THE EFFECT OF RESPONSE TIME ON SURVIVAL AMONG NON-TRAUMATIC OUT-OF-HOSPITAL CARDIAC ARREST PATIENTS IN THAILAND

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ABSTRACT:

Background: Out-of-hospital cardiac arrest (OHCA) is one of the leading causes of death among people around the world. Although Emergency Medical service (EMS) systems have been developed over the past decade to improve the quality of care, the survival rate to hospital for OHCA patients is still low. The objective of this study was to examine the effect of response time (time from emergency call to arrival on the scene) on the survival of non-traumatic OHCA patients in Thailand.

Methods: A national EMS database of Thailand including 19,472 OHCA patients receiving chest compressions by advanced life support (ALS) team, EMS Thailand between 2011 and 2013. Total of 9,951 non-trauma OHCA patients were considered in this study. Binary logistic mixed effect modeling was used to investigate the effect of response time and other potential risk factors on non-traumatic OHCA patients' survival. Imputation was used to investigate whether any bias was introduced though missing values.

Results: Among 9,951 non-trauma OHCA patients, 8,199 (82.42%) survived to hospital. Faster response time was associated with higher survival (OR = 0.97, 95% CI: 0.97, 0.98; $p < 0.001$). Other factors associated with survival among non-traumatic OHCA patients included patients who were administration of intravenous fluids (ORadj = 3.59, 95% CI : 3.15, 4.08, $p < 0.001$), OHCA occurring in urban location (ORadj = 1.49, 95% CI : 1.24,1.80; $p < 0.001$) and higher initial Glasgow coma score (GCS) (ORadj = 1.30 , 95% CI : 1.24,1.37; $p < 0.001$).

Conclusion: Early advanced care plays an important role in non-trauma OHCA patients' outcomes in Thailand. Early response time of the emergency medical services system is important for reducing non-traumatic OHCA patient mortality.

Keywords: Out-of-hospital cardiac arrest, Emergency medical services, Advanced life support, Response time, Thailand

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INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is one of the leading causes of mortality among people around the world. Although systems have been developed over the past decade to improve the quality of care, the survival rate to hospital for OHCA patients is still low [1] with reported overall survival rates between 4-22% [2-6].

Recent studies identify factors that potentially influence survival of OHCA patients, including: 1) Patient factors such as: etiology [2], Glasgow coma score (GCS) [7, 8], systolic blood pressure [9], age and gender [2] 2) Systematic factors including: Emergency medical services response time [6], period of time [3], day and geographical distance [3]

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and 3) Therapeutic factors including advanced airway management [10], cardiopulmonary resuscitation (CPR) [4, 6], medication [11], intravenous fluid administration [12] and automated external defibrillator (AED) [10]. In addition, these factors may relate to patient survival in rather complicated ways.

Several studies have shown that a short interval between collapse and the arrival of emergency medical service (EMS) teams is associated with desirable OHCA patient outcomes [13,14] and every minute without CPR among out of hospital cardiac arrest patients reduces the chance of survival by 7-10% per minute [15]. However, other studies report that response time could not be shown to be associated with the survival rate of OHCA patients [16, 17]. This inconsistency underscores the need to further investigate the effect of EMS response time on survival for OHCA patients. The major aim of this study is to determine the effect of response time on survival to hospital for non-traumatic OHCA patients in Thailand.

METHODS

Study design and setting

This study employed a national EMS database from the National Institute for Emergency Medicine (NIEM), Thailand [18]. The data are maintained and available, along with the study protocol and Case report form (CRF), from the DAMUS website (http://www.damus.in.th/damus/), developed by Medical Research Network of the Consortium of Thai Medical Schools, (MedResNet), Thailand. Data considered in the present study were OHCA patients with a non-trauma etiology, at least 15 years old, receiving CPR from Advanced Life Support (ALS) teams in Thailand between 2011 and 2013. Patients and relatives patients refusing treatment, dying before arrival on scene and response time over 90 min were excluded. This study was approved by the Ethics Committee, Khon Kaen University, Thailand (Permission No.HE57149, 18 June 2014).

