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Original Article

The change of serum and CSF BDNF level as a prognosis predictor in traumatic brain injury cases: A systematic review

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ABSTRACT

Background: Mortality predictions following traumatic brain injury (TBI) may be improved by including genetic risk in addition to traditional prognostic variables. One promising target is the gene coding for brain-derived neurotrophic factor (BDNF), a ubiquitous neurotrophin important for neuronal survival and neurogenesis.

Methods: A total of seven publications pertaining to BDNF in the study of traumatic head injury were included and reviewed. The majority of patients were male, that is, 483 (83.85%) patients, compared to 93 (16.15%) female patients. The median length of follow-up was 6 months (3 days–12 months). Measurement of the patient's initial condition was carried out by measuring the initial GCS of the patient at the time of admission across the five studies being 6.5. The median CSF BDNF levels in the unfavorable group being 0.2365 (0.19–0.3119) ng/ml, from favorable group which was 0.20585 (0.17–0.5526) ng/ml. The median serum BDNF level in the unfavorable group being 3.9058 (0.6142–13.0) ng/ml, from favorable group which was 4.3 (0.6174–23.3) ng/ml.

Results: Six studies reported on the sex distribution of patients, the majority of patients were male, that is, 483 (83.85%) patients, compared to 93 (16.15%) female patients. Six studies reported the number of patients per outcome group. The comparison of the number of patients in the two groups was quite balanced with the number of patients in the good group as many as 269 patients (55.5%) and the number of patients in the unfavorable group as many as 216 patients (44.5%). Measurement of the patient's initial condition was carried out by measuring the patient's initial GCS at the time of admission. It was reported in five studies, with the overall mean baseline GCS across five studies being 6.5 (3.2–8.8). Measurement of patient outcome was carried out by several methods, two studies used Glasgow Outcome Scale, Glasgow Outcome Scale Extended was used in two studies, and five studies used survival as a patient outcome measure. The patient's BDNF level was measured in CSF and/or serum. A total of four studies measuring BDNF CSF levels and serum BDNF levels. Measurement of BDNF levels in TBI patients conducted on patients in seven literatures showed that there were differences in the trend of BDNF levels from CSF sources and serum sources. Measurement of CSF BDNF levels CSF BDNF levels was reported in two of the seven literatures, with the median CSF BDNF level in the unfavorable group being 0.2365 (0.19–0.3119) ng/ml. CSF BDNF levels were higher than the median in the preferred group, which was 0.20585 (0.17–0.5526) ng/ml. The results of the analysis from three other literatures stated that there was a tendency for lower CSF BDNF levels in the preferred group. Serum BDNF levels were reported in two of the seven literatures, with the median serum BDNF level in the unfavorable group being 3.9058 (0.6142–13.0) ng/ml. This serum BDNF level was lower than the median in the preferred group, which was 4.3 (0.6174–23.3) ng/ml. The results of the analysis of four literatures reporting serum BDNF stated that there was a tendency for lower serum BDNF levels in the poor group. A risk assessment of bias for each study was performed using ROBINS-I because all included studies were non-RCT studies. Overall the results of the risk of bias analysis were good, with the greatest risk of confounding bias and outcome bias.

Conclusion: Serum BDNF levels were found to be lower in the unfavorable group than in the favorable group. This is associated with an increase in autonomic function as well as a breakdown of the blood–brain barrier which causes a decrease in serum BDNF levels. Conversely, CSF BDNF levels were found to be higher in the unfavorable group than in the favorable group. This is associated with an increase in the breakdown of the blood–brain barrier which facilitates the transfer of serum BDNF to the brain, leading to an increase in CSF BDNF levels.

