The response time threshold for predicting favourable neurological outcomes in patients with bystander-witnessed out-of-hospital cardiac arrest

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Abstract:

Objective

It is well established that the period of time between a call being made to emergency medical services (EMS) and the time at which EMS arrive at the scene (i.e., the response time) affects survival outcomes in patients who experienced out-of-hospital cardiac arrest (OHCA). However, the relationship between response time and favourable neurological outcomes remains unclear. We therefore aimed to determine a response time threshold in bystander-witnessed OHCA patients that is associated with positive neurological outcomes and to assess the relationship between response time and neurological outcomes in OHCA patients.

Methods

This study was a retrospective, observational analysis of data from 204,277 episodes of bystander-witnessed OHCA between 2006 and 2012 in Japan. We used classification and regression trees (CARTs) and receiver operating characteristic (ROC) curve analysis to determine the threshold of response time associated with favourable neurological outcomes (Cerebral Performance Category 1 or 2) one month after cardiac arrest.

Results

Both CARTs and ROC analyses indicated that a threshold of 6.5 min was associated with improved neurological outcomes in all bystander-witnessed OHCA events from cardiac origin. Furthermore, bystander cardiopulmonary resuscitation (CPR) prolonged the threshold of response time by 1 min (to 7.5 min). The adjusted odds ratios for favorable neurological outcomes in OHCA patients who received care within ≤ 6.5 min was 1.935 (95% confidential interval: 1.834−2.041, P<0.001).

Conclusions

A response time ≤ 6.5 min was closely associated with favourable neurological outcomes in all bystander-witnessed OHCA patients. Bystander CPR prolonged the response time threshold by 1 min.

Introduction

Survival rates following out-of-hospital cardiac arrest (OHCA) have long been used as an indicator of the effectiveness of emergency medical services (EMS). The pre-hospital predictors of survival rates include age, bystander eyewitness, bystander-initiated cardiopulmonary resuscitation (CPR), origin of cardiac arrest, primary electrocardiography rhythm, defibrillation, and time to CPR initiation.[1-8] The period of time from when a call is made to EMS to the point when EMS arrive at the scene (i.e., the response time) is another predictor. Several reports show that shorter EMS response times improve survival rates in OHCA patients.[9-13] Current recommended response times are based on an article published in 1979 that evaluated patient outcomes after OHCA from non-traumatic causes.[14] The authors reported that survival decreased significantly if basic life support (BLS) and advanced life support (ALS) were initiated within $\geq$ 4 min and $\geq$ 8 min of the event occurring, respectively. Mullie et al.[15] suggested that EMS providers should aim for a response time of $\leq$ 8 min. Chen et al.[16] and Sladjana et al.[17] reported that respectively 5.9 min and $\leq$ 4 min were the response time threshold associated with improved survival outcomes in OHCA patients.

Recently, reports showing neurological outcomes after cardiac arrest have been increasing.[18-20] Wang et al.[18] reported female patients from in-hospital cardiac arrest had worse neurological outcomes than male. Ameloot et al.[20] reported venous congestion was associated with unfavourable neurological outcomes in post cardiac arrest patients. However, there is no reports which analyse the relationship between response time and favourable neurological outcomes.

Therefore, we aimed to test our hypotheses that a response time is a predictor of favourable neurological outcomes in bystander-witnessed OHCA patients, and that there is a response time threshold for predicting favourable neurological outcomes. To do this, we used classification and regression trees (CARTs) and receiver operating characteristic (ROC) curve analysis. Furthermore, we assessed whether bystander CPR affected the response time threshold associated with favourable neurological outcomes.

Methods

Study design

This study was a retrospective analysis of prospectively collected data from the All-Japan Utstein Registry of OHCA patients. The registry was initiated in January 2005 as a prospective nationwide population-based registry of all OHCA patients transported to the hospital by EMS staff. It is managed by the Fire and Disaster Management Agency (FDMA). As the public has access to the data contained in the registry, the Institutional Review Board of Hokkaido University Hospital for Clinical Research waived the requirement to obtain written informed consent from patients included in the database, as well as the requirement to submit a study plan.

