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REVIEW

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Neuron-specific enolase in diagnosis and prognosis of delirium: a systematic review

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Abstract

Delirium, characterized by a sudden onset of neuropsychiatric symptoms, is a highly prevalent syndrome whose diagnosis is defined solely through clinical evaluation. Due to the often challenging reliability of assessments, especially in non-cooperative patients, there is a growing emphasis on exploring new reliable biomarkers, such as Neuron-Specific Enolase (NSE). NSE, an enzyme primarily found in neuronal and neuroendocrine tissues, has been clinically used to assess the prognosis of patients who have experienced traumatic or hypoxic brain injuries. Thus, the primary purpose of the present review is to examine the literature to determine whether NSE is applicable for diagnosis and/or prognosis of patients with delirium. Literature was searched using Pubmed, Lilacs and Scielo databases, and all published reports identified as potentially relevant were independently assessed by each reviewer. All relevant original studies were included and independent extraction of articles was performed by three authors using predefined data fields. Twenty one studies (2,311 patients) satisfied the entry criteria, among which only eight suggest a possible association between NSE and delirium, particularly in intensive care settings, and only one correlate NSE with delirium prognosis. Also, significant heterogeneity was observed among studies, varying across study design, setting, and methodologies. Furthermore, the majority of the selected studies presented severe methodological limitations, particularly small samples. In conclusion, this systematic review underscores the need for further research with larger, standardized studies to establish the reliability and validity of NSE as a diagnostic and prognostic tool for delirium. The current evidence does not sufficiently support its routine clinical application in assessing patients with delirium.

Keywords Delirium, Biomarkers, Neuron-specific enolase

Background

Delirium is a neuropsychiatric syndrome defined as a confusional state of sudden onset and fluctuating course, in which disturbances in attention and awareness represent a change from the baseline, and that is not better explained by an underlying neurocognitive disorder [1, 2].

The importance of delirium is evident in its incidence, morbidity, and costs for the health system. At least one-third of the hospitalized patients develop delirium, half of which at the admission and the other half during their stay [3]. Moreover, delirium is estimated to occur in

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around 15 to 25% of elderly patients submitted to major surgery, and 75% of patients at intensive care units under mechanical ventilation [3]. This high incidence leads to healthcare costs that are over 160 billion dollars each year in the USA [3].

Furthermore, even though delirium is, by definition, an acute condition, a significant number of patients maintain a degree of neurocognitive disability even after its resolution [4].

To diagnose delirium, medical professionals can only rely on their clinical suspicion, which proves to be a challenge, given that the neurocognitive impairment may be wrongly attributed to old age and other humor disorders. Therefore, it is estimated that only up to 12 to 35% of delirium cases are recognized [5].

The diagnostic criteria are stated in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), and they are very much similar to the very definition [2]. Hence, several questionnaires were developed and validated to help physicians assisting patients with disturbances of consciousness. The most widely used are the Confusion Assessment Method (CAM) and its brief version (bCAM); however, these tools might be impaired by the non-cooperative patient [6].

Considering the facts above, it is clear the importance of a biomarker that could identify patients with delirium [7]. A biomarker is defined as a characteristic that can be measured and assessed as an indicator of biological processes (normal or pathological) or as a response to therapeutic interventions [8, 9].

A biomarker's relevance is its ability to provide information on questions of interest adequately, and the validity represents the effectiveness in doing so [9]. So far, several biomarkers have been described as being able to diagnose delirium; however, none of them have been widely incorporated in clinical practice.

Neuron Specific Enolase (NSE) is a 78 kD gamma-homodimer and represents the dominant enolase-isoenzyme found in neuronal and neuroendocrine tissues. Its primary function is to catalyze the conversion of 2-phosphoglycerate to phosphoenolpyruvate and its levels in other tissues, except erythrocytes, are negligible [10].

Due to this organ-specificity, concentrations of NSE in cerebrospinal fluid and serum are often elevated in diseases resulting in acute neuronal destruction [11]. Elevated serum NSE levels can be found in coma patients after a hypoxic insult [12] or head trauma [13] and are usually related to a poor prognosis.

Therefore, the present review's primary purpose is to examine the literature to determine whether NSE is applicable for diagnosis and/or prognosis of patients with delirium.

Methods

Study design

This was a systematic review to evaluate NSE as a diagnostic and prognostic tool in delirium patients.

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Eligibility criteria

We included original observational studies (cohort, case-control and cross-sectional studies) that evaluated plasma or cerebrospinal fluid NSE levels among adult patients with delirium. There was no restriction in terms of year of publication, intervention or outcome. Non English or adult human studies, case reports, narrative reviews, and opinion articles were excluded.

Search strategy

A strategy for a literature search was developed and executed by a medical doctor with inputs from the study investigators. The search strategy was created using a combination of keywords and standardized index terms related to NSE and delirium.

The search strategy included the search terms (Delirium) AND (Neuron specific enolase OR enolase OR NSE).

The initial search was run in July 2024 in PubMed (66), Scielo (1) and Lilacs (2).

Study selection and data extraction

In the first phase, 3 investigators independently screened all titles and abstracts for eligibility.

