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EEG-ENHANCED PROGNOSTIC UTILITY OF SERUM VERSUS CEREBROSPINAL FLUID ESM-1 IN SEVERE TRAUMATIC BRAIN INJURY

EEG-POBOLJŠANA PROGNOSTIČKA KORISNOST SERUMA U ODNOSU NA CEREBROSPINALNU TEČNOST ESM-1 KOD TEŠKE TRAUMATSKE POVREDE MOZGA

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Summary

Background: To compare the prognostic value of serum versus cerebrospinal fluid (CSF) ESM-1 combined with EEG in severe traumatic brain injury (sTBI). This study aims to optimize biomarker detection strategies.
Methods: 98 sTBI patients (Glasgow Coma Scale [GCS] score 8) admitted from June 2023 to March 2025 were included. Serum and CSF samples were collected simultaneously from all patients after admission, and EEG monitoring was performed 48–72 hours post-injury. We employed enzyme-linked immunosorbent assay (ELISA) to measure serum ESM-1 and inflammatory factors (IL-6, TNF-α), and conducted chemiluminescence immunoassay (CLIA) to quantify CSF-ESM-1, S100β, and NSE. Multimodal EEG parameters were integrated with ESM-1 for joint modeling, with model efficacy in predicting 28-day mortality and adverse 6-month prognoses (defined as a GOS score of 1-3) evaluated by receiver operating characteristic (ROC) curve analysis.
Results: Both serum and CSF-ESM-1 levels showed a positive correlation with inflammatory factors (IL-6, TNF-α) and BBB injury markers (S100β, NSE) ($P<0.05$). CSF-ESM-1 combined with EEG exhibited significantly superior predictive efficacy for 28-day mortality than serum ESM-1 + EEG, while also demonstrating better performance in predicting poor prognosis at 6 months.
Conclusions: CSF-ESM-1, due to its direct reflection of the inflammatory-vessel injury microenvironment within the brain, has a significantly superior predictive efficacy when combined with EEG compared to serum ESM-1.

Keywords: endothelial cell-specific molecule-1, cerebrospinal fluid, electroencephalogram, severe traumatic brain injury, prognosis

Kratak sadržaj

Uvod: Cilj studije je bio da uporedi prognostičku vrednost ESM-1 analize u serumu u odnosu na cerebrospinalnu tečnost (CST) u kombinaciji sa EEG-om kod teške traumatske povrede mozga (sTMP). Cilj ove studije je optimizacija strategija detekcije biomarkera.
Metode: Uključeno je 98 pacijenata sa sTBI (Glazgovska skala kome [GCS] skor ≤8) primljenih od juna 2023. do marta 2025. godine. Uzorci seruma i CSF su prikupljeni istovremeno od svih pacijenata nakon prijema, a EEG monitoring je obavljen 48–72 sata nakon povrede. Koristili smo enzimski imunosorbentni test (ELISA) za merenje serumskog ESM-1 i inflamatornih faktora (IL-6, TNF-α) i sproveli hemiluminiscentni imunotest (CLIA) za kvantifikaciju CSF-ESM-1, S100β i NSE. Multimodalni EEG parametri su integrisani sa ESM-1 za zajedničko modeliranje, pri čemu je efikasnost modela u predviđanju mortaliteta u roku od 28 dana i nepovoljnih 6-mesečnih prognoza (definisanih kao GOS skor od 1–3) procenjenih analizom ROC krive (river operating characteristic).
Rezultati: Nivoi i seruma i CSF-ESM-1 pokazali su pozitivnu korelaciju sa inflamatornim faktorima (IL-6, TNF-α) i markerima povrede KMB (S100b, NSE) ($P<0,05$). CSF-ESM-1 u kombinaciji sa EEG-om pokazao je značajno superiornu prediktivnu efikasnost za mortalitet nakon 28 dana u odnosu na serumski ESM-1 + EEG, a istovremeno je pokazao i bolje performanse u predviđanju loše prognoze nakon 6 meseci.
Zaključak: CSF-ESM-1, zbog direktnog odraza mikrookruženja inflamatornog oštećenja krvnih sudova u mozgu, ima značajno superiorniju prediktivnu efikasnost kada se kombinuje sa EEG-om u poređenju sa serumskim ESM-1.

