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Review Article

The Role of Neuron Specific Enolase, S100B, Glial Fibrillary Acidic Protein, and Myelin Basic Protein as Prognostic and Survival Values in Traumatic Brain Injury: Systematic Review and Meta-analysis

Wibowo Artho Sutrisno[1], Prananda Surya Airlangga[1]*, Citrawati Dyah Kencono Wungu[2], Prihatma Kriswidyatomo[1], Hamzah[1], Bambang Pujo Semedi[1], Mahmudah[3]

ABSTRACT

Background: The high number of accidents and traumatic brain injuries, especially in the productive age group, causes a lot of morbidity and mortality. A fast and accurate examination method is needed for the diagnosis and treatment of traumatic brain injury. Nerve damage biomarkers such as Neuron Specific Enolase, S100B, Glial Fibrillary Acidic Protein, and Myelin Basic Protein, have been used globally both for research and daily use to determine the severity of traumatic brain injury. **Methods:** Searches and journal searches were carried out from Science Direct, Scopus, Springer Link, and PubMed, with the keywords "Neuron Specific Enolase", "S100B", "Glial Fibrillary Acidic Protein", "Myelin Basic Protein", and "Traumatic Brain Injury ". Screening was carried out using PRISMA 2021 to look for studies that met the criteria and were of sufficient study quality according to the Newcastle-Ottawa Scale. **Results:** Twenty-three studies were collected and further grouped based on outcomes, both prognostic and survival outcomes. Neuron Specific Enolase, S100B, and Glial Fibrillary Acidic Protein values were higher in poor outcomes (all p values < 0.001) and poor survival (all p values < 0.001) in traumatic brain injury. Myelin Basic Protein was not significant in poor outcome (p = 0.35), but was higher in poor survival (p < 0.001) in traumatic brain injury. **Conclusion:** Neuron Specific Enolase, S100B, and Glial Fibrillary Acidic Protein, can be used as markers for prognostic and survival value in traumatic brain injury. Myelin Basic Protein can be used as a marker for survival value in traumatic brain injury.

Key words: Neuron Specific Enolase, S100B, Glial Fibriallary Acidic Protein, Myelin Basic Protein, Prognostic Value, Survival, Traumatic Brain Injury.

Wibowo Artho Sutrisno[1], Prananda Surya Airlangga[1]*, Citrawati Dyah Kencono Wungu[2], Prihatma Kriswidyatomo[1], Hamzah[1], Bambang Pujo Semedi[1], Mahmudah[3]

[1]Department of Anesthesiology and Reanimation, Faculty of Medicine, Airlangga University - Dr Soetomo General Academic Hospital, Surabaya, INDONESIA.

[2]Department of Physiology and Medical Biochemistry, Faculty of Medicine, Airlangga University, Surabaya, INDONESIA.

[3]Department of Community Health, Faculty of Community Health, Airlangga University, Surabaya, INDONESIA.

Correspondence

Prananda Surya Airlangga

Department of Anesthesiology and Reanimation, Faculty of Medicine, Airlangga University - Dr Soetomo General Academic Hospital, Surabaya, INDONESIA.

E-mail: prananda-s-a@fk.unair.ac.id

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INTRODUCTION

Traumatic Brain Injury (TBI) is defined as changes in brain function or pathology caused by external forces where these changes consist of periods of loss or decreased level of consciousness, antegrade or retrograde memory loss, neurological deficits or changes in mental condition. The Centers for Disease Control and Prevention (CDC) recorded for 10 years that 521 – 823 / 100,000 people per year were hospitalized due to TBI with a mortality of around 17 – 18 / 100,000 people per year. Riskesdas (Basic Health Research) 2018, head injuries are ranked third in the ranking of injuries in Indonesia based on body parts. The behavior of the Indonesian people, as many as 23.9% do not wear helmets when driving, so head trauma due to traffic accidents is also the largest contributor to TBI cases.[1,2]

The pathophysiology of TBI is the occurrence of a primary insult caused by trauma, then a secondary insult occurs due to the inflammatory response due to the trauma which causes damage to the brain.[3] Biomarkers of brain damage have been investigated as potential tools for prognostic evaluation, one of which is Neuron Specific Enolase (NSE), which is a structural protein of the central nervous system, which will be upregulated to maintain homeostasis in the event of axonal damage[4] S100B and Glial Fibrillary Acidic Protein are biomarkers released during Glial cell damage, while Myelin Basic Protein is a biomarker of axon damage.[5–7]

MATERIALS AND METHODS

Search strategy and eligibility criteria. Searches were carried out using databases on PubMed, Science Direct, and Scopus. Search keywords are 'Neuron Specific Enolase' or 'NSE', 'Glial Fibrillary Acidic Protein' or 'GFAP', 'Myelin Basic Protein' or 'MBP', 'S100', with 'traumatic brain injury' or 'TBI'.

