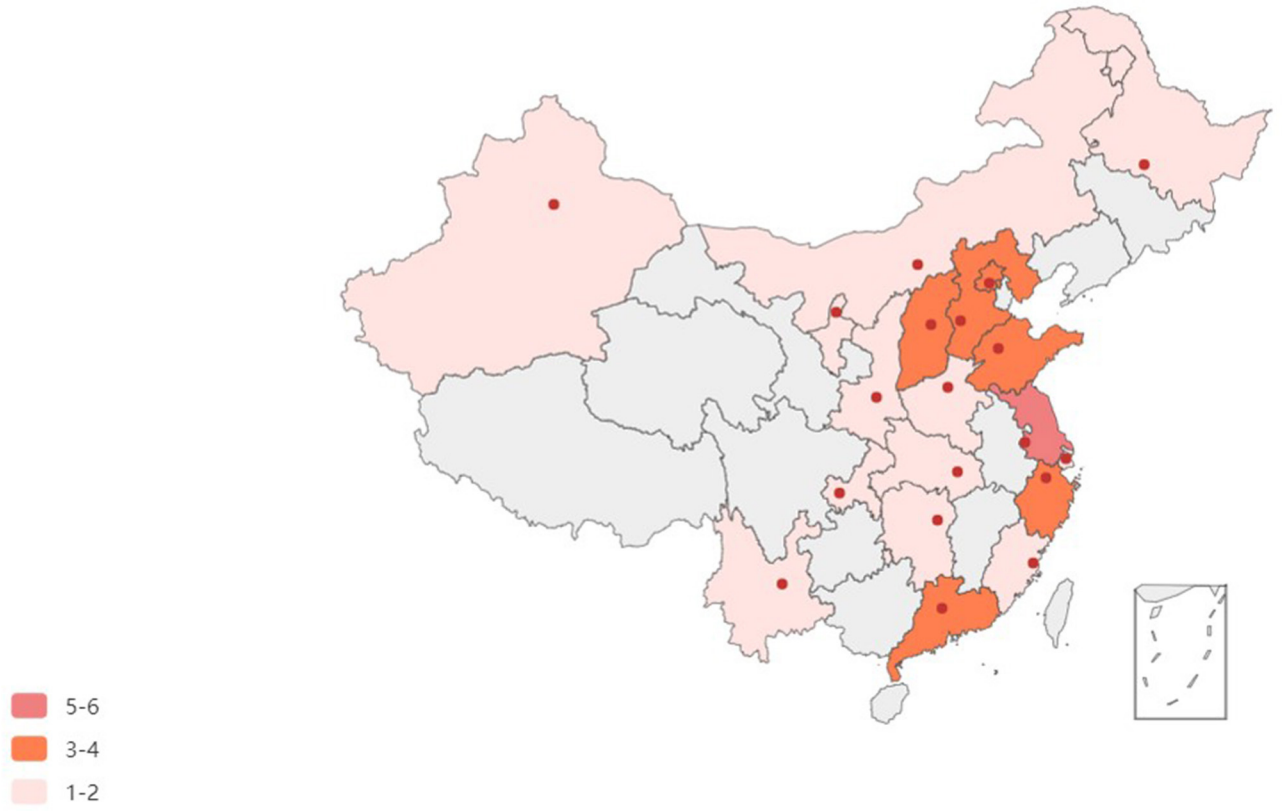

FIGURE 1 | Nationwide map of enrolled hospitals.

cities, with four or more hospitals located in Guangdong, Jiangsu, and Shanxi provinces (shown in **Figure 1**). The distribution of intubation frequency based on area is shown in **Figure 2**.

The number of ED intubations varied between different hospitals, even in the same province. The median was 21 intubations [interquartile range (IQR), 13.5–35.5]. **Figure 3** illustrates the total intubation numbers by the enrolled hospital.

In total, 953 intubations were performed by ED physicians (93.4%), 67 by anesthesiologists (6.3%), and 65 (6.4%) by nurses in the ED. The performing physicians were either attending physicians in 457 (44.8%) or resident physicians in 354 (34.7%) of the cases. In total, 643 (63.0%) reported being skilled in intubation (number of prior intubations >50). Intubations were slightly more likely to occur during off-hours between 5 pm and 8 am in 544 patients (53.3%) (**Table 1**).

In total, 685 patients (67.2%) who underwent intubation were male. The median age was 66 years, and 473 of patients (46.4%) were aged between 60 and 80. The causes for intubation were respiratory failure in 209 patients (20.5%), circulatory failure in 191 patients (18.7%), central nervous system disease in 362 patients (35.5%), cardiac arrest in 253 patients (24.8%), and "others" in five patients (0.5%). In addition, 797 (78.1%) subjects were intubated immediately on ED arrival (**Table 2**).

Looking at pre-intubation medications or fluid resuscitation, 631 patients (61.9%) were not pretreated at all, while 314 patients (30.8%) received vasoactive agents, and 179 patients (17.5%) received intravenous (IV) fluid resuscitation. In contrast, oxygenation-improving techniques (such as preoxygenation, denitrogenation, or apneic oxygenation) were much more common. Only 28 patients (2.7%) were not pre-oxygenated before intubation. Oxygenation-improving methods were nasal cannula in 330 patients (32.4%), oxygen masks in 206 patients (20.2%, including venturi and non-rebreather masks), noninvasive positive-pressure ventilation in 99 patients (9.7%), and high-flow oxygen delivery methods in 73 patients (7.2%). Bag-valve-mask ventilation was performed in 542 patients (53.1%).

Turning now to the intubation procedure itself, **Table 3** displays the variety of induction agents used for intubation in the ED. Less than half of the patients were given sedatives before intubation. The most popular drugs were propofol [used in 206 cases (20.2%)] and midazolam [used in 177 patients (17.4%)]. ED physicians rarely used analgesics before intubation, but when they did, they used IV fentanyl [in 42 patients (4.1%)]. In terms of muscle relaxation, scarcely any patients were paralyzed. For those who were, non-depolarizing muscle relaxants were used in 49 (4.8%) and depolarizing muscle relaxants in 5 (0.5%). Furthermore, compared with

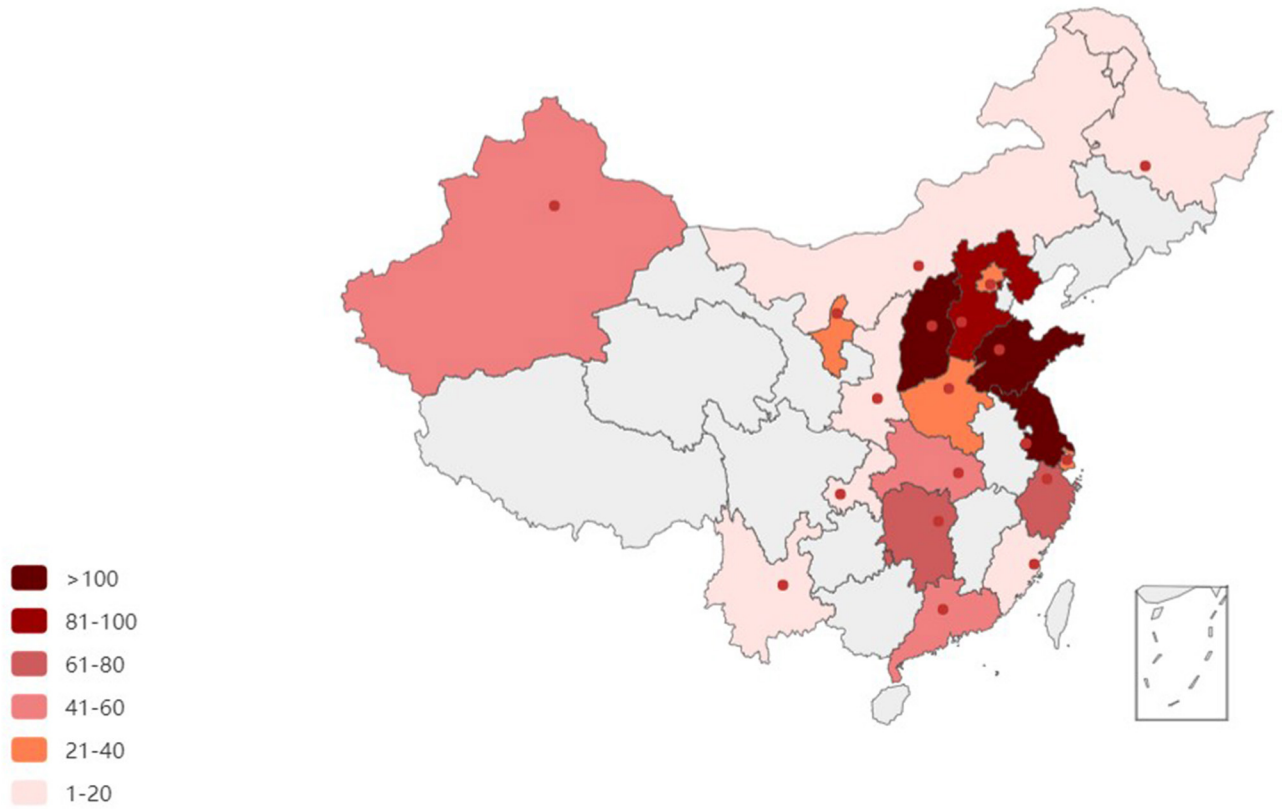

FIGURE 2 | Nationwide map of case distribution.

anesthesiologists (65.7%), the proportion using sedatives was significantly lower in emergency physicians (38.1%) ($p < 0.01$). As for muscle relaxants, anesthesiologists (10.4%) were about two times as likely to use these agents compared to emergency physicians (4.9%) ($p = 0.051$). In addition, fewer sedatives were utilized among patients intubated immediately on arrival (31.2 vs. 70.9%, $p < 0.01$).

With the steady worldwide increase in intubation equipment, Chinese ED physicians now have a plethora of options, from the traditional direct laryngoscope to a variety of direct and indirect visualization equipment. In this study, 819 intubations (80.3%) were performed using a video laryngoscope, greatly exceeding traditional direct laryngoscopy, which was still used in 192 cases (18.8%).

Looking at first pass success rates and remedies after failure, initial intubations were successful in 874 (85.7%) patients, while 125 (12.3%) required a second attempt, and 20 (2.0%) needed three attempts. In one patient (0.1%), attempts were finally given up as futile. When ED physicians faced first-pass intubation failure, the most common alternative strategy was to change to a more experienced operator, which accounted for 41.1% (60 of 146 first-pass failures) and 14.4% (21 of 146) opted to try again personally, and 10.3% (15 of 146) selected another intubation device. No supraglottic airway devices were used and no cricothyroidotomy procedures were performed.

Three aspects were considered in univariate regression screening for risk factors associated with initial intubation failure. From patient characteristics, sex ($p = 0.452$), age groups ($p = 0.295$), and concurrent diseases ($p = 0.005$) were included. The intubator's home department ($p = 0.831$), their professional rank ($p = 0.231$), and number of prior intubations ($p = 0.007$) were analyzed. Regarding intubation conditions, emergency intubation ($p = 0.127$), additional intubation devices utilized ($p = 0.643$), sedatives ($p < 0.001$), analgesia ($p = 0.138$), and muscle relaxants ($p = 0.001$) were considered. Unsurprisingly, there was an association between the professional rank of intubators and prior intubation numbers. Finally, the binary logistic model analyzed age, concurrent diseases, intubator department, prior intubation numbers, emergency intubation, devices, and three types of induction drugs. Hosmer and Lemeshow's test showed a good fit ($p = 0.462$). Results suggested that prior intubation numbers, the use of sedative agents, and the use of muscle relaxants were associated with first-pass success or failure rate. The more intubation once performed, the higher the success rate. However, using sedatives and muscle relaxants may increase the risks (see **Figure 4**).

Several kinds of complications may occur during tracheal intubation, especially in patients with serious underlying clinical conditions. Excluding patients with cardiac arrest, the remaining 767 patients experienced a variety of adverse events, including

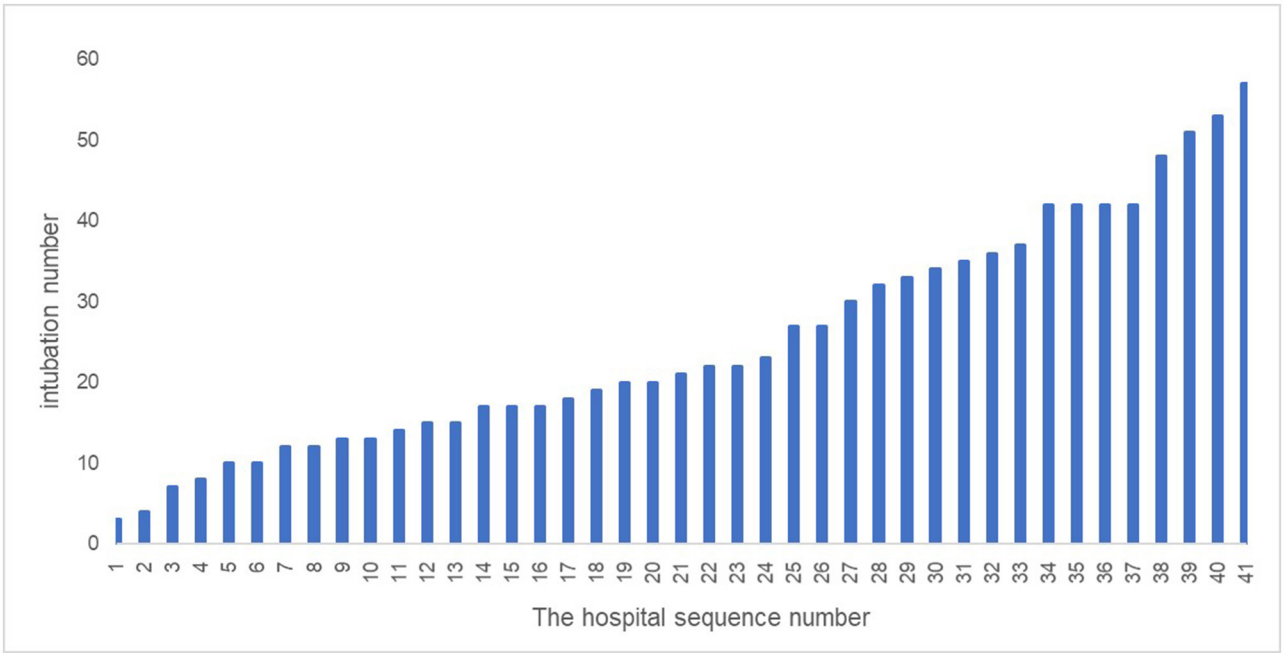

FIGURE 3 | Emergency department (ED) intubation frequency in each hospital in March 2021.

TABLE 1 | General characteristics of ED intubations.

Characteristics	*N* (%)
Intubation department	
Emergency department	953 (93.4%)
Anesthesiology department	67 (6.6%)
Intubation time	
On-hours (8 am–5 pm)	476 (46.7%)
Off-hours	544 (53.3%)
Intubation experience	
>50	643 (63.0%)
≤50	377 (37.0%)
Qualification	
Associate doctor and above	137 (13.5%)
Attending doctor	457 (44.8%)
Resident doctor	354 (34.7%)
Intern	7 (0.7%)
Nurse	65 (6.4%)

TABLE 2 | Characteristics of enrolled ED intubation patients.

Characteristics	*N* (%)
Sex	
Male	685 (67.2%)
Female	335 (32.8%)
Age	
18–40	84 (8.2%)
40–60	305 (29.9)
60–80	473 (46.4%)
80–100	158 (15.5)
Cause	
Respiratory failure	209 (20.5%)
Circulatory failure	191 (18.7%)
CNS disease	362 (35.5%)
Cardiopulmonary arrest	253 (24.8%)
Others	5 (0.5%)
Emergency intubation	797 (78.1%)

hypoxia in 97 cases (12.6%), hypotension in 48 (6.3%), aspiration in 29 (3.8%), and airway trauma in 22 (2.9%). Six patients suffered severe adverse events such as cardiac arrest or death (see **Figure 5**).

Among all subjects, blood pressure was detectable in 654 of 1,020 cases (64.1%). The median SBP was 130 mmHg before intubation and 121.5 mmHg after intubation. The median diastolic blood pressure (DAP) was 77 mmHg before and 72 mmHg after. The median mean arterial pressure (MAP) was 94.8 mmHg before and 88.8 mmHg after intubation. Wilcoxon signed-rank tests showed significant differences in blood pressure before and after the intubation ($p < 0.01$). After intubation, excluding patients with cardiac arrest, 219 of 617 patients (35.5%) were given vasoactive medications.

DISCUSSION

This national survey provided comprehensive intubation characteristics for ED patients in Chinese EDs. The overall ED

TABLE 3 | Induction agents used during ED intubations.

		N	Percent
Sedation			
	No sedative	613	60.1
	Midazolam	177	17.4
	Propofol	206	20.2
	Etomidate	22	2.2
	Ketamine	0	0
	Others	30	2.9
Analgesia			
	No analgesic	964	94.5
	Fentanyl	42	4.1
	Morphine	4	0.4
	Others	10	1.0
Muscle relaxants			
	No paralytic	967	94.7
	Rocuronium	39	3.8
	Succinylcholine	5	0.5
	Shunatracurium	8	0.8
	Others	2	0.2

intubation process, including pretreatment, preoxygenation, induction, device selection, and any complications related to the intubation procedure were examined. This study, which covered more than half of the country's provinces, was the first large-scale cross-sectional survey of ED intubation in China. This study found some widespread issues related to ED intubation, and in this discussion section, we aim to review these and provide specific goals for improving ED intubation success rates in the near future. Although it may be unrealistic to hope that ED complication rates match those of the surgical OR, we can still aim to get as close as possible to maximize patient safety in the ED.

Regarding ED patients who were intubated in this study, the majority were elderly male patients with multiple chronic diseases who needed urgent intubation. Almost a quarter of all ED intubations involved patients with cardiac arrest. Unfortunately, Khandelwal et al. recently found that cardiac arrest was a predictor for difficult tracheal intubation (6). This may play a role in the relatively low first-pass success and high complication rates seen in this study.

Emergency department physicians alone performed the intubation procedure in most cases, and among ED physicians, most reported being proficient at intubation. There are different staff assignments in various hospitals, and it was intriguing to see that nurses performed 65 (6.4%) intubations in this study. We learned that eight out of 41 (19.5%) hospitals in this study had protocols for intubation performed by nurses. Examining why nurses are intubating and potentially including nurses in intubation training may be wise in the future. In addition, it is worth noting that about half of all intubations occurred during off-hours when senior doctors were unavailable, and most ED physicians performing intubations were ED residents. On the one hand, this phenomenon emphasizes the importance of early intubation training for junior ED physicians. On the other hand, allocating senior ED physicians to the period of high incidence could improve the quality of health care and decrease complications.

Regarding intubation device selection, video laryngoscopy was more popular than traditional direct laryngoscopy in Chinese EDs in this study. However, there is still some controversy over the best choice of equipment. A systematic review identified improved glottic view and minor airway trauma in the use of video laryngoscopy patients, but no differences in intubation numbers or complication rates (7). A recent meta-analysis demonstrated that video laryngoscopy is associated with reduced numbers of esophageal intubations compared to direct laryngoscopy during emergency intubation (8). However, Jean et al. found that video laryngoscopy was related to higher rates of severe adverse events among ICU patients (9). For beginners, however, the use of video laryngoscopy does appear to decrease rates of intubation failure (10).

As for induction drugs, we found usage rates of the three most common medications in China to be low compared to other countries (11). The emergent condition of many patients may contribute to this phenomenon to some extent. Among patients using sedatives, propofol and midazolam were most commonly selected. Etomidate, a drug with little effect on circulation, has proven to be effective in patients with circulatory instability (12), but its use in Chinese EDs is very rare. Although this study did not delve into the reasons for the lack of sedative and muscle relaxant medications being used in ED intubations, a lack of standardized training or a lack of medication in the ED may be the cause. Airway guidelines have recently been updated in the anesthesiology and emergency medicine fields (13), but, as is the case in many countries, clinical physicians are slow to change their practice.

It is well-known that preoxygenation plays a vital role in maintaining oxygen saturation during intubation. Some have recommended that all critically ill patients should be pre-oxygenated (14). Our data showed that measures to improve oxygenation were adopted in almost all (97.4%) patients peri-intubation, but the incidence of hypoxia was still high. Previous meta-analyses have identified noninvasive positive pressure ventilation as being superior to other preoxygenation measures prior to intubation (15, 16). Recently, the utility of apneic oxygenation in non-breathing patients has been confirmed (17, 18), and the application of high flow oxygen inhalation equipment has also increased. However, limited equipment and some patient characteristics (altered mental status, facial hair, etc.) made routine noninvasive positive pressure ventilation or high flow oxygenation difficult in the ED. Bag-valve mask ventilation was still the dominant traditional method of preoxygenation domestically and overseas (19). Nasal cannulas, which do not provide a high fraction of inspired oxygen, were used in about 20% of patients. Since a high pre-intubation oxygen concentration can delay the time until oxygen saturation declines (20), the more oxygen provided during preoxygenation, the better outcome. Finally, this study did not query the detailed

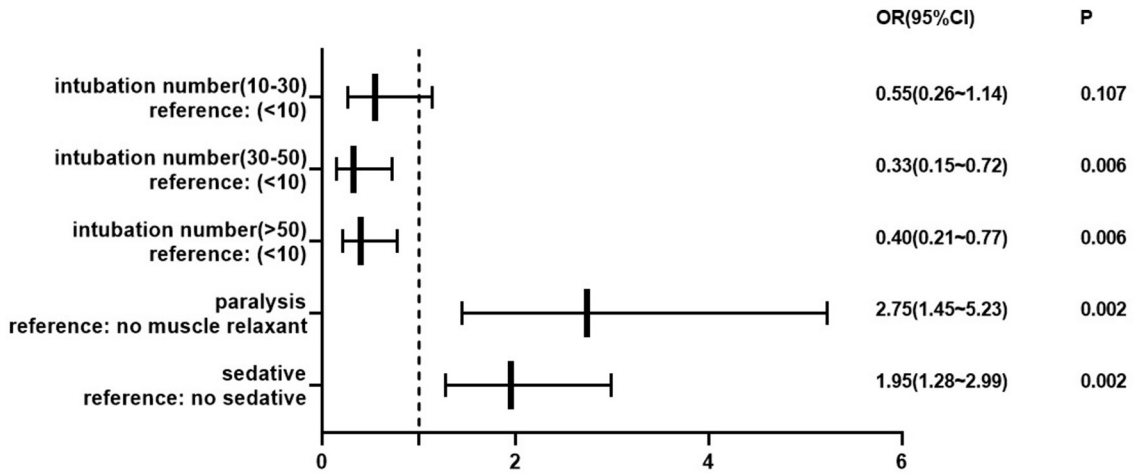

FIGURE 4 | Forest map of the risk of first-pass intubation attempt failure. The dotted line demarcates protective factors on the left and risk factors on the right. $P < 0.05$ represented statistically significant.

