Time point for transport initiation in out-of-hospital cardiac arrest cases with ongoing cardiopulmonary resuscitation: a nationwide cohort study in Japan

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Aim: This study aimed to investigate the time point of the decision to initiate transport with ongoing cardiopulmonary resuscitation (CPR) in Japan.

Methods: We analyzed adult out-of-hospital cardiac arrest (OHCA) cases that achieved return of spontaneous circulation (ROSC) before hospital arrival from the All-Japan Utstein Registry during 2015–2017. We constructed receiver operating characteristics (ROC) curves to illustrate the ability of achieving ROSC as a predictor of neurologically favorable outcomes as a function of increasing time points of resuscitation before ROSC. Furthermore, a multivariable logistic regression analysis was carried out to identify factors associated with outcomes.

Results: Of 373,993 OHCA patients with attempted resuscitation during 2015–2017, 22,067 patients with prehospital ROSC were included in our study. Patients were divided into the shockable initial rhythm (n=5,580) and nonshockable initial rhythm (n=16,487) cohorts. The ROC curves showed 10 min was the best test performance time point for a neurologically favorable outcome for shockable initial rhythm patients (sensitivity, 0.78; specificity, 0.53; area under the ROC curve [AUC], 0.70) and 8 min for nonshockable initial rhythm patients (sensitivity, 0.74; specificity, 0.77; AUC, 0.83). Multivariable logistic regression analyses revealed that CPR durations using the cut-off value were independently associated with better outcomes for both shockable initial rhythm patients (odds ratio, 2.09; 95% confidence interval, 1.81–2.42) and nonshockable initial rhythm patients (odds ratio, 3.34; 95% confidence interval, 2.92–3.82).

Conclusion: When Japanese emergency medical service (EMS) providers attend OHCA cases, the decision to initiate transport with ongoing CPR should be made at approximately 10 min after EMS providers initiate CPR for shockable initial rhythm patients and at approximately 8 min for nonshockable initial rhythm patients.

Key words: Ambulance, cardiopulmonary resuscitation, emergency medical service, out-of-hospital cardiac arrest, transportation of patient

INTRODUCTION

Emergency medical service (EMS) providers in Japan must initiate resuscitation efforts immediately for all out-of-hospital cardiac arrest (OHCA) patients who do not display obvious signs of death. Furthermore, since EMS providers cannot make the decision to terminate resuscitation efforts, resuscitation efforts must be continued until achievement of the return of spontaneous circulation (ROSC) or arrival at the hospital unless there are appropriate documents with Do Not Attempt Resuscitation (DNAR) orders. Therefore, it is beneficial for EMS providers to know when they should leave the scene with ongoing cardiopulmonary resuscitation (CPR) because transportation without ROSC could impair the quality of CPR and potential risks exist to both EMS providers and public safety when transporting during ongoing CPR.1

The time point at which patients without ROSC are transported to the hospital with ongoing CPR varies by region...
and agency. For example, although the statement was not based on previous research, the European Resuscitation Council guidelines in 2015 stated that the decision to transport with ongoing CPR should be considered after 10 min of advanced life support (ALS). Another report suggested that the optimal time for the decision to transport with ongoing CPR was between 8 and 15 min after EMS arrival. While these guidelines and previous studies suggested a time point for the decision to transport with ongoing CPR, the time point in Japanese prehospital settings remains unclear. Additionally, because termination of resuscitation (TOR) rules have not been adopted in Japan and ALS skills of EMS providers are quite limited compared to other countries, the time point should be investigated using data from Japanese OHCA registries. Furthermore, treatment strategies at the scene should be considered separately depending on the initial cardiac rhythm, as the first documented rhythm is associated with outcomes.

To address this knowledge gap, we analyzed the All-Japan Utstein Registry data to investigate the time point for the decision to initiate transport with ongoing CPR in a Japanese prehospital setting. We also compared the timing separately depending on the initial cardiac rhythm.

METHODS

Study design

This was a population-based, observational study using data from the All-Japan Utstein Registry, a prospective, nationwide, population-based registry of OHCA patients in Japan. Permission from the Fire and Disaster Management Agency (FDMA) was received to analyze the data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE) reporting statement for observational studies. This study was approved by the ethical committee of Kanazawa University (3709–1). The requirement for written informed consent was waived because the data were anonymous.

