

**Association between resuscitation time interval at the scene and neurological outcome after out-of-hospital cardiac arrest in two Asian cities**

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## ABSTRACT

*Background:* It is unclear whether the scene time interval (STI) for cardiopulmonary resuscitation (CPR) is associated with outcomes of out-of-hospital cardiac arrest (OHCA) or not.

*Methods:* A retrospective analysis based on two large population-based cohorts was performed for witnessed adult OHCA with presumed cardiac etiology from Seoul (2008-2010) and Osaka (2007-2009). The STI defined as time from wheel arrival at the scene to departure to hospital was categorized by short (less than 8 minutes), intermediate (8 to less than 16 minute), and long (16 min or longer) STI on the basis of sensitivity analysis. Primary outcome was good neurological outcome (cerebral performance category 1 or 2). Adjusted odds ratios (AORs) with 95% confidence intervals (CIs) were calculated to determine the association between STIs and outcomes comparing with the short STI group adjusting for potential risk factors and interaction products.

*Results:* Total 7,757 patients; 3,594 from Seoul and 4,163 from Osaka were finally analyzed. There were significant differences among STI groups for most potential risk variables. Survival to admission was higher in the intermediate STI group (35.7%) than in the short (31.8%) or long STI group (32.6%), respectively ( $p=0.004$ ). Survival to discharge was not different among groups (13.7%, 13.1%, 11.5%), respectively ( $p=0.094$ ). The intermediate STI

group had a significantly better neurological outcome compared with the short STI group (7.7% vs. 4.6%; AOR, 1.32; 95% CI, 1.03-1.71), while the long STI (6.6%) did not.

*Conclusion:* Data from two metropolitan cities demonstrated a positive association between intermediate STI from 8 to 16 minutes and good neurological outcome after OHCA.

## 1. Introduction

Out-of-hospital cardiac arrest (OHCA) is a major public health problem around the world.<sup>1</sup> Emergency medical service (EMS) factors have been known to be one of the major determinants for outcomes after OHCA as well as bystander performance and hospital post-resuscitation care.<sup>2-5</sup> Among EMS factors, response time interval (RTI) from call to arrival at the scene is known to be associated with outcomes, whereas the effect of scene time interval (STI) for cardiopulmonary resuscitation (CPR), from ambulance arrival at the scene to departure to hospital, is unclear.

Although some EMS systems like Osaka allow longer STI than others, in many Asian countries including Korea and Japan, EMS protocols do not basically allow them to stop CPR at the scene unless there is a return of spontaneous circulation (ROSC) and require scoop and run to the hospital emergency department (ED) while giving CPR during transport (Scoop and Run model).<sup>6-9</sup> In addition, advanced life support (ALS) procedures provided by EMS personnel on the scene are very limited. These protocols are very different from those in North America, Europe, and Australia, where EMS providers continue to perform CPR until getting the ROSC or stopping CPR for death declaration on the scene (Stay and Treat model).<sup>10,11</sup> The 2010 American Heart Association guideline has no comments regarding how long the EMS personnel stay at the scene to provide CPR or how many CPR cycles

are essential for scene CPR.<sup>10,11</sup>

We hypothesized that the STI staying at the scene to provide CPR is a key determinant for outcomes in OHCA in EMS systems because it is a very important treatment time interval after cardiac arrests. During this period, EMS personnel would provide various treatments at the scene including CPR, defibrillation, airway management, and fluid resuscitation.<sup>12</sup> The longer STI for CPR has a benefit of providing a likelihood of more stable and higher-quality CPR, while the shorter STI has a benefit of faster, more comprehensive and earlier advance care in ED. In contrast, there would be a disadvantage of delayed advance care by ED in the longer STI protocol, but more unstable CPR during ambulance transport in the shorter STI system. By comparing the outcomes according to STI for CPR, we can develop a more effective scene protocol for the EMS system. The present study aimed to determine the association between STI and neurological outcome after OHCA using two large population-based cohorts covering two metropolitan cities in Asia.

## **2. Methods**

### *2.1. Study method and materials*

The Seoul-Osaka Resuscitation Study (SORS) group is a volunteer-based collaborating study group between two communities' research scientists in Seoul Korea and Osaka Japan,

respectively. The study was approved by the institutional review boards of the study hospitals(Seoul National University and Osaka University).

## 2.2. Study setting

This study was done in two metropolitan cities, Seoul in Korea and Osaka in Japan. The population size was 9.9 million in Seoul (2009) and 8.8 million in Osaka (2010). Population density was 16,356 per km<sup>2</sup> in Seoul and 4,642 per km<sup>2</sup> in Osaka.

The EMS level is intermediate in both areas where the highest-qualified emergency medical technicians can give CPR with automatic external defibrillation (AED), perform advanced airway management, and insert intravenous fluid. EMS providers should not stop CPR unless there is a ROSC on the scene. In Seoul, EMTs are encouraged to “scoop and run” to a hospital emergency department while giving CPR during ambulance transport as soon as possible after giving one cycle of CPR followed by automatic external defibrillation. More than one cycle of CPR and rhythm analysis with/without shock at the scene, intravenous fluid resuscitation, advanced airway management, and drug infusion are not obligatory but optional in this system. EMS providers can choose their option according to families’ attitude, patient’s condition, self-confidence level for procedures, and expected transport time to ED. They give continuous CPR during ambulance transport.<sup>13</sup> In Osaka, EMTs are usually encouraged to stay around 10 minutes for interventions including three to four cycles of CPR with rhythm analysis



every 2 minutes, intravenous fluid resuscitation, advanced airway management, and drug infusion.<sup>14</sup> The emergency life-saving technician (ELST) systems in Osaka were started in 1991; specially-trained ELSTs began to use endotracheal intubation in July 2004, and administered adrenaline since July 2006, while the first-degree EMTs in Seoul can opt for the airway management from among Bag-Valve-Mask ventilation, supraglottic airway, and endotracheal intubation according to their preference. A system quality program was initiated in 1998 in the Osaka through Osaka Utstein Project, while the quality control was rare in Seoul until 2011.<sup>5,8,13-16</sup>

The number of ambulance crew per ambulance is three in both areas; first-degree EMT (intermediate EMT), second-degree EMT (basic EMT), and driver (first responder level) in Seoul, and three EMSs with at least one ELST (intermediate EMT) in Osaka. The first-degree EMTs in Seoul are usually graduates of EMT colleges with three- to four-year courses. In Osaka, there are two processes to qualify as an ELST.<sup>14</sup> The first is through the specialized education system in the fire department. The second way is through the education system in the EMT school and college.