Keywords: Brain-derived neurotrophic factor, Brain injury, Outcome, Traumatic brain injury

INTRODUCTION

Traumatic brain injury (TBI) is a medical condition that occurs as a result of traumatic events in the brain. TBI has become the main cause of mortality and disability in 2020, according to the World Health Organization, with over 10 million people impacted each year. Advanced age is a consistent determinant of TBI survival. Available data indicate that nearly 60% of TBI cases are caused by road traffic injuries worldwide; about 20–30% due to falls; 10% due to violence; and another 10% due to accidents at work and during sports. Recent literatures indicated that individuals who survive the acute phase after severe TBI have an increased risk of death during the postacute recovery phase and, on average, have a shorter life span compared to general population.[2,6]

Systemic biomarkers from the central nervous system (CNS) can provide information regarding the prediction of acute death after severe TBI. In addition, biomarkers describe TBI-specific pathology relevant to the molecular pathways they represent. While few studies have evaluated patterns of early biomarkers that predict mortality, less is known about how innate biological factors, such as genetics, interact with acute biomarkers to influence mortality.[16,19]

Brain-derived neurotrophic factor (BDNF), one of a group of neurotrophic proteins, is an autocrine factor that triggers cell development, differentiation, and regeneration. BDNF is also important for synaptic plasticity and regeneration of neuronal cells. BDNF has been known to have the effect of reducing the severity of secondary brain injury so that it can protect nerve cells and improve connections between these cells after trauma.[8]

BDNF, a neurotrophin expressed in the brain, is an attractive target for TBI intervention research because of its role in neuronal survival, neurogenesis, and plasticity. BDNF and its major receptors are found in various areas of the brain, including structures of the cortex, striatum, hypothalamus, septum, thalamus, and cerebellum. The highest levels of BDNF were found in the hippocampus structure.[1,10] BDNF has been extensively evaluated as a biomarker in affective disorders, where lower serum levels are associated with depressive episodes. Decreased serum BDNF levels have also been associated with mortality in the uninjured population.[14] Post-TBI, Kalish, and Phillips reported that serum BDNF levels decreased acutely and correlated with the severity of injury.[7]

Although the BDNF is known to have a protective effect on the incidence of TBI in terms of protection of nerve cells, the exact mechanism is still not clearly understood. Therefore, this study was designed to study usefulness of measuring BDNF levels as prognosticator of TBI.

MATERIALS AND METHODS

Eligibility criteria

Any studies investigating BDNF in patient with TBI will be included in this study. Literature with the following design: clinical, prospective, retrospective, and observational cohort trials.

Type of outcome measures

Clinical outcome measured with:

- Glasgow Outcome Scale (GOS)
- Glasgow Outcome Scale Extended (GOSE)
- Survival

Information sources

This systematic review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[11] Studies were obtained by searching electronic databases, PubMed DoAJ, and the Cochrane Library. We did apply language restriction to our search, only studies that in English were included in the study. We do not apply limit on the year of literature publication.

Search protocol

The study question was formed from the PICO. The authors used the following search keywords to search all trials registers and databases: ("Brain-derived Neurotrophic Factor" OR "BDNF" OR "Neurotrophic") AND ("Traumatic Brain Injury" OR "TBI" OR "Brain Injury").

Data collection and analysis

We screened all records on the title and abstract as a result of the search strategy. Three authors (AK, AMHT, and AT) independently assessed for inclusion all potential studies. The search results were first excluded based on the nonrelevancy of the titles followed with the abstracts. Non-English

publications were automatically excluded from the study. Articles were then assessed by all authors for potentially eligible clinical, prospective, retrospective, and observational cohort trials. The reasons of exclusion were noted. Included studies are resumed in Table 1.

Assessment of study quality and risk of bias in included studies

Review authors independently assessed risk of bias for each included study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions for nonrandomized studies, called as Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) for nonrandomized studies and Risk of Bias 2 for randomized studies. Any disagreement was resolved by discussion with the fourth author. We summarized judgments in "Risk of bias" tables along with the characteristics of the included studies and interpreted the results of meta-analyses in light of the overall "Risk of bias" assessment.

RESULTS

The literature search was conducted from multiple online databases. The online journal databases used in the search were PubMed (176 literature), Cochrane (eight literature), and DoAJ (two literature), and another nine studies were obtained by manual search, for a total of 195 studies. After the duplication screening, a total of 179 literatures were obtained then filtered through titles and abstracts and obtained 17 literatures. From these 17 literatures, the text was filtered thoroughly, and seven literatures were found that met the criteria. These seven were used to conduct a systematic review using qualitative data. The flowchart of the research literature search results is shown in Figure 1.

The authors summary of data from all seven studies included in the systematic review is shown in Table 1.

