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Clinical paper

External validation of the TiPS65 score for predicting good neurological outcomes in patients with out-of-hospital cardiac arrest treated with extracorporeal cardiopulmonary resuscitation

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Abstract

Aim: Estimating prognosis of patients treated with extracorporeal cardiopulmonary resuscitation (ECPR) is essential for selecting candidates. The TiPS65 score can predict neurological outcomes of patients with out-of-hospital cardiac arrest (OHCA) treated with ECPR. We aimed to perform an external validation of this score.

Methods: Data from the Japanese Association for Acute Medicine Out-of-Hospital Cardiac Arrest registry, a multicentred, nationwide, prospectively registered database, were analysed. All adult patients with OHCA and shockable rhythm and treated with ECPR between January 2018 to December 2019 were included. In the TiPS65 score, age, call-to-hospital arrival time, initial cardiac rhythm at hospital arrival, and initial pH value were used as predictors. The primary outcome was 30-day survival with favourable neurological outcomes (Cerebral Performance Category 1 or 2). Discrimination, using the *C*-statistic, and predictive performances of each score, such as sensitivity and specificity, were investigated.

Results: Of 590 included patients (517 [81.6%] men; median [interquartile range] age, 60 [50–69] years), 64 (10.8%) reported favourable neurological outcomes. The *C*-statistic of the TiPS65 score was 0.729 (95% confidence interval (CI): 0.672–0.786). When the cut-off of TiPS65 score was set to >1, the sensitivity and specificity were 0.906 (95%CI: 0.807–0.965) and 0.430 (95%CI: 0.387–0.473), respectively; conversely, when the cut-off was set to >3, they were 0.172 (95%CI: 0.089–0.287) and 0.971 (95%CI: 0.953–0.984), respectively.

Conclusions: The TiPS65 score shows reasonable discrimination and predictive performances. This score can be supportive in the decision-making process for the selection of eligible patients for ECPR in clinical settings.

Keywords: Out-of-hospital cardiac arrest, Extracorporeal cardiopulmonary resuscitation, Prediction model

Abbreviations: ECPR, extracorporeal cardiopulmonary resuscitation, OHCA, out-of-hospital cardiac arrest, ECMO, extracorporeal membrane oxygenation, VF, ventricular fibrillation, JAAM-OHCA, Japanese Association for Acute Medicine Out-of-Hospital Cardiac Arrest, EMS, emergency medical services, AED, automated external defibrillator, CPC, Cerebral Performance Category, IQR, interquartile range, CI, confidence interval, PPV, positive predictive value, NPV, negative predictive value, LR+, positive likelihood ratio, LR-, negative likelihood ratio

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Introduction

Extracorporeal cardiopulmonary resuscitation (ECPR) specifically refers to the deployment of veno-arterial extracorporeal membrane oxygenation (ECMO) before the return of spontaneous circulation (ROSC) during cardiac arrest, and it is considered as one of the advanced resuscitation procedures. Once initiated, the patient's blood is drained from a central vein and returned to the aorta after being pumped through a membrane lung to provide gas exchange and blood flow to vital organs in the absence of spontaneous circulation.[1] ECPR is expected to improve survival and neurological and functional recovery in patients with out-of-hospital cardiac arrest (OHCA), especially those with refractory ventricular fibrillation (VF).[2–5] However, ECPR requires significant financial and personnel resources[6,7] and is an invasive procedure that can cause serious adverse events such as bleeding, limb ischaemia, and infection.[8,9] Therefore, it is important to select appropriate candidates who are likely to be benefitted more from ECPR, rather than applying it to all patients with OHCA. Although an international expert consensus has recently been proposed,[10] validated criteria for the selection of patients for ECPR are insufficient. If the prognosis of the patients treated with ECPR can be predicted, then this may help clinicians select the appropriate patients.

