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Unveiling neurogenic biomarkers for the differentiation between sepsis patients with or without encephalopathy: an updated meta-analysis

Jiyun Hu[1†], Wenchao Li[1†], Shucai Xie[1], Ya Liao[1], Tao Chen[1], Xinrun Wang[1], Weiping Xia[1], Fang Huang[1], Zhaoxin Qian[1*] and Lina Zhang[1*]

Abstract

Background Sepsis-associated encephalopathy (SAE) is characterized by brain dysfunction in the context of sepsis and frequently leads to significant cognitive and neurological impairments, as well as an elevated risk of mortality. Accurate diagnosis of SAE is crucial for the timely initiation of optimal treatment and appropriate patient management. Neurogenic biomarkers hold promise as reliable serum diagnostic tools for the detection and longitudinal monitoring of SAE. This meta-analysis seeks to evaluate the diagnostic and prognostic utility of serum neurogenic biomarkers in patients with SAE.

Methods The study protocol was registered in the PROSPERO database (CRD42023408312) and conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A meta-analysis was conducted to comprehensively and critically evaluate the existing body of evidence regarding the use of serum neurogenic biomarkers: neuron-specific enolase (NSE), ubiquitin C-terminal hydrolase-L1 (UCH-L1), Tau, S100 calcium-binding protein β (S100β), and glial fibrillary acidic protein (GFAP) for the diagnosis and risk assessment of fatality in SAE. We conducted a systematic search of electronic bibliographic databases, including PubMed, Web of Science, Embase, Cochrane databases, CNKI, CQVIP, and WFSD. The quality and risk of bias of the selected studies were assessed using the QUADAS-2 tool. For biomarkers reported in two or more studies, pooled standardized mean differences and 95% confidence intervals were calculated. Heterogeneity among the included studies was examined using the I^2 statistic and random-effects model was applied owing to large heterogeneity.

Results Forty-two studies were included in our meta-analysis. The levels of serum neurogenic biomarkers were significantly higher in patients with SAE as compared to septic patients with no-encephalopathy (NE): NSE (standardized mean difference (SMD) 1.98 (95% CI 1.55–2.42), $P < 0.00001$); UCH-L1 (SMD 1.75 (95% CI 0.90–2.59), $P < 0.0001$); Tau (SMD 1.14 (95% CI 1.01–1.28), $P < 0.00001$); S100β (SMD 1.82 (95% CI 1.45–2.19), $P < 0.00001$); and GFAP (SMD 3.63 (95% CI 1.85–5.41), $P < 0.0001$). In addition, significantly lower serum neurogenic biomarkers levels were noted

[†]Jiyun Hu and Wenchao Li contributed equally to this work and should be regarded as co-first authors.

*Correspondence:
Zhaoxin Qian
xyqzx@csu.edu.cn
Lina Zhang
zln7095@csu.edu.cn

in septic patients with survivors as compared to non-survivors: NSE (SMD − 1.87 (95% CI − 2.43 to − 1.32), $P < 0.00001$); UCH-L1 (SMD − 1. 71 (95% CI − 2.24 to − 1.19), $P < 0.00001$); Tau (SMD − 0.57 (95% CI − 0.79 to − 0.35), $P < 0.00001$); S100β (SMD − 1.34 (95% CI − 1.88 to − 0.80), $P < 0.00001$). However, no significant differences in serum GFAP levels [SMD -7.98 (95% CI − 22.23–6.27), $P = 0.27$) were found between the surviving and non-surviving groups.

Conclusion The increased serum neurogenic biomarkers may be predictive of SAE and mortality for septic patients, which are expected to be applied as a reliable blood-based diagnostic tool for detection and longitudinal monitoring in SAE patients. However, results should be interpreted with caution due to the high heterogeneity among studies.

Highlights

1. This is the first systematic review and meta-analysis to evaluate serum neurogenic biomarkers potential in patients with sepsis-associated encephalopathy (SAE) and has the possibility of informing future clinical practice.
2. We used appropriate methodologies and quality assessment tools that may feed into an evidence-based clinical practice.
3. Serum neurogenic biomarkers may serve as a reliable blood-based diagnostic tool in SAE, which may provide a simple and effective reference for clinical treatment decisions.

Keywords Sepsis-associated encephalopathy, NSE, S100β, GFAP, UCH-1, Tau, Biomarker

Introduction

Sepsis is a leading cause of intensive care unit (ICU) admissions worldwide. Although the International Guidelines for Management of Sepsis and Septic Shock has been continuously updated from sepsis 1.0 in 1991 to sepsis 3.0 in 2016, and many new technologies for the treatment of sepsis have been emerged, no effective methods have been found to reduce the incidence and mortality of sepsis and sepsis-associated complications [1, 2]. Sepsis-associated encephalopathy (SAE) is characterized by acute cognitive impairment which has been linked to elevated mortality rates, prolonged hospital stays, and persistent cognitive deficits [3]. SAE is diagnosed through EEG abnormalities, mental status changes, clinical history, physical exams, lab tests, and neuroimaging. The cause of SAE is complex and not fully understood, making diagnosis and treatment difficult [4]. A growing amount of attention has been paid to precision medicine in recent years due to the continuous development of medical science, and there has been a growing interest in the discovery of different types of biomarkers with the development of precision medicine. A series of commonly used neurogenic biomarkers has garnered extensive use in investigating neuropsychiatric disorders including traumatic brain injuries (TBI), hypoxic-ischemic brain injuries, brain tumors, cerebral infarctions, cerebral hemorrhages, epilepsy, and ischemia/reperfusion cerebral injuries after cardiac arrest [5, 6]. The identification of biomarker signatures linked to specific aspects of SAE pathophysiology holds potential clinical significance in enhancing the characterization and risk stratification of TBI, thereby improving medical decision-making and enabling personalized therapeutic interventions. Consequently, there has been a concentrated effort in recent years to discover valuable serum biomarkers for SAE, resulting in the emergence of numerous potential candidates. As for currently used neurogenic biomarkers to diagnose SAE and assess its severity in clinical evaluations, they can be divided into two categories: neuronal cell damage markers including neuron-specific enolase (NSE), ubiquitin C-terminal hydrolase L1 (UCH-L1), and Tau; and glial cell damage markers including S100 calcium-binding protein β (S100β) and glial fibrillary acidic protein (GFAP) [7, 8].

The integration of neurogenic biomarkers tests holds promise for improving the diagnosis and prognosis of SAE, ultimately leading to better clinical management and patient outcomes. Currently, the field of medicine has transitioned from the traditional empirical medicine to the evidence-based medicine. Even so, serum neurogenic biomarkers in SAE are currently focused on research studies, and providing high-quality evidence for their adoption and routine use in clinical practice is paramount. Therefore, this systematic review and meta-analysis were undertaken to comprehensively summarize and critically evaluate the current body of evidence regarding the utilization of serum neurogenic biomarkers for the diagnosis and prognosis of SAE. A meta-analysis has the capacity to leverage the volume of data gathered from individual studies and allows for the examination of potential confounding factors that may influence the diagnostic and prognosis performance of biomarkers, as well as the detection of variations in the accuracy of different biomarker tests. The purpose of our meta-analysis was to evaluate the potential diagnostic and prognostic

value of serum neurogenic biomarkers including NSE, UCH-L1, Tau, S100β, and GFAP in patients with SAE.

Methods

Protocol/registration

Before conducting the analysis, we developed a protocol and registered it in PROSPERO (an international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; Registration No. CRD 42023408312). The study was conducted according to the original protocol registered with PROSPERO. Results were reported following Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) 2020 [9].