Setting

Japan has approximately 127 million residents in an area of 378,000 km². The FDMA of Japan supervises the nationwide EMS system, while the local fire stations operate the local EMS system. In 2017, there were 732 fire stations with dispatch centers in Japan. Each ambulance team consisted of three EMS providers, including at least one emergency lifesaving technician (ELST) who was certified to use semi-automated external defibrillators and to insert an intravenous line and an adjunct airway for OHCA patients. In addition, specially trained ELSTs are permitted to insert a tracheal tube and administer intravenous adrenaline under physician instructions on the phone.

All ambulance teams operate according to the protocols established by a local medical control council based on the Japan Resuscitation Council guidelines. According to FDMA guidelines, dispatcher-assisted CPR (DA-CPR) is commonly provided. Emergency medical service providers are obligated to initiate CPR for all OHCA patients, except for cases where there are signs of obvious death, such as rigor mortis. Furthermore, EMS providers cannot terminate CPR unless the local medical control council introduces DNAR protocols.

Participants

We identified all resuscitation-attempted OHCA cases by EMS with subsequent transport to the hospital during 2015–2017. We excluded patients that did not achieve ROSC, were less than 18 years of age, cases that were witnessed by EMS, cases in which a prehospital physician was involved, cases with a nonmedical cause, or cases with missing or insufficient data.

Variables

Clinically important confounders were selected according to previous studies and were included in a multivariable logistic regression analysis. The variables included age, gender, witnessed arrest, DA-CPR instruction, bystander CPR provision, prehospital defibrillation, presumed cardiac etiology, advanced airway management, adrenaline administration, response time, and CPR duration.

Data sources

The All-Japan Utstein Registry includes patient background, clinical characteristics, and time factors based on the Utstein recommendations for reporting OHCA cases. A data form was filled out by EMS providers along with the physician in charge and the data were subsequently transferred to the registration system on the FDMA data server. The data were then assessed by the FDMA. All OHCA survivors were followed up with an interview 1 month after the event by fire department personnel to assess their outcomes. A neurologically favorable outcome was defined using the Cerebral Performance Category (CPC) score where 1 is classified as good recovery and 2 as moderate disability. The CPC score was determined by a physician in collaboration with EMS providers. Prehospital ROSC was defined as any spontaneous palpable pulse confirmed by EMS providers. The
cause of arrest was presumed to be cardiac unless an obvious noncardiac cause was elicited. The cause of arrest was determined clinically by the physicians in charge after arrival at the hospital. The response time was calculated as the time from the emergency call to the time of contact with a patient by the EMS provider. Cardiopulmonary resuscitation duration was defined as the time from CPR initiation by the EMS provider to prehospital ROSC.

Outcomes

The primary outcome of this study was a neurologically favorable outcome defined as a CPC score of 1 or 2. The secondary outcome was 1-month survival.

Statistical analysis

We described the patients’ characteristics using the median and interquartile range (IQR) for continuous variables and number and percentage (%) for categorical variables. A $\chi^2$-test for nominal variables and a Mann–Whitney U-test for continuous variables were used to assess the univariate differences in background, clinical characteristics, time factors, and outcomes between shockable initial rhythm and nonshockable initial rhythm.

A receiver operating characteristics (ROC) curve was constructed with the corresponding area under the curve (AUC) to illustrate the ability of achieving ROSC (as a positive test) as a predictor of neurologically favorable outcomes as a function of increasing CPR duration. The true positive rate was the proportion of those achieving ROSC with an increasing time of resuscitation and subsequent neurologically favorable outcome. The true negative rate was the proportion of those who did not achieve ROSC with an increasing time of resuscitation and who demonstrated a neurologically unfavorable outcome. The time juncture of resuscitation that yielded the best test performance was determined.

Furthermore, a multivariable logistic regression analysis was undertaken to identify factors associated with outcomes. In a multivariable logistic regression analysis, we treated the variable of CPR duration as a binary variable using the cutoff value calculated by the ROC curve and AUC. All tests were two-tailed, and $P$-values of less than 0.05 were considered significant. EZR14 was used for all statistical analyses.

