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Original article

# Field termination-of-resuscitation rule for refractory out-of-hospital cardiac arrests in Japan

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ABSTRACT

*Background:* Guidelines for cardiopulmonary resuscitation (CPR) recommend using the universal termination-of-resuscitation (TOR) rule to identify out-of-hospital cardiac arrest (OHCA) patients eligible for field termination of resuscitation, thus avoiding medically futile transportation to the hospital. However, in Japan, emergency medical services (EMS) personnel are forbidden from terminating CPR in the field and transport almost all patients with OHCA to hospitals. We aimed to develop and validate a novel TOR rule to identify patients eligible for field termination of CPR.
*Methods:* We analyzed 540,478 patients with OHCA from 2011 to 2015 using a Japanese registry. Main outcome measures were specificity and positive predictive value (PPV) of the newly developed TOR rule in predicting 1-month mortality after OHCA.
*Results:* Recursive partitioning analysis in the development group ($n$ = 434,208) showed that EMS personnel could consider TOR if patients with OHCA met all of the following five criteria: (1) initial asystole, (2) arrest unwitnessed by a bystander, (3) age ≥81 years, (4) no bystander-administered CPR or automated external defibrillator use before EMS arrival, and (5) no return of spontaneous circulation after EMS-initiated CPR for 14 min. For patients meeting these criteria, specificity and PPV for predicting 1-month mortality were 99.2% [95% confidence interval (CI), 99.0–99.3%] and 99.7% (95% CI, 99.6–99.7%), respectively, for the development group and were 99.5% (95% CI, 99.3–99.7%) and 99.8% (95% CI, 99.7–99.9%), respectively, for the validation group. Implementation of this novel rule would reduce patient transports to hospitals by 10.6% in the development group and 10.4% in the validation group.
*Conclusions:* Having both high specificity and PPV of >99% for predicting 1-month mortality, our developed TOR rule may be applied in the field for Japanese patients with OHCA who meet all five criteria. Prospective validation studies and establishment of prehospital EMS protocol are required before implementing this rule.


## Introduction

The guidelines for cardiopulmonary resuscitation (CPR) recommend the universal basic life support (BLS) termination-of-resuscitation (TOR) rule to identify out-of-hospital cardiac arrest (OHCA) patients who are eligible for field termination of resuscitation, thus avoiding medically futile transportation to the hospital [1]. Under this rule, emergency medical services (EMS) personnel could terminate care for OHCA patients without transporting them to the hospital if all of the following three criteria are met after three full cycles of CPR: the arrest is not witnessed by EMS personnel, there are no shocks delivered, and there is no return of spontaneous circulation (ROSC). However, no TOR rules can be legally implemented in the field in Japan, and it is mandated that all cardiac arrest patients be transported to the emergency department (ED). We previously reported a TOR rule for emergency department (ED) physicians (the ED-TOR rule) immediately after patient arrival to the hospitals, to allow for better utilization of hospital healthcare resources in Japan [2]. The ED-TOR rule for deciding whether to withhold further resuscitation attempts or terminate ongoing resuscitation includes three criteria: no prehospital ROSC, non-shockable initial rhythm, and arrest unwitnessed by bystanders. The ED-TOR rule, however, has a

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relatively low specificity with 90.3% [95% confidence interval (CI), 89.4–91.1%] [2]. The American Heart Association and the European Resuscitation Council guidelines cautioned that prognostication for outcomes after cardiac arrest should be used cautiously if the 95% CI of a diagnostic test is between 90% and 95% due to its imprecision [3,4]. Moreover, our previous studies showed that both age and duration of CPR are critical components for predicting favorable outcomes after OHCA [5–9]. Therefore, to improve utilization of hospital healthcare resources, to reduce both attendant hazards for EMS personnel and unnecessary transportation of patients with OHCA, and to increase the availability of transport for other patients, a novel TOR rule with high specificity that incorporates age and the time the rule is applied is required.

Using a nationwide Japanese population-based registry, we aimed to develop and validate a novel TOR rule used in the field by EMS personnel that would allow them to decide whether to terminate ongoing resuscitation efforts.