There are 114 ambulance units available for service coverage of 24-hour/ 365 days in Seoul (2010) and 212 ambulance units in Osaka (2009). Hospital EDs for OHCA are categorized into four levels in Seoul including one regional ED (level 1) and 27 local EDs

(level 2). Level 1 and 2 EDs are covered by emergency physicians for 24/365 services and received approximately 80% of OHCA. In Osaka, there are 13 critical care medical centers (level 1) and 258 emergency centers (level 2). Level 1 ED can be used for very high criticality such as OHCA, severe trauma, and respiratory failure, and has received approximately 20% of OHCA, every year while level 2 EDs are used for moderate emergency conditions. The classification of ED levels differ by areas. The level 1 and some of level 2 hospitals in both cities usually provide therapeutic hypothermia and cardiac interventions (percutaneous coronary intervention and coronary bypass surgery).

### *2.3. Study population*

Study population was EMS-treated and bystander-witnessed adult (18 years and older) OHCA with presumed cardiac etiology. The study period was from Jan. 2008 to Dec. 2010 for Seoul and from Jan. 2007 to Dec. 2009 for Osaka. OHCA with non-cardiac etiology, not treated cases, and patients less than 18 years were excluded.

### *2.4. Data sources*

Data were collected from the EMS run sheet in Osaka and from the EMS run sheet and hospital medical record review in Seoul. Utstein factors including age, sex, location (public or private), and bystander CPR (yes or no), prehospital defibrillation, and primary ECG (ventricular fibrillation / tachycardia or not) were collected. Both data used the same

definition according to the Utstein data report form. In Osaka, first documented ECG was examined at the scene, while that in Seoul was examined for some patients at the scene and for most patients at the ED. Public access defibrillation was performed for several cases in Osaka while there was no case in Seoul because the PAD program started in 2010 in that city. Dataset details were reported in previous studies.<sup>5,8,13-16</sup>

The elapsed time intervals such as response time interval (RTI) from call to wheel arrival at scene, scene time interval (STI) from wheel arrival to departure to ED, and transportation time interval (TTI) from departure at the scene to arrival at ED were standardized and measured in both areas.

## *2.5. Outcome measure*

Primary outcome was good neurological outcome at hospital discharge (Seoul) and at one month after event (Osaka), which was defined as cerebral performance category 1 or 2. The secondary outcome was survival to discharge (Seoul) or one month survival (Osaka), and survival to admission.

Outcomes were collected by EMS providers one month after transporting patients to EDs in Osaka via telephone or fax contact to hospital. In Seoul, hospital medical record review was performed after hospital discharge. Medical record review was done by medical record experts employed at Korean Centers for Disease Controls and Prevention. Information on

neurological outcome was unavailable for six patients (0.2%) in Seoul and five cases (0.1%) in Osaka.

## *2.6. Main exposure variables*

We categorized the STI according to the sensitivity analysis. Restrictive cubic spline logistic analysis with five nodes was used to determine the cut-off value for categorizing STI subgroups. The analysis used two variables (scene time intervals and good neurological outcome) and unadjusted odds ratios (ORs) with 95% confidence intervals (95% CIs) of STI group to calculate according to STIs (unit= one min.) on the outcome. We decided STIs responding to the mean probability of survival as the two cut-off values in the curve. The STI was categorized with short STI, intermediate STI, and long STI using two cut-values.

## *2.7. Statistical analysis*

Demographic findings were described according to the two communities. Potential risk factors and outcomes were compared by STI groups. Continuous variables are described by mean with standard deviation or median with the interquartile range. Categorical variables are measured by number and percent. Descriptive analysis used the Student *t*-test for continuous variables and chi-square test for categorical variables. ANOVA test was used for the comparison among three STI groups.

Adjusted odds ratios and 95% confidence intervals on outcomes were calculated for each

STI group (reference=short STI) using multivariable logistic regression models. Potential risk factors were age, sex, RTI, TTI, place, bystander CPR, primary ECG, and prehospital defibrillation by layperson or EMS providers. These factors have been known to be associated with outcomes in many previous studies. Study city (Seoul and Osaka) would also be a potential risk although we adjusted for many relevant variables in the model. First, we tested interactions between STI and city on the outcomes because the two cities significantly showed the different STI distribution. After testing for interactions, the city level was also incorporated into the final model because there was no significant interaction.

We assessed the interaction between main exposure (STI) and other potential risk factors for main outcome using the chunk test and followed by backward elimination process for full model which included main exposure, potential risks, and all potential interaction products. We dropped out the interaction products according to the order of size of  $p$ -value  $> 0.01$  using the analysis of maximum likelihood estimates in the model. The interaction term with the biggest  $p$ -value was removed from the model and also assessed the remaining interaction terms. This backward elimination process was repeated to get final model where all potential confounders and significant interactions remained. If there was any significant interaction with  $p$ -value  $< 0.01$  between main exposure and other potential risks, we calculate adjusted ORs and 95% confidence intervals to estimate the summation of effect of the STI

plus effect modifiers on outcomes in each subgroup.

### 3. Results

Total 3,594 patients were enrolled from Seoul among 10,122 from 2008 to 2010 excluding EMS-not treated ( $n=1,511$ ), less than 18 years ( $n=232$ ), unwitnessed( $n=4,279$ ), and non-cardiac etiology ( $n=506$ ). A total of 4,163 patients among 21,032 patients from 2007 to 2009 in Osaka were included, excluding no-treated EMS ( $n=1,645$ ), less than 18 years old ( $n=335$ ), not bystander-witnessed ( $n=12,455$ ), and non-cardiac etiology ( $n=2,434$ ) (Fig.1).Of these, the proportion of female, elderly older than 70 years, public sites, bystander CPR performed, bystander and EMS defibrillation, ventricular fibrillation/tachycardia was significantly higher in Osaka than Seoul. Pre-hospitalROSC, survival to admission and survival to discharge (or one-month survival), and good neurological outcome weresignificantly better in Osaka than Seoul (Table 1).