Ključne reči: molekul-1 specifičan za endotelne ćelije, cerebrospinalna tečnost, elektroencefalogram, teška traumatska povreda mozga, prognoza

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Introduction

Severe traumatic brain injury (sTBI) is among the most common acute and critical conditions in neurosurgery, with a global annual incidence of approximately 103–156 per 100,000 people. The overall mortality rate of patients is as high as 30%-50%, and among the survivors, 60% suffer from permanent neurological dysfunction (1, 2). Accurate prognosis assessment is crucial for the early formulation of individualized treatment plans and improving patient outcomes (3). The Glasgow Coma Scale (GCS), imaging examinations, and the Glasgow Outcome Scale (GOS), which are currently the commonly used clinical assessment methods, all have limitations such as lag or subjectivity (4, 5). Searching for early, objective, and sensitive biomarkers combined with functional monitoring indicators has become a research hotspot in sTBI prognosis assessment.

In recent years, endothelial cell-specific molecule-1 (ESM-1) has attracted attention as a novel inflammation-vascular injury (pathophysiological interplay between endothelial dysfunction and neuroinflammation) biomarker (6). ESM-1 is mainly secreted by activated endothelial cells, which can reflect the degree of blood-brain barrier (BBB) disruption and the level of neuroinflammation; its serum level elevation is closely related to pathological processes such as cerebral ischemia and traumatic brain edema (7, 8). Electroencephalogram (EEG) directly reflects the cortical and subcortical functional status by dynamically capturing abnormal EEG activity, which has been proven to be able to predict the coma outcome and epilepsy risk of sTBI patients (9). However, most existing research focuses on the evaluation value of ESM-1 or EEG as a single indicator (10, 11), while reports on their combined application are relatively rare. Moreover, the distribution differences of ESM-1 in serum and cerebrospinal fluid (CSF) and its impact on prognosis have not been clearly defined.

Based on the current state of research, this study simultaneously examines ESM-1 levels in the serum and CSF of sTBI patients and, in combination with multimodal EEG parameters, clarifies the differences in prognostic evaluation value of ESM-1 from these two sources together with EEG. This study is expected to reveal the distinct prognostic implications of ESM-1 in the 'local brain' versus 'systemic circulation' states for sTBI, providing a basis for clinicians to select more precise biomarker detection samples (serum or CSF) and combined EEG assessment schemes. Ultimately, it aims to assist in early stratified management and individualized treatment of sTBI patients to reduce disability and mortality rates, holding significant clinical translational value.

Materials and Methods

Sample size estimation

This study is a prospective, observational, single-center study. The primary endpoint was the dichotomized 6-month Glasgow Outcome Score (GOS; good outcome: GOS 4–5; poor prognosis: GOS 1-3). Based on previous evidence (12), an area under the receiver operating characteristic (ROC) curve (AUC) of 0.80–0.85 was assumed for prognosis prediction by ESM-1 + EEG for sTBI patients. Using PASS 15.0, with a two-tailed $\alpha=0.05$, a test efficiency $1\text{-}\beta=0.80$, and an estimated AUC difference (serum ESM-1 + EEG vs CSF-ESM-1 + EEG) of 0.05, each group needed 87 patients. Considering a 10% attrition rate (e.g., loss to follow-up, death), we finally planned to include 98 patients (with each group actually analyzed ≥96 cases). Prior to initiation, the study obtained ethical approval from the institutional ethics committee.

Research participants and grouping

From June 2023 to March 2025, sTBI patients admitted to the neurosurgery intensive care unit (NICU) of our hospital were selected. Serum and CSF samples were collected synchronously from all 98 enrolled patients. Two prognostic assessment models, namely 'Serum ESM-1 + EEG' and 'CSF-ESM-1 + EEG', were constructed based on the sample source for comparative analysis.

Patient selection criteria

Inclusion criteria: Age range: 18–70; Fulfillment of the sTBI diagnostic criteria: GCS score at admission 8, with skull CT/MRI-confirmed intracranial injury (e.g., cerebral contusion and laceration, intracranial hematoma, diffuse axonal injury); injury-to-hospital time 24 hours; estimated ICU stay ≥72 hours and life expectancy ≥72 hours (non-acute phase death); provision of informed consent by the patient or legal representatives. Exclusion criteria: severe multiple organ failure; pre-existing nervous system diseases; pregnant or lactating women; refusal to participate in the research or withdrawal of informed consent.