The search was carried out until January 2024. Study inclusion criteria were: 1) observational research design, 2) patients with traumatic brain injury whose blood samples were taken to examine biomarkers; both NSE, S100B, GFAP, and MBP, 3) availability of outcome data, namely favorable and non-favorable outcomes (GOS or GOS-E), and survival (survivor or non-survivor). Exclusion criteria were: 1) articles with other comorbid diseases such as multiple sclerosis or meningitis, 2) articles in languages other than English, 3) articles with only abstracts, and 4) duplicate articles.

Data collection. Two researchers conducted independent searches and extracted articles. Two other researchers selected and screened articles. Researchers made a list of articles and checked for duplication of articles. The articles that have been obtained are studied in full text and evaluated for criteria according to the research concept. The

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assessment of each research study uses the Newcastle-Ottawa Scale, with a score of 0 – 9, which is taken with a journal score of ≥7.[8] Final conclusions are based on considerations from all researchers. Existing studies were collected according to PRISMA guidelines as shown in Figure 1.

Statistic analysis. Heterogeneity between studies was evaluated with the I^2 test. The SMD estimates of the collected studies were measured based on fixed effect or random effect assumptions. If $p < 0.05$, it indicates heterogeneity between studies, so a random effect model is used, and if vice versa, a fixed effect model is used. The 95% confidence intervals of the pooled SMD estimates were calculated. Egger's test was used with a number > 2 studies to look for publication bias. If the Egger test is significant ($p < 0.05$), then there is publication bias. Review Manager version 5.4 and Comprehensive Meta Analysis version 3 were used for this meta analysis. Journal selection using Mendeley for desktop version 1.19.

RESULTS

Twenty-three studies (Table 1) were collected and analyzed according to the PRISMA protocol as in Figure 1. A search for studies with predefined keywords was carried out using the existing study search engine, then selected using Mendeley for desktop software version 1.19. Selected studies were analyzed using Comprehensive Meta Analysis version 3 and RevMan 5.4 software. The summary results of the analysis can be seen in Table 2.

Neuron Specific Enolase (Figure 2). Forest plot for both variables (prognostic and survival), random effect model was carried out because $I^2 > 50\%$. For prognostics, Egger's p value was 0.11014 and overall $p < 0.001$, while for survival, Egger's p value was 0.50337 and overall $p < 0.001$.

S100B (Figure 3). $I^2 > 50\%$ for prognostic and survival so a random effect model is used. Both obtained Egger's p values of 0.07366 and 0.54178 with both $p < 0.001$.

GFAP (Figure 4). This time the fixed effect model is used because $I^2 < 50\%$. Prognostic and survival results were assessed as unbiased with Egger's p values of 0.32817 and 0.06698. Both $p < 0.001$.

MBP (Figure 5). For the prognostic value of MBP, a random effect model was used because $I^2 > 50\%$, but in contrast to the survival value a fixed effect model was used. Prognostics received an Egger's p value of 0.91211, but survival could not be processed because there were only 2 studies. Survival is $p < 0.001$, while prognostic value is p 0.35.

DISCUSSION

This meta-analysis study found that NSE, S100B, GFAP, and MBP, have a significant impact on the survival value of traumatic brain injury patients, with higher levels in non-survivors than survivors. For prognostic value, those that have significance are NSE, S100B, and GFAP, which have higher levels of non-favorable than favorable outcomes.

