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Clinical paper

Serum glial fibrillary acidic protein and protein gene product 9.5 for predicting neurological outcomes in cardiac arrest patients with cortical response to somatosensory evoked potentials

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Abstract

Aim: Predicting neurological prognosis after cardiac arrest remains challenging. Somatosensory evoked potential N20 absence is highly specific but lacks sensitivity. Glial fibrillary acidic protein and protein gene product 9.5 are potential biomarkers for brain injury, yet their roles in cardiac arrest patients with preserved somatosensory evoked potential N20 remain underexplored.

Methods: From January 2023 to December 2024, 69 cardiac arrest patients were enrolled, of whom 46 had preserved somatosensory evoked potential N20 responses. Serum glial fibrillary acidic protein, protein gene product 9.5 and neuron-specific enolase levels were measured at 72 h post-resuscitation. Patients were evaluated for neurological outcomes at 3 months using the Glasgow-Pittsburgh Classification of Cerebral Function scale. Receiver operating characteristic analysis determined biomarker thresholds for poor prognosis.

Results: In patients with preserved somatosensory evoked potential N20 responses, glial fibrillary acidic protein and protein gene product 9.5 levels were significantly higher in those with poor outcomes ($P < 0.001$). Glial fibrillary acidic protein (area under the curve = 0.908) had an optimal cutoff of 64.1 pg/mL (sensitivity 87.5%, specificity 82.4%) and a 100% specificity threshold of 149 pg/mL. Protein gene product 9.5 (area under the curve = 0.864) had an optimal cutoff of 448.4 pg/mL (sensitivity 87.5%, specificity 70.6%) and a 100% specificity threshold of 1253 pg/mL. The prognostic significance of combining serum glial fibrillary acidic protein, protein gene product 9.5, or neuron-specific enolase levels was explored, with glial fibrillary acidic protein + neuron-specific enolase achieving the highest area under the curve of 0.949 (0.882–1.000).

Conclusions: Serum glial fibrillary acidic protein and protein gene product 9.5 could be valuable predictors of poor neurological outcomes in cardiac arrest patients with cortical response to somatosensory evoked potential, though further studies are required to validate these findings.

Keywords: Out-of-hospital cardiac arrest, Somatosensory evoked potential, Glial fibrillary acidic protein, Protein gene product 9.5

Introduction

Cardiac arrest (CA) is a life-threatening emergency with a high mortality rate that usually results in severe disability for survivors.[1] The ability to accurately predict the neurological prognosis of patients after CA is critical to guide clinical decision-making and provide appropriate cares.[2] Current guidelines recommend a multimodal approach for neurological prognostication, including clinical examination, electrophysiology, serum biomarkers, and neuroimaging.[3] However, individual modalities have limitations in sensitivity and specificity, necessitating the use of combined predictive models to enhance accuracy. Integrating clinical, electrophysiological, imaging, and biomarker data could enhance specificity while maintaining high sensitivity in prognostic prediction.[4] A multimodal prognostic score incorporating electroencephalography, neuron-specific enolase (NSE), and clinical assessment achieved 97.5% sensitivity and an area under the curve (AUC) of 0.88 for predicting functional independence at three months.[5] Given these advancements, combining serum biomarkers with electrophysiological assessments, such as

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somatosensory evoked potential (SSEP), may refine prognostication strategies.

Bilateral or unilateral absence of cortical responses to SSEP is one of the most specific elements for poor prognosis, reflecting the primary somatosensory cortex and the thalamo-cortical loop injuries.[6,7] However, the sensitivity of SSEP N20 absence is relatively low, only about 30%.[3,8] To enhance SSEP sensitivity, novel brain injury biomarkers may be useful in screening for poor prognosis in CA patients presenting with SSEP N20. Glial fibrillary acidic protein (GFAP), an intermediate filament protein primarily expressed in astrocytes, is released when astrocytes are damaged.[9,10] Previous studies have demonstrated that increased serum GFAP levels are correlated with the severity of brain injury and can serve as a biomarker for predicting neurological outcomes in patients after cardiac arrest.[11,12] Protein gene product 9.5 (PGP 9.5), a ubiquitin C-terminal hydrolase, is widely distributed in the nervous system.[13] It has been shown to be elevated in the serum of resuscitated patients, suggesting its potential as a biomarker for evaluating neurological damage.[14,15] However, few studies have explored the relationship between these markers and the prognosis of CA patients with SSEP N20 presence.

