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

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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

Summary of Methods

- This study followed the PRISMA guidelines for systematic reviews and meta-analyses.

Search Strategy

A comprehensive literature search was conducted across four databases: Medline, Embase, Scopus, and Web of Science, up to October 21, 2023. A variety of keywords related to traumatic brain injury (TBI), NSE, and S100B were utilized, and no language restrictions were applied. Non-English studies were translated as necessary. Additional searches were conducted via Google and Google Scholar, and reference lists of included studies were also reviewed.

Study Selection

Duplicate records were removed, and two reviewers independently assessed titles and abstracts for eligibility, resolving disagreements with a senior reviewer. Eligible studies included prospective or retrospective cohorts, case-control studies, and randomized controlled trials that reported serum concentrations of NSE and S100B during the acute phase of TBI in adults. The review focused on mortality and unfavorable outcomes (measured by the Glasgow Outcome Scale). Studies comparing NSE and S100B concentrations in the same patients were prioritized.

Data Extraction

Data were independently extracted by two reviewers using Excel sheets for prognostic and diagnostic studies, capturing details on study characteristics, patient demographics, TBI specifics, laboratory data, outcome evaluations, and accuracy metrics (TP, FP, TN, FN). The earliest sampling times and longest follow-ups were used for analyses.

Risk of Bias Assessment

- Risk of bias was evaluated using the QUADAS-2(the Quality Assessment of Diagnostic Accuracy)
- Studies tool for diagnostic studies and the QUAPAS tool (the Quality Assessment of Prognostic Accuracy Studies)for prognostic studies, assessing various domains including patient selection and outcome measurement.

Statistical Analysis

- Data were analyzed using STATA 14.0. The standard deviation was calculated from standard errors when necessary, and pooled analyses of biomarkers were performed to derive standardized mean differences and confidence intervals. Sensitivity and specificity were pooled using diagnostic accuracy data with appropriate statistical tests to assess heterogeneity and publication bias.

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%).