We found the three peaks in the probability of survival in the restricted cubic spline curve; the first peak wasdownward around 5 min between 0 to 7 min, when the portion of intact neurological outcome was the lowest, the second upward around 12min between 8 to 15 min, when intact neurological outcome was highest, and the third downward around 18 min,in the interval of more than 16 min, when the outcomes were poor again. We selected two cut-off

values for categorizing the STI using 8 min and 16 min, respectively, responding to average value of good neurological outcome (6.4%) (Fig. 2). The STI was categorized with three groups; short STI for 0 to 7 min, intermediate STI for 8 to 15 min, long STI for 16 min, and longer.

There were significant differences among STI groups for city, gender, age group, place of arrest, bystander CPR, bystander defibrillation, defibrillation by EMS provider, primary ECG rhythms, RTI, but not TTI (Table 2). Survival to admission or to discharge and good neurological outcome was highest in the intermediate STI group (35.7%, 13.7%, 7.7%) compared to the short (31.8%, 13.1%, 4.6%) or the long STI group (32.6%, 11.5%, 6.6%), respectively (Table 3). The proportion of good neurological outcome in Seoul was the highest in the intermediate STI group (3.6%) while that in Osaka in the short STI group (11.4%). The proportion of prehospital ROSC in Seoul was the highest in intermediate STI group (4.2%) while that in Osaka in long STI group (17.6%). The outcomes by the STI groups were significantly different by city level. There was no significant interaction ( $p < 0.01$ ) between city level and STI group for prehospital ROSC ( $p = 0.711$ ), survival to admission ( $p = 0.724$ ), survival to discharge ( $p = 0.046$ ), and good neurological outcome ( $p = 0.265$ ).

In the final model (Table 4), intermediate STI was significantly associated with good neurological outcome (AOR=1.32, 95% CI: 1.03-1.71), while long STI was not (AOR=0.92,

95% CI;0.68-1.26), compared with short STI. Survival to discharge was significantly lower in long STI than in short STI (AOR=0.64, 95% CI;0.52-0.80), but not different in intermediate STI (AOR=0.88, 95% CI=0.74-1.05). Prehospital ROSC was significantly greater both in the intermediate STI group (AOR=2.78, 95% CI;2.18-3.54) and long STI group (AOR=4.23, 95% CI;3.26-5.49) compared to the short STI group. Survival to admission was not significantly associated with the STI groups.

Table 5 shows the summation of effect of STI and interactive effect modifiers on outcomes. Among OHCA patients who did not receive the bystander defibrillation, the adjusted ORs with 95% CIs for good neurological outcome was significantly higher in the intermediate STI group (AOR 1.40, 95% CI=1.08-1.82), but not different in long STI (AOR 1.01, 95% CI=0.74-1.39). However, either intermediate or long STI group was associated with worse neurological outcome among patients who received bystander defibrillation; AOR 0.20, 95% CI (0.05-0.92) in intermediate STI and AOR 0.09, 95% CI (0.02-0.44) in long STI group. Both intermediate and long STI were significantly associated with higher prehospital ROSC among patients who did not receive bystander defibrillation; AOR 2.94, 95% CI (2.29-3.78) in intermediate STI, AOR 4.58, 95% CI (3.50-5.98) in long STI group, respectively. The prehospital ROSC was significantly lower in the long STI group (AOR 0.24, 95% CI 0.06-0.98), but not in the intermediate



mediate STI group (AOR 0.33, 95% CI 0.09-1.21) among patients who received bystander defibrillation. There was no effect modifier on survival to discharge and to admission.

#### 4. Discussion

By use of data from two large population-based registries of OHCA in metropolitan cities, we successfully demonstrated the benefit of EMS activities during intermediate STI from 8 to 16 min for improving neurological outcome after OHCA.

In Osaka, the OHCA registry was started in 1998 based on the international guideline for reporting outcomes after OHCA (Utstein Osaka Project).<sup>14,15</sup> In Seoul, a similar OHCA registry was started in 2006,<sup>13,16</sup> and both registries remain on-going. Recently, in Asia, the attempt to develop an international registry of OHCA based on the Utstein style across countries is proceeding.<sup>17</sup> This international collaboration makes it possible to gather the large number of standardized data from two large areas such as this with different EMS systems, in order to evaluate these important issues.

These data suggest that EMS personnel should perform CPR on the scene at least 8 to 16 minutes before transport to the ED even in the intermediate EMS level where the ALS measurements are limited. The best STI should depend on many factors including EMS levels, the ALS measures the EMS personnel can provide, hospital levels, and EMS response times.

There are many differences in the EMS systems between Osaka and Seoul. Less than 10% of Seoul EMS providers inserted advanced airways, whereas Osaka providers usually selected more than 70% for advanced airways. This discrepancy would arise from the different CPR protocols employed in each area. Seoul EMS encourages EMS providers to give CPR with/without shock delivery if indicated and to run as soon as possible, while Osaka EMSs encourage providers to run after providing ALS measures including airway, fluid resuscitation, and CPR with/without shock delivery. As a result, Seoul showed very short STI (mean 6.8, standard deviation 4.2 min) while Osaka had a longer STI (mean 14.5, standard deviation 6.5 min). The longer STI in Osaka might be one of the reasons for the better outcome of Osaka than Seoul observed in this study. Improving neurological outcome in the intermediate STI group shown in this study covering two different areas suggests that this result shows the importance of EMS activities on the scene during early phase of cardiac arrest is robust across different EMS systems.

We assume that the lower quality of CPR during ambulance transport might be one of the possible explanations for the poorest outcome in the short STI group. It is well known that the quality of CPR is the key to improve outcomes after cardiac arrests.<sup>18,19</sup> CPR during ambulance transport is difficult and tended to show incorrect hand position, insufficient depth, and was interrupted.<sup>18-20</sup> Short STI and low-quality CPR during ambulance transport would

result in lower chance of ROSC in the early phase of cardiac arrest and worse neurologic outcome. Longer stay gives a chance to perform higher quality CPR and critical procedures during the very critical time window compared to earlier departure for ED.

In intermediate service level EMS, hospital level performance is strongly associated with survival.<sup>21,22</sup> Earlier intervention of advance life support measures would be beneficial in those who do not respond to treatments by EMS providers. In this study, we found the positive association between longer STI and prehospital ROSC as well as good neurological outcome. Longer CPR at the scene would be beneficial for achieving ROSC at the scene as well as final better neurological outcome. Although hospital care options were not adjusted in this study, a significant association between longer STI and ROSC before hospital arrival supports the idea that the longer stay and giving CPR are very important determinants in the EMS “Scoop and Run model.”

