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Clinical paper

A retrospective multi-centre cohort study: Pre-hospital survival factors of out-of-hospital cardiac arrest (OHCA) patients in Thailand

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Abstract

Objective: This study aimed to explore significant pre-hospital factors aecting the survivability of Out-of-Hospital Cardiac Arrest (OHCA) patients in countries with developing EMS systems.

Method: A retrospective cohort study was conducted examining data from January 1, 2017 to December 31, 2020 from Utstein Registry databases in Thailand, collected through Pan-Asian Resuscitation Outcomes Study (PAROS). Data were collected from three centres, including regional, suburban-capital, and urban-capital hospitals. The primary endpoint of this study was 30-day survival or discharged alive after an OHCA event. The multivariable risk regression was done by modified Poisson regression with robust error variance to explore the association between 30-day survival and pre-hospital factors with potential confounders adjustments.

Findings: Of 1,240 OHCA cases transferred by Emergency Medical Services (EMS), 42 patients (3.4%) were discharged alive after 30 days, including 22 (8.6%), 8 (3.0%), and 12 (1.7%) from regional, suburban-capital, and urban-capital centres, respectively. The initial arrest rhythm was 89.7% unshockable, with no significant variations across the three centres. Overall, bystander Cardiopulmonary Resuscitation (CPR) was 40.4%. However, bystander CPR with Automated External Defibrillator (AED) application was 0.8%. Bystander CPR significantly increased 30-day survival probability (aRR 1.88, 95% CI 1.01 to 3.51; *p* 0.049). Additionally, reducing the EMS response time by one minute significantly increased OHCA survivability (aRR 1.12, 95% CI 1.04 to 1.20; *p* 0.001).

Conclusions: Response time and bystander CPR are the factors that improve the 30-day survival outcomes of OHCA patients. In contrast, scene time, transport time, and pre-hospital advanced airway management didn't improve 30-day OHCA survival.

Keywords: Out-of-hospital cardiac arrest, Response time, Bystander CPR, Cardiac arrest, Response time interval, Cardiopulmonary resuscitation

Abbreviations: OHCA, Out-of-Hospital Cardiac Arrest, CPR, Cardiopulmonary Resuscitation, EMS, Emergency Medical Services

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Introduction

Out-of-hospital cardiac arrest (OHCA) is a global health concern.[1–3] From the meta-analysis in 2020, the global percentage of discharged alive OHCA patients accounted for 8.8% based on 141 included studies. The estimated survival rates showed significant differences among the regions, which were Oceania (16.2%), Europe (11.7%), North American (7.7%), and Asia (4.5%).[3] In Asia, most Emergency Medical Services (EMS) were recently developed, particularly in lower to middle-income countries. Moreover, previous studies demonstrated various survival to discharge rates of OHCA patients in the Asia-Pacific region, including Thailand, ranging from 0.5 to 8.5%.[4]

Several factors are known to be associated with improved survival probability and neurological outcomes. Basic Life Support (BLS) knowledge and skills, including recognizing cardiac arrest events, appropriate Cardiopulmonary Resuscitation (CPR) techniques, applying Automated External Defibrillator (AED), and calling EMS, are the key factors associated with patients survival.[5,6] Not only aforementioned pre-hospital factors but the EMS system, including the response time, initial treatment at the scene, patient evaluation, along with to-hospital-transportation also potentially increase survival rates and neurological outcomes.[6–8]

Since EMS plays a vital role in OHCA survivability, countries with developed EMS systems have more potential to increase OHCA survival.[4,9] EMS system development is a crucial factor for enhancing pre-hospital care and improved OHCA survival in countries with developing systems. A prior study in Thailand observed a bystander CPR rate of 15.8%, a bystander defibrillation rate of 0.3%, and a survival rate of 4.2%.[4] However, these data were obtained from a single centre which might not be applicable to OHCA in other regions. To date, data are still lacking to identify which factors are related to improving survival outcome, for instance, EMS response time and scene time. Moreover, when integrating with other studies from different populations in Thailand, a variation of survivability is likely to be regional.[4,7,10,11]

Therefore, additional evidence is warranted to establish the potential direction and national policy for EMS system improvement in countries where EMS systems have been recently developed. Therefore a retrospective multi-centre cohort study, which represented different contexts in Thailand, was conducted. This study aimed to explore the significant pre-hospital factors affecting the survivability of OHCA patients.