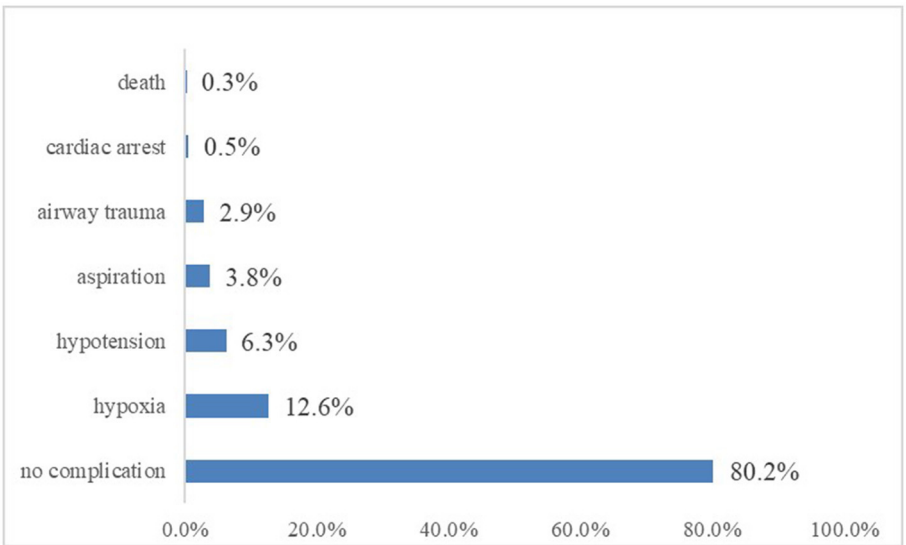

FIGURE 5 | Incidence of different complications during ED intubation.

process of how preoxygenation was performed. Future studies could focus on this point to explain the possible reasons behind the higher rates of hypoxia.

The Society for Airway Management in 2020 put forward consensus recommendations for airway management, including screening and pretreating patients for high risk of circulatory instability (21). However, in our investigation, among patients with hypotension (SBP <90 mmHg) before intubation, only 42% (175 of 422) received pretreatment. Neglecting pretreating circulatory problems in advance and incorrect use of induction agents may lead to more fluctuations in circulation. This was partly confirmed by a marked drop in blood pressure following intubation in this study. Overall, pretreatment before intubation and selecting proper induction medications are recommended areas for quality improvement in the future.

The first-pass intubation success rate has been associated with the incidence of adverse events during intubation (6) and is the most important statistic when it comes to intubations. Our results showed that 85.7% of patients were intubated successfully on the first attempt. This rate compares favorably to ED intubations in other countries, which range from 70.3 to 85% in several studies (2, 22–24). Unsurprisingly, physicians with greater intubation experience were associated with a higher intubation success rate. Unfortunately, using sedatives or muscle relaxants was associated with intubation failure in this study. This result is likely caused by selection bias or unmeasured confounders. One reason for the lower use of induction medications in Chinese EDs was

that the most uncooperative or irritable patients were considered for these medications, which may have increased the difficulty of intubation. In addition, drug selection and timing may also affect intubation quality. Physicians may rush to establish an artificial airway rather than wait for medications to take effect. Although physicians may have knowledge of induction medications, the medications themselves are not being widely used. The reasons for this may include local hospital protocols, anesthesia limitations, or lack of real-world training.

After failing intubation for the first time, the top three rescue choices were changing intubators, attempting again, or changing devices. A "cannot intubate and cannot ventilate" scenario occurred in only one patient, who, following the wishes of his family, had care withdrawn. Finally, no supraglottic equipment was used in any patient in this study. Nevertheless, many Chinese EDs are equipped with supraglottic airway equipment and cricothyrotomy kits, but they seem to be rarely used.

We found a complication rate of 19.8% for ED intubations. This was a relatively high percentage compared to other national-level ED studies which found complication rates of 8–28% (6, 22, 25). Examining these studies, the proportion of different adverse events was not consistent. Walls listed the top three complications were esophageal intubation, mainstem bronchus intubation, and hypotension (26). Graham found that severe hypotension, esophageal intubation, and critical desaturation happened most often (27). In this study, the most frequent adverse event encountered was hypoxia, followed by hypotension and aspiration. The relatively higher rate of adverse events may be partly due to patients' underlying medical conditions, such as pulmonary disease and circulatory shock. Previous research has shown that lower initial oxygen saturation is an independent predictor of hypoxia (28, 29). Similarly, pre-intubation hypotension was correlated to post-intubation hypotension (30). In the ED, it may not be possible to raise oxygenation or SBP to "normal" levels prior to initiating the intubation procedure, but we can still try to maximize these factors as much as possible.

LIMITATIONS

This study had some limitations. First, the survey only lasted 1 month, missing potential seasonal variations. Second, the number of hospitals chosen varied by region and some EDs enrolled only a small number of patients and may not represent a complete cross-section of all the intubations they performed. Third, this trial only focused on the short-term outcomes in the EDs. We still need further study into the long-term ED intubation outcomes, and a closer examination of controversial techniques, such as using cricoid pressure. Finally, this was a statistically descriptive cross-sectional study. The nature of the study is such that it can only uncover associations and cannot provide a further causal conclusion.

CONCLUSION

This study illuminated the current circumstances surrounding intubations in Chinese EDs, including a relatively high adverse event rate. Nation-wide standardized ED intubation training should be enhanced, with an emphasis on induction agent education. Repeat surveys in 5–10 years will help see if there are significant changes to ED intubation adverse event and medication utilization rates.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee, Peking Union Medical College Hospital. The certificate number was JS-2718. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JX and XY conceived and proposed the study. YD, HY, and JW were responsible for study design, statistical method selection, and drafting the manuscript. All authors reviewed and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.813833/full#supplementary-material

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Prediction of Ventricular Arrhythmias by QRS/QTc - Ratio in Citalopram or Escitalopram Intoxication

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Background: The U.S. Food and Drug Administration (FDA) has stated that citalopram and escitalopram should not be used at daily doses above 40 mg/20 mg due to risk for development of fatal ventricular arrhythmias like torsade de pointes (TdP). Yet, supratherapeutic serum concentrations of citalopram are common and predicting patients at risk for TdP is of high clinical value. Accordingly, we investigated whether QRS/QTc; developed for predicting TdP in hypothermic patients could be used in citalopram intoxication.

Methods: A total of 16 publications describing patients suffering from complications due to citalopram or escitalopram treatment, or intoxication with the same substances, were included after a systematic search. The main criterion for inclusion was admission ECG, either with given QRS and QTc values or with attached ECG-files that enabled calculation.

Results: QRS/QTc rather that QTc alone emerged as a marker of ventricular arrhythmia in the 16 included case reports, with highly significant ($p < 0.0005$) lower values in patients displaying ventricular arrhythmias.

Conclusion: Citalopram and escitalopram are extensively used in treatment of depressive disorders, and a large proportion of patients have supratherapeutic serum concentrations. Calculation of QRS/QTc in available case reports show that this novel ECG-marker has potential to predict patients at risk for developing ventricular arrhythmias.

Keywords: citalopram, escitalopram, long QT, ECG, QRS/QTc, arrhythmia, ventricular fibrilation, torsade de pointes (TdP)

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BACKGROUND

In 2011, The U.S. Food and Drug Administration (FDA) issued a Drug Safety Communication stating that the selective serotonin reuptake inhibitor (SSRI) citalopram should no longer be used at daily doses above 40 mg, due to risk of QT prolongation and fatal development of ventricular arrhythmias, like torsade de pointes (TdP) (1). Underlining the FDA recommendations, both

citalopram and its (S)-stereoisomer escitalopram was found to increase mortality risk compared to other anti-depressants, related to elevated incidence of ventricular arrhythmias in citalopram-users (2). Accordingly also escitalopram-doses are recommended to be restricted to a maximal daily dose of 20 mg (1).

Yet, escitalopram is extensively used in patients suffering from conditions such as depression and anxiety-disorders. More than 2% of the Norwegian population were prescribed escitalopram in 2020, making it both the most used SSRI and antidepressant drug in the Norwegian population (3). Generally, escitalopram in therapeutic doses is well tolerated but the high volume of users advocates the need for a tool to determine risk for adverse cardiac events. Predicting which patients that will develop such arrhythmias remains a significant clinical challenge. QTc alone does not give sufficient information to predict pro-arrhythmic activity in escitalopram-users and accordingly there is no well-established ECG value for assessing the risk of TdP (4).

QTc-prolongation with increased risk for TdP and cardiac arrest is a known complication in treatment with several psychopharmacological substances, but is relevant also in other patients groups and conditions like hypothermia (5). From pre-clinical and clinical data, we have recently developed the ECG-marker QRS/QTc that could predict risk for ventricular fibrillation (VF) and cardiac arrest with low core temperatures (6, 7). It is important to assess whether our findings also apply to predicting risk for developing ventricular arrhythmias in other patient groups with QTc-prolongation. Accordingly, intoxication with citalopram or escitalopram is a relevant condition. Successful identification of intoxicated patients at risk for developing ventricular arrhythmias could provide opportunity to initiate preventive pharmacological treatment before life-threatening arrhythmias arise. Accordingly, we have assessed case-reports describing emergency admission due to treatment or intoxication with either citalopram or escitalopram, where patients were undergoing electrophysiological monitoring with ECG-recordings.

METHODS

A literature search was conducted on April 13th, 2020 in the electronic PubMed database. All case reports retrieved for: #1 citalopram AND QRS AND QTC, #1 escitalopram AND QRS AND QTC, #3 citalopram AND cardiac arrest, #4 escitalopram AND cardiac arrest, #5 citalopram AND torsades de pointes, #6 escitalopram AND torsades de pointes, #7 citalopram AND overdose, and #8 escitalopram AND overdose, were assessed.

A total of 16 publications were included (8–23). The main criterion for inclusion of articles was that they had an admission ECG, either with given QRS and QTc values or with attached ECG-files that enabled us to calculate these parameters. Only case reports describing acute admission of patients suffering from complications due to citalopram or escitalopram treatment, or intoxication with the same substances, were included. Case reports lacking an admission ECG and case reports on children and neonates, were excluded. One case report with an admission ECG was excluded due to that this ECG was taken during monomorphic ventricular tachycardia, leaving us unable to assess ECG-timings prior to ventricular arrhythmia (24).

Studies were considered for inclusion based on the contents of the abstract. If this was inadequate or absent, the full text was assessed to examine whether they met inclusion criteria. Articles that were not detected through the literature search were found in reference-lists of included manuscripts or other literature reviews.

All data were normally distributed (assessed with Shapiro-Wilk's test) and passed a Brown-Forsythe test of equal variance. To assess differences between patients that did or did not experience ventricular arrhythmias, a two-tailed, unpaired *t*-test was used. Results are presented as mean ± Standard deviation. Differences were considered significant at $p < 0.05$.

RESULTS

A total of 16 case reports, concerning 11 female and five male patients aged 20–89 (mean 43) were included (**Table 1**). Twelve were admitted to hospital after complications related to intoxication with citalopram ($n = 9$) (dose range: 0.22–11.6 g) or escitalopram ($n = 3$) (0.14–0.4 g). Four patients were admitted due to serious side effects of using therapeutic doses of citalopram (0.08–0.04 g). Twelve of the patients had taken additional drugs or ethanol, either as part of their prescribed treatment regime or due to voluntary intoxication. Serum concentrations were available for five of the citalopram intoxications (mean 2,827 ng/mL) and one escitalopram intoxication (290 ng/mL).

A total of seven included patients had ventricular arrhythmias after admission and two of these died after final ECG-readings of pulseless tachycardia. In 5 of 7 patients, the ventricular arrhythmia was described as TdP. In the remaining nine patients, not developing ventricular arrhythmias, one went into sinus arrest after readings of increased QRS-widening but recovered and had no sequela. Other patients in this group also experienced sinus tachycardia, bradycardia or left bundle branch block during hospitalization, and the majority (6 of 9) were unconscious or experienced seizures at or after admission.

QRS/QTc value emerged as the best indicator of ventricular arrhythmia (**Figures 1–4** and **Table 2**) in the 16 included case reports, with highly significant lower values in the ventricular arrhythmia patient group (0.15 ± 0.02 vs. 0.24 ± 0.04, $p < 0.0005$). This difference was the most substantial between groups although both lower QRS values (90 ± 14 vs. 122 ± 23, $p < 0.01$) and longer QTc was found in the same patients (606 ± 78 vs. 508 ± 55, $p < 0.05$). There were no differences in heart rate (85 ± 17 vs. 81 ± 25).

DISCUSSION

Prolongation of the QT-interval is related to treatment with several psychopharmacological substances. The underlying challenge is to detect patients that are at risk for developing ventricular arrhythmias, like TdP, and take actions to reduce

TABLE 1 | Clinical data from the included patients, as given in the case-reports.

Case report	Age	Sex	Type of poisoning	Substance	Serum concentration (ng/mL)	Dose (g)	Other drugs	VT/VF
(1) Bin Salih et al. (19)	20	F	Intoxication	Citalopram	–	1.8	Ethanol	No
(2) Lung et al. (15)	21	M	Intoxication	Citalopram	522	11.6	Olanzapine Clonazepam	No
(3) Venkatraman et al. (20)	23	F	Intoxication	Citalopram	–	0.22	Lamotrigine Chlorphenamine Ethanol	No
(4) Cuenca et al. (22)	23	M	Intoxication	Citalopram	–	0.92	No	No
(5) Lung et al. (9)	24	F	Intoxication	Citalopram	400	1.8	Bupropion Clonazepam	Yes
(6) Farkas et al. (17)	25	F	Intoxication	Escitalopram	290	-	Lamotrigine	No
(7) Engebretsen et al. (16)	31	M	Intoxication	Citalopram	1,940	0.4	Ethanol	No
(8) Mohammed et al. (18)	33	F	Intoxication	Escitalopram	–	0.4	Lithium	No
(9) Kraai et al. (23)	35	F	Intoxication	Citalopram	7,300	–	Cannabis	Yes
(10) Deshmukh et al. (11)	40	F	Therapeutic dose	Citalopram	–	0.08	No	Yes
(11) Gregorio et al. (12)	48	F	Therapeutic dose	Citalopram	–	0.04	Furosemide	Yes
(12) Baranchuk et al. (21)	52	M	Intoxication	Escitalopram	–	0.14	Diazepam Zopiclone Lorazepam Morphine	No
(13) Liotier et al. (14)	54	F	Intoxication	Citalopram	–	–	Ethanol	Yes
(14) Kanjanauthai et al. (10)	81	M	Therapeutic dose	Citalopram	–	–	–	Yes
(15) Brucculeri et al. (8)	82	F	Intoxication	Citalopram	910	1.6	No	No
(16) Agosti et al. (13)	89	F	Therapeutic dose	Citalopram	–	0.04	Levosulpiride	Yes
Average ± SD	43 ± 23	–	–	–	2,464 ± 2,687	1.59 ± 3.09	–	–

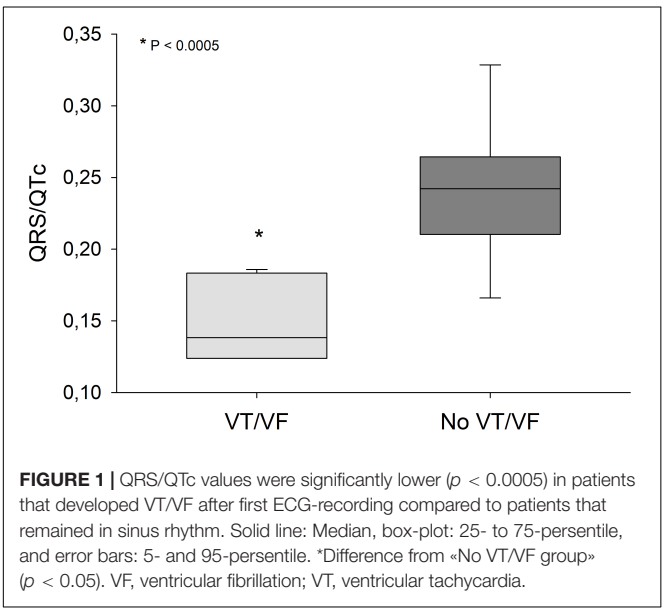

FIGURE 1 | QRS/QTc values were significantly lower ($p < 0.0005$) in patients that developed VT/VF after first ECG-recording compared to patients that remained in sinus rhythm. Solid line: Median, box-plot: 25- to 75-persentile, and error bars: 5- and 95-persentile. *Difference from «No VT/VF group» ($p < 0.05$). VF, ventricular fibrillation; VT, ventricular tachycardia.

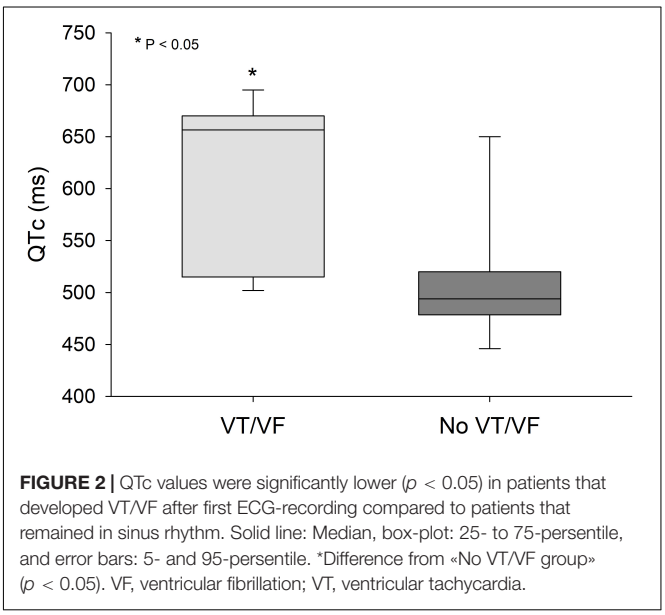

FIGURE 2 | QTc values were significantly lower ($p < 0.05$) in patients that developed VT/VF after first ECG-recording compared to patients that remained in sinus rhythm. Solid line: Median, box-plot: 25- to 75-persentile, and error bars: 5- and 95-persentile. *Difference from «No VT/VF group» ($p < 0.05$). VF, ventricular fibrillation; VT, ventricular tachycardia.

this risk. Here we present data advocating that the novel ECG-biomarker QRS/QTc has potential to predict predisposition to such arrhythmias and therefore serve as an ECG-marker of increased risk for cardiac arrest.

In recent publications we have found indication that QRS/QTc values below 0.2 were associated with increased risk for hypothermic cardiac arrest (5–7). The effects of hypothermia on the electrophysiology of the human heart are similar to those of citalopram- or escitalopram and other agents used to treat psychiatric disorders that prolong repolarization. While severe accidental hypothermia is uncommon, use of antidepressants is widespread. In Norway more than 6% of the population was

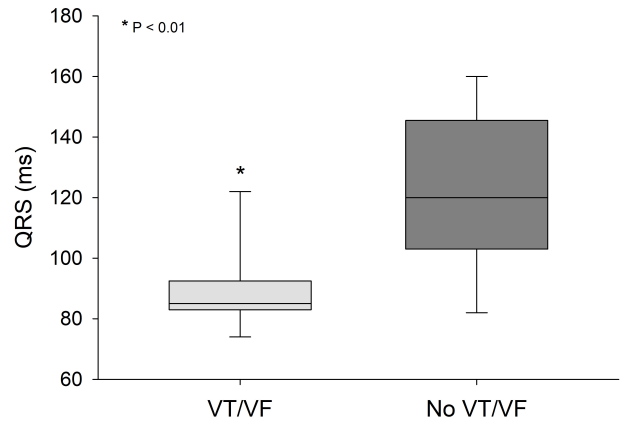

FIGURE 3 | QRS values were significantly lower ($p < 0.01$) in patients that developed VT/VF after first ECG-recording compared to patients that remained in sinus rhythm. Solid line: Median, box-plot: 25- to 75-persentile, and error bars: 5- and 95-persentile. *Difference from «No VT/VF group» ($p < 0.05$). VF, ventricular fibrillation; VT, ventricular tachycardia.

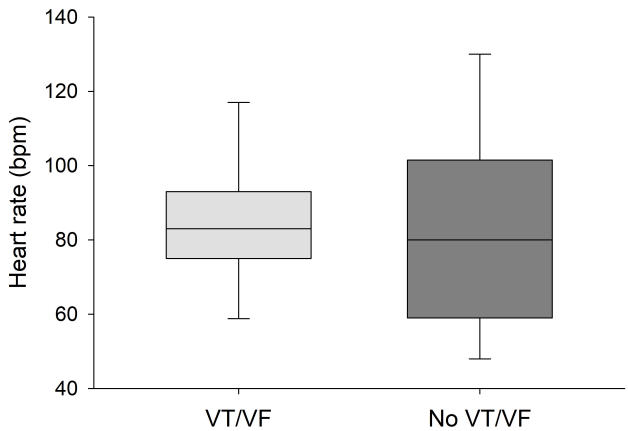

FIGURE 4 | No significant differences were found in heart rate between patients that developed VT/VF after first ECG-recording and patients that remained in sinus rhythm. Solid line: Median, box-plot: 25- to 75-persentile, and error bars: 5- and 95-persentile.

prescribed antidepressant drugs in 2020 (3), with even higher numbers in other European countries. A recent Spanish study showed that 8.6% of the general population used antidepressants (25). Greater age is associated with higher risk of cardiac disease, which could be complicated by more extensive use of drugs. Eleven percent of Norwegian senior residents are prescribed antidepressant drugs, with citalopram and escitalopram being among the most common substances. Twelve percent of users had serum concentrations of citalopram above the recommended reference range, with increasing risk of adverse effects (26).

In isolated guinea-pig cardiomyocytes it has been shown that citalopram inhibits the expression of hERG-channels available to generate repolarizing K^+-current, with an IC_{50} of 12.2 ng/mL (27). This concentration is more than 200-fold lower than the average serum concentration from 5 of the citalopram-intoxicated patients included in the present study, although direct comparison is difficult to due significant plasma protein binding of the drug. At higher concentrations, citalopram inhibits L-type Ca^{2+} channels (LTCC) (27). It has been advocated that citalopram-induced blockade of LTCCs mitigate the potential adverse effects of hERG-inhibition, by preventing early after depolarizations (EAD) and subsequent arrhythmias like TdP (28). The linking of anti-arrhythmic effects to QRS duration may be based in the ability of citralopram to block the Nav1.2 voltage gated sodium channel (VGSC) (29). The accompanying reduced myocardial excitability and potentially conduction velocity may contribute to the anti-arrhythmic properties under the same principle as Vaughan-Williams Class I anti-arrhythmic drugs (30). A similar logic can be used to explain the anti-arrhythmic effects of profound hypothermia where both QRS and QT are increased (5–7, 31). A mild reduction of excitability by inhibition of the VGSC and the associated reduced TdP-risk would not be detected by monitoring QTc-interval, which is prolonged predominately by effects on repolarization. Although long QT-interval is a common complication of citalopram- and other psychopharmacological treatments, to-date no reliable marker of arrhythmia-risk exists in these patients.

Given that citalopram-induced blockade of VGSC and LTCC may mitigate EAD-risk caused by hERG-inhibition, the risk of drug-induced arrhythmias due to hERG-blockade remains the dominant effects, as the IC_{50}-values of citalopram for inhibiting hERG is 10-fold lower than for inhibition of VGSC and LTCC (28). Individuals exposed to high concentrations of citalopram in the range above the threshold for hERG-inhibition and below VGSC channel-inhibition, could theoretically be at higher risk for developing TdP. QRS/QTc values would be low in such patients as opposed to higher QRS/QTc values in patients with the co-occurrence of reduced excitability/conduction velocity (prolonged QRS) and delayed repolarization (prolonged QTc).

