Chapter 5
Prediction in Neurological Outcomes in Cardiac Arrest Patients Before Inducing Targeted Temperature Management: Validation of CAST or cCAST

Mitsuaki Nishikimi

Abstract Not only a patient's family but also ICU physicians need information on the probability of a patient recovering from post-cardiac arrest syndrome (PCAS) before admitting to the intensive care unit (ICU) and initiating targeted temperature management (TTM). In this section, we introduced a novel prediction tool for evaluating the neurological prognosis in patients with PCAS before TTM, called a post-Cardiac Arrest Syndrome for Therapeutic hypothermia score (CAST) and condensed CAST (cCAST). They have been developed using retrospective analyses from data of 151 consecutive adult patients who were admitted to four hospitals within the last 5 years to undergo TTM after cardiac arrest. While the CAST was calculated by using eight factors and logistic regression formula, the cCAST was modified by, though using same factors, more simple formula. The cCAST of 3.5 or lower was associated with a 0.99 (95% CI, 0.94–1.00) sensitivity and a 0.73 (0.61–0.84) specificity predicting for a poor outcome and 6.5 or higher was with a 0.80 (0.71–0.88) and a 0.97 (0.89–1.00). The "cCAST" can be calculated more easily and is useful for estimating the prognosis of PCAS patients, describing patients' conditions to their family and making the decision before the initiation of TTM, as with the original CAST.

Keywords Post-cardiac arrest syndrome · Neurological prognosis · Targeted temperature management · CAST · cCAST

M. Nishikimi
Department of Emergency and Critical Care, Nagoya University Graduate School of Medicine, Nagoya, Japan

M. Aibiki, S. Yamashita (eds.), *A Perspective on Post-Cardiac Arrest Syndrome*,
https://doi.org/10.1007/978-981-13-1099-7_5

Abbreviations

95% CI	95% confidence interval
CAST	Post-cardiac arrest syndrome for therapeutic hypothermia score
cCAST	condensed CAST
CPC	Cerebral performance categories
ED	Emergency department
GCS	Glasgow Coma Scale
GWR	Gray matter attenuation to white matter attenuation ratio
ICU	Intensive care unit
PCAS	Post-cardiac arrest syndrome
TTM	Targeted temperature management

5.1 Introduction

5.1.1 The Estimation of Prognosis of PCAS Before the Initiation of TTM

Cardiac arrest typically occurs suddenly, and the families of patients are often confused on resuscitation and return of spontaneous circulation in the emergency department (ED). Objective information regarding recovery might be helpful to explain the patient's current status to his or her family clearly. Moreover, such information could also be helpful for the intensive care unit (ICU) physicians from the viewpoint of cost-effectiveness, because the cost of critical care for them is usually exorbitant, so the indications for the treatment in post-cardiac arrest syndrome (PCAS) patients should be decided more carefully [1]. Estimating the neurological prognosis immediately after the return of spontaneous circulation is challenging but important for the treatment of patients after cardiac arrest.

Previous studies have examined several factors that are available at the emergency department (ED) before the initiation of targeted temperature management (TTM) to determine their relation to the neurological prognosis of PCAS patients. For example, the duration of the resuscitation effort was shown to be correlated with a good functional outcome for patients with PCAS [2, 3]. In addition, other studies have revealed that pH [4], lactate [5, 6], and the Glasgow Coma Scale (GCS) [7, 8] are also related to neurological prognosis. However, these factors could not sufficiently separate patients with a good outcome from those with a poor outcome, indicating that a more "suitable scaling method" based on a combination of prognostic factors would be needed [9, 10].

Although several studies have described the use of a scoring system to estimate neurological outcome on the patient's arrival in the ED, these scoring systems did not focus on whether the patient had undergone TTM [4, 11–13]. Today, many intensivists perform TTM for the purpose of promoting a good recovery if intensive treatment is indicated. Logically, a scoring system for PCAS patients undergoing

TTM should be created using data from only PCAS patients treated with TTM, but not from all PCAS patients. Moreover, the factors used for these previous scoring systems were mostly limited to clinical history items, such as the time until ROSC, the initial rhythm, and the witness status. Potential candidate values used on their creation were not selected from blood and physical examination findings or imaging studies. If the scoring system for predicting the outcome of the PCAS patients is developed by the limited data of those undergoing TTM, furthermore the data including the other examinations such as blood and physical examination findings or imaging studies as well as clinical history, it is likely to be more suitable scoring system for them.