## Materials and methods

### *Study design*

This was a nationwide, population-based, observational study of all adults (aged ≥18 years) experiencing OHCA who received resuscitation performed by EMS personnel in Japan between January 1, 2011, and December 31, 2015. This study was conducted with the approval of the ethics committee of Kanazawa University, and informed consent was waived because of the anonymous nature of the data used (2012–032).

### *Study setting*

Japan has nearly 127 million residents living across an area of 378,000 $km^2$. The Fire and Disaster Management Agency (FDMA) of Japan supervises the nationwide EMS system, and local fire stations operate the local EMS systems. All EMS providers perform CPR according to the Japanese CPR guidelines [10]. EMS personnel are permitted to use several resuscitative methods, including automated external defibrillators (AEDs), insertion of an airway adjunct, insertion of a peripheral intravenous line, and administration of Ringers lactate solution. Further, certain emergency personnel are permitted to insert a tracheal tube and administer intravenous epinephrine. Importantly, Japanese law prohibits EMS personnel from terminating resuscitation in the field. Accordingly, most OHCA patients receive CPR administered by EMS providers and are subsequently transported to the hospital. Since 2006, emergency telephone dispatchers in Japan are required to provide CPR instructions for chest compression-only CPR if it is difficult for bystanders to administer rescue breathing [11].

### *Data collection and quality control*

The FDMA in Japan has launched an ongoing, prospective, population-based, observational study involving all OHCA patients who have received EMS treatment since 2005 [12]. Specifically, in cooperation with the physician in charge, EMS personnel at each treatment center record patient data using an Utstein-style template. The recorded data are then transferred to individual local fire stations and subsequently entered into the data registry system on the FDMA database. Ultimately, all data are stored in the nationwide database developed by the FDMA for public use. We obtained permission from the FDMA to analyze de-identified patient data contained within this database. Neurological outcomes were stratified using the Cerebral Performance Category (CPC) scale (category 1: good cerebral performance; category 2: moderate cerebral disability; category 3: severe cerebral disability; category 4: coma or vegetative state; and category 5: death) [13]. For all patients, the CPC category was determined by the attending physician.

### *Main outcome measures*

The main outcome measures were the specificity and positive predictive value (PPV) of the newly developed TOR rule for predicting 1-month mortality and 1-month unfavorable neurological outcome (CPC scale categories 3–5). Secondary outcome measures were those related to the BLS TOR rule [1].

### *Statistical analysis*

Continuous variables are expressed as median (25–75%) and mean with standard deviation, and categorical variables are expressed as percentages. As an estimate of effect size and variability, we reported the specificity, sensitivity, PPV, and negative predictive value (NPV) of TOR rules with 95% CIs. To compare the basic characteristics of patients between the development and validation groups, Wilcoxon and Kruskal–Wallis tests for continuous variables and chi-square tests for categorical variables were performed. From the results of our previous studies [2,5–9,14], we found that six prehospital variables (age, initial recorded rhythm, cardiac arrest witnessed by a bystander, bystander-administered CPR, duration of EMS-initiated CPR, and presence of prehospital ROSC) were crucial elements associated with favorable outcomes after OHCA. Using these six prehospital variables in the development group, we performed a recursive partitioning analysis to develop a novel TOR rule for predicting medically futile CPR (1-month survival rate of <1%) in patients with OHCA [1]. Recursive partitioning analysis creates a branching decision tree by dividing the patient population into subgroups according to the results of an analysis of the relationship between outcome proportions after OHCA and prehospital variables [14,15]. Recursive partioning was conducted using the maximized entropy index [16–18]. Ten-fold cross-validation was used to assess the predictive ability of the decision-tree model. We compared the performance of the novel TOR rule with that of the BLS rule for predicting 1-month mortality and 1-month unfavorable neurological outcome using the validation group.

All statistical analyses were performed using the JMP Pro statistical package, Version 14 (SAS Institute, Cary, NC, USA). All tests were two-tailed, with $p$-value <0.05 considered statistically significant.