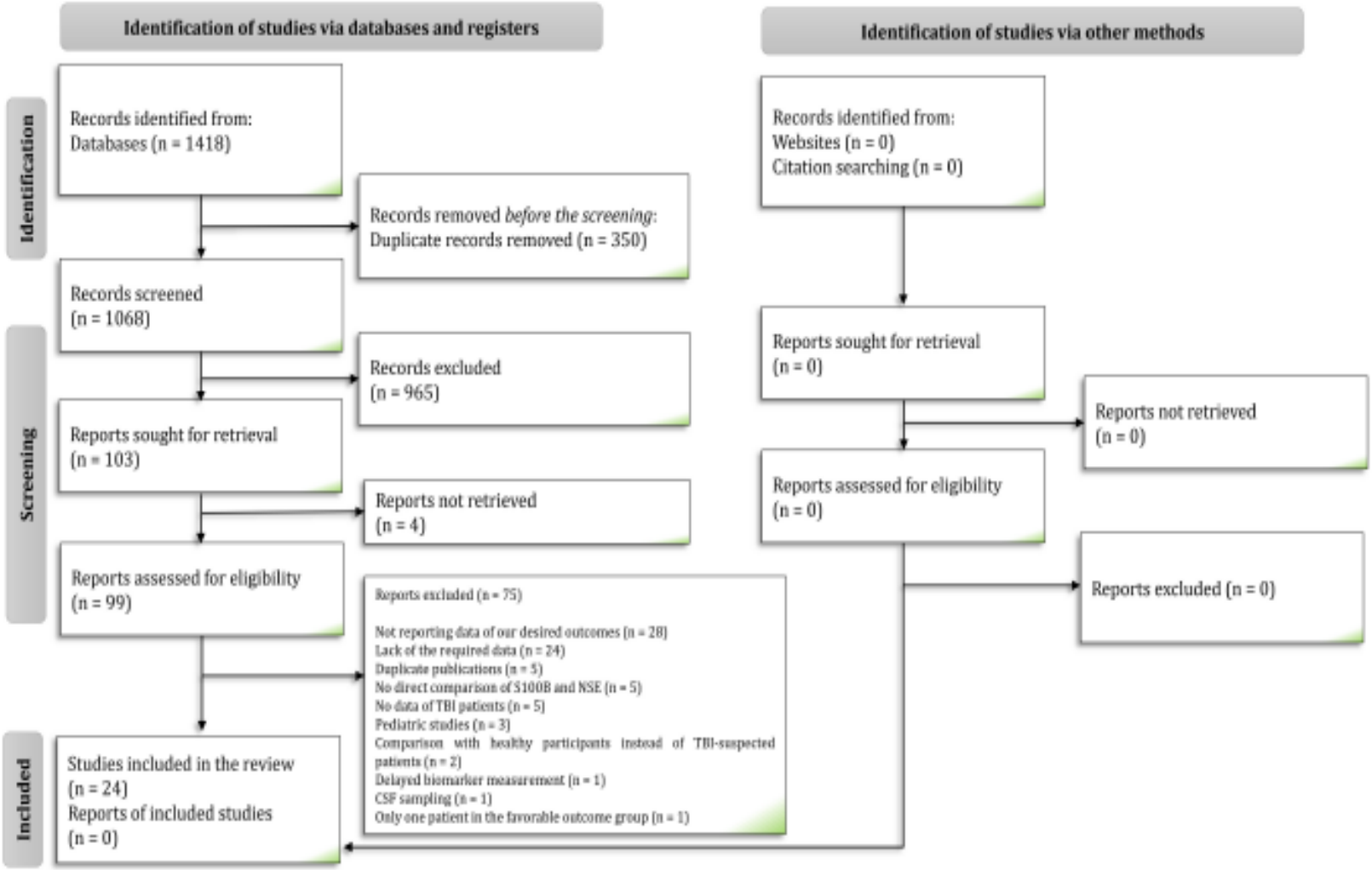


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the study selection process. TBI: traumatic brain injury; CSF: cerebrospinal fluid.

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.

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.