Search strategy

We searched the main English and Chinese databases from the establishment of the database to June 15, 2024. English databases include PubMed, Web of Science, MEDLINE, Embase, Cochrane Central Register of Controlled Trials; Chinese databases include Chinese National Knowledge Infrastructure (CNKI), Chongqing VIP database (CQVIP), and WFSD (Wanfang Data Knowledge Service Platform). The Medical Subject Heading (Mesh) headings or keywords as follows: ("markers" OR "biomarkers" OR "biological markers" OR "biological measures" OR "molecular predictor") AND ("sepsis," or "severe sepsis," or "septic shock," or "Sepsis-associated encephalopathy," or "Sepsis encephalopathy,"). The terms were applied to the title and keywords for EMBASE. The terms were applied to the title, abstract, and keywords for Web of Science. There were no restrictions on language. Further, we manually checked references and citations of the identified studies to determine if there were any other potentially eligible trials.

Inclusion and exclusion criteria

The meta-analysis focused exclusively on studies pertaining to the serum biomarker in patients with SAE. Studies that met the following criteria were identified: (1) all patients should meet the confirmed sepsis or septic shock definition, and experiments should be Sepsis-associated encephalopathy patients (SAE), controls should be septic patients with no-encephalopathy (NE); (2) evaluation of main biomarkers such as NSE, UCH-L1, Tau, S100β, and GFAP in serum samples. We included both prospective and retrospective studies without restrictions. The exclusion criteria were as follows: (1) duplicate publications or other types of patients; (2) studies lacking original or complete data; (3) animal studies or reviews; (4) not involving the selected biomarkers or biomarkers detected from other body fluids such as cerebrospinal fluid.

Quality assessment

Two independent reviewers, J.-Y.H. and L.-N.Z., conducted a study quality assessment using the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) assessment tool as recommended by the Cochrane Collaboration. The assessment focused on two domains: risk of bias and applicability, each with its own assessment protocol. The risk of bias within each domain was categorized as low, unclear, or high based on the methods employed to mitigate bias. Any disagreements were discussed and resolved by the entire review team.

Data extraction

Data were independently extracted by three reviewers from each included study according to the selection criteria, then reviewed and compared by the first author. Any disagreements were resolved by consensus. The data extracted included study characteristics (first author and year), participant characteristics (age, sex ratio, and sample size), and methodological characteristics (assay, cutoff, and collection time). For subsequent statistical analysis, the units of NSE, UCH-L1, Tau, S100β, and GFAP were unified. The data extracted encompassed various study characteristics (e.g., first author and year), participant characteristics (e.g., age, sex ratio, and sample size), and methodological characteristics (e.g., assay, cutoff, and collection time). Further details may be sought by engaging in direct communication with the primary authors to procure and authenticate the data whenever feasible. If there were several serum biomarkers collection time points in one study, we marked them separately at different time points, such as Zhou 2019(1d) and Zhou 2019 (3d).

Statistical analysis

To assess the diagnostic accuracy and predictive value of biomarkers in septic patients, the average serum NSE, UCH-L1, Tau, S100β, and GFAP levels were collected for those with and without encephalopathy, along with their respective standard deviations (SD). Additionally, the mean serum NSE levels were obtained for survivors and non-survivors, along with their corresponding SD. In instances where mean data were not provided, the approach outlined by Wan et al. was employed to calculate the mean and standard deviation (SD) using either the median and interquartile range (IQR) or median and range [10, 11]. These calculated values were then utilized to construct forest plots illustrating the standardized mean difference (SMD) of serum NSE, UCH-L1, Tau, S100β, and GFAP levels, with the results reported as SMD ± the 95% confidence interval (CI) for each respective patient cohort. Following the Cochrane

review guidelines, the *I*-squared (I^2) statistic was utilized to assess the impact of study heterogeneity on the outcomes of the meta-analysis. The fixed-effects or random-effects models were used according to the heterogeneities ($I^2 < 50\%$: fixed-effects models; $I^2 > 50\%$: random-effects models) [12]. Evaluation of potential publication bias was conducted using funnel plots, and sensitivity analysis was implemented to verify the dependability and coherence of the Meta-analysis results. Statistical software Review Manager version 5.4 (RevMan, The Cochrane Collaboration, Copenhagen) and STATA software (version 16.0, StataCorp, College Station, TX) were utilized for the entirety of the analyses. We considered a *P*-value of less than 0.05 significant for all analyses; for evaluating publication bias, we considered a *P*-value greater than 0.1 significant.

Results

Search results

The process of study selection is depicted in Fig. 1. A total of 60,769 relevant studies were identified using the search terms (PubMed: 12,589, Web of Science: 21,978, EMBASE: 21,686, Cochrane Library: 1415, CNKI: 914, WFSD: 1711, CQVIP: 476), with 47,343 duplicates excluded. Following a literature search and screening of titles and/or abstracts, 13,426 studies were identified, and then 13,217 studies were deemed irrelevant to the topic and excluded. After a full-text eligibility assessment, 167 studies were further excluded. Ultimately, 42 studies met all inclusion criteria and were included in the meta-analysis: 15 studies from the English database [13–27] and 27 studies from the Chinese database [28–54]. The selected details of the individual studies are listed in Table 1. In