Clinical prediction models can be useful tools for estimating the prognosis of patients in emergency departments. Recently, the TiPS65 scoring system was developed for predicting the neurological outcomes of adult patients with OHCA treated with ECPR using a nationwide OHCA registry in Japan.[11] It is a simplified score involving four variables, namely, time from call to hospital arrival, pH value, cardiac rhythm on hospital arrival, and age; the data that can be easily collected on hospital arrival. The TiPS65 scoring system showed good discrimination and calibration performance for predicting favourable neurological outcomes of patients with OHCA and shockable rhythm who were treated with ECPR.[11] Although many other prognostic prediction models have been developed for patients with OHCA,[12] very few have focused on patients requiring ECPR, and the existing models related to ECPR have included only patients with hypothermic cardiac arrest who underwent rewarming with ECPR.[13,14] Thus, TiPS65 is the only model that can predict outcomes in patients with OHCA treated with ECPR. However, this score has not yet been externally validated in other studies, and its reproducibility needs to be evaluated for further application. This study aimed to validate the predictive performance of the TiPS65 score using data different from the original study.

Methods

This study was reported according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[15] Study approval was granted by the Ethics Committee of the Kyoto University Graduate School of Medicine (R1045) and the participating hospitals. The requirement for individual patient consent was waived due to the observational nature of the study.

Study design and setting

This observational study analysed data from the Japanese Association for Acute Medicine Out-of-Hospital Cardiac Arrest (JAAM-OHCA) registry, a nationwide, multicentre, prospectively registered database of OHCA patients who are transported to hospitals in Japan. The details of the registry are described elsewhere.[16] In brief, the registry includes pre-hospitalisation information collected by emergency medical services (EMS) using the standardised Utstein-style template[17] and in-hospital data, including treatments and outcomes reported by the physicians or clinical data administrators, at each institution. As of December 2019, 83 hospitals in Japan, including university hospitals and/or tertiary critical care centres, were participating in this registry. In total, 57,754 patients have been registered from June 2014 to December 2019, and their data are currently available.

Data from January 2018 to December 2019 were used in the current validation study, while data from January 2014 to December 2017 were used in the score development study.[11] For the validation study, the duration was chosen as the period prior to publication of the original study. The validation study cohort included all participating 68 hospitals where eligible patients were treated, while the development cohort included 35 of these hospitals. Hence, our study can be regarded as a temporal and geographical validation study. As the same registry was used in both studies, the definitions of predictors and outcomes were identical.

Participants

We included all adult patients (age ≧18 years) with OHCA and shockable rhythm who were treated with ECPR. Patients with shockable rhythm were identified by any of the following parameters: those with VF or pulseless ventricular tachycardia confirmed by paramedics at the scene or clinicians at hospital arrival, those defibrillated by bystanders with public access automated external defibrillators (AEDs), or those defibrillated by paramedics before hospital arrival. ECPR was defined as emergency veno-arterial ECMO in patients who had sustained cardiac arrest at the time of hospital arrival. The decision to perform ECPR was made by the attending physician.

Patients who were not resuscitated in the hospital, such as those with rigor mortis or do-not-resuscitate orders, were excluded. The following were also excluded: patients transported to the participating hospitals after receiving any treatment at other hospitals, patients with traumatic cardiac arrest, patients with no pre-hospital data, patients with confirmed spontaneous resuscitation at the time of hospital arrival, and patients who opted out of the study. These eligibility criteria were the same as those used in the original development study.[11]

Outcome measurements

The Cerebral Performance Category (CPC) was used to determine the neurological outcomes, where CPC 1 denotes good cerebral performance; CPC 2, moderate cerebral disability; CPC 3, severe cerebral disability; CPC 4, coma or vegetative state; and CPC 5, death.[18] The primary outcome of our study was 30-day survival with favourable neurological outcomes, as defined by CPC 1 or 2. The CPC was determined by the attending physician. Since the original development study was not published during our study period, the outcomes were assessed without the use of the TiPS65 score.

Prediction model of interest

TiPS65 is the acronym of its constituent variables: Ti, time from the call for an ambulance to hospital arrival, ≤25 min; P, pH value on admission, ≥7.0; S, shockable rhythm on hospital arrival; and 65, age ≤ 65 years.[10] One point is assigned to each of these four predictors, and the total score ranges from 0 to 4 points. We used the same predictors that were used in the original study. All these variables can be measured objectively. The TiPS65 scoring system is summarised in Table 1.

Sample size estimation

In this study, we used the data that were not used in the original development study. It has been suggested that at least 100 events are required for the external validation of prediction models.[19] Although the number of events in the study cohort was expected to be less than 100, this registry is the largest database of patients with OHCA, including information about ECPR in Japan, and there is no alternative database available.