Japanese EMS system characteristics and procedures

The Japanese EMS system has been described in previously published research.[21-23] When cardiac arrest is diagnosed, CPR is provided by the EMS personnel according to international guidelines, including immediate initiation of chest compressions and bag-valve-mask ventilation.[27] If necessary, the specially trained EMS personnel insert an advanced airway device and employ the use of an automated external defibrillator, after which they attempt to gain peripheral venous access in order to administer 1 mg of epinephrine intravenously every 3−5 min until return of spontaneous circulation (ROSC) or arrival at the hospital, and CPR is performed throughout the transfer process.

Patient selection

The patients in this study were selected from among all patients in the All-Japan Utstein Registry who had experienced OHCA before the arrival of EMS personnel, and who were subsequently treated by EMS personnel and transported to a medical institution in Japan between January 1, 2006 and December 31, 2012. We excluded the following patients; those under 18 years of age; those whose OHCA episode had been witnessed by EMS personnel; those in whom spontaneous circulation had been restored before the arrival of EMS personnel; those from whose medical records data were missing; those for whom more than 120 min had elapsed from the emergency call being made to hospital arrival, or more than 60 min had elapsed from the emergency call being made to the initiation of CPR, and/or more than 120 min had elapsed from the initiation of CPR to hospital arrival; those who had been transferred under a physician's care and/or without specially-trained EMS personnel; those whose OHCA episode was not bystander-witnessed; and/or those in whom the response time was 0 min.

Data collection

The durations of each procedure was recorded using a timekeeping device employed by each EMS system. The device records the time of receipt of the emergency call by EMS, ambulance arrival at the scene, initial contact with the patient, initiation of CPR, and arrival at the hospital. Patient data included sex, age, initial cardiac rhythm, and time course of resuscitation, as well as whether a bystander had witnessed the episode of cardiac arrest and/or initiated CPR, whether the patient had been intubated, whether epinephrine had been administered, and whether spontaneous circulation had been restored before hospital arrival at the hospital. One month after the event, the EMS staff who had initially handled each OHCA patient case collected follow-up data regarding survival and neurologic status during a meeting with the medical control director at the hospital. The physicians in charge examined each patients and determined their neurological outcomes. If these patients were transferred other hospital, physicians at the hospital examined them and determined those outcomes. If these patients were discharged from the hospital, the EMS personnel conducted follow-up serach. A favourable neurological outcome was defined as a Cerebral Performance Category (CPC) score of 1 (good performance) or 2 (moderate disability). An unfavourable neurological outcome was defined as a score of 3 (severe cerebral disability), 4 (vegetative state), or 5 (death).[25-28] In partnership with the medical control director, emergency personnel summarized the data from each OHCA case according to the standardized Utstein style. These procedures were used to integrate data−collected at approximately 800 fire stations that maintain dispatch centres in 47 prefectures−which were integrated into the national registry system on the FDMA database server.

Statistical analysis

CARTs analysis was used to classify all included patients according to the response time threshold that predicted a favourable neurological outcome. The classification tree was cross-validated 10 times. In ROC curve analysis, optimal cut-off values for the response times that predicted favourable neurological outcomes were also calculated using the Youden Index. In addition, we performed CARTs analysis and ROC curve analysis for the following subgroups: cardiac-origin OHCA patients, OHCA patients who received bystander CPR, and cardiac-origin OHCA patients who received bystander CPR. Patient characteristics and outcomes were compared using the Mann-Whitney U test (for numerical variables) and the chi-squared test (for categorical variables). The adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for outcomes were assessed using logistic regression analysis that included the independent variables of age, sex, whether or not CPR had been initiated by a bystander, primary electrocardiography rhythm, type of life support provided by EMS personnel (defibrillation, advanced airway, intravenous line, epinephrine), origin of cardiac arrest, response time, the time from arrival at the scene to CPR initiation by EMS personnel, and the time from CPR initiation by EMS personnel to hospital arrival.

The IBM SPSS Statistics package version 23.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. A P value of <0.05 was considered to be statistically significant. Unless otherwise indicated, all numerical data are expressed as the median (interquartile range).