In the second phase, all studies considered potentially relevant were retrieved as full text and independently assessed for eligibility. The investigators were not blinded to the authors, journals, or results of the studies.

Pertinent data were independently extracted for all the studies using a standardized, predefined extraction form. The extracted data included author, journal, year, country, study type, included patients characteristics and main findings, which were paraphrased and adapted from the original publication results and conclusions. Unadjusted and adjusted effect estimates reported by the studies were extracted. Only data available in published manuscripts and abstracts were used.

Results

Initially, 69 articles were selected after searching the databases, and 2 duplicates were identified and excluded. Thus, 67 articles remained for the first phase of the analysis.

After reading the title and abstract, 23 articles were selected (not related to NSE and delirium, non english or adult human studies, editorials or reviews were

excluded), and then read in full by the reviewers. 2 studies were excluded in the second phase because they did not meet the inclusion criteria (lack of data about NSE or delirium-NSE correlation).

The 21 selected articles constitute this systematic review (Fig. 1; Tables 1 and 2).

Study design

Out of the twenty one articles selected, two were randomized clinical trials, six were case-control studies, and thirteen were cohorts.

Methodologies

Each study's sample sizes varied from 13 to 194, with a median value of 74 and an interquartile range of 44 to 120 patients.

Three out of twenty one studies determined a cutoff value for defining delirium, utilizing plasmatic NSE levels above the 95th percentile or above 12,5 µg/L [22, 24, 26].

Two out of twenty one studies took samples in varying time spams to evaluate NSE kinetics and release patterns before and after situations related to brain dysfunction [15, 17].

Most studies analyzed serum samples to determine NSE concentrations, as only Caplan et al. [19] and Zhang et al. [34] considered concentrations in cerebrospinal fluid.

The delirium diagnosis was confirmed with a clinical evaluation, carried out most frequently before and after exposure. Nonetheless, the delirium assessment tools varied, as five studies utilized the latest DSM criteria available at the time and thirteen studies utilized the Confusion Assessment Method (CAM) and its variations