Demographics

A total of seven literatures were included in our study. The total number of patients was 687 with a median age of 36 (1.3–74) years. Six studies reported on the sex distribution of patients, for a total sample of 576 patients. Of these six studies, the majority of patients were male, that is, 483 (83.85%) patients, compared to 93 (16.15%) female patients.

All patients were divided into two groups based on the final outcome, namely, favorable and unfavorable. A total of studies reported the number of patients per outcome group, for a total of 485 patients. There were 269 patients (55.5%) in the favorable group and 216 patients (44.5%) in the unfavorable group.

Measurement of initial condition and patient outcome

Measurement of the patient's initial condition was carried out by measuring the initial GCS of the patient at the time of admission. The median baseline GCS was reported in five studies only, with the overall median baseline GCS across the five studies being 6.5 (3.2–8.8).

Measurement of patient outcomes was carried out by several methods and some studies used more than 1 outcome measure. Two studies used GOS as well as GOSE as a measure of patient outcome. Five studies used survival as a measure of patient outcome.

The length of follow-up in seven studies was reported with certainty in six studies, and the other one study measured the length of stay in the intensive care unit/ICU. The median length of follow-up was 6 months (3 days–12 months).

Patients' BDNF levels were measured in CSF and/or serum. Failla *et al*.'s, 2015, study carried out measurements of both CSF and serum and was the only study to measure both.[5] A total of four studies measured CSF BDNF levels and serum BDNF levels, with 371 patients (41.73%) having CSF BDNF measurements and 518 patients (58.27%) having serum BDNF measurements. Sample measurement time ranged from 2 h to 1 week with two studies (Failla *et al*. and Munoz *et al*.) using weekly average BDNF levels.[5,13]

Demographic data and measurements of baseline conditions and patient outcomes in the literature included in this study are presented in a tabular summary in Table 2.

Measurement of BDNF levels in TBI patients

Measurement of BDNF levels in TBI patients conducted on patients in the seven literatures showed a difference between the trend of BDNF levels from CSF sources and serum sources. Each of these will be described below.

Measurement of BDNF CSF levels

BDNF CSF levels were reported in two of seven literatures, with the median CSF BDNF levels in the unfavorable group being 0.2365 (0.19–0.3119) ng/ml. The CSF BDNF level was higher than the median in the favorable group, which was 0.20585 (0.17–0.5526) ng/ml. The trend of lower CSF BDNF levels in the favorable group compared to the unfavorable group was also seen in reports from all four literatures reporting CSF BDNF levels, except in the 2009 Chiaretti *et al*. study which reported that lower CSF BDNF levels in the unfavorable group, but the results this was not statistically significant ($P = 0.37$).[3,5,13,18]

The results of the analysis of three other literatures stated that there was a tendency for lower CSF BDNF levels in the

Table 1: Summary of the studies included in the systematic review.

S. No.	Study (Author, Year)	Patient number	Age (median range)	Sex		Initial GCS (mean, range)	Outcome measurement (GOS, GOSE, Survival)	Patient number per group	Follow-up time	BDNF source	BDNF level (ng/ml)		Samples Taken Time (h)	Note
				M	F						Unfavorable	Favorable		
1.	Chiaretti *et al.*, 2009[3]	32	7.6 (1.3–15.6)	17	15	NM	GOS (unfavorable 1–3. favorable 4–5)	14 unfavorable: 18 favorable	6 mo	CSF	Not mentioned specifically, but shown in box plot charts: lower median in GOS≤3 (P=0.37)	Not mentioned specifically, but shown in box plot charts: higher median in GOS≥3 (P=0.37)	48 h	
2.	Di Battista *et al.*, 2015[4]	45.8±21.9	66	19		6.5±3.3	Survival, GOSE (unfavorable outcome 1–4. favorable 5–8),	50 unfavorable; 35 favorable 24 non survivors; 61 surVIVOrS	6 mo	serum	Not mentioned specifically; not significantly lower in unfavorable, significantly lower in died patient (P<0.05)	Not mentioned specifically, not significantly higher in favorable, significantly higher in lived patient (P<0.05)	24 h	
3.	Failla *et al.*, 2015[5]	202	37.7±16.3	163	39	7	Survival, GOS (died 1, unfavorable 2–3, favorable 4–5)	NM	6 mo	CSF	Died: 0.25+0.17 Unfavorable: not mentioned but significantly lower than died (P<0.05)	Not mentioned, not significantly lower than unfavorable (P>0.05), significantly lower than died (P<0.05).	Twice daily, Serum at 07.00 AM weekly average level used	Consistent lower CSF BDNF and higher serum BDNF in more favorable patients
										Serum	Died: 140.06+58.30 Unfavorable: not mentioned but not significantly higher than died (P=0.05), not significantly lower than favorable (P>0.05)	Not mentioned, not significantly higher than unfavorable and died (P>0.05)		
									12 mo	CSF	Died: 0.25+0.17 Unfavorable: not mentioned	Not mentioned, not significantly lower than		