5.1.2 Post–Cardiac Arrest Syndrome for Therapeutic Hypothermia Score (CAST)

Previously, we developed a "post-Cardiac Arrest Syndrome for Therapeutic hypothermia score (CAST)" for predicting the neurological outcome in patients with PCAS before the initiation of TTM [14, 15]. CAST was created in a multicenter, retrospective, observational study using a data of 151 adults who were admitted to four hospitals within the last 5 years to undergo TTM after cardiac arrest. It is calculated using eight categorized variables (initial rhythm, witnessed status and time until return of spontaneous circulation, pH, serum lactate, motor score according to the Glasgow Coma Scale, CT gray matter to white matter attenuation ratio, albumin, hemoglobin), which was strongly associated with neurological prognosis of PCAS patients at 30 days, and logistic regression formula (Figs. 5.1 and 5.2). The predictive accuracy of CAST has much higher as compared with previous reported scoring

Scrore	*0*	*1*	*2*	*3*
Initial Rhythm (X1)	*Shockable*	*Non Shockable*		
Witness / ROSC time (X2)	*< 20 min*	*20 min ≤*	*No Witness*	
pH (X3)	*≥ 7.31*	*7.30-7.16*	*7.15-7.01*	*7.00 ≥*
Lactate (X4)	*≤ 5.0*	*5.1-10.0*	*10.1-14.0*	*14.1 ≤*
GCS M (X5)	*≥ 2*	*1*		
GWR (X6)	*≥ 1.201*	*1.200-1.151*	*1.150 ≥*	
Alb (X7)	*≥ 3.6*	*3.5-3.1*	*3.0 ≥*	
Hb (X8)	*≥ 13.1*	*13.0-11.1*	*11.0 ≥*	

Fig. 5.1 The categorical classification of eight variables. *ROSC time* time until return of spontaneous circulation; *GCS M* motor scale according to Glasgow Coma Scale; *GWR* gray matter to white matter attenuation ratio; *Alb* albumin; *Hb* hemoglobin. This figure was cited from a figure of Nishikimi's article [14]

a

	Correlation Coefficient
Initial Rhythm	*0.570 (a1)*
Witness / ROSC time	*1.040 (a2)*
pH	*1.167 (a3)*
Lactate	*0.338 (a4)*
GCS M	*2.225 (a5)*
GWR	*1.480 (a6)*
Alb	*1.077 (a7)*
Hb	*0.595 (a8)*
intercept	*-5.282 (a9)*

b

Scrore (A) = a1 x X1+a2 x X2 ...+a9

a: correlation coefficient
X: categorized variables in Fig.5.1

$$\textbf{Probability For Good Outcome} = \frac{(e^{-A})}{1 + (e^{-A})}$$

Fig. 5.2 Calculation used for the *post-Cardiac Arrest Syndrome for Therapeutic hypothermia score* (*CAST*). Using the categorical classification of eight variables (Fig. 5.1) and the correlation coefficients for the data (**a**), the resulting scores and probability of a good outcome were calculated (**b**). *ROSC time* time until return of spontaneous circulation; *GCS M* motor scale according to Glasgow Coma Scale; *GWR* gray matter to white matter attenuation ratio; *Alb* albumin; *Hb* hemoglobin. This figure was cited from a figure of Nishikimi's article [14] (partially modified)

system for PCAS [4, 12], but the calculation was a little complex. It needs some electronic devices for the calculation [16, 17]. Simplified version of CAST, which can be calculated more easily but has similar predictive accuracy, may be needed. Thus, the aim of this study is to develop the simplified version of the original CAST, which can calculate in an easier manner, condensed CAST (cCAST).