In this study, we aimed to investigate the value of serum GFAP and PGP 9.5 in predicting neurological outcomes in post-cardiac arrest patients with cortical response to SSEP. By analyzing the correlation between these biomarkers and neurological prognosis, we sought to determine their predictive ability, identify optimal thresholds, and provide clinicians with more reliable prognostic information.

Materials and methods

Study population

From January 2023 to December 2024, all consecutive adult patients with out of hospital cardiac arrest (OHCA) admitted to the Emergency Intensive Care Unit (EICU) of Beijing Chao-yang Hospital were screened for eligibility in the study. The following patients were included: patients with comatose state defined as a Glasgow coma scale (GCS) $\leq$ 8 with a GCS motor < 3. The following patients were excluded: patients younger than 18 years of age, patients with brain death diagnosis, patients with combined brain injury (stroke, cerebral hemorrhage, etc.), patients awake before SSEP, patients who died within 48 h post CA, and patients whose family members did not agree to be enrolled.

All patients were temperature controlled by maintaining a target temperature of 33 °C for 24 h using an Arctic Sun® (Arctic Sun® 5000, BD, USA) feedback controlled surface cooling device. The patient's body temperature was then gradually increased to 37 °C with a rewarming rate of 0.1 °C/h. Other treatment protocols were provided according to the international guidelines for post-cardiac arrest care.[16] SSEP recordings were performed using neuron spectrum-5 (Neurosoft, Russia). SSEP were recorded in patients still comatose 72 h after ROSC and 48 h after sedation discontinuation. Patients with reproducible cortical potential on both sides were classified as patients with SSEP N20 present.

Neurologic outcome was assessed 3 months after resuscitation using the Glasgow-Pittsburgh Classification of Cerebral Function (CPC) scale. The CPC score ranges from 1 to 5, with a score of 1 indicating good performance, 2 indicating moderate disability, 3 indicating severe disability, 4 indicating a vegetative state, and 5 indicating brain death or death. Neurological prognosis was categorized as good prognosis (CPC 1–2) and poor prognosis (CPC 3–5). The neurological evaluation was performed by independent assessors who were blinded to the biomarker results. Follow-up assessments were conducted either face-to-face or via telephone. The study was approved by the Ethics Committee of Beijing Chaoyang Hospital (No. 2023-ke-780). Written informed consent was obtained from all patients and/or legal representatives.

Data collection

Demographic and resuscitation data, and clinical and laboratory data were collected upon admission. Clinical data included age, gender, co-morbidities, as well as the cause and characteristics of the cardiac arrest. Serum neuron-specific enolase (NSE) concentration was routinely tested by the hospital laboratory, with a normal reference range of 0–16.3 ng/ml at 72 h after ROSC. The ethylenediamine tetraacetic acid (EDTA) anticoagulant blood was collected from patients at 72 h after ROSC, and samples were centrifuged immediately upon collection. Serum GFAP and PGP 9.5 concentrations were determined with a compact automated immunoanalyzer (Aceso80A; Sophonix Co., Ltd, Beijing, China) based on a chemiluminescent enzyme immunoassay and the assay results were obtained within 30 min. The normal reference range for serum GFAP concentration is 0–22 pg/ml and for PGP 9.5 concentration is 0–320 pg/ml.

Statistical analyses

For data with skewed distributions, the median, 25th and 75th percentiles were used to represent the variables. The Kruskal-Wallis test was used for multiple comparisons, and the Mann-Whitney *U* test was used for between-group comparisons. Qualitative parameters were tested using the $\chi 2$ test, and further analyses were performed using continuity correction or Fisher's exact test. Receiver operating characteristic (ROC) curves and area under the ROC curve (AUC) were analyzed. Prognostic parameters including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated based on the optimal thresholds determined by ROC curve analysis using the Youden index. The Z-test formula was used for AUC comparison. All statistical tests were two-tailed tests, and P values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 24.0 software (IBM, Chicago, IL, USA) and GraphPad Prism 6 (GraphPad, La Jolla, CA).