RESULTS

Patient enrolment

The selection criteria for the participants of this study are shown in Figure 1. During 2015–2017, the database recorded 373,993 resuscitation-attempted OHCAs by EMS with subsequent transport to a hospital in Japan. Of these, we excluded 334,946 patients that did not achieve ROSC, 658 patients that were less than 18 years of age, 6,012 cases that were witnessed by EMS, 4,763 cases with a prehospital physician involved, 1,738 cases with a nonmedical cause, and 3,809 records with missing or insufficient data. We included the remaining 22,067 cases in the current analysis.

Table 1 displays the patient characteristics and outcomes. Overall, the median age was 76 years (IQR, 65–85 years) and 62.9% were men. Furthermore, the median CPR duration was 12.0 min (IQR, 6.0–12.0 min). Of these, 5,580 (25.3%) demonstrated a shockable initial rhythm and 16,487 (74.7%) demonstrated a nonshockable initial rhythm. Those with a shockable initial rhythm were significantly younger than those with a nonshockable initial rhythm. The proportions of male gender, witnessed arrests, bystander CPR provisions, prehospital defibrillations, and presumed cardiac etiologies in the shockable initial rhythm group were significantly higher than those in the nonshockable initial rhythm group. Additionally, advanced airway management and adrenaline administration were undertaken more often in the nonshockable initial rhythm group than in the shockable initial rhythm group. Response times and CPR durations were shorter in the shockable initial rhythm group than in the nonshockable initial rhythm group. Regarding outcomes, the shockable initial rhythm group had a higher 1-month survival rate and was more likely to experience a
neurologically favorable outcome than the nonshockable initial rhythm group.

**Relationship between probability of outcome and CPR duration**

The sensitivities and specificities of CPR duration and a neurologically favorable outcome for the shockable initial rhythm patients are displayed in a ROC curve with an AUC of 0.70 (Fig. 2). The ROC curve showed 10 min was the best test performance time point and this time had the highest sensitivity (0.78) and specificity (0.53). In the group of nonshockable initial rhythm patients, the best test performance time point was 8 min according to the ROC curve, and the highest sensitivity and specificity values were 0.74 and 0.77, respectively (AUC, 0.83; Fig. 3).

The probability of outcome changed as the CPR duration increased for shockable initial rhythm patients, as shown in Figure 4. For patients who achieved ROSC within 10 min, the probability of a neurologically favorable outcome was 64.7% (2,291 of 3,541), and the probability of a neurologically unfavorable outcome was 35.3% (1,250 of 3,541). Likewise, the probabilities of outcomes for nonshockable initial rhythm patients are shown in Figure 5. For patients who achieved ROSC within 8 min, the probability of a neurologically favorable outcome was 29.3% (1,396 of 4,762), and the probability of a neurologically unfavorable outcome was 70.7% (3,366 of 4,762).

**Factors associated with outcomes**

A multivariable logistic regression analysis revealed various factors associated with the outcomes. Cardiopulmonary resuscitation durations using the cut-off value calculated by the ROC curve and AUC (shockable, within 10 min; nonshockable, within 8 min) were independently associated with better outcomes for both shockable initial rhythm patients (OR, 2.09; 95% CI, 1.81–2.42 for neurologically favorable outcome; and 1.91; 1.64–2.23 for 1-month survival) and nonshockable initial rhythm patients (3.34; 2.92–3.82 for neurologically favorable outcome, 2.08; 1.89–2.28 for 1-month survival). Witnessed arrest was more likely to increase the odds of outcomes for both shockable and nonshockable initial rhythm patients. In contrast, older age, adrenaline administration, and prolonged response times were commonly associated with worse outcomes in both groups (Table 2).
DISCUSSION

In this analysis of nationally representative data from 22,067 OHCA cases, we revealed that a longer CPR duration was independently associated with a worse outcome, regardless of the initial cardiac rhythm. When considering the time point of the decision to initiate transport with ongoing CPR, we found that the decision should be made approximately 10 min after the EMS initiated CPR for shockable initial rhythm patients and approximately 8 min after initiation for nonshockable initial rhythm patients. To the best of our knowledge, this is the first study to reveal the time point for the decision to initiate transport with ongoing CPR in a Japanese prehospital setting.