EEG monitoring

Within 48–72 hours after admission (EEG monitoring was conducted within 48–72 hours post-admission, as this window is considered a critical period for the onset and progression of brain injury, allowing for the capture of early electrophysiological abnormalities), a digital video EEG device (Nicolet-One, USA) was used, with 19 electrodes placed according to the international 10–20 system, to

record at least 30 minutes of EEG signals in a calm (EEG signals were recorded for at least 30 min in a resting, awake state with eyes closed, in a quiet environment to minimize artifacts), awake state. The recordings were independently interpreted by two senior neurophysiologists (Kappa value > 0.8), and the absolute power of α, β, θ, and δ waves was extracted.

Laboratory tests

ELISA was employed for serum ESM-1 detection due to its well-established performance for serum biomarkers. CLIA was chosen for CSF ESM-1 quantification given its higher sensitivity, which is advantageous for detecting potentially lower analyte concentrations in CSF.

Fasting blood and CSF were collected 24 hours after admission. Serum: Following collection, the fasting venous blood sample underwent centrifugation (anticoagulant-free, 3000×g, 10 minutes, 4 °C) to obtain serum. CSF: CSF was obtained by lumbar puncture or external ventricular drainage, followed by immediate centrifugation (3000×g, 10 minutes, 4 °C) to remove cell debris. ① Sample pretreatment: The supernatant was used for detection. As for CSF, if the protein content was too high (>100 mg/dL), it was concentrated to 50 μL using a 10 kDa ultrafiltration tube (Millipore, UFC501096), and then brought up to 500 μL with a PBS buffer (pH 7.4). ② Sample addition and incubation: 100 μL each of the standard, quality control, and sample was added to the wells of the antibody-coated microplate and incubated with shaking at room temperature for 2 hours. After discarding the liquid, the plate was washed 3 times with a washing buffer (PBST, containing 0.05% Tween-20), with a 1-minute standing interval between washes. ③ Antibody binding and color development: A biotin-labeled secondary antibody (diluted 1: 1000) was added and incubated at room temperature for 1 hour. After washing, horseradish peroxidase (HRP)-labeled streptavidin was added for a 30-minute room-temperature incubation. Development was conducted with a substrate solution (TMB) in the dark for 15 minutes, and then the reaction was terminated with a stopping solution (2 mol/L H_2SO_4). ④ Determination: The absorbance at 450 nm wavelength was read by the microplate reader, with 620 nm as the reference wavelength for correction. A standard curve was plotted with the concentration of the standard as the abscissa and the absorbance as the ordinate. Similarly, the concentrations of inflammatory factors IL-6 and TNF-α in patient serum were measured following the above steps. Intra-assay coefficient of variation (CV) <10% and inter-assay CV <15% were required.

Chemiluminescence immunoassay (CLIA; Roche cobas e 601) was used to detect S100β and NSE. The standards were diluted at the gradient of 0, 0.1, 0.5, 2, 10, 50, 100, and 200 ng/mL and added to the microplate. Standard, sample, and quality control samples were added at 50 μL per well, followed by oscillating incubation at room temperature for 2 hours. After liquid removal, the plate was washed with a washing buffer in triplicate, with 1-minute standing between each wash. Next, 50 μL of biotin-labeled capture antibody was added to incubate at room temperature for 1 hour. After washing, 50 μL of streptavidin-labeled acridinium ester was added for light-tight incubation for 5 minutes. An enhanced chemiluminescent substrate was then introduced, with chemiluminescence signals detected with the microplate reader. A four-parameter logistic regression standard curve was plotted with the standard concentration as the abscissa and the RLU value as the ordinate. An intra-batch CV <5% and an inter-batch CV <10% were ensured.

Statistical methods

We used SPSS 30.0 to analyze and process the collected data. The comparison of normally distributed measurement data ($\bar{x}\pm s$) was conducted using the independent sample t-test, while the comparison of non-normally distributed data [M (P25, P75)] was performed using the Mann-Whitney U test. Correlation was analyzed using the Pearson correlation coefficient. The diagnostic value was analyzed using receiver operating characteristic (ROC) curve analysis, and combined detection was conducted using logistic regression. The diagnostic performance was assessed based on ROC-AUC. For multiple correlation analyzes (e.g., ESM-1 with inflammatory markers and BBB injury markers), the Bonferroni correction was applied to adjust the significance level, controlling the family-wise error rate. Statistical significance was defined as a P-value <0.05.