Results

Patient characteristics

During the study period, a total of 108 OHCA patients were screened. After excluding patients with brain death diagnosis (n = 12), combined brain injury (n = 9), awake before SSEP (n = 6), as well as 7 patients who passed away within 48 h of admission and 5 patients who were lost to follow up. Eventually, 69 patients were included in the study cohort. Eventually, 17 (24.6%) and 52 (75.4%) patients were respectively assigned to the CPC 1–2 and CPC 3–5 groups at 90-days after ROSC. Bilateral SSEP N20 was present in 29 of 52 patients in CPC 3–5 subgroups. The flowchart was shown in Fig. 1. There were no significant differences in age, sex, comorbidities, and etiology between patients with and without cortical response to SSEP. The serum NSE, GFAP and PGP 9.5 concentrations in CPC 3–5 group were significantly higher

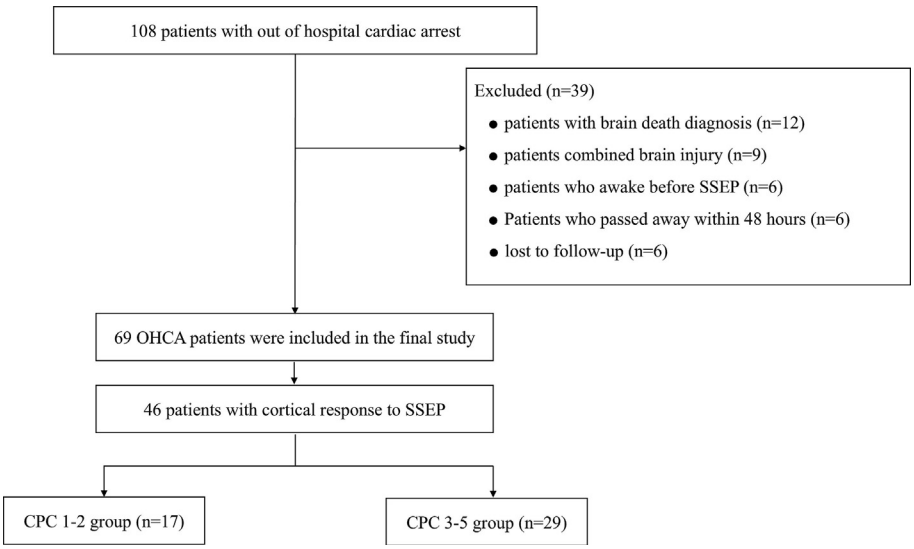

Fig. 1 – Flow diagram of patients based on CONSORT.

than CPC 1–2 group (P < 0.001). The baseline characteristics of the patients were shown in Table 1.

Value of serum GFAP and PGP 9.5 in patients with SSEP N20 present

GFAP levels were higher in patients with poor outcome compared to patients with good outcome in resuscitated patients with SSEP N20 present (288.6 [70.4–2069] pg/mL vs. 34.2 [28.5–60.1] pg/mL P < 0.001). A detailed data was presented in Table 2. The AUC of the levels of serum GFAP for predicting poor prognosis was 0.908 in CA patients with SSEP N20 present (P = 0.964, Fig. 2A). The ROC curve analysis showed that the optimal threshold of serum GFAP for predicting poor prognosis in resuscitated patients with SSEP N20 present was 64.1 ng/ml (sensitivity 87.5%, specificity 82.4%, PPV 87.5%, NPV 82.4%). Sensitivities and cut-off values for high specificity of GFAP are presented in Table 4. The cutoff value for 100% specificity of GFAP in the CA patients with SSEP N20 was 149 pg/mL. The detailed results were presented in Table 4.