Variables considered in the present study were: (1) Patient factors: *Age, Sex, Initial Glasgow Coma Score (GCS), Initial oxygen saturation, Initial blood sugar;* (2) Systematic & Geographic factors: *EMS response time was defined as the time from dispatch call receipt to ALS unit arrival on scene), Location (urban/rural),* and (3) Therapeutic factors: *Ambu bag ventilation, Pocket mask ventilation, Suctioning the airway, Endotracheal intubation, Automated External Defibrillator* (*AED*) and *Intravenous fluid administration.*

Measurements

The primary outcome for this study was survival to admission to hospital *(yes/no). Survival to admission* was defined as OHCA patients who received resuscitation by ALS team of EMS Thailand and did not die before admission to hospital and those *dying* on scene after the ALS team had arrived or during transportation after unsuccessful resuscitation were as "*not surviving*". Those dying before arrival of the ALS team on the scene were excluded.

Statistical analysis

All variables were summarized using descriptive statistics with frequencies (percentages) used for categorical variables, and means (standard deviations) for continuous variables. Crude and adjusted estimates of associations (represented by odds ratios) were obtained using binary mixed effects logistic regression. A mixed effect approach was used to adjust for a possible "province" clustering effect, so province was included as a random effect in the mixed models. The best model was identified using the purposeful selection of covariates approach [19]. Purposeful selection of covariates (PSC) is a rater involved process. Briefly, PSC allows all "potentially" important variables in to the model ($p<0.25$) then sequentially excludes for reasons of non-statistical significance, but also rechecks their statistical significance in later steps, along with their potential for inclusion as a confounder (change the study effect OR > 20%). As response time is the study effect, this predictor was forced into the model. To investigate the potential bias introduced by missing values, multiple imputation was used to generate multiple replicate datasets and results from the subsequent analysis of the imputed data were compared to the complete case analysis. All statistical analysis was conducted using R statistical software (version 3.0.3) [20]. Mixed effect modeling was performed using the R library lme4 [21] and multiple imputation was conducted using the R library mi [22].

RESULTS

During the study period, 19,472 OHCA patients were attended by ALS team in Thailand, of which 9,951 of which were non-trauma OHCA. A total of 9,086 OHCA patients were not eligible for our analysis because of traumatic etiology, refusal of treatment and / or under 15 years of age.

Table 1 presents the characteristics of non-traumatic OHCA patients included in the present study. Of 9,951 non-traumatic OHCA patients

Table 1 Non-traumatic OHCA patients' characteristics

Variables	n (%) or mean ± SD	
Patient factors		
Female sex	3,176	(31.93%)
Age (year)	59.40	± 17.50
Initial Glasgow coma score	3.55	± 2.29
Initial oxygen saturation (%)	67.66	± 29.25
Initial blood sugar (mg %)	158.18	± 100.25
Systematic & Geographic factors		
EMS response time (min)	10.96	± 7.42
Urban location	3,857	(38.77 %)
Therapeutics factors		
Ambu bag ventilation	8,283	(83.26 %)
Endotracheal intubation	1,772	(17.81 %)
Intravenous fluid administration Automated external defibrillator	8,237	(82.82 %)
Suctioning the airway	1,255	(12.68 %)
Automated external defibrillator	681	(6.85 %)
Survival to hospital	8,199	(82.42 %)

Table 2 Unadjusted and adjusted odds ratio from both complete case and imputed data analysis for survival to admission in hospital of non-traumatic OHCA patients

Effects	Complete case (n=2,889)			Multiple imputation (n=9,951)	
	$OR_{unadjust}$	OR_{adjust}	95%CI	OR_{adjust}	95%CI
EMS response time (min)	0.97***	0.97 ***	0.97, 0.98	0.97***	0.96, 0.98
Oxygen cannula	2.06***	1.24	0.99, 1.54	1.58***	1.21, 2.06
Ambubag ventilation	1.21*	1.24**	1.07, 1.43	1.24*	1.03, 1.48
Suctioning the airway	1.60***	1.25**	1.06, 1.47	1.39**	1.12, 1.72
IV fluid[†]	3.55***	3.59 ***	3.15, 4.08	3.79***	3.25, 4.42
Automated external defibrillator	0.96*	0.76*	0.61, 0.96	0.85	0.64, 1.12
Female sex	1.15*	1.15*	1.03, 1.28	1.16*	1.02, 1.33
Urban location	1.65***	1.49 ***	1.24, 1.80	1.49***	1.2, 1.86
Initial Glasgow coma score	1.26***	1.30***	1.24, 1.37	1.21***	1.15, 6.64
Age	1.01				
Initial oxygen saturation	1.02				
Initial blood sugar	1.00				
Endotracheal intubation	1.43				