Results

Patient selection

During the study period, 822,460 patients with OHCA were transferred to the hospital by EMS personnel. Of these, 70,993 patients were excluded as they had not experienced an actual cardiac arrest, or spontaneous circulation had been restored before EMS personnel arrival, or they were younger than 18 years. In addition, there were 87,941 patients for whom data were missing, 2,754 for whom more than 120 min had elapsed from the emergency call to hospital arrival, or for whom more than 60 min had elapsed from the emergency call to CPR initiation, and/or for whom more than 120 min had elapsed from CPR initiation to hospital arrival. We also excluded 56,177 patients who were transferred to the hospital with a physician and/or without specially-trained EMS personnel, 400,140 patients whose OHCAs were not bystander-witnessed, and 178 patients in whom the response time was 0 min. After these exclusions, 204,277 remaining patients were included in the analysis (Figure 1).

Cumulative rates for favourable neurological outcomes and bystander-witnessed OHCA events

Figure 2 shows the cumulative rates for favourable neurological outcomes (line graphs) and the cumulative number of bystander-witnessed OHCA events (bar charts) during the first 20 min of response time. In all OHCA patients (Figure 2A), the cumulative rates for favourable neurological outcomes decreased as response times increased, and plateaued after 10 min of response time. In addition, the cumulative rates for favourable neurological outcomes in patients who received bystander CPR were consistently higher than the cumulative rates for all patients. In patients with OHCA of cardiac origin (Figure 2B), the trend for the cumulative rates for favorable neurological outcomes and the cumulative number of OHCA patients were similar to the trend for all patients. Lastly, the cumulative rates for favourable neurological outcomes in patients with cardiac arrest were consistently higher than the cumulative rates for all patients.

Response time threshold

CARTs analysis for predicting a favourable neurological outcome revealed that the response time threshold for favourable neurological outcomes for all bystander-witnessed OHCA patients was 6.5 min (Figure3A). In OHCA patients who received bystander CPR, the response time threshold for favourable neurological outcomes was 7.5 min (Figure 3B). In patients with OHCA of cardiac origins, the response time threshold was the same as the threshold for all OHCA patients (Figures 3C and 3D). ROC curve analysis revealed that the same response time threshold was associated with predicting a favourable neurological outcome for each subgroup (Table 1).

Comparison of patients characteristics between early and late response groups

Table 2 shows the characteristics of all OHCA patients, and Supplementary Table 1 shows the characteristics of all OHCA patients who received bystander CPR. Those patients were divided into 2 groups according to response time threshold. There were significant differences between the groups regarding all variables except for origin of cardiac arrest.

Adjusted odds ratios for prognoses

Table 3 shows the adjusted ORs for outcomes in all OHCA patients who received care in ≤ 6.5 min adjusted for all the covariates listed in Table 2. Table 3 shows the ORs for outcomes when response time was modelled as a continuous variable. For all OHCA patients, the rates of ROSC, 1-month survival, and favourable neurological outcomes were significantly higher for patients in the ≤ 6.5 min response time group compared to patients in the >6.5 min response time group. Supplementary Table 2 shows the adjusted ORs for outcomes for OHCA patients who received bystander CPR and who received EMS care in ≤ 6.5 min adjusted for all covariates listed in Supplementary Table 1. In OHCA patients who received bystander CPR, the rates for ROSC, 1-month survival, and favourable neurological outcomes were significantly higher for patients in the ≤ 7.5 min response time group compared to patients in the >7.5 min response time group. Tables 3 and Supplementary Table 2 also show the ORs for outcomes when response time was modelled as a continuous variable.

Discussion

This study used CARTs and ROC curve analysis to determine the response time threshold that associated with favourable neurological outcomes in patients with bystander-witnessed OHCA. Our results indicated that a response time threshold of 6.5 min was closely associated with favourable neurological outcomes in this patients group. Furthermore, our study showed that bystander CPR increased the response time threshold by 1 min.

To the best of our knowledge, the present report is the first assessing the relationship between EMS response times and neurological outcomes among OHCA patients. Although several reports have shown that response time affects survival in OHCA patients, these reports did not describe neurological outcomes, nor did they explain their rationale for using a particular threshold.[9-13] Further, most of these reports were based on research by Eisenberg et al.[14] who reported a response time threshold of 4 min. Eisenberg et al. stratified OHCA patients into blocks of 2-min response times and then assessed the relationship between response time and survival. They noted that survival rates definitely decreased when the response time increased from 4−6min. We theorize that the response time threshold associated with favourable neurological outcomes was longer in our study (6.5 min) compared to the response time threshold associated with increased survival rates reports in past studies (4 min) as a result of improved knowledge of basic life support among the general public as well as improvements in EMS prehospital treatment.