(Contd...)

Table 1: (*Continued*).

S. No.	Study (Author, Year)	Patient number	Age (median range)	Sex		Initial GCS (mean, range)	Outcome measurement (GOS, GOSE, Survival)	Patient number per group	Follow-up time	BDNF source	BDNF level (ng/ml)		Samples Taken Time (h)	Note
				M	F						Unfavorable	Favorable		
											but not significantly lower than died (*P*>0.05)	unfavorable (*P*>0.05), significantly lower than died (*P*<0.05)		
										Serum	Died: 140.06+58.30 Unfavorable: not mentioned but not significantly higher than died (*P*>0.05), not significantly lower than favorable (*P*>0.05)	Not mentioned, not significantly higher than Unfavorable (p>0,05), significantly higher than died (*P*<0.05)		
4.	Korley *et al.*, 2016[18]	111	41, 42, 47	NM	NM	NM	GOS (favorable=8. unfavorable<8)	78 unfavorable; 33 favorable	6 mo	Serum	7.1 (2.8–13.0). not significantly lower (*P*=0.05)	7.9 (4.0–23.3) not significantly higher (*P*=0.05)	Within 24 h	Very low serum BDNF (14.2 ng/ml) Significantly associated with GOS<8 (OR 4.16; 95% CI 1.48–11.70)
5.	Munoz *et al.*, 2017[13]	117	36.16–74	99	18	7.6-7	Survival	26 non survivors; 91 survivors	6 mo	CSF	0.21±0.02, significantly higher (*P*<0.05)	0.18+0.01 significantly lower (*P*<0.05)	Twice daily D0-D6, mean used	Significantly lower CSF BDNF in favorable patients; significantly higher CSF BDNF in favorable patients found in 1st 24 h
6.	Simon *et al.*, 2015[7]	120	34.8±13.1	0	5.8±2.7	5.8±2.7	Survival	42 non survivors: 78 survivors	ICU stay (ICU mortality)	Serum	0.7116±0.0974. not significant (*P*<0.05)	0.7002=0.0828 not significant (*P*>0.05)	Within 12 h	
7.	Stefani *et al.*, 2017[18]	20	29.16–53	2	6.4–8	6.4–8	Survival	6 nonsurvivors; 14 survivors	3 days	CSF	0.2630 (0.2165–0.3119), not significantly higher (*P*>0.05)	0.2317 (0.1740–0.5526), not significantly lower (*P*>0.05)	2 h and 4 h	

GOS: Glasgow Outcome Scale, GOSE: Glasgow Outcome Scale Extended, BDNF: Brain-derived neurotrophic factor