Data collection

We extracted relevant clinical information such as sex, age, bystander cardiopulmonary resuscitation (CPR), initial rhythm at the scene and hospital arrival, and 30-day survival status from the registry. The definitions of the variables are listed in Additional file eTable 1. To calculate the TiPS65 score for the patients, the continuous variables included in the score were categorised according to the cut-offs specified in the 'Prediction model of interest' section. We performed nonparametric missing value imputation using the 'missForest' algorithm in R package.[20] Missing values were imputed by an algorithm with a random forest using the other variables in the matrix as predictors. The imputation approach was repeated until prediction accuracy was stable. Then the matrix with no missing values was returned. We included all available patient characteristics and outcomes in the matrix applying this imputation method. Furthermore, we performed a complete case analysis using the data with no missing value for the four variables of the TiPS65 score as a sensitivity analysis. The details of missing data are available in Additional file eTable 2.

Table 1 – TiPS65 scoring system.

Variable	Score
Time from call to hospital arrival $\leq$ 25 min	1
pH $\geq$ 7.0	1
Shockable on hospital arrival	1
Age $\leq$ 65 years	1
Sum	4

Abbreviations: TiPS65, time from call to hospital arrival; pH, pH in initial blood gas assessment; shockable, shockable rhythm on hospital arrival.

Statistical analysis

Patient characteristics were described using medians and interquartile ranges (IQRs) for continuous variables and numbers and percentages for categorical variables. To assess the discrimination performance, we calculated the *C*-statistic and 95% confidence intervals (CIs) for the TiPS65 score. We showed the observed outcome probabilities with 95% CIs for each score. In addition, we visually compared the observed outcomes and the predictive probabilities of the outcomes for each TiPS65 score category (0, 1, 2, 3–4) derived from the original study[11] using a bar plot.

We considered the need for updating the model by evaluating the discrimination and calibration performances and by using a closed testing procedure,[21] a method that compared the following model updates: 1) updating the intercept; 2) updating both, intercept and slope; and 3) re-estimating the model coefficients. *P* values < 0.05 were considered statistically significant in the closed test procedure. In this updating evaluation, we used the logistic regression formula developed in the original study[11] (Additional file eAppendix 1). To assess the prognostic accuracy for each TiPS65 score, we calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR−) with 95% CIs. Moreover, we performed a decision curve analysis to assess the net benefit and clin-

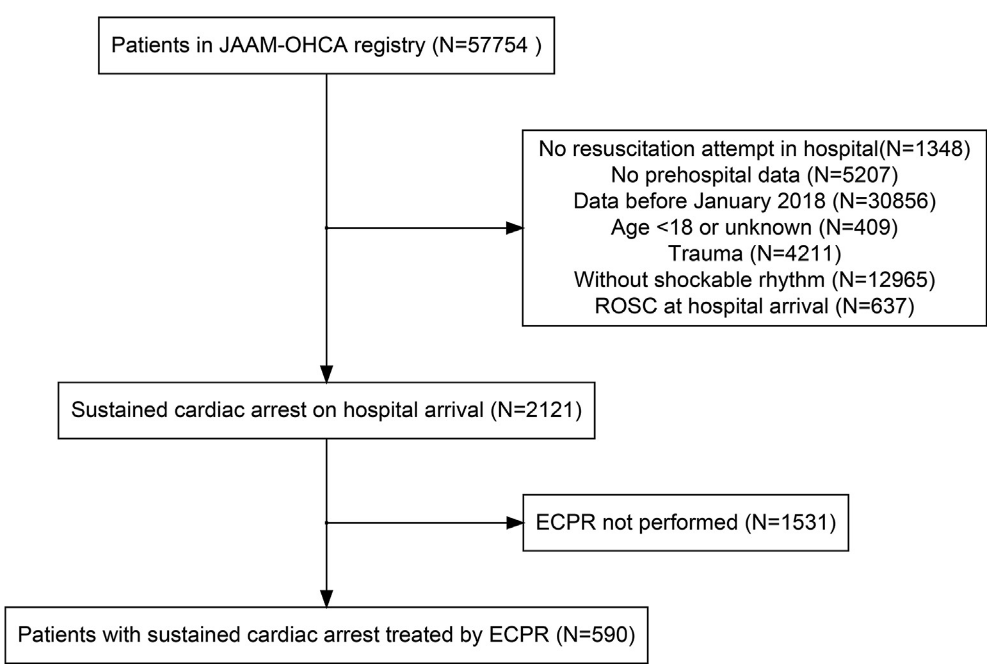

Fig. 1 – Study flowchart. JAAM-OHCA, Japanese Association for Acute Medicine Out-of-Hospital Cardiac Arrest; ROSC, return of spontaneous resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation.

