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REVIEW ARTICLE

Diagnostic and Prognostic Values of S100B versus Neuron Specific Enolase for Traumatic Brain Injury; a Systematic Review and Meta-analysis

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Abstract: **Introduction:** Traumatic brain injury (TBI) represents a significant global health burden. This systematic review delves into the comparison of S100B and Neuron-Specific Enolase (NSE) regarding their diagnostic and prognostic accuracy in TBI within the adult population. **Methods:** Conducted on October 21, 2023, the search identified 24 studies encompassing 6454 adult patients. QUADAS-2 and QUAPAS tools were employed to assess the risk of bias. The analyses aimed to evaluate the diagnostic and prognostic performance of S100B and NSE based on sensitivity, specificity, and area under the curve (AUC). The outcomes were detecting intracranial injury, mortality, and unfavorable outcome. **Results:** Pooled data analysis tended towards favoring S100B for diagnostic and prognostic purposes. S100B exhibited a diagnostic AUC of 0.74 (95% confidence interval (CI): 0.70-0.78), sensitivity of 80% (95% CI: 63%-90%), and specificity of 59% (95% CI: 45%-72%), outperforming NSE with an AUC of 0.66 (95% CI: 0.61–0.70), sensitivity of 74% (95% CI: 53%-88%), and specificity of 46% (95% CI: 24%-69%). Notably, both biomarkers demonstrated enhanced diagnostic value when blood samples were collected within 12 hours post-injury. The analyses also revealed the excellent diagnostic ability of S100B with a sensitivity of 99% (95% CI: 4%-100%) and a specificity of 76% (95% CI: 51%-91%) in mild TBI patients (AUC = 0.89 [0.86–0.91]). In predicting mortality, S100B showed a sensitivity of 90% (95% CI: 65%-98%) and specificity of 61% (95% CI: 39%-79%), slightly surpassing NSE's performance with a sensitivity of 88% (95% CI: 76%-95%) and specificity of 56% (95% CI: 47%-65%). For predicting unfavorable outcomes, S100B exhibited a sensitivity of 83% (95% CI: 74%-90%) and specificity of 51% (95% CI: 30%-72%), while NSE had a sensitivity of 80% (95% CI: 64%-90%) and specificity of 59% (95% CI: 46%-71%). **Conclusion:** Although neither biomarker has shown promising diagnostic performance in detecting abnormal computed tomography (CT) findings, they have displayed acceptable outcome prediction capabilities, particularly with regard to mortality.

Keywords: Brain Injuries, Traumatic; Brain Concussion; Brain Contusion; Brain Hemorrhage, Traumatic; S100 Calcium Binding Protein Beta Subunit; S100 Proteins

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1. Introduction

Acute traumatic brain injury (TBI) is characterized by the temporary or permanent alteration of neurological functions as a result of external mechanical forces (1). TBI represents a significant global health burden, with its incidence rate having increased over the past few decades translating to a large portion of visits to the emergency rooms (2, 3). In clinical practice, the Glasgow Coma Scale (GCS) is traditionally utilized to classify TBI severity into three main groups, namely mild (GCS scores of 13-15), moderate (GCS scores of 9-12), and severe (GCS scores of 3-8) (4).

Empirical non-contrast computed tomography (CT) scans have long been considered the gold standard for detecting intracranial injuries, even in cases of mild TBI, given the potential possibility of non-negligible injuries in this group (5). Although mild TBI accounts for over 90% of all TBI admissions, less than 20% of them have demonstrable intracranial injuries in head CT scans (6-8). Thus, due to the low diagnostic yield of CT scans, particularly in cases of mild TBI, as well as the associated cost implications and potential radiation hazards, there is ongoing debate surrounding the triaging of patients for CT acquisition in TBI presentations to the emergency rooms.

Currently, various guidelines and clinical decision rules have been implemented to aid physicians in the selective acquisition of CT scans among TBI patients. Although these al-

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gorithms share many similar components, they mainly rely on neurological examination findings and patient-reported symptoms, which may be subject to examiner bias or unreliable in cases where the patient is intoxicated (9). Concordantly, multiple validation studies have reported inconsistent sensitivity and specificity for the administration of these rules in clinical practice. As a result, the urging quest for more objective and reliable indices to optimize the diagnostic and therapeutic pathways of TBI patients has become the foundation for research on blood-based biomarkers involved in the pathological process of TBI.

Through the last decades, a multitude of biomarkers with distinct functions, such as structural, vascular, coagulative, and inflammatory roles in TBI, have been introduced (10). Among them, S100B Calcium Binding Protein B (S100B), an astroglial calcium homeostasis regulator, and Neuron Specific Enolase (NSE), a neuronal enzyme engaged in glycolytic pathways, are the two most extensively studied serum biomarkers proposed as adjunctive diagnostic and prognostic tools (11). Currently, S100B has been recommended by the Scandinavian Neurotrauma Committee (SCN) to be employed in the course of managing mild TBI patients (12).

S100B is mainly secreted in the extracellular space by astrocytes, Schwann cells, and myeloid-derived cells (13). Adipocytes, chondrocytes, lymphocytes, bone marrow and melanoma cells are other sources of S100B production (14). NSE is mainly found in neurons and different brain disorders including TBI and stroke have been associated with its raise in serum and cerebrospinal fluid (CSF) (15). The main methods of measuring these biomarkers are electrochemiluminescence immunoassay, enzyme-linked immunosorbent assay, line immunoassay, radioimmunoassay, and chemiluminescent immunoassay (16-21). Glial fibrillary acidic protein (GFAP) is another detectable biomarker in serum following TBI and showed some benefits in mild TBI diagnosis (22). Numerous large validation studies, systematic reviews, and meta-analyses have been conducted to gain insight into the diagnostic and prognostic values of individual biomarkers and to indirectly compare their performance characteristics in the context of TBI (23, 24). While S100B and NSE biomarkers have both demonstrated their utility as diagnostic and prognostic markers, a direct comparison of their respective diagnostic and prognostic values is yet to be established. Such a comparison would be helpful for researchers to prioritize which biomarkers to investigate in their forthcoming studies and for health policymakers to make informed decisions. In light of this, we have designed a systematic review and meta-analysis to compile all available evidence related to the direct comparison of S100B and NSE in terms of their diagnostic or prognostic performance.

2. Methods

We reported results based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (25).

2.1. Search strategy

We performed a literature search using 4 databases; Medline (via PubMed), Embase, Scopus, and Web of Science (Until October 21st, 2023). To maximize sensitivity, we used a wide variety of Mesh terms, Emtree terms, and synonyms for traumatic brain injury, NSE, and S100B and combined them properly (Appendix 1). We applied no language restrictions. Studies in languages other than English were translated as required, using DocTranslator or Google Translate. We conducted a manual search in the Google search engine and Google Scholar and reviewed the first five pages to retrieve other relevant studies. We also reviewed the bibliography of included studies and the included studies in previously published systematic review studies, to make sure we have not missed any relevant studies.