A previous study that used ROC curves revealed that the optimal timing of the decision to initiate transport with ongoing CPR was between 8 and 15 min after the EMS initiated CPR for shockable initial rhythm patients and approximately 8 min after initiation for nonshockable initial rhythm patients. To the best of our knowledge, this is the first study to reveal the time point for the decision to initiate transport with ongoing CPR in a Japanese prehospital setting.

A previous study that used ROC curves revealed that the optimal timing of the decision to initiate transport with ongoing CPR was between 8 and 15 min for presumed cardiac causes of OHCA that achieved prehospital ROSC.\textsuperscript{4} This was consistent with the results of our study. Additionally, another study reported that transport should be considered at time points between 8 and 24 min for patients who were extracorporeal cardiopulmonary resuscitation (ECPR) candidates.\textsuperscript{15} However, these previous studies were undertaken in the United States or European countries, where TOR rules are generally adopted and study settings and the population are very different from settings and populations in Japan. Paramedics in the United States or European countries demonstrate higher ALS skills when compared to Japanese EMS providers. Therefore, these study results might not be applicable when it comes to a prehospital setting in Japan. Furthermore, treatment strategies at the scene of an OHCA should be thought of independently contingent on the initial cardiac rhythm, as the first documented rhythm is associated with outcomes.\textsuperscript{5–7} The present study builds on these prior reports and extends them by using domestic OHCA data in Japan.

Overall, as previous studies have reported, patients with a nonshockable initial rhythm seem to have longer CPR durations when compared to patients with a shockable initial rhythm.\textsuperscript{16,17} One of the reasons for this observation could be that patients with a nonshockable initial rhythm are more likely to receive ALS procedures, including adrenaline.

Fig. 2. Receiver operating characteristics (ROC) curve for patients with out-of-hospital cardiac arrest and shockable initial rhythm. At the time juncture of 10 min, 2,291 of the total 2,926 patients who had neurologically favorable outcomes achieved return of spontaneous circulation (ROSC) (sensitivity 0.783 [2,291 of 2,926]) and 1,404 of the total 2,654 patients who had neurologically unfavorable outcomes did not achieve ROSC (specificity of 0.529 [1,404 of 2,654]). AUC, area under the ROC curve.

Fig. 3. Receiver operating characteristic (ROC) curve for patients with out-of-hospital cardiac arrest and nonshockable initial rhythm. At the time juncture of 8 min, 1,396 of the total 1,888 patients who had neurologically favorable outcomes achieved return of spontaneous circulation (ROSC) (sensitivity 0.739 [1,396 of 1,888]) and 11,233 of the total 14,599 patients who had neurologically unfavorable outcomes did not achieve ROSC (specificity of 0.769 [11,233 of 14,599]). AUC, area under the ROC curve.
administration and advanced airway management. Adrenaline administration by EMS personnel plays an important role in achieving ROSC, especially for the nonshockable initial rhythm group. In addition, the proportion of cases with adrenaline administration and advanced airway management was significantly higher in the nonshockable initial rhythm group than in the shockable initial rhythm group in the current study. Nevertheless, the ROC curves indicated that the best test performance time point was significantly shorter in the nonshockable initial rhythm group than in the shockable initial rhythm group, which could indicate that the causes of arrest could be fatal for nonshockable initial rhythm patients. Neurologically favorable outcomes for this cohort could be determined in the early stages of the resuscitation process, regardless of ALS treatments.

There are two major differences in the EMS systems of Japan and other developed nations, namely TOR rules and ALS skills. In other developed nations, protocol for dealing with OHCA patients is to stay at the scene and provide ALS procedures in hopes of achieving ROSC. However, EMS providers in Japan must transport OHCA patients to the hospital, as TOR rules have not been adopted in prehospital settings in Japan. Therefore, EMS providers in Japan tend to prioritize early transport to the hospital regardless of ROSC. Notably, because the ALS skills of Japanese EMS providers are quite limited compared to paramedics in other countries, fewer treatments may be available on the scene. Therefore, transportation in the early stages of the resuscitation process may be reasonable in Japan. However, numerous studies have reported an association between intra-arrest CPR and poor outcomes. Transport during an active resuscitation could deteriorate the quality of CPR as well as inhibit an EMS provider’s ability to treat possible reversible causes of the OHCA, which could lead to poorer outcomes. Furthermore, intra-arrest CPR could place the ambulance staff and others at risk of serious injuries or death; therefore, if the time point of the decision to initiate transport with ongoing CPR is identified, outcomes could be improved by the EMS providers staying on the scene until a proper time point and aiming for ROSC at the scene, which could be associated with a higher quality of CPR. This study suggests new treatment strategies for Japanese EMS providers; that is, staying on the scene and aiming for ROSC for at least 10 min after initiation of CPR for shockable initial
rhythm patients and at least 8 min for nonshockable initial rhythm patients.