Results

Detection results

Table I presents the EEG and ESM-1 test results of all patients. ESM-1 was found to be present at a generally high level in both the serum and CSF of sTBI patients. Moreover, the absolute power of β, θ, and δ waves was significantly higher than the reference values, while the absolute power of α waves was lower. All 98 enrolled sTBI patients were included in the analysis. Prospective follow-up at 28 days and 6 months was completed for all participants, with no loss to follow-up.

Table I Baseline data and examination results of the patients.

Test items	Data
Age	54.18±6.02
Gender, (male vs. female)	58 (59.18) vs.40 (40.82)
Admission time (h)	14.56±6.09
GCS score	5.08±1.92
Serum -ESM-1 (pg/mL)	13.69±4.46
CSF-ESM-1 (pg/mL)	10.35±4.08
Θ waves (μV^2)	5.81±0.68
δ waves (μV^2)	6.88±0.82
β waves (μV^2)	5.77±0.74
α waves (μV^2)	1.99±0.61
IL-6 (pg/mL)	13.28±4.07
TNF-α (pg/mL)	19.86±4.82
S100β (mg/L)	0.25±0.08
NSE (ng/mL)	30.19±4.46
Mechanism of injury (open *vs.* closed)	56 (57.14) vs.42 (42.86)
Pathological processes (primary *vs.* secondary)	62 (63.27) vs. 36 (36.73)
Undergo surgical treatment	72 (73.47)
Combined hypertension	36 (36.73)
Combined diabetes mellitus	44 (44.90)

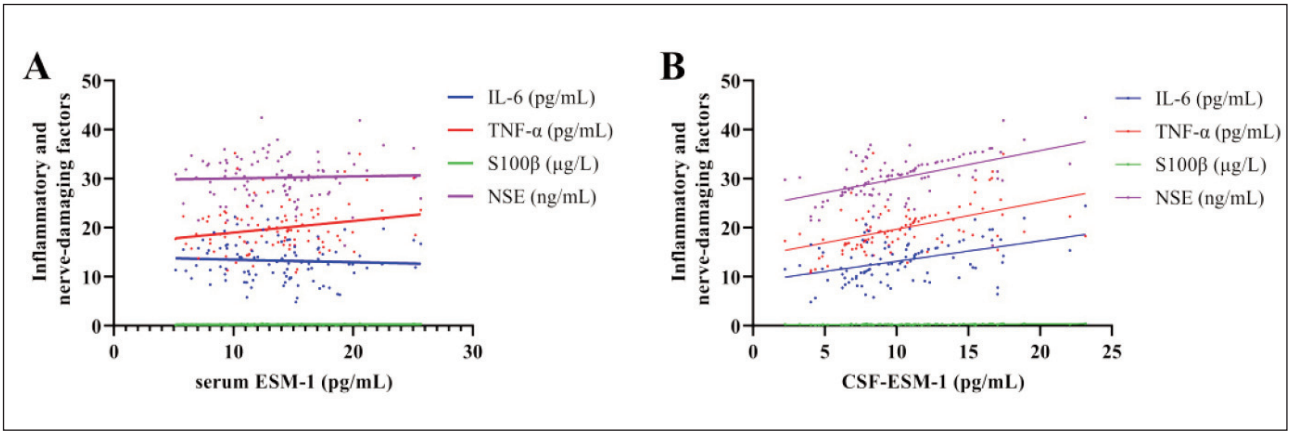

Figure 1 Correlation of ESM-1 and inflammatory factors /BBB damaging factors. (A) Correlation analysis of serum -ESM-1 and IL-6, TNF-α, S100β, NSE. (B) Correlation analysis between CSF-ESM-1 and IL-6, TNF-α, S100β, NSE.

Correlation of ESM-1 with inflammatory reaction and BBB injury

Correlation analysis showed that CSF-ESM-1 was positively correlated with inflammatory factors IL-6 (r=0.417), TNF-α (r=0.470) (P<0.05), as well as BBB injury biomarkers S100β (r=0.522) and NSE (r=0.524) (P<0.05). It is suggested that the higher the ESM-1 level, the more severe the inflammatory response and BBB damage in patients. Serum ESM-1 was only positively correlated with TNF-α (r=0.219, P<0.05) (*Figure 1*).