Methods

Study design, setting, and population

We conducted a retrospective cohort study examining data from January 1, 2017 to December 31, 2020 of the three Utstein Registry databases in Thailand. Data were collected through the Pan-Asian Resuscitation Outcomes Study (PAROS). We included patients with OHCA who were 18 years of age or older and excluded all traumatic patients. Cardiac arrest was defined and confirmed by the absence of circulation signs. Non-EMS patients, transported by private cars and first responders, were also excluded from this study. Data were collected from three centres, including a regional hospital (Maharaj Nakorn Chiang Mai Hospital), a suburban-capital hospital (Siriraj Hospital), and an urban-capital hospital (Rajavithi Hospital). Each centre has its own EMS system and protocols. The characteristics of the three EMS centres are described in Table 1. Each centre submitted anonymized patient data in both EMS and hospital parts. The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Chiang Mai University. (Study code: COM-2564–08134) The requirement for individual informed consent was waived. The study flow diagram is provided in Fig. 1.

Data collection and quality control

Data were collected through PAROS, the system based on the Utstein template guidelines for reporting OHCA. The quality and accuracy of data collection across the three centres were partially ensured by using a standardized database and its relational database properties. Moreover, there was a PAROS orientation at the national OHCA conference to ensure that data collection and data entry patterns and methods were consistent. The information included details of the patient's age, gender, ethnicity, witness status, initial rhythm, the shock delivered, time course, bystander CPR, airway management, intravenous treatment, return of spontaneous circulation (ROSC), hospital resuscitation, one-month survival, and neurological status one month after the event. The paper data form was filled out either by the EMS personnel in charge of the patients or the physician in the emergency room responsible for the patients. The data from the paper forms were then later entered into the PAROS registry system by the centre's coordinator or medical personnel. The data of each centre can only be accessed by the centre. If a data form was incomplete, the PAROS system would flag each incomplete case. The centre coordinator would correct and add the missing information. The completed data for this study were retrieved independently, with each centre's authorization and ethical approval. As a well-organized follow-up of all cases in each centre was not successful, some Cerebral Performance Category (CPC) results were missed, and it was not possible to retrieve them at the time of analysis.

Variables

The primary endpoint of this study was 30-day survival or discharged alive after an out-of-hospital cardiac arrest event. Pre-hospital information of OHCA patients was retrieved from the PAROS database, including a history of witnessed arrest, bystander CPR, bystander CPR with AED application, pre-hospital advanced airway management, and pre-hospital defibrillation. Time responses of the EMS systems in three centres were calculated and divided into three main periods, which consist of a response time (a time EMS received the call to the time of EMS arrival at the scene), scene time (the time of EMS arrival at the scene to the time of EMS departure from the scene) and transport time (the time of EMS departure from scene to arrival at the emergency department). Patient characteristics, co-morbidity, estimated Charlson Co-morbidity Index (CCI), first arrest shockable rhythm, witnessed arrest, and cause of arrest, which are the potential confounders of OHCA survival, were also provided for the explanatory analysis. The Charlson Co-morbidity Index in our study was an estimated score because the score from co-morbidity variables was assumed in some predictors (e.g., +1 score from having heart diseases that might be either or both (+1) previous MI and (+1) congestive heart failure).

Statistical methods

Descriptive analysis was performed using frequency and percentage for categorical data, estimates, and variation for continuous data.

Table 1 – Comparison of EMS Centres Characteristics.

Hospital/service region	Urban capital	Suburban capital	Regional
City	Bangkok	Bangkok	Chiang Mai
Service area population	1,200,000	103,800	50,000
Population density (per km^2)	15,000	8,650	8,300
No. of ambulances	7 ALS teams, 15 BLS teams (including network organization)	1 ALS team 1 BLS per shift	1 ALS team 1 BLS per shift
No. of hospitals	1	1	1
No. of participating EMS Agencies	3	2	6
Ambulance:population ratio	1:68,100	1:50,000	1:25,000
Type of providers	EMS doctor, EMS Nurse, EMT-B	Emergency nurse practitioner, EMT	EMT,Paramedic, Doctor, Nurse
Operation of ambulance	Hospital-based and non-profit community	Hospital-based and non-profit community	Hospital-based and non-profit community
Tiered response	BLS and ALS	BLS and ALS	BLS and ALS
Resuscitation protocol	Both Scoop and Run and Stay and Play	Scoop and Run	Scoop and Run

EMT, Emergency Medical Technician; EMT-B, Emergency Medical Technician Basic; ALS, Advanced Life Support; BLS, Basic Life Support.