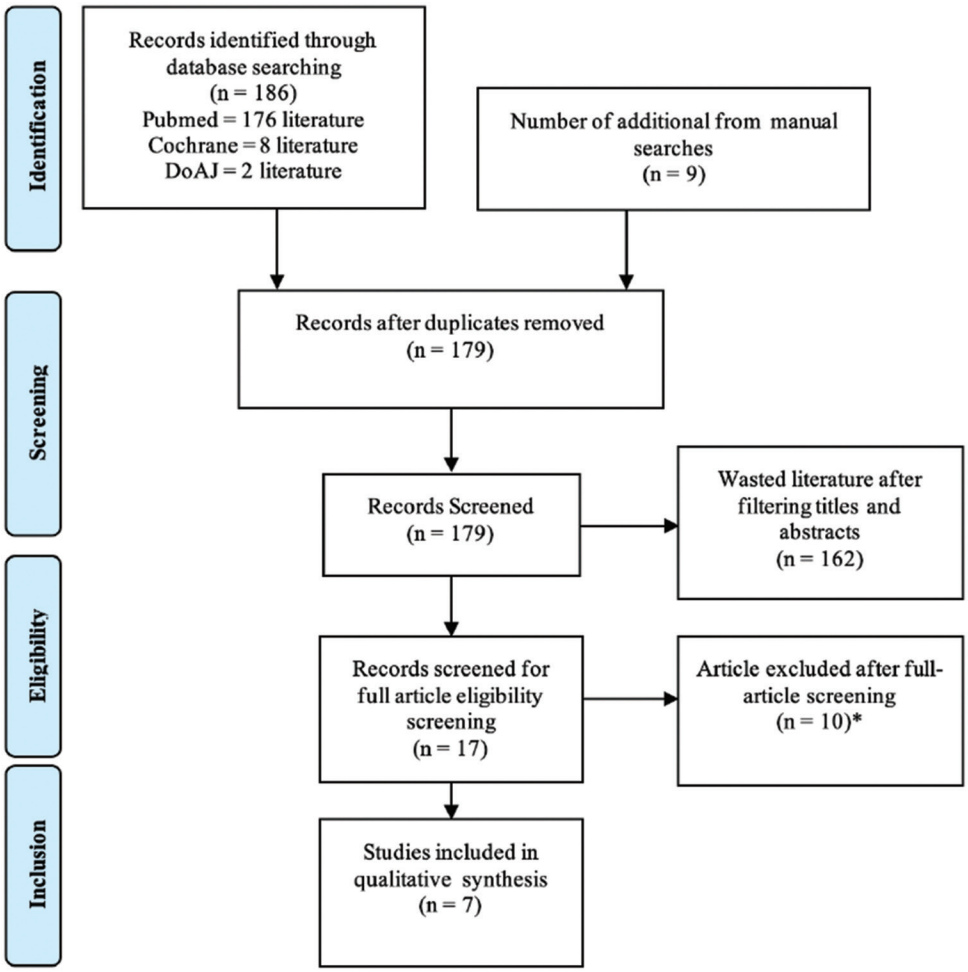

Figure 1: PRISMA guidelines flowchart.

favorable group. Studies by Failla *et al*. and Munoz *et al*. which obtained weekly average CSF BDNF levels showed significant results, meanwhile, a study by Stefani *et al*. taking CSF BDNF samples at 2 and 4 h posthospitalization demonstrated negligible findings.[5,13,18]

Measurement of serum BDNF level

Serum BDNF levels were reported in two of the seven literatures, with the median serum BDNF level in the unfavorable group being 3.9058 (0.6142–13.0) ng/ml. This serum BDNF level was lower than the median in the favorable group, which was 4.3 (0.6174–23.3) ng/ml.[8,17] The trend of lower CSF BDNF levels in the unfavorable group compared to the favorable group was also seen in reports from all six literatures reporting serum BDNF levels.[4,5,8,17]

The results of the analysis of four literatures reporting serum BDNF stated that there was a tendency for lower serum BDNF levels in the unfavorable group. This result was not significant between the unfavorable group and the favorable group, but significantly lower serum BDNF levels were reported in the nonsurvival group compared to the survival group in the 2015 study by Di Battista *et al*.[4] Failla *et al*., 2015, study also showed serum BDNF rates, which was significantly lower in the nonsurvival group than in the favorable group at month 12.[5]

Risk of bias

The risk assessment of bias for each study was carried out using ROBINS-I because all included studies were non-RCT studies. Overall the results of the risk analysis of bias were good, with the greatest risk of confounding bias and outcome bias. The results of the risk assessment of bias with ROBINS-I are shown in Figure 2.

DISCUSSION

This study was conducted by means of a systematic literature search of all literature that report assessing patients' BDNF levels and is associated with TBI patient outcomes. The literature study systematically produced seven literatures

Table 2: Summary of demographic characteristics and data from studies included in the systematic review.