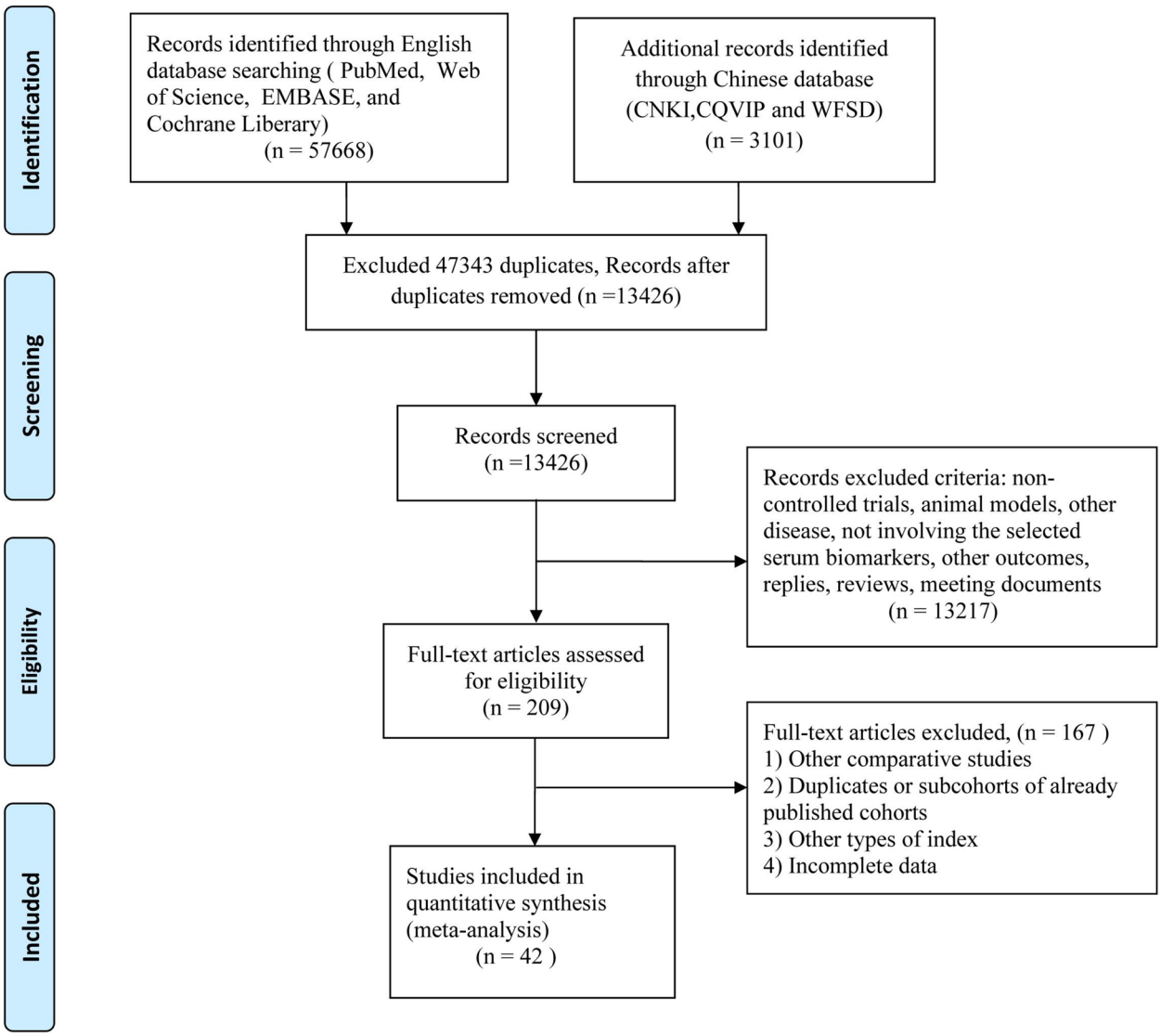

Fig. 1 The process of study selection

the current meta-analysis, as for neuronal cell damage markers, we collected 1315 clinical samples from SAE patients and 1463 clinical samples from NE which examined serum NSE; 138 clinical samples from SAE patients and 144 clinical samples from NE which examined serum UCH-L1; and 493 clinical samples from SAE patients and 497 clinical samples from NE which examined serum Tau. As for glial cell damage markers, there were 1401 SAE clinical samples and 1591 NE clinical samples respectively which examined serum S100β; and there were 385 SAE clinical samples and 486 NE clinical samples respectively which examined serum GFAP. This information is very interesting from the clinical aspect of serum neurogenic biomarkers selection. Of these, NSE and S100β have been most extensively studied and widely used.

Quality assessment

An assessment of quality using the QUADAS-2 tool is presented in Figs. 2 and 3, and the quality of the included studies varied. After the quality assessment of each biomarker, we had fewer concerns about the applicability of the included studies to the review question compared to concerns about the risk of bias. High-risk of bias was mainly focused on index tests and high- applicability concerns mostly from reference standards. This can probably be explained because different diagnostic criteria of SAE were used in the various studies, and our study included only English and Chinese literature, and literatures in other languages were not searched, which may have resulted in a language bias.

Meta-analysis results

Correlation between the levels of serum neurogenic biomarkers and SAE

In our study, through exploratory analysis, we found associations between some serum neurogenic biomarkers and SAE. Whether serum levels of these biomarkers (NSE, UCH-L1, Tau, S100β, and GFAP) differ between SAE and NE, remains therefore unclear. For this comparison, we analyzed serum samples from septic patients with and without clinical suspicion of SAE by a meta-analysis (Fig. 4). Twenty-one studies reported serum NSE levels in the SAE group between the NE group. As shown, the heterogeneity test demonstrated significant differences among studies ($I^2=95\%$, $P<0.00001$); therefore, the random-effects model was applied, and there was a statistically significant difference between serum NSE levels in SAE patients and NE patients [SMD 1.98 (95% CI 1.55–2.42), $P<0.00001$]. There are only two studies that reported serum UCH-L1 levels in the SAE group between the NE group, and the heterogeneity test demonstrated significant ($I^2=89\%$, $P=0.003$). There was also a statistically significant difference between serum UCH-L1 levels in SAE patients and NE patients (SMD 1.75 (95% CI 0.90–2.59), $P<0.0001$). And there are three studies reported serum Tau levels with a lower heterogeneity ($I^2=28\%$, $P=0.19$), the levels of serum Tau during SAE patients were significantly higher than NE patients (SMD 1.14 (95% CI 1.01–1.28), $P<0.00001$). In addition to that, there was a statistically significant difference between serum S100β levels (SMD 1.82 (95% CI 1.45–2.19), $P<0.00001$) and GFAP levels (SMD 3.63 (95% CI 1.85–5.41), $P<0.0001$) in SAE patients and NE patients. A summary of the number and characteristics of primary articles identified for each biomarker is presented in Table 2. In brief, the results of the meta-analysis indicated that the serum levels of neurogenic biomarkers in the SAE group were significantly higher than those observed in the NE group. These findings suggest the differences in serum levels of neurogenic biomarkers between septic patients with or without SAE.

Comparison of serum NSE levels between survival and death

We further collected studies that detected serum neurogenic biomarkers between the surviving and non-surviving group (Fig. 5). There are also significant differences between serum NSE levels (SMD − 1.87 (95% CI − 2.43 to − 1.32), $P<0.00001$); UCH-L1 levels (SMD − 1. 71 (95% CI − 2.24 to − 1.19), $P<0.00001$); Tau levels (SMD − 0.57 (95% CI − 0.79 to − 0.35), $P<0.00001$); S100β levels (SMD − 1.34 (95% CI − 1.88 to − 0.80), $P<0.00001$) between surviving and non- surviving group. But there were no significant differences in serum GFAP levels (SMD − 7.98 (95% CI − 22.23–6.27), $P=0.27$) between the surviving and non-surviving groups. The sample size of GFAP was relatively small, so the results may not necessarily represent survival and death outcomes. It displayed septic patients who died had significantly higher serum NSE, UCH-L1, Tau, and S100β concentrations at baseline than those of survivors.

Publication bias and sensitivity analysis

We assessed the impact of publication bias by visual inspection of the funnel plot which is in Fig. 6. Potential publication bias may exist in association between levels of serum neurogenic biomarkers and SAE due to the funnel plot being asymmetric on visual inspection. Besides this, a sensitivity analysis was conducted utilizing a leave-one-out methodology to assess the robustness of the primary analyses. As illustrated in Fig. 7, the association between serum neurogenic biomarker levels and SAE remained consistent upon the exclusion of any single study. This indicates that no individual study significantly influenced the overall outcome, thereby affirming the statistical stability of the meta-analysis findings.