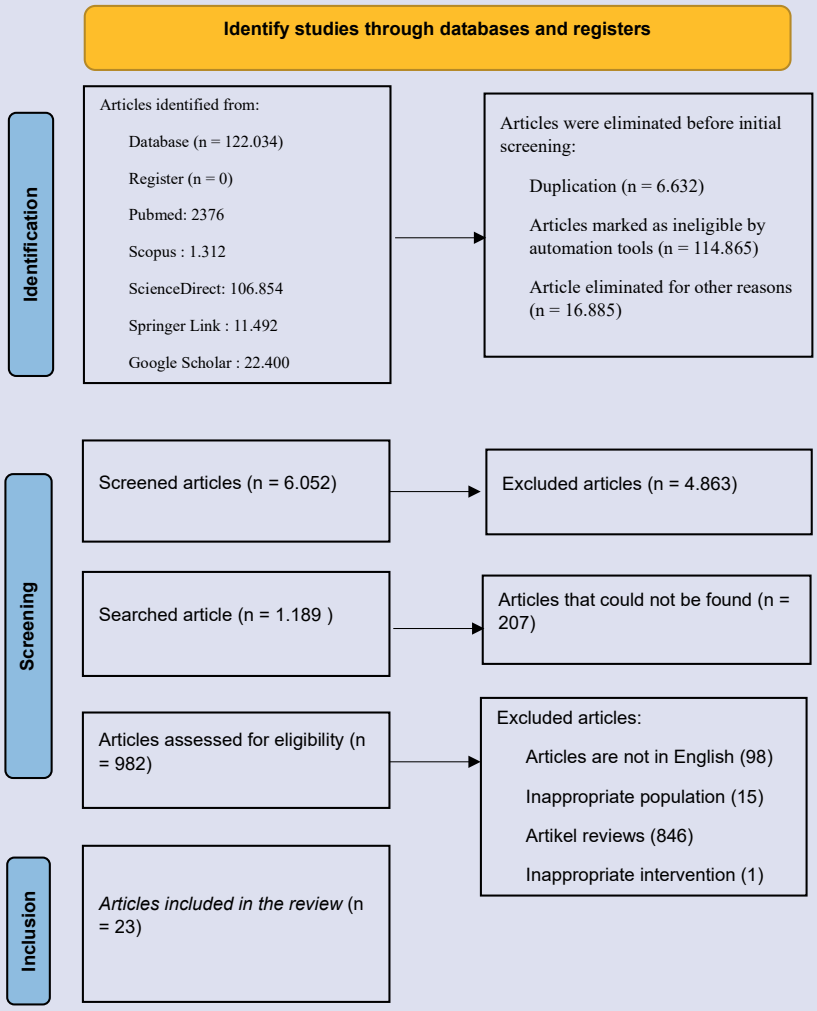

Figure 1. PRISMA flowchart guides in study search and screening.