ical usefulness of the score[22] for our validation cohort. The following four strategies for selecting patients for ECPR were compared: selecting all patients for the intervention (treat all), selecting no patients (treat none), selecting patients using predicted probability based on age alone, and selecting patients using the TiPS65 score. The net benefit and decision curve analysis are detailed in Additional file eAppendix 2. All statistical analyses were performed using R software (version 4.1.0).

Results

Patient characteristics

Of the 57,754 patients in the JAAM-OHCA registry, 590 patients treated with ECPR were included in the analysis (517 [87.6%] men; median [IQR] age, 60 [50–69] years) (Fig. 1; Table 2). Most patients had witnessed cardiac arrest (78.1%), and more than half had received bystander CPR (58.3%); 151 (26%) had survived the 30-day period, and 64 (10.8%) showed favourable neurological outcomes after 30 days. Other patient characteristics including pre- and in-hospital data are listed in Table 2. The characteristics of this validation cohort were generally comparable to those of the TiPS65 development cohort (Additional file eTable 3). The characteristics of the complete case analysis cohort are summarised in Additional file eTable 4.

Model performance

The *C*-statistic of the TiPS65 score was 0.729 (95%CI: 0.672–0.786). The proportions of observed outcomes for TiPS65 scores of 0, 1, 2, 3, and 4 with 95%CIs were 0.0% (0.0–9.0%), 3.1% (1.1–6.6%), 12.2% (8.2–17.2%), 18.2% (11.5–26.7%), and 42.3% (23.4–63.1%), respectively (Fig. 2). The complete case analysis showed generally similar results (Additional file eFigure 1). The predicted probabilities derived from the original TiPS65 study and observed outcomes for each TiPS65 score category are described in Additional file eFigure 2. Although the TiPS65 score tended to slightly overestimate the probabilities of outcomes for patients with high scores, these were generally consistent. The calibration plot of the logistic regression formula prediction model is also illustrated in Additional file eFigure 3. Since the intercept was −0.273, we considered it may be appropriate to update the model. However, the closed test showed no statistically significant difference between the original and the updated models; hence, we retained the original

Table 2 – Patient characteristics.

		30-day neurological outcome	
Characteristic	Overall, N = 590	Favourable, N = 64	Unfavourable, N = 526
Men	517 (87.6)	55 (85.9)	462 (87.8)
Age, years			
Median	60 (50, 69)	56 (45, 64)	61 (51, 69)
18–64	358 (60.7)	48 (75.0)	310 (58.9)
65–74	166 (28.1)	12 (18.8)	154 (29.3)
≥75	66 (11.2)	4 (6.2)	62 (11.8)
Witnessed	461 (78.1)	56 (87.5)	405 (77.0)
Bystander CPR	344 (58.3)	37 (57.8)	307 (58.4)
Shock by public access AEDs	64 (10.8)	7 (10.9)	57 (10.8)
Shock by paramedics	572 (96.9)	62 (96.9)	510 (97.0)
Initial rhythm confirmed by paramedics at the scene			
Shockable[a]	473 (80.2)	54 (84.4)	419 (79.7)
Nonshockable[b]	117 (19.8)	10 (15.6)	107 (20.3)
Initial rhythm on hospital arrival			
Shockable[a]	347 (58.8)	56 (87.5)	291 (55.3)
Nonshockable[b]	243 (41.2)	8 (12.5)	235 (44.7)
Time from call to hospital arrival, min			
Median	31 (25, 38)	27 (22, 35)	31 (26, 39)
≤25	153 (25.9)	28 (43.8)	125 (23.8)
26–35	240 (40.7)	21 (32.8)	219 (41.6)
36–45	135 (22.9)	10 (15.6)	125 (23.8)
>45	62 (10.5)	5 (7.8)	57 (10.8)
Treated by tertiary centre	559 (95)	60 (94)	499 (95)
Initial pH on hospital arrival			
Median	6.96 (6.86, 7.06)	7.02 (6.88, 7.13)	6.95 (6.85, 7.04)
≥7.0	221 (37.5)	34 (53.1)	187 (35.6)
6.9–7.0	163 (27.6)	12 (18.8)	151 (28.7)
6.8–6.9	125 (21.2)	11 (17.2)	114 (21.7)
<6.8	81 (13.7)	7 (10.9)	74 (14.1)
Time from call to blood gas, min	44 (35, 58)	45 (35, 58)	44 (35, 58)
Time from call to ECPR start, min	55 (46, 67)	48 (42, 60)	56 (47, 68)