Table 1 Specific basic characteristics of the main included studies

Study and year	Biomarkers	SAE group			NE group			Sample collection time	Assay
		No. (males/female)	Age	Biomarker levels	N0. (males/female)	Age	Biomarker levels		
Chen 2019 [49]	S100β	42	Total: 68 ± 5.4	0.53 ± 0.28	58		0.19 ± 0.09	ICU admission	ELISA
Cui 2022 [28]	NSE; S100β; GFAP	79 (45/34)	72.78 ± 4.01	**NSE:** 24.84 ± 3.28 **S100β**: 0.53 ± 0.09 **GFAP**: 2.03 ± 0.47	121 (70/51)	72.86 ± 4.60	**NSE**: 10.69 ± 4.31 **S100β**: 0.25 ± 0.06 **GFAP**: 0.21 ± 0.08	Within 48 h	FICA
Erikson 2019 [25]	S100β	10 (4/6)	62.4 (49–70.5)	0.30 (0.19–0.59)	12 (10/2)	61.8 (60.1–78.5)	0.15 (0.07–0.30)	When CAM-ICU assessed	CLIA
Feng 2017 [16]	NSE; S100β	36 (21/15)	52 ± 14	**NSE**: 1d: 19.28 (13.00, 30.52); 3d: 16.03 (9.40, 21.29) **S100β**: 1d: 0.33 (0.15, 0.54); 3d: 0.19 (0.10, 0.29)	23 (14/9)	57 ± 15	**NSE**:1d:16.61(7.58,22.01) ;3d:11.39(8.49,15.00) **S100β**:1d:0.23(0.16,0.53); 3d:0.10(0.05,0.17)	1, 3 d	CLIA
Guo 2021 [17]	NSE; S100β	30 (17/13)	57.61 ± 4.16	**NSE**: 10.16 ± 2.11 **S100β**: 0.27 ± 0.06	90(42/48)	56.91 ± 4.85	**NSE**:8.62 ± 1.62 **S100β**:0.18 ± 0.04	NA	ELISA
Hu 2020 [51]	S100β	40	NA	1 h: 0.50351 ± 0.41551 3d: 0.36315 ± 0.2466 5d: 0.0683 ± 0.02235	40	NA	1 h:0.14208 ± 0.06362 3d:0.07384 ± 0.02233 5d:0.06617 ± 0.01959	1 h, 3 d, 5 d	
Jiang 2021 [52]	S100β	26 (18/8)	42.45 ± 3.48	0.16446 ± 0.02921	38(27/11)	41.2 ± 3.5	0.12784 ± 0.02224	4 h	ELISA
Kang 2022 [53]	S100β	22 (14/8)	27.5 (11.3–54.5) months	1.8 ± 0.2	25 (14/11)	21.0 (9.0–32.5) months	1.1 ± 0.3	Within 24 h	ELISA
Li 2019 [46]	S100β	28	NA	0.92 ± 0.15	102	NA	0.76 ± 0.13	1 d	ELISA
Li 2022 [22]	NSE; S100β	21 (13/8)	37 ± 5	**NSE**: 12 h:18.4 ± 2.2; 24 h: 26.3 ± 1.8; 48 h: 21.8 ± 2.0 **S100β**: 12 h: 2.38 ± 0.21; 24 h: 3.52 ± 0.16; 48 h: 2.45 ± 0.18	20 (12/8)	38 ± 4	**NSE**: 12 h:18.4 ± 2.2; 24 h: 26.3 ± 1.8; 48 h: 21.8 ± 2.0 **S100β**: 12 h: 2.38 ± 0.21; 24 h: 3.52 ± 0.16; 48 h: 2.45 ± 0.18	12, 24, 48 h	NA
Li 2022–2 [50]	Tau	31 (21/10)	58.29 ± 12.20	1.03 ± 0.33	41(28/13)	61.41 ± 11.18	0.88 ± 0.25	Within 24 h	ELISA
Liao 2017 [48]	S100β	28 (20/8)	55 ± 13	1 h: 0.5 ± 0.24 3d: 0.58 ± 0.33	10 (8/2)	51 ± 16	1 h: 0.14 ± 0.08 3d:0.19 ± 0.11	1 h, 3 d	ELISA
Lin 2024 [47]	Tau	112(60/52)	44.45 ± 5.38	12 h: 9.56 ± 2.84 24 h: 11.30 ± 3.40 48 h: 9.81 ± 2.92	112(56/56)	45.91 ± 4.60	12 h: 6.70 ± 2.02 24 h: 7.81 ± 2.36 48 h: 6.89 ± 2.07	12, 24, 48 h	ELISA
Lu 2016 [23]	NSE; S100β	34 (24/10)	59.15 ± 8.8	**NSE**: 10.02 ± 1.48; **S100β**: 1.21 ± 0.15	52 (33/19)	58.39 ± 8.14	**NSE**: 9.86 ± 0.91; **S100β**: 0.98 ± 0.20	NA	NA
Nguyen 2014 [24]	S100β	107	Total: 65 ± 14	ICU admission:0.13 (0.06, 0.49) 4d:0.12 (0.08, 0.24)	21		ICU admission: 0.51 (0.18, 0.97) 4d: 0.08 (0.04, 0.13)	ICU admission, 4 d	RIA

Table 1 (continued)

Study and year	Biomarkers	SAE group			NE group			Sample collection time	Assay
		No. (males/female)	Age	Biomarker levels	N0. (males/female)	Age	Biomarker levels		
Meng 2020 [30]	NSE	82 (43/39)	59.54 ± 17.36	9.84 ± 2.21	96 (42/54)	60.32 ± 17.38	7.56 ± 1.72	NA	CLIA
Nong 2021 [31]	NSE	48 (26/22)	8.13 ± 2.12	20.28 ± 2.69	48 (25/23)	8.68 ± 2.71	12.18 ± 3.27	1 d	ELISA
Wang 2020 [32]	NSE; S100β	30(17/13)	50.5 ± 2.3	**NSE**: 27.20 ± 3.25 **S100β**: 0.28 ± 0.04	30 (19/11)	50.8 ± 2.5	**NSE**: 15.77 ± 3.50 **S100β**: 0.17 ± 0.02	1 d	WB
Wang 2022 [42]	NSE; S100β	45(29/16)	55.42 ± 14.63	**NSE**: 1d: 21.52 (14.47, 31.28);3d: 15.98 (9.36, 21.08) **S100β**: 1d: 0.32 (0.162, 0.579); 3d: 0.18 (0.116, 0.307)	35 (22/13)	56.37 ± 15.74	**NSE**: 1d: 15.87 (9.16, 21.49);3d: 10.74 (8.49, 16.09) **S100β**: 1d: 0.092 (0.068, 0.181); 3d: 0.063 (0.034, 0.121)	1, 3 d	ELISA
Wu 2019 [26]	UCH-L1; GFAP	58	NA	**UCH-L1**: 7.968 (7.018–8.736) **GFAP:** 0.696 (0.540–0.871)	47	NA	**UCH-L1**: 6.396 (5.771–6.977) **GFAP:** 0.436 (0.316–0.532)	Within 24 h	ELISA
Wu 2020 [18]	S100β	59(38/21)	54 ± 15	1d: 0.291 (0.174–0.478) 3d: 0.226 (0.129–0.447)	45 (32/13)	58 ± 14	1d: 0.157 (0.09–0.218) 3d: 0.089 (0.053–0.136)	1, 3 d	ELISA
Tan 2024 [45]	NSE	80(42/38)	71.55 ± 6.87	5.25 ± 1.00	97 (50/47)	71.88 ± 6.76	2.81 ± 1.21	1d	ELISA
Xiao 2022 [33]	NSE	46(20/26)	42.78 ± 8.75	22.18 ± 5.49	103 (46/57)	40.26 ± 9.22	15.30 ± 3.21	ICU admission	ELISA
Yan 2019 [19]	NSE; S100β; GFAP	58(44/14)	55.8 ± 16.4	**NSE**: 24.4(15.7, 37.5) **S100β**: 0.5(0.3, 1.3) **GFAP:** 2.1(0.7, 3.7)	94 (60/34)	55.0 ± 18.3	**NSE**: 10.6(5.0, 16.6) **S100β**: 0.3(0.1,0.5) **GFAP:** 0.2(0.1, 0.6)	Within 24 h	ELISA
Yao 2014 [20]	NSE; S100β	48 (33/15)	56 ± 16	**NSE**: 24.87 (31.73, 12.73) **S100β**: 0.306 (0.157,0.880)	64 (40/24)	52 ± 17	**NSE**: 15.49 (9.88–21.46) **S100β**: 0.095 (0.066–0.177)	1 d	ECLIA
Yu 2020 [35]	NSE; S100β	90 (49/41)	53.61 ± 12.74	**NSE**: 9.48 ± 1.32 **S100β**: 0.96 ± 0.14	90 (47/43)	52.89 ± 11.65	**NSE**: 7.62 ± 1.28 **S100β:** 0.71 ± 0.12	NA	ELISA
Yu 2022 [36]	NSE; S100β	67 (37/30)	70.3 ± 8.3	**NSE:** 9.62 ± 1.76 **S100β**: 1.03 ± 0.32	95 (51/44)	69.7 ± 8.6	**NSE:** 7.32 ± 1.35 **S100β**: 0.75 ± 0.21	NA	ICA
Yuan 2020–1 [37]	NSE	128 (77/51)	58 .6 ± 13 .5	13 .86 ± 8 .47	56 (35/21)	56.7 ± 15 .4	5.63 ± 2.91	NA	ECLIA
Yuan 2020–2 [38]	NSE	52 (21/34)	56.32 ± 7.04	1d: 28.85 (15.78, 38.37) 3d: 21 (12.47, 26.22)	16 (8/8)	53.71 ± 4.21	1d: 16.80 (6.61, 21.28) 3d: 11.98 (7.93, 14.34)	1, 3 d	CLIA
Zhang 2016 [21]	NSE; S100β	29 (20/9)	55.55 ± 12.72	**NSE:** 43.92 ± 14.66 **S100β**: 2.50 ± 0.49	28 (13/15)	56.21 ± 12.85	**NSE:** 13.16 ± 1.43 **S100β**: 0.61 ± 0.26	Within 24 h	ELISA
Zhao 2019 [54]	Tau	27 (16/11)	64.4 ± 14.2	91.90 ± 35.14	82 (48/34)	57.8 ± 12.5	58.18 ± 29.17	ICU admission	ELISA