2.2. Study selection

We combined the records from the search in the four databases and removed duplicates using EndNote version X9 (Thomson Reuters). Two reviewers (HZ and SR) independently scanned titles and abstracts of the records and found potentially eligible citations. Disagreements were deliberated and resolved at the discretion of the senior reviewer (MY).

We included prospective or retrospective cohorts, case-control studies, and randomized controlled trials (RCTs in which there were adequate data on the untreated arm of the trial), which reported data on the serum concentrations of NSE and S100B in the acute phase of TBI with any severity in adult patients. The review outcomes for the prognostic performance were: 1- mortality, 2- unfavorable outcome using Glasgow outcome scale (GOS) and Glasgow outcome scale-extended (GOSE). Our desired outcome for the diagnostic performance was the presence of any traumatic injury in the brain CT scan. In order to compare the biomarkers directly, we only included studies that reported the concentrations of NSE and S100B in the same set of patients. Studies reporting one or more quantitative levels of the biomarkers and at least one of the follow-up outcome measures were eligible. We excluded studies involving patients below 15 years old, non-traumatic brain injuries, duplicate publications, those lacking a direct comparison of S100B and NSE, those with delayed biomarker measurement, cerebrospinal fluid sampling, and those without data on the desired outcome.

2.3. Data extraction

Using two separate Excel sheets for prognostic and diagnostic studies, two reviewers (SR and HZ) independently extracted data including study characteristics (first author, publication year, country, study period, and study design), patient characteristics (age and gender), details of TBI (severity, closed or penetrating, and presence of extracranial injury), laboratory aspects of S100B and NSE (type of assay, admission to sampling interval, cutoff, and mean + standard deviation (SD) in outcome and non-outcome groups), out-

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come evaluation (outcome definition and outcome measurement time), and prognostic or diagnostic accuracy data (true positive (TP), false positive (FP), true negative (TN), and false negative (FN)). If two articles reported data on the same patients, we included the article with the largest sample size. We retained all biomarker assessments and all outcome measurements to have freedom for a subgroup or sensitivity analysis. However, we used the earliest sampling time and longest follow-up of every unique observation for our analyses unless otherwise stated. In our analyses, a GOS of 3 or less and a GOSE of 4 or less were considered comparable unfavorable outcomes. All data were extracted from the included studies' texts, tables, and figures. If we had to extract data from figures, we used PlotDigitizer software. In diagnostic studies, we defined positive TBI as the presence of any trauma-related injury in the brain CT scan performed on admission.

2.4. Risk of bias assessment

We evaluated the risk of bias for the diagnostic studies included using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool, which evaluates patient selection, index test, reference standard, and flow and timing domains (26). For the prognostic studies, we used the Quality Assessment of Prognostic Accuracy Studies (QUAPAS) tool, which evaluates the applicability and risk of bias in participants, index test, outcome, flow and timing, and analysis (27).

2.5. Statistical analysis

Analyses were performed using STATA 14.0 statistical software. All studies were summarized and divided based on their outcome. Since a number of the included studies reported standard errors (SEs) instead of SD, SD was calculated by multiplying SE by the square root of the number of patients in the group. For direct comparison, the study results were pooled together using mean and SD of the biomarkers in the outcome and non-outcome groups, and a standardized mean difference (SMD) and 95% confidence interval (CI) was calculated and reported.

For calculating pooled sensitivity and specificity, TP, TN, FP, and FN values were the priority in the data collection process. If the aforementioned data was not reported in the articles, the data were extracted by employing calculations on reported sensitivity and specificity. Analyses were performed using the "Midas" package of STATA, which pools article diagnostic and prognostic accuracy data using a bivariate binary regression modeling framework. The results were provided as pooled sensitivity, specificity, and area under the summary receiver operating characteristic curve (SROC) with a 95% confidence interval (95% CI).

To measure the heterogeneity between studies, I2 statistics were performed. We applied a subgroup analysis to studies that included data of mild TBI patients. We applied Egger's Test to identify publication bias in studies we pooled to calculate and compare SMDs, and Deeks' Funnel Plot Asymmetry Test for diagnostic and prognostic accuracy meta-analysis.

3. Results

3.1. Study identification and selection

We found 1418 records in databases searching. After duplicate removal, we screened 1070 records, from which we reviewed 103 full-text documents. 78 articles were excluded for a variety of reasons (Figure 1). Finally, this review included 24 studies. Nine papers investigated diagnostic yield (16-20, 28-31) and 15 papers investigated prognostic performance (21, 32-45) of S100B and NSE in TBI. No extra articles were retrieved through manual search.

3.2. Diagnostic values of S100B and NSE in detection of TBI

3.2.1. Study characteristics

The search for gathering data regarding the diagnostic performance of S100B and NSE in traumatic brain injury resulted in nine eligible studies (n = 5515) (16-20, 28-31). Eight studies were prospective and one study (20) was retrospective observational. The earliest sampling time was on admission/within 3 hours post-injury for six studies, up to 6 hours for one study, and up to 24 hours for two studies. The outcome in all studies was defined as the presence of injury detected in brain CT scan. Five studies included patients with or without extracranial injuries and three studies included patients with isolated head injuries without significant extracranial injuries. In one study, the presence of extracranial injuries was unknown. Six studies included patients with blunt TBI and one study included patients with penetrating and blunt TBI. In two studies, the type of TBI was unknown. Three studies only included patients with mild TBI (GCS 13-15)(18, 19, 31), one study included mild to moderate TBI (29), and six studies included all severities of TBI (16, 17, 20, 28, 30). Table 1 summarizes the characteristics of the included studies.

3.2.2. Quality assessment and publication bias for diagnostic studies

Table 2 shows a detailed assessment of risk of bias using QUADAS-2 tool. The risk of bias was unclear in three studies in patient selection domain, high in one study and unclear in one study in index test domain, and low in all studies in reference standard and flow and timing domain. There was low concern for applicability of all included studies for the review question.

We assessed the publication bias for the diagnostic value of S100B and NSE in predicting intracranial injury. There was no evidence of publication bias (Figures 4a & b).

