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Clinical paper

Multimodal approach for neurologic prognostication of out-of-hospital cardiac arrest patients undergoing targeted temperature management

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Abstract

Aim: Since the introduction of targeted temperature management (TTM), the accuracy and timing of prognostic tests for post-cardiac arrest patients have changed. Although previous studies have demonstrated the effectiveness of a multimodal approach in assessing the prognosis of TTM patients, few studies have investigated an optimised strategy that sequentially combines different prognostic modalities. This study identified an optimal sequential combination of prognostic modalities to predict poor neurologic outcomes in patients undergoing TTM.

Methods: We performed a retrospective analysis using TTM management registry data. All patients underwent an identical sequence of prognostic tests at fixed timings. The sequence included brain computed tomography (CT), serum neuron-specific enolase (NSE), electrophysiological examination, neurologic examination, and diffusion-weighted imaging. We used hierarchical classification and regression tree analysis to find the optimal prognostic model. The primary measure was a poor neurologic outcome at one month after cardiac arrest.

Results: A total of 192 patients were included and 103 patients (53.6%) had poor neurologic outcomes. The final model consisted of brain CT, serum NSE, electroencephalogram, somatosensory-evoked potentials, and pupil light reflex. Our model predicted poor outcomes with a 0% false positive rate. Moreover, our model had an area under the receiver operating characteristic curve value of 0.911 (95% confidence interval, 0.872–0.950), which was significantly higher than that of each prognostic modality alone.

Conclusions: Our stepwise model showed excellent prognostic ability to predict poor outcomes at one month after cardiac arrest and may be used to minimise the risk of false pessimistic predictions in patients undergoing TTM.

Keywords: Targeted temperature management, Prognostication, Cardiac arrest, Prediction model

Introduction

Since the introduction of targeted temperature management (TTM), the accuracy and timing of diagnostic tests for predicting a poor outcome in comatose post-cardiac arrest patients have changed because of TTM-induced attenuation of brain injury and the influence of sedative and neuromuscular blocking agents used to induce and maintain hypothermia.[1–7] Therefore, current guidelines recommend delayed prognostication after TTM, based on multiple prognostic

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modalities such as neurologic and electrophysiological examinations, biochemical marker assessment, and neuroimaging.[7–9] Previous studies have demonstrated that a multimodal approach is effective in assessing the prognosis of patients undergoing TTM.[9–12] However, to our knowledge, no research has been conducted to develop a systematic strategy using sequentially combined prognostic modalities based on quantitative analysis for patients undergoing TTM. Two review articles suggested stepwise multimodal algorithms for outcome prognostication after cardiac arrest; however, these algorithms were developed based solely on the reviewed evidence and were not validated clinically.[13,14]

The goal of our study was to identify an optimal sequential combination of prognostic modalities for predicting neurologic outcomes in patients undergoing TTM after resuscitation from out-of-hospital-cardiac arrest (OHCA) using quantitative analysis.

Methods

Study design and setting

The study was approved by the Institutional Review Board of Yonsei University College of Medicine, Severance Hospital (no. 4-2017-1048). The requirement of consent from patients for using their data was waived because of the retrospective study design. We performed a retrospective analysis of prospective cohort data collected from September 2011 to December 2016. A critical pathway (CP) for post-resuscitation care including TTM in patients with return of spontaneous circulation (ROSC) after OHCA was developed and has been utilised at our institution since September 2011. Patients who recover spontaneous circulation after OHCA are selected for CP activation according to the following criteria: age >18 years, ROSC >20 min, comatose state after ROSC, time after ROSC <4 h, and family's consent to TTM. Exclusion or deactivation criteria are as follows: normothermia after rewarming (CP completion), severe active bleeding, persistent arrhythmia with haemodynamic instability, refractory shock, death, transfer to other facilities, and family's request for withdrawal of life-sustaining treatment (WLST) before rewarming. After CP activation, a team consisting of emergency physicians, cardiologists, intensivists, and neurologists treat patients according to predefined algorithms and guidelines. Until April 2014, the target temperature was set at 32–34 °C, and later, it was set to below 36 °C when the arrest cause was presumed to be cardiogenic, and to 32–34 °C when it was presumed to be non-cardiogenic. Standardised sedation drugs, analgesia, and neuromuscular blocking agents were administered during TTM.[3]