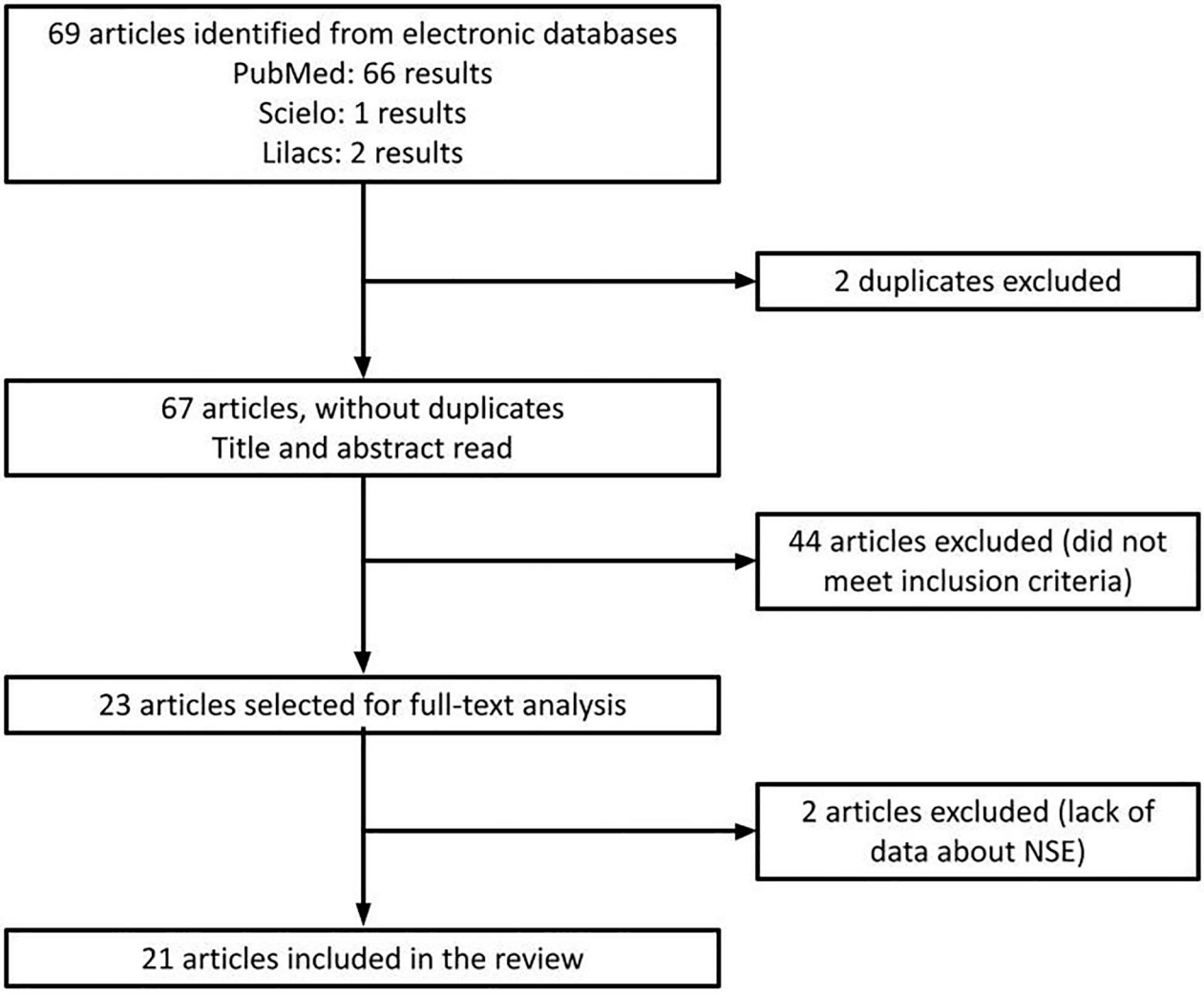

Fig. 1 Diagram of studies selection

Table 1 Key characteristics of included studies

Study	Journal	Year	Country	Study type	Delirium assessment tool
Stelzl et al. [14]	Eur J Emerg Med	1995	Germany	Cohort	DSM-III-R
Herrmann et al. [15]	Eur J Cardiothorac Surg	1999	Germany	Cohort	DSM-IIIR DRS (severity)
Rasmussen et al. [16]	Br J Anaesth	2000	Denmark	Case-control	DSM-III
Herrmann et al. [17]	Stroke	2000	Germany	Cohort	DSM-IIIR DRS (severity)
van Munster et al. [18]	BMC Neurol	2009	Netherlands	Case-control	CAM DRS-R-98 (severity) DOS
Caplan et al. [19]	J Gerontol A Biol Sci Med Sci	2010	Australia	Cohort	CAM DI
Grandi et al. [20]	J Crit Care	2011	Brazil	Case-control	CAM-ICU
Macedo et al. [21]	Braz J Psychiatry	2013	Brazil	Case-control	CAM-ICU
Anderson et al. [22]	J Crit Care	2016	EUA	Cohort	CAM-ICU (medical record review)
Kozak et al. [23]	Neurol Neurochir Pol	2017	Turkey	Case-control	DSM IV DRS
Anderson et al. [24]	J Heart Lung Transplant	2018	EUA	Cohort	Medical record review
Gailiusas et al. [25]	Acta Med Litu	2019	Lithuania	Cohort	CAM-ICU
Erikson et al. [26]	Acta Anaesthesiol Scand	2019	Finland	Cohort	CAM-ICU (Finnish version)
Li et al. [27]	J intensive Care Med	2019	China	Randomized clinical trial	CAM-ICU
Mietani et al. [28]	PLoS One	2021	Japan	Cohort	CAM-ICU ICDSC
Hollinger et al. [29]	J Clin Anesth	2021	Switzerland	Randomized clinical trial (placebo controlled, double blind)	DOS Nu-DESC ICDSC
Gao et al. [30]	Ann Palliat Med	2021	China	Case-control	No information
Menzenbach et al. [31]	Biomedicines	2021	Germany	Cohort	CAM (hospital ward) CAM-ICU DOS 4AT score
de Alencar et al. [32]	Sci Rep	2023	Brazil	Cohort	CAM
Nübel et al. [33]	J Cardiovasc Dev Dis	2023	Germany	Cohort	CAM-ICU
Zhang et al. [34]	Curr Med Res Opin	2024	China	Cohort	CAM-ICU

(CAM-ICU). Only three studies considered neither DSM criteria nor CAM to diagnose delirium.

Results of individual studies

Eight studies found statistically significant variation in plasma or CSF NSE levels in patients with and without delirium [15, 19, 20, 22, 24, 28, 30, 33, 34], while other eleven did not [14, 16–18, 23, 25–27, 29, 31, 32].

One study concluded that NSE might have prognostic value, for its higher levels being related to a higher risk of delirium and overall mortality [20], while other three did not [15, 21, 34].

Limitations and bias

Ten authors acknowledged that they worked with small sample sizes [15, 19, 20, 23, 24, 26, 27, 32–34]. Other limitations stated were also related to the small number of participants, such as lower incidence of cases [20, 22, 27, 33] and the rigidity of exclusion criteria [21, 23, 27, 28, 31].

Three out of twenty one authors declared limitations in the post-analytical phase, for instance, hemolysis [14] and the difference between peripheral and CNS samples [18, 32].

We did not observe any limitations reported in four studies [16, 17, 25, 30], even though some of the limitations discussed by other authors could also be applied to them.