In this study, we applied ROC curve analysis and identified “optimal” cut-off time points for initiating transport with ongoing CPR. However, the time points might not be optimal for clinical situations. For example, if an OHCA case with ventricular fibrillation occur in an urban area where the time to the nearest tertiary center with ECPR capacity is 1 min, early transport could be beneficial because the duration of low-quality CPR due to transport can be minimized. In contrast, if in a rural area and a mechanical chest compression device is available, staying on the scene more than 10 min is reasonable. As Figure 4 shows, more than 50% of patients had a good outcome even after 30 min. Emergency medical service providers are required to show the ability to judge how to offer the best possible care for their patients and we believe that this study provides support for their judgements.

In terms of subsequent steps for dealing with OHCA patients in Japan, EMS systems in Japan should be improved. For example, TOR rules should be applied and Japanese EMS providers should be trained in advanced ALS skills. Furthermore, cooperating emergency physicians, air ambulances, and doctor cars should be utilized further to provide early advanced medical care. Simultaneously, all emergency physicians in Japan need to understand the circumstances in which Japanese EMS providers operate and the limitations of their activities.

Our study has several potential limitations. First, because of the limited data of the All-Japan Utstein Registry, the time point when patients achieved ROSC is not known for every case. Some patients might receive ongoing CPR, while others might not. The results in our study could have been different if the background of each patient was the same. Second, this study did not take into consideration the quality of EMS intervention or hospital management (e.g., the use of mechanical chest compression devices, therapeutic hypothermia, or ECPR), which could have affected patient outcomes.

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A PPROVAL OF THE research protocol with approval no. and committee number: The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Committee of Kanazawa University, Approval No. 3709–1.

Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.
Conflict of Interest: None.

Table 2. Factors associated with outcomes among Japanese patients with out-of-hospital cardiac arrest

|                  | Neurologically favorable outcome | One-month survival |
|------------------|---------------------------------|--------------------|
|                  | Shockable, adjusted OR (95% CI) | Nonshockable, adjusted OR (95% CI) |
| CPR duration†    | 2.09 (1.81–2.42)                | 3.34 (2.92–3.82)   |
| Age (for one-increment of year) | 0.96 (0.95–0.96) | 0.98 (0.97–0.98)   |
| Male gender      | 1.09 (0.93–1.26)                | 1.20 (1.07–1.35)   |
| Witnessed arrest | 1.47 (1.26–1.72)                | 1.48 (1.31–1.68)   |
| DA-CPR instruction | 1.01 (0.88–1.16)        | 0.82 (0.73–0.93)   |
| Bystander CPR provision | 1.63 (1.41–1.88) | 0.86 (0.76–0.98)   |
| Prehospital defibrillation‡ | 1.52 (1.04–2.22) | 2.39 (2.04–2.81)   |
| Presumed cardiac etiology | 2.06 (1.55–2.74) | 1.72 (1.53–1.93)   |
| Advanced airway management | 0.65 (0.56–0.74) | 0.57 (0.50–0.66)   |
| Adrenaline administration | 0.31 (0.26–0.37) | 0.22 (0.18–0.26)   |
| Response time§ (for one-increment of minute) | 0.94 (0.92–0.96) | 0.97 (0.95–0.98)   |

CI, confidence interval; CPR, cardiopulmonary resuscitation; DA-CPR, dispatcher-assisted CPR; OR, odds ratio.
†Time from CPR initiation by emergency medical service (EMS) provider to prehospital return of spontaneous circulation. Binary variables using the cut-off value, calculated by the receiver operating characteristic (ROC) curve and area under the ROC curve, were used (shockable, within 10 min; nonshockable, within 8 min).
‡Defibrillation was performed by layperson or EMS providers.
§Time from emergency call to time of contact with a patient by EMS provider.

DISCLOSURE

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