Some reports suggest that bystander CPR is associated with improved survival and neurological outcomes in OHCA patients; however, these reports do not address the relationship between bystander CPR and response time.[29, 30] The present study is the first report that specifically demonstrates that bystander CPR may prolong the response time threshold associated with favourable neurological outcomes in OHCA patients. These results may be useful during the development and execution of bystander CPR education programs, and may help non-healthcare providers understand the importance of providing CPR.

We originally hypothesized that the response time threshold for patients with OHCA from cardiac origins would be longer compared to the threshold for patients with OHCA from all causes. However, our study demonstrated that response time threshold was the same for patients with both OHCA from cardiac cause as well as OHCA from non-cardiac causes. This may be due to the fact that the number of patients with favourable neurological outcomes after OHCA from non-cardiac origins in not high. In the present study, the number of patients with favourable outcomes after OHCA from non-cardiac origins was 1,165; conversely, the number of patients with favourable neurological outcomes after OHCA from all causes was 7,100. As a result, the small number patients with favourable neurological outcomes after OHCA from non-cardiac causes might not affect the response time threshold for all patients. In fact, when CARTs analysis was used to classify patients with OHCA from non-cardiac origins according to the response time threshold associated with favourable neurological outcomes, a response time threshold was not detected.

Conclusion

In this study, we found that an EMS response time of ≤6.5 min was closely associated with favourable neurological outcomes for all bystander-witnessed OHCA patients. In addition, bystander CPR extended the response time threshold by 1 min. However, our study has several limitations. First, this was a retrospective study. However, it would not be possible to study this subject prospectively. Second, we were unable to analyse the effect of in-hospital procedures, or how post-arrest hypothermia or percutaneous coronary interventions may have affected patient prognosis. Despite these limitations, our results have significant implications for EMS, emergency care, and cardiac care practitioners.

Conflicts of Interest

None to declare

Acknowledgments

None to declare

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Figure Legends

Figure 1. Study participant selection

OHCA, out-of-hospital cardiac arrest; EMS, emergency medical services; CPR, cardiopulmonary resuscitation

Figure 2. Cumulative rates for favourable neurological outcomes and number of bystander-witnessed OHCA patients

The left vertical line and line graph represent the cumulative favourable neurological outcome rates and the right vertical line and bar chart represent the cumulative number of bystander-witnessed OHCA patients. The horizontal line represents the response time. Figure A shows all bystander-witnessed OHCA patients and Figure B shows bystander-witnessed OHCA patients with cardiac origin during the first 20 min of response time.