Table 1 (continued)

Study and year	Biomarkers	SAE group			NE group			Sample collection time	Assay
		No. (males/female)	Age	Biomarker levels	N0. (males/female)	Age	Biomarker levels		
Zhao 2020 [40]	NSE; S100β	22 (13/9)	64.7 ± 12.2	**NSE**: 9.44 ± 1.02 **S100β**: 0.92 ± 0.11	78 (45/33)	65.1 ± 11.8	**NSE**: 7.45 ± 1.66 **S100β**: 0.72 ± 0.22	1 d	ELISA
Zhao 2022-1 [43]	NSE; S100β; GFAP	28 (16/12)	55.89 ± 16.55	**NSE**: 9.85 ± 2.40 **S100β**: 0.99 ± 0.28 **GFAP**: 176.23 ± 62.78	32 (18/14)	55.23 ± 16.71	**NSE**: 7.31 ± 1.32 **S100β**: 0.61 ± 0.15 **GFAP**: 45.09 ± 18.76	NA	ELISA
Zhao 2022-2 [44]	NSE	46 (24/22)	NA	9.12 ± 1.05	117 (62/55)	NA	8.53 ± 0.92	ICU admission	NA
Zhou 2019 [41]	NSE	38 (22/16)	53.74 ± 14.35	1d: 17.28 ± 5.47 3d: 23.03 ± 4.96	46 (24/22)	54.66 ± 15.72	1d: 16.87 ± 4.46 3d: 20.43 ± 3.34	1, 3 d	ELISA
Zhu 2022 [27]	NSE	86 (51/35)	55.45 ± 6.71	9.67 ± 1.03	100 (54/46)	55.48 ± 6.89	6.05 ± 0.34	Within 24 h	ELISA

SAE Sepsis-associated encephalopathy patients, *NE* No-encephalopathy septic patients, *NA* Not announced, *h* hour, *d* day, *m* month, *ELISA* Enzyme-linked immunosorbent assay, *ECLIA* Electrochemiluminescence immunoassay, *CLIA* Chemiluminescence immunoassay, *ICA* Immunochromatography assay, *FICA* Fluorescence immunochromatography assay, *RIA* Radioimmunoassay *WB* Western blotting

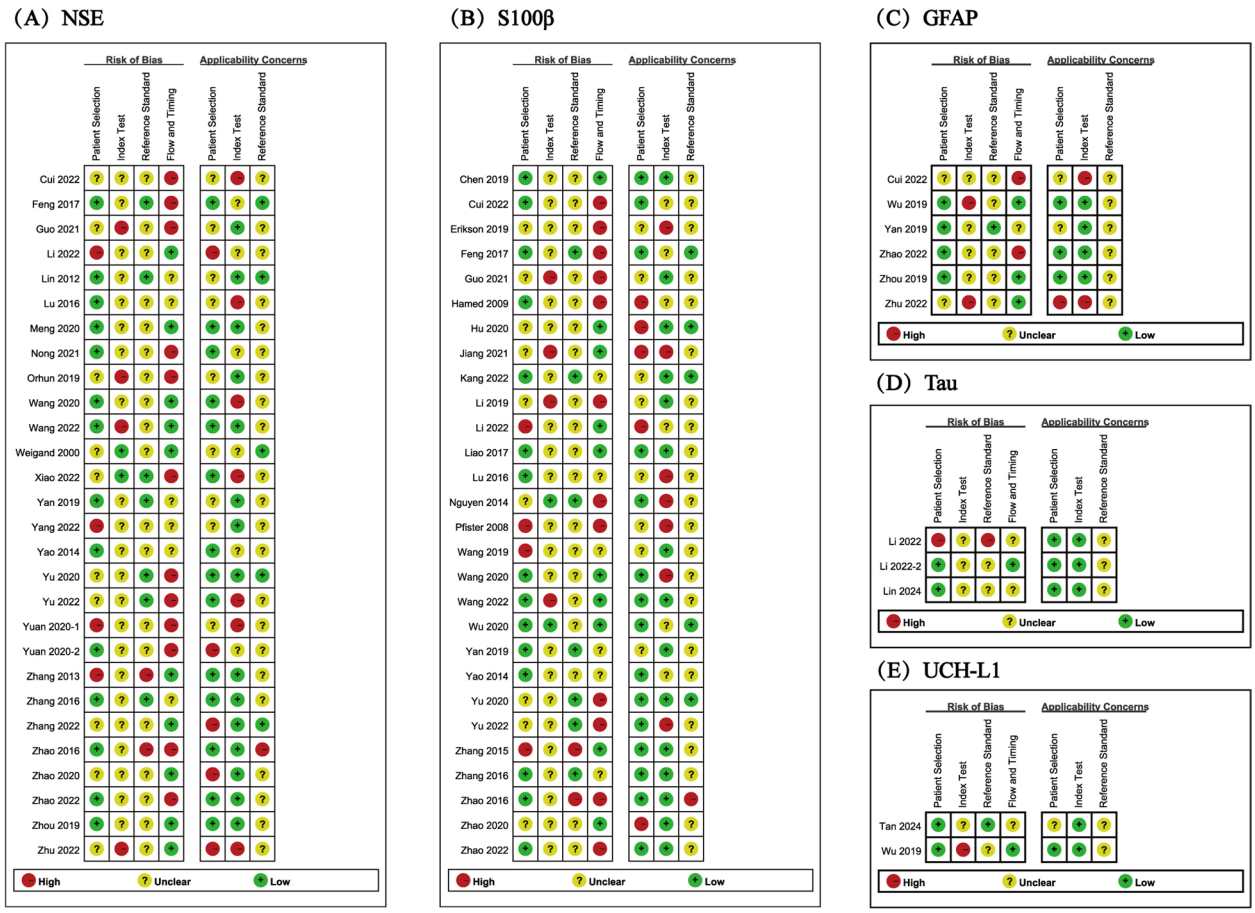

Fig. 2 Quality assessment of the included studies: risk of bias and applicability concerns summary (**A**: NSE, B: S100β; **C**: GFAP; **D**: Tau; **E**: UCH-L1)