Levels of PGP 9.5 were markedly elevated in CPC 3–5 group compared with CPC 1–2 group in in resuscitated patients with SSEP

Table 1 – Baseline demographic data and arrest characteristics.

Variables	CPC 1–2	CPC 3–5	P value
n	17	52	
Ages (years)	58 (56–63)	61 (53–66)	0.896
Male, n (%)	10 (58.8%)	31 (59.6%)	0.954
Comorbidities, n (%)			
Cardiovascular disease	7 (41.2%)	26 (50.0%)	0.527
Diabetes	5 (29.4%)	18 (34.6%)	0.693
Hypertension	9 (52.9%)	31 (59.6%)	0.628
Chronic respiratory disease	3 (17.7%)	7 (13.5%)	0.977
Suspected Cardiac arrest etiology, n (%)			0.501
Cardiac	10	31	
Respiratory	6	13	
Other	1	8	
Bystander CPR, n (%)	6 (35.3%)	13 (25.0%)	0.410
Initial rhythm, n (%)			0.429
shockable rhythms	7 (41.2%)	16 (30.8%)	
non-shockable rhythms	10 (58.8%)	36 (69.2%)	
Time to ROSC, min	16 (12–21)	22 (17–27)	0.001
Serum NSE (ng/mL)	31.9 (25.4–48.8)	72.8 (55.0–114.4)	<0.001
Serum GFAP (pg/mL)	234.2 (68.5–360.1)	519.6 (271.4–1572)	<0.001
Serum PGP 9.5 (pg/mL)	347.7 (277.0–544.3)	1287.0 (526.0–4547.0)	<0.001
SSEP responses, n (%)			–
Bilaterally or unilaterally absent	0	23	
Bilaterally present	17	29	

Data are shown as median and interquartile range unless otherwise indicated.

CPC cerebral performance category, CPR Cardiopulmonary resuscitation, NSE neuron specific enolase, GFAP glial fibrillary acidic protein, PGP 9.5 protein gene product 9.5, ROSC return of spontaneous circulation, SSEP Somatosensory evoked potentials.

Table 2 – Baseline demographic data and arrest characteristics of patients with cortical response to SSEP.

Variables	CPC 1–2	CPC 3–5	P value
n	17	29	
Ages (years)	58 (56–64)	63 (59–67)	0.361
Male, n (%)	10 (58.8%)	13 (44.8%)	0.360
Comorbidities, n (%)			
Cardiovascular disease	7 (41.2%)	16 (55.2%)	0.360
Diabetes	5 (29.4%)	11 (37.9%)	0.558
Hypertension	9 (52.9%)	20 (69.0%)	0.277
Chronic respiratory disease	3 (17.7%)	4 (13.8%)	0.941
Suspected Cardiac arrest etiology, n (%)			0.545
Cardiac	10	15	
Respiratory	6	9	
Other	1	5	
Bystander CPR, n (%)	6 (35.3%)	9 (31.0%)	0.766
Initial rhythm, n (%)			0.650
shockable rhythms	7 (41.2%)	18 (62.1%)	
non-shockable rhythms	10 (58.8%)	11 (37.9%)	
Time to ROSC, min	16 (12–21)	24 (18–29)	0.002
Serum NSE (ng/mL)	31.9 (25.4–48.8)	63.8 (51.6–98.9)	0.001
Serum GFAP (pg/mL)	34.2 (28.5–60.1)	288.6 (70.4–2069)	<0.001
Serum PGP 9.5 (pg/mL)	347.7 (277.0–544.3)	1684.0 (508.7–4946.0)	<0.001

Data are shown as median and interquartile range unless otherwise indicated.

CPC cerebral performance category, CPR Cardiopulmonary resuscitation, NSE neuron specific enolase, GFAP glial fibrillary acidic protein, PGP 9.5 protein gene product 9.5, ROSC return of spontaneous circulation, SSEP Somatosensory evoked potentials.