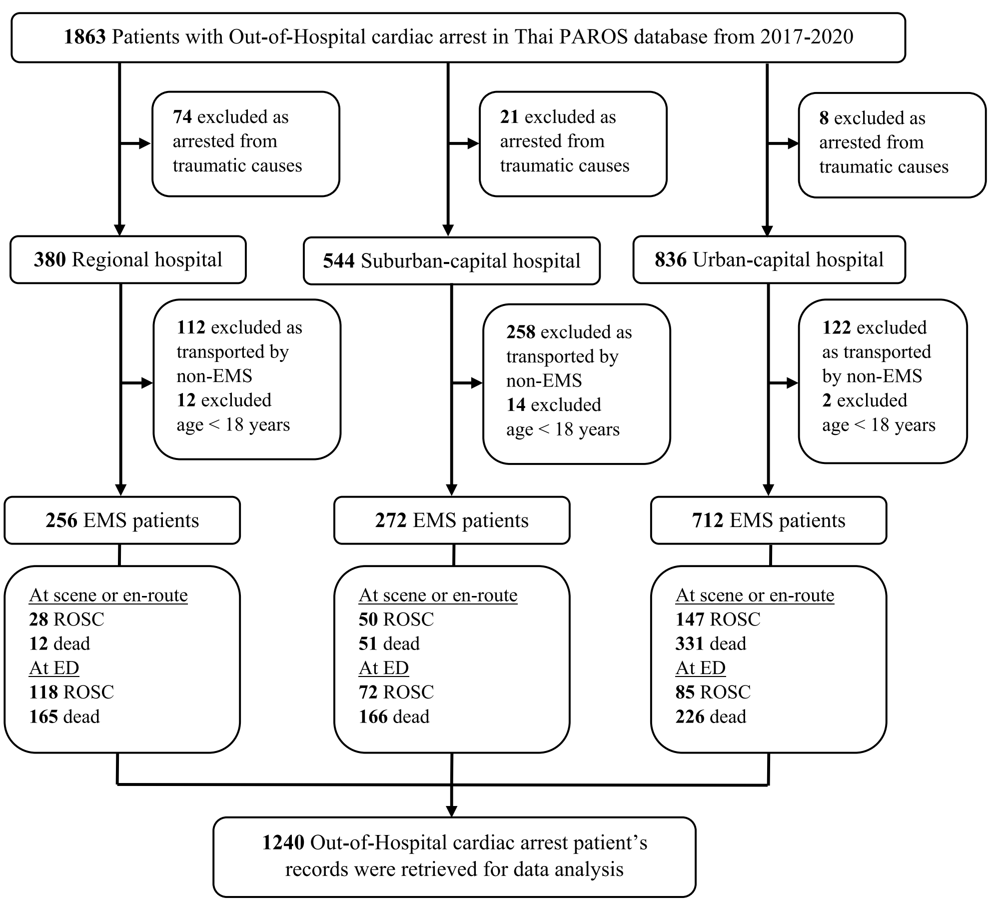

Fig. 1 – Flow Diagram of a Retrospective Cohort Study in OHCA Patients. EMS, Emergency Medical Services; OHCA, Out-of-Hospital Cardiac Arrest; PAROS, Pan-Asian Resuscitation Outcomes Study; ROSC, Return of Spontaneous Circulation.

Chi-square test of independence was applied to the categorical univariable comparison between the three EMS centres. For continuous data, ANOVA and Kruskal-Wallis test with post-hoc adjustment was performed for parametric and non-parametric data, respectively. The multivariable risk regression was done by modified Poisson regression with robust error variance to explore the association between 30-day survival and pre-hospital factors. These included response time, scene time, transport time, bystander CPR, pre-hospital defibrillation, and pre-hospital advanced airway management. The potential confounders adjustment were pre-defined by established evidence including age, gender, ethnicity, first arrest shockable rhythm, cardiac aetiology, estimated Charlson Co-morbidity Index, and witnessed arrest. All statistical analysis was performed via the ***STATA*** software package (Stata Corp. 2019. Stata Statistical Software: Release 16. College Station, TX: Stata Corp LLC.).

