International Journal of Research in Medical Sciences
Ate A et al. Int J Res Med Sci. 2023 Jan;11(1):289-301
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20223653

Meta-Analysis

Systematic review and meta-analysis of biomarker proinflammation of depression in traumatic brain injury

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Received: 29 October 2022
Accepted: 03 December 2022

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ABSTRACT

Depression is one of the long-term complications of traumatic brain injury (TBI) associated with the inflammatory process. This study aims to analyze the role of proinflammatory biomarkers on depression due to TBI and determine the types of proinflammatory biomarkers of depression in TBI. This systematic review and meta-analysis used the preferred reporting items for systematic reviews and meta-analyses (PRISMA) protocol with the population, intervention, comparison, outcome method. The selected research articles consisted of 4 cohort studies and 2 cross-sectional studies. Participants were all participants who experienced TBI without any previous infectious disease and neurobehavior disorders. Article searches are limited to the last 10 years using digital libraries including Pubmed, Science Direct, Wiley, Google Scholar. Assessment of the risk of bias using the ROBINS-1 tool, research quality using the GradePro application, and meta-analysis using review manager software 5.4.1. The results of a meta-analysis of proinflammatory biomarkers of depression using 2 cross-sectional studies showed a risk of bias and a moderate level of certainty. The most common types of proinflammatory biomarkers are IL-6, TNF-α, and IL-10. These proinflammatory biomarkers are markers of depression in TBI and have an effect on depression in TBI, especially in recurrent TBI and high post-traumatic stress disorder with depression accompanied by an increase in the concentration value of these biomarkers. Increased proinflammatory biomarkers IL-6, TNF-α, and IL-10 were found in depression with TBI. This proinflammatory biomarker has a significant relationship so that it can be used as a marker of depression in TBI.

Keywords: Depression in TBI, IL-6, IL-10, TNF-α

INTRODUCTION

Traumatic brain injury (TBI) is one of the biggest causes of death worldwide and can cause disability in human life and affect quality of life. A study conducted by James stated that in 2016, there were 27.08 million new cases of TBI with the prevalence rate increasing by 8.4% from 1990 to 2016. The incidence rate of TBI in developing countries is generally higher, such as in India 160 per 100,000. In Indonesia itself, the data from baseline health research (Riskesdas) showed that the proportion of head injuries was around 11.9% of the injured patient population. The incidence of head injuries in North Sulawesi based on Riskesdas data in 2018 reached 15.45% with a prevalence rate in the Manado of 20.08%.[1,2]

A study conducted by Mac Donald stated that depression in TBI was found at 6-12 months post-TBI correlated with the severity of TBI. A study conducted by Singh

showed that about 56% of the population experiencing TBI had depressive symptoms at 10 weeks post-injury. A study conducted by Lavoie explained that the risk of depression among individuals with traumatic brain injury was much higher than what was seen in the general population. Approximately 25-50% of people with TBI will develop major depression within the first year after TBI and more than 60% of people will develop it within 7 years of brain injury. The severity of the injury, number of injuries, age at injury, and other factors influence the relative likelihood of post-TBI depression, but only a few escape the risk that TBI may contribute to depression.[3,4]

Several meta-analytical studies that have been summarized in a number of research studies from O'Brien, Kohler, and Leighton that support the theory of inflammatory depression are correlative and depending on the presence of increased cytokines in the blood of individuals who experience depression compared to healthy controls. A meta-analysis by Kohler of 82 studies specifically showed that peripheral levels of many cytokines and chemokines, including IL-6 and TNF, were elevated in people with major depressive disorder compared with healthy controls. Studies from Howren, Dowlati, Haapakoski, Goldsmith, Köhler suggested that there was direct evidence of inflammation in depression from cross-sectional meta-analyses of inflammatory markers in depression. Inflammatory biomarkers that play a role are increased concentrations of C-reactive protein (CRP), interleukin 6 (IL-6), circulating interleukin-12 (IL-12) and tumour necrosis factor-α (TNF-α), and reduced interleukin-4 (IL-4) in acute depression.[5,6]