Discussion

Delirium is the outcome of a multifactorial process that culminates in the acute confusional state and not a proper disease [1]. Therefore, it may be better comprehended as an "acute brain failure" in many ways, similar to heart failure and other organic dysfunctions. The difference is the lack of biomarkers that could reliably define the diagnosis and prognosis, which would serve a similar

Table 2 Included patients characteristics and main findings of the selected studies

Study	Included patients	Main findings
Stelzl et al. [14]	13 patients with circulatory arrest due to acute cardiopulmonary failure	Only one patient developed a prolonged delirium, whose NSE levels ranged from 10 ug/mL to 36 ug/mL. Other patient's enzyme levels ranged from 8 ug/mL to 412 ug/mL. No correlation was assumed between NSE levels and the presence of delirium.
Hermann et al. [15]	36 patients undergoing valve replacement and/or coronary artery bypass grafting surgery	Three patients undergoing valve replacement developed delirium at the first postoperative examination, whose NSE-values were found above the 75% percentiles 6 h and 20 h after surgery. No associations were found between the delirium data at 1-week and 6-month follow-up and the NSE release pattern.
Rasmussen et al. [16]	65 patients undergoing elective major abdominal surgery, aged 60 years or older	After operation, eight patients had delirium. No statistical correlation was found between delirium and non-delirium patients and the levels of NSE at 24 h ($p=0.19$), 48 h ($p=0.41$) or 72 h ($p=1.0$) after surgery.
Hermann et al. [17]	74 patients who underwent elective coronary artery bypass grafting or valve replacement surgery and who showed no severe neurological deficits after surgery	Seven patients presented with delirium at the first postoperative assessment. The area under the receiver operating characteristic curve of NSE did not differ significantly between patients with and without delirium.
van Munster et al. [18]	120 patients aged 65 years or older who were acutely admitted with hip fracture to the medical center	62 patients had delirium. Mean NSE level was 11.7 ng/L both in delirium (samples were the first samples during the delirious episode) and no delirium patients (samples of comparable postoperative day) ($p=0.97$). No significant difference was observed in NSE levels in patients with different subtypes (hyperactive, hypoactive or mixed) ($p=0.41$), nor between patients with known vs. unknown subtype. Also, NSE did not correlate with delirium severity ($p=0.32$).
Caplan et al. [19]	20 hospitalized patients with delirium without clinical improvement after 5 days of treatment and 20 outpatients with known Alzheimer's dementia (control group)	NSE levels in cerebrospinal fluid were lower in patients with delirium compared to those with Alzheimer's dementia ($P<0.001$). CSF NSE levels were significantly correlated with CAM ($P=0.028$), DI ($P=0.014$). No statistically significant correlations were found between the NSE and the other indices [APACHE ($p=0.298$), IADL ($P=0.449$) and Barthel ($p=0.991$)].
Grandi et al. [20]	60 patients (30 delirium and 30 non-delirium) retrospectively selected from 130 patients admitted to the ICU for more than 24 h	Mean NSE concentration at admission was significantly higher in delirium when compared to non-delirium patients ($p=0.001$), whereas NSE level the day before delirium was not ($p=0.321$), as NSE levels decreased during ICU stay. The area under the receiver operating characteristic curve to the diagnosis of delirium was 0.72 for NSE levels at admission. When patients who earlier developed delirium were separately analyzed, it was determined that serum NSE levels at admission were significantly higher only at this group, but not in patients who later developed delirium ($p<0.05$). Also, admission NSE levels were higher in non survivor delirious patients when compared with survivors ($p=0.04$).
Macedo et al. [21]	70 patients admitted to the ICU (35 patients who developed delirium and 35 who did not)	When analyzing delirium and non-delirium patients separately, there were no significant differences in NSE levels between survivors and non-survivors.
Anderson et al. [22]	124 patients admitted to the ICU for sepsis	All patients had detectable NSE on admission to the ICU, and the median plasma concentration of NSE was 6.6 µg/L (interquartile range 4.1–13.8). Thirty-four patients developed delirium. Higher plasma NSE concentrations at ICU admission were associated with increased risk of delirium. Each 2-fold increase in the plasma NSE concentration was associated with a 5.2% (95% CI 3.2–7.2, $P<0.001$) increased risk of delirium after adjusting for APACHE III score and receipt of sedative and analgesic infusions.
Kozak et al. [23]	60 patients with acute ischemic stroke admitted to the hospital within the first 24 h of stroke onset	There was no significant difference between the delirious and non-delirious patients in respect of NSE values ($p=1.0$). In addition, serum baseline levels of the enzyme were similar in the two groups.
Anderson et al. [24]	155 patients undergoing lung transplantation	Delirium occurred in 57 (36.8%) patients for a median of 4 days (interquartile range [IQR] 2 to 7 days). All patients had detectable NSE plasma levels 24 h after reperfusion, with a median concentration of 11.3 µg/liter (interquartile range [IQR] 8.1 to 14.7). Higher plasma NSE concentrations were significantly associated with post-operative delirium. Patients with a plasma NSE concentration at the 75th percentile (14.7 µg/liter) had a 15.1% (95% CI 2.5 to 27.7; $p=0.019$) absolute increased risk of post-operative delirium compared with patients with a plasma NSE concentration at the 25th percentile (8.1 µg/liter).
Gailiusas et al. [25]	44 patients undergoing elective coronary artery bypass grafting and/or valve procedures	8 patients developed postoperative delirium. After surgery, NSE significantly increased in the whole sample ($p=0.002$), but when comparing delirium and non-delirium patients, NSE was significantly higher in the delirium group ($p=0.042$).
Erikson et al. [26]	22 patients with septic shock admitted to the ICU	Ten patients had delirium, whose mean NSE was 23.0 [13.2–28.0] $P=0.771$. 17 patients achieved the cut-off value of 12.5 µg/L adopted for NSE, 8 of whom developed delirium.