## Results

Over the 5-year study period, data for 629,471 patients were compiled in the FDMA database. Fig. 1 shows the inclusion and exclusion criteria for participants in the present study. Among 605,573 adult patients (aged ≥18 years) who were treated by EMS personnel, we excluded patients with EMS-witnessed OHCA ($n$ = 49,388) and those without information on EMS resuscitation time ($n$ = 14,286), prehospital ROSC time ($n$ = 1413), 1-month outcome ($n$ = 7), and initial cardiac rhythm ($n$ = 1). Finally, 540,478 patients (85.9% of registered patients) with OHCA were eligible for enrolment in this study. Patients were divided into a development group (2011–2014; $n$ = 434,208) and a validation group (2015; $n$ = 106,270). The characteristics of study participants are shown in Table 1. Age, EMS response time, and the proportion of patients with bystander-administered CPR, a presumed cardiac cause of arrest, and epinephrine administration were significantly higher among patients in the validation group than in the development group (all $p$ < 0.001). The proportion of patients with initial shockable rhythm and use of advanced airway

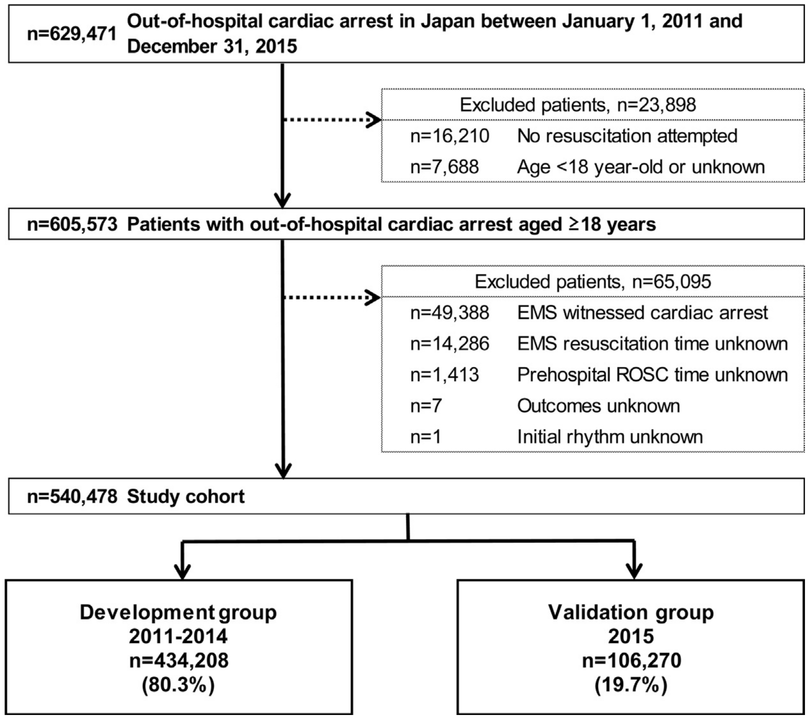


**Fig. 1.** Study profile and selection of the study population. EMS, emergency medical services; ROSC, return of spontaneous circulation.