Research conducted by Juengst explained that overall levels of cytokines soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule-1 (sICAM-1), and soluble FAS (sFAS) were associated with significant increases in the risk of developing depression 6 months post-TBI. Another study showed that high IL-8 was obtained within 24-48 hours of post-TBI. There is evidence that IL-1 and IL-6 levels are elevated in the cerebrospinal fluid of patients with depression. Higher blood levels of C-reactive protein (CRP) compared to controls were found in depressed patients. There are studies showing that serum levels of brain-specific proteins, such as S100B, glial fibrillation acid protein, TAU protein, neurofilament light/NF-L and ubiquitin C-terminal hydrolase-L1 predict the presence of lesions in TBI and poor outcome post-TBI. High levels of CRP and IL-6 are observed as early biomarkers of cognitive symptoms of depression.[6-9]

Based on this background, it is known that there have been many studies related to proinflammatory biomarkers of depression in patients with traumatic brain injury, but there are still few data from systematic studies and meta-analyses regarding the significance of proinflammatory biomarkers of depression in post-traumatic brain injury patients. Researchers are interested in conducting research with this method to produce the latest medical scientific evidence.

METHODS

This study is a systematic study and a meta-analysis which is carried out regularly and logically according to the PRISMA protocol.[10,11] The inclusion criteria in this study were all participants who had TBI, without acute infectious diseases such as pneumonia, urinary tract infections (UTI), gastrointestinal infections, brain infections, and disorders of neurobehavior. This study uses a research design including cross-sectional, retrospective case-control, and prospective cohort studies that addressed or evaluated the association of proinflammatory biomarkers of depression in traumatic brain injury. The outcome of this study is a type of proinflammatory biomarker of depression in TBI. Diagnosis of depression with the diagnostic and statistical manual of mental disorders IV-V (DSM IV, DSM-V), Halminton questionnaire and patient health questionnaire-9 (PHQ-9), Montgomery-Asberg depression rating scale (MADRS), Beck depression inventory (BDI), Zung self-rating depression scale, Raskin depression rating scale, and diagnostic instruments used to diagnose depression in the local country. The research method used had the same research design as the biomarkers studied and the number of pro-inflammatory biomarkers that had been studied the most. The researcher included the research output, namely the type of pro-inflammatory biomarker for depression. Exclusion criteria in this study included research published in a symposium book or dissertation proceeding book that has not been published, population with co-morbidities such as infectious diseases and previous history of neurobehavior or depressive disorders.

RESULTS

The collection of research articles would be carried out through digital libraries including Pubmed/Medline, Willey Online Library, Science Direct, Google Scholar, and Neurona. The search for research articles was limited to the time of publication, namely the last 10 years between 2011-2021. The risk assessment of bias used the risk of bias in non-randomized studies-of interventions (ROBINS-1) tool and obtained 5 research articles with moderate risk of bias and 1 risk study with high bias. Assessment of research quality used the GradePro application. Meta-analysis studies were obtained in 2 cross-sectional articles because they had homogeneous data from the types of inflammatory biomarkers studied and same research design and calculation of results using review manager software 5.4.1 and research results were presented in the form of forest plots.[12-16]

An initial search yielded 8273 articles from Pubmed/Medline, Wiley Online Library, Science Direct, Google Scholar, and Neurona as well as 41 additional

manually identified articles. The number of duplicated articles were 63 articles. The number of excluded articles was 8222 so 29 articles were eligible for this research. Twenty-three articles were excluded because they did not meet the criteria, did not meet the outcomes, and did not meet the research design so that 6 studies that met the inclusion criteria were obtained, including 4 cohort studies and 2 cross-sectional studies.