Table II Results of the regression analysis.

	B	S.E.	Wals	P	OR	95%CI
Serum ESM-1	0.226	0.069	10.604	0.001	1.254	1.094–1.437
α	1.438	0.468	9.431	0.002	4.214	1.683–10.553
β	0.717	0.337	4.516	0.054	1.048	0.357–3.965
δ	1.132	0.433	6.827	0.009	3.101	1.327–7.249
θ	-0.983	0.525	3.498	0.061	0.374	0.134–1.048

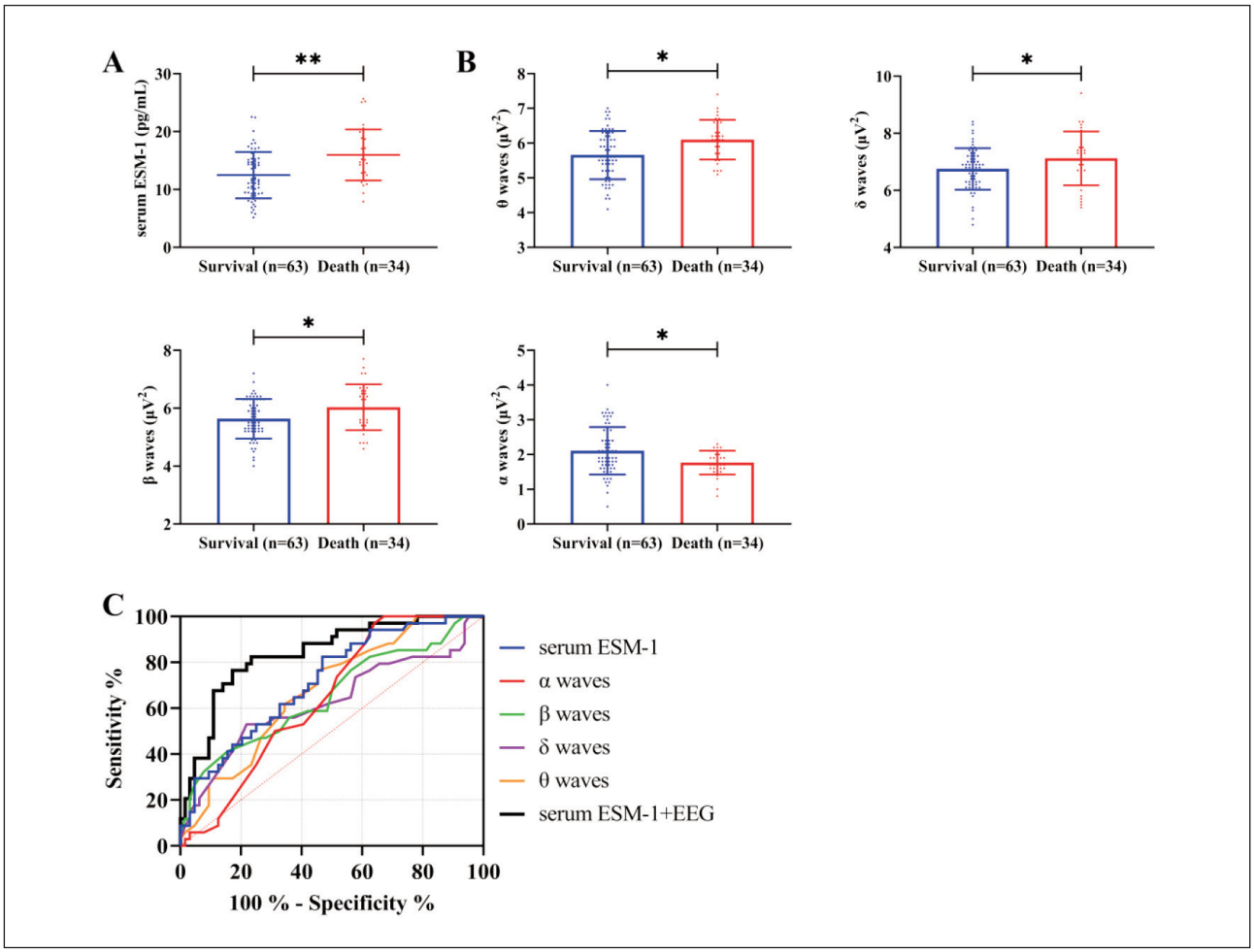

Figure 2 Predictive effect of serum-ESM-1 + EEG on mortality within 28 days in patients with sTBI. (A) comparison of serum -ESM-1 between patients who died and those who survived. (B) comparison of EEG results (α, β, θ, and δ waves) between dead and surviving patients. (C) ROC curve of serum -ESM-1 + EEG for predicting death in sTBI patients. **P<0.01, *P<0.05.