OHCA, out-of-hospital cardiac arrest

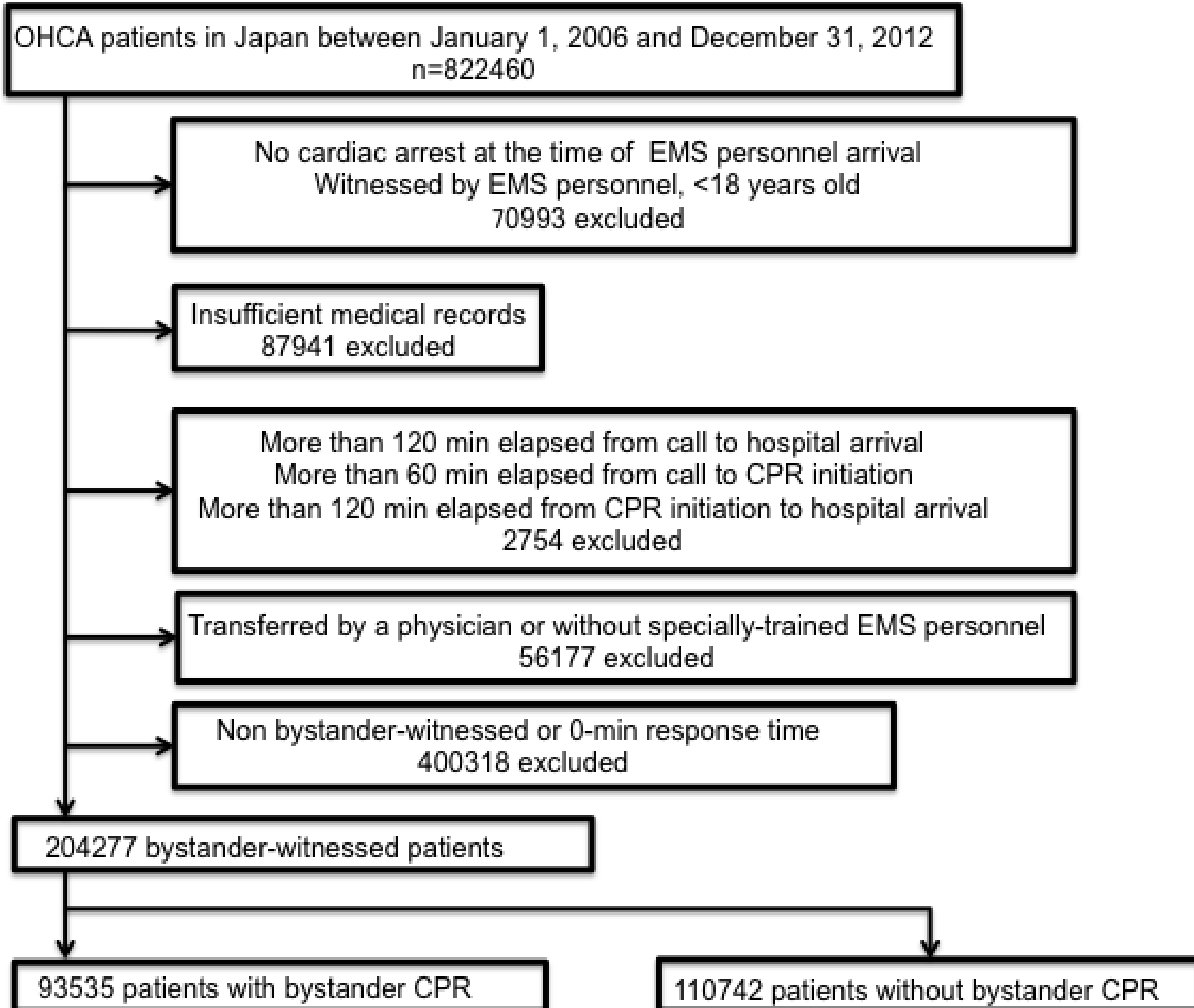
Figure 3. Stratification of bystander-witnessed OHCA according to response time

using CARTs analysis

Figures A and B show the CARTs analyses for all bystander-witnessed OHCA patients and Figures C and D show the analyses for bystander-witnessed OHCA patients with OHCA of cardiac origin. The response time threshold for positive neurological outcomes was 6.5 min in bystander-witnessed OHCA patients with or without bystander CPR and 7.5 min in those who received bystander CPR. Figures C and D show bystander-witnessed OHCA patients with cardiac origin. The response time threshold in these patients was the same compared to the response time threshold for all bystander-witnessed OHCA patients.