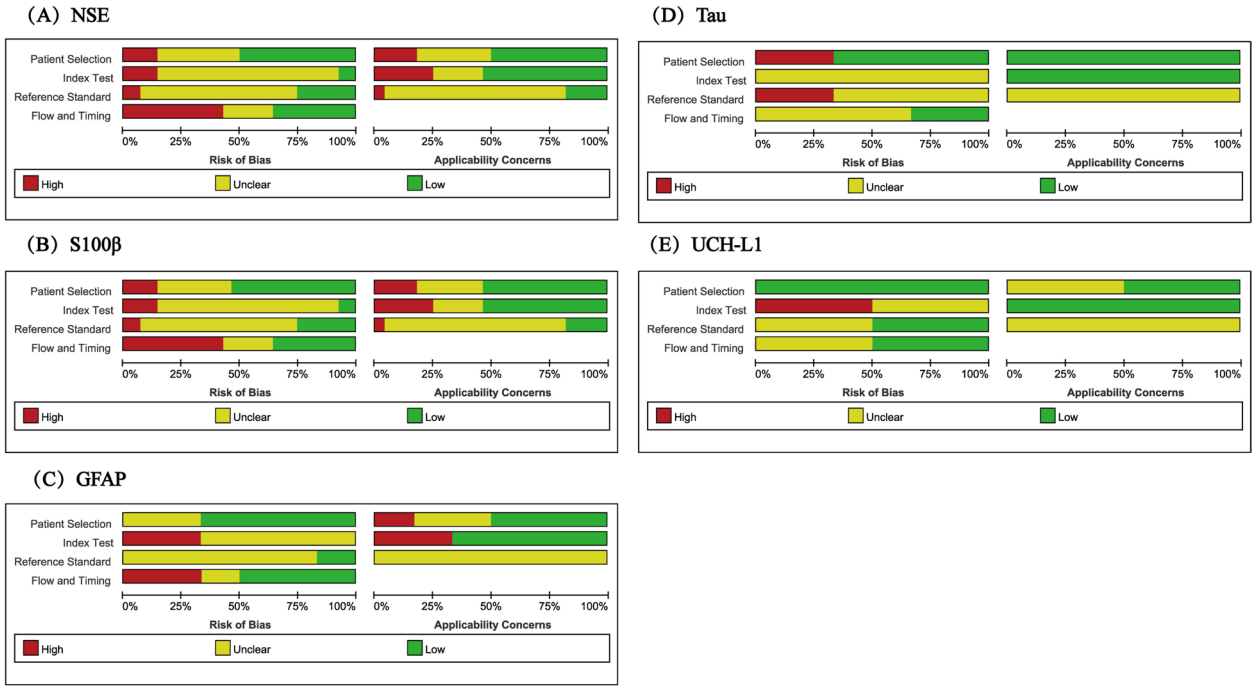

Fig. 3 Quality assessment of the included studies: risk of bias and applicability concerns graph (**A**: NSE, **B**: S100β; **C**: GFAP; **D**: Tau; **E**: UCH-L1)

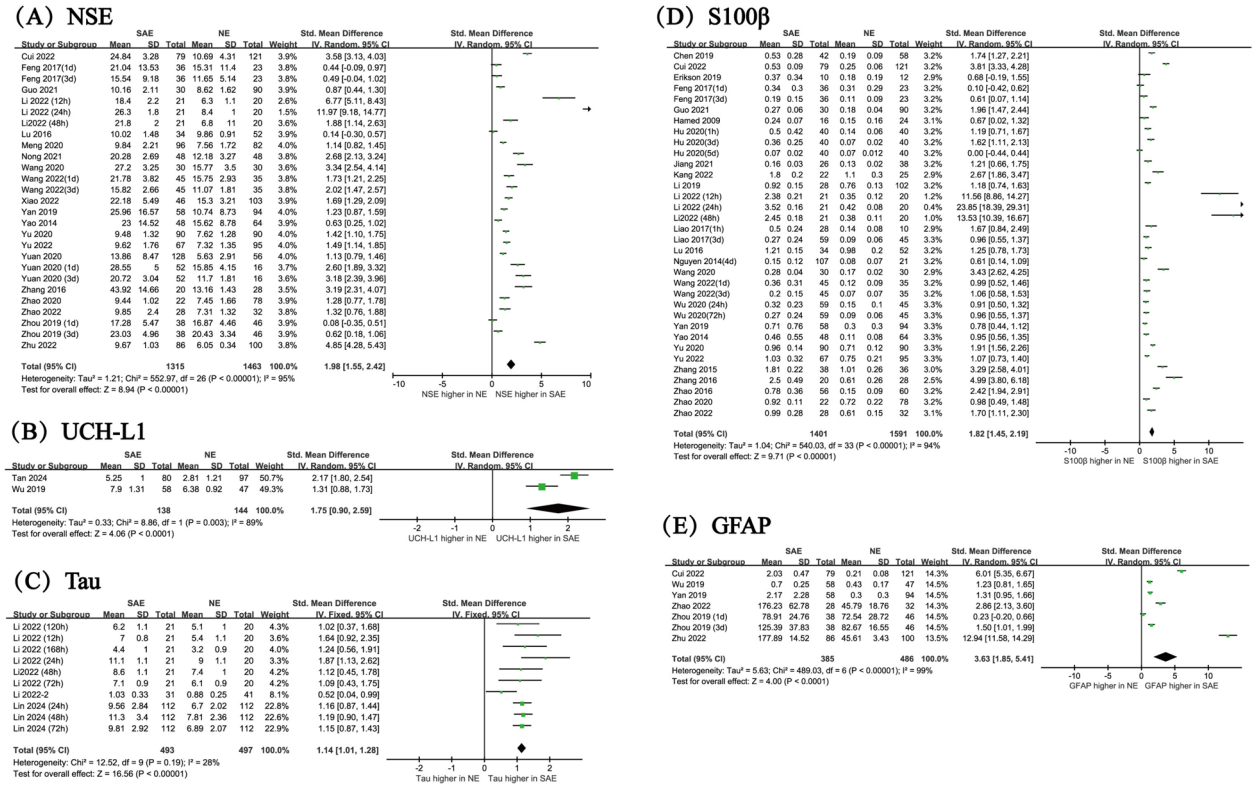

Fig. 4 Forest plot evaluating the association between serum neurogenic biomarkers levels and SAE (**A**: NSE; **B**: UCH-L1; **C**: Tau; **D**: S100β; **E**: GFAP)

Table 2 Summary of the number and characteristics of primary studies identified for each serum neurogenic biomarker

Biomarker	No. of studies	Heterogeneity	Statistical analysis results	
		I^2	SMD (95%CI)	*P*
NSE	21	95%	1.98 (1.55, 2.42)	< 0.00001
UCH-L1	2	89%	1.75 (0.90, 2.59)	< 0.0001
Tau	3	28%	1.15 (0.97,1.32)	< 0.00001
S100β	27	94%	1.82 (1.45, 2.19)	< 0.00001
GFAP	6	99%	3.63 (1.85, 5.41)	< 0.0001

Discussion

As a result of the complications caused by sepsis, patients with SAE experience increased mortality and poor outcomes, its onset and development are characterized by rapid changes, complicated illness state, and difficult treatment. In the absence of an unambiguous definition and highly accurate diagnostic tools, ICU physicians always rely on their own clinical skills and experience to diagnose SAE. And exclusion diagnosis was adopted for the diagnosis of SAE [55, 56]. We focused on neurogenic biomarkers for which promising scientific evidence of analytical and clinical validity is available and which therefore, are likely to be rapidly transferable to the clinical practice of SAE diagnosis and prognosis; namely NSE, UCH-L1, Tau, S100β, and GFAP. This meta-analysis aimed to analyze the serum neurogenic biomarkers levels in sepsis patients with or without encephalopathy. We further found that the levels of above serum neurogenic biomarkers except GFAP were significantly lower in surviving patients as compared to non-surviving patients. These findings were consistent throughout the studies. The purpose of our study was to explore the diagnostic and prognostic value of serum neurogenic biomarkers in patients with SAE for predicting the clinical status and malignant potential of sepsis, which warrants further investigation as a predictive biomarker.