Continuous variables are described as median (IQR, interquartile range). Categorical variables are described as number (%).

CPR, cardiopulmonary resuscitation; AED, automated external defibrillator; ECPR, extracorporeal cardiopulmonary resuscitation.

[a] Shockable: ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT).

[b] Nonshockable: pulseless electrical activity (PEA) and asystole.

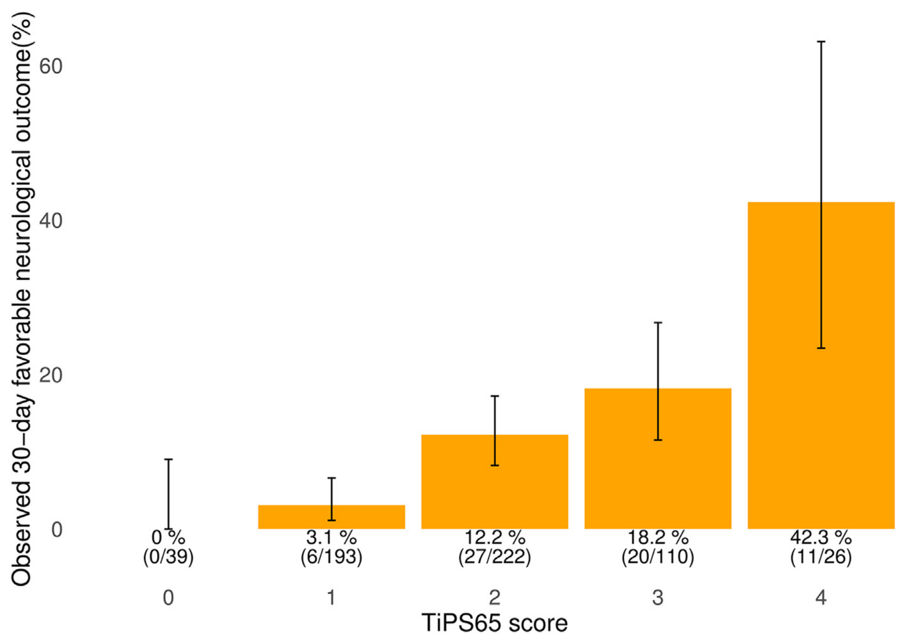

Fig. 2 – Proportion of observed outcomes by each TiPS65 score. The values in parentheses represent the numbers of outcomes and patients for each score.

model. The details of the updated models are summarised in Additional file eFigure 4–6.

The predictive accuracies (sensitivity, specificity, PPV, NPV, LR+, LR−) are summarised in Table 3. When the cut-off of TiPS65 score was set to > 1, the sensitivity and specificity were 0.906 (95%CI: 0.807–0.965) and 0.430 (95%CI: 0.387–0.473), respectively; conversely, when the cut-off was set to > 3, they were 0.172 (95%CI: 0.089–0.287) and 0.971 (95%CI: 0.953–0.984), respectively. The complete case analysis also showed similar results (Additional file eTable 5). Furthermore, we performed a decision curve analysis (Additional file eFigure 7). The net benefit of using this score was greater than that of using other strategies at almost all threshold probabilities.