Predictive effect of serum ESM-1 + EEG on patient mortality

According to statistics, the 28-day mortality rate of 98 patients was 34.69% (34/98). Compared to survivors, the serum ESM-1 of the deceased was higher (P<0.05). A joint detection model (-19.334 + 0.268 × serum ESM-1 + 1.471 × δ waves + 1.074 × α waves) of serum ESM-1 and EEG for predicting patient mortality was established through regression analysis [Variables (θ and β waves) were excluded from the final serum ESM-1+EEG model through backward stepwise regression based on the Akaike

Table III Results of the regression analysis.

	B	S.E.	Wals	P	OR	95%CI
CSF-ESM-1	0.511	0.124	17.098	<0.001	1.667	1.308–2.124
α	1.193	0.551	4.691	0.030	3.296	1.120–9.700
β	0.756	0.377	4.021	0.045	2.129	1.017–4.455
δ	1.320	0.504	6.867	0.009	3.745	1.395–10.053
θ	-1.221	0.602	4.111	0.043	0.295	0.091–0.960

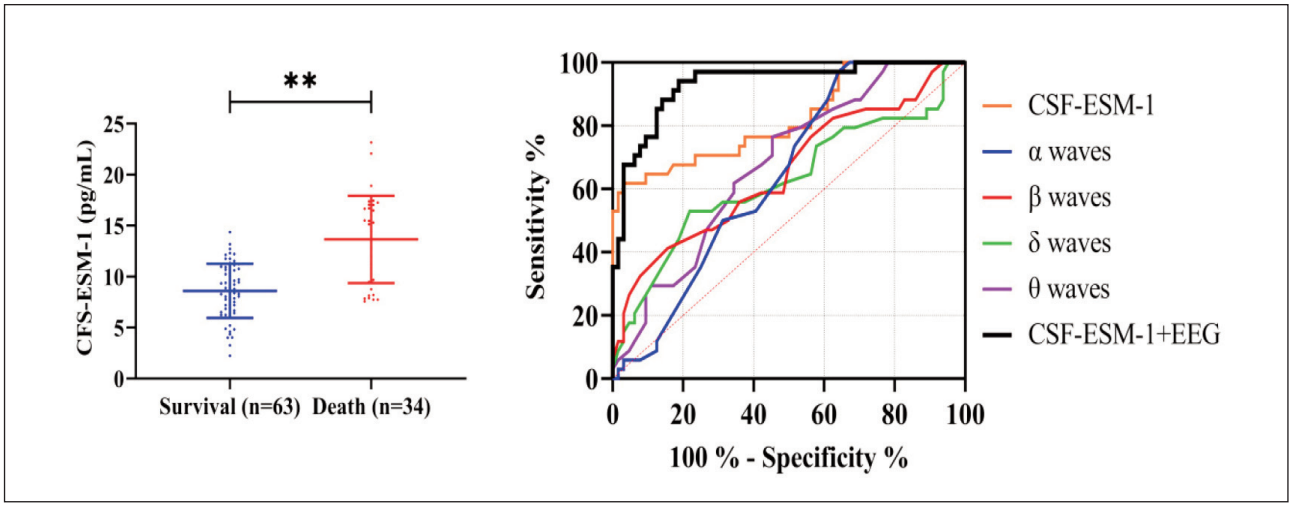

Figure 3 Predictive effect of CSF-ESM-1 + EEG on mortality within 28 days in patients with sTBI. **P<0.01.