5.2 Methods

5.2.1 Study Design

A multicenter, retrospective, observational study was performed. The same patients' data had been retrospectively analyzed for developing the original score. A data of 151 adults who were admitted to four hospitals within the last 3–5 years to undergo TTM after cardiac arrest was reanalyzed: 54 patients treated at Nagoya University Hospital between April 2011 and March 2016, 23 patients treated at Chutouen General Medical Center between April 2013 and March 2016, 64 patients treated at Japan Red Cross Maebashi Hospital between April 2011 and March 2016, and ten patients treated at Komaki City General Hospital between April 2012 and March 2016. Eligible patients were all PCAS patients who were treated with TTM. They were excluded if they were traumatic cardiac arrest patients, or pediatric patients (age <18 years), or did not have lived independently prior to experiencing cardiac arrest.

5.2.2 Participating Hospital

The four participating hospitals are all tertiary emergency medical centers (Japanese centers for emergency patients with serious or life-threatening conditions): Nagoya University Hospital is an academic hospital; and Chutouen General Medical Center, Japan Red Cross Maebashi Hospital, and Komaki City General Hospital are general hospitals. Nagoya University Hospital and Japan Red Cross Maebashi Hospital are both located in a city and have 1035 and 592 beds each, including 26 and 12 ICU beds, respectively; these hospitals, respectively, treat about 12,000 and 20,000 emergency patients each year. Chutouen General Medical Center and Komaki City General Hospital are both located in the countryside and have 500 and 558 beds each, including 10 and 30 ICU/CCU beds; these hospitals treats about 20,000 and 30,000 emergency patients per year.

5.2.3 Data Set

Data was collected retrospectively from electronic chart reviews, including the clinical histories (age, sex, situation surrounding the cardiac arrest), cardiac rhythms, physical examinations (GCS, mydriasis), results of blood examinations (C-reactive protein [CRP], albumin [Alb], hemoglobin [Hb], glucose, creatinine, pH, lactate), cranial CT scan images, and clinical courses after admission. The gray matter attenuation to white matter attenuation ratio (GWR) was measured using the method described in previous report [15]. Physical examination was obtained just after return of spontaneous circulation, and results of blood examinations were obtained about 15 min before and after return of spontaneous circulation. CT scan images were obtained using an Aquilion64 (TOSHIBA) or SOMATOM Definition Flash (SIEMENS) within 6 h after the patient's cardiac arrest event.

5.2.4 Protocol of TTM

TTM was considered for cardiac arrest patients who were in a coma (GCS ≤8) after ROSC without remarkable hemodynamic instability or a "Do Not Attempt to Resuscitation" directive. A temperature between 34 and 36 °C was targeted by the infusion of cold fluids in combination with surface cooling, an ice pack and cold blanket, or a surface cooling device with a computerized automatic temperature control (Arctic Sun 2000 TTM; Bard Medical Louisville, CO). After the targeted temperature had been maintained for 24 h, rewarming to 36 °C was performed at a rate of 0.2 °C/4 h. Propofol, dexmedetomidine, midazolam, fentanyl, and rocuronium were used for sedation, analgesia, and muscle relaxation according to individual clinician preferences. At all the participating hospitals, the ventilator settings, fluid infusion, and doses of vasopressors, sedatives, and analgesics were adjusted so that the mean arterial pressure, pCO_2, and urine output were ≥80 mmHg, 35–45 mmHg, and ≥ 0.5 mL/kg/h, respectively, to maintain cerebral perfusion.

5.2.5 Neurological Outcome

We used the cerebral performance categories (CPC) at 30 days to estimate the neurological outcomes as with the original score [18]. The categories were grouped into either a good outcome (1–2) or a poor outcome (3–5).

5.2.6 Statistical Analysis

The statistical method for the development of CAST was shown in our previous study [15]. R software was used for all the statistical analyses.