We found that bystander defibrillation was a strong effect modifier of STI on good neurological outcome and prehospital ROSC. If the patient did not receive bystander defibrillation, intermediate STI was associated with good neurological outcome while both the intermediate and long STI groups were associated with worse outcome among patients who received bystander defibrillation. These findings would be supported by the three phase model of CPR (1. electrical phase, from the time of cardiac arrest to approximately 4 minutes

following the arrest; 2. circulatory phase, from approximately 4 to 10 minutes after cardiac arrest; 3. metabolic phase, extending beyond approximately 10 minutes after cardiac arrest).<sup>23</sup>

When OHCA patient does not receive any defibrillation by bystanders, the intermediate STI which means longer CPR time by the EMS personnel at the scene would have benefit because the patient is not under the electrical phase. On the other hand, among patients who has shosckable rhythm and consequently receive the bystander defibrillation in the early electrical phase, the benefit of longer STI would be disappeared. These findings can be considered for developing CPR protocol in scoop and run EMS model.

Different from our “Scoop and Run” model, which has been argued as better for safety as well as quality of CPR<sup>24,25</sup> and widely introduced in many Asian countries, most systems in North America and European EMS allow EMS providers to go on CPR until archiving ROSC or CPR termination under medical oversight unless there is a response. The best timing for stopping CPR on the scene and starting transport to the ED should be different in a “Stayand Treat Model” where EMS providers can provide more ALS measures. However, there still should be additional advanced treatments that can only be provided after hospital arrival; moreover, some studies showed the effectiveness of these treatments.<sup>26,27</sup> In addition, recently, a large observational study of in-hospital cardiac arrest reported that the duration of resuscitation attempts varied between hospitals and suggested that the timing of termination

of resuscitation might be too short and that efforts to systematically increase the duration of resuscitation could improve survival after cardiac arrests.<sup>28</sup> The appropriate STI should be also discussed in this type of EMS system.

Although we found STI effective for good neurological outcome after OHCA in this study, the appropriate CPR protocol during this phase is unclear. Theoretically, the short STI from 0 to 7 min would give a chance for four cycles of CPR and rhythm analysis, and median STI from 8 to 15 min would give four more cycles of CPR and rhythm analysis based on the current CPR guideline.<sup>10</sup> STI of 8 to 16 min is not too short to allow EMS resuscitation including CPR, shocks, and some advanced treatments at the scene for OHCA victims. In Arizona, more simplified and compression highlighted CPR protocol was encouraged for EMS providers to provide continuous high-quality CPR at least 8 min without any procedures to interrupt the CPR continuity, and its effectiveness was reported.<sup>29,30</sup> A CPR protocol for EMS providers to provide high-quality CPR during resuscitation on the scene should also be established.

This study has some limitations. First, it is not a randomized controlled trial on the effects of scene time intervals on OHCA outcomes. Although we adjusted for potential risk confounders, it was limited. The second limitation derives from the study setting. This study was conducted at an intermediate service level at which EMS providers should run to ED

while giving CPR during ambulance transport unless there is any ROSC. The study results have limitation to be generalized. The third drawback is that we did not directly measure the treatment options during the scene stay. We just regarded the scene time interval as a treatment time including giving CPR, airway management, shock delivery, and intravenous fluid resuscitation. However, the scene time also include the time usage for failed intubation and reattempts, technical errors, not to mention the time searching for the patient. Therefore, the scene time interval does not always mean actual treatment time at the scene. Fourth, we did not measure the CPR quality directly, for example, compression depth, CPR fraction, CPR interruption for any procedure. These items are really of crucial importance to improve the outcomes of OHCA. A final limitation should be pointed out. Post-resuscitation care procedures including therapeutic hypothermia and cardiac intervention have been proved very critical interventions for survived patients after OHCA for good neurologic outcome as well as survival to discharge.<sup>31</sup> The two cities had very different hospital care systems. Seoul had one level-1 and 27 level-2 EDs and Osaka had 13 level-1 critical care centers. However, service level, capacity, procedure, and protocol in two cities were neither standardized and nor measured in this study. Therefore, we could not adjust for the hospital level, capacity, and post-resuscitation care procedures. These incomplete adjustments might cause bias for study results.

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## 398 **5. Conclusion**

399 Based on a large population-based cohort covering two metropolitan cities, we found  
400 a positive association between intermediate STI from 8 to 16 minutes and good neurological  
401 outcome after OHCA. A better EMS resuscitation protocol should be developed considering  
402 this important resuscitation time period on the scene.

403

## 404 **Conflict of interest**

405 There are no conflicts of interest to declare.

406

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## 411 **References**

412 1. Nichol G, Thomas E, Callaway CW, et al. Resuscitation Outcomes Consortium  
413 Investigators. Regional variation in out-of-hospital cardiac arrest incidence and outcome.  
414 JAMA 2008;300:1423-31.

- 415 2. Stiell IG, Wells GA, Field B, et al. Ontario Prehospital Advanced Life Support Study  
416 Group. Advanced cardiac life support in out-of-hospital cardiac arrest. N Engl J Med  
417 2004 ;351:647-56.
- 418 3. Spaite DW, Hanlon T, Criss EA, et al. Prehospital cardiac arrest: the impact of  
419 witnessed collapse and bystander CPR in a metropolitan EMS system with short response  
420 times. Ann Emerg Med 1990;19:1264-9.
- 421 4. Stiell IG, Wells GA, DeMaio VJ, et al. Modifiable factors associated with improved  
422 cardiac arrest survival in a multicenter basic life support/defibrillation system: OPALS Study  
423 Phase I results. Ontario Prehospital Advanced Life Support. Ann Emerg Med 1999;33:44-50.
- 424 5. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-  
425 hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557-63.
- 426 6. Ahn KO, Shin SD, Suh GJ, et al. Epidemiology and outcomes from non-traumatic  
427 out-of-hospital cardiac arrest in Korea: A nationwide observational study. Resuscitation  
428 2010;81:974-81.
- 429 7. Ma MH, Chiang WC, Ko PC, et al. Outcomes from out-of-hospital cardiac arrest in  
430 Metropolitan Taipei: does an advanced life support service make a difference? Resuscitation  
431 2007;74:461-9.
- 432 8. Kitamura T, Iwami T, Kawamura T, Nagao K, Tanaka H, Hiraide A; Implementation



433 Working Group for the All-Japan Utstein Registry of the Fire and Disaster Management  
 434 Agency. Nationwide public-access defibrillation in Japan. *N Engl J Med* 2010;362:994-1004.