[*] *p < 0.05,* [**] *p < 0.01,* [***] *p < 0.001*

[†]IV fluid: Intravenous fluid administration

considered, 8,199 patients (82.42%) survived to hospital. 3,176 patients (31.93%) were female, and the mean age was 59.40 years old (SD = 17.50). In the sample 3,857 (38.77%) patients lived in an urban location, and 1,772 patients (17.81%) had non-traumatic OHCA with endotracheal intubation. The mean response time was 10.96 min (SD = 7.42).

Table 2 shows the factors associated with survival to hospital of non-traumatic OHCA patients. In a bivariate analysis, survival to hospital was significantly higher for patients with lower EMS response times with every extra minute of response time leading to a 3% reduction in the odds of survival (OR = 0.97, 95% CI: 0.96, 0.98; p < 0.001). Intravenous fluids administration (OR = 3.55, 95% CI: 3.06, 4.12), urban location (OR = 1.65, 95% CI: 1.33, 2.05) and higher initial GCS (OR = 1.26, 95% CI: 1.18, 1.35) were all associated with increased patient survival in the bivariate analysis.

In the complete-case multivariable analysis, response times were associated with survival in non-traumatic OHCA patients (OR_{adj} = 0.97, 95% CI: 0.97, 0.98; p < 0.001). The similarity between the crude and adjusted odds ratio for the response time effect suggests that neither patient nor therapeutic factors confounded the response time effect substantially. In addition, the response time effect remained largely unchanged in the imputed data analysis suggesting that, at least for the response time effect, missing values did not lead to substantial biases in the estimation of the response time effect.

Patients who were administered intravenous fluids had 3.59 times the odds of survival relative to patient without intravenous fluid (OR_{adj} = 3.59, 95% CI : 3.15, 4.08, p < 0.001). Urban location and initial GCS were also associated with increased survival to hospital in non-traumatic OHCA patients (OR_{adj} = 1.49, 95% CI : 1.24,1.80; p < 0.001 and OR_{adj} =

1.30, 95% CI : 1.24,1.37; p < 0.001, respectively).

The results from the imputation analysis suggest most effects (most notably the response time) remain largely unchanged, suggest little evidence for missing value bias. In no case was did the direction of association change, but there was some effects for which there was a change in the magnitude of the effect, to the point of changing statistical significance. The oxygen cannula effect in the complete case analysis was not statistically significant, whereas this effect was identified as highly significant (p<0.001) in the imputed analysis. Conversely, AED was significant in the complete case analysis, but not in the multiple imputation analysis (Table 2). The main purpose of conducting the imputed analysis was to gauge whether observations were systematically missing, or whether they were missing at random. The minimal difference between the complete case and imputed analysis suggest only small amounts of bias were introduced though missing values.

DISCUSSION

Our results suggest that in Thailand, survival among non-traumatic OHCA patients is considerably higher than others countries [2, 3]. One possible explanation might be that we measured a short term patient outcome (survival to hospital admission), rather than longer-term survival. Following patients to discharge would be more informative, and provide stronger evidence of the effectiveness of the EMS system. However, the problem with considering longer-term outcomes is that in-hospital intervention, often dictated by the nature and severity of the cardiac arrest, then come into play.

EMS response time of ALS units in Thailand seems slower (mean=10.96 min) when compared with response times in other countries [13, 14]. Unfortunately, only 13% of critical patients have access to the EMS [23]. It is essential that the policy should expand EMS system to increase percentage of patient access in Thailand.