Table 2 (continued)

Study	Included patients	Main findings
Li et al. [27]	26 patients admitted to the ICU for more than 96 h receiving continuous sedation and analgesia for ≥ 48 h.	54 patients developed delirium. The area under the receiver operating characteristic curve for predicting the development of delirium on the day when delirium was diagnosed was 0.724 (CI 95%: 0.532–0.916).
Mietani et al. [28]	117 patients who underwent elective cancer surgery under general anesthesia, irrespective of the affected organ	41 patients were clinically diagnosed with postoperative delirium. NSE levels were significantly higher in the delirium group when compared to the non-delirium one ($p < 0.0001$). Using a cut-off value of 201.2 ng/mL, the area under the curve (AUC) for serum NSE level in predicting delirium was 0.87 (sensitivity, 0.76; specificity, 1.00; 95% confidence interval, 0.79–0.95). Multivariate logistic regression analysis showed that NSE was associated with postoperative delirium ($p < 0.0001$).
Hollinger et al. [29]	182 patients admitted for elective surgery (randomized into haloperidol, ketamine, haloperidol + ketamine and placebo groups)	14 of patients developed postoperative delirium and had mean NSE levels of 19.7 µg/l in the preoperative period ($p = 0.8$), while 10 had mean levels of 16.8 µg/l in the postoperative period ($p = 0.9$). There were no significant changes in perioperative NSE levels in patients with delirium (median − 5.1 [-9; 14.3], $P = 0.56$).
Gao et al. [30]	98 patients with combined severe craniocerebral injury (GCS ≤ 8) and delirium (research group), and 90 patients who had a physical examination during the same period (control group)	The expression levels of NSE in the research group were higher than those in the control group ($P < 0.001$). Research group patients were followed up for a period of 30 days when transferred out of the ICU. By the end of the follow-up, 37 patients died and 61 patients survived. The expression levels of NSE in the death group were higher than those in the survival group ($P < 0.001$). Multivariate analysis showed that abnormally elevated levels of NSE were independent risk factors for the prognosis of research group patients. Also, the average survival time of the high NSE level group was shorter than that of the low-level group ($P < 0.05$).
Menzenbach et al. [31]	118 patients over the age of 60 admitted for elective surgery lasting at least 60 min	33 patients had delirium (20 from the 1st to the 2nd postoperative day and 13 from the 3rd to the 5th). NSE tended to be different in patients with postoperative delirium, but without statistical significance in relation to the control group ($p = 0.39$), even after propensity score matching ($p = 0.26$).
de Alencar et al. [32]	194 patients aged 65 years or older, admitted to the ED of a tertiary hospital and hospitalized for less than 24 h	46 patients were diagnosed with delirium − 25 on admission (prevalent delirium) and 21 during hospital stay (incident delirium). Plasma NSE concentration at ED admission was not associated with an increased risk of delirium diagnosis during hospitalization ($p = 0.57$), even when only patients at risk of developing delirium were evaluated (i.e., those without delirium at enrollment) ($p = 0.87$). Also, NSE levels were not associated with the delirium pathology (enzyme levels measured before and during delirium were compared) ($p = 0.88$).
Nübel et al. [33]	135 patients undergoing elective TAVR (Transfemoral Aortic Valve Replacement) classified as high surgical risk patients	After TAVR, patients with postoperative delirium (POD) had a higher median NSE level compared to patients without POD after TAVR (4.42 ng/mL vs. 2.33 ng/mL, $p = 0.024$). The median relative increase in NSE was 40.4% (13.1–138.0) in patients with POD versus 17.3% (3.3–43.4) in those without POD ($p = 0.17$). Adjusted for preoperative NSE levels, the relative increase in NSE had an OR 1.0 [95% CI 0.995–1.01], $p = 0.40$, for POD. Compared to the group of patients with an NSE elevation < 20%, patients with an NSE elevation > 20% had an OR 2.45 [95% CI 0.43–13.84], $p = 0.31$, for POD.
Zhang et al. [34]	101 sepsis patients (patients with infection or suspected infection and sequential organ failure assessment (SOFA) scores of ≥ 2)	NSE levels in the Sepsis-Associated Encephalopathy (SAE) group were higher than in the non-SAE group with a statistically significant difference for both serum (11.67 (9.80–12.62) vs. 10.05 (9.12–11.34), respectively, $p = 0.002$) and cerebrospinal fluid (9.89 (8.46–11.02) vs. 8.54 (7.83–9.34), respectively, $p < 0.001$) measurements. When plasma NSE ≥ 8.81 ng/ml, the ability to identify SAE of AUC = 0.687, specificity = 0.605, sensitivity = 0.714; When cerebrospinal fluid NSE ≥ 10.04 ng/ml, the ability to identify SAE of AUC = 0.711, specificity = 0.816, sensitivity = 0.635. Also, NSE levels in the survival group did not present statistical significance when compared with the non-survival group for both serum (11.98 (11.09–15.32) vs. 11.45 (9.73–12.45), respectively, $p = 0.079$) and cerebrospinal fluid (9.60 (8.96–11.44) vs. 9.89 (8.45–10.70), respectively, $p = 0.815$) measurements.

purpose that troponin and brain natriuretic peptides do for heart failure [35, 36].