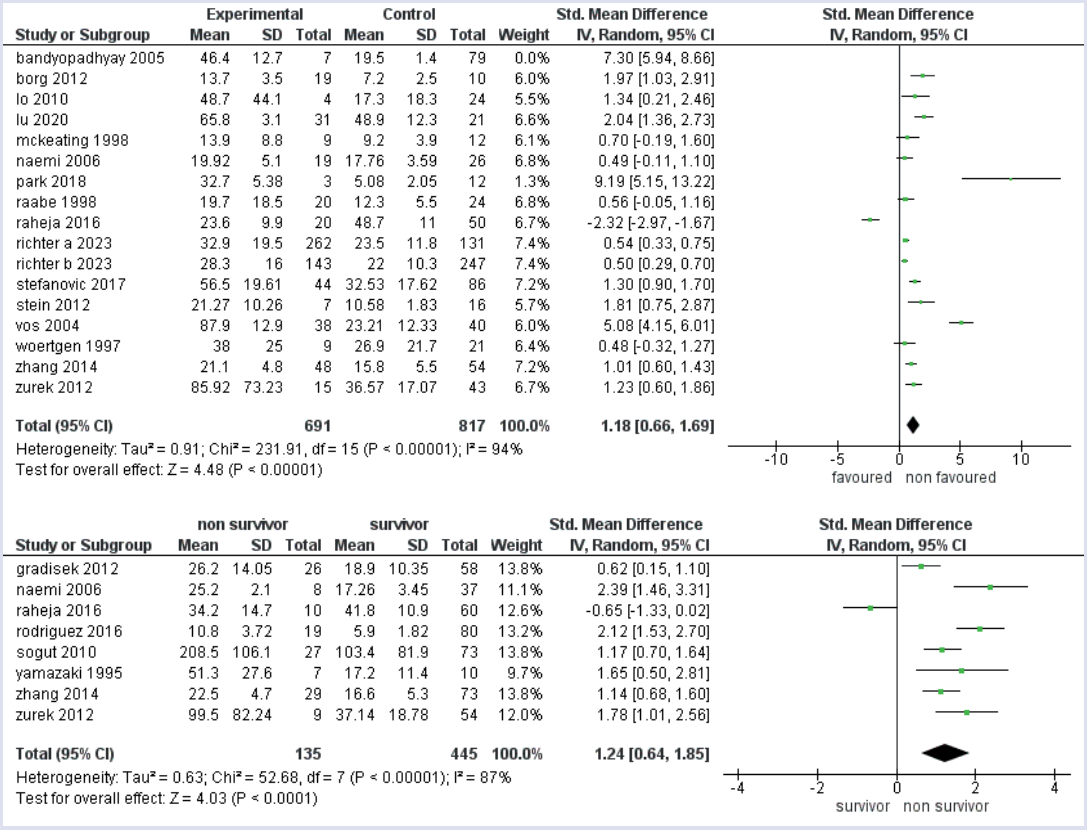

Figure 2. NSE levels on outcomes in traumatic brain injury patients.

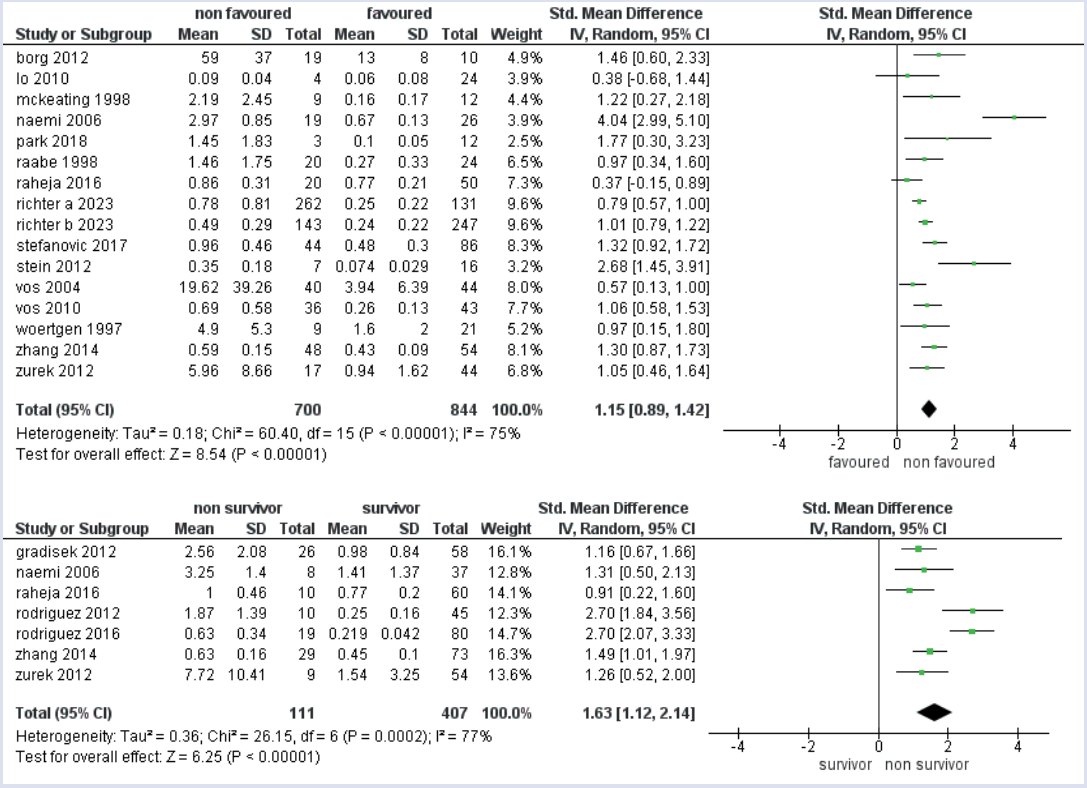

Figure 3. S100B levels on outcomes in traumatic brain injury patients.