We included patients for whom the CP was activated and completed without deactivation. All patients who completed the CP underwent an identical sequence of prognostic tests at fixed timings according to the CP protocol. The sequence included brain computed tomography (CT), serum neuron-specific enolase (NSE), electrophysiological examination, neurologic examination, and diffusion-weighted magnetic resonance imaging (MRI).

Neurological prognostication

Brain CT

Brain CT scanning was the first element of standard prognostic assessment of the enrolled patients. Images were obtained within 2 h of cardiac arrest. The grey-to-white matter attenuation ratio (GWR) was measured by one investigator (J.H.K.), blinded to the patients' neurologic outcomes, using the Picture Archiving and Communication System (PACS, Centricity, GE Healthcare, Milwaukee, WI, USA). as previously described.[15,16] A circular measuring cursor (0.1–0.15 cm^2) was placed in regions of interest, and the average attenuation in Hounsfield Units (HU) was recorded. At the basal ganglia level, values were recorded bilaterally for the caudate nucleus (CN), putamen (PU), corpus callosum (CC), thalamus (THL), and posterior limb of the internal capsule (PIC). The GWR in the basal ganglia was calculated according to previously reported methods as follows:GWR basal ganglia = (CN + PU)/(CC + PIC)

We recorded HU values bilaterally for the medial cortex and medial white matter at the level of the centrum semiovale (MC1 and MWM1, respectively) and high convexity area (MC2 and MWM2, respectively). The GWR in the cerebrum was calculated as follows:GWR cerebrum = (MC1 + MC2)/(MWM1 + MWM2)

The average GWR was calculated as the mean of the basal ganglia GWR and cerebrum GWR.[16]

Serum NSE

According to our CP protocol, serum NSE analysis was performed at 24 h after cardiac arrest. The NSE values were assessed by an electrochemiluminescence immunoassay (Cobas 6000 analyser, Roche Diagnostics, Mannheim, Germany) with a normal range of <16.3 μg/L; an investigator collected the NSE values from electronic records.

Electrophysiological examinations

All patients underwent daily portable electroencephalogram (EEG) monitoring from 24 to 72 h after cardiac arrest. EEG recordings were interpreted by board-certified neurologists, and a dichotomised determination (malignant or benign) was made based on previous studies.[4,13,17] We defined a pattern as malignant if it contained alpha coma, burst suppression, generalised suppression, postanoxic status epilepticus, or nonreactive EEG. Bilateral somatosensory-evoked potentials (SSEPs) were recorded from 48 to 72 h after cardiac arrest. SSEP findings were interpreted by a board-certified neurologist. Patients with bilateral absence of N20 were classified as non-responders.

Neurologic examination

The pupil light reflex (PLR) and corneal reflex tests were performed by neurologists at ≥72 h after cardiac arrest. Our study defined a favourable responder as one with both reflexes found in both eyes.

Brain diffusion-weighted imaging (DWI)

Brain DWI was performed 3 days after cardiac arrest. All imaging findings were interpreted by board-certified radiologists blinded to the patients' outcomes. They classified high-signal findings according to the ischemic site. The sites included the frontal cortex, parietal cortex, temporal cortex, occipital cortex, basal ganglia-thalamus, cerebellum, and brain stem. If diffuse cortical high-signal changes were present on DWI, we counted four regional injury sites (frontal, parietal, temporal, and occipital cortices). An injury site was counted once in a given anatomical area, even though the high-signal changes appeared on several imaging slices. An injury site was considered to belong to two different anatomical areas when it crossed two lobes. We calculated the sum of the areas interpreted as showing high-signal change among the seven classified areas.[8]