Neuron Specific Enolase is an intracellular enzyme, located almost exclusively in neurons and neuroendocrine tissues [10]. This fact prompted its use as a marker of neuronal injury. There is no consistent evidence that, in patients with delirium, neuronal death occurs. However, other central nervous system injury markers, like S100B, have been reported to reflect the delirium severity [7].

Therefore, in this review, we evaluated serum NSE levels' applicability as a diagnostic and prognostic tool to assess patients with delirium. We selected twenty one papers, published from 1995 to 2024, that evaluated the relationship between serum or CSF NSE levels and the occurrence of delirium. Due to the wide variation in study design, participants, interventions, data, and outcomes reported, we decided to describe the studies, their results, their limitations, and possible bias.

Only eight studies concluded that NSE could have any value for identifying or giving the prognosis of patients

with delirium [15, 19, 20, 22, 24, 28, 30, 33, 34]. All of these studies, except one [19], were conducted in intensive care units. Although there is no logical explanation for this finding, it can be supposed that these patients received a higher degree of attention to changes in consciousness levels, making it more probable that delirium could be identified.

This systematic review suffers significantly from its study pool's vast heterogeneity, which leads to an impossibility to create a meta-analysis. The data published in these studies have almost no similarity between each other, as seen in the delirium assessment: the assessment tool varied significantly, and the time of evaluation varied even further.

Besides that, the number of patients included in each study was very small for the designed purpose. The three largest studies included around 177 patients [24, 29, 32] and, notoriously, presented opposite results. As a comparison, one of the first studies to report the usefulness of troponin to diagnose myocardial infarction enrolled 388 patients [37]. Also, selection bias is also very plausible in this systematic review, the size of which we could not predict due to the incapability of creating a funnel plot.

Although a discussion about the limitations was supposed to be found in each paper, some did not present it. All the others discussed the matter, pointing out the small samples and even analytical troubles responsible for negative results. Anderson and colleagues [22] even stated that the varying results across studies might be explained by different outcome definitions or the difference in pathophysiologic mechanisms leading to delirium in different patient populations.

Conclusion

In conclusion, the present data and findings concerning NSE measurements are not sufficient to be clinically applied in the neurobehavioral and/or neurocognitive diagnoses or prognosis of a patient that presents to the emergency room or to the intensive care unit. Thus, further data is necessary to support any claims that NSE is a diagnostic or prognostic tool for patients with delirium.

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Author contributions
F. K. S., R. S. S. and M. M. M. independently screened all titles and abstracts for eligibility and read in full the selected papers. F. K. S., G. M. D. P., V. M. R. B., R. S. S. and M. M. M. extracted and presented the data of the included articles. All authors discussed and reviewed the manuscript.

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Data availability
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. Lancet Lond Engl. 2014;383(9920):911–22. https://doi.org/10.1016/S0140-6736(13)60688-1
2. European Delirium Association, American Delirium Society. The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer. BMC Med. 2014;12(1):141. https://doi.org/10.1186/s12916-014-0141-2. http://bmcmedicine.biomedcentral.com/articles/
3. Eidelman LA, Putterman D, Putterman C, Sprung CL. The spectrum of septic encephalopathy. Definitions, etiologies, and mortalities. JAMA. 1996;275(6):470–3. https://doi.org/10.1001/jama.1996.03530300054040
4. Ciampi A, Bai C, Dyachenko A, McCusker J, Cole MG, Belzile E. Latent class analysis of the multivariate delirium index in long-term care settings. Int Psychogeriatr. 2019;31(1):59–72. https://doi.org/10.1017/S1041610218000510
5. Boucher V, Lamontagne M-E, Nadeau A, Carmichael P-H, Yadav K, Voyer P, et al. Unrecognized incident delirium in older emergency department patients. J Emerg Med. 2019;57(4):535–42. https://doi.org/10.1186/s12877-020-01536-5
6. Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium? Value of bedside instruments. JAMA. 2010;304(7):779–86. https://doi.org/10.1001/jama.2010.1182
7. Khan BA, Zawahiri M, Campbell NL, Boustani MA. Biomarkers for delirium–a review. J Am Geriatr Soc. 2011;59(Suppl 2):S256–261. https://doi.org/10.1111/j.1532-5415.2011.03702.x
8. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69(3):89–95. https://doi.org/10.1067/mcp.2001.113989
9. Strimbu K, Tavel JA. What are biomarkers? Curr Opin HIV AIDS. 2010;5(6):463–6. https://doi.org/10.1097/coh.0b013e32833ed177
10. Isgrò MA, Bottoni P, Scatena R. Neuron-specific enolase as a biomarker: biochemical and clinical aspects. Adv Exp Med Biol. 2015;867:125–43. https://doi.org/10.1007/978-94-017-7215-0_9
11. Laterza OF, Modur VR, Crimmins DL, Olander JV, Landt Y, Lee J-M, et al. Identification of novel brain biomarkers. Clin Chem. 2006;52(9):1713–21. https://doi.org/10.1373/clinchem.2006.070912
12. You Y, Park JS, Min J, Yoo I, Ahn HJ, Cho Y, et al. The usefulness of neuron-specific enolase in cerebrospinal fluid to predict neurological prognosis in cardiac arrest survivors who underwent target temperature management: a prospective observational study. Resuscitation. 2019;145:185–91. https://doi.org/10.1016/j.resuscitation.2019.09.027
13. Mercier E, Tardif P-A, Cameron PA, Émond M, Moore L, Mitra B, et al. Prognostic value of neuron-specific enolase (NSE) for prediction of post-concussion symptoms following a mild traumatic brain injury: a systematic review. Brain Inj. 2018;32(1):29–40. https://doi.org/10.1080/02699052.2017.1385097
14. Stelzl T, von Bose MJ, Hogl B, Fuchs HH, Flugel KA. A comparison of the prognostic value of neuron-specific enolase serum levels and somatosensory evoked potentials in 13 reanimated patients. Eur J Emerg Med. 1995;2(1):24–7. https://doi.org/10.1097/00063110-199503000-00006
15. Herrmann M, Ebert AD, Tober D, Hann J, Huth C. A contrastive analysis of release patterns of biochemical markers of brain damage after coronary artery bypass grafting and valve replacement and their association with the