Citalopram and escitalopram are mainly subject to hepatic metabolism by CYP2C19. CYP2C19-mutations that reduce metabolism could therefore explain high serum concentrations (26) of the mother compound (escitalopram/citalopram) compared to the metabolite demethylcitalopram in some patients. Other metabolites include didemethylcitalopram via CYP2D6 metabolism. Neither of these metabolites contribute to the pharmacologic activity, and normally exist in the plasma in small quantities. Although not contributing to the antidepressant effect of citalopram or escitalopram, demethylcitalopram and didemethylcitalopram are electrophysiologically active metabolites, inhibiting both the IKr and IKs potassium channels (32), theoretically reducing QRS/QTc values. Didemethylcitalopram appears the most cardiotoxic and has been associated with unexpected and sudden death in dogs (33), probably due to species-specific metabolic differences as humans generally have lower didemethylcitalopram-concentrations (32). Nevertheless, some patients appear to have high didemethylcitalopram serum-concentrations after therapeutic escitalopram-doses at 20 mg or less per day (34). Drug interactions as well as genetic variation of CYP2C19

TABLE 2 | ECG-data from the included patients as given in the case-reports or calculated from included ECG-recordings.

Case report	Age	QRS (ms)	QT (ms)	QTc (ms)	HR (bpm)	QRS/QTc	VT/VF
(1) Bin Salih et al. (19)	20	82	428	494	80	0.17	No
(2) Lung et al. (15)	21	160	400	487	85	0.33	No
(3) Venkatraman et al. (20)	23	120	352	470	107	0.26	No
(4) Cuenca et al. (22)	23	108	446	446	60	0.24	No
(5) Lung et al. (9)	24	85	411	515	93	0.17	Yes
(6) Farkas et al. (17)	25	98	392	496	96	0.2	No
(7) Engebretsen et al. (16)	31	124	344	506	130	0.25	No
(8) Mohammed et al. (18)	33	117	479	491	63	0.24	No
(9) Kraai et al. (23)	35	92	360	502	117	0.18	Yes
(10) Deshmukh et al. (11)	40	74	357	535	90	0.14	Yes
(11) Gregorio et al. (12)	48	83	620	670	75	0.12	Yes
(12) Baranchuk et al. (21)	52	145	727	650	48	0.22	No
(13) Liotier et al. (14)	54	83	600	670	75	0.12	Yes
(14) Kanjanauthai et al. (10)	81	92.5	572	695	83	0.13	Yes
(15) Brucculeri et al. (8)	82	146	544	534	58	0.27	No
(16) Agosti et al. (13)	89	122	650	657	59	0.19	Yes
Average ± SD	43 ± 23	108 ± 25	480 ± 118	551 ± 82	82 ± 22	0.20 ± 0.06	–

and CYP2D6 could therefore alter serum concentrations of citalopram metabolites and cause individual differences in cardiac toxicity of citalopram and escitalopram. Therapeutic drug monitoring would not reveal patients at such risk, unless the metabolites are monitored as well as citalopram concentrations. Accordingly, QRS/QTc values could potentially reveal patients with CYP2C19 and CYP2D6 metabolism that biases these patients toward pro-arrhythmic activity when using escitalopram or citalopram.

Use of antidepressants is also common in intended intoxications. Recently, suicide rates among older women in the United States has been increasing, and toxicology reports show that 47% of overdoses were positive for antidepressants (35). Accordingly, both unintentional and intentional citalopram-intoxications are relevant conditions both for general practitioners, psychiatrists and in emergency medicine. An ECG-marker more reliable than QTc for detecting risk of TdP in exposed patients would be of high clinical value, both in the emergency room after intoxications and as a simple screening tool in patients with citalopram or escitalopram prescriptions.

Prolongation of QT-interval and increased risk of TdP, triggered by drugs, is termed "acquired long QT syndrome" (aLQTS) (36). In vulnerable patients, with underlying genetic substrates, aLQTS is triggered more easily. A third of patients that present with aLQTS have congenital LQTS mutations (36). Accordingly, close monitoring is necessary to prevent unexpected death due to QT-prolongation and TdP, during treatment with psychopharmaca. Currently there is no well-established ECG value for assessing the risk of TdP (4). To speculate; the relation we find between QRS/QTc-values and VF in citalopram and escitalopram-intoxication could be due to undetected, congenital LQTS mutations. Accordingly, there is potential that QRS/QTc could serve as an inexpensive tool to detect underlying genetic disposition for aLQTS, both in intoxications and therapeutic use of drugs known to increase risk for TdP.

LIMITATIONS

The current systematic review of case-reports cannot reveal possible underlying mechanisms that could explain which patients that develop TdP and cardiac arrest after intoxication with escitalopram or citalopram. Such mechanisms could include LQTS mutations but also interaction with or simultaneous intoxication with other drugs that were not detected in the included cases and that could have affected QRS/QTc-values.

CONCLUSION

Citalopram and escitalopram are extensively used in treatment of depressive disorders, and a large proportion of patients have serum concentrations that exceed recommended reference intervals for safe treatment. Ventricular arrhythmias like torsades des pointes and cardiac arrest is a potential and life-threatening complication of such supratherapeutic serum concentrations. Calculation of QRS/QTc in available case reports show that this novel ECG-marker has potential to predict patients at risk for developing ventricular arrhythmias.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

ED carried out the systematic search and screened case-reports for inclusion. ED and GS evaluated the data, wrote the manuscript, contributed to the article, and approved the submitted version.

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Non-Invasive Monitoring of Core Body Temperature for Targeted Temperature Management in Post-Cardiac Arrest Care

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Importance: Accurate monitoring of core body temperature is integral to targeted temperature management (TTM) following cardiac arrest. However, there are no reliable non-invasive methods for monitoring temperature during TTM.

Objectives: We compared the accuracy and precision of a novel non-invasive Zero-Heat-Flux Thermometer (SpotOn^{TM}) to a standard invasive esophageal probe in a cohort of patients undergoing TTM post-cardiac arrest.

Design, Setting, and Participants: We prospectively enrolled 20 patients undergoing post-cardiac arrest care in the intensive care units at the London Health Sciences Centre in London, Canada. A SpotOn^{TM} probe was applied on each patient's forehead, while an esophageal temperature probe was inserted, and both temperature readings were recorded at 1-min intervals for the duration of TTM.

Main outcomes and Measures: We compared the SpotOn^{TM} and esophageal monitors using the Bland–Altman analysis and the Pearson correlation, with accuracy set as a primary outcome. Secondary outcomes included precision and correlation. Bias exceeding 0.1°C and limits of agreement exceeding 0.5°C were considered clinically important.

Results: Sixteen (80%) of patients had complete data used in the final analysis. The median (interquartile range) duration of recording was 38 (12–56) h. Compared to the esophageal probe, SpotOn^{TM} had a bias of 0.06 ± 0.45°C and 95% limits of agreement of −0.83 to 0.95°C. The Pearson correlation coefficient was 0.97 (95% confidence interval 0.9663–0.9678), with a two-tailed $p < 0.0001$.

Conclusion and Relevance: The SpotOn^{TM} is an accurate method that may enable non-invasive monitoring of core body temperature during TTM, although its precision is slightly worse than the predefined 0.5°C when compared to invasive esophageal probe.

Keywords: critical care, heart arrest, hypothermia, induced, brain injuries, thermometers, technology

INTRODUCTION

Implementation of targeted temperature management (TTM) protocols is an important component of post-cardiac arrest care that is associated with improved neurologic outcomes (1, 2). TTM protocols generally include rapid cooling, maintenance, rewarming, and hyperthermia prevention stages that are delivered over 24–72 h following cardiac arrest (3–5). Recent evidence suggests that targeted normothermia and prevention of hyperthermia in a subset of patients within the post-cardiac arrest period may be as effective as hypothermia in improving post-cardiac arrest outcomes (6). Accurate monitoring of core body temperature is a critical component of TTM, and current guidelines recommend using invasive esophageal, nasopharyngeal, bladder, endotracheal cuff, or pulmonary artery temperature sensors to achieve this goal (3–5).

A novel temperature monitor (SpotOn^{TM}, 3M, Minnesota, USA) is an attractive non-invasive alternative for tracking core body temperature during TTM. SpotOn^{TM} is applied to the forehead, creates an isothermic tunnel under the measurement site by insulating heat loss from the skin surface, and estimates core body temperature using the zero-heat-flux technology (7). In perioperative settings, SpotOn^{TM} showed good correlation, accuracy, and precision when compared to esophageal, nasopharyngeal, and pulmonary artery sensors (8–10) and was better than bladder temperature sensors (10). However, these studies only measured temperatures for up to 9 h and did not compare the SpotOn^{TM} monitor during TTM, which employs wider temperature ranges and longer measurement duration (up to 72 h).

The aim of this study was to assess the accuracy, precision, and correlation of the SpotOn^{TM} monitor compared to a standard invasive core body temperature monitor in cardiac arrest patients undergoing TTM.

MATERIALS AND METHODS

Study Design and Patients

This was a prospective observational single-center study that recruited consecutive patients with cardiac arrest admitted to two intensive care units (ICUs) at the London Health Sciences Centre in London, Canada. Inclusion criteria were age $\geq$18 years with in- and out-of-hospital cardiac arrest who were eligible for TTM as per established hospital protocols developed in accordance with the current practice guidelines (3). Exclusion criteria were immediate plan to withdraw life-sustaining measures, inability to obtain consent, skin rash or infection over the forehead, or medical tape allergy. The study was approved by the Western University Health Sciences Research Ethics Board (Protocol # 109432). We obtained signed informed consent from substitute decision-makers prior to commencing study procedures.

Study Procedures

Following study enrollment, we initiated simultaneous recording of the patient's core body temperatures using SpotOn^{TM} and

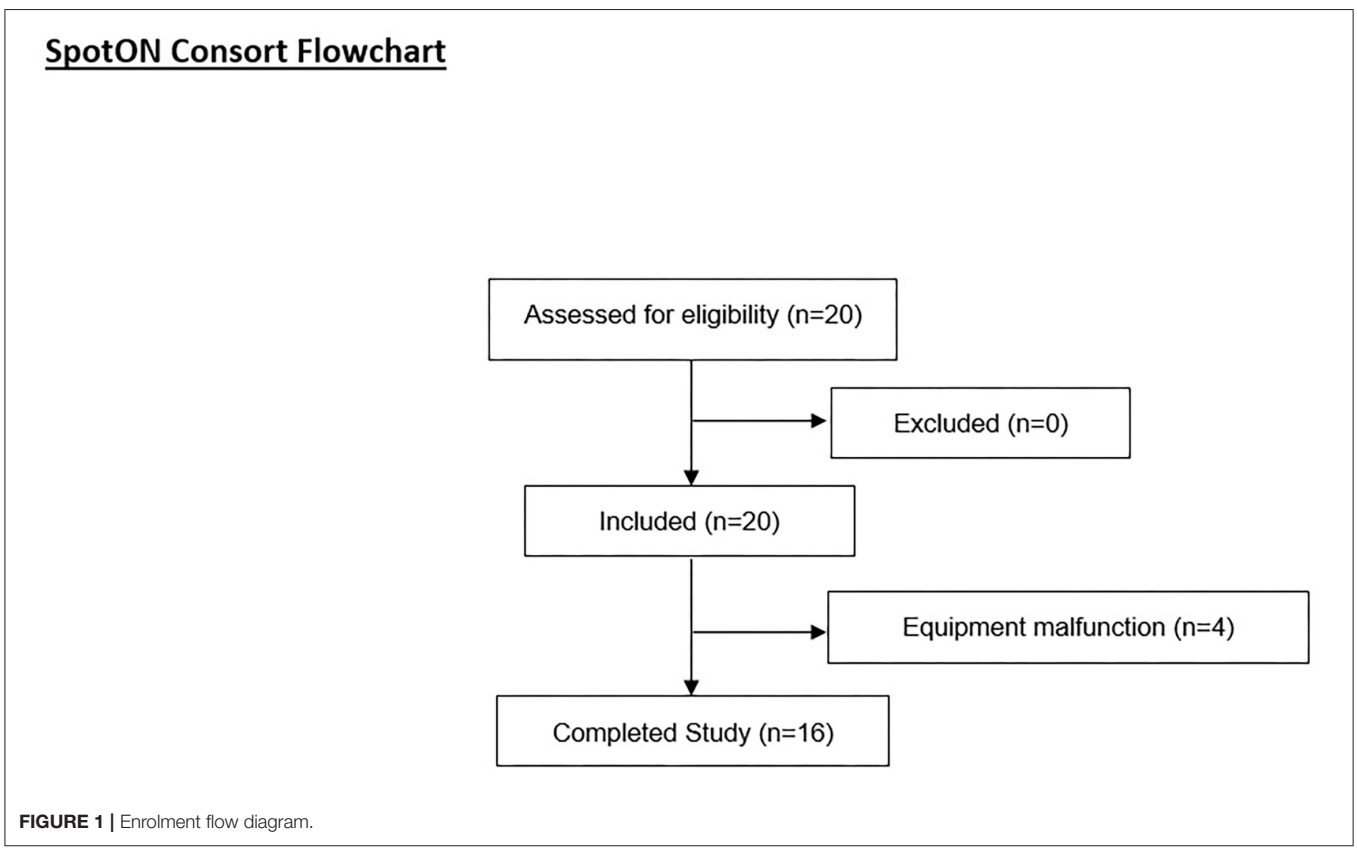

FIGURE 1 | Enrolment flow diagram.

esophageal temperature probes for the duration of the TTM protocol. The TTM protocol at our hospital included cooling, maintenance, rewarming, and hyperthermia prevention for up to 72 h following cardiac arrest. In each patient, we used the pressure-sensitive adhesive to secure the SpotOn™ temperature probe to the patient's forehead as per the product monograph. We then connected the probe to the SpotOn™ central portable console and initiated temperature measurement. All patients had esophageal temperature probes inserted as per our institutional TTM protocol. We used an automated data capture module (MediCollector®, USA) to simultaneously record temperatures from both the SpotOn™ and esophageal temperature probes at 1-min intervals for the duration of the TTM protocol. We used case report forms for each patient to record demographic data, type of cardiac arrest, comorbidities, duration of TTM protocol, and temperature recording from the medical chart.

TABLE 1 | Patient demographics.

Subjects	**16**
Sex (M:F)	11:5
Age (IQR)	65.5 (54–71.5)
IHCA	7 (43.8%)
OHCA	9 (56.2%)
VT or VF	4 (25%)
PEA or asystole	12 (75%)
Cooling—hours (IQR)	24 (24–24)
Recording—hours (IQR)	38.14 (11.69–56.10)
Comorbidities	
Coronary disease	0 (0%)
Congestive heart failure	3 (18.75%)
Diabetes	5 (31.25%)
Hypertension	9 (56.25%)
Chronic kidney disease	3 (18.75%)
Dyslipidemia	6 (37.5%)
COPD	2 (12.5%)

IQR, interquartile range; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; VT, ventricular tachycardia; VF, ventricular fibrillation; PEA, pulseless electrical activity; COPD, chronic obstructive pulmonary disease.

Data Analysis and Statistics

Statistical analysis was performed using GraphPad Prism version 8.3 (GraphPad Software®, San Diego, CA, USA). Continuous variables were reported using medians and interquartile ranges (IQRs) for non-normally distributed data or means and standard deviations for normally distributed data, and categorical variables were reported as frequencies (%). The primary endpoint for this study was accuracy between the SpotOn™ and esophageal temperature probes, measured as bias using the Bland–Altman analysis. Secondary outcomes include precision, measured as limits of agreement using the Bland–Altman analysis, and correlation, measured using the Pearson correlation coefficient.

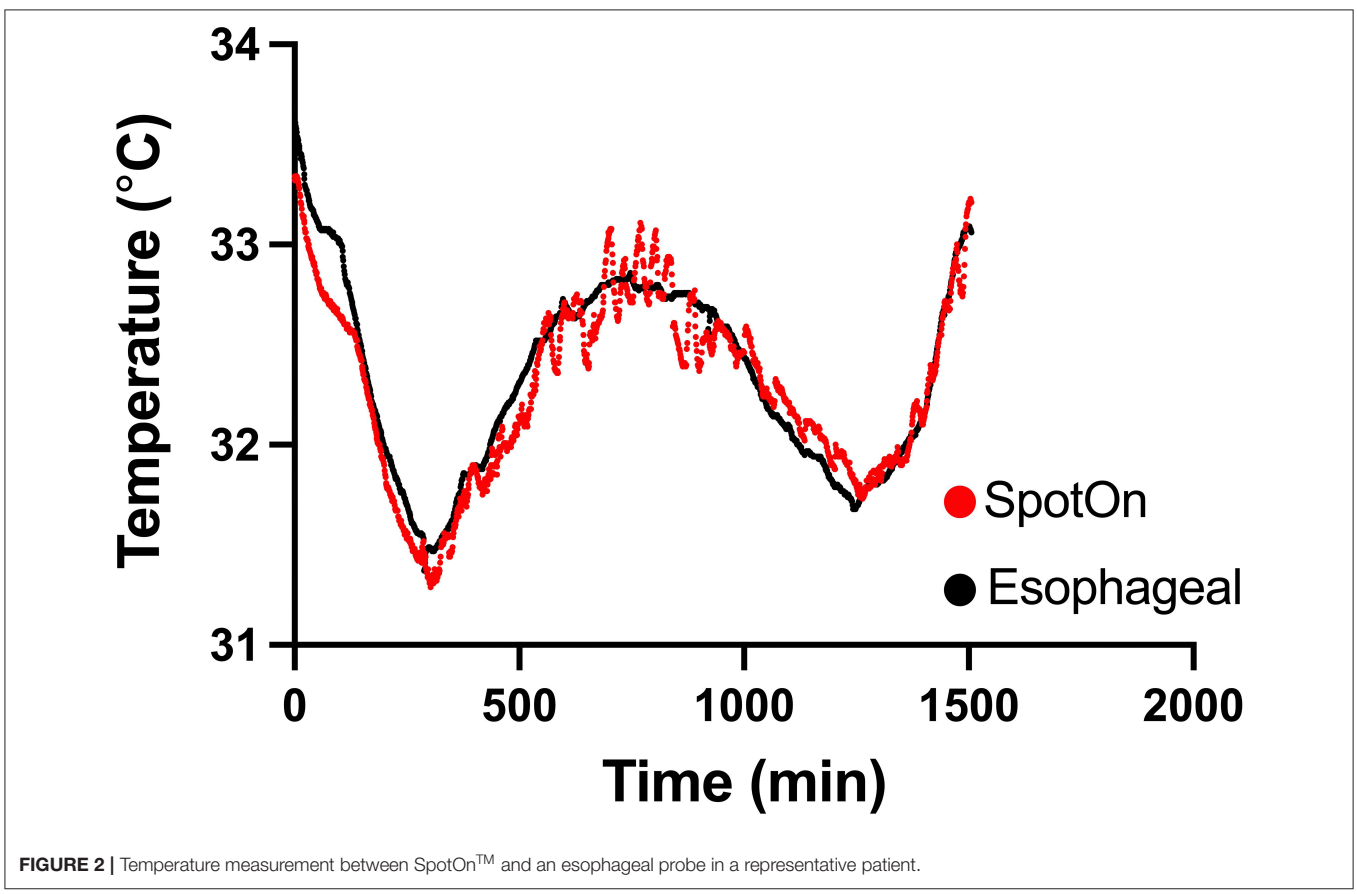

FIGURE 2 | Temperature measurement between SpotOn™ and an esophageal probe in a representative patient.

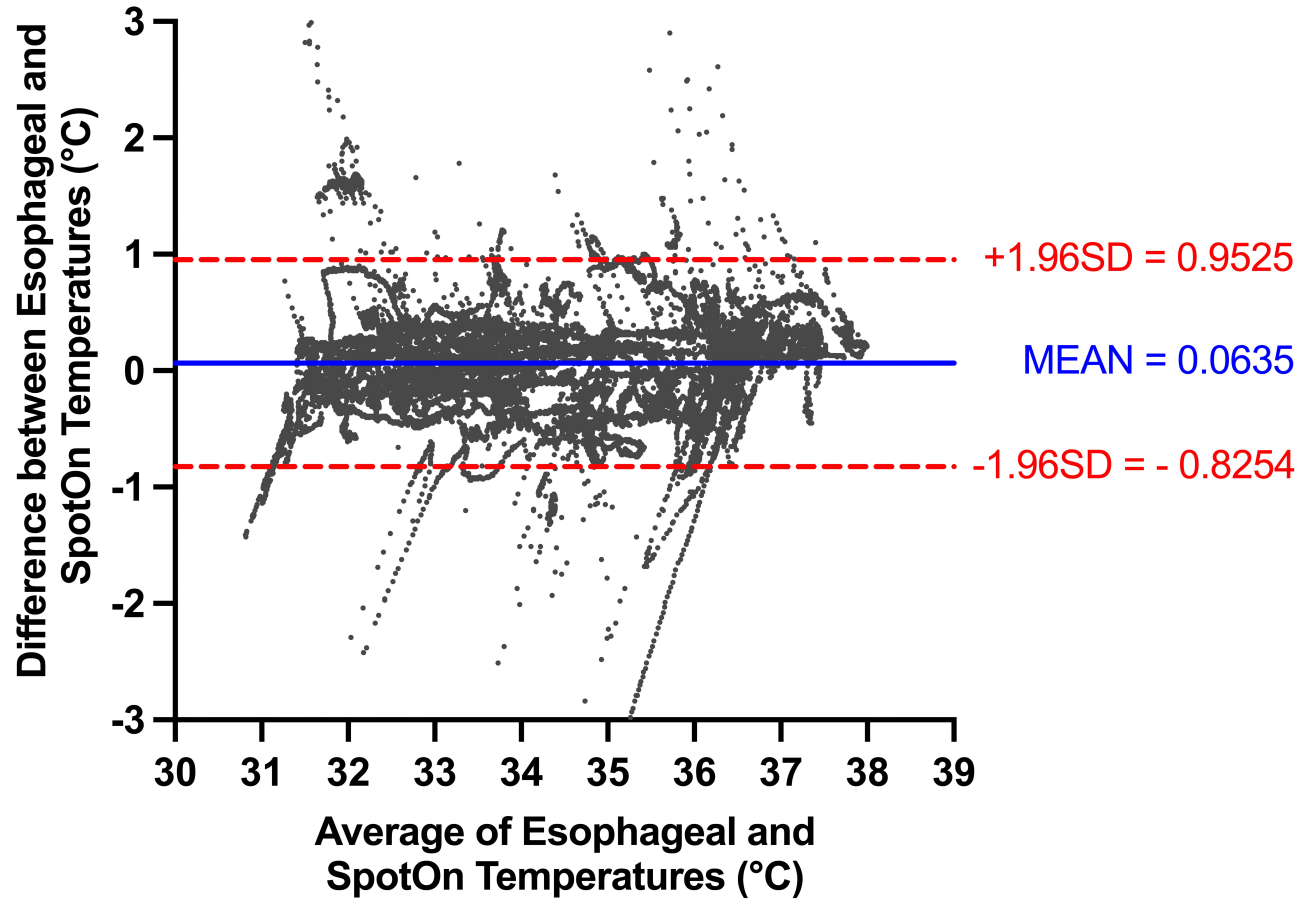

FIGURE 3 | Bland-Altman analysis comparing SpotOn™ and the esophageal temperature probe.