Outcome measures

The primary measure was the neurologic outcome at the time of one month after cardiac arrest. Neurologic outcomes were classified into five categories according to the Cerebral Performance Category (CPC). We defined a good outcome as a CPC score of 1 or 2.[18]

Statistical analyses

Statistical analyses were conducted using SAS (version 9.3, SAS Inc., Cary, NC, USA) and the R package (version 3.2.5, http://www.R-project.org). Categorical variables are described as frequencies (%), while continuous variables are described as means ± standard deviation (SD). The independent t-test was used for continuous variables while the chi-square or Fisher's exact test was used for categorical variables. We included all prognostic tests to develop an optimal model predicting poor neurologic outcomes by using a hierarchical classification and regression tree (CART),[19,20] considering the time of the test. Each test was entered into the hierarchical CART analysis in the sequence suggested by current guidelines. If the test times overlapped, such as those suggested for SSEP and EEG, these tests were entered into the analysis at the same time. In this manner, we included the brain CT GWR first in the hierarchical CART analysis followed by the serum NSE results. We included the results of electrophysiological examinations in the next step, and finally included neurologic examinations and DWI.

In the CART analysis, a binary classification tree was developed through consecutive splits, dividing the patients into more homogeneous subgroups at each node. The prognostic test with the greatest capacity to distinguish between good and poor neurologic outcomes was selected at each node. The discriminative power of a node decreased with each division. Among the models created by hierarchical CART analysis, we selected the model that had the largest area under the receiver operating characteristic curve (AUROC) and the lowest false positive rate (FPR) considering the clinical relevance. If a prognostic test was not performed, we assumed that its result would be good, considering clinical relevance. Because this is likely to cause selection bias, we conducted an additional hierarchical CART analysis for patients who performed all prognostic tests, as a sensitivity analysis. The discriminative ability of the hierarchical CART model and each prognostic test to predict one-month neurologic outcomes was evaluated by FPR, false negative rate (FNR), and AUROC values with their 95% confidence intervals (CIs). The generalised estimating equation (GEE) method was used to compare FPR and FNR among the prognostic tests including the CART model, and a standard bootstrap method with resampling 1000 times was used to compare the AUROC value of the final model with that of other prognostic modalities. Differences with $p < 0.05$ were considered statistically significant.

To assess inter-rater reliability of brain CT GWR measurement, another investigator, who was blinded to the results of brain CT GWR, measured the GWR of 30 cases that were randomly selected. The agreement between the two measurement values was assessed using the intraclass correlation coefficient (ICC).[21,22] ICC statistics were 0.896 (95% CI, 0.775–0.954) for GWR basal ganglia, 0.946 (95% CI, 0.880–0.976) for GWR cerebrum, and 0.948 (95% CI, 0.885–0.977) for average GWR; this demonstrated almost perfect agreement for all GWRs.

Results

During the study period, the CP for TTM was activated in a total of 273 patients. Of these, 81 patients were excluded due to deactivation before CP completion. Eventually, 192 patients were included in our study (Fig. 1). Among them, 103 patients experienced poor neurologic outcomes, while the remaining 89 patients had a good outcome at one month after cardiac arrest. The baseline characteristics of the study population are shown in Table 1. Brain CT, serum NSE, and SSEP were significantly less frequently performed in patients with a good neurologic outcome, whereas brain DWI was performed less frequently in patients with a poor neurologic outcome.

A hierarchical CART analysis was performed to develop an optimal multimodal approach composed of various prognostic tests for predicting neurologic outcomes. The final model with six nodes was composed of brain CT, serum NSE, EEG, SSEPs, and PLR.