neurobehavioral outcome after cardiac surgery. Eur J Cardiothorac Surg. 1999;16(5):513–8. https://doi.org/10.1016/s1010-7940(99)00245-6
16. Rasmussen LS, Christiansen M, Rasmussen H, Kristensen PA, Moller JT. Do blood concentrations of neurone specific enolase and S-100 beta protein reflect cognitive dysfunction after abdominal surgery? ISPOCD group. Br J Anaesth. 2000;84(2):242–4. https://doi.org/10.1093/oxfordjournals.bja.a013410
17. Herrmann M, Ebert AD, Galazky I, Wunderlich MT, Kunz WS, Huth C. Neurobehavioral outcome prediction after cardiac surgery: role of neurobiochemical markers of damage to neuronal and glial brain tissue. Stroke. 2000;31(3):645–50. https://doi.org/10.1161/01.str.31.3.645
18. van Munster BC, Korse CM, de Rooij SE, Bonfrer JM, Zwinderman AH, Korevaar JC. Markers of cerebral damage during delirium in elderly patients with hip fracture. BMC Neurol. 2009;9:21. https://doi.org/10.1186/1471-2377-9-21
19. Caplan GA, Kvelde T, Lai C, Yap SL, Lin C, Hill MA. Cerebrospinal fluid in long-lasting delirium compared with Alzheimer's dementia. J Gerontol Biol Sci Med Sci. 2010;65(10):1130–6. https://doi.org/10.1093/gerona/glq090. Epub 2010 Jun 7.
20. Grandi C, Tomasi CD, Fernandes K, Stertz L, Kapczinski F, Quevedo J, Dal-Pizzol F, Ritter C. Brain-derived neurotrophic factor and neuron-specific enolase, but not S100β, levels are associated to the occurrence of delirium in intensive care unit patients. J Crit Care. 2011;26(2):133–7. https://doi.org/10.1016/j.jcrc.2010.10.006. Epub 2010 Nov 23.
21. Macedo RC, Tomasi CD, Giombelli VR, Alves SC, Bristot Mde L, Locks MF, Petronilho F, Grandi C, Quevedo J, Dal-Pizzol F, Ritter C. Lack of association of S100β and neuron-specific enolase with mortality in critically ill patients. Braz J Psychiatry. 2013;35(3):267–70. https://doi.org/10.1590/1516-4446-2012-0835
22. Anderson BJ, Reilly JP, Shashaty MGS, Palakshappa JA, Wysoczanski A, Dunn TG, Kazi A, Tommasini A, Mikkelsen ME, Schweickert WD, Kolson DL, Christie JD, Meyer NJ. Admission plasma levels of the neuronal injury marker neuron-specific enolase are associated with mortality and delirium in sepsis. J Crit Care. 2016;36:18–23. https://doi.org/10.1016/j.jcrc.2016.06.012. Epub 2016 Jun 23.
23. Kozak HH, Uğuz F, Kılınç İ, Uca AU, Serhat Tokgöz O, Akpınar Z, Özer N. Delirium in patients with acute ischemic stroke admitted to the non-intensive stroke unit: incidence and association between clinical features and inflammatory markers. Neurol Neurochir Pol. 2017;51(1):38–44. https://doi.org/10.1016/j.pjnns.2016.10.004. Epub 2016 Oct 24.
24. Anderson BJ, Chesley CF, Theodore M, Christie C, Tino R, Wysoczanski A, Ramphal K, Oyster M, Kalman L, Porteous MK, Bermudez CA, Cantu E, Kolson DL, Christie JD, Diamond JM. Incidence, risk factors, and clinical implications of post-operative delirium in lung transplant recipients. J Heart Lung Transpl. 2018;37(6):755–62. https://doi.org/10.1016/j.healun.2018.01.1295. Epub 2018 Feb 2.
25. Gailiušas M, Andrejaitienė J, Širvinskas E, Krasauskas D, Švagždienė M, Kumpaitienė B. Association between serum biomarkers and postoperative delirium after cardiac surgery. Acta Med Litu. 2019;26(1):8–10. https://doi.org/10.6001/actamedica.v26i1.3949
26. Erikson K, Ala-Kokko TI, Koskenkari J, Liisanantti JH, Kamakura R, Herzig KH, Syrjälä H. Elevated serum S-100β in patients with septic shock is associated with delirium. Acta Anaesthesiol Scand. 2019;63(1):69–73. https://doi.org/10.1111/aas.13228. Epub 2018 Aug 5.