**Table 1**
Baseline characteristics of study participants.

| Characteristic | All patients ($N$ = 540,478; 100%) | Development group ($n$ = 434,208; 80.3%) | Validation group ($n$ = 106,270; 19.7%) | $p$-Value |
|---|---|---|---|---|
| Age (years) | | | | |
| Median (25–75%) | 79 (68–86) | 79 (67–86) | 80 (68–87) | <0.001 |
| Mean (SD) | 75.3 (15.7) | 75.1 (15.7) | 75.7 (15.5) | <0.001 |
| Male | 305,310 (56.5) | 245,246 (56.5) | 60,064 (56.5) | 0.82 |
| Witnessed cardiac arrest | 192,637 (35.6) | 154,673 (35.6) | 37,964 (35.7) | 0.53 |
| Bystander-administered CPR | 263,991 (48.8) | 209,210 (48.2) | 54,781 (51.6) | <0.001 |
| AED use by bystander before EMS arrival at the site | 6199 (1.1) | 4913 (1.1) | 1286 (1.2) | 0.03 |
| Initial shockable rhythm | 37,908 (7.0) | 31,032 (7.2) | 6876 (6.5) | <0.001 |
| Presumed cardiac cause | 322,293 (59.6) | 258,083 (59.4) | 64,210 (60.4) | <0.001 |
| Use of advanced airway management | 220,443 (40.8) | 178,516 (41.1) | 41,927 (39.5) | <0.001 |
| Epinephrine administration | 85,720 (15.9) | 66,440 (15.3) | 19,280 (18.1) | <0.001 |
| Prehospital AED administration by EMS personnel | 51,330 (9.5) | 41,378 (9.5) | 9952 (9.4) | 0.10 |
| EMS response time (min) | | | | |
| Median (25–75%) | 7 (6–9) | 7 (5–9) | 7 (6–9) | <0.001 |
| Mean (SD) | 7.66 (3.28) | 7.64 (3.29) | 7.74 (3.21) | <0.001 |
| Prehospital EMS-initiated CPR duration (min) | | | | |
| Median (25–75%) | 23 (17–29) | 23 (17–29) | 23 (17–29) | 0.48 |
| Mean (SD) | 23.6 (9.0) | 23.6 (9.1) | 23.6 (9.0) | 0.48 |
| Prehospital ROSC | 40,917 (7.6) | 32,285 (7.4) | 8632 (8.1) | <0.001 |
| 1-Month survival | 22,104 (4.1) | 17,649 (4.1) | 4455 (4.2) | 0.06 |
| 1-Month neurologically intact survival | 10,750 (2.0) | 8543 (2.0) | 2207 (2.1) | 0.02 |

Values are reported as $n$ (%) unless otherwise indicated.
AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; ROSC, return of spontaneous circulation; SD, standard deviation.

management was significantly lower in the validation group than in the development group (all $p < 0.001$). The validation group had significantly higher prehospital ROSC and 1-month neurologically intact survival than the development group (prehospital ROSC: 8.1% vs. 7.4%, $p < 0.001$; 1-month neurologically intact survival: 2.1% vs. 2.0%, $p = 0.02$). However, there was no significant difference in 1-month survival between the two groups (4.1% vs. 4.2%, $p = 0.06$).

The result of recursive partitioning analysis for the development group in predicting 1-month mortality along with a flow chart algorithm of the new TOR rule in the field is depicted in Fig. 2. The novel TOR rule was defined if patients with OHCA met all five of the following criteria: (1) initial asystole, (2) arrest unwitnessed by a bystander, (3) age ≥81 years, (4) no bystander-administered CPR or AED use before EMS arrival at the site, and (5) no ROSC after EMS-initiated CPR for 14 min. With respect to the fifth criterion of the new TOR rule, we regarded the 5266 patients who either arrived at the hospital or achieved prehospital ROSC in ≤14 min of EMS-initiated CPR as having not met the fifth criterion of the new TOR rule. In this scenario, we assumed that all patients had ROSC just after arrival at the hospital.

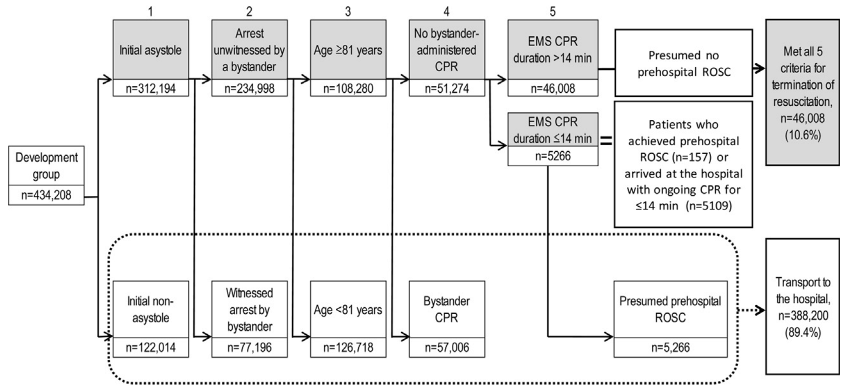


**Fig. 2.** Recursive partitioning analysis for predicting 1-month mortality in the development group with a flow chart algorithm of the novel termination-of-resuscitation rule in the field. CPR, cardiopulmonary resuscitation; EMS, emergency medical services; ROSC, return of spontaneous circulation.