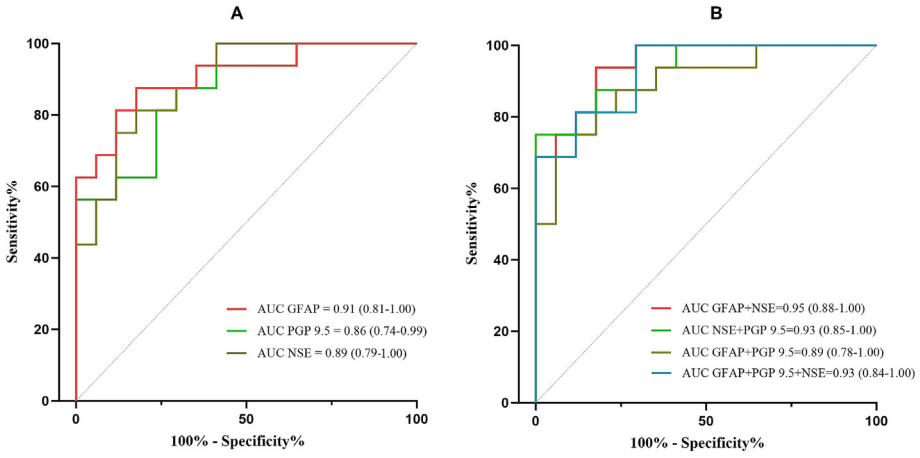

Fig. 2 – Receive operating characteristic curve for predicting poor prognosis in cardiac arrest patients with SSEP N20 present. Receiver operating characteristic curves for single biomarker prediction of poor prognosis (A): GFAP (Light Red) 0.91, PGP 9.5 (blue-green) 0.86, NSE (Brown Yellow) 0.89. Receiver operating characteristic curves of combined biomarkers predicting poor prognosis (B): GFAP + NSE (Light Red) 0.95, PGP 9.5 + NSE (blue-green) 0.93, GFAP + PGP 9.5 (Brown Yellow) 0.89, and GFAP + PGP 9.5 + NSE (blue) 0.93. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

N20 present (1684.0 [508.7–4946.0] pg/mL vs. 347.7 [277.0–544.3] pg/mL P < 0.001). The AUC of serum PGP 9.5 concentrations for predicting poor prognosis was 0.864 (Table 3 and Fig. 2A). The best cutoff of serum PGP 9.5 for predicting poor prognosis in resuscitated patients with SSEP N20 present was 448.4 pg/mL (sensitivity 87.5%, specificity 70.6%, PPV 73.7%, NPV 85.7%). Sensitivities and cut-off values for high specificity of PGP 9.5 were presented in Table 4. The cutoff value for 100% specificity of PGP 9.5 in the CA patients with SSEP N20 presence was 1253 pg/mL. Similarly, the cutoff value for 100% specificity of NSE was 71.5 ng/mL. The detailed results were presented in Table 4.

We further explored the prognostic significance of a combination of serum GFAP, serum PGP 9.5 or serum NSE levels in patients with cortical response to SSEP. Among these combinations, GFAP + NSE exhibited the highest AUC at 0.949 (0.882–1.000). However, using the Z-test, we found that the differences in AUC between GFAP + NSE and other combinations, including PGP 9.5 + NSE (AUC = 0.930), GFAP + PGP 9.5 (AUC = 0.893), and GFAP +

Table 3 – Area under the curve of various parameters for predicting poor prognosis in cardiac arrest patients with SSEP N20 present.

Variable	AUC	P value	95% Confidence interval	
			Lower limit	Upper limit
Serum GFAP	0.908	<0.001	0.807	1.000
Serum PGP 9.5	0.864	<0.001	0.742	0.986
Serum NSE	0.893	<0.001	0.788	0.999
Serum GFAP + Serum NSE	0.949	<0.001	0.882	1.000
Serum PGP 9.5 + Serum NSE	0.930	<0.001	0.848	1.000
Serum GFAP + Serum PGP 9.5	0.893	<0.001	0.785	1.000
Serum GFAP + Serum PGP 9.5 + Serum NSE	0.930	<0.001	0.844	1.000

NSE neuron specific enolase, GFAP glial fibrillary acidic protein, PGP 9.5 protein gene product 9.5, SSEP Somatosensory evoked potentials.