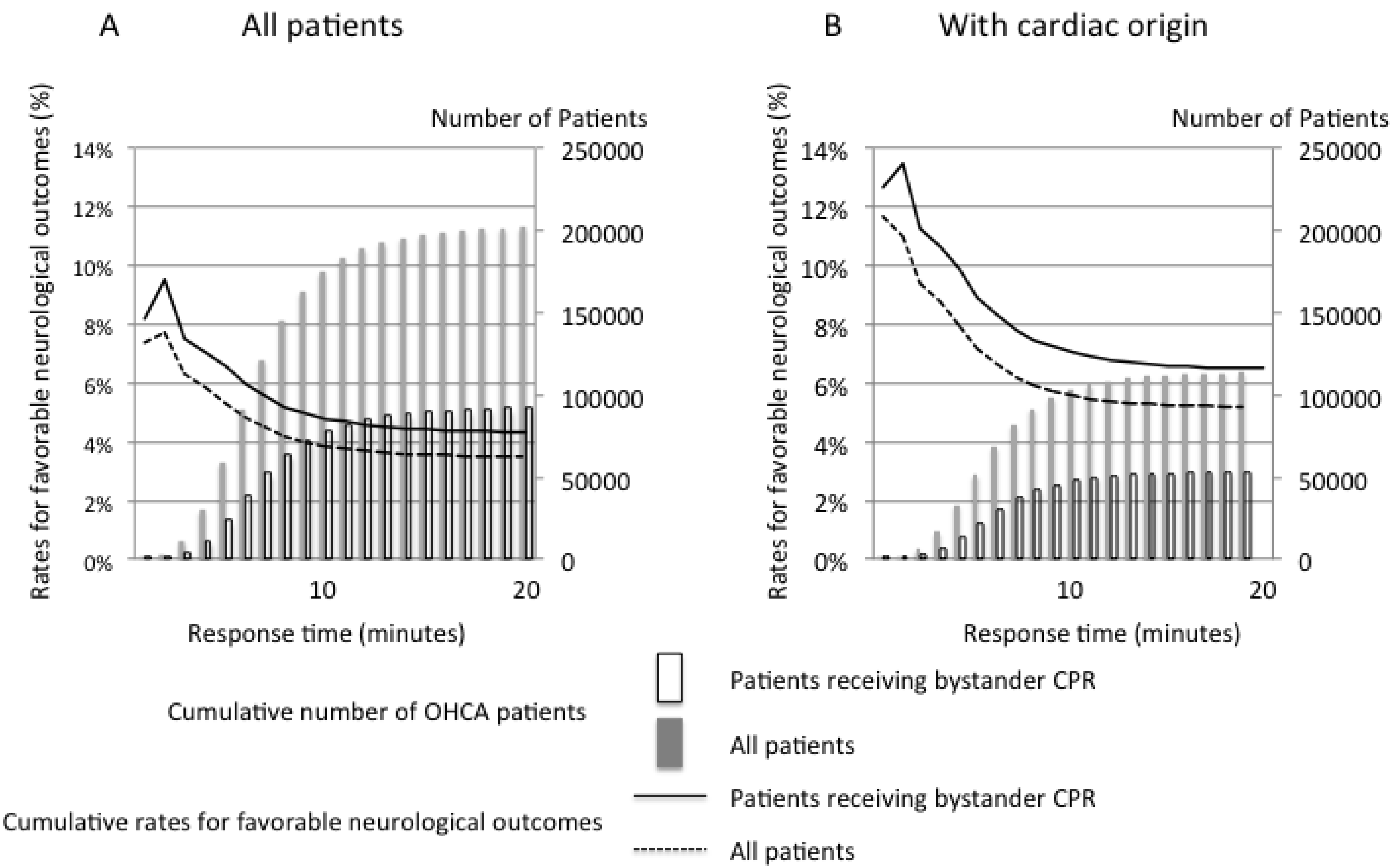
OHCA, out-of-hospital cardiac arrest; CPR, cardiopulmonary resuscitation; CARTs, classification and regression trees

Figure 1



OHCA patients in Japan between January 1, 2006 and December 31, 2012
n=822460
No cardiac arrest at the time of EMS personnel arrival
Witnessed by EMS personnel, <18 years old
70993 excluded
Insufficient medical records
87941 excluded
More than 120 min elapsed from call to hospital arrival
More than 60 min elapsed from call to CPR initiation
More than 120 min elapsed from CPR initiation to hospital arrival
2754 excluded
Transferred by a physician or without specially-trained EMS personnel
56177 excluded
Non bystander-witnessed or 0-min response time
400318 excluded
204277 bystander-witnessed patients
93535 patients with bystander CPR
110742 patients without bystander CPR

Figure 2



A
All patients
Rates for favorable neurological outcomes (%)
Number of Patients
14%
12%
10%
8%
6%
4%
2%
0%
250000
200000
150000
100000
50000
0
10
20
Response time (minutes)
B
With cardiac origin
Rates for favorable neurological outcomes (%)
Number of Patients
14%
12%
10%
8%
6%
4%
2%
0%
250000
200000
150000
100000
50000
0
10
20
Response time (minutes)
Cumulative number of OHCA patients
Patients receiving bystander CPR
All patients
Cumulative rates for favorable neurological outcomes
Patients receiving bystander CPR
All patients