**Table 2**
Performance of new termination-of-resuscitation rule in predicting 1-month mortality.

| Variables | Development group (*N* = 434,208) | | Validation group (*N* = 106,270) | |
|---|---|---|---|---|
| | Fulfilled 5/5 criteria (*n* = 46,008; 10.6%) | Did not fulfill criteria (*n* = 388,200; 89.4%) | Fulfilled 5/5 criteria (*n* = 11,090; 10.4%) | Did not fulfill criteria (*n* = 95,180; 89.6%) |
| Death, *n* | 45,859 | 370,700 | 11,069 | 90,746 |
| Survival, *n* | 149 | 17,500 | 21 | 4434 |
| Survival rate, % (95% CI) | 0.32 (0.28–0.38) | 4.51 (4.44–4.57) | 0.19 (0.12–0.29) | 4.66 (4.53–4.79) |
| Sensitivity, % (95% CI) | 11.0 (10.9–11.1) | | 10.9 (10.7–11.1) | |
| Specificity, % (95% CI) | 99.2 (99.0–99.3) | | 99.5 (99.3–99.7) | |
| PPV, % (95% CI) | 99.7 (99.6–99.7) | | 99.8 (99.7–99.9) | |
| NPV, % (95% CI) | 4.5 (4.2–4.8) | | 4.7 (4.1–5.3) | |

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

**Table 3**
Classification accuracy of new termination-of-resuscitation rule in predicting 1-month unfavorable neurological outcome.

| Variables | Development group (*N* = 434,208) | | Validation group (*N* = 106,270) | |
|---|---|---|---|---|
| | Fulfilled 5/5 criteria (*n* = 46,008; 10.6%) | Did not fulfill criteria (*n* = 388,200; 89.4%) | Fulfilled 5/5 criteria (*n* = 11,090; 10.4%) | Did not fulfill criteria (*n* = 95,180; 89.6%) |
| CPC 3–5, *n* | 45,988 | 379,677 | 11,086 | 92,977 |
| CPC 1–2, *n* | 20 | 8523 | 4 | 2203 |
| Rate of patients with CPC 1–2, % (95% CI) | 0.04 (0.03–0.07) | 2.20 (2.15–2.24) | 0.04 (0.01–0.09) | 2.31 (2.22–2.41) |
| Sensitivity, % (95% CI) | 10.8 (10.7–10.9) | | 10.7 (10.5–10.8) | |
| Specificity, % (95% CI) | 99.8 (99.6–99.9) | | 99.8 (99.5–99.9) | |
| PPV, % (95% CI) | 100.0 (99.9–100) | | 100.0 (99.9–100) | |
| NPV, % (95% CI) | 2.2 (1.9–2.5) | | 2.3 (1.8–3.0) | |

CI, confidence interval; CPC, Cerebral Performance Category; PPV, positive predictive value; NPV, negative predictive value.

**Table 4**
Classification accuracy of basic life support termination-of-resuscitation rule in predicting 1-month mortality in the validation group.

| Application time of the BLS TOR rule | At 6 min of EMS-initiated CPR | | At 14 min of EMS-initiated CPR | | At 30 min of EMS-initiated CPR | |
|---|---|---|---|---|---|---|
| Validation group (*N* = 106,270) | Fulfilled 3/3 criteria (*n* = 94,295; 88.7%) | Did not fulfill criteria (*n* = 11,975; 11.3%) | Fulfilled 3/3 criteria (*n* = 92,467; 87.0%) | Did not fulfill criteria (*n* = 13,803; 13.0%) | Fulfilled 3/3 criteria (*n* = 89,652; 84.4%) | Did not fulfill criteria (*n* = 16,618; 15.6%) |
| Death, *n* | 92,581 | 9234 | 91,297 | 10,518 | 88,852 | 12,963 |
| Survival, *n* | 1714 | 2741 | 1170 | 3285 | 800 | 3655 |
| Survival rate, % | 1.8 (1.7–1.9) | 22.9 (22.2–23.7) | 1.3 (1.2–1.3) | 23.8 (23.1–24.5) | 0.9 (0.8–1.0) | 22.0 (21.4–22.6) |
| Sensitivity, % (95% CI) | 90.9 (90.8–91.1) | | 89.7 (89.5–89.9) | | 87.3 (87.1–87.5) | |
| Specificity, % (95% CI) | 61.5 (60.0–62.9) | | 73.7 (72.4–75.0) | | 82.0 (80.9–83.1) | |
| PPV, % (95% CI) | 98.2 (98.1–98.3) | | 98.7 (98.7–98.8) | | 99.1 (99.0–99.2) | |
| NPV, % (95% CI) | 22.9 (21.4–24.5) | | 23.8 (22.4–25.3) | | 22.0 (20.7–23.4) | |