RESULTS

We enrolled 20 consecutive patients in the study. Four (20%) patients had incomplete data due to failure of the recording equipment and were excluded from data analysis. The remaining 16 patients (5 women) were included in the final analysis (**Figure 1**). Their clinical characteristics are summarized in **Table 1**. Median (IQR) age was 66 years (54–72) years, 9 (56%) patients had an out-of-hospital cardiac arrest, 4 (25%) had a shockable rhythm, 8 (50%) had pulseless electrical activity, and the three most common comorbidities were hypertension (56%), dyslipidemia (38%), and diabetes (31%). The median (IQR) duration of the TTM protocol was 24 (24–24) h and the median recording time was 38 (12–56) h. **Figure 2** shows a sample recording from a representative patient.

Combining data across all patients with multiple observations per patient, we had 29,750 sets of data points from the two temperature probes. All patients within the study underwent rapid cooling as part of TTM, although their temperature target varied at the discretion of the treating physician. Temperatures detected by the esophageal probe ranged from 29.4 to 37.9°C. Within this range, there were no temperatures that were not able to be detected by the SponOn™ probe. For our primary outcome (accuracy), the bias measured using the Bland–Altman analysis was 0.06 ± 0.45°C (**Figure 3**). For our secondary outcomes, the precision as measured by the Bland–Altman analysis 95% limits of agreement was −0.83 to 0.95°C (**Figure 3**). The correlation analysis between the two modalities showed a Pearson coefficient of 0.967 (95% confidence interval 0.966–0.968), with a two-tailed $p < 0.0001$ (**Figure 4**).

Furthermore, we stratified the data to determine the accuracy and precision of the SpotOn™ temperature probe across three temperature ranges: normothermia (≥36.0°C), mild hypothermia (34.0–35.9°C), and deep hypothermia (<34.0°C). In the normothermia group (≥36.0°C), there were 8,226 pairs of temperature measurements, with a bias of 0.05 ± 0.43°C and 95% limits of agreement of −0.79 to 0.88°C. In the mild hypothermia group (34.0–35.9°C), there were 7,417 pairs of temperature measurements with a bias of 0.03 ± 0.49°C and 95% limits of agreement of 0.93–1.00°C. In the deep hypothermia group (<34.0°C), there were 14,107 pairs of temperature measurements with a bias of 0.09 ± 0.45°C and 95% limits of agreement of −0.79 to 0.97°C (**Figure 5**).

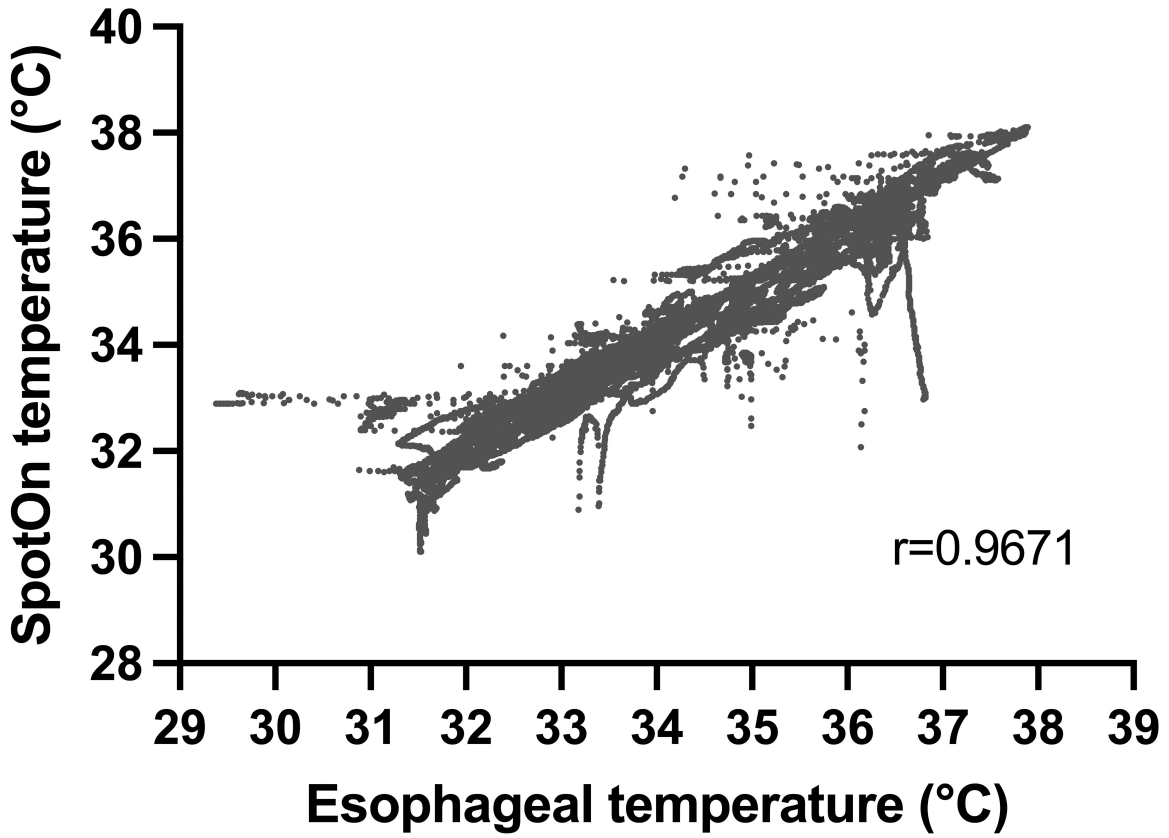

FIGURE 4 | Correlation between temperature measurement using SpotOn™ and the esophageal temperature probe.

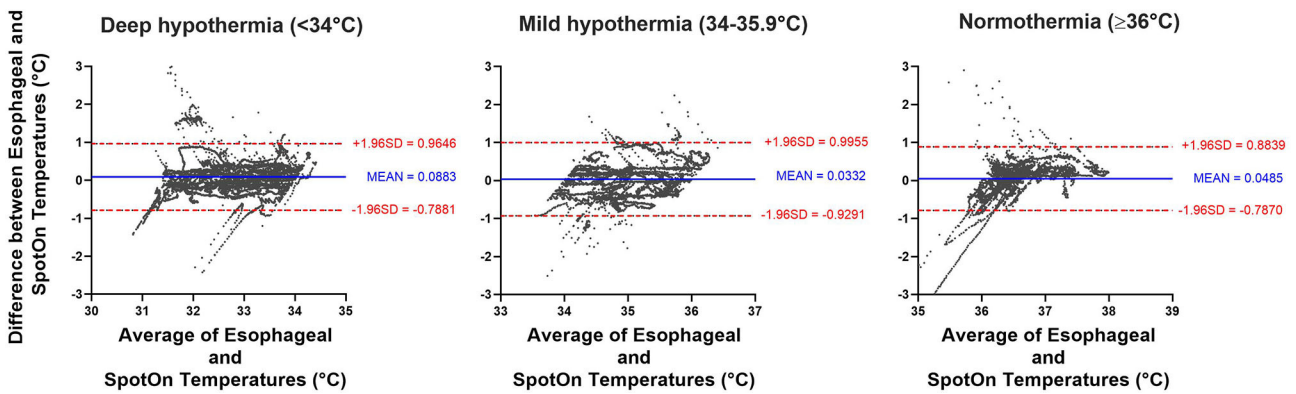

FIGURE 5 | Bland-Altman analysis comparing SpotOn™ and esophageal temperature probes in different temperature ranges, including deep hypothermia (<34°C), mild hypothermia (34–35.9°C), and normothermia (≥36°C).

DISCUSSION

Targeted temperature management is a fundamental component of post-cardiac arrest care that relies on accurate and precise monitoring of core body temperature (3–5). Current guidelines recommend using esophageal, nasopharyngeal, bladder, endotracheal cuff, and pulmonary artery temperature sensors for monitoring of core body temperature during TTM (3–5). However, these monitors are invasive and may not be readily available in all centers. In this study, we measured the accuracy and precision of the SpotOn™ against the invasive esophageal probe in patients undergoing TTM. Our results suggest that the SpotOn™ monitoring device has an accuracy consistent with what was acceptable in prior studies (11), although its precision

is just outside the previously accepted 95% limits of agreement of $<0.5^{\circ}$C (9).

The SpotOn™ thermometer has acceptable accuracy and precision for continuous core body temperature monitoring in perioperative settings (8–10) and during TTM (12, 13). Our work compliments these studies by providing a larger dataset spanning broader temperature ranges during TTM (13). Although they have become standard of care, invasive temperature monitors still have associated risks. For example, the risks associated with esophageal probes include vomiting and aspiration, tracheal misplacement and endotracheal tube cuff leak, and mucosal injury that can lead to bleeding, especially in patients with post-cardiac arrest due to concurrent acidosis, hypothermia, and use of therapeutic anticoagulation and platelet inhibitors (14). In contrast, the SpotOn™ monitor is non-invasive and easy to apply. The only potential drawbacks of the SpotOn™ device include restrictions with application in patients with adhesive allergies and potential for skin breakdown with extensive use, although these adverse events were seen neither in our study nor in a prior study that used SpotOn™ for the duration of time that was similar to TTM protocols (13).

An added benefit of the SpotOn™ thermometer is that its placement over the forehead provides an indirect measure of the brain temperature. Given that the purpose of TTM is to limit secondary brain injury by accurately titrating brain temperature, non-invasive monitoring of brain temperature by the SpotOn™ thermometer may be more clinically relevant than monitoring of core body temperature at non-brain sites. In the future, selective brain cooling while maintaining body normothermia may enable neurologic benefits of TTM while minimizing systemic side effects associated with whole-body cooling (15). In these cases, non-invasive monitoring of brain temperature using SpotOn™ would be highly relevant.

Our study had several limitations. We enrolled only 20 patients at a single-center and 4 patients were excluded due to a failure of data recording equipment. While the remaining 16 patients is a small sample size, long duration and high frequency of temperature recording resulted in a large dataset spanning a broad range of temperatures, enabling a robust comparison between the two temperature monitoring modalities. Although this large dataset of paired measurements derives a significant statistical power in determining the agreement between the two devices, one limitation is that our patient sample size was too small to stratify our results into clinical subgroups. Future larger studies can assess the accuracy and precision of the SpotOn™ temperature probe during TTM among clinical subgroups stratified by age, sex, and body mass index.

While the "gold standard" for temperature monitoring is considered the pulmonary artery catheter (16), we compared SpotOn™ performance against the esophageal temperature probe since pulmonary artery catheters are no longer used routinely in patients with post-cardiac arrest in our units. The precision and accuracy of the esophageal temperature probe relative to the pulmonary artery catheter have been previously demonstrated in another study (16). The esophageal temperature probes were placed using standard operating procedures for our ICU and were confirmed using chest X-ray. While one study showed that incorrect position of nasopharyngeal probe placement can affect accuracy of temperature measurement by approximately 0.2°C (17), confirming accurate placement of our esophageal probes beyond chest X-ray using modalities, such as CT scanning, was beyond the standard of care in our patients with post-cardiac arrest. Considering these limitations, we chose to use esophageal probes as a reference standard instead of pulmonary artery catheters.

Another possible limitation of our study was a small proportion of outlying data included in our analysis. The main cause of this was due to dislodgement or detachment of either the SpotOn™ or the esophageal temperature probe. Unfortunately, this occurs commonly during routine post-cardiac arrest care due to nursing care, imaging studies, invasive procedures, and interventions. Given that we were measuring temperatures every minute, even a short period of probe dislodgement or detachment can lead to a sizable number of outliers. However, given that we had an extensive number of data points, the amount of outlying data was not likely significant enough to have a substantial impact on the results. Lastly, shivering may also impact the accuracy of SpotOn™ measurements, although we did not assess this specifically in our study.

CONCLUSION

The SpotOn™ monitor is an accurate method for continuous temperature monitoring in patients with post-cardiac arrest, although its precision is slightly worse than the predefined 0.5°C when compared to the invasive esophageal probe. This device is an encouraging alternative to invasive probes for monitoring core body temperature during targeted temperature management, but larger studies will be required to confirm this in various patient populations. Furthermore, the possibility of indirect brain temperature measurement warrants further investigation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Western University Health Sciences Research Ethics Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TT, JD, and MS were responsible for data collection. KF, MS, and AH performed the data analysis. KF and MS wrote the first draft of the manuscript. All authors contributed to the review and revisions of the manuscript. All authors contributed to the article and approved the submitted version.

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Hyperoxia Is Not Associated With 30-day Survival in Out-of-Hospital Cardiac Arrest Patients Who Undergo Extracorporeal Cardiopulmonary Resuscitation

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Introduction: The appropriate arterial partial pressure of oxygen (PaO_2) in patients undergoing extracorporeal cardiopulmonary resuscitation (ECPR) for out-of-hospital cardiac arrest (OHCA) remains unclear. The present study aimed to investigate the relationship between hyperoxia and 30-day survival in patients who underwent ECPR.

Materials and Methods: This single-center retrospective cohort study was conducted between January 2010 and December 2018. OHCA patients who underwent ECPR were included in the study. Exclusion criteria were (1) age < 18 years, (2) death within 24 h after admission, (3) return of spontaneous circulation at hospital arrival, and (4) hypoxia (PaO_2 < 60 mmHg) 24 h after admission. Based on PaO_2 at 24 h after admission, patients were classified into normoxia (60 mmHg ≤ PaO_2 ≤ 100 mmHg), mild hyperoxia (100 mmHg < PaO_2 ≤ 200 mmHg), and severe hyperoxia (PaO_2 > 200 mmHg) groups. The primary outcome was 30-day survival after cardiac arrest, while the secondary outcome was 30-day favorable neurological outcome. Multivariate logistic regression analysis for 30-day survival or 30-day favorable neurological outcome was performed using multiple propensity scores as explanatory variables. To estimate the multiple propensity score, we fitted a multinomial logistic regression model using the patients' demographic, pre-hospital, and in-hospital characteristics.

Results: Of the patients who underwent ECPR in the study center, 110 were eligible for the study. The normoxia group included 29 cases, mild hyperoxia group included 46 cases, and severe hyperoxia group included 35 cases. Mild hyperoxia was not significantly associated with survival, compared with normoxia as the reference (adjusted odds ratio, 1.06; 95% confidence interval: 0.30–3.68; $p = 0.93$). Severe hyperoxia was also not significantly associated with survival compared to normoxia (adjusted odds ratio, 1.05; 95% confidence interval: 0.27–4.12; $p = 0.94$). Furthermore, no association was observed between oxygenation and 30-day favorable neurological outcomes.

Conclusions: There was no significant association between hyperoxia at 24 h after admission and 30-day survival in OHCA patients who underwent ECPR.

Keywords: blood gas analysis, cardiopulmonary resuscitation, extracorporeal membrane oxygenation, hyperoxia, post-cardiac arrest syndrome, cardiac arrest

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) remains a major health burden worldwide (1). The American Heart Association reports that at the time of hospital discharge, the survival rate of patients with OHCA is approximately 10%, which remains low despite advances in cardiopulmonary resuscitation (CPR) and post-cardiac arrest syndrome care (2).

Extracorporeal cardiopulmonary resuscitation (ECPR) is the administration of veno-arterial extracorporeal membrane oxygenation (ECMO) to cardiac arrest patients who are refractory to conventional CPR (3). The main purpose of ECPR is to restore circulation and gas exchange, and it has been shown to improve clinical outcomes after OHCA (4–6). ECMO provides time for interventions that are necessary for achieving adequate spontaneous circulation, including percutaneous coronary intervention, pulmonary thrombectomy, and rewarming.

Some studies have reported that hyperoxia contributes to the deterioration of patients with post-cardiac arrest syndrome (7). Therefore, the latest guidelines for cardiac arrest management recommend avoiding hyperoxia after the return of spontaneous circulation (8, 9). During ECPR, the sweep gas provides supraphysiological levels of oxygenation, which can exacerbate post-cardiac arrest syndrome. However, clinical studies evaluating hyperoxia associated with ECPR are few (10–12). Furthermore, in previous studies, the site of blood sample collection for blood gas analysis was not specified (10–12). Therefore, the influence of hyperoxia on neurological outcome and mortality in patients who undergo ECPR for OHCA remains unclear.

The purpose of this study was to investigate the relationship between oxygenation and survival and favorable neurological outcome in adult patients who underwent ECPR.

MATERIALS AND METHODS

Study Design and Setting

This retrospective study was conducted in a tertiary emergency center that serves a population of approximately 1,800,000 in the eastern Tokyo metropolitan area of Japan. The institutional review board of Tokyo Metropolitan Bokutoh Hospital approved the study. The requirement for informed consent was waived because of the observational study design that posed minimal risk to patients and preserved their anonymity. An opportunity to opt out from the registry was provided for patients and their respective families.

Participants

Adult OHCA patients (≥ 18 years old) who underwent ECPR between January 2010 and December 2018 were included in the study. The following were the exclusion criteria: (i) age < 18 years, (ii) death within 24 h after admission, (iii) restoration of spontaneous circulation upon hospital arrival, and (iv) hypoxia (partial pressure of arterial oxygen [PaO_2] < 60 mmHg) 24 h after admission.

The indications for ECPR at the study center were one of the following: (i) initial shockable rhythm, time from arrest to hospital arrival < 30 min, witness of cardiac arrest by a bystander, and age < 65 years; or (ii) witness of cardiac arrest by emergency medical service personnel, presumed reversible etiology (e.g., cardiac disease, pulmonary embolism, incidental hypothermia, and drug overdose), and age < 70 years (13). Outside these circumstances, ECPR was performed at the discretion of the emergency physician. ECPR was performed in the emergency room immediately after hospital arrival. Both the outflow and inflow cannulas were inserted percutaneously into contralateral or ipsilateral femoral vessels by emergency physicians. For the femoral artery, 15/16 Fr cannulas were used; for the femoral vein, 21/22 Fr cannulas were used. The blood circuit set, including a pump and membrane oxygenator, was primed using normal saline with 3,000 units of heparin. The ECMO pump flow rate was set between 3 and 4 L/min at the discretion of the emergency physician. After the ECMO pump was turned on, an arterial line was inserted into the right radial or brachial artery, and it reflected cerebral oxygenation.

Data Collection

Data (patients' demographics, cardiac arrest characteristics, treatment, laboratory data, and outcomes) were retrieved from the electronic medical records. The following patients' demographics and pre-hospital data were collected: age, sex, witness status (emergency medical service personnel or others), bystander CPR, etiology of cardiac arrest (cardiac or non-cardiac), initial cardiac rhythm, pre-hospital adrenaline administration, and pre-hospital shock delivery. In addition, the following in-hospital factors and outcomes were retrieved: time from arrest to ECMO pump-on, blood gas analysis data (pH, PaO_2, partial pressure of arterial carbon dioxide [$PaCO_2$], bicarbonate ion concentration [HCO_3^-], and lactate level), intra-aortic balloon pump use, percutaneous coronary intervention, and cerebral performance category 30 days after cardiac arrest. Every 4 h, at most, blood samples for gas analysis were obtained from an arterial line inserted into the right radial artery or brachial artery.

Abbreviations: CI, confidence interval; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; OR, odds ratio.

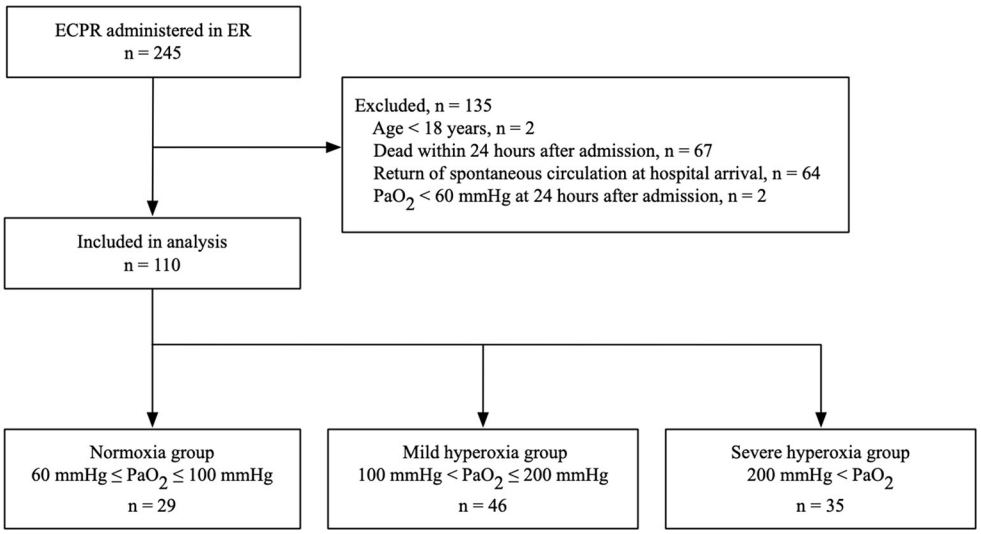

FIGURE 1 | Flowchart of study patients who underwent ECPR. ECPR, extracorporeal cardiopulmonary resuscitation; ER, emergency room; PaO_2, arterial partial pressure of oxygen.

TABLE 1 | Demographic and pre-hospital characteristics of the study population.

Factor	Overall (*n* = 110)	Normoxia (*n* = 29)	Mild hyperoxia (*n* = 46)	Severe hyperoxia (*n* = 35)	*p*-value
Age, years	59 [45–64]	61 [46–64]	56 [45–65]	53 [45–62]	0.27
Male	96 (87.3)	25 (86.2)	39 (84.8)	32 (91.4)	0.71
Witness of cardiac arrest					0.042
by EMS personnel	41 (37.3)	11 (37.9)	23 (50.0)	7 (20.0)	
by others	57 (51.8)	14 (48.3)	21 (45.7)	22 (62.9)	
Bystander CPR	74 (67.3)	19 (65.5)	36 (78.3)	19 (54.3)	0.072
Cardiac origin	89 (80.9)	25 (86.2)	33 (71.7)	31 (88.6)	0.14
Initial cardiac rhythm monitored					0.25
VF	68 (61.8)	19 (65.5)	23 (50.0)	26 (74.3)	
Pulseless VT	5 (4.5)	1 (3.4)	4 (8.7)	0 (0.0)	
PEA	29 (26.4)	6 (20.7)	15 (32.6)	8 (22.9)	
Asystole	8 (7.3)	3 (10.3)	4 (8.7)	1 (2.9)	
Prehospital adrenaline administration	92 (83.6)	20 (69.0)	43 (93.5)	29 (82.9)	0.021
Prehospital shock delivery	79 (71.8)	23 (79.3)	28 (60.9)	28 (80.0)	0.11

Continuous variables are presented as median [interquartile range]. Categorical variables are presented as count (percentage).
CPR, cardiopulmonary resuscitation; EMS, emergency medical service; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia.

Exposure and Definition

The eligible patients were divided into the following three groups according to their PaO_2 levels 24 h after admission: normoxia group, 60 mmHg $\leq$ PaO_2 $\leq$ 100 mmHg; mild hyperoxia group, 100 mmHg $<$ PaO_2 $\leq$ 200 mmHg; and severe hyperoxia group, 200 mmHg $<$ PaO_2 (14).

Outcome Measures

The primary outcome was 30-day survival after cardiac arrest. The secondary outcome was 30-day favorable neurological outcome after cardiac arrest. A favorable neurological outcome was defined as cerebral performance category 1 or 2. The possible cerebral performance categories were 1) good cerebral recovery, 2) moderate cerebral disability, 3) severe cerebral disability, 4) coma or vegetative state, and 5) death or brain death (15).

Statistical Analyses

Continuous variables are presented as medians and interquartile ranges, while categorical variables are presented as counts and percentages. Continuous variables were

TABLE 2 | In-hospital variables and clinical outcomes of the study population.