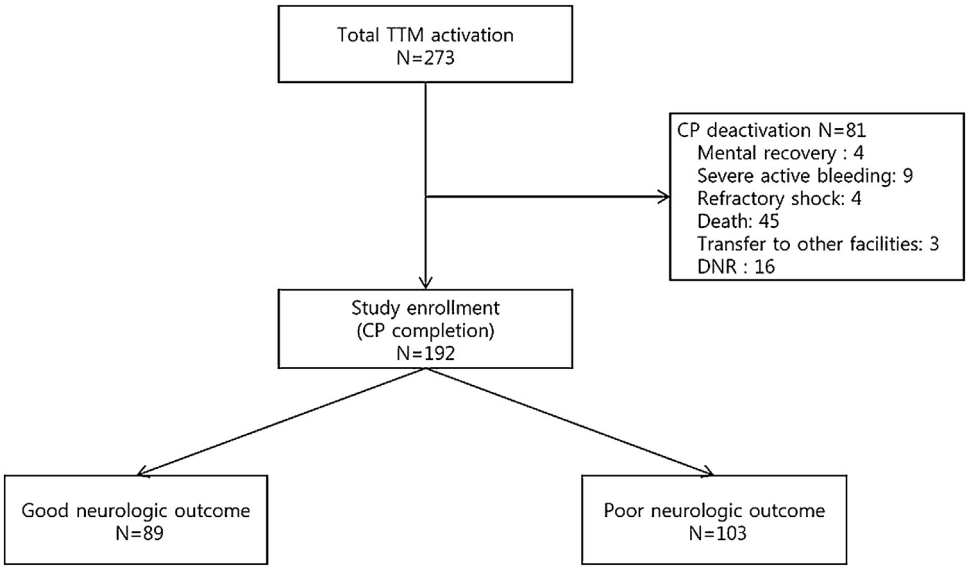

Fig. 1 – Flow diagram of patient eligibility.

Table 1 – Baseline characteristics of the study population.

Variable	Total	Outcome		p-Value
		Good	Poor	
Age, years	59.536 ± 15.875	57.258 ± 16.484	61.505 ± 15.135	0.064
Sex, male	141 (73.44)	72 (80.90)	69 (66.99)	0.030
Bystander CPR				0.052
Performed	113 (58.85)	59 (66.29)	54 (52.43)	
Not performed	79 (41.15)	30 (33.71)	49 (47.57)	
Witnessed arrest				0.023
Witnessed	124 (64.58)	65 (73.03)	59 (57.28)	
Not performed	68 (35.42)	24 (26.97)	44 (42.72)	
Initial rhythm				<0.001
Non-shockable	112 (58.33)	29 (32.58)	83 (80.58)	
Shockable	80 (41.67)	60 (67.42)	20 (19.42)	
Time to ROSC, minute	26.438 ± 17.965	19.551 ± 16.259	32.388 ± 17.295	<0.001
Brain CT				
Performed	174 (90.63)	72 (80.9)	102 (99.03)	<0.001
Not performed	18 (9.38)	17 (19.1)	1 (0.97)	
Serum NSE				
Performed	125 (65.1)	47 (52.81)	78 (75.73)	<0.001
Not performed	67 (34.9)	42 (47.19)	25 (24.27)	
EEG				
Performed	182 (94.79)	82 (92.13)	100 (97.09)	0.192
Not performed	10 (5.21)	7 (7.87)	3 (2.91)	
SSEPs				
Performed	127 (66.15)	52 (58.43)	75 (72.82)	0.036
Not performed	65 (33.85)	37 (41.57)	28 (27.18)	
Pupil light reflex				
Performed	192 (100.00)	89 (100.00)	103 (100.00)	>0.999
Not performed	0 (0.00)	0 (0.00)	0 (0.00)	
Corneal reflex				
Performed	173 (90.1)	81 (91.01)	92 (89.32)	0.696
Not performed	19 (9.9)	8 (8.99)	11 (10.68)	
MRI with DWI				
Performed	133 (69.27)	70 (78.65)	63 (61.17)	0.009
Not performed	59 (30.73)	19 (21.35)	40 (38.83)	

Values are shown as mean ± SD or number (percentage). CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; CT, computed tomography; NSE, neuron-specific enolase; EEG, electroencephalogram; SSEPs, somatosensory-evoked potentials; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging.