Table 4 – Serum NSE, GFAP and PGP 9.5 specificity, cut-off levels and sensitivity in cardiac arrest Patients with SSEP N20 present.

Variable	Cutoff Level	Specificity (95% CI)	Sensitivity (95% CI)
Serum NSE (ng/mL)	71.5	1.00 (0.82–1.00)	0.44 (0.23–0.66)
	67.2	0.94 (0.73–1.00)	0.44 (0.23–0.67)
	63.8	0.94 (0.73–0.99)	0.50 (0.28–0.72)
Serum GFAP (pg/mL)	149	1.00 (0.81–1.00)	0.63 (0.39–0.82)
	95.5	0.94 (0.73–0.99)	0.63 (0.39–0.82)
	79.2	0.94 (0.73–0.99)	0.69 (0.44–0.86)
Serum PGP 9.5 (pg/mL)	1253	1.00 (0.81–1.00)	0.56 (0.33–0.76)
	984	0.94 (0.73–1.00)	0.56 (0.33–0.77)
	628	0.88 (0.66–0.98)	0.63 (0.39–0.82)

NSE neuron specific enolase, GFAP glial fibrillary acidic protein, PGP 9.5 protein gene product 9.5, SSEP Somatosensory evoked potentials.

PGP 9.5 + NSE (AUC = 0.930), were not statistically significant (all P > 0.05). Our analysis also revealed that none of the comparisons between biomarker combinations and individual biomarkers reached statistical significance (all p-values > 0.05). Notably, GFAP alone (AUC = 0.908) outperformed the combination of GFAP + PGP 9.5 (AUC = 0.893) in predicting poor prognosis. The detailed data are presented in Table 3 and Fig. 2B.

Discussion

In this study, we investigated the value of serum GFAP and PGP 9.5 in predicting neurological outcomes in post-cardiac arrest patients with cortical response to SSEP. Our results demonstrated that serum levels of GFAP and PGP 9.5 were significantly higher in patients with poor neurological outcomes compared to those with favorable outcomes. The AUC values indicated that both GFAP and PGP 9.5 had good predictive abilities for poor prognosis in patients with SSEP N20 present. The prognostic significance of combining serum GFAP, PGP 9.5, or NSE levels was explored, with GFAP + NSE achieving the highest AUC at 0.949 (0.882–1.000). These findings suggest that GFAP and PGP 9.5 can aid in identifying poor prognosis in CA patients who retain SSEP cortical responses, offering valuable insights for clinical decision-making.

Bilateral or unilateral absence of SSEP N20 has long been regarded as a highly specific indicator of poor prognosis in post-cardiac arrest patients, reflecting significant cortical or thalamocortical injury.[17] Although the intracerebral conduction pathways for SSEP remain intact, abnormal injury in other localized brain regions associated with conscious perception and processing may also lead to unfavorable neurological prognosis.[18] Therefore, the sensitivity of this method remains limited. By incorporating biomarkers such as GFAP and PGP 9.5, it becomes possible to stratify patients with intact SSEP N20 responses and enhance early prediction of neurological outcomes. GFAP, indicative of astrocytic injury, and PGP 9.5, reflective of neuronal damage, provide complementary data about the extent of brain injury beyond what is captured by electrophysiological assessments alone.[19] Therefore, incorporating biomarker screening addresses the limitations of relying solely on SSEP N20 and ensures more comprehensive prognostic evaluations.