Factor	Overall (n = 110)	Normoxia (n = 29)	Mild hyperoxia (n = 46)	Severe hyperoxia (n = 35)	*p*-value
Time from arrest to ECMO pump-on, min	40 [31–49]	36 [23–47]	39 [31–47]	44 [37–52]	0.085
Percutaneous coronary intervention	45 (40.9)	16 (55.2)	13 (28.3)	16 (45.7)	0.054
Intra-aortic balloon pump	79 (71.8)	20 (69.0)	32 (69.6)	27 (77.1)	0.77
PaO_2 12 h after admission, mmHg	217 [141–317]	172 [100–263]	190 [130–273]	326 [258–457]	<0.001
$PaCO_2$ 12 h after admission, mmHg	35 [32–39]	35 [32–41]	33 [30–38]	37 [34–41]	0.051
pH 12 h after admission	7.33 [7.27–7.39]	7.31 [7.27–7.38]	7.35 [7.31–7.44]	7.29 [7.23–7.35]	0.016
HCO_3^- 12 h after admission, mEq/L	18.3 [15.5–19.9]	17.4 [15.0–19.5]	19.2 [17.1–21.4]	17.6 [15.1–19.3]	0.027
Lactate 12 h after admission, mEq/L	3.2 [2.3–5.4]	3.8 [2.5–6.7]	3.0 [2.2–4.3]	3.9 [2.5–5.9]	0.12
Mean blood pressure 12 h after admission, mmHg	82 [68–98]	81 [68–91]	87 [75–102]	79 [55–97]	0.088
PaO_2 24 h after admission, mmHg	145 [99–237]	80 [73–94]	135 [121–156]	297 [240–419]	<0.001
$PaCO_2$ 24 h after admission, mmHg	36 [32–40]	37 [34–40]	34 [32–40]	38 [36–41]	0.096
pH 24 h after admission	7.36 [7.29–7.42]	7.35 [7.29–7.39]	7.40 [7.32–7.43]	7.32 [7.21–7.38]	0.004
HCO_3^- 24 h after admission, mEq/L	20.4 [17.5–21.9]	19.2 [16.9–20.9]	21.3 [20.0–22.3]	18.6 [15.7–22.2]	0.011
Lactate 24 h after admission, mEq/L	2.2 [1.4–3.8]	2.7 [1.4–3.7]	1.7 [1.2–2.5]	3.5 [2.1–5.7]	0.001
Mean blood pressure 24 h after admission, mmHg	79 [64–91]	78 [63–89]	82 [73–94]	71 [56–89]	0.044
30-day survival	52 (47.3)	13 (44.8)	27 (58.7)	12 (34.3)	0.096
30-day favorable neurological outcome	14 (12.7)	2 (6.9)	8 (17.4)	4 (11.4)	0.41

Continuous variables are presented as median [interquartile range]. Categorical variables are presented as count (percentage).
HCO_3^-, bicarbonate ion; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; ECMO, extracorporeal membrane oxygenation.

analyzed with the Kruskal-Wallis test, and categorical variables in the three groups were analyzed with a Fisher's exact test.

We used multiple propensity score analysis to adjust and control for multiple confounding factors in the comparison of the three groups (16). A multiple propensity score is the conditional probability of a patient being categorized into one of three or more groups, given baseline covariates. First, we created a multinomial logistic regression model by setting one of the three PaO_2 groups as the dependent variable. The following covariates were used to calculate the multiple propensity scores: age, sex, type of witness, bystander administration of CPR, initial cardiac rhythm, pre-hospital shock delivery, pre-hospital adrenaline administration, etiology, percutaneous coronary intervention, intra-aortic balloon pump use, and time from arrest to ECMO pump-on. Second, we performed binomial logistic regression analysis to determine the adjusted odds ratios (ORs) of the PaO_2 level group for 30-day survival or 30-day favorable neurological outcome after cardiac arrest, adjusting for multiple propensity scores and variables at 24 h after admission, including $PaCO_2$, pH, HCO_3^-, lactate level, and mean blood pressure.

In addition, we performed sensitivity analysis using a similar multiple propensity score, grouping patients by PaO_2 12 h after admission.

ORs and 95% confidence intervals (CIs) were calculated. All statistical tests were two-sided, and p values <0.05 were considered significant. All statistical analyses were conducted using Statistical Package for the Social Sciences version 26.0 for Mac (IBM Corp., Armonk, NY, USA).

RESULTS

Patient Enrollment

Between January 2010 and December 2018, 245 patients underwent ECPR in the emergency room of the study center. After excluding 2 patients under 18 years, 67 patients who died within 24 h after admission, 64 patients with return of spontaneous circulation at hospital arrival, and 2 patients with PaO_2 < 60 mmHg at 24 h after admission, 110 patients were finally included in the study (**Figure 1**).

Patients' Characteristics and Outcomes

Demographic and pre-hospital characteristics of the patients are shown in **Table 1**. The median age was 59 years (interquartile range, 45–64 years), and 87.3% of the patients were men. Witness status and pre-hospital adrenaline administration were significantly different among groups. In-hospital variables, including blood gas data and clinical outcomes, are shown in **Table 2**. The median PaO_2 level 24 h after admission was 145 mmHg (interquartile range, 99–237 mmHg) in all patients. A total of 29, 46, and 35 patients were categorized into the normoxia, mild hyperoxia, and severe hyperoxia groups, respectively (**Figure 1**). The pH, HCO_3^-, lactate level, and mean arterial blood pressure 24 h after admission were significantly different among groups. There was no statistically significant difference in 30-day survival or 30-day favorable neurological outcome among the three groups.

Logistic Regression Analysis

The results of the multivariate logistic regression analyses for 30-day survival and 30-day favorable neurological outcome

TABLE 3 | Multivariate logistic regression analyses of 30-day survival and 30-day favorable neurological outcome after cardiac arrest.

	Adjusted OR (95% CI)	*p*-value
30-day survival		
Normoxia	Reference	
Mild hyperoxia	1.06 (0.30–3.68)	0.93
Severe hyperoxia	1.05 (0.27–4.12)	0.94
30-day favorable neurological outcome		
Normoxia	Reference	
Mild hyperoxia	1.66 (0.26–10.65)	0.60
Severe hyperoxia	1.12 (0.15–8.39)	0.91

A multiple propensity score was calculated after adjusting for the following factors: age, sex, type of witness, bystander administration of CPR, initial cardiac rhythm, pre-hospital shock delivery, pre-hospital adrenaline administration, etiology, percutaneous coronary intervention, intra-aortic balloon pump use, and time from arrest to ECMO pump-on. Adjusted ORs were calculated controlling for the multiple propensity score and variables at 24 h after admission, including $PaCO_2$, pH, HCO^{3-}, lactate level, and mean blood pressure.
CI, confidence interval; OR, odds ratio.

are shown in **Table 3**. Mild hyperoxia was not significantly associated with survival, compared with normoxia as reference (adjusted OR, 1.06; 95% CI: 0.30–3.68; $p = 0.93$). Furthermore, severe hyperoxia was not significantly associated with survival, compared to normoxia (adjusted OR, 1.05; 95% CI: 0.27–4.12; $p = 0.94$).

Mild and severe hyperoxia were not significantly associated with 30-day favorable neurological outcome, compared with normoxia as reference (adjusted OR, 1.66; 95% CI: 0.26–10.65; $p = 0.60$; adjusted OR, 1.12; 95% CI: 0.15–8.39; $p = 0.91$, respectively).

Sensitivity Analysis

The results of the sensitivity analysis (that is, multivariate logistic regression analysis performed after grouping the patients by PaO_2 level at 12 h after admission) were also similar. Mild and severe hyperoxia were not significantly associated with 30-day survival when compared with normoxia as reference (adjusted OR, 4.93; 95% CI: 0.61–39.9; $p = 0.14$; adjusted OR, 2.58; 95% CI: 0.32–20.8; $p = 0.37$, respectively).

DISCUSSION

Main Findings

We investigated the relationship between hyperoxia and clinical outcomes in adult patients who underwent ECPR, focusing on PaO_2 levels 24 h after admission. After adjusting for multiple confounders, both mild and severe hyperoxia were not significantly associated with 30-day survival and favorable neurological outcome.

Effect of Hyperoxia in Patients With Cardiac Arrest

Hyperoxia increases the production of reactive oxygen species during reperfusion injury, leading to oxidative damage to mitochondrial respiration and cerebral energy metabolism. Oxidative modification of mitochondrial proteins can inactivate cerebral pyruvate dehydrogenase complex (17). Furthermore, oxidative stress activates the mitochondrial permeability transition pore, releasing NAD(H) into the cytoplasm and depleting cofactors essential for metabolism (18). This results in metabolic failure, which can lead to decreased brain glucose and oxygen consumption, increased lactate production, and delayed neuronal death (19).

Several observational studies and meta-analyses have shown that hyperoxia after cardiac arrest is associated with poor neurological outcomes and increased mortality (20–23). Therefore, current post-resuscitation guidelines recommend avoiding prolonged hyperoxia (8, 9).

Effect of Hyperoxia in Patients Undergoing ECPR

Supraphysiological hyperoxia frequently occurs during veno-arterial ECMO, such as that administered during ECPR, depending on the fractional delivered oxygen concentration setting of the sweep gas (12). Therefore, cardiac arrest patients undergoing ECPR are at a high risk of hyperoxia.

Previous studies have reported an association between exposure to hyperoxia and poor clinical outcomes (mortality and impaired neurological status) in cardiac arrest patients who undergo ECPR (10–12). The results of those previous studies are not consistent with those of the present study. However, confounding factors were not adjusted or controlled for in the previous studies (10–12). In addition, the site from which blood samples for gas analysis were obtained in those studies is unclear (11, 12). Therefore, the PaO_2 levels used in the studies may not have been representative of cerebral oxygenation.

Clinical Applications and Strengths of the Present Study

In this study, we focused on the PaO_2 levels measured during ECMO and found that avoiding hyperoxia may not improve the clinical outcomes of patients who undergo ECPR. These results may be useful in the administration of ECMO to cardiac arrest patients during ECPR. More important than oxygenation are the prognostic determinants in patients undergoing ECPR, and they should not be downplayed by overemphasis on hyperoxia.

Our study has several strengths. First, we used blood samples from the right upper limb for blood gas analysis, which allowed us to investigate the relationship between cerebral oxygenation and prognosis. Second, we evaluated the effect of hyperoxia on clinical outcomes after controlling for various confounders using multiple propensity scoring.

Study Limitations

This study has several limitations. First, this was a single-center retrospective cohort study with a small sample size; therefore, the study was probably underpowered to detect significant differences. Second, we did not adjust for cardiac function as a possible confounder. Peripheral veno-arterial ECMO is usually performed during ECPR (24). The retrograde blood flow from the ECMO mixes with the antegrade blood flow from the patient's own heart, creating a watershed condition called the Harlequin

syndrome (North-South syndrome) (25). Therefore, the cardiac function of the patient is an important factor. However, we were unable to collect data on cardiac function. Furthermore, in this study, we only analyzed blood gas data at 12 and 24 h after admission. Therefore, the effects of oxygenation in the shorter or longer term are unknown. Well-designed studies that will eliminate or minimize these limitations are therefore required in the future.

CONCLUSIONS

In OHCA patients who underwent ECPR, no significant association was found between hyperoxia at 24 h after admission and 30-day survival. These results may be useful in the administration of ECMO to cardiac arrest patients during ECPR. However, a well-designed study is needed to overcome the specific problems associated with ECMO administration, including Harlequin syndrome.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because approval from the Ethics Committee of the study institution is necessary for accessing them. Requests to access the datasets should be directed to MaK, kashiura@me.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Tokyo Metropolitan Bokutoh Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MaK conceived this study. MiK and KS collected the data. MiK and MaK statistically analyzed the data. MiK, MaK, and HY interpreted the data. MiK drafted the manuscript. All the authors contributed substantially to the study design, approved the manuscript, and agree to be accountable for this work.

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Targeted Temperature Management for Cardiac Arrest Due to Non-shockable Rhythm: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background: Targeted temperature management (TTM) is recommended in adult patients following cardiac arrest (CA) with any rhythm. However, as to non-shockable (NSR) CA, high-quality evidence of TTM supporting its practices remains uncertain. Thus, we aimed to conduct a systematic review and meta-analysis with randomized controlled trials (RCTs) to explore the efficacy and safety of TTM in this population.

Methods: We searched PubMed, Embase, and Cochrane library databases for potential trials from inception through Aug 25, 2021. RCTs evaluating TTM for CA adults due to NSR were included, regardless of the timing of cooling initiation. Outcome measurements were mortality and good neurological function. We used the Cochrane bias tools to evaluate the quality of the included studies. Heterogeneity, subgroup analyses, and sensitivity analysis were investigated to test the robustness of the primary outcomes.

Results: A total of 14 RCTs with 4,009 adults were eligible for the final analysis. All trials had a low to moderate risk of bias. Of the included trials, six compared NSR patients with or without TTM, while eight compared pre-hospital to in-hospital TTM. Pooled data showed that TTM was not associated with improved mortality (Risk ratio [RR] 1.00; 95% CI, 0.944–1.05; $P = 0.89$, $I^2 = 0\%$) and good neurological outcome (RR 1.18; 95% CI 0.90–1.55; $P = 0.22$, $I^2 = 8\%$). Similarly, use of pre-hospital TTM resulted in neither an improved mortality (RR 0.99, 95% CI 0.97–1.03; $I^2 = 0\%$, $P = 0.32$) nor favorable neurological outcome (RR 1.13, 95% CI 0.93–1.38; $I^2 = 0\%$, $P = 0.22$). These results were further confirmed in the sensitivity analyses and subgroup analyses.

Conclusions: Our results showed that using the TTM strategy did not significantly affect the mortality and neurologic outcomes in CA survival presenting initial NSR.

Keywords: non-shockable rhythm, cardiac arrest, targeted temperature management, neurological outcome, meta-analysis

INTRODUCTION

Cardiac arrest (CA) is a common public health problem with an estimated annual incidence rate of 28–55 per 100,000 person-years (1). Despite the advances in cardiopulmonary resuscitation (CPR) technology, the overall mortality rate is still high, up to 90% (2). Target temperature management (TTM) has been considered as an effective therapy to improve the neurological prognosis of comatose CA survivors after the return of spontaneous circulation (ROSC) (3). The mechanism may be related to the decrease in core body temperature, which reduces inflammation and cell damage after ischemia-reperfusion injury, and promotes the brain neurons healing by reducing cerebral oxygen demand and intracranial pressure (4). Thus, the use of TTM in CA survivors had been recommended consistently by published CPR guidelines (3, 5). However, the guidelines were challenged by the most recent trial conducted by Dankiewicz et al. (6), which concluded that in patients with coma after out-of-hospital cardiac arrest, targeted hypothermia did not improve survival or neurologic good outcome rates.

CA is a highly heterogeneous entity. Many factors will affect the effect of sub-hypothermia. Among them are the two types of presenting ECG rhythm in CA patients: a shockable rhythm (SR, ventricular fibrillation, or ventricular tachycardia) or a non-shockable rhythm (NSR, asystole, or pulseless electrical activity) during CA have received the most attention (7). Currently, the guidelines recommend TTM for CA survivors with SR or NSR (3). However, compared with CA survivors with SR having conclusive evidence of TTM to support their use, studies focusing on TTM for NSR survivors have reported conflicting results (7–9). Most current clinical recommendations are based on the consensus of expert opinions and extrapolate the potential benefits of TTM in NSR patients from the evidence of SR survivors (3, 4).

Recently, several high-quality RCTs evaluating the effect of TTM in CA patients have been published (6, 8, 10–13), and most of them focus on the subgroup of NSR survivors. Therefore, with the aid of the increased power of meta-analytic techniques, we aimed to review the relevant and available RCTs to describe the effectiveness of TTM in CA survivors with initial NSR.

METHODS

We conducted the current systematic review following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement (**Appendix 1**), and the review protocol had been published in the journal of Medicine (14).

Abbreviations: CA, cardiac arrest; CI, confidence interval; ICU, intensive care unit; IHCA, in-hospital cardiac arrest; ILCOR, International Liaison Committee on Resuscitation; IQR, interquartile range; LOS, length of stay; MD, mean difference; NSR, non-shockable rhythm; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; RR, risk ratio; RCTs, randomized controlled trials; SD, standard deviations; SR, shockable rhythm; TTM, targeted temperature management.

Eligibility Criteria

Studies were considered eligible if they investigated the efficacy and safety of TTM strategy in CA survivors presenting an initial NSR were included, regardless of the methods (evaporative cooling, infusion of cold saline, and surface or systemic cooling), timing (in-hospital or pre-hospital cooling), duration of TTM, or targeted temperature (32–36°C). We excluded studies conducted in neonates, children, pregnant, and studies that did not report data on survival. In addition, articles in abstract form without predefined data available or reviews or case series were also excluded.

Search Strategy

We conducted a comprehensive systematic electronic search through PubMed, Cochrane library, and Embase databases from inception to Aug 15, 2021 (the last search) for potential RCTs, without language restriction. Boolean terms (OR and AND), Medical Subject Headings (MeSH), Emtree, and keywords were used in the search strategy. The search terms included "targeted temperature management," "Therapeutic hypothermia," "advanced cardiac life-support," "cardiac arrest," "cardiopulmonary resuscitation," and "heart arrest." The details of the research strategy was summarized in **Appendix 2**. Reference lists of relative articles were also manually checked to ensure the inclusion of all possible publications on this topic.

Data Extraction and Quality Assessment

Two reviewers (Y-BZ and YY) extracted data independently from included studies on the first author' last name, publication year, study design (blinding or open-label; single or multi-centers), country where the study was conducted, study period, sample size, therapeutic regimens, follow-up duration, patient characteristics as well as all predefined outcomes. We appraised the risk of bias of the included RCTs using the Cochrane Collaboration tool for assessing the risk of bias (15). Discrepancies were identified and resolved through discussion.

Outcome Measures

The primary outcome measure was mortality (considering the longest follow-up reported by the authors). The secondary outcome was good neurological function defined as a Cerebral Performance Category (CPC) score of 1 or 2. If trials only reported good neurological recovery, we considered this outcome to be CPC 1 or CPC 2 (16).

Statistical Analysis

We pooled categorical data with risk ratios (RR) and continuous data with the mean difference (MD) using the Mantel-Haenszel, Inverse Variance fixed-effect, or Der Simonian and Laird random-effects model if needed. Some studies reported median as the measure of treatment effect, with accompanying interquartile range (IQR). Before data analysis, we estimated mean from median and standard deviations (SD) from IQR using the methods described in previous studies (17). Heterogeneity was quantified using the I^2 statistic and its P-value. Studies with an $I^2 > 50\%$ indicate significant heterogeneity (18).

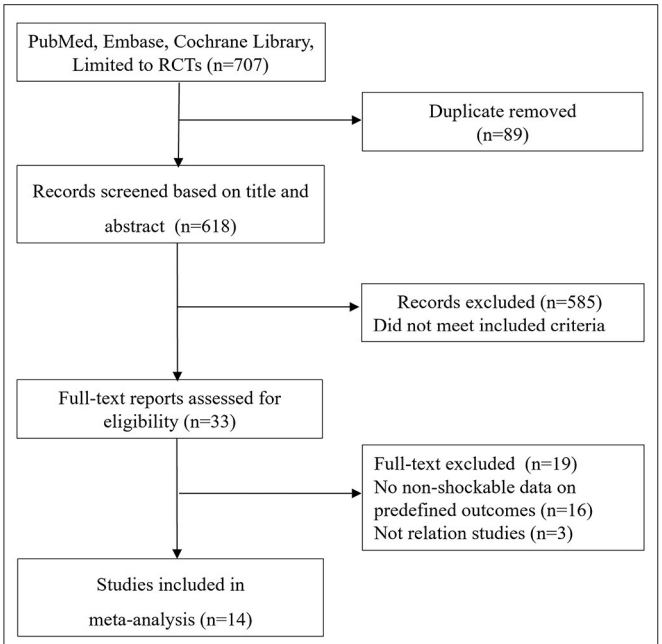

FIGURE 1 | Selection process for studies included in the meta-analysis.

To obtain more robust results, we estimated the pooled effect with their 95% CI if at least three studies with sufficient data available in each predefined outcome. Sensitivity analyses were performed by excluding trials that potentially biased the results. We further conducted subgroup analyses to test the robustness of the primary outcomes basing on the important clinical features (i.e., follow-up [short-term or long-term mortality; short-term mortality was defined as 28 days, ICU or hospital mortality, or mortality within 90 days of randomization, while long-term mortality was defined as a mortality rate of more than 180 days], by-stander CPR% [<50% or ≥50%], sample size [≥200 or <200], design [single-center or multi-centers], and OHCA% [100% or <100%]). Publication bias was evaluated by visually inspecting funnel plots. A two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed using Review Manager, Version 5.3.

RESULTS

Trial Identification

The de-duplicated results yielded 707 abstracts. The screen of abstracts and titles identified a total of 34 relevant studies for the following full-text review. **Figure 1** shows a flowchart for the selection of studies. The excluded studies based on the full-text evaluation with exclusion reasons were summarized in **Appendix 2**. Finally, 14 RCTs (6, 10–13, 19–27) met the study inclusion criteria, of which six (6, 10, 11, 19–21) were comparing NSR patients with or without TTM while eight (12, 13, 22–27) were comparing NSR patients receiving pre-hospital or in-hospital TTM.

Quality of the Studies

The quality of the included RCTs was low to moderate risk of bias (**Appendix 3**). However, funnel plots did not show skewed distributions, suggesting no publication bias was involved (**Appendix 4**).

Study Characteristics

Tables 1, **2** shows the characteristics of the 14 included RCTs. Of these studies, 2 were single-center trials (19, 20), and 12 were multi-center trials (6, 10–13, 21–27). These RCTs were published between 2007 and 2021 from the France ($n = 3$), USA ($n = 2$), Australia ($n = 2$), Belgium ($n = 2$), Canada ($n = 1$), and multi-site ($n = 4$). A total of 4,009 NSR survivors were included in the final analysis (sample size ranging from 10 to 776 patients), with 2,022 patients in the TTM group and 1,987 patients in the non-TTM group. As to the initial rhythm, 11 RCTs included patients with SR or NSR (6, 12, 13, 19–21, 23–27), while the remaining three included only patients with NSR (10, 11, 22). Cooling methods varied among the RCTs, such as trans-nasal evaporative cooling, infusion of cold saline, and surface or systemic cooling.

Outcomes

With or Without TTM

Six studies compared NSR survivors with or without TTM, and all reported outcomes of mortality (6, 10, 11, 19–21). Of the 677 patients in the TTM group, 542 died, compared to 520 of 646 patients in the non-TTM group. The pooled analysis suggested TTM did not affect the mortality (RR = 1.00; 95% CI, 0.944–1.05; $P = 0.89$, $I^2 = 0\%$) (**Figure 2A**). Five studies focused on neurological outcomes as interests (10, 11, 19–21). Pooled analysis showed the good neurological outcome was comparable between the TTM group and non-TTM groups ($n = 1{,}232$; RR 1.39; 95% CI 0.92–2.11; $P = 0.11$, $I^2 = 0\%$) (**Figure 2B**).

In the sensitivity analysis, excluding any single test did not significantly change the overall combined OR of the survival (P-value ranged from 0.21 to 0.87) and neurological outcomes (P-value ranged from 0.19 to 0.98). Similarly, subgroup analyses based on study design, sample size, country, or initial rhythm showed no differences in the survival outcomes and good neurological outcomes (**Table 2**) between the TTM and non-TTM groups (**Table 3**).