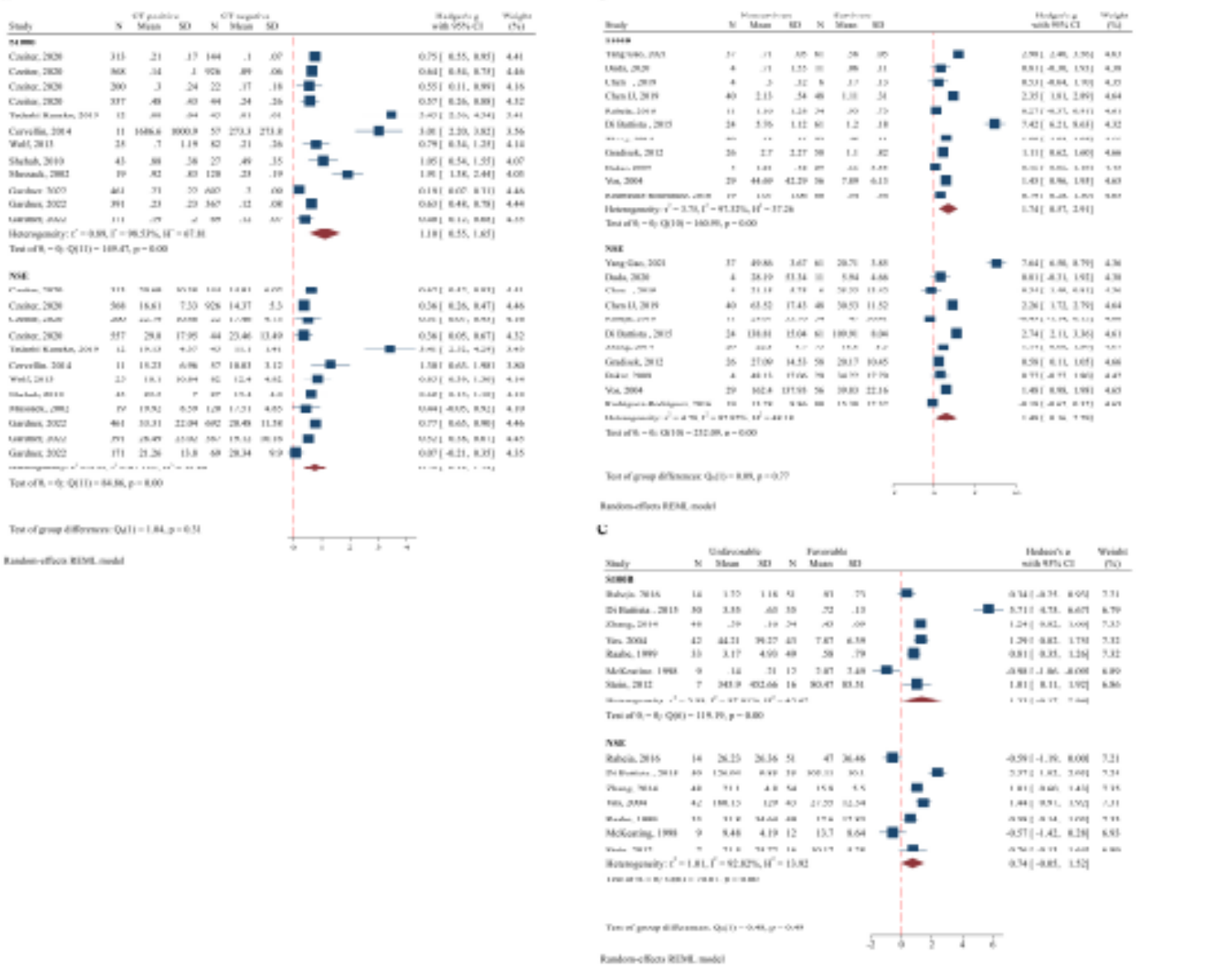
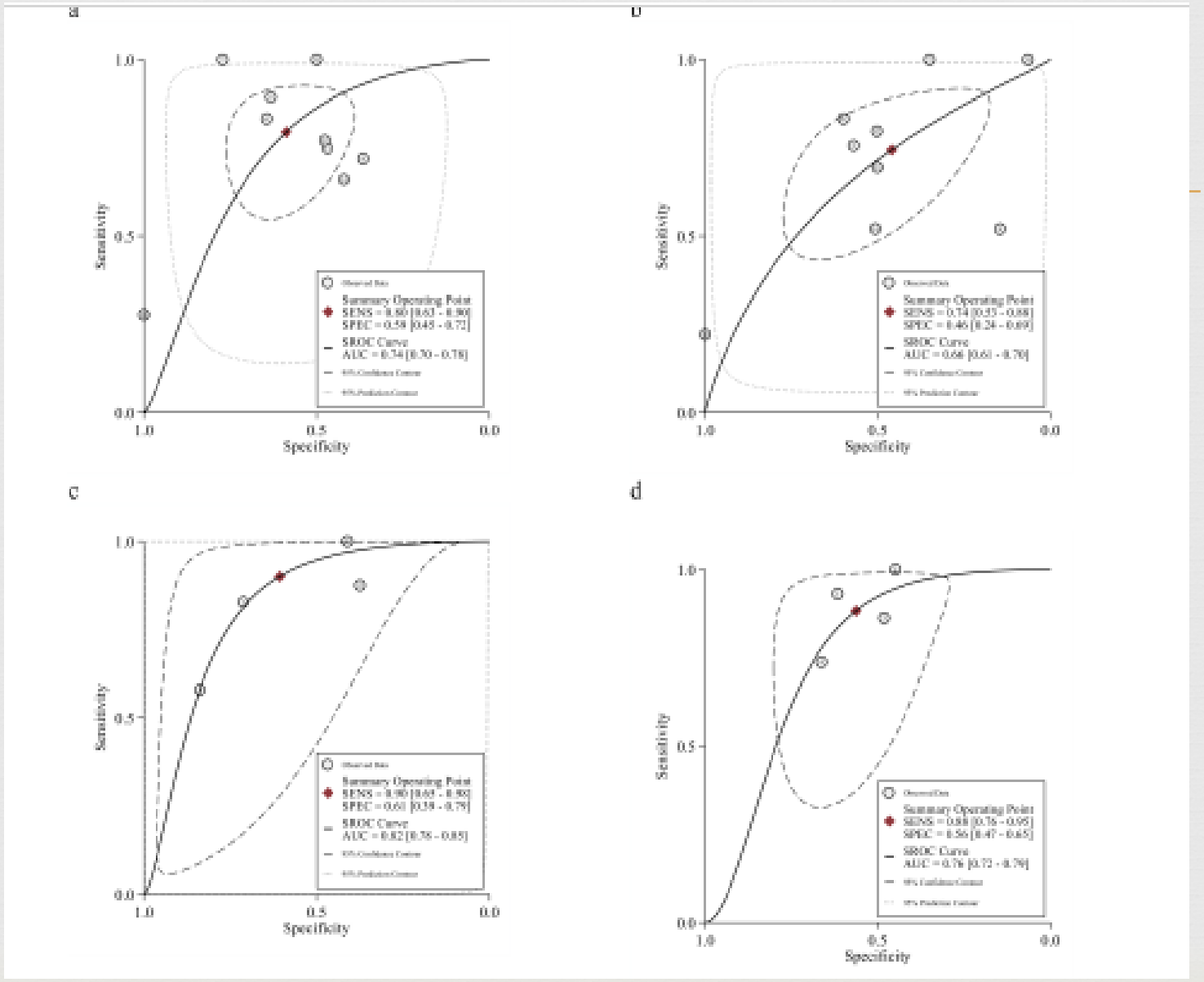
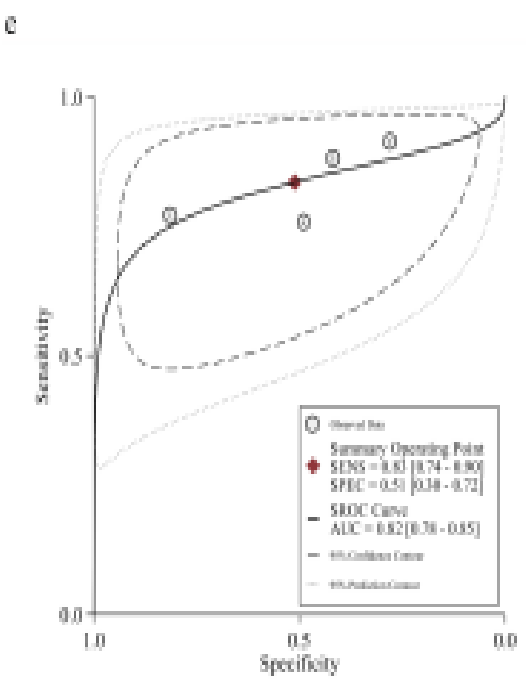