Results

Patient characteristics

Between 2017 and 2020, 1760 reported non-traumatic OHCA cases in Thai PAROS were collected from three distinct EMS locations. As shown in Fig. 1, 520 individuals were excluded from non-EMS transfers and pediatric cases under 18 years. Of 1240 cases transferred by EMS, 42 patients (3.4%) were discharged alive after 30 days, including 22 (8.6%), 8 (3.0%), and 12 (1.7%) from regional, suburban capital, and urban capital EMS centres, respectively. Table 2 shows how the distribution of patient characteristics differed between three EMS centres. Male patients were the majority in all centres, with no significant differences in male gender percentages across regional (66.4%), suburban capital (61.0%), and urban capital (65.7%) EMS centres (p 0.324). There was a significant variation in the mean age (years ± SD) of patients in regional, suburban capital, and urban capital centres, which were 54.4 ± 21.8, 66.1 ± 17.3, and 61.8 ± 19.1, respectively ($p < 0.001$). The proportion of Thai patients and other nationalities in the three centres also significantly differed ($p < 0.001$), particularly in the urban capital centre where the majority were other nationalities (62.4%). In contrast, most of the patients in regional (85.2%) and sub-urban hospitals (98.5%) were Thai. Cases in both capital centres had a significantly higher prevalence of heart disease, hypertension, type 2 diabetes, and cancer than those in the regional centre. As a result, we calculated the estimated Charlson Co-morbidity Index (CCI), which indicated an individual's baseline morbidity and mortality risk. Also, the mean estimated CCI of the patients from these centres differed significantly. Although presumed cardiac aetiology was the leading cause of cardiac arrest in regional (46.9%) and suburban capital centres (45.2%), 60.0% of OHCA patients delivered by urban-capital EMS had cardiac arrest for reasons other than cardiac aetiology (33.3%), and the proportion of cardiac arrest causes still significantly varied by centres ($p < 0.001$). In our study, the initial arrest rhythm was 89.7% unshockable, with no significant variations across the three EMS centres. Lastly, the locations of OHCA occurrences were reported differently. The most prevalent site was the home residence, which accounted for 50.4% in the regional area, 83.5% in the suburban capital area, and 81.3% in the urban capital area ($p < 0.001$).

Pre-hospital factors and EMS time response

From Table 2, other key pre-hospital factors, which include witnessed arrest, bystander CPR, and bystander CPR with AED applied, all revealed a significant difference between the three centres, except for pre-hospital defibrillation. The percentage of arrests was significantly different in the three areas. It was highest in the suburban capital area (73.9%), in the urban capital area (55.5%), and in the regional area (50.0%) ($p < 0.001$). The incidence of bystander CPR also significantly varied; highest in the suburban capital area (46.0%), in the urban capital area (43.5%), and the regional area (25.8%) ($p < 0.001$). However, bystander CPR with AED application was only 0.8% nationally. The percentage of pre-hospital advanced airway management varied depending on each centre's local protocols. As indicated in Table 3, regional EMS median response time, median scene time, and median transport time were significantly faster than EMS centres in the capital area. Comparing the two capital EMS centres, urban EMS response time was considerably shorter than suburban EMS. Despite this, urban EMS median scene time and median transport time were longer than suburban capital EMS. Overall, the box plot of EMS response times is illustrated in Fig. 2.

Associated predictors of OHCA survivability in pre-hospital period

The multivariable analysis with potential confounders adjustment is reported in Table 4. Bystander CPR significantly increased the 30-day discharged alive probability by 1.88 times. Additionally, reducing the EMS response time by one minute significantly increased OHCA survivability. However, other predictors, including pre-hospital defibrillation, pre-hospital advanced airway management, shortened scene time, and transport time, were not shown to be significantly associated.

Discussion

In this study, OHCA 30-day survival rates in the three hospitals were significantly different; regional hospital (8.6%), suburban capital hospital (3.0%), and urban capital hospital (1.7%). However, many factors influenced OHCA survivability in different contexts. Therefore, we aimed to determine the association of pre-hospital predictors and 30-day survival of OHCA patients in Thailand, which is a low-middle-income country and has a developing EMS system. Our results showed that a decrease of one minute in the response time was significantly associated with increasing survivability of OHCA patients. Furthermore, receiving bystander CPR is another important predictor that independently increased OHCA survival. Nevertheless, the benefit of bystander AED application and pre-hospital defibrillation were inconclusive from our results because approximately 89.7% of the cases had an initially unshockable rhythm, and the number of bystander AED applications was too low. However, pre-hospital advanced airway management, scene time, and transport time were conclusively not associated with the 30-day survival of OHCA patients.