Figure 3

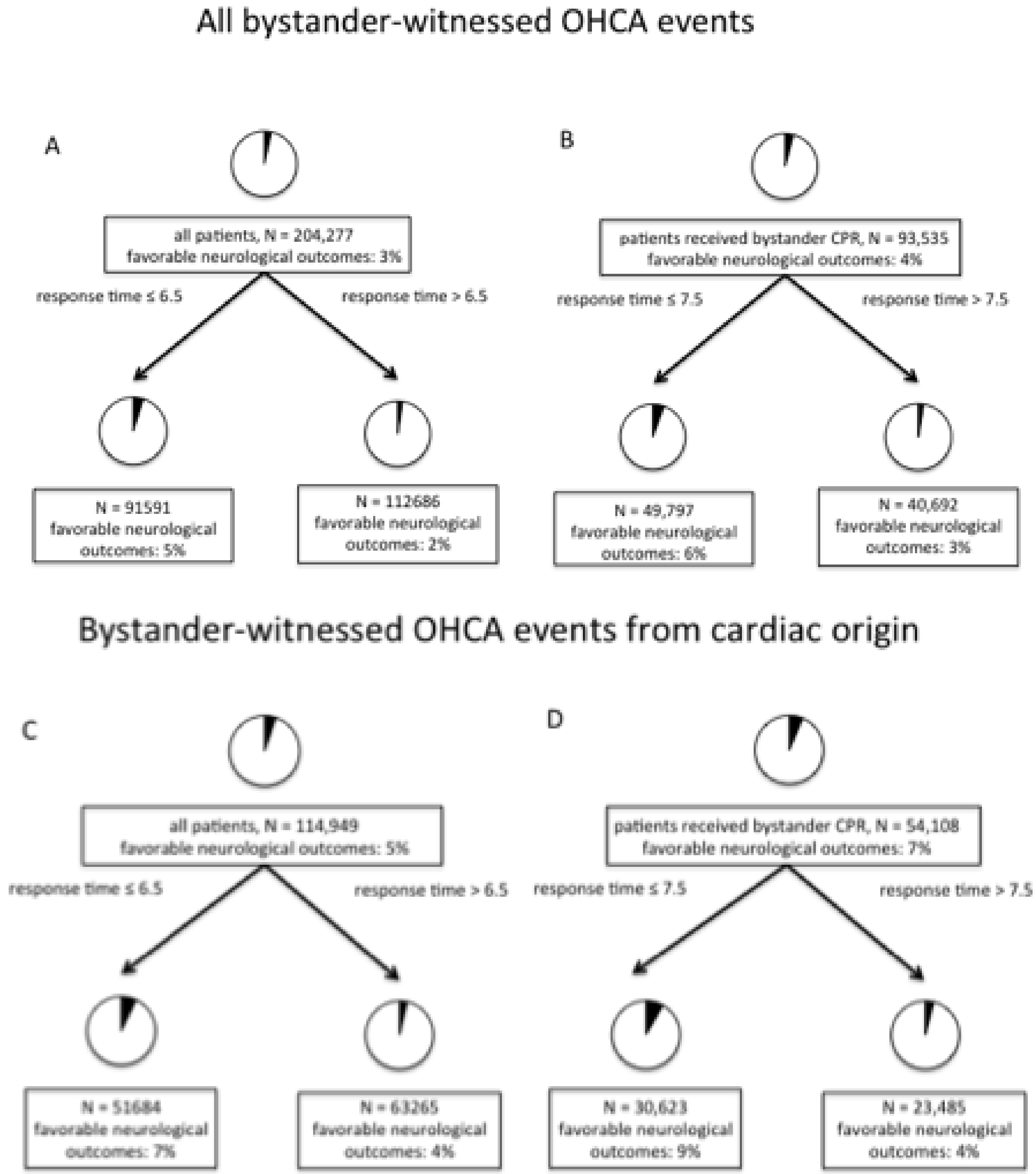

All bystander-witnessed OHCA events
A
all patients, N = 204,277
favorable neurological outcomes: 3%
response time ≤ 6.5
response time > 6.5
N = 91591
favorable neurological outcomes: 5%
N = 112686
favorable neurological outcomes: 2%
B
patients received bystander CPR, N = 93,535
favorable neurological outcomes: 4%
response time ≤ 7.5
response time > 7.5
N = 49,797
favorable neurological outcomes: 6%
N = 40,692
favorable neurological outcomes: 3%
Bystander-witnessed OHCA events from cardiac origin
C
all patients, N = 114,949
favorable neurological outcomes: 5%
response time ≤ 6.5
response time > 6.5
N = 51684
favorable neurological outcomes: 7%
N = 63265
favorable neurological outcomes: 4%
D
patients received bystander CPR, N = 54,108
favorable neurological outcomes: 7%
response time ≤ 7.5
response time > 7.5
N = 30,623
favorable neurological outcomes: 9%
N = 23,485
favorable neurological outcomes: 4%

Table 1. Receiver operating characteristics (ROC) curve analysis of response time

	AUC	95% Confidence Interval			Response Time
		Lower	Upper	P-value	Cut-Off Value
All patients with bystander-witnessed OHCA	0.628	0.622	0.634	<0.001	6.5
Patients who received bystander CPR	0.622	0.614	0.613	<0.001	7.5
Patients with bystander-witnessed OHCA of cardiac origin	0.629	0.622	0.636	<0.001	6.5
Patients who received bystander CPR	0.624	0.615	0.633	<0.001	7.5

AUC, area under curve; OHCA, out-of-hospital cardiac arrest; CPR, cardiopulmonary resuscitation.

Table 2. Characteristics of all bystander-witnessed OHCA patients according to response time

Response Time	≤ 6.5 minutes n = 91591	> 6.5 minutes n = 112686	
Age, years	78 (66−86)	78 (66−86)	<0.001
Male sex	54699 (59.7)	67889 (60.2)	0.016
CPR initiated by bystander	38867 (42.4)	54668 (48.5)	<0.001
Origin of cardiac arrest			
Cardiac	51684 (56.4)	63265 (56.1)	0.194
Non-cardiac	39907 (43.6)	49421 (43.9)	