3.2.3. Diagnostic performance of S100B and NSE in TBI

We pooled studies reporting blood concentrations of NSE and S100B and their association with presence or absence of intracranial injury in brain CT scans of patients with suspected TBI on admission. We excluded three studies because they used healthy individuals without head trauma as the

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control group (34, 46, 47). We observed a significant association between increased blood concentrations of S100B and the presence of injury in brain CT scan (SMD = 1.10 [95% CI: 0.55 to 1.65], p < 0.0001; I2 = 98.53%). Similarly, there was a significant association between increased blood concentrations of NSE and the presence of injury in brain CT scan (SMD = 0.75 [95% CI: 0.35 to 1.15], p < 0.0001; I2 = 97.11%). Both biomarkers had equal performance when comparing the difference in biomarker levels between CT positive and CT negative groups (Figure 2a) (p = 0.31). We also calculated pooled sensitivity and specificity using seven studies with adequate data. The sensitivity and specificity of S100B for detecting intracranial injury in brain CT scans were 80% (95% CI: 63% - 90%) and 59% (95% CI: 45% - 72%), respectively [AUC = 0.74 (0.70 – 0.78)] (Figure 3a). The sensitivity and specificity of NSE for detecting intracranial injury in brain CT scans were 74% (95% CI: 53% - 88%) and 46% (95% CI: 24% - 69%), respectively (AUC = 0.66 [0.61 – 0.70]) (Figure 3b).

In a sensitivity analysis, when sampling time was within 12 hours post-injury, the specificity of S100B was raised while maintaining the same sensitivity (sensitivity = 80% (95% CI: 36% - 97%), specificity = 80% (95% CI: 60% - 91%), and AUC = 0.86 (0.83 – 0.89)). The same happened for NSE, when sampling time was within 12 hours post-injury, the specificity was raised with no significant alteration in sensitivity (sensitivity = 70% (95% CI: 27% - 94%), specificity = 62% (95% CI: 13% - 94%), and AUC = 0.72 (0.67 – 0.75)).

3.3. Prognostic values of S100B and NSE in TBI patients

3.3.1. Study characteristics

The search for gathering data regarding the prognostic performance of S100B and NSE in TBI resulted in 15 eligible studies (n = 939) (21, 32-45). Eight studies were prospective observational, one study was retrospective observational, two studies were post-hoc of a randomized clinical trial (RCT), and four studies did not clearly mention the study design. Eleven studies assessed severe TBI patients. Sampling time was within 12 hours in seven studies, within 24 hours in three studies, within 28 hours in one study, within 36 hours in one study, and within 48 hours post-injury in one study. There were two studies that used mean or peak level of biomarkers in multiple samples as the predictor of outcome. Two studies followed patients during hospital stay, two studies for 1 month, one study for 3 months, six studies for 6 months, and four studies for 12 months (Table 3). In cases of multiple sampling or multiple outcome measurements, we used the earliest sample and longest follow-up, respectively, in the meta-analysis.

3.3.2. Quality assessment and publication bias for prognostic studies Table 4 shows a detailed assessment of risk of bias using QUAPAS tool. In thirteen studies, the risk of bias was unclear in the patient selection domain, due to unclear study design or unclear sampling method in retrospective studies. Five studies had a high risk of bias in index test domain. One was because of using two different assays for S100B and the others were for using the optimal cutoff, and not a prespecified cutoff for dichotomizing patients in low- and high-level of biomarker group. In flow and timing and analysis domains, one study had a high risk of bias and two studies had unclear risk of bias, due to the uncertainty about including all patients in the analysis and availability of data on outcome for all patients. There was low concern for applicability of all included studies for the review question.

We assessed the publication bias for the prognostic value of S100B and NSE in predicting intracranial injury. The analysis showed no evidence of publication bias (Figures 4c & d).

3.3.3. Ability of S100B and NSE in predicting mortality in TBI

We pooled studies reporting blood concentrations of S100B and NSE and their association with mortality in TBI patients. We observed a significant association between increased blood concentrations of S100B and mortality (SMD = 1.74 [95% CI: 0.57 to 2.91], p < 0.0001; I2 = 97.32%). Similarly, there was a significant association between increased blood concentrations of NSE and mortality (SMD = 1.48 [95% CI: 0.16 to 2.79], p < 0.0001; I2 = 97.92%). Both biomarkers had equal performance when comparing the difference in biomarker levels between mortality and survival groups (p = 0.77) (Figure 2b). We also calculated pooled sensitivity and specificity using four unique studies with adequate data (40, 42, 44, 45). The sensitivity and specificity of S100B for predicting mortality were 90% (95% CI: 65% - 98%) and 61% (95% CI: 39% - 79%), respectively (AUC = 0.82 [0.78 – 0.85]) (Figure 3c). The sensitivity and specificity of NSE for predicting mortality were 88% (95% CI: 76% - 95%) and 56% (95% CI: 47% - 65%), respectively (AUC = 0.76 [0.72 – 0.79]) (Figure 3d).

3.3.4. Ability of S100B and NSE in predicting unfavorable outcome in TBI

We pooled studies reporting blood concentrations of S100B and NSE and their association with unfavorable outcome using GOS or GOSE in TBI patients. We observed a significant association between increased blood concentrations of S100B and unfavorable outcome (SMD = 1.33 [95% CI: -0.17 to 2.84], p < 0.0001; I2 = 97.81%). Similarly, there was a significant association between increased blood concentrations of NSE and unfavorable outcome (SMD = 0.74 [95% CI: -0.05 to 1.52], p < 0.0001; I2 = 92.82%). Both biomarkers had equal performance when comparing the difference in biomarker levels between favorable and unfavorable outcome groups (p = 0.49) (Figure 2c). We also calculated pooled sensitivity and specificity using four unique studies with adequate data (21, 40, 44, 45). The sensitivity and specificity of S100B for predicting unfavorable outcome were 83% (95% CI: 74% - 90%) and 51% (95% CI: 30% - 72%), respectively (AUC = 0.82 [0.78 – 0.85]) (Figure 3e). The sensitivity and specificity of NSE for predicting unfavorable outcome were 80% (95% CI: 64% - 90%) and 59% (95% CI: 46% - 71%), respectively (AUC = 0.73 [0.69 – 0.77]) (Figure 3f).

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3.4. Evidence appraisal using GRADE

Overall, the GRADE assessment demonstrated "Moderate" certainty in the body of evidence for the diagnostic value of S100B and NSE in TBI, and "low" to "moderate" certainty for the prognostic yield of S100B and NSE in predicting mortality and unfavorable outcome. The certainty for diagnostic performance of S100B and NSE, and also the prognostic performance of S100B for predicting mortality was downgraded one level due to moderate heterogeneity. Whereas, the certainty for prognostic yield of S100B and NSE in predicting unfavorable outcome, and NSE for mortality was downgraded two levels due to severe heterogeneity (Table 5).