OHCA is a critical health problem because the probability of recovery remains low despite the process being potentially reversible. After adjusting for potential confounders in a logistic mixed effect regression analysis, our study demonstrates that reduced EMS response time leads to substantially better patient outcomes. The similarity of the results from our analyses with and without imputation suggests that missing data led to minimal bias in our complete case analysis. To the best of our knowledge, this study is the first, large, multicenter study to demonstrate the association between response times and survival to hospital for non-traumatic OHCA patients in Thailand.

The American Heart Association (AHA) suggested that to improve OHCA patient outcomes, the 5 links in the adult Chain of Survival must be practical. For the pre-hospital area, this optimization incorporates early access, rapid launch of CPR, quick defibrillation, effective advanced care and post-cardiac arrest care [24]. Although public basic life support training and civic education campaigns continue to achieve effective bystander CPR, there is little that could be possible to improve patient survival unless the emergency response system is activated in a timely manner.

Consistent with previous studies, earlier emergency medical services response time is associated with OHCA patients survival [6, 14, 25]. However, most previous studies consider the long term survival of patients, that is, survival to hospital discharge, and one-month survival. Few studies have considered short term patient outcomes such as survival to hospital or the return of spontaneous circulation (ROSC) [15-17]. We decided to assess survival to hospital rather than long-term survival because we aim to elucidate prognostic factors in the pre-hospital setting policy and targets for EMS survival. In contrast, long-term survival depends on hospital treatment, including critical care, and other advanced treatments of underlying diseases [26]. Further research to evaluate longer-term survival would be desirable.

The present study also identified other interesting factors associated with OHCA patient survival to hospital. For example, intravenous fluid administration, urban location, and initial Glasgow coma score were all identified as important factors. The multivariate logistic mixed effect regression analysis in this study identified that for non-traumatic OHCA patients that had been administrated intravenous fluid, the odds of survival were shown to be 3.59 times higher than those who did not receive intravenous fluid. However, in terms of long term survival, other studies have found pre-hospital use of intravenous administration or lactated Ringer's solution is not associated with survival [12, 27].

Non-traumatic OHCA patients who lived in an urban location demonstrated a higher chance of survival, with 1.49 times the odds of survival relative to those living in rural areas, even after adjusting for response time. However, even after adjusting for response time, we demonstrate that rural patients prognosis is worse than urban patients above and beyond the effect of response time [28].

Our study demonstrates higher Glasgow coma

score was also shown to be associated with increased chance of survival to hospital. This finding is consistent with several studies which demonstrated that initial Glasgow coma scale is associated with patient outcomes [7, 8].

LIMITATIONS

The present study was an observational nation-wide study with a number of limitations. First, high levels of missing data were present which may lead to some bias in any subsequent analysis. To investigate the effect of missing values, we conducted multiple iterative regression imputation and found that the direction of the various effects never changed between the complete case and imputed data analysis, and the magnitude of effects changed little. The significance of the effects varied between the results of the complete case and imputed analysis in only three instances (Oxygen cannula, Ambu bag ventilation and AED) and this may be explained by the additional power of the imputed data analysis, which was based on a substantially larger sample.

A second potential limitation was that the data considered in the present study were non-traumatic OHCA patients receiving care from ALS teams from 76 of the 77 provinces of Thailand. The last province, Bangkok is only partially present in the data set (5%). This is due to an administrative issue in this province where several EMS systems are running simultaneously, only one of which, falls under the auspices of the National Institute for Emergency Medicine.

Finally, most previous studies of OHCA patients have used the Utstein-Style reporting templates [6, 14, 29, 30] but our data collection involved the use of a case record form (CRF) of the EMS, Thailand, a general purpose CRF. Consequently, some potentially important predictors were not measured (e.g., witnessed, bystander CPR).

CONCLUSION

For non-traumatic OHCA patients attended by ALS teams, reduced EMS response times were demonstrated to increase the likelihood of survival to hospital. Early advanced care on non-traumatic OHCA patient should be a major priority.

CONFLICT OF INTEREST STATEMENT

There is no conflict of interest related to this study.

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