Pre-hospital or In-hospital TTM

All eight trials reported outcome of mortality (1,345 in pre-hospital group and 1,341 in in-hospital group) (12, 13, 22–27). The pooled mortality rate was similar when we compared the pre-hospital TTM group with the in-hospital TTM group (8 trials, $N = 2{,}682$; RR 0.99, 95% CI 0.97–1.01, $I^2 = 0$) (**Figure 3A**). Five RCTs focused on neurological outcomes as interests. When pooled, the result showed no difference in favorable neurological outcome (6 trials, $N = 1{,}955$; RR 1.13, 95% CI 0.93–1.18, $I^2 = 0$) (**Figure 3B**).

DISCUSSION

In the current meta-analysis, we included 14 RCTs focusing on CA survivors with NSR to evaluate the prognosis of TTM for

TABLE 1 | Characteristics of the studies included in current systemic review and meta-analysis.

First author, year	Design	Research periods	Conducted country	Cooling method	TT (°C) TTM	TT(°C) Control	Sample size	OHCA (%)	Follow-up (days)
Dankiewicz et al. (6)	P, OL, MC	2017–2020	Multi-sites	Mixed	33	<37.8°C	259/231	100	180
Lascarrou et al. (11)	P, OL, MC	2014–2018	France	Mixed	33	37°C	284/297	78	90
Frydland et al. (10)	P, OL, MC	2010–2013	Multi-sites	Mixed	33	36°C	96/82	100	180
Laurent et al. (21)	P, OL, MC	2000–2002	France	Systemic	32–33	No cooling	5/5	100	180
Hachimi-Idrissi et al. (20)	P, OL, SC	1999–2002	Belgium	External	33	37°C	17/16	100	180
Hachimi-Idrissi et al. (19)	P, OL, SC	1999–2000	Belgium	External	34	<38°C	16/14	100	14
Nordberg et al. (13)	P, OL, MC	2010–2018	Multi-sites	TNE	32–34	HC: 32–34°C	198/199	100	90
Scales et al. (27)	P, OL, MC	2012–2016	Canada	Cold saline/External	32–34	No cooling	155/169	100	Hospitalization
Bernard et al. (12)	P, OL, MC	2010–2014	Australia	Cold saline	33	No cooling	327/313	100	Hospitalization
Debaty et al. (24)	P, OL, MC	2009–2012	France	Cold saline/External	32–34	HC: 32–34°C	87/90	100	365
Bernard et al. (22)	P, OL, MC	2005–2007	Australia	Cold saline	33	HC: 32–34°C	82/81	100	Hospitalization
Castre'n et al. (23)	P, OL, MC	2008–2009	Multi-sites	TNE	34	HC: 34°C	66/69	100	Hospitalization
Kim et al. (25)	P, OL, MC	2004–2006	USA	Cold saline	<34	No cooling	34/40	100	Hospitalization
Kim et al. (26)	P, OL, MC	2007–2012	USA	Cold saline	<34	No cooling	396/380	100	Hospitalization

CPR, cardiac pulmonary resuscitation; MC, multi-centers; NA, not available; OHCA, out-of-hospital cardiac arrest; OL, open-label; P, prospective; HC, hospital-cooling; SC, single-center; TT, targeted temperature; TNE, trans-nasal evaporative; TTM, target temperature management.

TABLE 2 | Characteristics of the patients included in current systemic review and meta-analysis.

First author, year	TTM group/Control group								
	Sample size	Asystole%	PEA%	Bystander-CPR%	CA to ROSC time, minute	Age, year	Male,%	Mortality %	Good neurological outcome
Dankiewicz et al. (9)	259/231	48/43	45/49	82/78	25/25	NA	NA	77/74	NA
Lascarrou et al. (11)	284/297	78/81	12/12	70/69	NA	67/67	65/63	81/83	13/14
Frydland et al. (10)	96/82	63	37	54	25/30	67	76	84/84	13/0
Laurent et al. (21)	5/5	100/87	0/13	NA	25/14	52/58	80/80	83/100	0/13
Hachimi-Idrissi et al. (20)	17/16	88/76	12/24	19/12	35/34	73/74	69/59	75/88	10/6
Hachimi-Idrissi et al. (19)	16/14	75/86	25/14	14/6	33/34	74/77	64/56	81/93	17/0
Nordberg et al. (13)	198/199	NA	NA	65/60	30/27	64/66	75/76	95/94	4/5
Scales et al. (27)	155/169	NA	NA	44/48	NA	68/69	70/61	92/92	14/13
Bernard et al. (12)	327/313	62/61	37/38	66/67	NA	65/64	75/74	98/99	NA
Debaty et al. (24)	87/90	91/90	9/10	50/52	27/30	66/69	72/71	98/99	NA
Bernard et al. (22)	82/81	50/37	50/63	44/38	29/29	64/61	69/59	87/89	12/9
Castre'n et al. (23)	66/69	71/67	29/33	36/46	32/30	66/64	72/78	94/96	25/14
Kim et al. (25)	34/40	NA	NA	67/74	NA	67/65	67/74	94/80	NA
Kim et al. (26)	396/380	53/53	44/48	54/52	NA	68/68	55/54	81/84	29/25

CA, cardiac arrest; CPR, cardiac pulmonary resuscitation; NA, not available; OHCA, out-of-hospital cardiac arrest; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; TTM, target temperature management.

these patients. Most included studies were low to medium risk of bias in quality. Our results showed that TTM did not significantly improve survival or neurological outcomes in CA patients with NSR than those who did not. Meanwhile, early starting cooling strategies such as prehospital TTM showed no more benefits in such a patient population. These results were further supported by subgroup analysis and sensitivity analysis.

Comparison With Previous Studies

Our results showed that many CA survivors with NSR received TTM despite no high-quality evidence to support its use. This may be due to the recommendations of the CPR guidelines (3, 5), which had consistently recommended TTM for CA survivors with both SR and NSR. However, the recommendation for the NSR patients is mainly based on an extrapolation of SR patients but no clear evidence. The latest 2021 guideline has been modified to suggest TTM for adult CA patients with initial NSR who remain unresponsive after ROSC (3). However, it is still a weak recommendation and is from very low-quality evidence.

So far, there have been 3 meta-analyses published on this topic with inconsistent results (7–9). However, the main problem of

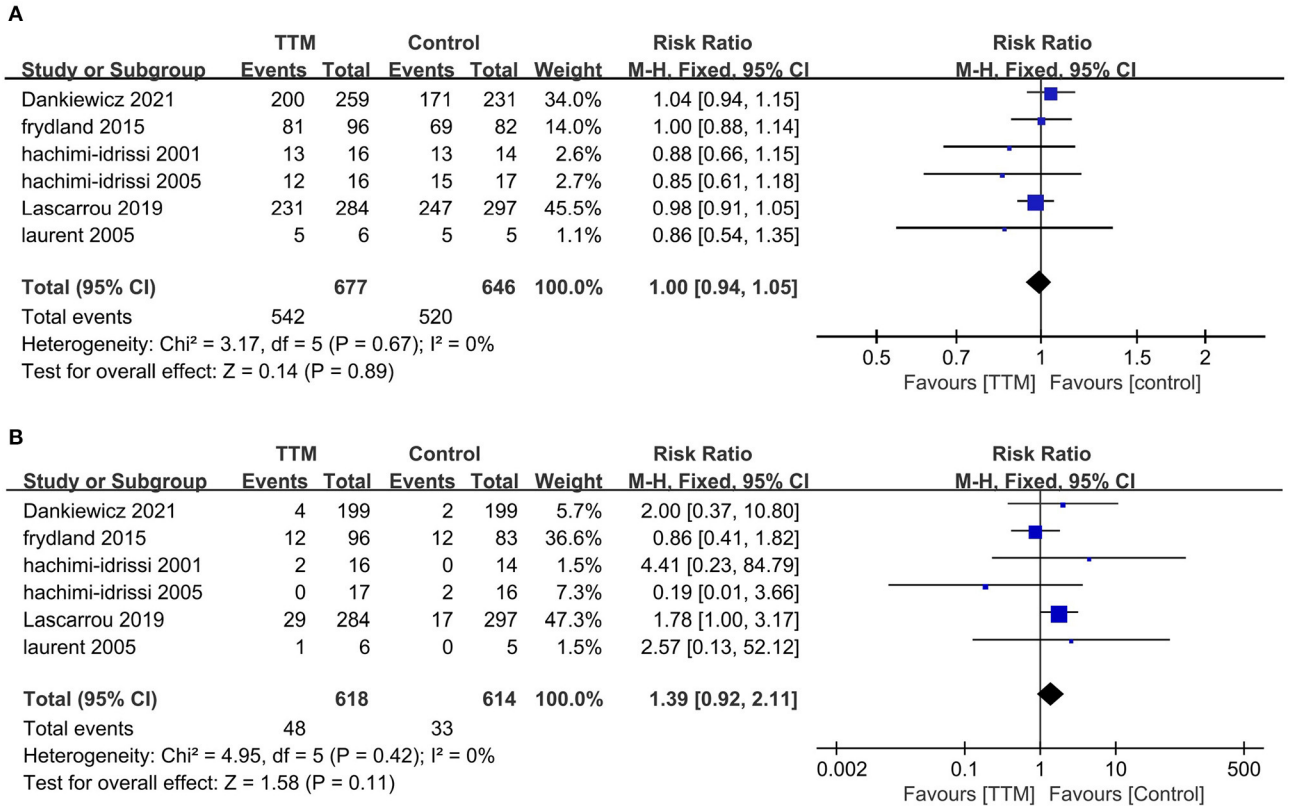

FIGURE 2 | Forest plot of the non-shockable rhythm survivors with or without targeted temperature management. **(A)** Mortality; **(B)** Good neurological outcome.

these articles was the inclusion of most observational studies but only a small number of RCTs, leading to a high risk of bias and random error in these studies. To address the limitations of the previous meta-analysis, we only included RCTs and added several recent published trials, with a total sample size of 4,009 patients in the current study (6, 10–13, 19–27). Thus, our sample size allowed for better statistical power and other sensitivities and subgroup analyses. The results of subgroup and sensitivity analyses for ICHA initial rhythm, study start date, study design, OHCA%, and recent and long-term prognosis corroborated the robustness of our findings. Thus, our results provide conclusive evidence regarding the impact of TTM on mortality and neurologic outcomes of CA survivors with initial NSR.

It is also worth noting that the International Liaison Committee on Resuscitation (ILCOR) recently published a systematic review that there was no improvement in survival or favorable neurologic outcome in TTM groups compared with normothermia groups. The prehospital cooling groups also showed no benefits in survival or favorable neurologic outcome in comparison with on prehospital cooling groups. These findings may warrant an update of international cardiac arrest guidelines (28).

Explaining Our Findings

We found TTM did not benefit CA patients with initial NSR concerning the mortality and neurological prognosis. Some might contribute to this. On the one hand, NSR has a marked impact on the CA prognosis, not only the reduced chances of obtaining ROSC but also the chances of surviving hospital discharge. The CA patients' leading cause of death is the neurological injury from anoxic brain damage, independent of initial rhythm (29, 30). The potential mechanism of TTM included anti-oxidant, anti-apoptotic and anti-inflammatory effects and a decrease in the accumulation or release of excitotoxic amino acids (4, 28, 31). The positive results from animal studies and trials led to the inclusion of TTM in the guidelines (32, 33). However, NSR survivors have more poor prognostic factors than those of SR (26, 34). As shown in our results, NSR survivors were usually older, had more comorbidities, and suffered an increased risk of multiple organ dysfunction. Thus, those risks might partly weaken the advantages of TTM application.

On the other hand, the included studies spanned an extensive range of periods, during which CPR and CA guidelines have been updated several times (3, 5). CA prognosis might benefit from several improved techniques such as bystander

TABLE 3 | Subgroup analysis of the primary outcome based on TTM strategy.

		Studies number	Patient, number	Event in the intervention group	Event in the control group	Risk ratio (95% CI)	I^2	*P*
With or without TTM		**6**	**1323**	**TTM group**	**Non-TTM group**	1.00 [0.94, 1.05]	0%	0.90
Follow-up	Short-term	3	219	99 of 118	87 of 101	0.97 [0.87, 1.09]	0%	0.66
	Long-term	3	1099	437 of 557	426 of 542	1.00 [0.94, 1.06]	0%	0.97
Sample size	>200	2	1071	431 of 543	418 of 528	1.01 [0.95, 1.07]	3%	0.85
	<200	4	247	105 of 132	95 of 115	0.86 [0.71, 1.05]	16%	0.16
Design	MC	4	652	517 of 645	492 of 615	1.00 [0.95, 1.06]	0%	0.90
	SC	2	63	25 of 32	28 of 31	0.86 [0.69, 1.07]	0%	0.18
OHCA%	<100	1	581	231 of 284	247 of 297	0.98 [0.91, 1.05]	–	–
	100	5	1249	512 of 639	487 of 610	1.01 [0.95, 1.06]	0%	0.85
Bystander CPR%	≥50	3	1249	512 of 639	487 of 610	1.01 [0.95, 1.06]	0%	0.85
	<50	3	74	30 of 38	33 of 36	0.86 [0.71, 1.05]	0%	0.14
Pre- or In-hospital TTM		**8**	**2686**	**Pre-hospital TTM**	**In-hospital TTM**	0.99 [0.97, 1.01]	0%	0.85
Follow-up	Short-term	8	2686	1220 of 1345	1231 of 1341	0.99 [0.97, 1.01]	0%	0.85
	Long-term	–	–	–	–	–	–	–
Sample size	>200	4	2137	970 of 1076	970 of 1061	0.99 [0.96, 1.01]	0%	0.31
	<200	4	549	250 of 269	261 of 280	1.00 [0.95, 1.04]	34%	0.88
Design	MC	8	2686	1220 of 1345	1231 of 1341	0.99 [0.97, 1.01]	0%	0.85
	SC	–	–	–	–	–	–	–
Bystander CPR%	≥50	5	2064	945 of 1042	936 of 1022	0.99 [0.97, 1.02]	21%	0.48
	<50	3	622	275 of 303	295 of 319	0.98 [0.94, 1.03]	0%	0.45
Bystander CPR%	≥50	8	2686	1220 of 1345	1231 of 1341	0.99 [0.97, 1.01]	0%	0.85
	<50	–	–	–	–	–	–	–

CPR, cardiac-pulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; TTM, targeted temperature management.

intervention, advanced cardiac life support, emergency cardiac catheterization, and optimal support for brain functions (3). Therefore, these techniques may limit the theoretical benefits of TTM to reduce free radical-mediated reperfusion injury in hypoxic brain injury.

Additionally, the prehospital cooling strategy also showed no more prognosis benefits in NSR patients after CA than those receiving TTM after hospital arrival. Several reasons might help explain the negative findings. First, prehospital cooling patients have more re-arrest episodes and pulmonary edema due to the infusion of a large amount of cold intravenous saline immediately after ROSC (26). Meanwhile, the rapid infusion can also cause an increase in right atrium pressure, which may reduce coronary perfusion pressure and, therefore, myocardial perfusion (35). Second, the drop in temperature by rapid infusion of cold saline might be too slight. As shown in the study by Bernard et al., the authors found no differences in outcomes when cooling was initiated before hospital arrival between the groups (12). Third, prehospital cooling did not significantly reduce the time to targeted temperature. Scales et al. (27) reported that achieving a target temperature of <34°C within 6-h of hospital arrival was not significantly different between CA survivors with or without prehospital cooling patients. In addition, studies have shown that lower myocardial temperature increases the rate of successful defibrillation. However, this does not affect patients with NSR (36).

Research Limitations

Our study has several limitations. First, all of the included RCTs are open-label designs. This might result in the selection bias of our research. Second, CA is a highly heterogeneous entity, and many factors may affect the efficacy of TTM, such as the cooling methods, sedative drugs, timing, and shivering monitoring methods. Third, although we had used subgroup analyses and sensitivity analysis to explore the possible confounding factors, our results may be affected by unmeasured factors. Fourth, prognostic assessment methods varied among the included studies. Some clinicians chose telephone interviews rather than face-to-face interviews. Fifth, the non-TTM CA survivors varied in the temperature management, such as target 36°C to < 38°C or no cooling, which may affect the robustness of our conclusions. Finally, the included CA patients have different underlying diseases, demographic characteristics and use different disease severity scoring standards. However, due to the number of studies, we cannot further perform subgroup analysis to clarify this point.

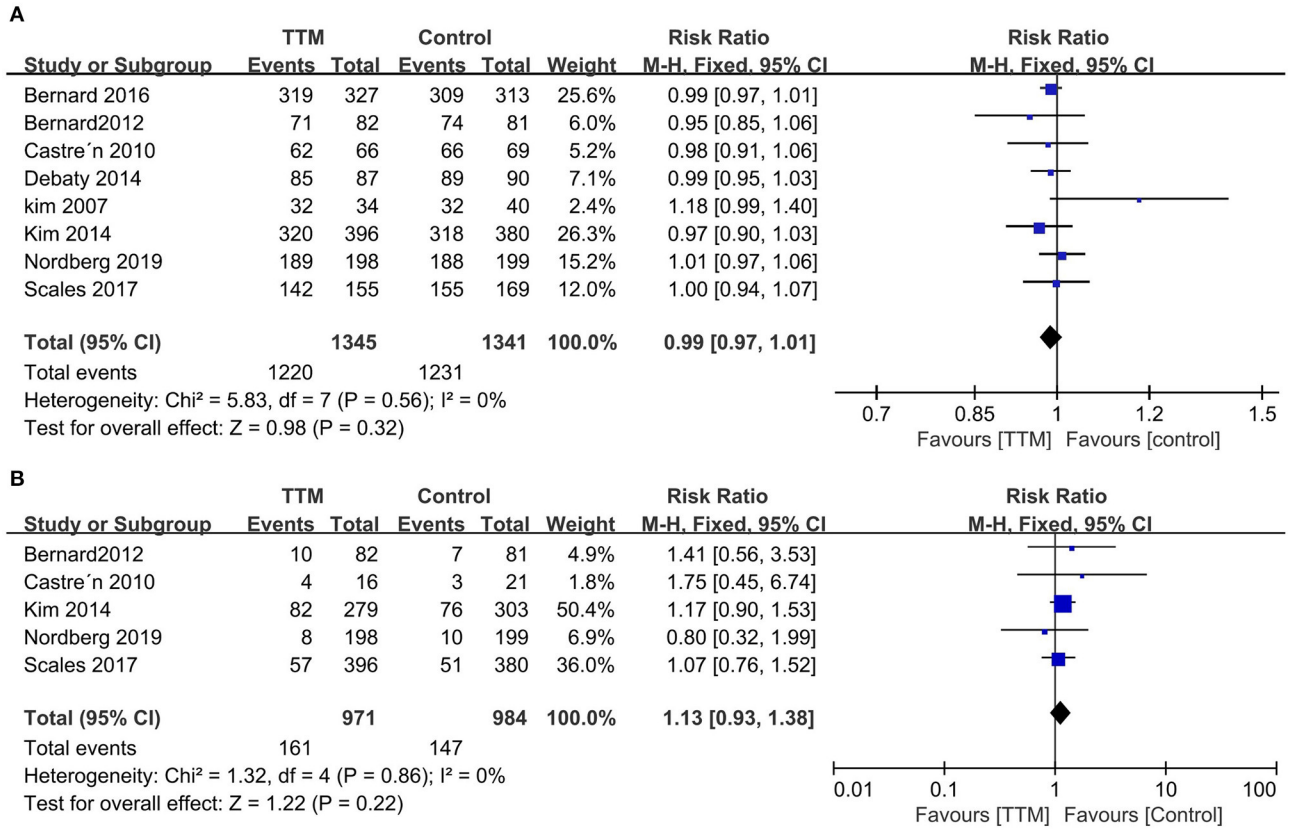

FIGURE 3 | Forest plot of the targeted temperature management used in pre-hospital or in-hospital survivors with non-shockable rhythm. **(A)** Mortality; **(B)** Good neurological outcome.

CONCLUSIONS

Among patients with NSR, the use of TTM showed no more benefits than usual care in survival and favorable neurological outcomes. However, our results were based on observational findings and warranted a randomized clinical trial to assess the efficacy of TTM for such a patient population.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

Y-BZ contributed to conception and design and drafted the manuscript. YY and Y-BZ contributed to searching the scientific literature and data interpretation. J-ZF and YR helped to collect the data and performed statistical analyses. H-BH was responsible for the integrity of the work as a whole, from inception to publication of the article. All authors read and approved the manuscript.

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SUPPLEMENTARY MATERIAL

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REVIEW
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Traumatic Cardiac Arrest: Scoping Review of Utilization of Resuscitative Endovascular Balloon Occlusion of the Aorta

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Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) is increasingly used in trauma resuscitation for patients with life-threatening hemorrhage below the diaphragm and may also be used for patients with traumatic cardiac arrest (TCA). Resuscitative thoracotomy with aortic cross clamping (RT-ACC) maneuver was traditionally performed for patients with TCA due to hemorrhagic shock; however, REBOA has been substituted for RT-ACC in selected TCA cases. During cardiopulmonary resuscitation (CPR) in TCA, REBOA increases cerebral and coronary perfusion, and temporary bleeding control. Both animal and clinical studies have reported the efficacy of REBOA for TCA, and a recent observational study suggested that REBOA may contribute to the return of spontaneous circulation after TCA. Although multiple questions remain unanswered, REBOA has been applied to trauma fields as a novel technology.

Keywords: traumatic cardiac arrest, Resuscitative Endovascular Balloon Occlusion of the Aorta, return of spontaneous circulation (ROSC), mortality, review

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INTRODUCTION

The mortality of traumatic cardiac arrest (TCA) remains high and was estimated to be 97.6% by a recent systematic review (1). The main cause of TCA is hemorrhagic shock (2); severe hemorrhage leads to decreased circulatory volume and the systemic pressure during chest compressions may be inadequate to achieve return of spontaneous circulation (ROSC).

Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) is a resuscitative measure for the augmentation of cardiac and cerebral perfusion by controlling blood flow in the proximal aorta and hemorrhage from the distal portion. REBOA was first used more than 50 years ago (3); REBOA has been used for the treatments of ruptured abdominal aneurysm (4), postpartum hemorrhage (5), and trauma (6). Brenner et al. (6) first reported the use of REBOA for blunt and penetrating injuries associated with end-stage shock. Since then, REBOA became one of the modern technologies in trauma fields (7) and an increasing number of studies have been conducted on REBOA.