Interpretation and generalizability

In our study, the percentage of discharged alive OHCA patients was similar to a previous study.[4] When compared to other countries with advanced EMS systems, the survival rate of OHCA in Thailand is lower.[3,12,13] In developing EMS countries, such as Thailand, measuring OHCA survival is an important first step in identifying those procedures that can improve survival outcomes. The national policy should focus on reducing response time, increasing bystander

Table 2 – Comparison of OHCA patient characteristics and outcomes in three hospitals.

Patient Characteristics	Thailand OHCA Data Collection Centres (Total = 1240)						*P-value*
	Regional hospital (n = 256)		Suburban-capital hospital (n = 272)		Urban-capital hospital (n = 712)		
	N	(%)	N	(%)	N	(%)	
Age, mean ± SD, year	54.4 [a]	±21.8	66.1[b]	±17.3	61.8[c]	±19.1	< 0.001
Male	170	66.4	166	61.0	468	65.7	0.324
Ethnicity							
Thai	218	85.2	268	98.5	268	37.6	< 0.001
Other	38	14.8	4	1.5	444	62.4	
Co-morbidity							
Heart disease	25	9.5	60	26.1	126	17.7	0.015
Diabetes Mellitus	36	14.1	65	23.9	151	21.2	0.013
Cancer	14	5.5	32	13.9	73	10.3	0.007
Hypertension	62	24.2	97	35.6	209	29.4	0.015
Renal disease	23	8.9	25	10.9	65	9.1	0.707
Respiratory disease	18	7.0	15	6.5	59	8.3	0.321
Dyslipidemia	19	7.4	21	7.7	33	4.6	0.093
Stroke	13	5.1	26	9.56	44	6.2	0.084
HIV	3	1.2	2	0.7	7	1.0	0.875
Other	49	19.14	35	12.87	107	15.0	0.125
Estimate Charlson Co-morbidity Index (CCI), mean ± SD2 [a]	±2		4[b]	±2	3[c]	±2	< 0.001
Location type							
Home Residence	129	50.4	227	83.5	579	81.3	< 0.001
Street/Highway	55	21.5	15	5.5	53	7.4	
Public/Commercial Building	54	21.1	16	5.9	58	8.2	
Healthcare Facility	15	5.8	9	3.3	15	2.1	
Other	3	1.2	5	1.8	7	1.0	
Cause of arrest							
Presumed Cardiac Aetiology	120	46.9	123	45.2	237	33.3	< 0.001
Respiratory	60	23.4	41	15.1	48	6.7	
Other	76	29.7	108	39.7	427	60.0	
First arrest rhythm							
vShockable rhythm	32	12.5	31	11.4	65	9.1	0.253
Unshockable rhythm	224	87.5	241	88.6	647	90.9	
Witnessed arrest	128	50.0	201	73.9	395	55.5	< 0.001
Bystander CPR	66	25.8	125	46.0	310	43.5	< 0.001
Bystander CPR with AED application	0	0.0	2	0.7	8	1.1	0.224
Pre-hospital defibrillation	45	17.6	65	24.9	126	17.7	0.031
Pre-hospital advanced airway management	109	42.6	136	50.0	511	71.8	< 0.001
Discharged alive	22	8.6	8	3.0	12	1.7	< 0.001
Cerebral Performance Categories Scale 1–2	1	4.5	3	37.5	-	-	
Cerebral Performance Categories Scale 3–4	-	-	1	12.5	1	8.4	
Unknown/Missing	21	95.5	4	50.0	11	91.6	

Significant pairwise comparison by Tukey's method ($p < 0.05$): [a] regional vs. suburban-capital, [b] suburban- capital vs. urban-capital, [c] urban-capital vs. regional.

Table 3 – Comparison of EMS times in pre-hospital period between three hospitals.

Times (minutes)	Thailand OHCA Data Collection Centres (Total = 1240)						*P-value*
	Regional hospital (n = 256)		Suburban-capital hospital (n = 272)		Urban-capital hospital (n = 712)		
	median	(IQR)	median	(IQR)	median	(IQR)	
Response time	7 [a]	(4–9)	11[b]	(9–15)	8[c]	(4–13)	< 0.001
Scene time	15 [a]	(9–22)	20[b]	(13–26)	22[c]	(15–33)	< 0.001
Transport time	4 [a]	(2–9)	9[b]	(7–11)	11[c]	(7–18)	< 0.001

Significant pairwise comparison by Bonferroni's method ($p < 0.05$): [a] regional vs. suburban-capital, [b] suburban- capital vs. urban-capital, [c] urban-capital vs. regional.