27. Li Y, Yu ZX, Ji MS, Yan J, Cai Y, Liu J, Yang HF, Jin ZC. A pilot study of the use of dexmedetomidine for the control of delirium by reducing the serum concentrations of brain-derived neurotrophic factor, neuron-specific enolase, and S100B in polytrauma patients. J Intensive Care Med. 2019;34(8):674–81. https://doi.org/10.1177/0885066617710643. Epub 2017 Jun 1.
28. Mietani K, Hasegawa-Moriyama M, Inoue R, Ogata T, Shimojo N, Kurano M, Sumitani M, Uchida K. Elevated neuron-specific enolase level is associated with postoperative delirium and detection of phosphorylated neurofilament heavy subunit: a prospective observational study. PLoS ONE. 2021;16(11):e0259217. https://doi.org/10.1371/journal.pone.0259217
29. Hollinger A, Rüst CA, Riegger H, Gysi B, Tran F, Brügger J, Huber J, Toft K, Surbeck M, Schmid HR, Rentsch K, Steiner L, Siegemund M. Ketamine vs. haloperidol for prevention of cognitive dysfunction and postoperative delirium: a phase IV multicentre randomised placebo-controlled double-blind clinical trial. J Clin Anesth. 2021;68:110099. https://doi.org/10.1016/j.jclinane.2020.110099. Epub 2020 Oct 22.
30. Gao Y, Duan J, Ji H, Lu W. Levels of S100 calcium binding protein B (S100B), neuron-specific enolase (NSE), and cyclophilin A (CypA) in the serum of patients with severe craniocerebral injury and multiple injuries combined with delirium transferred from the ICU and their prognostic value. Ann Palliat Med. 2021;10(3):3371–8. https://doi.org/10.21037/apm-21-424
31. Menzenbach J, Frede S, Petras J, Guttenthaler V, Kirfel A, Neumann C, Mayr A, Wittmann M, Coburn M, Klaschik S, Hilbert T. Perioperative vascular biomarker profiling in elective surgery patients developing postoperative delirium: a prospective cohort study. Biomedicines. 2021;9(5):553. https://doi.org/10.3390/biomedicines9050553
32. de Alencar JCG, Garcez FB, Pinto AAS, Silva LOJE, Soler LM, Fernandez SSM, Van Vaisberg V, Gomez Gomez LM, Ribeiro SML, Avelino-Silva TJ, Souza HP. Brain injury biomarkers do not predict delirium in acutely ill older patients: a prospective cohort study. Sci Rep. 2023;13(1):4964. https://doi.org/10.1038/s41598-023-32070-0
33. Nübel J, Buhre C, Hoffmeister M, Oess S, Labrenz O, Jost K, Hauptmann M, Schön J, Fritz G, Butter C, Haase-Fielitz A. Association between neuron-specific enolase, memory function, and postoperative delirium after transfemoral aortic valve replacement. J Cardiovasc Dev Dis. 2023;10(11):441. https://doi.org/10.3390/jcdd10110441. PMID: 37998499; PMCID: PMC10672434.
34. Zhang N, Xie K, Yang F, Wang Y, Yang X, Zhao L. Combining biomarkers of BNIP3 L, S100B, NSE, and accessible measures to predict sepsis-associated encephalopathy: a prospective observational study. Curr Med Res Opin. 2024;40(4):575–582. https://doi.org/10.1080/03007995.2024.2322059. Epub 2024 Mar 5. PMID: 38385550.
35. Lee C-C, Huang S-S, Yeo YH, Hou Y-T, Park JY, Inoue K, et al. High-sensitivity-cardiac troponin for accelerated diagnosis of acute myocardial infarction: a systematic review and meta-analysis. Am J Emerg Med. 2020;38(7):1402–7. https://doi.org/10.1016/j.ajem.2019.11.035
36. Doust JA, Pietrzak E, Dobson A, Glasziou P. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. BMJ. 2005;330(7492):625. https://doi.org/10.1136/bmj.330.7492.625
37. Katus HA, Remppis A, Neumann FJ, Scheffold T, Diederich KW, Vinar G, et al. Diagnostic efficiency of troponin T measurements in acute myocardial infarction. Circulation. 1991;83(3):902–12. https://doi.org/10.1161/01.cir.83.3.902

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