BLS, basic life support; CI, confidence interval; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; PPV, positive predictive value; NPV, negative predictive value; TOR, termination of resuscitation.

Results for performance of the novel TOR rule in predicting 1-month mortality are shown in Table 2. In the development group, 10.6% (46,008/434,208) of patients met all five criteria and had a survival rate of 0.32% (95% CI, 0.28–0.38%). The new TOR rule had a specificity of 99.2% (95% CI, 99.0–99.3%) and PPV of 99.7% (95% CI, 99.6–99.7%). In the validation group, 10.4% (11,090/106,270) of patients met the five criteria and had a survival rate of 0.19% (95% CI, 0.12–0.29%). The new TOR rule had a specificity of 99.5% (95% CI, 99.3–99.7%) and PPV of 99.8% (95% CI, 99.7–99.9%).

The classification accuracy of the novel TOR rule in predicting 1-month unfavorable neurological outcome is shown in Table 3. The rates of CPC category 1–2 in patients who met all five criteria for the new TOR rule were 0.04% (0.03–0.07) and 0.04% (0.01–0.09) in the development and validation groups, respectively. The specificities of the novel TOR rule for the development and validation groups were 99.8% (95% CI, 99.6–99.9%) and 99.8% (95% CI, 99.5–99.9%), respectively. The PPV of the novel TOR rule for the development and validation groups was 100% (95% CI, 99.9–100%) and 100% (95% CI, 99.9–100%), respectively.

The classification accuracy of the BLS TOR rule in predicting 1-month mortality in the validation group, according to the application time of the BLS TOR rule is shown in Table 4. When the BLS TOR rule was applied at 6 min of EMS-initiated CPR, the specificity and PPV of the BLS TOR rule in patients meeting the three criteria of the BLS TOR rule were 61.5% (95% CI, 60.0–62.9%) and 98.2% (98.1–98.3%), respectively, with a survival rate of 1.8% (95% CI, 1.7–1.9%). When the BLS TOR rule was applied at 14 and 30 min of EMS-initiated CPR, the specificity of the BLS rule in patients who met the three criteria was 73.7% (95% CI, 72.4–75.0%) and 82.0% (95% CI, 80.9–83.1%), respectively. The PPV of the BLS TOR rule applied at 14 and 30 min was 98.7% (95% CI, 98.7–98.8%) and 99.1% (95% CI, 99.0–99.2%), respectively. When applying the novel TOR rule at 33 min of EMS-initiated CPR in the validation group, the specificity and PPV reached 100% (95% CI, 99.9–100.0%) and 100% (95% CI, 99.8–100%), respectively.

## Discussion

We developed and validated a novel TOR rule to guide EMS personnel in considering whether to terminate resuscitation for patients with refractory OHCA in the field. A new TOR rule was defined in patients meeting all of the following five criteria: initial asystole, arrest unwitnessed by a bystander, age ≥81 years, no bystander-administered CPR or defibrillator use before EMS arrival at the site, and no ROSC after EMS-initiated CPR for 14 min. If a patient with OHCA meets all five criteria, EMS personnel in charge should consider terminating resuscitation before transport to the hospital. The present study demonstrated that the novel TOR rule had specificity of 99.5% in the validation group, which means that the false positive rate was 0.5%, and the PPV was 99.8% for predicting 1-month mortality (Table 2). Moreover, patients who met the novel TOR rule had a 1-month survival rate of less than 1% (0.32% and 0.19% in the development and validation groups, respectively), which is commonly regarded as the threshold of medical futility [1,19]. Using the validation data set, we compared the classification accuracy of the BLS TOR rule with that of the novel TOR rule in predicting 1-month mortality. The novel TOR rule had higher specificity and PPV than the BLS TOR rule in predicting 1-month mortality after applying the rules at 14 min of EMS-initiated CPR (Tables 2 and 4). These findings suggest that the new TOR rule is preferable to the BLS TOR rule in the field in Japan.