Description		Measure (%)
Sample number	n	687 samples
Unfavorable	n	216 samples (44.5%)
Favorable	n	269 samples (55.5%)
Median age	Median (min–max)	36 years (1.3–74)
Sex		
Male	n	483 samples (83.85%)
Female	n	93 samples (16.15%)
Initial GCS	Median (min–max)	65 (32–8.8)
Outcome measurement		
GOS	n	Two studies
GOSE	n	Two studies
Survival	n	Five studies
Follow-up length	Median (min–max)	6 months (3 days–12 months)
BDNF Source		
LCS	n	371 samples (41.73%)
Serum	n	518 samples (58.27%)
Sample obtained timing	Range	2 h – weekly average
CSF BDNF level (ng/ml)		
Unfavorable	Median (min–max)	0.2365 (0.19–03119)
Favorable	Median (min–max)	0.20585 (0.17–0.5526)
Serum BDNF level (ng/ml)		
Unfavorable	Median (min–max)	3.9058 (0.6142–13.0)
Favorable	Median (min–max)	4.3 (0.6174–23.3)

GOS: Glasgow Outcome Scale, GOSE: Glasgow Outcome Scale Extended, BDNF: Brain-derived neurotrophic factor

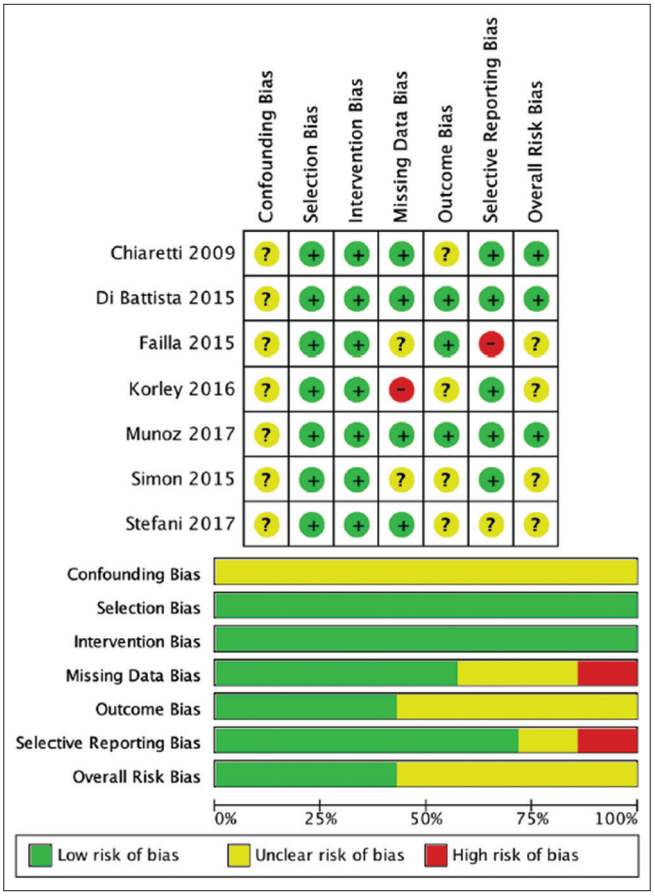

Figure 2: Figure Robins I Assessment.

which were used for qualitative analysis. BDNF can be used to predict the outcome of TBI patients, both from serum BDNF and CSF BDNF. BDNF levels can even be used to assess long-term outcomes and mortality up to 12 months after trauma.[5]

Because this test is still relatively unpopular, the ability to check BDNF is still not evenly distributed and there is no definite level number associated with the outcome in TBI patients, so this test is not routinely performed. Several studies are also still debating the benefits of this examination.[3,8,17,18] Therefore, the role of BDNF in predicting the outcome of TBI patients is interesting to discuss.

Demographics

The study of seven literatures resulted in a total of 687 patients. The median age obtained from this study was 36 years with the youngest age 1.3 years and the oldest 74 years. Six studies reported on the sex distribution of patients, for a total sample of 576 patients. Of these six studies, the majority of patients were male, that is, 483 (83.85%) patients, compared to 93 (16.15%) female patients. Various studies have revealed sex differences in TBI. They noted that the number of male patients was higher than that of women, due to the increased likelihood of injury in males, due to the high rates of traffic mobility and risky sports activities in males compared to females.[9,12]

All patients were generally divided into two groups based on the final outcome, namely, favorable and unfavorable. Six studies reported the number of patients per outcome group, for a total of 485.[3-5,8,17,18] The comparison of the number of patients in the two groups was fairly balanced with the total number of patients in the favorable group being 269 patients (55.5%) and the total number of patients in the unfavorable group being 216 patients (44.5%).