Discussion

Key observations and strengths

In this multicentre cohort study, the TiPS65 score showed reasonable external validity for predicting the neurological outcomes of patients with OHCA treated with ECPR. The *C*-statistic of the model was 0.729 (95%CI: 0.672–0.786), which is comparable to the *C*-statistic reported in the original development study (0.741, 95%CI: 0.682–0.792). At a cut-off score of >1, the TiPS65 score showed high sensitivity (0.906, 95%CI: 0.807–0.965), while at a cut-off score of >3, it showed high specificity (0.971, 95%CI: 0.953–0.984).

The TiPS65 score has some advantages compared to other models for OHCA patients. First, clinical prediction models need to be externally validated to ensure reproducibility and generalisability before they are applied in clinical practice, but some of the models for patients with OHCA have not been externally validated for different data or settings.[23–25] However, we have conducted rigorous temporal and geographical external validation of the TiPS65 scoring system using a nationwide registry. Second, the TiPS65 score includes variables that are available immediately after the arrival of patients with OHCA at the hospital. Previous studies suggested that prolonged low-flow duration before ECPR resulted in unfavourable neurological outcomes.[26,27] Hence, a prompt decision to initiate ECPR is desirable. In a previous study, current heart disease and ECMO blood flow were suggested to be prognostic factors for patients after ECPR,[28] but information regarding these parameters, which could be used in decision-making for the application of ECPR, is difficult to obtain during the initial period of resuscitation. However, the TiPS65 variables such as age, time, and initial rhythm are routinely collected from patients at hospital arrival, and the pH value can be obtained by blood gas analysis during femoral cannulation, which can help in deciding the initiation of ECPR.

Interpretation of the results

The TiPS65 score slightly overestimated the probabilities of favourable outcomes, especially for patients with high scores. This could be because the absolute number of outcomes in the population was small. However, in most clinical settings, the threshold probability for implementing ECPR is assumed to be approximately 20–25%, based on the mean probability of good neurological outcomes reported in a previous systematic review.[29] Accordingly, even if the predictive probability for good prognosis is overestimated, such as at TiPS65 scores of 3 or 4, it would not have a significant impact on the decision-making process for the implementation of ECPR. Moreover, the calibration intercept (−0.273) was lower than the ideal value of 0, indicating that the incidence of outcomes was lower in this validation cohort than in the original cohort, but the actual difference of the incidence was small (10.8 vs 12.4%). This may be the reason why the closed test result did not support updating the TiPS65 model. Our study sample size was small, and this could have compromised the model's performance including the intercept and the statistical power of the tests for model updates.

Table 3 – Predictive accuracy of the TiPS65 score for each cut-off score.

Values of TiPS65	Sensitivity [95% CI][†]	Specificity [95% CI][†]	PPV [95% CI][†]	NPV [95% CI][†]	LR+ [95% CI][†]	LR− [95% CI][†]
>0	1.000 [0.944–1.000]	0.074 [0.053–0.100]	0.116 [0.091–0.146]	1.000 [0.910–1.000]	1.080 [1.054–1.106]	–
>1	0.906 [0.807–0.965]	0.430 [0.387–0.473]	0.162 [0.125–0.204]	0.974 [0.945–0.990]	1.589 [1.426–1.771]	0.219 [0.102–0.471]
>2	0.484 [0.358–0.613]	0.800 [0.764–0.834]	0.228 [0.160–0.308]	0.927 [0.899–0.949]	2.420 [1.783–3.284]	0.645 [0.508–0.819]
>3	0.172 [0.089–0.287]	0.971 [0.953–0.984]	0.423 [0.234–0.631]	0.906 [0.879–0.929]	6.027 [2.894–12.550]	0.853 [0.763–0.954]

The predictive performance is calculated to predict good neurological outcomes.
CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR−, negative likelihood ratio.
† Confidence intervals were estimated according to the definition of Clopper and Pearson.