Corneal reflexes and brain DWI data were removed from our final model (Fig. 2). All 18 patients with a brain CT GWR of ≤1.1 had poor neurologic outcomes (Node 6). Among the patients with no brain CT or a brain CT GWR of >1.1, 33 patients with a serum NSE value of >67.4 μg/L had poor neurologic outcomes (Node 5). Of 96 patients with no findings suggesting a poor neurologic outcome in all splits, 16 patients (16.67%) did have poor neurologic outcomes (Node 1). Table 2 shows the odds ratio for predicting a poor neurologic outcome of each node in the CART.

The prognostic performance of the final CART model for poor neurologic outcomes compared to that of each test is shown in Table 3. All prognostic modalities revealed significant differences between the good and poor outcome groups. The final CART model predicted poor outcomes with a 0% FPR (95% CI, 0%–0%). A GWR of <1.1 within 2 h, serum NSE level of >67.4 μg/L at 24 h, and bilateral absence of N20 in SSEP at 48–72 h also showed an FPR of 0% (95% CI, 0%–0%). However, the FNR of the CART model was 20.5% (95% CI, 13.1%–28.0%), which was lower than that of GWR, NSE, and SSEP (all $p < 0.01$). Moreover, our CART model had an AUROC value of 0.9110 (95% CI, 0.8719–0.9502), which was significantly higher than the AUROC value of each prognostic modality alone (all $p < 0.01$) (Fig. 3). The additional CART analysis for patients who performed all prognostic tests showed that the FPR value remained 0, FNR was 17.1% (95% CI, 4.7%–29.6%), and the AUROC value was 0.953 (95% CI, 0.911–0.995).

Discussion

We showed that a prediction model containing initial brain CT, serum NSE, EEG, SSEPs, and PLR had the optimal sequential combination for predicting poor neurologic outcomes in patients undergoing TTM after ROSC from OHCA. This model had a better prognostic performance than that of each component prognostic modality alone.

Multiple previous studies have tested the predictive power of specific modalities in evaluating neurological outcomes in comatose patients after OHCA.[9,12,17,23–28] The evidence has shown that multimodal assessment demonstrates good performance in predicting neurologic outcome; however, an optimal combination of prognostic modalities has not been proposed.[6,7,29] Moreover, if the test times overlap, such as those suggested for SSEP and EEG, it is important to decide which test result should be included first.