4. Discussion

Following a comprehensive search, we have gathered valuable insights into the direct comparative performance of two frequently studied biomarkers in the field of traumatic brain injury (TBI). The results demonstrated that both biomarkers have comparable performance, with S100B exhibiting slightly better diagnostic and prognostic capabilities than NSE in TBI. Moreover, our analysis has uncovered that the clinical significance of these two biomarkers is more pronounced in prognostic contexts than in diagnostic scenarios. This is due to the potentially lethal consequences of overlooking patients with cranial injuries during emergency room evaluations, which is far more serious than misidentifying patients' future functional outcomes.

Results of the meta-analysis implied that both biomarkers performed poorly in predicting trauma-related injuries in CT imaging, with S100B showing higher sensitivity and specificity than NSE. With the advent of brain-specific biomarkers such as Glial Fibrillary Acidic protein (GFAP) and Ubiquitin C-Terminal Hydrolase L1 (UCH-L1) that offer higher sensitivity and specificity, the application of NSE and S100B, which have been shown to have a high rate of missing injuries with undeniable consequences, is no longer justified (24, 48).

Most of the international guidelines have recommended the use of imaging in all patients sustaining moderate or severe TBI. Therefore, the measurement of biomarkers would be exploited mainly in aiding emergency physicians in the selective CT imaging of mild/minimal TBI patients.

Only three studies have directly targeted mild TBI and the rest provided inadequate data on this subgroup of patients. Thus, conducting a subgroup analysis on mild TBI patients would result in an imprecise confidence interval and clinically useless and even misleading results.

Unlike diagnostic purposes, the significance of serum biomarkers for predicting mortality and functional outcome is more pronounced in moderate and severe TBI, given the higher morbidity and mortality rates in these groups. As such, the majority of studies investigating the prognostic efficacy of biomarkers were conducted on severe TBI cases. Our analysis has revealed that both NSE and S100B have shown accepting performance in predicting mortality and functional outcomes, with the performance of S100B being slightly superior to NSE. S100B and NSE have been shown to correlate with the extent of damage represented by damage burden and volumetric assessment of lesions in the imaging (49). Additionally, they exhibit a correlation with other clinical factors that are associated with brain damage and subsequent outcomes, such as intracranial pressure and cerebral perfusion pressure in cases of severe TBI (50). Nonetheless, the systematic review and meta-analysis on the potential of the GCS and Full Outline of Unresponsiveness as predictive tools indicated that readily used scoring systems hold a higher value in forecasting mortality and disability outcomes among patients with traumatic brain injuries (51).

Based on our meta-analysis, we found that patients who had positive results in CT scan had notably higher levels of S100B and NSE in their serum as compared to TBI patients who did not show any signs of intracranial abnormality. Moreover, the concentration of both biomarkers was significantly greater among those who did not survive or had higher levels of disability. Previous reports have suggested that both biomarkers also originate from sources outside the cranium, as evidenced by the increase of S100B levels in polytrauma patients without head injuries and the surge in NSE levels following hemolysis (11, 24). Our objective was to assess the accuracy of these biomarkers, given the presence of non-cranial injuries. Unfortunately, a dearth of studies involving isolated head trauma patients precludes this analysis. Nevertheless, the biomarkers' performance would be more representative if the patient only suffered from head trauma. This is implicitly supported by the heightened specificity displayed by both biomarkers when only patients with mild TBI were considered, as these individuals are thought to be less likely to have extracranial injuries. Moreover, one should note that not all injuries caused by head trauma are visible in CT scan images. In fact, some lesions, such as diffuse axonal injury, small contusions, and microhemorrhages, are only demonstrable with magnetic resonance imaging or diffuse tensor imaging, which are not routinely performed in emergency rooms (52, 53). Thus, some false positive results from these two biomarkers may have sustained injuries only visible in such advanced imaging modalities.

In the wake of the relatively short half-life of S100B (up to 120 mins), we conducted a sensitivity analysis that excluded studies with sampling times beyond 12 hours (54). The results of our study indicate that the timing of biomarkers' sampling plays a crucial role in the accuracy of their diagnostic yield for TBI. Our findings demonstrate that early sampling is associated with higher levels of specificity for both biomarkers, while late sampling is linked to a higher rate of false positives. This conclusion agrees with the Scandinavian Neurotrauma Committee's guideline, which recommends assessing S100B levels within the first six hours of injury to aid in selective imaging decisions for mild TBI (55). In contrast to S100B, NSE exhibits a longer half-life of approximately 30 hours and reaches its peak 12 hours after injury (56, 57). This

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explains why its sensitivity decreases with early sampling. However, the longer half-life of NSE may also lead to delayed washout time of extracranial sources of NSE in serum, which can interfere with its diagnostic and prognostic performance (58).

While delayed sampling may compromise the diagnostic value of biomarkers, it can prove beneficial in achieving prognostic objectives. TBI is an intricate, multifaceted process that involves both primary insult and subsequent secondary damage. The secondary damage can exacerbate the primary injury or give rise to chronic symptoms, even in the absence of any visible abnormality in the medical imaging (59). The damage can result from a variety of factors, including axonal stretching, microglial activation, excitotoxicity, and neuroinflammation, all of which can compromise the integrity of the blood-brain barrier and cause brain biomarkers to leak into the circulation (60, 61). As a result, the accuracy of diagnostic measurements can be compromised, with false positives being a common occurrence when measurements are taken after a delay.

Conversely, delayed sampling may reflect the evolving damage or ongoing recovery, thus aiding in timely and tailored care in at-risk patients (62, 63). In the current study, we opted for the earliest value of biomarkers in the course of admission for assessing the diagnostic and prognostic value. In consideration of the kinetics of NSE and S100B and the dynamic process of TBI, it is presumed that serial sampling of biomarkers, encompassing bulk release or peak and mean value, can yield a higher predictive value and provide a more accurate representation of the damage course. Consequently, it is imperative to undertake further research to compare the value of serial measurements of these biomarkers in the context of TBI.

5. Limitations and considerations

To the best of our knowledge, this is the first study that provides a direct comparison between two extensively recognized biomarkers of brain injury. However, we acknowledge that our review is subject to some limitations that require caution in interpreting our results. Significant heterogeneity was observed in all outcomes across both biomarkers. However, the limited number of studies and inadequately presented information hampered us in identifying the potential source of the heterogeneity. We postulate that several factors relating to study design and conduction may contribute to the observed heterogeneity. First, the definition of pathological damage rendering a positive CT scan result for intracranial damage varied among the included studies. While some studies adopted a conservative approach of only including parenchymal damages, others even included isolated skull fractures as an outcome. Moreover, the variability in the analytical methods and reagents utilized presents a significant challenge in comparing the studies on this topic. Consequently, the power of comparability among studies is hindered. Furthermore, many studies failed to report the threshold used for S100B and NSE or had retrospectively adopted a cutoff point derived from a ROC curve, which may overestimate the performance of biomarkers.