Changes in the condition of sepsis are a dynamic process, so peaks of various serum neurogenic biomarkers emerged at various ages. And due to the clearance half-life of different biomarkers varies, and dynamic changes occurring as brain injury progresses, the optimal time to reflect the markers needs to be determined [57]. For example, NSE has a half-life of about 24–30 h and peaks at 48–72 h after cardiac arrest, and it has historically been recommended to use NSE levels for prognostic purposes in the first 72 h after cardiac arrest in comatose cardiac arrest survivors [58, 59]. For most studies in our meta-analysis, serum sample collection times were ICU admission or within 24 h, so it is still poorly understood whether there is a critical time window for different serum neurogenic biomarkers during SAE. A more significant number of clinical samples with more clinical features-especially different time windows of serum collection time may be required for the upcoming studies.

The clinically selected biomarkers can not only be used to confirm the diagnosis, but also determine the severity

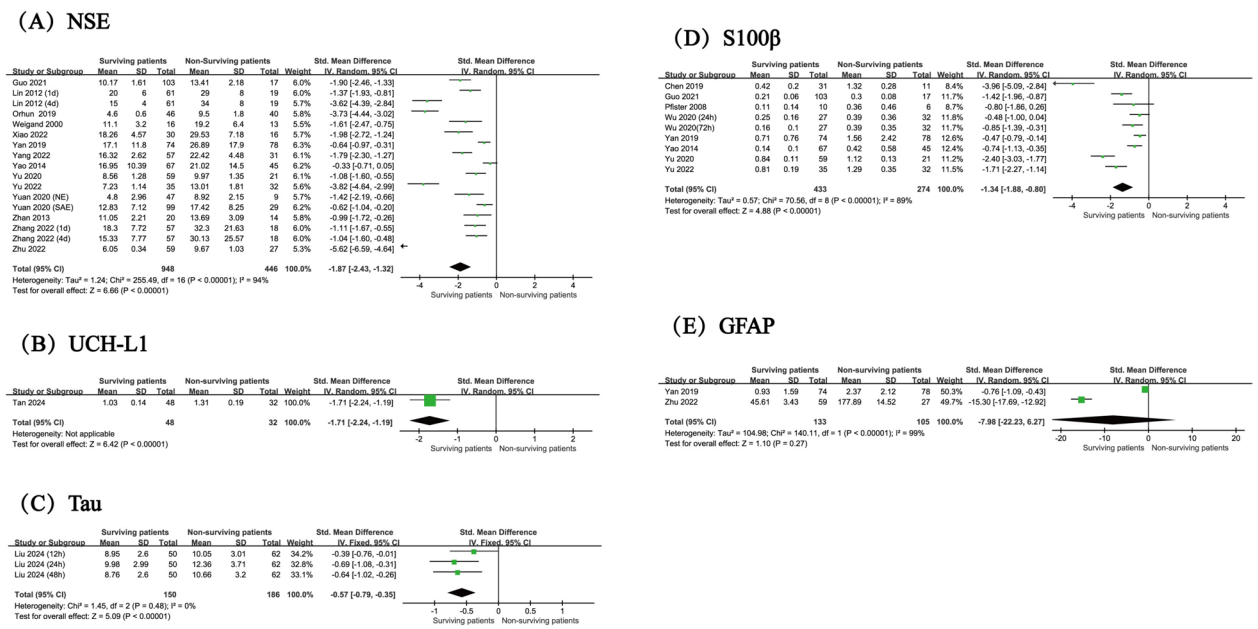

Fig. 5 Forest plot evaluating the association between serum neurogenic biomarkers levels and outcomes (**A**: NSE; **B**: UCH-L1; **C**: Tau; **D**: S100β; **E**: GFAP)

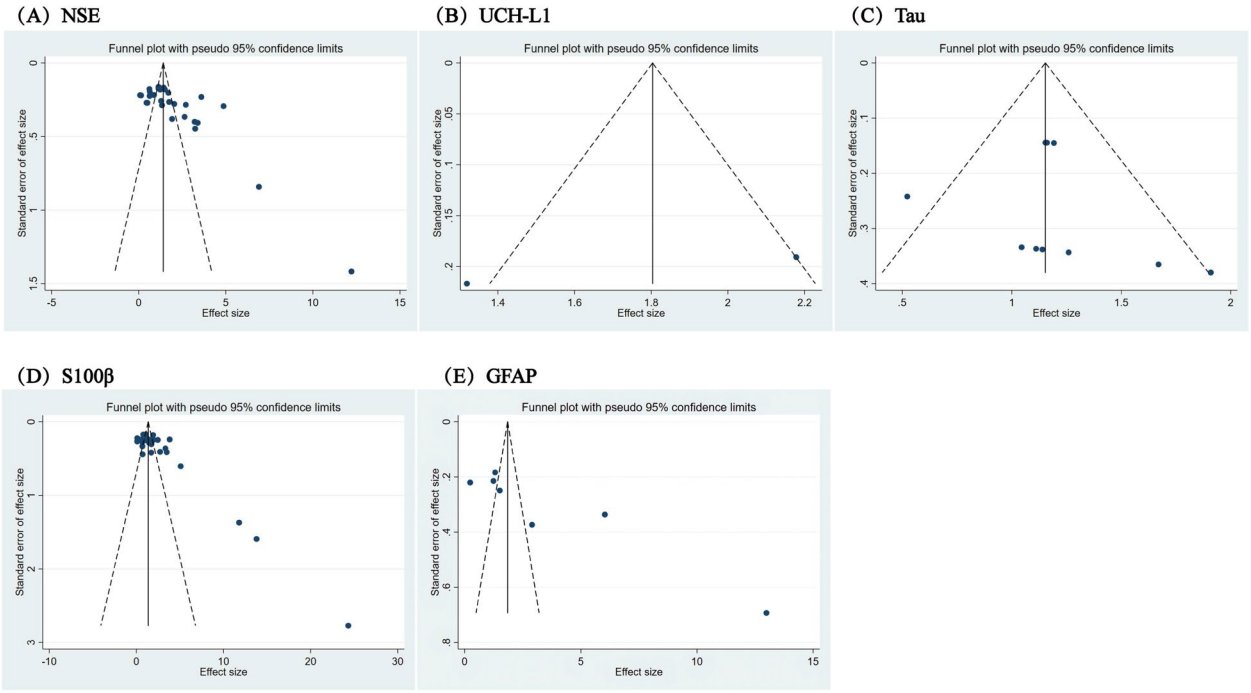

Fig. 6 Funnel plot for evaluating the publication bias from studies on assessment of levels of serum neurogenic biomarkers between SAE and NE patients (**A**: NSE; **B**: UCH-L1; **C**: Tau; **D**: S100β; **E**: GFAP)