Our findings align with recent literature emphasizing the value of serum biomarkers in predicting neurological outcomes in CA patients. Previous studies have established that elevated serum GFAP and PGP 9.5 levels correlate with the severity of brain injury in resuscitated patients.[20,21] However, few studies have focused specifically on CA patients with preserved SSEP N20 responses. Compared to previous studies, this study highlights the unique contribution of these biomarkers in a subset of patients who are typically challenging to assess using conventional methods. Previous research has demonstrated that the combination of N20-baseline < 0.88 μV and NSE > 60 μg/mL predicts poor neurological outcomes in CA patients with a sensitivity of 36% (95% CI: 31–41) and a specificity of 100% (95% CI: 100–100).[22] These findings are consistent with our study, which showed that in CA patients with preserved SSEP N20 responses, NSE > 71.5 μg/mL predicted poor outcomes with a sensitivity of 0.44 (95% CI: 0.23–0.66) and a specificity of 1.00 (95% CI: 0.82–1.00). Importantly, our study extends these findings by incorporating serum GFAP and PGP 9.5 into the prognostic

framework. Both biomarkers showed excellent predictive performance, with GFAP achieving an AUC of 0.908 and PGP 9.5 an AUC of 0.864 in patients with SSEP N20 responses. Furthermore, the integration of GFAP and NSE enhanced the overall predictive ability compared to NSE alone. This suggests that GFAP and PGP 9.5 not only complement existing markers like NSE but also provide additional insights into astrocytic and neuronal injury, which are critical for comprehensive prognostication.

These findings underscore the importance of a multimodal biomarker approach to improve sensitivity without compromising specificity, ultimately refining the prognostic toolkit for clinicians managing CA patients. Our study emphasizes the value of combining serum biomarkers (GFAP, PGP 9.5, and NSE) and SSEP to predict neurological outcomes in post-CA patients. The integration of model is particularly critical in guiding the withdrawal of life-sustaining therapy (WLST), a complex clinical decision that requires highly specific tools to minimize the risk of premature or inappropriate withdrawal in potentially recoverable patients.[3,23] Supporting this multimodal approach, a previous study demonstrated the predictive power of combining clinical examination, biomarkers, electrophysiology, and brain imaging.[4] Combining these parameters increased specificity when compared to individual predictors.[4] Another study developed a multimodal score using EEG, NSE, and clinical examination, achieving a high sensitivity of 97.5% and an AUC of 0.88 in predicting favorable outcomes (CPC 1–2) at three months.[5] These studies collectively support the idea that a multimodal approach enhances prognostic accuracy, and moving forward, the development of multi-parameter models will be pivotal in advancing clinical research and improving patient care in post-cardiac arrest management.

Limitations

This study has several limitations. First, the sample size was relatively small, and the cohort was derived from a single center, which may limit the generalizability of the findings. Future studies with larger, multi-center cohorts are warranted to validate these results. Second, monitoring these biomarkers at multiple time points after resuscitation may provide valuable insights into the trajectory of brain injury and recovery, offering a more comprehensive understanding of their prognostic value. Longitudinal studies are necessary to explore how the levels of these biomarkers evolve over time and to identify the optimal timing for biomarker measurement. Third, while GFAP and PGP 9.5 show strong prognostic value in our study and prior research, the thresholds identified here may not apply universally. Given that our study was based on a specific temperature protocol (33 °C for 24 h with gradual rewarming), these thresholds may differ under alternative treatment strategies. Validation in diverse cardiac arrest cohorts, including those with varying protocols, etiologies, and comorbidities, is essential before clinical implementation.

Conclusions

This study highlights the potential of serum GFAP and PGP 9.5, alone or in combination with NSE, as valuable prognostic biomarkers in post-cardiac arrest patients with cortical response to SSEP. These findings have important clinical implications, although further research is warranted to overcome the identified limitations and optimize the clinical application of these biomarkers.

CRediT authorship contribution statement

Chenchen Hang: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rui Shao:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xingsheng Wang:** Writing – review & editing, Data curation, Conceptualization. **Luying Zhang:** Writing – review & editing, Data curation, Conceptualization. **Weijie Cheng:** Writing – review & editing, Data curation, Conceptualization. **Zihao Jiang:** Writing – review & editing, Data curation, Conceptualization. **Ziqi Zhong:** Writing – review & editing, Validation, Supervision, Resources. **Le An:** Writing – review & editing, Supervision, Software, Resources, Project administration, Methodology, Data curation, Conceptualization. **Ziren Tang:** Writing – review & editing, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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