Our review did not investigate the combined performance of S100B and NSE, despite evidence suggesting that NSE had limited additional benefit to the discriminatory value of S100B due to the high correlation between these two biomarkers (58). In our study, we focused exclusively on serum biomarkers, as we found CSF to have limited utility in mild and moderate cases of TBI. However, more recently, there has been a growing debate surrounding the use of S100B levels in saliva. This non-invasive method of assessing biomarkers has shown great promise for future studies, given its rapid assessment and potential for providing valuable insights into TBI (64). Lastly, the results of our review cannot be applied to the pediatric population, as we excluded them from our analysis. Therefore, future studies are necessary to establish the superior prognostic and diagnostic performance of S100B over NSE in the pediatric population.

6. Conclusions

The results indicate that S100B is superior to NSE for both prognostic and diagnostic purposes in TBI patients. Although neither biomarker has shown promising diagnostic performance in detecting abnormal CT findings, they have displayed acceptable outcome prediction capabilities, particularly with regard to mortality. Henceforth, we propose that forthcoming inquiries prioritize the examination of S100B over NSE, with greater emphasis on their prognostic values.

7. Declarations

7.1. Acknowledgments

None.

7.2. Competing interests

None of the authors has any conflict of interest to declare.

7.3. Ethics approval

This study approved by Ethics Committee of Shahid Beheshti University of Medical Sciences (Ethics code: IR.SBMU.RETECH.REC.1401.226).

7.4. Funding and support

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7.5. Consent for publication

Not applicable.

7.6. Data availability

The datasets generated and analyzed during the current study are available from the corresponding author upon rea-

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sonable request.

7.7. Using Artificial intelligence chatbots

None.

7.8. Authors contribution

Study design: MY
Data gathering: SRD, HZ
Analysis: MY, HZ
Interpretation: SRD, HZ, AT
Drafting: SRD, HZ
Revising: All authors
Reading and approving the final manuscript: All authors

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Table 1: Characteristics of the diagnostic studies

Study	Design	TBI severity	Type of head trauma	Co-injury	N	Age + SD	Male (N)	S100B assay	Sampling time	NSE assay
Czeiter, 2020	PO	All	Open and closed	Yes	2774	NR	NR	ECLIA	First 24h post-injury	ECLIA
Carabias, 2019	PO	All	Closed	Yes	115	45.67+22.52	79	CLIA	On admission	ECLIA
Cervellin, 2014	PO	Mild	NR	NR	68	52.75+15.05	44	Immunoassay	Within 3h post-injury	Immuno-fluorimetric
Gardner, 2022	PO	All	Closed	Yes	2151	51.6+6.9	240	ECLIA	First 24h post-injury	ECLIA
Honda, 2010	RO	All	NR	Yes	34	NR	21	ELISA	Within 3h post-injury	ELISA
Kaneko, 2019	PO	Mild to moderate	Closed	No	57	69.5+5.23	22	ELISA	Within 3h post-injury	ELISA
Mussack, 2002	PO	Mild	Closed	No	139	41.36+24.04	106	LIA	First 6h post-injury	ECLIA
Shehab, 2010	PO	All	Closed	Yes	70	40.8+8	52	ELISA	On admission	ELISA
Wolf, 2013	PO	Mild	Closed	No	107	59+23	60	ECLIA	Within 3h post-injury	ECLIA

TBI: traumatic brain injury; PO: prospective observational, RO: retrospective observational; NR: not reported; N: number of patients; ECLIA: electrochemiluminescence immunoassay; ELISA: enzyme-linked immunosorbent assay; LIA: line immunoassay; h: hours CLIA: chemiluminescent immunoassay; SD: standard deviation.

Table 2: Risk of bias assessment for the diagnostic studies

Study	Risk of Bias				Applicability		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Czeiter, 2020	☺	☺	☺	☺	☺	☺	☺
Carabias, 2019	☺	☺	☺	☺	☺	☺	☺
Cervellin, 2014	☺	?	☺	☺	☺	☺	☺
Gardner, 2022	☺	☺	☺	☺	☺	☺	☺
Honda, 2010	?	☺	☺	☺	☺	☺	☺
Kaneko, 2019	?	☺	☺	☺	☺	☺	☺
Mussack, 2002	☺	☹	☺	☺	☺	☺	☺
Shehab, 2010	?	☺	☺	☺	☺	☺	☺
Wolf, 2013	☺	☺	☺	☺	☺	☺	☺
Czeiter, 2020	☺	☺	☺	☺	☺	☺	☺
Carabias, 2019	☺	☺	☺	☺	☺	☺	☺
Cervellin, 2014	☺	?	☺	☺	☺	☺	☺
Gardner, 2022	☺	☺	☺	☺	☺	☺	☺
Honda, 2010	?	☺	☺	☺	☺	☺	☺
Kaneko, 2019	?	☺	☺	☺	☺	☺	☺
Mussack, 2002	☺	☹	☺	☺	☺	☺	☺
Shehab, 2010	?	☺	☺	☺	☺	☺	☺
Wolf, 2013	☺	☺	☺	☺	☺	☺	☺

☹: High risk; ☺: Low risk; ?: unclear.

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Table 3: Characteristics of the prognostic studies

Study	Design	TBI severity	Type[1]	Co-injury	N	Age (year)	Male (N)	Sampling time	Follow-up	S100B assay	NSE assay
Baker, 2009	Post-hoc of RCT	Severe	Closed	No	33	42.3+20.7	23	Within 48h post-admission (peak)	1 M	ELISA	ELISA
Chen, 2019	NR	Severe	NR	Yes	10	35.1+14.4	7	Within 24h post-admission	Hospital stay	ECLIA	ECLIA
Chen JJ, 2019	NR	Severe	NR	No	88	44.1+15.3	61	Within 72h post admission	1 M	ECLIA	ECLIA
Di Battista, 2015	PO	Moderate to severe	Open and closed	No	85	45.8+21.9	66	24h post injury	6 M	ELISA	ELISA
Duda, 2020	PO	All	NR	NR	15	NR	NR	Within 2h post-admission	Hospital stay	ELISA	ELISA
Gradisek, 2012	PO	Moderate to severe	NR	Yes	84	46+21	73	On admission	12 M	LIA	LIA
McKeating, 1998	NR	All	NR	Yes	21	39+13.8	17	Within 96h post-admission (Mean)	6 M	RIA	RIA
Olivecrona, 2009	RO	Severe	Closed	Yes	48	35.5+15.2	31	Within 24h after injury	3 M	LIA	LIA
Raabe, 1999	PO	Severe	NR	Yes	82	44.2+14.2	66	2-28h after injury	6 M	RIA and LIA	RIA
Raheja, 2016	Post-hoc of RCT	Severe	NR	Yes	65	NR	NR	Within 8h after injury	12 M	ELISA	ELISA
Rodríguez-Rodríguez, 2016	PO	Severe	NR	No	99	37+15.8	80	Within 6h post-injury	6 M	ECLIA	ECLIA
Stein, 2012	PO	Severe	NR	No	24	30.7+12.3	21	On admission	12 M	ELISA	ELISA
Vos, 2004	PO	Severe	Closed	Yes	85	40+13.5	61	Within 36h after injury	6 M	LIA	LIA
Yang Gao, 2021	RO	Severe	Open and closed	Yes	98	39.6+8.6	53	Within 12h before transfer from ICU	1 M	ELISA	ELISA
Zhang, 2014	PO	Severe	NR	No	102	40.5+15.3	68	<6h after injury	6 M	ELISA	ELISA