435 9. Ong ME, Ng FS, Anushia P, et al. Comparison of chest compression only and  
 436 standard cardiopulmonary resuscitation for out-of-hospital cardiac arrest in Singapore.  
 437 *Resuscitation* 2008;78:119-26.

438 10. Hazinski MF, Nolan JP, Billi JE, et al. Part 1: Executive summary: 2010 International  
 439 Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science  
 440 With Treatment Recommendations. *Circulation* 2010;122:S250-75.

441 11. Sandroni C, Nolan J; European Resuscitation Council. ERC 2010 guidelines for adult  
 442 and pediatric resuscitation: summary of major changes. *Minerva Anesthesiol.* 2011;77:220-6.

443 12. Shin SD, Hock Ong ME, Tanaka H, et al. Comparison of Emergency Medical  
 444 Services Systems Across Pan-Asian Countries: A Web-based Survey. *Prehosp Emerg Care*  
 445 2012;16:477-496.

446 13. Shin SD, Ahn KO, Song KJ, Park CB, Lee EJ. Out-of-hospital airway management  
 447 and cardiac arrest outcomes: a propensity score matched analysis. *Resuscitation* 2012;83:313-  
 448 9.

449 14. Kajino K, Iwami T, Kitamura T, et al. Comparison of supraglottic airway versus  
 450 endotracheal intubation for the pre-hospital treatment of out-of-hospital cardiac arrest.

451 CritCare 2011;15:R236.

452 15. Iwami T, Kawamura T, Hiraide A, et al. Effectiveness of bystander-initiated cardiac-  
453 only resuscitation for patients with out-of-hospital cardiac arrest. *Circulation* 2007;116:2900-  
454 7.

455 16. Park CB, Shin SD, Suh GJ, et al. Pediatric out-of-hospital cardiac arrest in Korea: A  
456 nationwide population-based study. *Resuscitation* 2010;81:512-7.

457 17. Ong ME, Shin SD, Tanaka H, et al. Pan-Asian Resuscitation Outcomes Study  
458 (PAROS): rationale, methodology, and implementation. *Acad Emerg Med* 2011;18:890-7.

459 18. Olasveengen TM, Wik L, Steen PA. Quality of cardiopulmonary resuscitation before  
460 and during transport in out-of-hospital cardiac arrest. *Resuscitation* 2008;76:185-90.

461 19. Krarup NH, Terkelsen CJ, Johnsen SP, et al. Quality of cardiopulmonary  
462 resuscitation in out-of-hospital cardiac arrest is hampered by interruptions in chest  
463 compressions—A nationwide prospective feasibility study. *Resuscitation* 2011;82:263-9.

464 20. Wang HC, Chiang WC, Chen SY, et al. Video-recording and time-motion analyses of  
465 manual versus mechanical cardiopulmonary resuscitation during ambulance transport.  
466 *Resuscitation* 2007;74:453-60.

467 21. Shin SD, Suh GJ, Ahn KO, Song KJ. Cardiopulmonary resuscitation outcome of out-  
468 of-hospital cardiac arrest in low-volume versus high-volume emergency departments: An

469 observational study and propensity score matching analysis. *Resuscitation* 2011;82:32-9.

470 22. Kajino K, Iwami T, Daya M, et al. Impact of transport to critical care medical centers  
471 on outcomes after out-of-hospital cardiac arrest. *Resuscitation* 2010;81:549-54.

472 23. Weisfeldt ML, Becker LB. Resuscitation after cardiac arrest: a 3-phase time-sensitive  
473 model. *JAMA* 2002;288:3035-8.

474 24. Kahn CA, Pirralo RG, Kuhn EM. Characteristics of fatal ambulance crashes in the  
475 United States: an 11-year retrospective analysis. *Prehosp Emerg Care* 2001;5:261-9.

476 25. Sasson C, Hegg AJ, Macy M, Park A, Kellermann A, McNally B; CARES  
477 Surveillance Group. Prehospital Termination of Resuscitation in Cases of Refractory Out-of-  
478 Hospital Cardiac Arrest. *JAMA* 2008;300:1432-8.

479 26. Nagao K, Kikushima K, Watanabe K, et al. Early induction of hypothermia during  
480 cardiac arrest improves neurological outcomes in patients with out-of-hospital cardiac arrest  
481 who undergo emergency cardiopulmonary bypass and percutaneous coronary intervention.  
482 *Circ J* 2010;74:77-85.

483 27. Gaieski DF, Boller M, Becker LB. Emergency cardiopulmonary bypass: a promising  
484 rescue strategy for refractory cardiac arrest. *Crit Care Clin* 2012;28:211-29.

485 28. Goldberger ZD, Chan PS, Berg RA, et al; American Heart Association Get With The  
486 Guidelines—Resuscitation (formerly National Registry of Cardiopulmonary Resuscitation)

487 Investigators. Duration of resuscitation efforts and survival after in-hospital cardiac arrest: an  
488 observational study. *Lancet* 2012;380:1473-81.

489 29. Bobrow BJ, Spaite DW, Berg RA, et al. Chest compression-only CPR by lay rescuers  
490 and survival from out-of-hospital cardiac arrest. *JAMA* 2010;304:1447-54.

491 30. Bobrow BJ, Clark LL, Ewy GA, et al. Minimally interrupted cardiac resuscitation by  
492 emergency medical services for out-of-hospital cardiac arrest. *JAMA* 2008;299:1158-65.

493 31. Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: Post-cardiac arrest care: 2010  
494 American Heart Association guidelines for cardiopulmonary resuscitation and emergency  
495 cardiovascular care. *Circulation* 2010;122:S768-86.

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500 **Legend to Figures**

501 **Fig. 1.** Patient enrollment flow in both study sites.