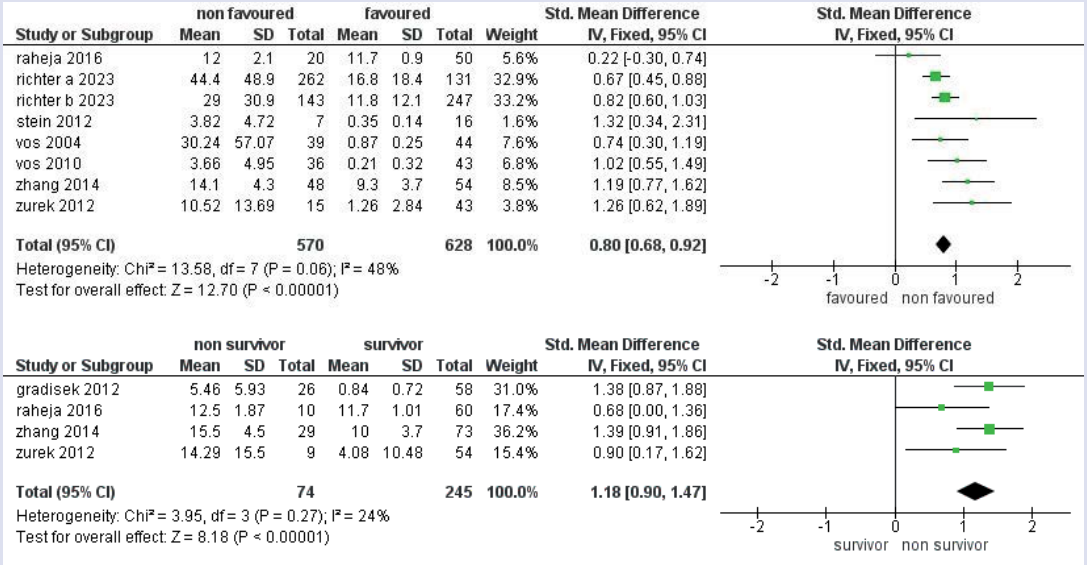

Figure 4. GFAP levels on outcomes in traumatic brain injury patients.

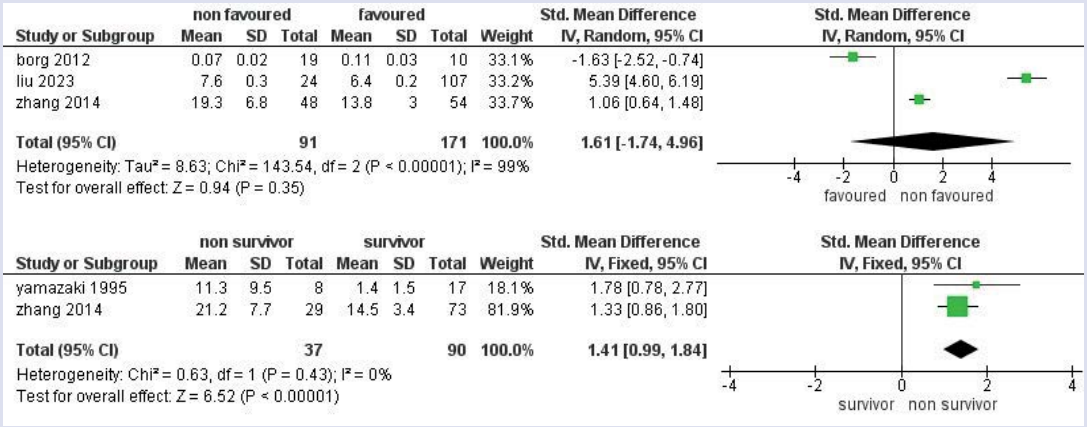

Figure 5. MBP levels on outcomes in traumatic brain injury patients.

Increased NSE is considered a marker of neuronal injury and is found in blood serum and cerebro spinal fluid.[32] Research in Serbia in 2017 showed NSE levels taken serially in the blood serum of TBI patients (6 hours, 24 hours, 48 hours and 72 hours after TBI), showing significant levels for prognostic outcomes.[33] Zurek and Fedora showed that NSE levels of more than 50 ng/ml indicated a lethal outcome.[31] Structural damage to nerve cells causes leakage of NSE into the extracellular compartment and bloodstream, so NSE can be detected in serum after neuronal death due to TBI or cerebrovascular accident.[34]

Levels of S100B, which originates from astrocytes, are considered a marker of astroglial injury.[35] Naeimi demonstrated that S100B levels above 2 µg/L indicated lethality in TBI patients in 2006.[16] S100B can be used to demonstrate prognostic outcomes of TBI patients in the ED, thereby reducing resource use.[36] The release of S100B from Schwann cells after peripheral nerve damage has been shown, in addition to the central nervous system, to promote macrophage recruitment and Schwann cell migration, thereby facilitating repair of injured peripheral nerves.[37,38]