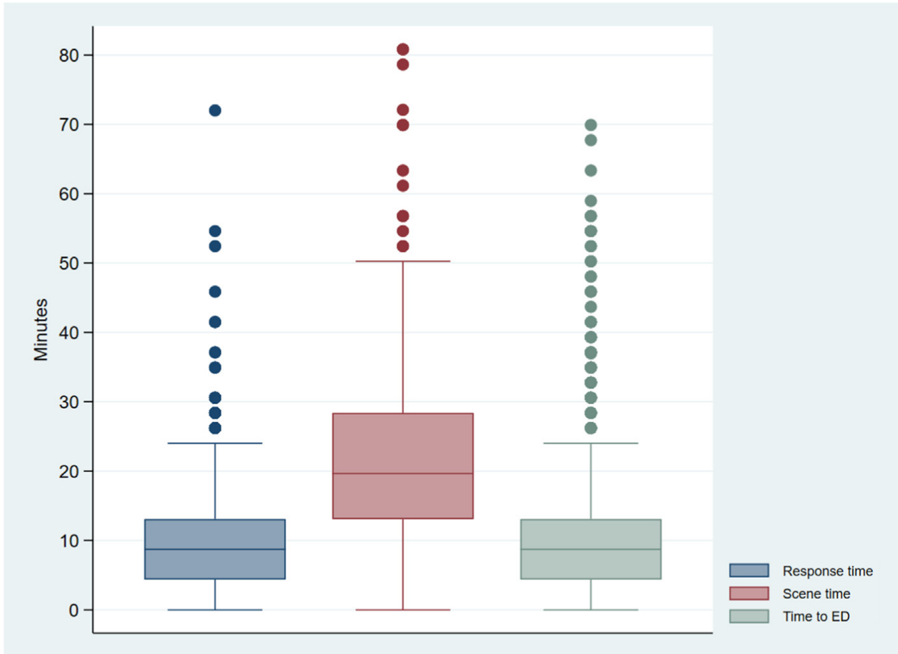

Fig. 2 – Overall EMS times of three hospitals in Thailand. Overall EMS times of three hospitals: Median response time (IQR) was 9 minutes (4–13). Median scene time was 20 minutes (13–28). Median time to ED was 9 minutes (4–13).

Table 4 – Predictors of discharged alive OHCA patients during pre-hospital period by the Multivariable risk regression analysis.

Pre-hospital Predictors	Adjusted relative risk	95% CI	*P-value*
Decreasing response time (minute)	1.12	1.04–1.20	0.001
Decreasing Scene time (minute)	1.03	0.99–1.07	0.112
Decreasing Transport time (minute)	1.00	0.99–1.01	0.936
Bystander CPR	1.88	1.01–3.51	0.049
Pre-hospital defibrillation	1.30	0.46–3.68	0.619
Pre-hospital advanced airway management	0.82	0.41 – 1.62	0.563

Adjusted variables in the explanatory model: age, gender, ethnicity, first arrest shockable rhythm, cardiac aetiology, estimate Charlson Co-morbidity Index, witnessed arrest.

CPR and expanding registry participation. Considering the distinctiveness of various pre-hospital factors among each centre, reducing response time and increasing bystander CPR independently increase the OHCA survival similar to other previous studies.[6–8,14–17]

In countries with developed EMS systems where 60.8% were shockable, bystander CPR with AED application (16.1%) and pre-hospital defibrillation(35.8%) were found to be significantly associated with OHCA survival.[17–20] In our study, bystander CPR with AED application (0.8%) and pre-hospital defibrillation (19.0%) were very low compared to countries with developed EMS systems. Our study showed that pre-hospital defibrillation was not associated with the OHCA survival due to the mentioned factors. Our findings were similar to previous studies in countries with developing EMS systems.[4,21,22]

In our study, the pre-hospital period, scene time, and transport time did not affect the OHCA survival rate. The only significant period is the response time regardless of the hospital location, setting, and patient characteristics.[8,14–16] Also, pre-hospital airway management did not affect the OHCA survival rate in the same way.[23,24] In conclusion, early bystander CPR and prompt EMS care are associated with improved OHCA survival outcomes. Further efforts to expand registry participation and strengthen the chain of survival at the community level will advance OHCA care in Thailand's maturing EMS systems.