This article reviewed the current and future use of REBOA during TCA, including animal and human data. Literature was searched using PubMed database published between 1900 and 2020. The key words used for the search were combinations of "aortic balloon occlusion," "intra-aortic balloon occlusion (IABO)," "REBOA," and "traumatic cardiac arrest." Though utilization of REBOA

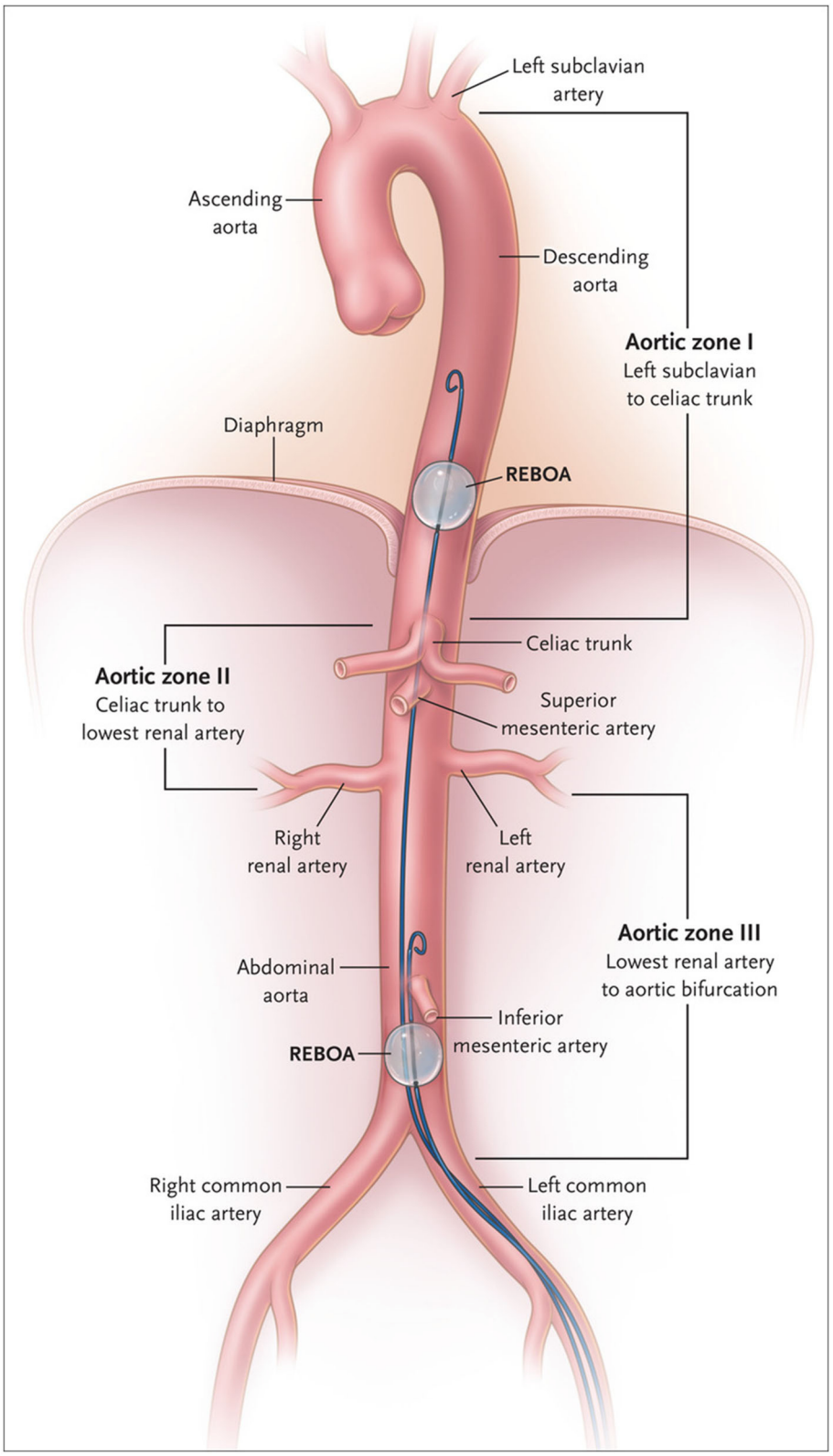

FIGURE 1 | Classification of aortic zone using Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA). In Zone I, safe positioning of the balloon for control of infradiaphragmatic hemorrhage is shown; in Zone III, positioning for control of massive pelvic hemorrhage in the absence of a simultaneous abdominal source of hemorrhage is shown. From King (11). Copyright © 2022 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

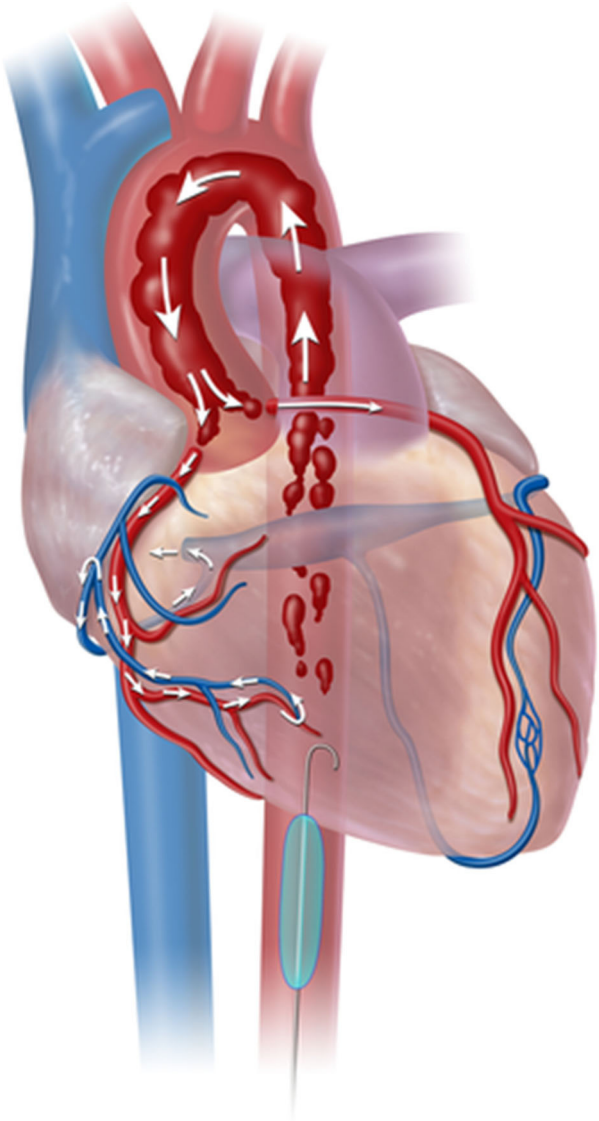

FIGURE 2 | Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) deployment in aorta Zone 1. Zone 1 aortic occlusion with REBOA allows the cardiac output generated from cardiopulmonary resuscitation to be directed toward cardiac and cerebral vessels. From Nowadly et al. (14). Copyright © 2020 Reprinted with permission from J Am Coll Emerg Physicians Open.

for non-traumatic cardiac arrest (NTCA) has been also spotlight and debated, the major difference between TCA and NTCA exists especially in pathophysiology, and we did not discuss the use of REBOA for NTCA in this scoping review.

Indications of REBOA in TCA

Anatomical Aspect

The indication of use of REBOA in TCA should be discussed based on the anatomical and physiological aspects. REBOA is generally indicated for use in patients with bleeding below the diaphragm. The use of REBOA for patients with major hemorrhage above the diaphragm, such as traumatic brain injury (8) or thoracic injury (9), could increase hemorrhage. The joint statement from American College of Surgeons Committee on Trauma stated that REBOA is contraindicated in the setting of major thoracic hemorrhage or pericardial tamponade (10). REBOA is placed in Zone 1 or 3 (**Figure 1**) (11). Zone 1 is the distal thoracic aorta, which is selected for the control of severe intra-abdominal or retroperitoneal hemorrhage, or in patients with traumatic arrest (12). Zone 3 is the distal abdominal aorta, which is selected for patients with severe pelvic, junctional, or proximal lower extremity hemorrhage (11, 12).

Physiological Changes After REBOA Deployment After TCA

Current expert consensus and clinical guidelines state that trauma patients with an initial systolic blood pressure <90 mmHg who do not respond at initial fluid or blood product administration are potential candidates for REBOA use (12, 13). However, REBOA is modestly indicated for TCA patients, albeit with limited evidence. Current guidelines state that REBOA is indicated for patients arriving in arrest from injury due to presumed life-threatening hemorrhage below the diaphragm; in these patients, REBOA should be used within the same time period as resuscitative thoracotomy-aortic cross clamping (RT-ACC) (12). The physiological indication of REBOA for TCA includes patients with signs of life on arrival, which is comparable to the indications of RT-ACC. Physiologically, aortic occlusion (AO) during hemorrhagic shock including TCA results in increases in coronary blood flow (**Figure 2**) (14), cardiac output, mean arterial pressure, carotid blood flow, and partial oxygen pressure of the brain (15, 16). AO simultaneously minimize the major hemorrhage below the diagram maintaining proximal aortic pressure, and contributing to resuscitation and surgical repair of hemorrhage (17).

Superiority of REBOA to RT-ACC for TCA

RT-ACC is maximally invasive procedure and produces additional severe thoracic injury (17), on the other hands, REBOA is less invasive. Another feature of REBOA is that we could control of distal organ perfusion by adjusting balloon volume. If TCA patient was resuscitated by initial resuscitation, the hemodynamics may be controlled using the inflation balloon volume. If the resuscitated patients could maintain acceptable hypotension (permissive hypotension), partial REBOA could maintain the distal organ perfusion and prevent the ischemic complications (18). Besides, adjusting balloon volume enabled to temporarily control the bleeding, carry out surgical treatment in a bloodless field and identify the site of bleeding (19). AO by RT-ACC cannot be unlocked unless hemostatic treatment performed, and the distal organ perfusion was not maintained.

Notably, REBOA does not interrupt closed chest-compressions, which is a significant advantage for TCA patients (20). A prospective observational study of 22 REBOA cases and 28 RT cases analyzed the interruptions in the chest compressions and reported fewer interruptions in patients who had received REBOA compared to RT. Compression was

TABLE 1 | Summary of previous studies of mortality of REBOA for TCA.

References	Type of study	Place of study	Duration	Patient indication	Outcomes of REBOA patients (%)
Moore et al. (18)	Dual-center retrospective	United States	Jan 2012–Jun 2013	REBOA vs. RT-ACC	In-hospital mortality: 7/7 (100) Mortality in ED: 4/7 (57.1%)
Dubose et al. (27)	Prospective observational, multicenter	United States	Nov 2013–Feb 2015	REBOA vs. RT-ACC	N.A
Brenner et al. (28)	Prospective observational, multicenter	United States	Nov 2013–Jan 2017	REBOA vs RT-ACC	In-hospital mortality: 54/56 (96.4%) Mortality in ED: 29/56 (51.8%)
Brenner et al. (29)	Retrospective observational, single-center	United States	Feb 2013–Jan 2017	REBOA	In-hospital mortality: 45/50 (90.0%) Morality in ED: 39/50 (78.0%) ROSC: 29/50 (58.0%)
Yamamoto et al. (30)	Retrospective cohort, multicenter	Japan	Jan 2004–Mar 2019	REBOA vs. RT-ACC	In-hospital mortality: 139/144 (96.5%)
Moore et al. (31)	Prospective observational multicenter	United States	May 2017–Jun 2018	REBOA	In-hospital mortality: 16/17 (94.1%) Mortality in ED: 7/10 ROSC: 10/17 (58.8%)

REBOA, resuscitative endovascular balloon occlusion of the aorta; TCA, traumatic cardiac arrest; RT, resuscitative thoracotomy; ACC, aortic cross-clamping; NA, not applicable.

continued 86.5% of the time for REBOA and 35.7% of the time for RT (20). R Adams Cowley Shock Trauma Center confirmed that the end-tidal carbon dioxide value after aortic occlusion was higher in REBOA compared to RT-ACC, and the rate of ROSC was higher in REBOA compared to RT-ACC [20/33 (60.1%) vs. 5/18 (33.3%), respectively; $p = 0.04$] (21). Conversely, the disadvantage of REBOA is that it may take longer to perform AO by REBOA compared to RT-ACC. The team at R Adams Cowley Shock Trauma Center reported that the time to AO was shorter for RT-ACC compared to REBOA [median time to AO was 317.5 (IQR 227–551) s for RT-ACC vs. 474 (IQR 431–572) s for REBOA] (22). However, REBOA had shorter time to AO once arterial access was established [median time to AO was 245 (179–295.5) s once common femoral artery (CFA) access was established] (22). In addition, REBOA with a wire-free device was commercialized in the USA to achieve earlier time to AO (23). REBOA with a wire-free device could be directly inserted into the aorta without guidewire and this device can be inserted by one provider, and shorten the time to AO (23). Conventional REBOA is inserted by over the wire technique and long stiff guidewire is needed.

Additionally, we described the superiority of RT-ACC compared to REBOA. First, TCA patients with thoracic injury should be resuscitated by RT-ACC, which could immediately control major hemorrhage from the thoracic regions and the shock from cardiac tamponade. Therefore, multiply injured patients with thoracic injury tended to be selected by RT-ACC (24). Second, CFA access is generally difficult among TCA patients compared to hypotensive patients (22, 25). Besides, even if CFA access was achieved, REBOA sometimes may not be deployed for patients with severely tortuous aorta (25). Therefore, it is preferable to select RT-ACC for TCA patients with difficulty in CFA access or severe aortic tortuosity.

Practically, the conversion from RT-ACC to REBOA was reported and previous report showed 30 cases among 106 REBOA cases were RT and REBOA combined cases (26). After TCA patients underwent RT-ACC and achieved ROSC, the patient would suffer from loss of body heat that was potentially caused by exposed pleural cavity and oozing from the incision site of chest. Then, closing the chest wall after RT and converting from RT to REBOA could be a practical choice.

Clinical Research of REBOA for TCA

Most clinical research regarding REBOA in trauma fields excluded TCA patients and limited evidence exists for the utilization of REBOA in TCA (**Table 1**). The mortality of REBOA patients significantly varies with the presence or absence of vital signs necessitating CPR (28). Therefore, previous investigators excluded the TCA patients. An observational prospective study from the American Association for the Surgery of Trauma (AAST) Aortic Occlusion (AO) for Resuscitation in Trauma compared REBOA and RT-ACC for trauma patients requiring AO, including those with TCA (27). In this cohort, 34.7% of REBOA patients (16/46) underwent CPR during initial AO by REBOA and the mortality of REBOA patients who underwent CPR was unknown. In this study, the mean time from initiation of procedure to successful AO did not vary between REBOA and RT-ACC (6.6 vs. 7.2 min, respectively; $p = 0.842$) (30); therefore, the clinical use of REBOA for TCA may be feasible as an alternative to RT-ACC (30). Subsequent reports from the American Association for the Surgery of Trauma (AAST) Aortic Occlusion (AO) (Aorta-2) for Resuscitation in Trauma showed no statistical difference in terms of mortality among TCA patients between REBOA and RT-ACC (96.4 vs. 97.7%, respectively) (27). A trauma registry from Japan (Japan Trauma Data Bank) reported a possible survival benefit of REBOA for TCA compared to RT-ACC (29). The major difference between Aorta-2 and JTDB was whether the time of initiation of CPR was known or not. JTDB did not report whether REBOA was inserted before or after CPR (29). A single center study from the R Adams Cowley

Shock Trauma Center reported comparable mortality of 90.0% and ROSC of 58.0% (29/50) among TCA patients (31). A recent prospective observational study at US 6 Level-1 trauma centers reported that 59% achieved ROSC among TCA patients (32). Taken together, the conclusion was that REBOA in TCA patients due to non-compressible torso hemorrhage below the diagram is preferable (32).

Unresolved Problems of REBOA for TCA

A joint statement from the American College of Surgeons Committee on Trauma (ACS COT) and the American College of Emergency Physicians suggest a longest occlusion time of <15 min for Zone 1 (12). TCA patients already exposed to ischemia were more prone to ischemia-reperfusion injury; therefore, it is unclear how long the TCA patient can accept the Zone 1 inflation. Expert opinion recommends deflating the balloon if the TCA patient tolerates the deflation by proximal aortic pressure. Full occlusion can be switched to partial occlusion once TCA patients achieve ROSC; however, the switch from full to partial occlusion is practically difficult until definitive hemostatic treatment is completed (33).

Another problem to consider is REBOA-related complications (28, 34). Although REBOA is less invasive, major complications may occur. Recent review summarized the complications with associated REBOA, and noted complications can arise in arterial access (i.e., vessel injuries, embolization, air emboli, and peripheral ischemia), balloon inflation (i.e., rupture of the balloon and aortic injury), during occlusion (i.e., other arterial injury, retroperitoneal hemorrhage, lactic acidosis, organ dysfunction, and limb ischemia), deflation (i.e., ischemic reperfusion injury), and removal of the sheath (i.e., distal thrombus and arterial dissection) (34). A nationwide database study (American College of Surgeons Trauma Quality Improvement Program data set) reported high complication rates such as acute kidney injury and lower leg amputations (35) and we had to know REBOA may cause serious complications. REBOA has been a more advanced and lower profile device (36) and complication rates were expected to be lower (36); however, several complications still exist (32).

CONCLUSIONS

REBOA is one of the modern technologies among the trauma field, which has led to a paradigm shift. Recent clinical evidence suggests that the efficacy of REBOA was comparable to RT-ACC for TCA patients; in addition, REBOA may contribute to achieving ROSC and additional definitive hemostatic treatment. However, the mortality of TCA patients remains high and further prospective studies are warranted to validate the efficacy of REBOA for TCA patients.

AUTHOR CONTRIBUTIONS

MA conceived the idea for this scoping review and drafted the manuscript. TA revised the manuscript. Both authors critically reviewed and approved the final manuscript.

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External validation of the Survival After ROSC in Cardiac Arrest (SARICA) score for predicting survival after return of spontaneous circulation using multinational pan-asian cohorts

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Aim: Accurate and timely prognostication of patients with out-of-hospital cardiac arrest (OHCA) who attain return of spontaneous circulation (ROSC) is crucial in clinical decision-making, resource allocation, and communication with family. A clinical decision tool, Survival After ROSC in Cardiac Arrest (SARICA), was recently developed, showing excellent performance on internal validation. We aimed to externally validate SARICA in multinational cohorts within the Pan-Asian Resuscitation Outcomes Study.

Materials and methods: This was an international, retrospective cohort study of patients who attained ROSC after OHCA in the Asia Pacific between January 2009 and August 2018. Pediatric (age <18 years) and traumatic arrests were excluded. The SARICA score was calculated for each patient. The primary outcome was survival. We used receiver operating characteristics (ROC) analysis to calculate the model performance of the SARICA score in predicting survival. A calibration belt plot was used to assess calibration.

Results: Out of 207,450 cases of OHCA, 24,897 cases from Taiwan, Japan and South Korea were eligible for inclusion. Of this validation cohort, 30.4%

survived. The median SARICA score was 4. Area under the ROC curve (AUC) was 0.759 (95% confidence interval, CI 0.753–0.766) for the total population. A higher AUC was observed in subgroups that received bystander CPR (AUC 0.791, 95% CI 0.782–0.801) and of presumed cardiac etiology (AUC 0.790, 95% CI 0.782–0.797). The model was well-calibrated.

Conclusion: This external validation study of SARICA demonstrated high model performance in a multinational Pan-Asian cohort. Further modification and validation in other populations can be performed to assess its readiness for clinical translation.

KEYWORDS

out-of-hospital cardiac arrest, return of spontaneous circulation, prognosis, survival, resource allocation, emergency department, retrospective cohort study, scoring system

Introduction

Out-of-hospital cardiac arrest (OHCA) is a key healthcare challenge for emergency care systems globally, (1) with an estimated incidence of 96 per 100,000 person-years (2). While the pooled incidence of return of spontaneous circulation (ROSC) is 29.7%, only 8.8% achieved 30-day survival globally (3) and 5.8% in the Asia Pacific (4). Advanced interventions post-ROSC can improve mortality in well-selected patients, (5) but also come with significant costs estimated at USD 333,844 per person (6).

The initiation of advanced post-resuscitation efforts often follows after ROSC, in what some authors have described as a "technological imperative" of the physician. Physicians may continue care just because it is available, even if it may not be beneficial to the patient (7). Difficult decisions hence ensue, especially in Asian populations, where such medical decisions often involve the extended family, (8) who might have difficulty comprehending the issue of medical futility under time pressure (9). Accurate prognostication can help frame the family's expectations and allow for better guidance of decisions, potentially avoiding futile care and facilitating efficient allocation of intensive care resources. However, studies have shown that only 50–70% of physicians are able to accurately predict survival (10). Previous studies have also shown that emergency physicians subjectively terminate resuscitation efforts earlier if there are perceived poor prognostic factors, which may not necessarily be objectively associated with patient outcomes (11). The provision of clear objective clinical decision tools that predict outcomes may hence be used to guide the extent of resuscitative efforts.

A recent systematic review by Gue et al identified several existing OHCA prognostication risk scores with good predictive ability (12). However, the clinical relevance of these scores was noted to be limited by difficulty in computation, recall bias and unavailability of data at the time the patient is in the emergency department (ED). In response to this unmet need, we recently developed the Survival After ROSC In Cardiac Arrest (SARICA) score (13) using real world data from Singapore applied to AutoScore, (14, 15) an interpretable machine learning score generator. SARICA consists of three variables: pre-hospital ROSC, age and initial heart rhythm. On the internal validation cohort, SARICA achieved an area under the curve (AUC) of 0.869 (95% confidence interval 0.839–0.900). There is a pressing need to validate SARICA in external cohorts to further understand its potential for clinical implementation.

In this study, we aimed to externally validate the SARICA score in multinational cohorts within the Pan-Asian Resuscitation Outcomes Study (PAROS).

Materials and methods

Study design and setting

We conducted a retrospective cohort study using data from the PAROS registry. PAROS is a clinical research network comprising thirteen countries across the Asia Pacific, and collects out-of-hospital cardiac arrest data. Participating communities are required to submit all core variables regarding each arrest (including bystander CPR, out-of-hospital defibrillation, ROSC in the ED), including information from both Emergency Medical Services and participating hospitals (4). Communities with existing cardiac arrest registries contributed data *via* an export field entry process into the PAROS registry. All data was further verified by designated coordinators in each participating community. Further checks were performed by the trial coordinating center

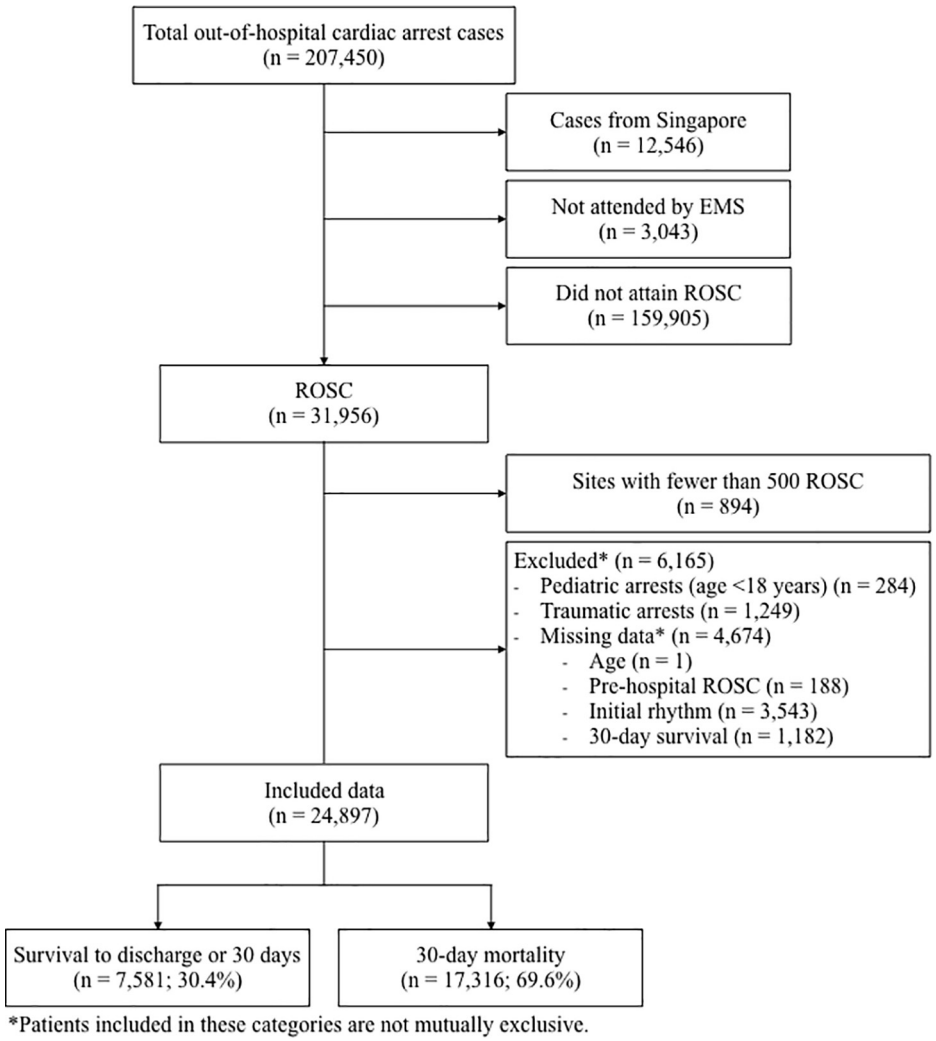

FIGURE 1
Population flow diagram showing cohort selection. EMS, emergency medical services; ROSC, return of spontaneous circulation.

that ensured clarification of logical inconsistencies and missing data through source verification. Further information regarding data collection has been previously described (4).