502 Finally, 7,759 patients (3,594 from Seoul and 4,163 from Osaka) were enrolled in this study.

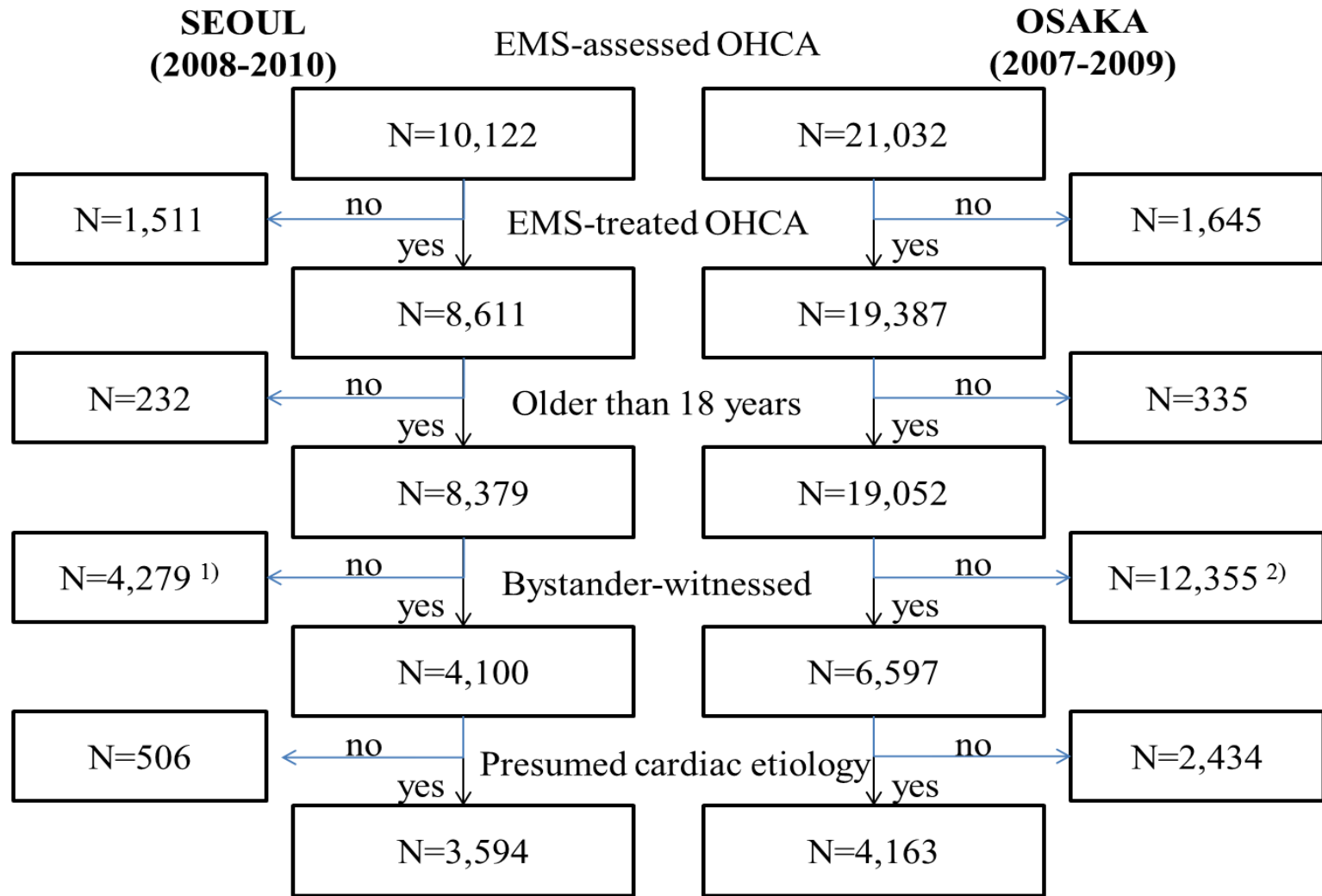
503 EMS, emergency medical service; OHCA, out-of-hospital cardiac arrest.

504 **Fig. 2.** Estimated probability and 95% confidence intervals of survival with good neurological  
505 outcome as a function of the STI using 5-knots restricted cubic spline univariate logistic  
506 regression model.

507 The dark solid line indicates the average probability of survival with good neurological  
508 outcome. The red dot lines are cut-off values corresponding to average probability.