Confounding factors

Examination of BDNF levels to evaluate and estimate the outcome of TBI patients to date is an additional examination

that has not been routinely performed. Therefore, there are several things that confound this situation. First, the source and timing of BDNF collection varies greatly, depending on the health facility. Second, the method of assessing BDNF levels also varies greatly, depending on each health facility. Finally, the time of patient follow-up and assessment of patient outcomes also differed between studies, making it difficult to interpret the data homogeneously. The author realizes that these three factors act as confounding factors, so the discussion of these factors is carried out in this study.

Measurement of the patient's initial condition

Measurement of the patient's initial condition was carried out by measuring the initial GCS of the patient at the time of admission. The median baseline GCS was reported in five studies, with the overall median baseline GCS across the five studies being 6.5 (3.2–8.8). This is in accordance with the theory that BDNF is indeed more valued in severe brain injury, considering that in cases of mild and moderate brain injury, the BDNF number is not much different between favorable and nonfavorable patients.[4,5,13,17,18]

Patient outcome measurement

Measurement of patient outcomes was carried out by several methods and some studies used more than 1 outcome measure.

Five studies used survival as a measure of patient outcome. Several studies show that indeed, BDNF is more significant for showing survival outcomes than differ favorable and unfavorable outcomes.[4,5]

Patient outcome follow-up

The length of follow-up in seven studies was reported with certainty in six studies, and the other one study measured the length of stay in the intensive care unit/ICU. The median length of follow-up was 6 months (3 days–12 months). It seemed that studies which had longer than 6-month median follow-up would likely to show significant outcome compared to the one with shorter median follow-up.[4,5,13]

Measurement of BDNF levels in patients

Patients' BDNF levels were measured in CSF and/or serum. Failla *et al*.'s, 2015, study carried out measurements of both CSF and serum and were the only study to measure both. A total of four studies measured CSF BDNF levels and serum BDNF levels, with 371 patients (41.73%) having CSF BDNF measurements and 518 patients (58.27%) having serum BDNF measurements. Sample measurement time ranged from 2 h to 1 week with two studies using weekly average BDNF levels.[5,13]

Measurement of BDNF levels in TBI patients commonly uses CSF or serum samples. CSF BDNF levels tend to be low in favorable patients, and conversely, serum BDNF levels tend to be high in favorable patients.[5] It can be seen that significant findings were more prone to be found in studies which measure the average weekly BDNF levels. However, keep in mind that the assessment of BDNF levels in studies other than Failla *et al*. and Munoz *et al*. which showed significant results. BDNF was calculated in the early 24 h posttraumatic, except for Chiaretti *et al*. study.[3] This was explained in the study of Munoz *et al*. where it was initially hypothesized that, before the first 24 h, serum BDNF levels would be higher in the unfavorable group due to the acute stress response.[13]

The results of various studies show an increase in serum BDNF levels in the early phase and a decrease after 24 h in the unfavorable group due to the acute stress response which initially causes an increase in serum BDNF in severe TBI conditions in the first 24 h. Furthermore, an increase in autonomic function causes activation of the HPA axis, leading to a decrease in serum BDNF levels after 24 h.[5,13,15] In addition, this is because the transit of serum BDNF to the brain acutely after TBI causes a decrease in serum BDNF levels and an increase in CSF BDNF levels in unfavorable patients after 24 h posttraumatic.[5,13,15]

Measurement of BDNF levels in TBI patients

Measurement of BDNF levels in TBI patients conducted on patients in the seven literatures showed a difference between the trend of BDNF levels from CSF sources and serum sources. There was a trend of higher serum BDNF levels in the more favorable group and, conversely, the trend of lower CSF BDNF levels in the unfavorable group.[5,13] Each of these will be described below.