The 2010 American Heart Association guidelines [1] recommend that the BLS TOR rule be applied after three 2-min cycles of CPR and AED analysis, i.e. 6 min of EMS-initiated CPR. However, the time juncture of BLS TOR rule application in the field has varied from unindicated time [20–23] to four 2-min intervals of CPR (i.e. 8 min of EMS-initiated CPR) [24]. Grunau et al. [25] stated that when applied at 6 min of resuscitation, the BLS TOR rule had a false positive rate of 2.1% in an analysis of 6994 patients with EMS-treated OHCA in British Columbia; however, the BLS TOR rule at 30 min demonstrated specificity of 100% and PPV of 100%. Those authors suggested that EMS personnel might consider TOR rule application at resuscitation points later than 6 min. In the present study, we found very low specificity for the BLS TOR rule when applied at 6 min of EMS-initiated resuscitation and at 30 min of EMS-initiated resuscitation (Table 4).

Recently, using data from the All-Japan Utstein Registry between 2008 and 2012, Shibahashi et al. reported a new TOR rule for EMS personnel in the field that would be applied immediately after arrival at the site without EMS-CPR efforts [26]. Their results showed that EMS personnel can evaluate patients with OHCA who meet the following criteria: unshockable initial rhythm, arrest unwitnessed by bystanders, and age ≥73 years. Although this TOR rule had the PPV of 99.0% (95% CI, 98.9–99.0%) for predicting 1-month mortality, the specificity was 92.3% (95% CI, 91.8–92.7%). Namely, their rule had a false positive rate of 7.7% (95% CI, 7.3–8.2%), which is graded as serious for its imprecision because the upper limit of the 95% CI for the false positive rate was greater than 5% [4]. Our novel TOR rule in the field had a false positive rate of <1% for predicting both 1-month mortality and 1-month unfavorable neurological outcomes, which is superior compared to Shibahashi's TOR rule.

Another Japanese study from SOS-KANTO 2012 Study Group showed a new TOR rule for physicians in the ED after arrival at the hospitals [27]. They suggested that ED physicians can terminate resuscitation efforts when patients meet all of the following criteria: arrest unwitnessed by bystanders, asystole as an initial rhythm, and asystole at hospital arrival. The rule had a higher specificity [98.6% (95% CI, 97.3–99.4%)] and PPV [99.8% (95% CI, 99.7–99.9%)] for predicting 1-month mortality than our previous developed ED-TOR rule [27]. The TOR rule developed by SOS-KANTO 2012 Study Group after arrival at hospitals may be useful considering present Japanese EMS systems. However, EMS personnel have to transport almost all patients with OHCA to hospitals according to Japanese law.

Despite the recommendations from guidelines [1], reported rates of TOR in the field vary from 0% to 67% [28–32]. When applying the new TOR rule at 14 min of EMS-initiated CPR, the reduction in the patient transport rate to the ED is anticipated to be 10% (approximately 11,000 patients per year in Japan) (Table 2). Reducing the number of transports for OHCA patients may help reduce the number of ambulances dispatched, shorten EMS response time, and ultimately improve survival in OHCA patients [33]. However, in Japan, EMS personnel cannot pronounce death on the scene for OHCA patients. Therefore, when implementing the novel TOR rule in the field, a new prehospital protocol should be established in Japan. This may include the approval of TOR efforts by an on-call physician or real-time contacting of medical control, as well as mandatory reporting or notification to the police after termination of resuscitation.

As previous studies have shown that population density is independently associated with survival after OHCA [34–36], one concern for implementation of the novel TOR rule is whether the rule could be applied throughout Japan regardless of the population density. Table 5 shows the results of classification accuracy assessment of the novel TOR rule in predicting 1-month mortality in the validation group according to geographic regions in Japan. The novel TOR rule had a specificity of >99.4% with a false positive rate <0.6%; it had a PPV of >99.8% for predicting 1-month mortality in both rural and urban areas. Taken together, the new TOR rule may be applied throughout Japan.