Primary ECG rhythm			
VF/VT	14540 (15.9)	13905 (12.3)	<0.001
PEA/Asystole	77051 (84.1)	98781 (87.7)	
Life support by EMS personnel			
Defibrillation	17632 (19.3)	18329 (16.3)	<0.001
Advanced airway management	43156 (47.2)	56814 (50.5)	<0.001
Intravenous line inserted	27175 (29.8)	37776 (33.6)	<0.001
Epinephrine administered	12157 (13.4)	18715 (16.7)	<0.001
Time, minutes			
Time from arrival at the scene to CPR initiation	1 (1−2)	1 (1−2)	<0.001
Time from CPR initiation to arrival at the hospital	21 (16-27)	23 (18-29)	<0.001
Outcome			
ROSC	11608 (12.7)	10274 (9.1)	<0.001
1 month survival	9064 (9.9)	6516 (5.8)	<0.001
CPC 1 or 2	4466 (4.9)	2634 (2.3)	<0.001

Data are expressed as a number (%) or median (interquartile range)

OHCA, out-of-hospital cardiac arrsst; CPR, cardiopulmonary resuscitation; ECG, electrocardiography; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; EMS, emergency medical services; AED, automated external defibrillator; ROSC, return of spontaneous circulation; CPC, Cerebral Performance Category.

Table 3. Adjusted[1] odds ratios for outcomes in all bystander-witnessed OHCA patients

Response Time	**≤ 6.5 min**	**Per Min Shorter**
ROSC		
aOR	1.519	1.088
95% CI	1.475-1.565	1.082-1.094
P-value	<0.001	<0.001
1 month survival		
aOR	1.652	1.123
95% CI	1.595-1.712	1.115-1.130
P-value	<0.001	<0.001
CPC 1or 2		
aOR	1.935	1.164
95% CI	1.834-2.041	1.151-1.176
P-value	<0.001	<0.001

[1] Adjusted for age, sex, bystander-initiated CPR, origin of cardiac arrest, primary electrocardiography rhythm, life support methods provided by EMS personnel, response time, the time from arrival at the scene to CPR initiation by EMS personnel, the time from CPR initiation by EMS personnel to hospital.

OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; CPR, cardiopulmonary resuscitation; aOR, adjusted odds ratio; CI, confidence interval; CPC, Cerebral Performance Category; EMS, emergency medical services.