5.3 Results

5.3.1 Simplified Version of CAST: Condensed CAST (cCAST)

The eight variables (initial rhythm, witnessed status and time until return of spontaneous circulation, pH, serum lactate, motor score according to the Glasgow Coma Scale, gray matter to white matter attenuation ratio, albumin, hemoglobin) on the original CAST were used for the development of cCAST, and the categorization was also performed as with the original (Fig. 5.1). First, the coefficients of the eight items in the cCAST were created by simplifying the correlation coefficients in the logistic regression analysis used for the original (initial rhythm, 0.570, was converted to 0.5; witnessed status and time until return of spontaneous circulation, 1.040 to 1.0; pH, 1.167 to 1.0; serum lactate, 0.338 to 0.5; motor score according to the Glasgow Coma Scale, 2.225 to 2.0; gray matter to white matter attenuation ratio, 1.480 to 1.5; albumin, 1.077 to 1.0; hemoglobin, 0.595 to 0.5). By using the simplified correlation coefficients and categorized variables, the cCAST has been developed (Fig. 5.3). If the score point is high, the probability of PCAS prognosis is poor, and if the score point is low, the probability is good.

Next, for the classification of cCAST, we created the scatter diagram using the all data (Fig. 5.4). Looking at this, we considered we could classify the prognosis most clearly when we set the threshold to 4 and 6. A cCAST of 3.5 or lower was associated with a 0.99 (95% CI, 0.94–1.00) sensitivity and a 0.73

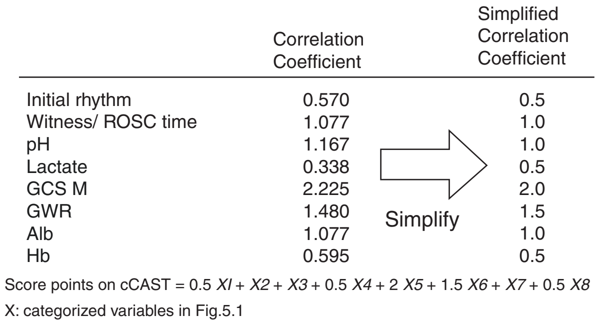

Fig. 5.3 The method to simplify the original CAST. The correlation coefficients in the logistic regression analysis used for the original CAST was simplified for the development of condensed CAST as shown in the figure. By using the simplified correlation coefficients and categorized variables, the cCAST has been developed. *ROSC time* time until return of spontaneous circulation; *GCS M* motor scale according to Glasgow Coma Scale; *GWR* gray matter to white matter attenuation ratio; *Alb* albumin; *Hb* hemoglobin

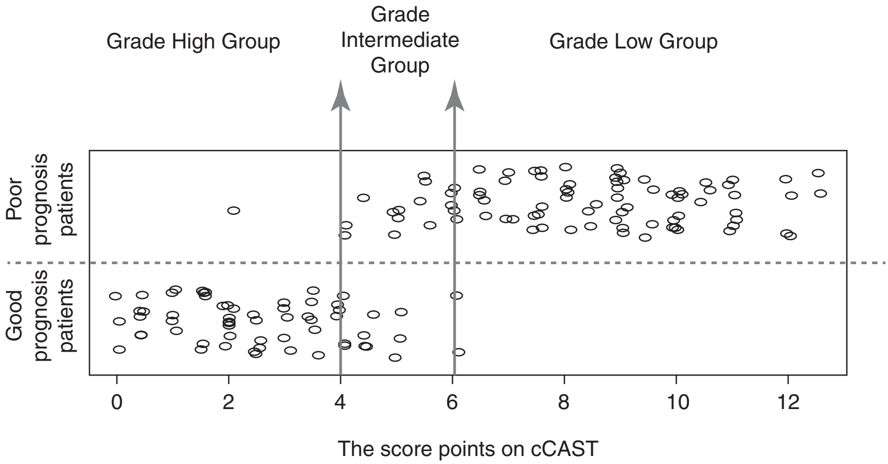

Fig. 5.4 The scatter diagram of the all analyzed patients showing relationship between their score points on cCAST and their neurological outcomes. Looking at this, we considered we could classify the prognosis the most clearly when we set the threshold to 4 and 6

(0.61–0.84) specificity for a poor outcome, and 6.5 or higher was with a 0.80 (0.71–0.88) and a 0.97 (0.89–1.00). Here, specificity measures the proportion of poor prognosis patients who were correctly identified as such. Using these thresholds, we created three grades in cCAST; Grade High (≤3.5), Grade Intermediate (4–6), and Grade Low (6.5 ≤). The 2% (1/48) of all patients classified into the Grade High group (score ≤3.5), 55% (17/31) into the Grade Intermediate group (4–6), and 97% (70/72) into the Grade Low group (≥ 6.5) showed poor outcomes (Table 5.1).