Clinical implications

Our findings have some important implications for actual clinical settings. First, the TiPS65 score can assist the decision-making process for initiating ECPR. For example, if the score is 1 or 0, the LR− for a good prognosis is adequately low; hence, most physicians would consider it reasonable not to perform ECPR. In contrast, if the score is 4, the LR+ for a good prognosis is high; therefore, aggressive treatment with ECPR can be considered. If the score is 2 or 3, the probability of a good prognosis is estimated to be approximately 15%. Since this is not considered a sufficient threshold for all clinicians to implement ECPR, the decision-making should be based on the experience of the physician, patient values, and circumstances. Thus, the TiPS65 score can promote appropriate allocation of medical resources and prevent unnecessary resuscitation attempts. Second, the TiPS65 score may help researchers select the target populations for future clinical trials. ECPR should be used only for those patients who would benefit from it;[30] therefore, it is important to select eligible candidates for studies examining the efficacy of ECPR. The eligibility criteria of recent randomised controlled trials (RCTs) of ECPR versus conventional CPR for OHCA are discordant,[5,31] contributing to the heterogeneity of the results. Hence, models such as the TiPS65 score can be used to develop standardised eligibility criteria for clinical trials. In addition, our results may contribute to the development of tailored treatment strategies for this group of patients.

Limitations

This study has several limitations. First, the indications for ECPR and patient management practices after ECPR at the participating hospitals were not specified. However, since the Japanese EMS system and medical insurance system is well developed and most of the included hospitals were university hospitals and/or tertiary critical care centres, we assumed that the patients received standard care including ECPR based on standard clinical practice guidelines. Second, if the treatment strategy is determined according to the variables of the TiPS65 score, it can lead to a self-fulfilling prophecy bias, which increases the risk of overestimating model performance.[32] However, we believe this bias was minimised because our study period did not extend beyond the date of publication of the original study. Third, there were only 26 of 590 at the TiPS65 cut-off score of >3. Hence the accuracy in the estimates of the predictive performance may be limited. Fourth, this study did not examine the impact of the utilisation of the TiPS65 score on clinical outcomes. The effectiveness of treatment strategies based on this score should be examined in future interventional studies. Finally, the generalisability of theTiPS65 score to other countries has not been validated, since our study focused on temporal and geographic validation and evaluation of the reproducibility of the model performance in the context of the Japanese population only. Model performance tends to decline in settings with different proportions of outcomes and effects of predictors.[33] Therefore, further studies are needed to assess the validity of this scoring system in other independent settings.

Conclusion

We validated the TiPS65 score externally for predicting the neurological outcomes of patients with OHCA treated with ECPR; the score showed favourable discrimination and predictive performances.

The use of this score is expected to be helpful in the decision-making process for initiating ECPR in actual clinical settings.

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Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available as it is not permitted by the Ethics Committee. Data are available from the corresponding author on reasonable request.

Conflict of interests

Yohei Okada has received funding from the ZOLL Foundation, an overseas research scholarship from the Fukuda Foundation for Medical Technology, and the International Medical Research Foundation.

Other authors declare that they have no competing interests.

CRediT authorship contribution statement

Yuto Makino: Conceptualization, Methodology, Software, Resources, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Yohei Okada:** Conceptualization, Methodology, Writing – review & editing. **Taro Irisawa:** Investigation, Resources, Project administration. **Tomoki Yamada:** Investigation, Resources. **Kazuhisa Yoshiya:** Investigation, Resources. **Changhwi Park:** Investigation, Resources. **Tetsuro Nishimura:** Investigation, Resources. **Takuya Ishibe:** Investigation, Resources. **Hitoshi Kobata:** Investigation, Resources. **Takeyuki Kiguchi:** Investigation, Resources. **Masafumi Kishimoto:** Investigation, Resources. **Sung-Ho Kim:** Investigation, Resources. **Yusuke Ito:** Investigation, Resources. **Taku Sogabe:** Investigation, Resources. **Takaya Morooka:** Investigation, Resources. **Haruko Sakamoto:** Investigation, Resources. **Keitaro Suzuki:** . **Atsunori Onoe:** Investigation, Resources. **Tasuku Matsuyama:** Formal analysis, Data curation. **Satoshi Matsui:** Formal analysis, Data curation. **Norihiro Nishioka:** Formal analysis, Data curation. **Satoshi Yoshimura:** Formal analysis, Data curation. **Shunsuke Kimata:** Formal analysis, Data curation. **Shunsuke Kawai:** Formal analysis, Data curation. **Ling Zha:** Formal analysis, Data curation. **Kosuke Kiyohara:** . **Tetsuhisa Kitamura:** Validation, Data curation, Writing – review & editing, Funding acquisition. **Taku Iwami:** Conceptualization, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2022.11.018.

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