GFAP originates from ependymal cell filaments and its increase is considered a marker of astroglial injury.[39] For GFAP, Gradisek observed that higher values were obtained in non-survivor patients, while Vos found that levels > 1.5 µg/L indicated high lethality.[11,27] The GFAP protein is not routinely secreted into the blood and is only released after cells die or are injured.[40,41]

MBP is a biomarker of injury to the myelin sheath and is considered a marker of oligodendrocyte injury.[29] Zhang reported that increasing MBP levels above 16.9 µg/ml indicated worse survival rates in TBI patients.[30] MBP levels do not increase immediately after injury, instead the peak occurs at 48 – 72 hours after TBI reflecting axonal injury, this is why several studies on MBP stated that the levels with prognostic outcomes were not very significant.[39]

This research is expected to strengthen scientific evidence regarding the use of TBI biomarkers in determining diagnosis and prognosis in TBI. The brain is very complex and varies in the number and types of cells it contains, so it is unlikely that a single biomarker in one cell can reliably predict the outcome and outcome of TBI.[7] The author still hopes for an accurate and cheap diagnostic and prognostic modality, especially for areas that do not have adequate radiology and laboratory equipment, such as in large cities.

Table 1. Characteristic Studies.

Study	Country	Design	Age	Sample Size	Entry Criteria	Outcome	Observation time	Biomarkers examined
Bandyopadhyay, 2005[9]	USA (Milwaukee)	Retrospektif	0 – 18 years	86	Mild TBI – severe TBI (GCS 3 – 15)	GOS	During hospital treatment	NSE
Borg, 2012[10]	Canada (Toronto)	Observasional case control	16 – 89 years	50	GCS ≤ 14, or GCS 15 but was unaware event	CT scan, GOS	2 weeks – 1 month	NSE, S100B, MBP
Gradisek, 2012[11]	Slovenia	Cohort prospective	15 – 87 years	84	Moderate TBI – severe TBI (GCS ≤ 12)	survival	12 months	NSE, S100B, GFAP
Liu, 2023[12]	China(Chengyang)	Retrospektif	≥ 18 years	131	Mild TBI (GCS 13 – 15), Moderate TBI (GCS 9 – 12), Severe TBI (GCS 3 – 8)	GOS-E	6 months	MBP
Lo, 2010[13]	Britania	Cohort prospective	0 – 15 years	28	Mild TBI – severe TBI (GCS 3 – 13)	GOS-E	6 months	NSE, S100B
Lu, 2020[14]	China	Cohort prospective	18 – 65 years	52	Severe TBI (GCS 3 – 8)	GOS-E	6 months	NSE
Mckeating, 1998[15]	Britania	Cohort prospective	17 – 69 years	21	TBI ringan sampai berat (GCS 3 – 13)	GOS-E	6 months	NSE, S100B
Naemi, 2006[16]	Austria (Vienna)	Cohort prospective	16 – 86 years	45	Mild TBI – severe TBI (GCS < 9 – GCS > 12)	GOS-E, CT scan	6 months	NSE, S100B
Park, 2018[17]	South Korea (Daegu)	Cohort prospective	4 – 18 years	15	Mild TBI – severe TBI (GCS < 9 – GCS > 12)	GOS-E	6 months	NSE, S100B
Raabe, 1998[18]	German	Cohort prospective	16 – 83 years	44	Severe TBI (GCS 3 – 8)	GOS-E	6 months	NSE, S100B
Raheja, 2016[19]	India	Cohort prospective	18 – 65 years	107	Severe TBI (GCS 4 – 8)	GOS-E	6 dan 12 months	NSE, S100B, GFAP
Richter, 2023[20]	Europe	Cohort prospective	16 – 95 years	872	Moderate TBI – Severe TBI (GCS ≤ 12)	GOS-E	6 months	NSE, S100B, GFAP
Rodriguez, 2012[21]	Spain	Cohort prospective	> 14 years	55	Severe TBI (GCS 3 – 8)	survival	During hospital treatment	NSE, S100B
Rodriguez, 2016[22]	Spain	Cohort prospective	> 14 years	99	Severe TBI (GCS 3 – 8)	survival	During hospital treatment and 6 months	S100B
Sogut, 2010[23]	Turkey	Cohort prospective	1 – 49 years	100	Mild TBI – severe TBI (GCS 3 – 15)	survival	During hospital treatment	NSE
Stefanovic, 2017[24]	Serbia	Cohort prospective	18 – 65 years	130	Mild TBI – severe TBI (GCS ≤ 8 – 15)	GOS, CT scan kepala	2 weeks	NSE, S100B
Stein, 2012[25]	Maryland, USA	Cohort prospective	19 – 64 years	23	TBI berat (GCS < 9)	GOS-E	12 months	NSE, S100B, GFAP
Vos, 2004[26]	Netherland	Cohort prospective	15 – 81 years	85	Severe TBI (GCS ≤ 8)	GOS-E	6 months	NSE, S100B, GFAP
Vos, 2010[27]	Netherland	Cohort prospective	18 – 91 years	79	Moderate TBI – severe TBI (GCS ≤ 12)	GOS-E	6 months	S100B, GFAP
Woertgen, 1997[28]	German	Cohort prospective	17 – 73 years	30	Severe TBI (GCS < 9)	GOS	During hospital treatment	NSE, S100B
Yamazaki, 1995[29]	Japan	Cohort prospective	14 – 91 years	25	Mild TBI – severe TBI (GCS 3 – 15)	survival	During hospital treatment	NSE, MBP
Zhang, 2014[30]	China(Hangzhou)	Cohort prospective	18 – 78 years	102	Severe TBI (GCS ≤ 8)	GOS-E	6 months	NSE, S100B, GFAP, MBP
Zurek, 2012[31]	Ceko	Cohort prospective	0 – 19 years	63	TBI	Survival, GOS-E	6 months	NSE, S100B, GFAP