Table 5.1 The proportion of poor outcome patients in each group

cCAST	Grade	Proportion of poor outcome
≤3.5	High	1/48 (2%)
4–6	Intermediate	17/31 (55%)
6.5 ≤	Low	70/72 (97%)

Data are presented as absolute frequencies with percentages

5.4 Discussion

5.4.1 Clinical Use of cCAST

In this study, we created cCAST, which can estimate the prognosis of PCAS patients before the initiation of TTM without calculator. According to the scoring points, we set three grades: Grade High (≤3.5), Grade Intermediate (4–6), and Grade Low (6.5 ≤). While Grade High and Intermediate showed a certain possibility of recovery to a good outcome, Grade Low did not. Since TTM could increase the overall cost of care for all cardiac arrest survivors, the indications should be decided more carefully. Unfortunately, patients who do not have any likelihood of recovery may not be candidates for the critical care treatment including TTM. Thus, still challenging, it appeared that the PCAS patients who are classified into Grade Low may not be candidates for TTM.

However, we have to take care of the use of this scoring system. Note that it shows only the probability of outcome in a general population, not the precise probability for an individual patient [19]. Although predictive scores can be used to help guide decision-making and risk assessment for individual patients, their results are not absolute. Of course, the final therapeutic strategy should be decided after taking different factors into account (e.g., the results of discussions with family members, the patient's own wishes, the societal ethos, etc.), although the results of the scoring system can be used to guide judgment. Most importantly, a patient's exact neurological prognosis cannot be predicted without making decisive examinations, such as an electroencephalogram [15].

This condensed score can be also calculated using eight clinical parameters that are broadly available before the initiation of TTM. But if this scoring system could be combined with a neurological-specific marker or examination, such as NSE or S-100 or an electroencephalogram, it might be possible to predict patient outcome even more precisely. It would be of great interest to predict the neurological outcomes of PCAS patients using this scoring system and other tests before the initiation of TTM.

5.4.2 A Possibility of Further Simplification of cCAST

In future study, we have a plan for further simplification of cCAST by cutting down the value of GWR from the variables for cCAST. The GWR is one of the strongest tools for objectively measuring to detect the hypoxic encephalopathy, and many previous studies reported that GWR was beneficial for the estimation of PCAS prognosis [18, 20], but the calculation is a little complex, and the brain CT examination needs to be performed for the calculation. Some hospitals cannot always perform the brain CT examination before the initiation of TTM because of several factors such as shortage of radiology technician during night. If we can create the scoring system without the calculation of GWR, it would become useful for broader population.

5.4.3 Limitation

The predictive accuracy of the CAST and cCAST is limited because they were created using retrospective data, even though its generalizability is likely to be high since it was developed using data from multiple centers. The endpoint used in this study was 30 days. Although the outcome at 30 days has been used in a few studies that have attempted to establish a predictive score for cardiac arrest patients [4, 21], it may be better to set longer-term endpoints such as outcome at 90 days for predicting the future clinical course of the patients more accurately [22]. Further prospective validation of the CAST and cCAST and a study examining the utility of these scores for predicting long-term prognosis would be useful.

5.4.4 A Possibility of the Risk Classification for PCAS Using CAST

Finally, we describe a possibility that the CAST may be used for the risk classification of PCAS. After previous TTM trial showed no effect of therapeutic hypothermia as compared with normothermia [23], the optimal targeted setting temperature during TTM for PCAS remains unclear. One of the possible reasons why the aforementioned study failed to show a beneficial of TTM at lower targeted setting temperature is that the subject population in that study included PCAS patients of all grades, including the highest and lowest grade, of severity. Logically, the effect size of TTM at lower targeted temperature would be expected to differ according to the severity of PCAS, and there may be a group with a particular severity who has more benefit from it. In actual clinical practice, we may feel that if the PCAS patients had several signs for poor prognosis prediction (if their cardiac arrest was no witness, the time until return of spontaneous circulation was over 1 h, and they had the presence of findings of hypoxic encephalopathy in their brain CT), they may remain poor outcome even if they underwent TTM at lower targeted temperature. On the other hand, we may feel that if they had several signs for good prognosis prediction (if their cardiac arrest was with witness and bystander and the time until return of spontaneous circulation was only 1 min), they will show good outcome even if they did not undergo TTM at lower targeted temperature. The group who had most