This study might be helpful to other countries with similar developing EMS systems. The population in this study was also mainly urban-like many conducted studies in capital and regional cities.[4] However, the regional centre still could not represent a rural area as it possessed a regional level hospital, so this study might not be applicable to a rural setting with lower resources, less professional medical support, and more difficulties in transportation. Future research should include rural areas in the study. In developing EMS countries, reducing response time and increasing bystander CPR should be one of the first priorities in the EMS development process and policy making decisions.[4,21,22]

Strength and limitations

This study is a multi-centre study in different settings, which represented both regional and capital areas and included a large OHCA patient data in Thailand, a developing EMS system country. Furthermore, all patient data were collected in a standardized database system, which was specifically designed for the OHCA study. Therefore, our study results could represent the performance of the EMS in other countries with similar developing EMS systems and provide development and policy for EMS systems in the future.

There were some limitations in this study. First, the population of this study were only OHCA patients who were delivered by EMS; therefore, the survival rates in this study might be overestimated. Non-EMS cases were excluded since the estimated arrest time could not be collected accurately in the non-EMS cases. Second, there are some factors affecting survival, including quality CPR, CPR duration, and pharmacotherapy which could not be shown in this study. Event outcomes, including 1-year-survivability and neurological outcomes, were also not shown in this study. Well-organized follow-up of cases in each centre was not successful, Cerebral Performance Category (CPC) results were lost, and it was not possible to trace them at the time of analysis. Third, the three centres that we collected data from might not represent all rural areas of the country. Lastly, it should be mentioned that the regression analysis may be underpowered since the multivariable risk regression included many dependent variables (both the explanatory variables and confounders). The association between pre-hospital defibrillation and outcome was not shown to have statistical significance because of the imprecise effect estimation by the explanatory model. Although our multivariable analysis was affected by the number of variables in the model, there is sufficient power to detect the precise effect estimation of our main interest predictors, including time responses of EMS and bystander CPR.

Conclusion

Response time and bystander CPR are the factors improving 30-day survival outcomes of OHCA patients among the three centres, which are improvable factors and could be improved by changes in government policy. Reducing EMS response time and increasing bystander CPR are the important goals that should be taken into consideration in countries developing their EMS systems. In addition, increasing the number of public AEDs should be encouraged. In contrast, scene time, transport time, and pre-hospital advanced airway management, regardless of the hospital setting and patient characteristics, didn't improve 30-day OHCA survival.

CRediT authorship contribution statement

The project administration and data validation in each hospital was performed by Jirapong Supasaovapak, Sattha Riyapan, and Wachira Wongtanasarasin. The study methodology was designed by Wachiranun Sirikul, Chanodom Piankusol, and Borwon Wittayachamnankul.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data collection at Rajavithi hospital was facilitated with contributions from Mr.Panjasilpa Somboon and Mr.Saichol Saengchan. Data collection at Siriraj hospital was facilitated with contributions from Ms.Bongkot Somboonkul and Dr.Pakorn Roongsaenthong. Data collection at Maharaj Nakorn Chiang Mai hospital was facilitated with contributions from Ms.Sunisa Taja and Ms.Pannarat aramrerng. Parts of the manuscript were written by Ms.Pitchaya Singhavejsakul, Mr.Komchan Wattanasil, Mr.Nat Ungrungseesopon, and Mr.Sarunsorn Krintratun.

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Author contribution

The idea for the article was initiated by **Wachiranun Sirikul** and **Chanodom Piankusol**. Data acquisition was performed by **Borwon Wittayachamnankul, Sattha Riyapan, Jirapong Supasaovapak, Wachira Wongtanasarasin,** and **Bryan McNally**. **Wachiranun Sirikul** performed data analysis. Interpretation of the study results was done by **Wachiranun Sirikul, Chanodom Piankusol,** and **Borwon Wittayachamnankul**. The first draft of the manuscript was written by **Wachiranun Sirikul** and **Chanodom Piankusol,** and all authors commented on a previous version of the manuscript. The final work was critically revised by **Bryan McNally**. All authors read and approved the final manuscript.

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