Figure 2: Forrest plots demonstrating the standardized mean difference (SMD) of S100B and NSE blood levels in traumatic brain injury (TBI) patients by (a) presence or absence of intracranial lesion in brain computed tomography (CT) scan; (b) mortality or survival; (c) unfavorable or favorable outcome.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


a
b
c
d
Sensitivity
Specificity
1.0
0.5
0.0
Summary Operating Point
SROC Curve
AUC = 0.74 [0.70 - 0.78]
AUC = 0.68 [0.61 - 0.74]
AUC = 0.82 [0.78 - 0.85]
AUC = 0.76 [0.72 - 0.79]



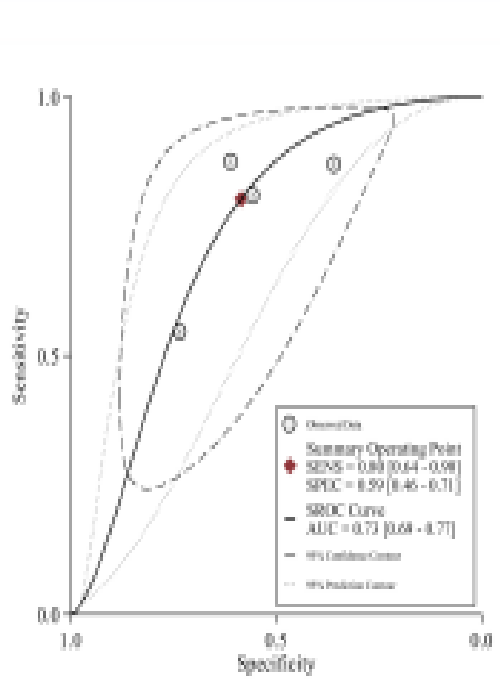
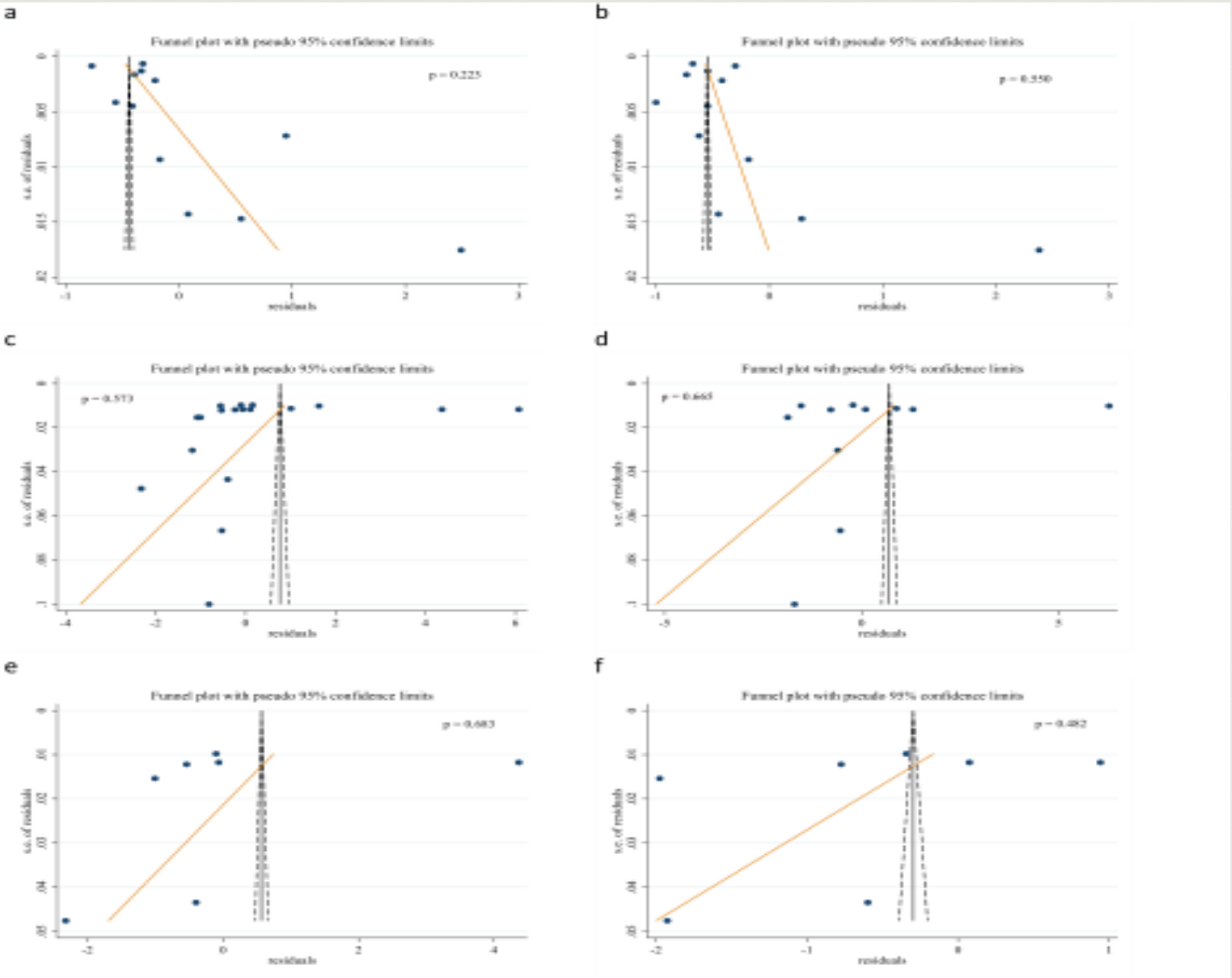