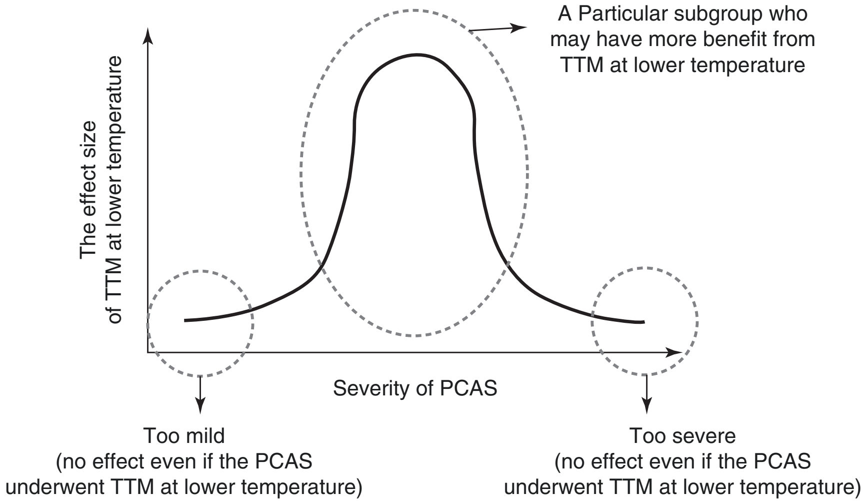

Fig. 5.5 Schema of our hypothesis. The group who had most benefit from TTM at lower targeted temperature may be not too severe and not too mild group, in other words, the intermediate group according to their severity. *TTM* targeted temperature management; *PCAS* post-cardiac arrest syndrome

benefit from TTM at lower targeted temperature may be not too severe and not too mild group, in other words, the intermediate group according to their severity (Fig. 5.5).

Considering that the CAST is the score for predicting the neurological prognosis in PCAS patients before the initiation of TTM, the probability for good prognosis on CAST may be able to be converted to their severity, and it may be also useful for the risk classification of PCAS treated with TTM. For example, the patients who showed poor prognosis on CAST may be regarded as “severe PCAS,” and such patients may show a poor outcome regardless of the targeted temperature in TTM. On the other hand, the patients who showed good prognosis on CAST may be regarded as “mild PCAS,” and such patients may show a good outcome regardless of the targeted temperature in TTM. Based on our assumption, it would be great interest of investigating the correlation between the targeted setting temperature in TTM and the neurological outcome among the intermediate score group patients on CAST in future study.

5.5 Conclusion

The cCAST can be calculated more easily and is useful for estimating the prognosis of PCAS patients, explaining patients’ conditions to their family, and possibly making the decision before the initiation of TTM, as with the original. Further prospective validation of the CAST and cCAST would be needed.