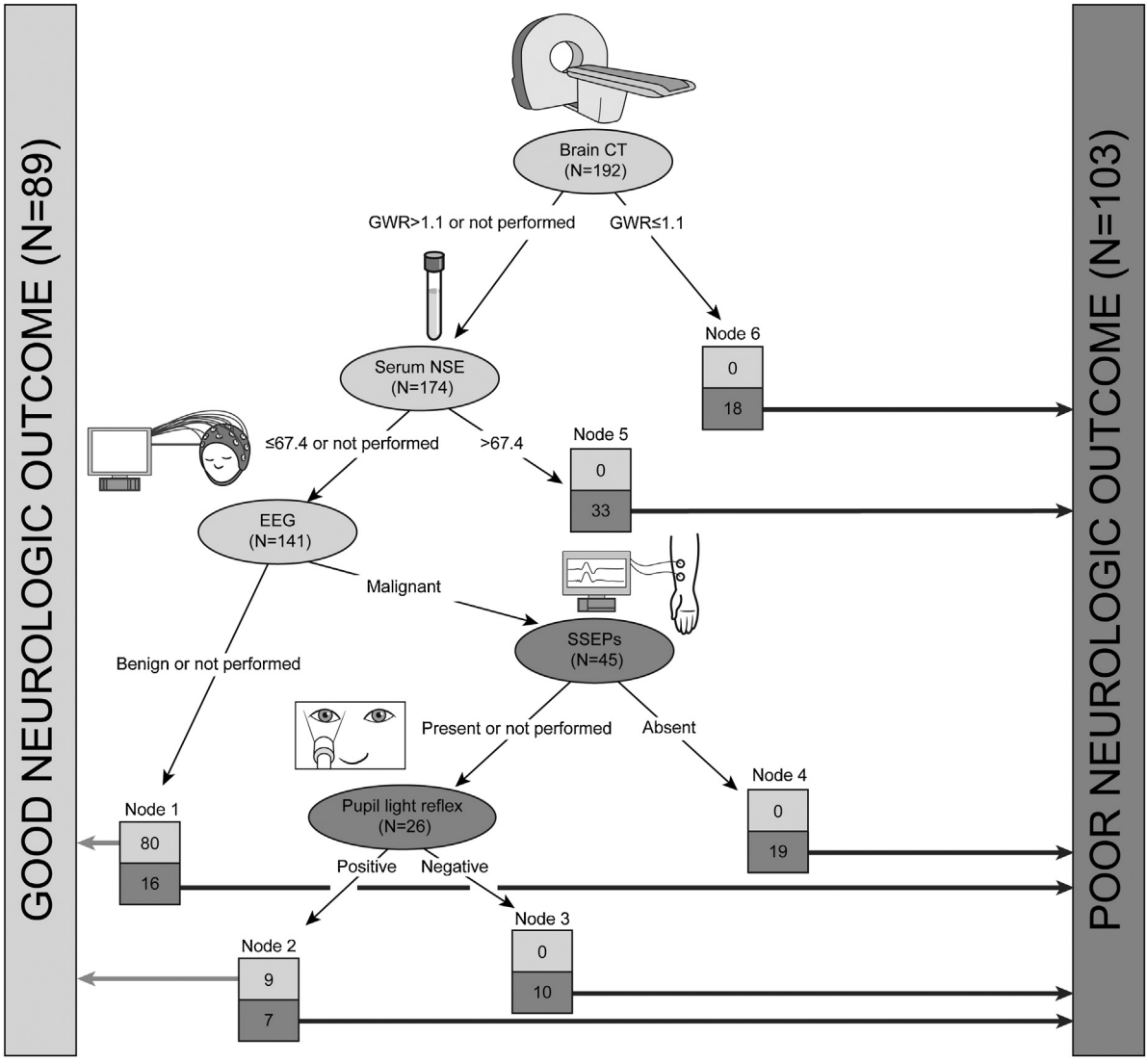

Fig. 2 – Final prediction model for poor neurologic outcomes.

Therefore, we attempted to determine the optimum combination for predicting prognosis, including all prognostic testing, with considerations for test timing. Based on hierarchical CART analysis, the corneal reflex and DWI were unnecessary for our final CART model; EEG was selected before SSEP to distinguish between good and poor neurologic outcomes with the greatest prognostic capacity.

Occasionally, in clinical practice, not all prognostic tests for neurologic outcome evaluation are performed.[12] For example, patients who are already starting to awaken do not need additional prognostic tests. In addition, all modalities for prognostic prediction are not available at every facility because smaller hospitals have insufficient resources.[14] Consistent with these reports, the present study also showed that patients with favourable neurologic outcomes had undergone fewer tests than patients with a poor outcome, and some patients could not undergo all prognostic modalities. Therefore, a new multimodal approach considering clinical variables such as mental status alteration, test availability, and optimal test time is needed. Our prediction model is designed for use even when some prognostic tests cannot be performed. Furthermore, it was developed by including study populations receiving standardised management during post-resuscitation care, in order to minimise the cohort heterogeneity found in previous studies.

Table 2 – Odds ratios for predicting poor neurologic outcomes of each node in the final prediction model.

Node	Outcome		OR	p-Value
	Good	Poor		
Node 1	80 (83.33)	16 (16.67)	Ref	
Node 2	9 (56.25)	7 (43.75)	3.852 (1.255–11.820)	0.018
Node 3	0 (0.00)	10 (100.00)	102.448 (4.986–999.999)	0.003
Node 4	0 (0.00)	19 (100.00)	190.312 (10.171–999.999)	<0.001
Node 5	0 (0.00)	33 (100.00)	326.788 (18.278–999.999)	<0.001
Node 6	0 (0.00)	18 (100.00)	180.534 (9.594–999.999)	<0.001

Values are shown as numbers (percentage). OR, odds ratio.