This observational study has several potential limitations. First, the novel TOR rule misclassified 21 survivors in the present

**Table 5**
Classification accuracy of the novel termination-of-resuscitation rule in predicting 1-month mortality in the validation group according to geographic regions in Japan.

| Valuables | Rural area[a] ($N$ = 26,134) | | Urban area ($N$ = 80,136) | |
|---|---|---|---|---|
| | Fulfilled 5/5 criteria ($n$ = 2654, 10.2%) | Did not fulfill criteria ($n$ = 23,480, 89.8%) | Fulfilled 5/5 criteria ($n$ = 8436, 10.5%) | Did not fulfill criteria ($n$ = 71,700, 89.5%) |
| Death, $n$ | 2648 | 22,481 | 8421 | 68,265 |
| Survival, $n$ | 6 | 999 | 15 | 3435 |
| Survival rate (95% CI), % | 0.23 (0.10–0.49) | 4.25 (4.00–4.52) | 0.18 (0.11–0.29) | 4.79 (4.64–4.95) |
| Sensitivity (95% CI), % | 10.5 (10.2–10.9) | | 11.0 (10.8–11.2) | |
| Specificity (95% CI), % | 99.4 (98.7–99.7) | | 99.6 (99.3–99.8) | |
| PPV (95% CI), % | 99.8 (99.5–99.9) | | 99.8 (99.7–99.9) | |
| NPV (95% CI), % | 4.3 (3.2–5.7) | | 4.8 (4.1–5.6) | |

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.
[a] The rural area is constituted of 19 prefectures with population of less than 200 inhabitants per km$^2$.

validation study, resulting in a misclassification rate of 0.19% (21/11,090). Four of these patients were documented as having a good CPC score (score of 1 on a scale of 1–5) at 1 month after OHCA, 3 as having severe disability (CPC score of 3), and 14 as having coma (CPC score of 4). A recent study in Japan showed that patients with cardiac arrest on hospital arrival due to acute myocardial infarction had a survival rate of 15% at hospital discharge after aggressive in-hospital treatments (i.e. percutaneous coronary intervention, coronary artery bypass graft) [37]. This remarkably good result implies that the novel TOR rule cannot be ethically applied by EMS systems in Japan. However, we were unable to access the original patient records to determine the factors that contributed to the outcomes of the 21 patients who survived for 1 month after cardiac arrest. Nevertheless, the novel TOR rule had a PPV of 99.8% for predicting lack of survival, which is within the acceptable range used by medical ethicists for defining futility [1,19,20,23]. Second, the actual etiology of cardiac arrest was not fully verified. Some patients who met the criteria of the novel TOR rule may have had accidental hypothermia, which is a reversible cause of OHCA; therefore, the new TOR rule may overestimate these patients. Third, we may have underestimated the number of patients who met the novel TOR rule criteria. Some patients who met four of the novel TOR rule criteria (initial asystole, unwitnessed arrest by bystander, age >81 years, and no bystander-administered CPR) in the prehospital setting and who arrived at the hospital before 14 min of EMS-initiated CPR did not actually achieve in-hospital ROSC. Because we did not have in-hospital data, the number of patients who actually achieved in-hospital ROSC was unknown. Fourth, the different job roles and experience levels of the EMS providers might influence the quality of EMS-initiated CPR and prehospital ROSC after OHCA. However, we could not evaluate the quality of EMS CPR due to insufficient data. Fifth, caution must be exercised when generalizing these results to other EMS systems or other countries. Finally, prospective validation studies are required before implementation of the novel TOR rule in the field with a reliable medical protocol system.

## Conclusions

We developed and validated a novel TOR rule in the field for refractory OHCA patients who meet all the established criteria, with specificity of >99% and PPV of >99%. Prospective validation studies and establishment of prehospital EMS protocols are required prior to implementation of this rule in Japan.


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## Conflict of interest

The authors declare that there is no conflict of interest.


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