1: type of head injury. Age is presented as mean ± standard deviation (SD). TBI: traumatic brain injury, RCT: randomized clinical trial; PO: prospective observational, RO: retrospective observational; NR: not reported; N: number of patients; h: hours; M: month(s); ECLIA: electrochemiluminescence immunoassay, ELISA: enzyme-linked immunosorbent assay, LIA: line immunoassay, RIA: radioimmunoassay; ICU: intensive care unit.

Table 4: Risk of bias assessment for the prognostic studies

Study	Risk of Bias					Applicability			
	Patient selection	Index test	Outcome	Flow and timing	Analysis	Participants	Index test	Outcome	Flow & timing
Baker, 2009	?	☺	☺	☺	☺	☺	☺	☺	☺
Chen, 2019	?	☺	☺	☺	☺	☺	☺	☺	☺
Chen JJ, 2019	?	☺	☺	☺	☺	☺	☺	☺	☺
Di Battista, 2015	?	☺	☺	☺	☺	☺	☺	☺	☺
Duda, 2020	☺	☺	☺	☺	☺	☺	☺	☺	☺
Gradisek, 2012	?	☺	☺	☺	☺	☺	☺	☺	☺
McKeating, 1998	?	☺	☺	☺	☺	☺	☺	☺	☺
Olivecrona, 2009	☺	☹	☺	☺	☺	☺	☺	☺	☺
Raabe, 1999	?	☹	☺	☺	☺	☺	☺	☺	☺
Raheja, 2016	?	☺	☺	☹	☹	☺	☺	☺	☺
Rodríguez-Rodríguez, 2016	?	☹	☺	☺	☺	☺	☺	☺	☺
Stein, 2012	?	☺	☺	?	?	☺	☺	☺	☺
Vos, 2004	?	☹	☺	?	?	☺	☺	☺	☺
Yang Gao, 2021	?	☺	☺	☺	☺	☺	☺	☺	☺
Zhang, 2014	?	☹	☺	☺	☺	☺	☺	☺	☺

☹: High risk; ☺: Low risk; ?: unclear.

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Table 5: Certainty of evidence for diagnostic and prognostic performance of S100B and NSE

Outcomes	No	Study design	Risk of bias	Inconsistency[1]	Indirectness	Imprecision	Publication bias	Quality of evidence
S100B								
Intracranial injury	7	Diagnostic/Prognostic	Not[2]	Serious	Not Serious	None	No[3]	Moderate ⊕⊕⊕⊖
Mortality	11	Diagnostic/Prognostic	Not	Serious	Not Serious	None	No	Moderate ⊕⊕⊕⊖
Unfavorable outcome	11	Diagnostic/Prognostic	Not	Very Serious Not Serious	None	No	Low	⊕⊕⊖⊖
NSE								
Intracranial injury	7	Diagnostic/Prognostic	Not	Serious	Not Serious	None	No	Moderate ⊕⊕⊕⊖
Mortality	11	Diagnostic/Prognostic	Not	Very Serious	Not Serious	None	No	Low ⊕⊕⊖⊖
Unfavorable outcome	11	Diagnostic/Prognostic	Not	Very Serious	Not Serious	None	No	Low ⊕⊕⊖⊖

1: The authors judged the inconsistency by the examination of effect estimates. 2: Not Serious. 3: No evidence of publication bias. Serious inconsistency implies that the effect estimates are all favoring the same directions, but I2 > 75% and lack of overlap in confidence intervals are evident in the forest plots. In cases where therewere effects estimates in both directions and I2 > 75%, the inconsistency was judged as very serious and downgraded by two levels. No: number of studies.

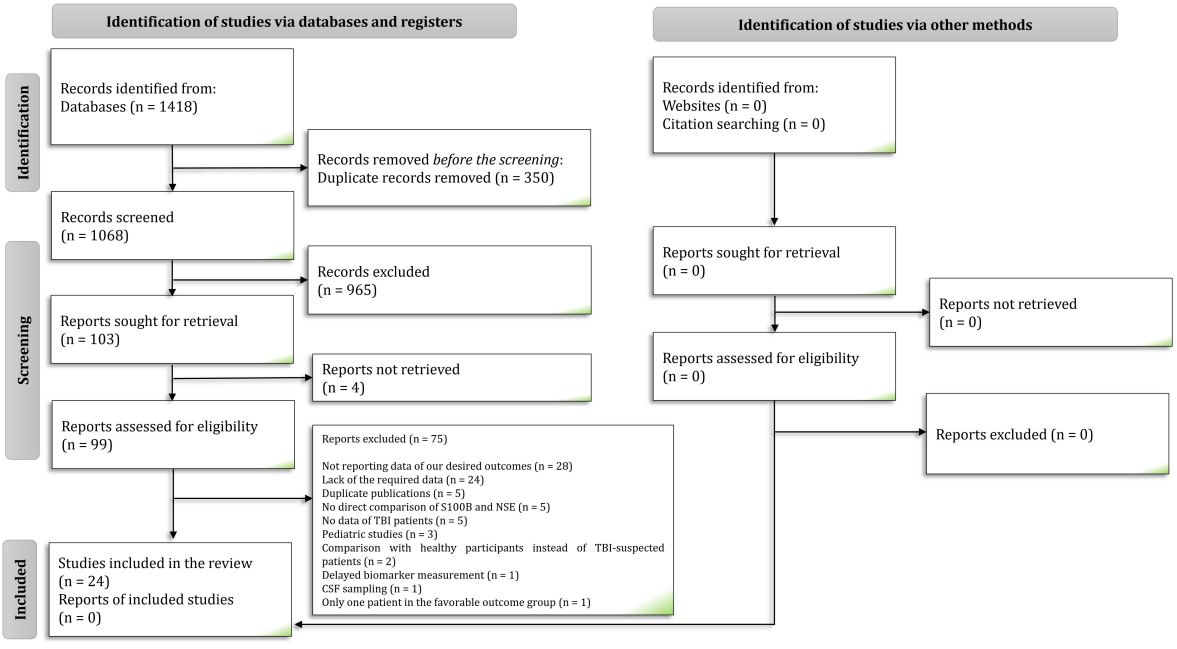

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the study selection process. TBI: traumatic brain injury; CSF: cerebrospinal fluid.