Table 3 – Predictive power of prognostic modalities for poor neurologic outcomes compared to that of the final prediction model.

Finding of modalities	Outcome		P-value	FPR (95% CI)	AUROC (95% CI)
	Good	Poor			
Brain CT			0.002	0 (0–0)	0.782 (0.727–0.837)
GWR ≤ 1.1	0 (0)	18 (17.65)			
GWR > 1.1	72 (100)	84 (82.35)			
Serum NSE			<0.001	0 (0–0)	0.782 (0.727–0.837)
>67.4	0 (0)	44 (56.41)			
≤67.4	47 (100)	34 (43.59)			
EEG			<0.001	10.11 (3.85–16.38)	0.853 (0.802–0.905)
Malignant	9 (10.98)	80 (81.63)			
Benign	73 (89.02)	18 (18.37)			
SSEPs			<0.001	0 (0–0)	0.833 (0.780–0.887)
Absense	0 (0)	50 (66.67)			
Presense	52 (100.00)	25 (33.33)			
Pupil light reflex			<0.001	2.99 (0–7.06)	0.804 (0.755–0.854)
Negative	2 (2.25)	65 (63.11)			
Positive	87 (97.75)	38 (36.89)			
Corneal reflex			<0.001	1.67 (0–4.91)	0.814 (0.764–0.865)
Negative	1 (1.23)	59 (64.13)			
Positive	80 (98.77)	33 (35.87)			
MRI with DWI			<0.001	35.23 (25.25–45.21)	0.731 (0.662–0.800)
Sum of high signal area ≥1	31 (44.29)	57 (90.48)			
Sum of high signal area = 0	39 (55.71)	6 (9.52)			
Final prediction model			<0.001	0 (0–0)	0.911 (0.872–0.950)
Poor	0 (0)	80 (77.67)			
Good	89 (100)	23 (22.33)			

Values are number (percentage). FPR, false positive rate; AUROC, area under the receiver operating characteristic curve; CT, computed tomography; GWR, grey matter to white matter attenuation ratio; NSE, neuron-specific enolase; EEG, electroencephalogram; SSEPs, somatosensory-evoked potentials; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging.

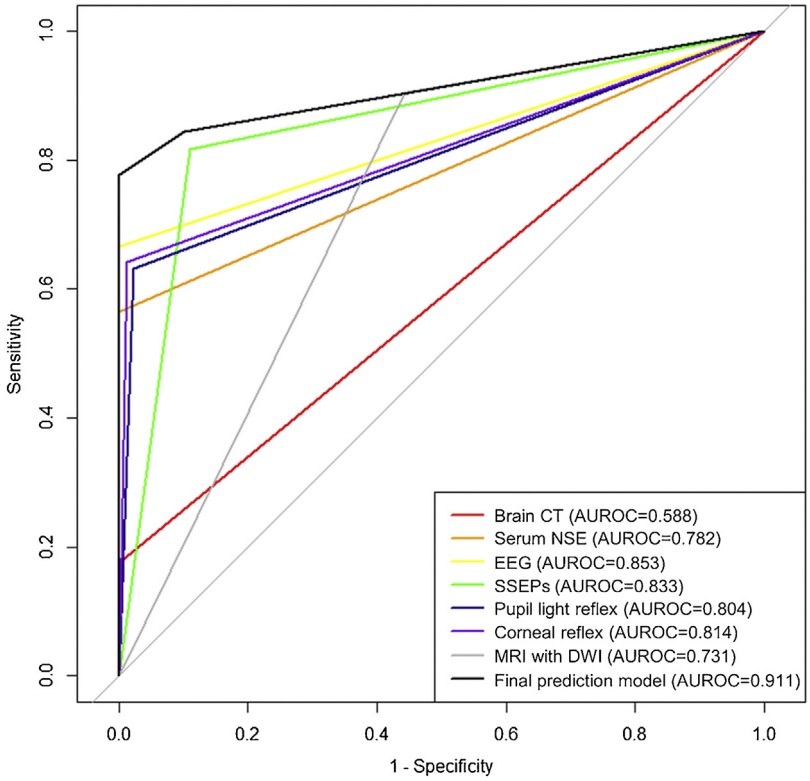

Fig. 3 – Comparison of the area under the receiver operating characteristic curve of the final prediction model and that of each prognostic modality.