Measurement of CSF BDNF levels

BDNF CSF levels were reported in two of seven literatures, with the median CSF BDNF levels in the unfavorable group being 0.2365 (0.19–0.3119) ng/ml. This CSF BDNF level was higher than the median in the favorable group, which was 0.20585 (0.17–0.5526) ng/ml.[13,18]

The trend of lower CSF BDNF levels in the favorable group compared to the unfavorable group was also seen in reports from all four literatures reporting CSF BDNF levels, except for 2009 Chiaretti *et al*. study which reported on the contrary, lower CSF BDNF levels in the unfavorable group, but the results this was not statistically significant ($P = 0.37$).[3]

The results of the analysis of three other literatures stated that there was a tendency for lower CSF BDNF levels in the favorable group. Two studies from Failla *et al*. and Munoz *et al*. showed statistically significant results.[5,13] The study from Stefani *et al*. in 2017 showed insignificant results. The

sample measurement in this study is different from the study sample measurement by Failla *et al*. and Munoz *et al*. which took weekly average CSF BDNF levels, whereas Stefani *et al*.'s study took CSF BDNF samples at 2 and 4 h posttreatment.[18]

This is consistent with the theory that after severe TBI, there is a more significant disruption of the blood–brain barrier, causing an acute transfer of serum BDNF to the brain after TBI, leading to a decrease in serum BDNF levels and an increase in CSF BDNF levels in unfavorable patients.[5,13,15]

The insignificance of the results in some studies could be due to the delay required for the transfer of serum BDNF to the CSF within 24 h posttraumatic. In the study of Munoz *et al*., where it was hypothesized that, before the first 24 h, CSF BDNF levels could be lower in the unfavorable group because it takes time to transit from serum BDNF to the brain acutely after TBI causing a decrease in serum BDNF levels and an increase in CSF BDNF levels in unfavorable patients after 24 h posttrauma.[5,13,15]

Measurement of serum BDNF level

Serum BDNF levels were recorded in two of the seven studies, with the unfavorable group having a median serum BDNF level of 3.9058 (0.6142–13.0) ng/ml. This blood BDNF level was lower than the favorable group's median, which was 4.3 (0.6174–23.3) ng/ml.[13,18]

The pattern of decreased CSF BDNF levels in the unfavorable group compared to the favorable group was also evident in serum BDNF level findings from all four literatures. The results of the analysis of four literatures reporting serum BDNF stated that there was a tendency for lower serum BDNF levels in the unfavorable group. This result was not significant between the unfavorable group and the favorable group, but significantly lower serum BDNF levels were reported in the nonsurvival group compared to the survival group in 2015 Di Battista *et al*. study.[4] Failla *et al*.'s, 2015, study also showed significantly lower serum BDNF levels in the nonsurvival group than the favorable group at 12 months.[5]

The decrease in serum BDNF levels in the unfavorable group is thought to be due to an increase in autonomic function in patients with more severe conditions so that activation of the HPA axis causes a decrease in BDNF levels.[5,13,15] In addition, this is because the acute transfer of serum BDNF to the brain after TBI causes a decrease in serum BDNF levels and an increase in CSF BDNF levels in unfavorable patients.[5,13,15]

The insignificance of the results of the included studies could be due to the premature sampling time, the majority of which were within the first 24 h. According to the literature study, there is a delay required for the transfer of serum BDNF to the CSF within 24 h after trauma. In addition, in acute conditions, before 24 h, the response to acute stress results in an increase in serum BDNF first before a decrease in serum BDNF then because the increase in autonomic function in patients with more severe conditions causes activation of the HPA axis and suppresses BDNF levels.[5,13,15]

CONCLUSION

Serum BDNF levels were found to be lower in the unfavorable group than in the favorable group. This is associated with an increase in autonomic function as well as a breakdown of the blood–brain barrier which causes a decrease in serum BDNF levels. Conversely, CSF BDNF levels were found to be higher in the unfavorable group than in the favorable group. This is associated with an increase in the breakdown of the blood–brain barrier which facilitates the transfer of serum BDNF to the brain, leading to an increase in CSF BDNF levels.

Yet, serum BDNF and CSF levels have the potential to be outcome predictors in brain injury patients, especially those with severe conditions. Specific measurement methods and timing are required for the use of BDNF levels as predictors that can be widely used in everyday clinical practice.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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