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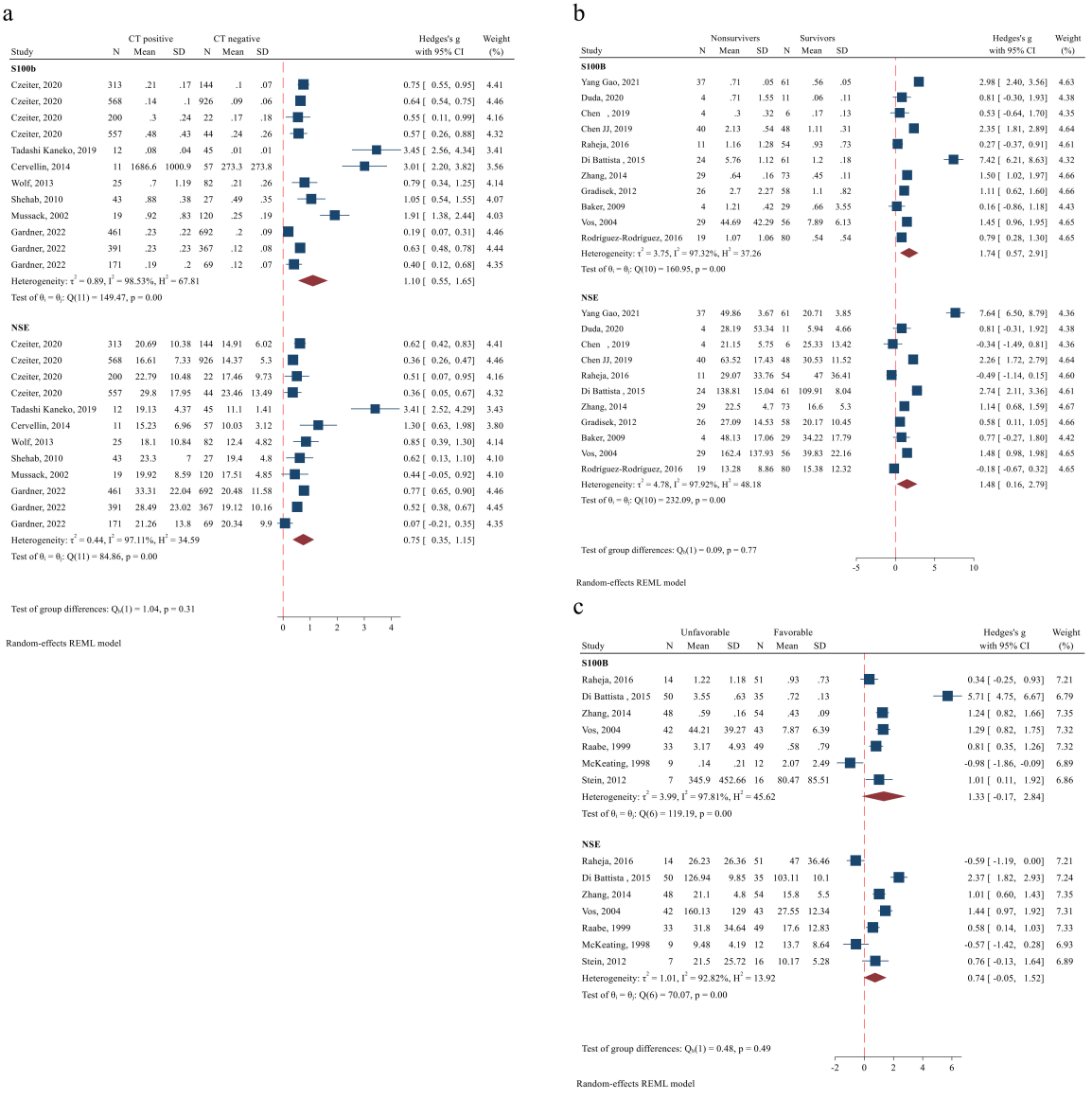

Figure 2: Forrest plots demonstrating the standardized mean difference (SMD) of S100B and NSE blood levels in traumatic brain injury (TBI) patients by (a) presence or absence of intracranial lesion in brain computed tomography (CT) scan; (b) mortality or survival; (c) unfavorable or favorable outcome. SD: standard deviation; CI: confidence interval.