Rossetti et al. proposed a stepwise approach including clinical examination, EEG, and SSEP recording as mandatory steps. They reported that if a patient remained comatose despite the absence of poor-outcome evidence, intensive management should be continued while the two core prognostic methods (clinical examination and EEG) were periodically reassessed.[14] These authors also noted that serum NSE levels and brain MRI were limited to the role of optional confirmatory tests. Taccone et al. also proposed a sequential multimodal prognostic algorithm. They emphasised that neurologic examination and EEG findings suggesting a poor prognosis through continuous monitoring before and after sedation and the bilateral absence of N20 after rewarming increased the accuracy of a poor neurologic prognosis. DWI and high NSE levels should be considered as additional tools and not be used to make an early final decision.[13] Our results are in line with these recommendations, which emphasised the role of core prognostic modalities such as electrophysiological and neurologic examinations. In a population showing no evidence of a poor neurologic prognosis in brain CT and serum NSE findings, the results of two electrophysiological examinations predicted 100% (19 patients) of poor outcomes. Furthermore, if the two electrophysiological tests were contradictory, PLR findings in the final step could predict 100% (10 patients) of poor neurologic outcomes.

Previous studies have suggested that loss of differentiation between grey and white matter, reflected as a decreased GWR on CT, predicts a poor outcome in cardiac arrest patients.[11,16,30,31] Consistent with these findings, GWR in patients with poor neurologic outcomes in the present study was significantly lower than that in patients with good outcomes. Specifically, the cut-off GWR value in our study was 1.1, consistent with previous studies.[11,32,33] Current guidelines also recommend that the GWR on brain CT obtained within 2 h after cardiac arrest be used to predict poor outcomes in OHCA patients.[6,7] In addition, brain CT is required to identify the arrest cause, such as cerebral haemorrhage. Therefore, it is reasonable to designate brain CT as the first step in the prognosis evaluation process.

Our CART model could not predict the poor outcomes of 23 cases (Node 1: 16 cases, Node 2: 7 cases), even though the test results predicted favourable neurologic outcomes. These findings show that it may not be possible to identify all patients with a poor prognosis even if the tests are carried out sequentially. However, in only 5 out of 16 inconsistent cases in Node 1, all three prognostic modalities were performed corresponding to that node. Of the 7 cases in node 2, SSEP recording was not performed in 3. Therefore, it is possible that if all prognostic modalities had been performed, the discrepancy rate might be reduced. Therefore, additional studies that can overcome these shortcomings are needed.

The present study has several limitations. The main limitation of our study is that it comprises a retrospective analysis of prospective cohort data collected from a single centre; therefore, our model could exhibit over-fitting because the entire dataset was used to develop the model. Our stepwise model should therefore be applied to a new dataset and prospectively validated, prior to implementation. Second, patients who showed a good neurologic outcome in our study population were less likely to undergo prognostic tests than patients who had poor neurologic outcomes, which suggests the possibility of the selection bias found in previous studies. However, patients with a good prognosis often awaken during post-resuscitation care, and additional testing may be unnecessary. Third, our study did not examine long-term neurological outcomes because we used one-month CPC as the primary outcome. Finally, the self-fulfilling prophecy regarding prognosis is an important issue; the present study cannot be free from this potential bias, although there were no enrolled patients who died or whose family wanted WLST within 3 days of cardiac arrest. This bias is common to the vast majority of prognostication studies; unfortunately, we could not evaluate prognostic factors in a fully blinded manner.

Conclusions

We developed a sequential prediction model that had better prognostic performance than that of any single prognostic modality. This prediction model may be used to minimise the risk of false pessimistic predictions and reduce erroneous WLST in the post-resuscitation care of OHCA patients.

Conflict of interest statement

There are no conflicts of interest to declare.

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