Participants

We included all OHCA cases between January 2009 and August 2018 that attained ROSC. OHCA was defined as the absence of pulse, unresponsiveness, and apnea; ROSC was defined as regaining a palpable pulse. Cases that were not attended to by Emergency Medical Services (EMS) were excluded. Countries with fewer than 500 patients who attained ROSC were excluded due to small effect size. Data from Singapore was excluded as that data had previously formed the derivation and internal validation cohorts (13). Pediatric arrests (age <18 years) and traumatic arrests were excluded. Cases with missing data (of key variables required in computation of the SARICA score, and the primary outcome) were excluded. This study was approved by SingHealth Centralised Institutional Review Board (CIRB ref: 2013/604/C) and Domain Specific Review Board (ref: C/10/545 and 2013/00929) with waiver of informed consent.

Calculation of survival after ROSC in cardiac arrest score

The SARICA score was calculated as described in the original SARICA paper (13). SARICA comprises three variables: age, pre-hospital ROSC and initial shockable rhythm. For age, in years, it awarded 0 points for age ≥80, 1 point for age 60 to 79, 2 points for age 40 to 59 and 3 points for age <40.

Pre-hospital ROSC was awarded 4 points, and initial shockable rhythm was awarded 3 points. The sum of the scores from each variable formed the SARICA score, with the total score ranging from 0 to 10 points.

Outcomes

The primary outcome was survival, which was defined as survival to hospital discharge or being alive in hospital at 30 days. Secondary outcome was good neurological recovery at 30 days post-arrest, defined as Glasgow-Pittsburgh cerebral performance category (CPC) scores 1 to 2.

Statistical methods

Data preparation, descriptive analysis, and receiver operating curve (ROC) analysis were performed using IBM SPSS Statistics 25.0 (Armonk, NY, United States). Descriptive statistics were generated to compare the characteristics of survivors and non-survivors. Data was reported as mean and standard deviation (SD) for continuous variables and percentages for categorical variables. Bivariable analysis by survival was performed with a chi-squared test for categorical variables, and independent samples *t*-test for continuous variables. We performed ROC analysis on the overall cohort, and subsequently on pre-determined subgroups. Sensitivity and specificity were calculated for each of the SARICA scores. A calibration belt plot was then constructed to assess model calibration.

This study did not venture to identify a threshold score as it is outside the scope of our study; clinical application of such a scoring would be highly dependent on the population it is applied to, as determining distribution of resources based on predicted mortality would depend highly on resource availability. Instead, we aim to validate the performance of the original SARICA score, which similarly, did not propose any cut-off.

Results

There was a total of 207,450 cases of OHCA reported to the PAROS registry from January 2009 to August 2018. A total of 12,546 cases from Singapore, 3,043 that were not attended by EMS and 159,905 cases that did not attain ROSC, were excluded. Of the 31,956 who did attain ROSC, 6,165 cases (3% of total population) were excluded due to missing data. Of the 12 remaining countries in the PAROS registry, 9 countries (with a total of 894 cases) were further excluded as they each had fewer than 500 patients with ROSC. The remaining countries included in the analysis were Japan, South Korea and Taiwan. Finally, 24,897 cases qualified for analysis. The population flow diagram in Figure 1 demonstrates the selection of study participants.

Characteristics of study population

The clinical characteristics of the study cohort, along with comparisons of survivors vs. non-survivors, are shown in Table 1. The cohort had a mean age of 69.3 (SD 16.0) years, and 64.1% were male. A total of 7,581 patients (30.4%) survived to hospital discharge or 30 days. Survivors, compared to non-survivors, were younger (64.2 vs. 71.6 years old, $p < 0.001$) and more likely to be male (70.5 vs. 61.2%, $p < 0.001$). Compared to non-survivors, a greater proportion of survivors had a witnessed arrest (79.7 vs. 64.3%, $p < 0.001$), bystander cardiopulmonary resuscitation (CPR) (46.0 vs. 41.4%, $p < 0.001$), and bystander automated external defibrillator (AED) use (3.7 vs. 2.1%, $p < 0.001$). Significantly more survivors had an initial shockable rhythm compared to non-survivors (47.2 vs. 14.1%, $p < 0.001$), and received pre-hospital defibrillation (51.5 vs. 19.3%, $p < 0.001$). A lower proportion of survivors received pre-hospital drug administration (13.3 vs. 22.5%, $p < 0.001$) and insertion of advanced airway (24.1 vs. 49.9%, $p < 0.001$). A total of 73.2% of survivors had pre-hospital ROSC as compared to 40.9% of non-survivors ($p < 0.001$).

Calculated survival after ROSC in cardiac arrest score for study population

The median SARICA score was 4 (IQR 1-5). The proportion of patients who survived or had a good neurological outcome by each SARICA score level is shown in Table 2. There was a monotonic relationship between SARICA score and proportion of survivors. There was also a visible positive correlation with good neurological outcome; only 1.4% of patients with SARICA score 0 survived with good neurological outcome, while 74.1% of patients at SARICA score 10 survived with good neurological outcome.

Score validation

The AUC for predicting survival was 0.759 (95% CI 0.753–0.766), indicating acceptable diagnostic accuracy. AUC for predicting good neurological outcome was 0.744 (95% CI 0.732–0.755), which was also acceptable. The respective receiver operating characteristics (ROC) curves can be seen in Figure 2.

Receiver operating characteristics analysis on predetermined subgroups showed acceptable diagnostic accuracy across most subgroups in predicting survival (see Table 3). The score exhibited reduced diagnostic

TABLE 1 Clinical characteristics of the study cohort, with comparison between survivors and non-survivors.

	All, *n* (%)	Survivors, *n* (%)	Non-survivors, *n* (%)	*P*-value
Total	**24,897**	**7,581 (30.4%)**	**17,315 (69.5%)**	–
Gender, male	15,948 (64.1%)	5,348 (70.5%)	10,600 (61.2%)	<0.001
Age in years, mean	69.3 ± 16.0	64.2 ± 16.3	71.6 ± 15.3	<0.001
Age in years				<0.001
<40	1,290 (5.2%)	626 (8.3%)	664 (3.8%)	
40 to 59	4,946 (19.9%)	2,081 (27.5%)	2,865 (16.5%)	
60 to 79	11,000 (44.2%)	3,458 (45.6%)	7,542 (43.6%)	
≥80	7,661 (30.8%)	1,416 (18.7%)	6,245 (36.1%)	
Past medical history				
Heart disease	3,844 (29.6%)	1,052 (32.1%)	2,792 (28.7%)	<0.001
Diabetes mellitus	2,418 (31.5%)	543 (26.5%)	1,875 (33.3%)	<0.001
Hypertension	3,632 (46.9%)	887 (42.8%)	2,745 (48.4%)	<0.001
Hyperlipidemia	227 (3.3%)	83 (4.5%)	144 (2.9%)	<0.001
Renal disease	729 (10.6%)	169 (9.2%)	560 (11.1%)	<0.001
Respiratory disease	630 (9.1%)	145 (7.9%)	485 (9.6%)	<0.001
Stroke	867 (12.9%)	177 (9.6%)	690 (13.5%)	<0.001
Cancer	881 (12.6%)	139 (7.5%)	742 (14.5%)	<0.001
Details of arrest				
Witnessed arrest	16,596 (69.%)	5,893 (79.7%)	10,703 (64.3%)	<0.001
Bystander CPR	10,633 (42.8%)	3,480 (46.0%)	7,153 (41.4%)	<0.001
Bystander AED use	399 (2.6%)	190 (3.7%)	209 (2.1%)	<0.001
Initial shockable rhythm	6,017 (24.2%)	3,582 (47.2%)	2,435 (14.1%)	<0.001
Pre-hospital defibrillation	7,252 (29.1%)	3,906 (51.5%)	2,246 (19.3%)	<0.001
Pre-hospital advanced airway inserted	11,228 (45.7%)	2,709 (24.1%)	8,519 (49.9%)	<0.001
Pre-hospital drug administered	4,862 (19.7%)	1,001 (13.3%)	3,861 (22.5%)	<0.001
Pre-hospital adrenaline given	4,822 (25.5%)	983 (16.3%)	3,839 (29.8%)	<0.001
Pre-hospital ROSC	12,639 (50.8%)	5,552 (73.2%)	7,087 (40.9%)	<0.001

ROSC, return of spontaneous circulation; CPR, cardiopulmonary resuscitation; AED, automated external defibrillator.

TABLE 2 Distribution of clinical outcomes by SARICA score level, along with sensitivity and specificity for each cut-off.

Score cut-off	Proportion of study population (%)	Proportion of survivors within the score (%)	Proportion of survivors with good neurological outcome within the score (%)	Sensitivity (%)	Specificity (%)
≥0	100	9.2	1.4	100	0.0
≥1	85.9	13.6	2.8	95.7	18.4
≥2	67.7	17.2	3.2	87.6	41.1
≥3	60.1	19.0	3.4	83.3	50.1
≥4	57.5	25.5	9.9	81.7	53.1
≥5	40.5	35.2	17.4	67.4	71.3
≥6	23.2	41.5	26.0	47.5	87.4
≥7	18.0	43.5	25.0	40.3	91.8
≥8	14.5	68.4	50.9	35.4	94.6
≥9	6.3	80.5	67.0	17.1	98.3
≥10	1.4	86.8	74.1	4.0	99.7

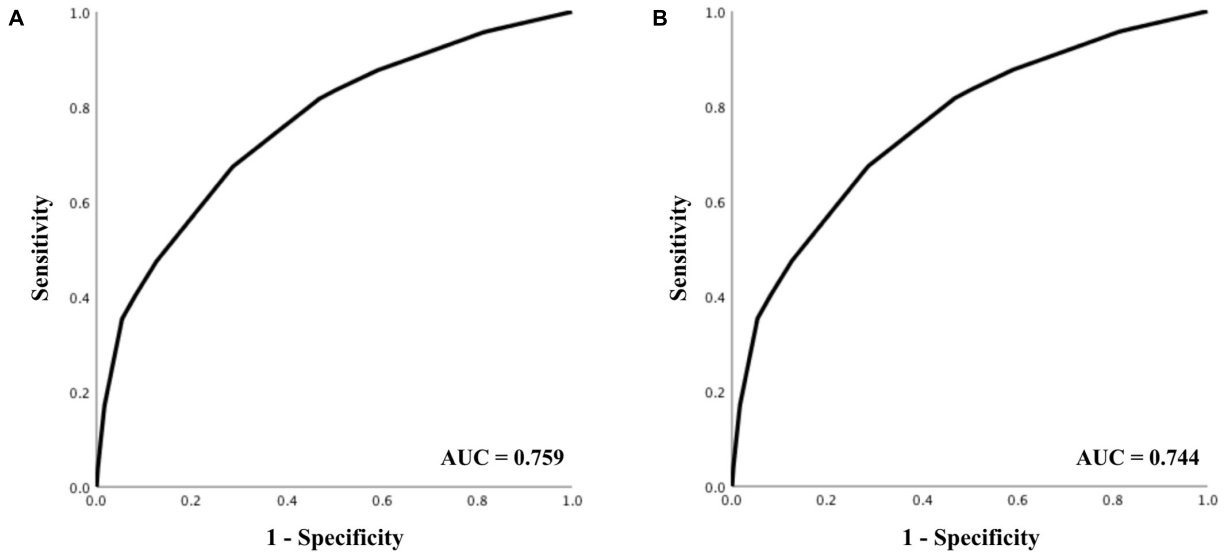

FIGURE 2
Receiver operating characteristics analysis for prediction of **(A)** 30-day survival, and **(B)** good neurological outcome.

TABLE 3 Subgroup analysis–survival rate, area under the curve.

Subgroup	Survival (%)	AUC (95% CI)
Total cohort	30.4%	0.759 (0.753–0.766)
Subgroups by site		
Japan	33.2%	0.759 (0.751–0.767)
Korea	26.0%	0.771 (0.756–0.786)
Taiwan	26.4%	0.695 (0.676–0.715)
Witnessed arrest	35.5%	0.754 (0.747–0.762)
Unwitnessed arrest	20.2%	0.740 (0.725–0.754)
Bystander CPR	32.7%	0.791 (0.782–0.801)
Bystander AED	47.6%	0.746 (0.698–0.793)
Pre-hospital defibrillation	53.9%	0.753 (0.741–0.764)
Pre-hospital airway	24.1%	0.731 (0.720–0.743)
Pre-hospital drug administration	20.6%	0.654 (0.633–0.674)
Pre-hospital adrenaline	20.4%	0.652 (0.632–0.672)
Defibrillation in ED	24.7%	0.750 (0.723–0.777)
Advanced airway inserted in ED	23.6%	0.746 (0.729–0.763)
Presumed cardiac etiology	33.1%	0.790 (0.782–0.797)
Presumed respiratory etiology	31.4%	0.630 (0.602–0.658)

accuracy in two subgroups–administration of adrenaline pre-hospital (AUC 0.652), and presumed respiratory etiology of cardiac arrest (AUC 0.630), but improved diagnostic accuracy in subgroups that received bystander CPR (AUC 0.791) and of presumed cardiac etiology (AUC 0.790).

Calibration performance

A calibration belt plot was used to plot observed outcome vs. predicted probability (Figure 3). The calibration was deemed very good as the calibration belt approximated the line $y = x$.

Discussion

This external validation study of SARICA in a multinational Pan-Asian cohort demonstrated good model performance (both accuracy and calibration). SARICA exhibited reduced diagnostic accuracy among patients who received pre-hospital adrenaline and those of respiratory etiology. It exhibited improved diagnostic accuracy among patients who received bystander CPR and those of presumed cardiac etiology. This is the first external validation study of the SARICA score.

Several other scores have been created as prognostic tools for patients after ROSC, including NULL-PLEASE, OHCA, and rCAST, each of which exhibit good predictive value

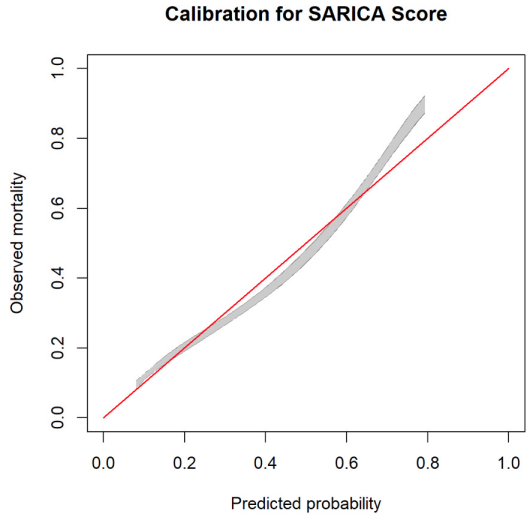

FIGURE 3
Calibration plot for SARICA score showing calibration belts (at 80% [gray] and 95% [dark gray] confidence levels).

(AUC >0.8) (12). However, these scores require variables not immediately attainable on arrival to the emergency department (e.g., serum lactate, pH level, cause of arrest) or variables that are subject to recall bias (e.g., duration of low-flow or no-flow time), or require complex calculations and a score calculator for interpretation. SARICA employs three easily obtainable, routinely available, and objective variables (age, initial shockable rhythm, and pre-hospital ROSC) to offer accurate prediction of prognosis–fulfilling an unmet clinical need in accurate and timely prognostication in the emergency department.

The AUC in our external validation study is lower than that of the internal validation study (AUC 0.759 as compared to 0.869). This appears to be a common feature in prediction scores for OHCA, including the OHCA, (16) NULL-PLEASE (17), and CAHP (18) scores. A possible reason could be the heterogeneity in different healthcare systems–including differences in ambulance arrival time, prevalence and use of AEDs, expertise of first responders–which can contribute to varying outcomes. There was inadequate data for subgroup analysis for evaluation of these possible confounders.

Differences in cultural attitudes toward life-sustaining treatment (LST) can also confound outcomes and contribute to the variation in survival rate between populations at the same SARICA level.

Withholding of LST is prevalent in East Asia, and can contribute to falsely low survival rates. A study by Phua et al. (19) revealed that 70% of physicians in Asian countries would almost always or often withhold LST, and 82% would implement do-not-resuscitate orders, for patients with no real chance of recovering a meaningful life. Interpretation and selection of this patient group remains highly subjective, and can result in limitation of care for patients with perceived poor prognosis, resulting in a falsely low survival rate. This may result in a self-fulfilling prophecy where patients of presumed poor prognosis are denied medical care, thereby decreasing survival rates.

On the other hand, withdrawal of LST, or lack thereof, can also confound survival rates. Among the 3 studied populations, only Taiwan permits withdrawal of LST with persistent vegetative state (20). Korea only allows withdrawal of LST in patients who are imminently dying, (21) while Japan has no official law regarding withdrawal of LST, with a previous survey showing that physicians' fear of criminal prosecution has contributed to avoidance of withdrawal of LST (22). Asian families also play an important role in medical decision making, (23) and these decisions often lean toward prolonging life (24).

At SARICA score 0 to 2, our study population demonstrates higher survival rates, but 80% of these patients are of poor neurological outcome. This may suggest decreased rates of withdrawal of life-sustaining treatment (LST) despite poor neurological recovery. A total of 71 to 80% of ICU physicians in Japan, Taiwan and Korea believe that withholding care and withdrawing care are ethically dissimilar, compared to 41% in Singapore, the original study population for SARICA (19). This mindset that withdrawing LST is ethically unacceptable can contribute to high survival rates despite poor neurological outcomes at low SARICA scores.

Nevertheless, an AUC of 0.759 with good calibration indicates a respectable predictive accuracy. Within our study, other factors that demonstrated good correlation with survival were pre-hospital defibrillation (OR 4.44, 95% CI 4.18–4.71), witnessed arrest (OR 2.18, 95% CI 2.04–2.32) and public location of arrest (OR 2.40, 95% CI 2.26–2.55). These factors have been proven to correlate with eventual survival (4, 25) and are also included in other predictive scores such as NULL-PLEASE, (26) CaRdiac Arrest Survival Score, (27) and Cardiac Arrest Hospital Prognosis score (28). They also remain in line with our aim of employing objective variables that are easily obtained in the emergency department, without being subject to recall bias. However, their inclusion did not substantially improve overall model performance (measured by AUC) as shown in the parsimony plot of the original SARICA derivation paper (13).

Moving forward, despite good model performance, clinical implementation of the SARICA score remains limited at present. Clinical scoring systems require a specific cut-off to guide clinical decision making, however, identifying a specific cut-off remains beyond the scope of our study. Firstly, a sensible cut-off for one setting may be irrelevant for another. A sensible cut-off is one that rations life-sustaining resources (including intensive care unit beds, among others)

rationally, which would depend highly on the availability of resources. A healthcare system that faces severe resource limitation may hence be compelled to accept a higher specificity to reduce its false-positive rate, in order to conserve scarce resources. Secondly, prior to recommending a cut-off point, there is a necessary step of determining how many levels the score should have. The original derivation study arbitrarily used a 10-point scale, however, it could be that a 20-point scale is required to produce the sensitivity and specificity desired.

Limitations

There are several limitations of our study. First, similar to cohort selection in the original SARICA derivation publication, (13) we excluded cases that were not attended by EMS, traumatic arrests, and pediatric cases. These may limit the generalizability of our results to these subgroups of OHCA patients. However, we note that these collectively comprised only 2% of all cases. The clinical implementation process of SARICA would therefore require education of clinicians on patient groups on which SARICA lacked robust validation data so far. Second, we had to exclude cases that had missing data for any of the three variables required to compute SARICA. The proportion of missing data varied across sites. However, it is unlikely that the missing data would skew overall survival, hence we believe the robustness of our analysis is not in question. Third, neurological recovery was assessed through CPC score at 30 days post-arrest. As patients may progress in their neurological recovery beyond this point, eventual neurological outcome may not be accurately reflected. Evaluation of CPC score also requires assessment of community-level functioning that is difficult to perform while inpatient, and may further affect accuracy of the assessment. Lastly, a strong cultural influence on withdrawal and withholding of life support in East Asia also confounds outcomes–clinicians are averse toward withdrawal of LST, resulting in higher rates of survival with poor neurological outcome, but are inclined toward withholding of LST, where a self-fulfilling prophecy of perceived poor outcome may result in inadequate escalation of care and falsely low survival rates.

Conclusion

This external validation study of SARICA demonstrated high model performance (AUC 0.759) in a multinational Pan-Asian cohort. However, further validation is required before clinical application. This can include further increasing the number of score levels to create a score with higher specificity and a lower false positive rate. Further analysis to determine a threshold score and additional validation in populations outside East Asia will also aid in improving the score for clinical application.

Membership of the pan-asian resuscitation outcomes study clinical research network participating site investigators

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Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the SingHealth Centralised Institutional Review Board Domain Specific Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

MR, FZ, NS, NL, and AH contributed to conception and design of the study. MR, FX, NS, PP, MM, SD, HT, MO, NL, and AH were involved in data curation. MR and FX performed the statistical analysis. MR, FX, and AH wrote the first draft of the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

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Conflict of interest

MO reports funding from the Zoll Medical Corporation for a study involving mechanical cardiopulmonary resuscitation devices; grants from the Laerdal Foundation, Laerdal Medical, and Ramsey Social Justice Foundation for funding of the Pan-Asian Resuscitation Outcomes Study; an advisory relationship with Global Healthcare SG, a commercial entity that manufactures cooling devices; and funding from Laerdal Medical on an observation program to their Community CPR training Centre Research Program in Norway. He has a licensing agreement and patent filed (Application no: 13/047,348) with ZOLL Medical Corporation for a study titled "Method of predicting acute cardiopulmonary events and survivability of a patient." He is also the co-founder and scientific advisor of TIIM Healthcare, a commercial entity which develops real-time prediction and risk stratification solutions at triage. AH was supported by the Estate of Tan Sri Khoo Teck Puat (Khoo Clinical Scholars Programme), Khoo Pilot Award (KP/2019/0034), Duke-NUS Medical School and National Medical Research Council (NMRC/CS_Seedfd/012/2018).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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