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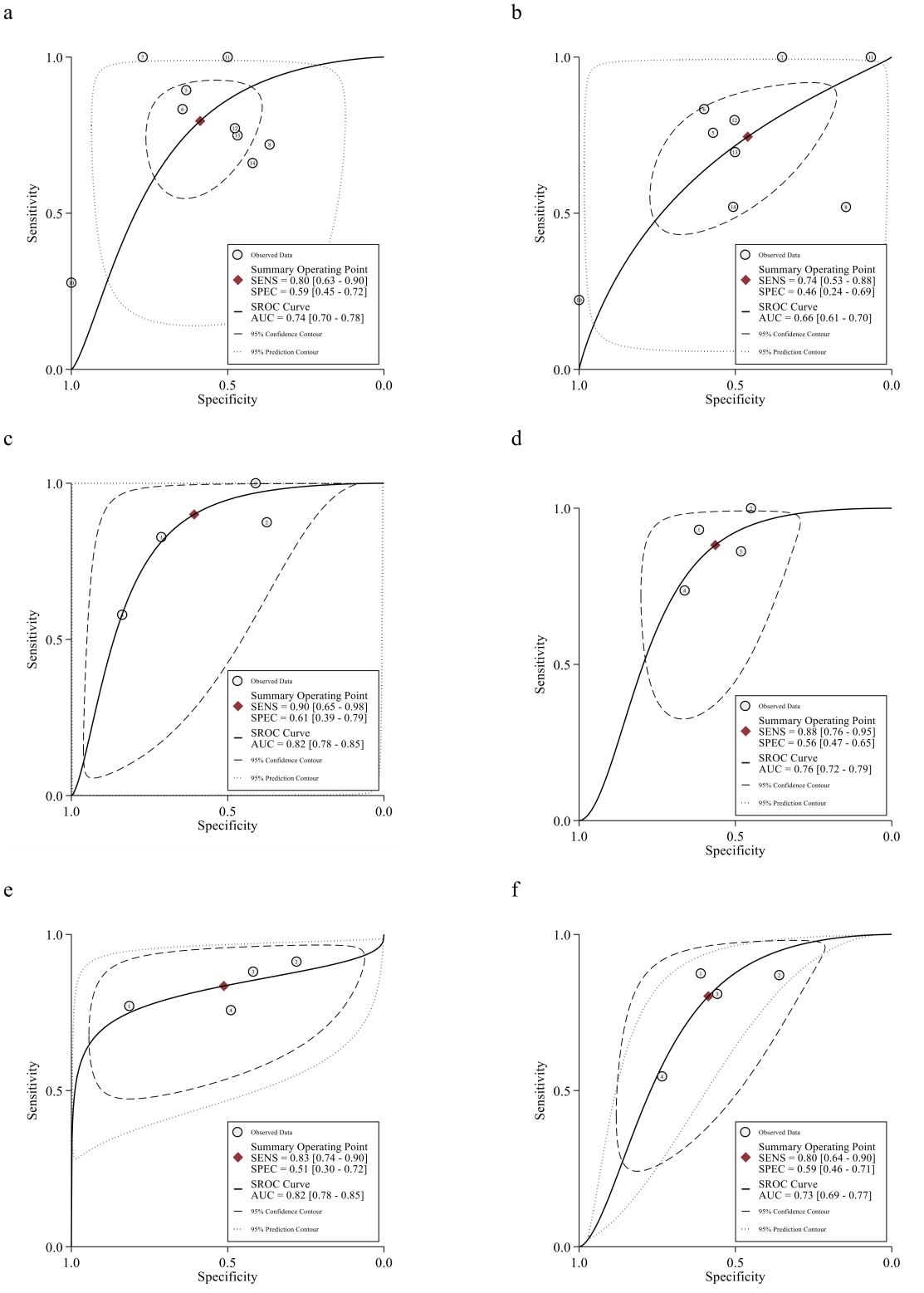

Figure 3: The summary receiver operating characteristic (SROC) curves. (a-b) depict the diagnostic performance of S100B (a) and NSE (b) in detecting intracranial injury. (c-d) show the prognostic yield of S100B (c) and NSE (d) in predicting mortality. (e-f) demonstrate the prognostic performance of S100B (e) and NSE (f) in predicting the unfavorable outcome. SENS: sensitivity; SPEC: specificity; AUC: area under the curve.

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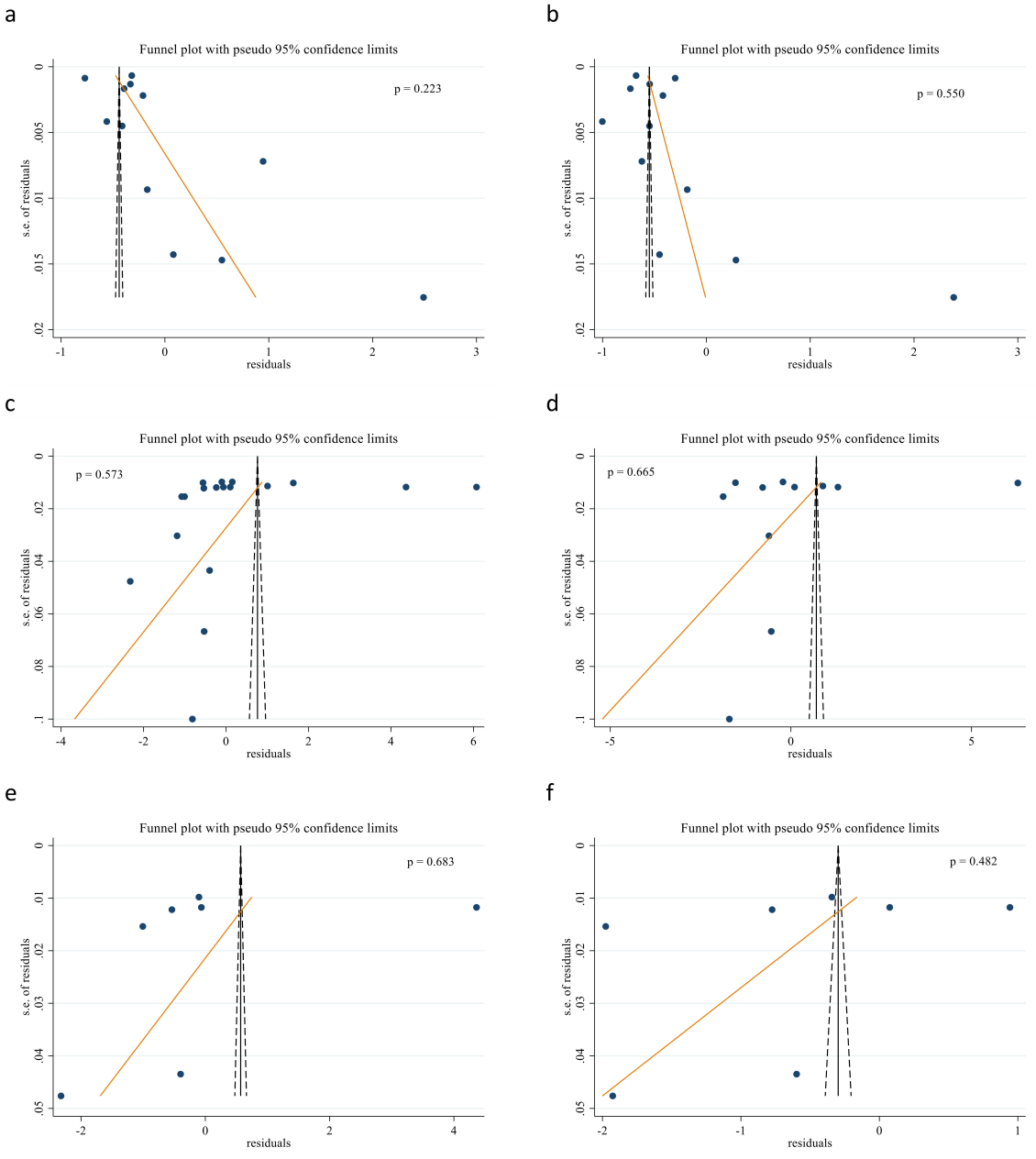

Figure 4: Funnel plot asymmetry tests using Egger's test for investigating a possible publication bias. The analysis revealed no evidence of publication bias in studies assessing the diagnostic performance of S100B (a) and NSE (b). Similarly, no evidence of publication bias was observed in studies investigating the association of mortality with S100B (c) and NSE (d) serum levels, as well as in studies investigating the association between unfavorable outcome and S100B (e) and NSE (f) serum levels.

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