Table 2. Summary of Analysis.

Covariates	Case / total (n[%])	Model	JS	MD*/SMD**	95% CI	P Egger	P Het	p
Non favourable outcome NSE	698 / 1594 (43.78%)	Random	17	1.18**	[0.66 – 1.69]	0.11014	< 0.00001	< 0.00001
Non favourable outcome S100B	700 / 1544 (45.33%)	Random	16	1.15**	[0.89 – 1.42]	0.07366	< 0.00001	< 0.00001
Non favourable outcome GFAP	570 / 1198 (47.57%)	Fixed	8	0.80**	[0.68 – 0.92]	0.32817	0.06	< 0.00001
Non favourable outcome MBP	91 / 262 (34.73%)	Random	3	1.61**	[-1.74 – 4.96]	0.91211	< 0.00001	0.35
NSE mortality	135 / 580 (23.27%)	Random	8	1.24**	[0.64 – 1.85]	0.50337	< 0.00001	< 0.0001
S100B mortality	111 / 518 (21.42%)	Random	7	1.63**	[1.12 – 2.14]	0.54178	0.0002	< 0.00001
GFAP mortality	74 / 319 (23.19%)	Fixed	4	1.18**	[0.90 – 1.47]	0.06698	0.27	< 0.00001
MBP mortality	37 / 127 (29.13%)	Fixed	2	1.41**	[0.99 – 1.84]	NA	0.43	< 0.00001

The limitations of this study are: 1) heterogeneity between studies is very high and there are still few studies, especially MBD, 2) this study did not directly compare TBI biomarkers, and 3) the age of the study patients was not grouped.

CONCLUSION

Neuron Specific Enolase, S100B, Glial Fibrillary Acidic Protein, and Myelin Basic Protein, are significant as survival values for traumatic brain injury, the levels of which are higher in non-survivors than survivors. Meanwhile, as a prognostic value, NSE, S100B, and GFAP are significant with higher non-favorable outcomes than favorable outcomes. The hopes for the future are: 1) conducting research by differentiating the age of the subjects so that the research is more specific and effective, 2) creating a separate meta-analysis research that discusses direct comparisons between TBI biomarkers, and 3) creating in-depth primary research on MBP.

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CONFLICTS OF INTEREST

There's no conflict of interest to inform.

ETHICS CLEARANCE

This research has been registered in PROSPERO (International Prospective Register of Systematic Reviews with number CRD420234495141.

AUTHOR'S CONTRIBUTION

All authors made substantial contributions to the conception and design of the study, the collection of the data, the analysis and interpretation of data, the drafting of the article, the critical revision of the article for important intellectual content, and the final approval of the version to be published.

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