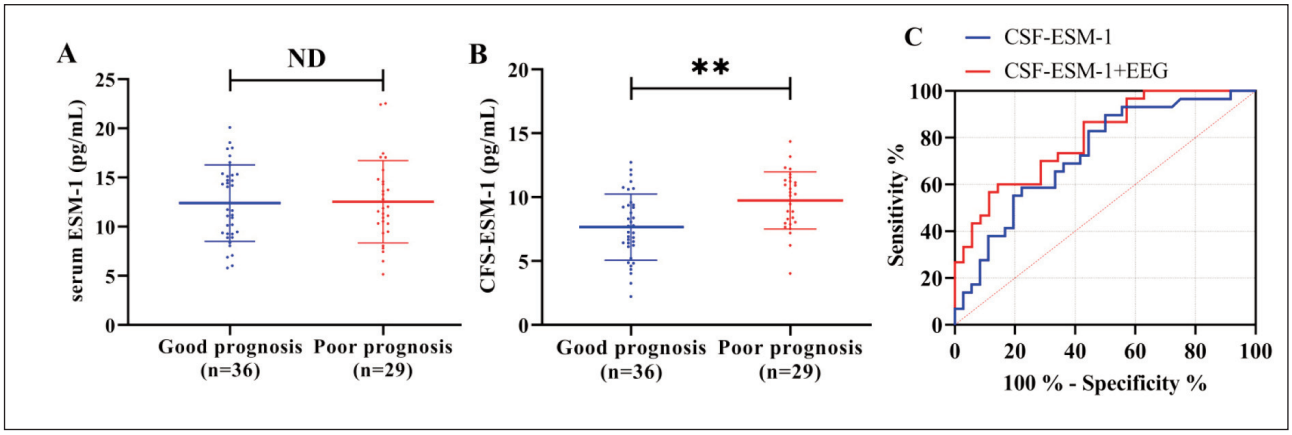

Figure 3 Predictive effect of CSF-ESM-1 + EEG on mortality within 28 days in patients with sTBI. **P<0.01.

Information Criterion (AIC) to achieve model parsimony, as they did not contribute significantly to the predictive power]. According to ROC curve analysis, the sensitivity of this model for predicting patient mortality within 28 days was 76.47%, the specificity was 82.81%, and the AUC was 0.838 (95%CI=0.756-0.921, P<0.001) (*Table II* and *Figure 2*).

Predictive effect of CSF-ESM-1 + EEG on patient mortality

Similarly, we identified higher CSF-ESM-1 levels in dead patients compared to survivors (P<0.05). The combined detection [-23.683 + 0.511 × CSF-ESM-1 + 1.193 × waves + 0.756 × δ waves + 1.320 × β waves+(-1.221) × α waves] of CSF-ESM-1 and EEG had a sensitivity and specificity of 94.12% and 81.25%, respectively, for predicting patient mor-

tality within 28 days (AUC = 0.932; 95%CI=0.879-0.984, P<0.001) (*Table III* and *Figure 3*).

Predictive effect of serum ESM-1/CSF-ESM-1 + EEG on poor prognosis

Prognostic follow-up successfully tracked all the subjects, with 6 additional patient deaths. The GOS of the patients who finally survived was (2.97±1.27) at 6 months. Based on the GOS scoring results, 36 patients were included in the good prognosis group and 29 patients in the poor prognosis group. There was no significant difference in serum ESM-1 between the good prognosis group and the poor prognosis group (P>0.05), while CSF-ESM-1 was lower in the good prognosis group relative to the poor prognosis group (P<0.05). When used in combination for predicting adverse outcomes, CSF-ESM-1 and EEG showed an AUC of 0.798 (95%CI=0.693-0.903, P<0.05; sensitivity: 60.00%, specificity: 85.71%), outperforming serum ESM-1 + EEG detection (*Figure 4*).

Discussion

This study systematically evaluated the prognostic value of ESM-1 in sTBI by simultaneously detecting ESM-1 levels in the serum and CSF of 98 sTBI patients and combining them with EEG parameters. The primary findings are listed below: ① Levels of ESM-1 in serum and CSF were significantly positively correlated with inflammatory factors (IL-6, TNF-α) and BBB injury biomarkers (S100β, NSE), suggesting that ESM-1 can serve as a biomarker for inflammation-vascular injury after sTBI. ② CSF-ESM-1 + EEG had better predictive performance for 28-day mortality and 6-month poor prognosis than serum ESM-1 + EEG, supporting the stronger association between local elevation of ESM-1 in the brain and neurological deterioration.