509 STI, scene time interval

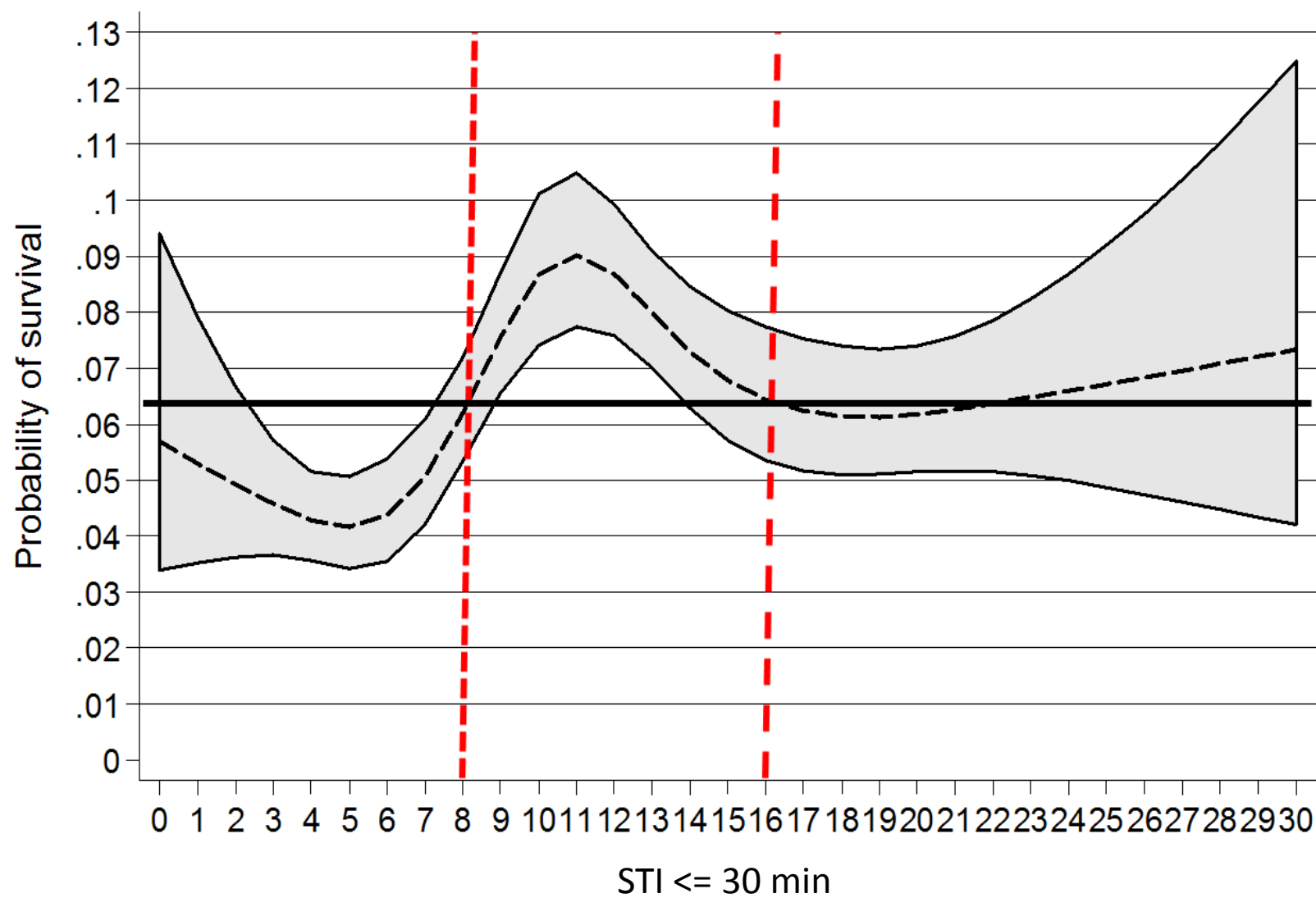
# Figure 1



1) 338 witnessed by EMS provider and 3,941 not witnessed by lay person

2) 1,482 witnessed by EMS provider and 10,973 not witnessed by lay person

# Figure 2



**Table 1**

Seoul and Osaka demographic findings.

	Total		Seoul		Osaka		<i>p</i>
Number of cases, <i>n</i> , %	7,757	100.0	3,594	100.0	4,163	100.0	
Year, <i>n</i> , %							
2007	1,317	17.0	0	0.0	1,317	31.6	NA
2008	2,508	32.3	1,108	30.8	1,400	33.6	
2009	2,645	34.1	1,199	33.4	1,446	34.7	
2010	1,287	16.6	1,287	35.8	0	0.0	
Female, gender, <i>n</i> , %	2,713	35.0	1,156	32.2	1,557	37.4	<0.001
Age, mean, SD	68.7	16.0	64.8	15.6	72.5	15.3	<0.001
Age group, <i>n</i> , %							
10-19 years	17	0.2	10	0.3	7	0.2	<0.001
20-29 years	126	1.6	77	2.1	49	1.2	
30-39 years	263	3.4	173	4.8	90	2.2	
40-49 years	600	7.7	397	11.0	203	4.9	
50-59 years	1,041	13.4	636	17.7	405	9.7	
60-69 years	1,606	20.7	808	22.5	798	19.2	
70-79 years	1,932	24.9	860	23.9	1,072	25.8	
Older than 80 years	2,172	28.0	633	17.6	1,539	37.0	
Public place, <i>n</i> , %	2,001	25.8	677	18.8	1,324	31.8	<0.001
Bystander CPR, <i>n</i> , %	2,004	25.8	257	7.2	1,747	42.0	<0.001
Bystander defibrillation, <i>n</i> , %	89	1.1	0	0.0	89	2.1	<0.001
EMS defibrillation, <i>n</i> , %	1,703	22.0	515	14.3	1,188	28.5	<0.001
Primary ECG, <i>n</i> , %							
VF/pulseless VT	1,293	16.7	352	9.8	941	22.6	<0.001
PEA	1,742	22.5	358	10.0	1,384	33.2	
Asystole	4,704	60.6	2,878	80.1	1,826	43.9	
Unknown	18	0.2	6	0.2	12	0.3	
Elapsed time intervals, mean, SD							
Response time interval	7.3	3.1	7.0	3.4	7.5	2.8	<0.001
Scene time interval	10.9	6.8	6.8	4.2	14.5	6.5	<0.001
Transportation time interval	7.3	5.1	7.3	5.1	7.2	5.1	0.375
Prehospital time interval	25.4	9.8	21.2	7.9	29.0	9.8	<0.001
Outcomes, <i>n</i> , %							
Prehospital ROSC	755	9.7	110	3.1	645	15.5	<0.001
Survival to admission	2,608	33.6	1,033	28.7	1,575	37.8	<0.001
Survival to discharge	1,008	13.0	400	11.1	608	14.6	<0.001
Good neurological outcome	496	6.4	127	3.5	369	8.9	<0.001

CPR, cardiopulmonary resuscitation; EMS, emergency medical service; ECG, electrocardiography; ROSC, return of spontaneous circulation; SD, standard deviation; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity.



**Table 2**

Distribution of risk factors and outcomes by scene time intervals.