References

1. Gajarski RJ, Smitko K, Despres R, Meden J, Hutton DW. Cost-effectiveness analysis of alternative cooling strategies following cardiac arrest. Springerplus. 2015;4:427.
2. Reynolds JC, Frisch A, Rittenberger JC, Callaway CW. Duration of resuscitation efforts and functional outcome after out-of-hospital cardiac arrest: when should we change to novel therapies? Circulation. 2013;128(23):2488–94.
3. Kaneko T, Kasaoka S, Nakahara T, Sawano H, Tahara Y, Hase M, et al. Effectiveness of lower target temperature therapeutic hypothermia in post-cardiac arrest syndrome patients with a resuscitation interval of </=30 min. J Intensive Care. 2015;3(1):28.
4. Seeger FH, Toenne M, Lehmann R, Ehrlich JR. Simplistic approach to prognosis after cardiopulmonary resuscitation-value of pH and lactate. J Crit Care. 2013;28(3):317 e313–20.
5. Mullner M, Sterz F, Domanovits H, Behringer W, Binder M, Laggner AN. The association between blood lactate concentration on admission, duration of cardiac arrest, and functional neurological recovery in patients resuscitated from ventricular fibrillation. Intensive Care Med. 1997;23(11):1138–43.
6. Kliegel A, Losert H, Sterz F, Holzer M, Zeiner A, Havel C, et al. Serial lactate determinations for prediction of outcome after cardiac arrest. Medicine (Baltimore). 2004;83(5):274–9.
7. Grossestreuer AV, Abella BS, Leary M, Perman SM, Fuchs BD, Kolansky DM, et al. Time to awakening and neurologic outcome in therapeutic hypothermia-treated cardiac arrest patients. Resuscitation. 2013;84(12):1741–6.
8. Golan E, Barrett K, Alali AS, Duggal A, Jichici D, Pinto R, et al. Predicting neurologic outcome after targeted temperature management for cardiac arrest: systematic review and meta-analysis. Crit Care Med. 2014;42(8):1919–30.
9. Young GB. Clinical practice. Neurologic prognosis after cardiac arrest. N Engl J Med. 2009;361(6):605–11.
10. Oddo M, Rossetti AO. Early multimodal outcome prediction after cardiac arrest in patients treated with hypothermia. Crit Care Med. 2014;42(6):1340–7.
11. Hayakawa K, Tasaki O, Hamasaki T, Sakai T, Shiozaki T, Nakagawa Y, et al. Prognostic indicators and outcome prediction model for patients with return of spontaneous circulation from cardiopulmonary arrest: the Utstein Osaka project. Resuscitation. 2011;82(7):874–80.
12. Goto Y, Maeda T, Goto Y. Decision-tree model for predicting outcomes after out-of-hospital cardiac arrest in the emergency department. Crit Care. 2013;17(4):R133.
13. Adrie C, Cariou A, Mourvillier B, Laurent I, Dabbane H, Hantala F, et al. Predicting survival with good neurological recovery at hospital admission after successful resuscitation of out-of-hospital cardiac arrest: the OHCA score. Eur Heart J. 2006;27(23):2840–5.
14. Nishikimi M, Matsuda N, Matsui K, Takahashi K, Ejima T, Liu K, et al. CAST: a new score for early prediction of neurological outcomes after cardiac arrest before therapeutic hypothermia with high accuracy. Intensive Care Med. 2016;42(12):2106–7.
15. Nishikimi M, Matsuda N, Matsui K, Takahashi K, Ejima T, Liu K, et al. A novel scoring system for predicting the neurologic prognosis prior to the initiation of induced hypothermia in cases of post-cardiac arrest syndrome: the CAST score. Scand J Trauma Resusc Emerg Med. 2017;25(1):49.
16. CAST for iPad. https://geo.itunes.apple.com/jp/app/meidai-score-for-ipad/id1065338535?mt=8. Accessed 20 Jan 2018.
17. CAST for iPhone. https://geo.itunes.apple.com/jp/app/meidai-score-for-iphone/id1067612773?mt=8. Accessed 20 Jan 2018.
18. Takahashi N, Satou C, Higuchi T, Shiotani M, Maeda H, Hirose Y. Quantitative analysis of brain edema and swelling on early postmortem computed tomography: comparison with antemortem computed tomography. Jpn J Radiol. 2010;28(5):349–54.
19. Nielsen N. Predictive scores, friend or foe for the cardiac arrest patient. Resuscitation. 2012;83(6):669–70.

20. Metter RB, Rittenberger JC, Guyette FX, Callaway CW. Association between a quantitative CT scan measure of brain edema and outcome after cardiac arrest. Resuscitation. 2011;82(9):1180–5.
21. Aschauer S, Dorffner G, Sterz F, Erdogmus A, Laggner A. A prediction tool for initial out-of-hospital cardiac arrest survivors. Resuscitation. 2014;85(9):1225–31.
22. Becker LB, Aufderheide TP, Geocadin RG, Callaway CW, Lazar RM, Donnino MW, et al. Primary outcomes for resuscitation science studies: a consensus statement from the American Heart Association. Circulation. 2011;124(19):2158–77.
23. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. N Engl J Med. 2013;369(23):2197–206.