The superiority of CSF-ESM-1 + EEG to serum ESM-1 + EEG in evaluating sTBI can be explained from the following two aspects: ① Biological source specificity: ESM-1 is mainly secreted by activated endothelial cells, and endothelial cells in the brain parenchyma account for more than 20% of the total endothelial cells in the human body, with increased permeability after BBB disruption (13). Following sTBI, brain endothelial cells are directly exposed to the injury microenvironment. Hence, the increase in ESM-1 in the CSF directly reflects the local inflammatory reaction and the degree of BBB injury in the brain. In contrast, serum ESM-1 not only originates from the brain vascular endothelium but is also influenced by inflammation in peripheral tissues (e.g., the lungs, liver, intestines) (14). For example, post-traumatic systemic inflammatory response syndrome (SIRS) can lead to non-specific elevation of serum ESM-1, weakening its association with neural injury (15). In this study, the correlation coefficient of serum ESM-1 with IL-6 and TNF-α was statistically lower than that of CSF-ESM-1, confirming the dilution effect of peripheral interference on serum ESM-1. ② Proximity in anatomical position: CSF, as a direct 'liquid biopsy' of brain parenchyma, has proteomic characteristics highly homologous to the interstitial fluid of brain tissue (16). Following sTBI, cerebral ESM-1 enters the CSF through a damaged BBB, with its concentration changes synchronizing with core pathological processes such as neuronal injury and glial cell activation (17). However, serum ESM-1 needs to cross the BBB through passive diffusion or active transport, resulting in temporal and spatial delays. Animal experiments have shown that after intracerebral injection of ESM-1, its concentration in the CSF peaks within 2 hours, whereas the concentration in the serum takes 6 hours to rise significantly (18). This time lag may limit the predictive efficacy of serum ESM-1 in the early stages of sTBI (e.g., within 24 hours post-injury), and the predictive advantage observed in the CSF group in this study, with sampling within 24 hours of admission, is consistent with this mechanism.

Previous studies have mostly separately evaluated the prognostic value of ESM-1 or EEG. For instance, For example, Sun H et al. found that elevated serum ESM-1 increased the risk of early atherosclerosis (19). The report by Chen W et al. indicates that the absence of EEG reactivity predicts poor prognosis with a sensitivity of 78% and a specificity of 73% (20). In this study, by combining two biomarkers, the predictive performance was significantly enhanced (AUC: 0.838-0.932), and for the first time, the differences between serum- and CSF-derived ESM-1 were compared. Similar to studies by Lam AD et al., this study confirms that combining CSF biomarkers with EEG can optimize prognostic stratification, although their research focused on tau protein rather than ESM-1 (21). This suggests that different combinations of biomarkers may be applicable for assessing specific pathological mechanisms.

Based on our findings, the following clinical translational pathways are proposed: ① For sTBI patients requiring precise prognostic evaluation (such as those planned for surgical intervention or mild hypothermia treatment), it is recommended to simultaneously collect CSF and serum samples to reduce interference from peripheral inflammation. ② Continuous EEG monitoring can be combined with dynamic changes in ESM-1 to construct a time series prediction model. For instance, the timing of the CSF-ESM-1 peak may correspond to the phase of increased slow-wave activity on EEG, potentially indicating a peak period of secondary brain injury. ③ For patients with high CSF-ESM-1 expression and widespread EEG suppression, intensified neuroprotection treatment (e.g., targeted anti-inflammatory drugs,

BBB repair agents) is required. ④ Whereas for cases with serum ESM-1 elevation, the influence of systemic complications (such as sepsis) should be evaluated.

It is worth noting that although the sample size was estimated to be 98 cases using the PASS software, the actual number of deaths was only 26 cases, which may result in insufficient power for subgroup analysis. In the future, a larger sample size is needed to verify the external validity of the critical value. Furthermore, given that this study was conducted in a single medical center, there may be biases in the patient population characteristics (e.g., injury mechanism, treatment strategy), warranting multi-center collaboration for verification. Moreover, CSF sampling was conducted within 24 hours of admission, failing to dynamically track the temporal variation pattern of ESM-1. Subsequent sampling points at early (6 hours) and late (72 hours) stages could be added to analyze the kinetic characteristics of ESM-1.

Conclusion

The combination of CSF-ESM-1 and EEG demonstrates significantly superior prognostic predictive efficacy compared to serum ESM-1 combined with EEG in patients with sTBI. When feasible, prioritizing CSF sampling for ESM-1 assessment alongside multimodal EEG monitoring can enhance early risk stratification and guide personalized management in sTBI.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Not applicable.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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