	Total		Short (0=<STI<8)		Intermediate (8=<STI<16)		Long (16=<STI)		<i>p</i>
Total, N, %	7,757	100.0	2,739	100.0	3,314	100.0	1,704	100.0	
Year, N, %									
2007	1,317	17.0	135	4.9	712	21.5	470	27.6	<0.001
2008	2,508	32.3	840	30.7	1,064	32.1	604	35.4	
2009	2,645	34.1	919	33.6	1,138	34.3	588	34.5	
2010	1,287	16.6	845	30.9	400	12.1	42	2.5	
City, N, %									<0.001
Seoul	3,594	46.3	2,353	85.9	1,119	33.8	122	7.2	
Osaka	4,163	53.7	386	14.1	2,195	66.2	1,582	92.8	
Gender, N, %									
Male	5,044	65.0	1,866	68.1	2,086	62.9	1,092	64.1	<0.001
Female	2,713	35.0	873	31.9	1,228	37.1	612	35.9	
Age group, mean, SD	68.7	16.0	65.1	16.0	70.0	15.6	72.1	15.5	
Age<65 years	2,741	35.3	1,217	44.4	1,075	32.4	449	26.3	
Age>=65 years	5,016	64.7	1,522	55.6	2,239	67.6	1,255	73.7	<0.001
Place of arrest, N, %									
Public	2,001	25.8	726	26.5	877	26.5	398	23.4	
Private	5,333	68.8	1,807	66.0	2,262	68.3	1,264	74.2	
Unknown	423	5.5	206	7.5	175	5.3	42	2.5	<0.001
Bystander CPR, N, %									
No	5,753	74.2	2,409	88.0	2,279	68.8	1,065	62.5	
Yes	2,004	25.8	330	12.0	1,035	31.2	639	37.5	<0.001
Bystander defibrillation, N, %									
No	7,668	98.9	2,726	99.5	3,265	98.5	1,677	98.4	
Yes	89	1.1	13	0.5	49	1.5	27	1.6	<0.001
EMS defibrillation, N, %									
No	6,054	78.0	2,301	84.0	2,520	76.0	1,233	72.4	
Yes	1,703	22.0	438	16.0	794	24.0	471	27.6	<0.001
Primary ECG, N, %									
VF/pulseless VT	1,293	16.7	342	12.5	601	18.1	350	20.5	
PEA	1,742	22.5	381	13.9	810	24.4	551	32.3	
Asystole	4,722	60.9	2,016	73.6	1,903	57.4	803	47.1	
Unknown	18	0.2	8	0.3	4	0.1	6	0.4	
Elapsed time intervals, N, %									
Response time, mean, SD	7.3	3.1	7.0	3.1	7.4	2.8	7.6	3.5	<0.001
Transportation time interval, mean, SD	7.3	5.1	7.1	5.1	7.2	4.9	7.9	5.4	<0.001
Prehospital time, mean, SD	25.4	9.8	18.7	6.5	25.7	6.5	35.5	10.5	<0.001

STI, scene time interval from ambulance wheel arrival to departure (unit: minute.); CPR, cardiopulmonary resuscitation; EMS, emergency medical service; ECG, electrocardiography; ROSC, return of spontaneous circulation; SD, standard deviation; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity.

**Table 3**

Outcomes after OHCA by scene time interval group and city.

City	Outcome	Total		Short 0<=STI<8 min		Intermediate 8<=STI<16 min		Long 16<=STI min		<i>P</i>
		N	%	N	%	N	%	N	%	
Total	Total	7,757		2,739		3,314		1,704		
	Preshospital ROSC	755	9.7	97	3.5	374	11.3	284	16.7	< 0.001
	Survival to admission	2,608	33.6	871	31.8	1,182	35.7	555	32.6	0.004
	Survival to discharge	1,008	13.0	359	13.1	453	13.7	196	11.5	0.094
	Good neurological outcome	496	6.4	127	4.6	256	7.7	113	6.6	< 0.001
Seoul	Total	3,594		2,353		1,119		122		
	Preshospital ROSC	110	3.1	58	2.5	47	4.2	5	4.1	0.017
	Survival to admission	1,033	28.7	704	29.9	303	27.1	26	21.3	0.041
	Survival to discharge	400	11.1	280	11.9	107	9.6	13	10.7	0.121
	Good neurological outcome	127	3.5	83	3.5	40	3.6	4	3.3	0.986
Osaka	Total	4,163		386		2,195		1,582		
	Preshospital ROSC	645	15.5	39	10.1	327	14.9	279	17.6	< 0.001
	Survival to admission	1,575	37.8	167	43.3	879	40.0	529	33.4	< 0.001
	Survival to discharge	608	14.6	79	20.5	346	15.8	183	11.6	< 0.001
	Good neurological outcome	369	8.9	44	11.4	216	9.8	109	6.9	0.001

OHCA, out-of-hospital cardiac arrest; STI, scene time interval; ROSC, return of spontaneous circulation.

**Table 4**

Association between scene time intervals and outcomes after OHCA.

Outcomes Scene time interval	Total	Outcome		Crude OR			Adjusted OR		
	N	N	%	OR	95% CI		OR	95% CI	
Prehospital ROSC, total	7,757	755	9.7						
0=<STI<8 min	2,739	97	3.5	Reference			Reference		
8=<STI<16 min	3,314	374	11.3	3.47	2.76	4.36	2.78	2.18	3.54
16=< STI min	1,704	284	16.7	5.45	4.29	6.92	4.23	3.26	5.49
Survival to admission, total	7,757	2,608	33.6						
0=<STI<8 min	2,739	871	31.8	Reference			Reference		
8=<STI<16 min	3,314	1,182	35.7	1.19	1.07	1.32	1.10	0.98	1.24
16=< STI min	1,704	555	32.6	1.04	0.91	1.18	0.94	0.82	1.09
Survival to discharge, total	7,757	1,008	13						
0=<STI<8 min	2,739	359	13.1	Reference			Reference		
8=<STI<16 min	3,314	453	13.7	1.05	0.91	1.22	0.88	0.74	1.05
16=< STI min	1,704	196	11.5	0.86	0.72	1.04	0.64	0.52	0.80
Good neurological outcome, total	7,757	496	6.4						
0=<STI<8 min	2,739	127	4.6	Reference			Reference		
8=<STI<16 min	3,314	256	7.7	1.72	1.38	2.14	1.32	1.03	1.71
16=< STI min	1,704	113	6.6	1.46	1.13	1.90	0.92	0.68	1.26

ROSC, return of spontaneous circulation; STI, scene time interval from wheel arrival to departure; OR, odds ratio; CI, confidence interval.

Adjusted ORs were calculated by adjusting for city, age, gender, response time interval, transportation time interval, place, bystander cardiopulmonary resuscitation, defibrillation by lay person, defibrillation by emergency medical service (EMS) providers, and primary ECG rhythm in the model.

**Table 5**

Association between scene time interval and outcomes considering the effect of interaction terms.

Outcomes	Effect modifier	Scene time interval						
		<8 min	8-16 min			>= 16 min		
Good neurological outcome			AOR	95% CI		AOR	95% CI	
	Bystander defibrillation							
	No	Reference	1.40	1.08	1.82	1.01	0.74	1.39
Prehospital ROSC	Yes	Reference	0.20	0.05	0.92	0.09	0.02	0.44
	Bystander defibrillation							
	No	Reference	2.94	2.29	3.78	4.58	3.50	5.98
	Yes	Reference	0.33	0.09	1.21	0.24	0.06	0.98

ROSC, return of spontaneous circulation; AOR, adjusted odds ratio; CI, confidence interval.

AORs were calculated by contrast estimate for all corresponding interaction variables adjusting for potential confounders in the final model.