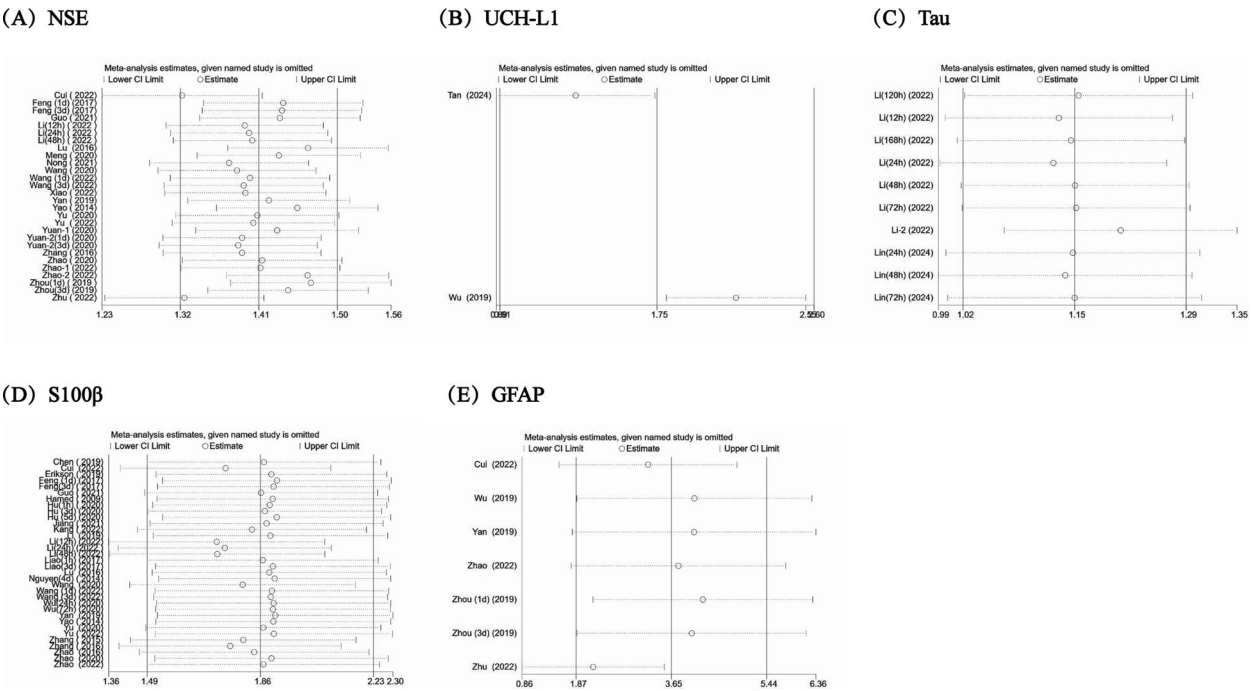

Fig. 7 Sensitivity analyses for studies of serum neurogenic biomarkers between SAE and NE patients (**A**: NSE; **B**: UCH-L1; **C**: Tau; **D**: S100β; **E**: GFAP)

of the disease and provide the basis for subsequent treatment. Aside from the above biomarkers, there are several other biomarkers that could be potential for predicting the risk of SAE such as neurofilament light (NFL), microtubule-associated protein 2 (MAP2), brain-derived neurotrophic factor (BDNF), mitochondrial DNA (mtDNA), and miRNAs [60, 61]. NFL is a cytoskeletal protein exclusive to neurons which has been suggested as a biomarker for assessing neuronal cytoskeleton stability and axonal damage, it can play a more active role in the clinical management of SAE [62]. In the original protocol of study design, we considered also included NFL in our meta-analysis, while there are only two studies that reported NFL levels in cerebrospinal fluid [63] and plasma [64] between the SAE group and NE group after a systematic and rigorous search, which prevented the conduct of a meta-analysis. As a new type of biomarker, NFL may provide new insights for biomarker development of SAE. However, more research is needed in the future.

Moreover, there are also other factors that can potentially influence clinical judging when neurogenic biomarkers are used. For instance, NSE can be generated in various tissues within the human body, thereby necessitating the exclusion of non-neurological disease factors during the analysis of NSE outcomes. NSE levels are also influenced by various factors including age, sex, and muscle injury, among others [65]. Furthermore, NSE cannot be detected in hemolyzed samples because it exists in erythrocytes and platelets; therefore, hemolysis results in increased serum NSE levels, which may affect accuracy and clinical results [66]. Consequently, it is imperative to comprehensively consider multiple confounders for the clinical application of neurogenic biomarkers. Although neurogenic biomarkers exhibit high sensitivity and specificity in certain instances, they should not be regarded as a substitute for clinical manifestations or other diagnostic tests. Instead, it necessitates a combined analysis of other indicators and clinical manifestations for an accurate assessment. The combination of serum neurogenic biomarkers and other serum biomarkers such as procalcitonin (PCT) and C-reactive protein (CRP) can further confirm diagnosis, prognosis, and guide treatment.

Our meta-analysis possesses several notable strengths. Firstly, most prior studies only focused on one biomarker during SAE [67, 68], this systematic review and meta-analysis aimed at evaluating all the potential serum neurogenic biomarkers (NSE, UCH-L1, Tau, S100β, and GFAP) in patients with SAE, thereby offering valuable insights for future clinical practice. Secondly, we employed rigorous methodologies and quality assessment tools consistent with evidence-based clinical practice standards. Furthermore, the results of our sensitivity analysis indicated that the pooled effect model is both robust and reliable. This meta-analysis is subject to several limitations that warrant consideration. Firstly, significant heterogeneity was observed which is a common challenge in meta-analyses of observational studies, it is important to note that the presence of substantial heterogeneity among studies poses challenges in determining the most effective discrimination cutoff values and optimal sampling collection time. Secondly, publication bias could not be entirely eliminated, potentially distorting the evidence derived from the included clinical studies and thereby limiting the generalizability of the findings to other contexts. Lastly, the search criteria employed may have overlooked unpublished articles and preliminary results from ongoing studies. Nevertheless, work is continuing on improving the process to eliminate these defects. More researches are still needed in the future including longitudinal studies and validation in diverse populations. It is imperative to acknowledge that the use of serum neurogenic biomarkers as a diagnostic tool necessitates a comprehensive evaluation in conjunction with clinical manifestations and alternative diagnostic tests. It is probably better to predict SAE and prognosis by sequentially determining a series of neurogenic biomarkers than by using just one value.

Conclusion

Overall, we identified and selected the five most commonly used serum neurogenic biomarkers of SAE: NSE, UCH-L1, Tau, S100β, and GFAP. Our meta-analysis suggested that the occurrence of SAE and mortality outcome is strongly associated with levels of the above biomarkers, which may be used to assist clinical diagnoses and the monitoring of the severity or progression of SAE patients. However, due to the intrinsic limitations of the included studies, the results of this meta-analysis need cautious interpretation, and for more details and evidences, further studies are warranted hereafter.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-025-02784-5.

Supplementary Material 1. AMSTAR 2 Checklist.

Supplementary Material 2. PRISMA 2020 checklist.

Authors' contributions

Jiyun Hu, Wenchao Li, Shucai Xie, Ya Liao, Tao Chen, Xinrun Wang, Weiping Xia, Zhaoxin Qian, and Lina Zhang contributed to the conception and design of the study. The manuscript of the protocol was drafted by Jiyun Hu and Lina Zhang and critically revised by Shucai Xie, Fang Huang, and Ya Liao. The search strategy was developed by Tao Chen, Xinrun Wang, and Weiping Xia. Zhaoxin Qian and Lina Zhang assessed the quality of the study. Jiyun Hu and Wenchao Li wrote the first draft of the manuscript. Zhaoxin Qian and Lina Zhang wrote sections of the manuscript. All authors contributed to the manuscript revision

and read and approved the submitted version. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author details
[1]Department of Critical Care Medicine, Hunan Provincial Clinical Research Center for Critical Care Medicine, National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China.

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