Figure 3: The summary receiver operating characteristic (SROC) curves. (a-b) depict the diagnostic performance of S100B (a) and NSE (b) in detecting intracranial injury. (c-d) show the prognostic yield of S100B (c) and NSE (d) in predicting mortality. (e-f) demonstrate the prognostic performance of S100B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

- **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) serumlevels.


a
Funnel plot with pseudo 95% confidence limits
p = 0.225
s.e. of residuals
residuals
b
Funnel plot with pseudo 95% confidence limits
p = 0.550
s.e. of residuals
residuals
c
Funnel plot with pseudo 95% confidence limits
p = 0.573
s.e. of residuals
residuals
d
Funnel plot with pseudo 95% confidence limits
p = 0.665
s.e. of residuals
residuals
e
Funnel plot with pseudo 95% confidence limits
p = 0.683
s.e. of residuals
residuals
f
Funnel plot with pseudo 95% confidence limits
p = 0.482
s.e. of residuals
residuals

Discussion

- This study highlights the comparative performance of two biomarkers, S100B and NSE, in traumatic brain injury (TBI). The findings indicate that S100B has slightly superior diagnostic and prognostic capabilities compared to NSE. Importantly, the clinical significance of these biomarkers is more pronounced in prognostic contexts due to the critical nature of accurately assessing cranial injuries in emergency settings.

- The meta-analysis revealed that both biomarkers generally performed poorly in predicting trauma-related injuries on CT scans, although S100B showed better sensitivity and specificity than NSE. With newer brain-specific biomarkers like GFAP and UCH-L1 emerging, the utility of S100B and NSE, which often miss injuries, is being questioned. Current guidelines recommend imaging for moderate to severe TBI, making biomarkers more relevant for aiding selective imaging in mild cases.

- Most studies focused on moderate to severe TBI, where both biomarkers effectively predicted mortality and functional outcomes, with S100B showing slightly better performance. Both biomarkers correlate with injury severity and other clinical factors, but traditional scoring systems like the Glasgow Coma Scale (GCS) may be more reliable in predicting outcomes.

- The study also noted that patients with positive CT findings had significantly higher serum levels of both biomarkers, particularly among those who did not survive or had severe disabilities. However, both biomarkers can originate from non-cranial sources, complicating their assessment in polytrauma patients.

- The study emphasizes the importance of early biomarker sampling, as later measurements are linked to higher false positive rates. S100B, with a short half-life, should ideally be measured within six hours post-injury, while NSE's longer half-life might lead to delayed detection of extracranial sources affecting its diagnostic accuracy.

- While delayed sampling can hinder diagnostic value, it may be beneficial for prognostic assessment as it can reflect ongoing brain damage. Serial measurements may provide a more accurate picture of TBI progression, suggesting a need for further research on the value of such approaches in clinical practice.

Limitations and considerations

- This study is the first to directly compare two well-known biomarkers of brain injury, S100B and NSE. However, there are several limitations to consider when interpreting the results. Notable heterogeneity was found across the studies, partly due to varying definitions of what constitutes a positive CT scan for intracranial damage, as well as differences in analytical methods. Additionally, many studies did not clearly report the thresholds for S100B and NSE, which could skew performance evaluations.

- The review did not assess the combined effectiveness of S100B and NSE, despite evidence suggesting that NSE offers limited additional benefit due to its high correlation with S100B. The study focused on serum biomarkers, noting that cerebrospinal fluid (CSF) has limited utility in mild to moderate traumatic brain injury (TBI) cases. There's ongoing interest in using S100B levels in saliva as a non-invasive assessment method.

- Lastly, the findings do not apply to pediatric populations, which were excluded from the analysis. Future research is needed to determine the relative effectiveness of S100B and NSE in diagnosing and prognosticating TBI in children

Conclusions

- 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.

Thanks for your attention