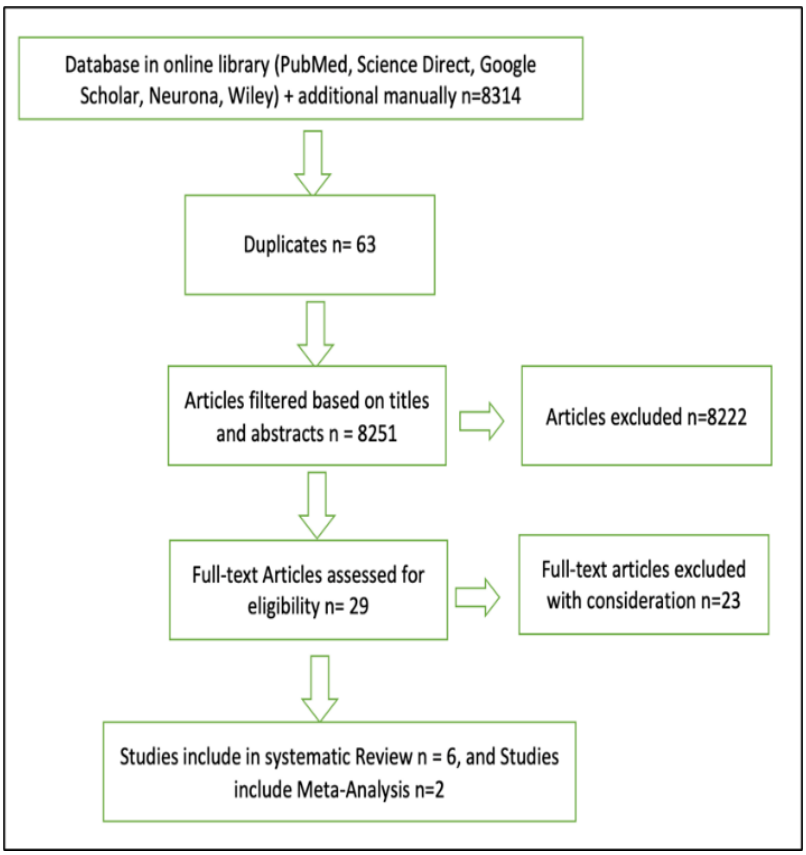

Figure 1: Literature selection process with PRISMA diagram.[11]

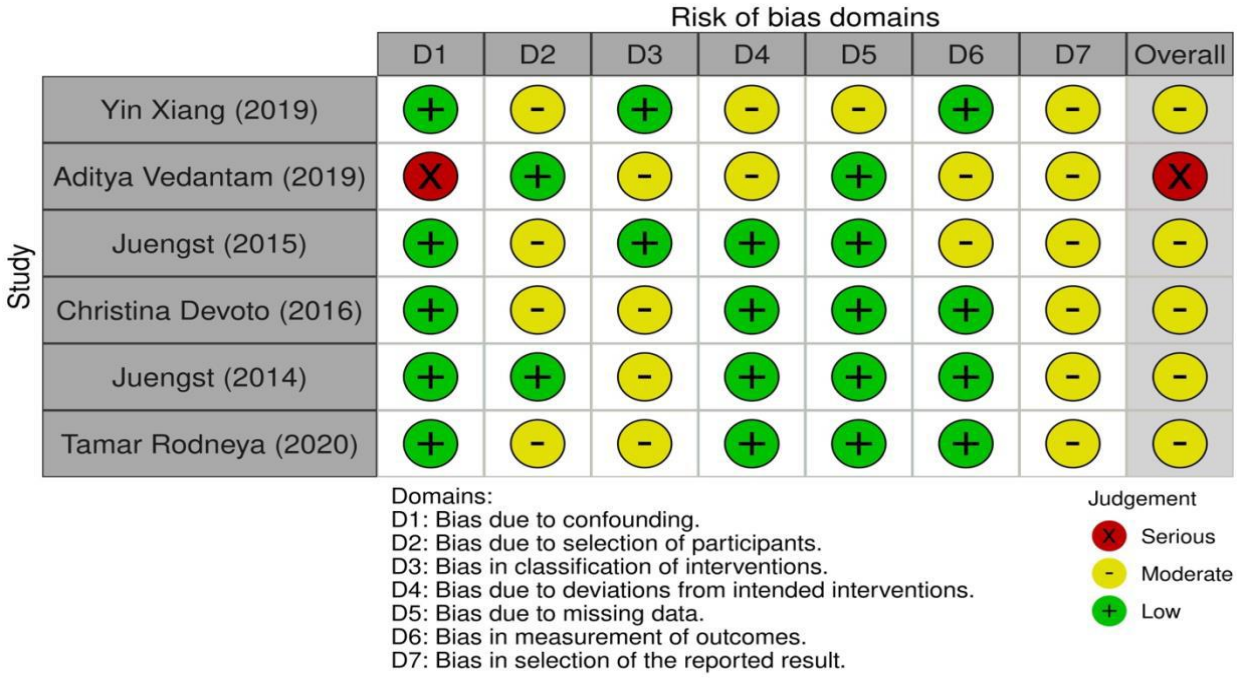

Figure 2: Summary of the risk assessment of bias in the study under study/inclusion.[13]

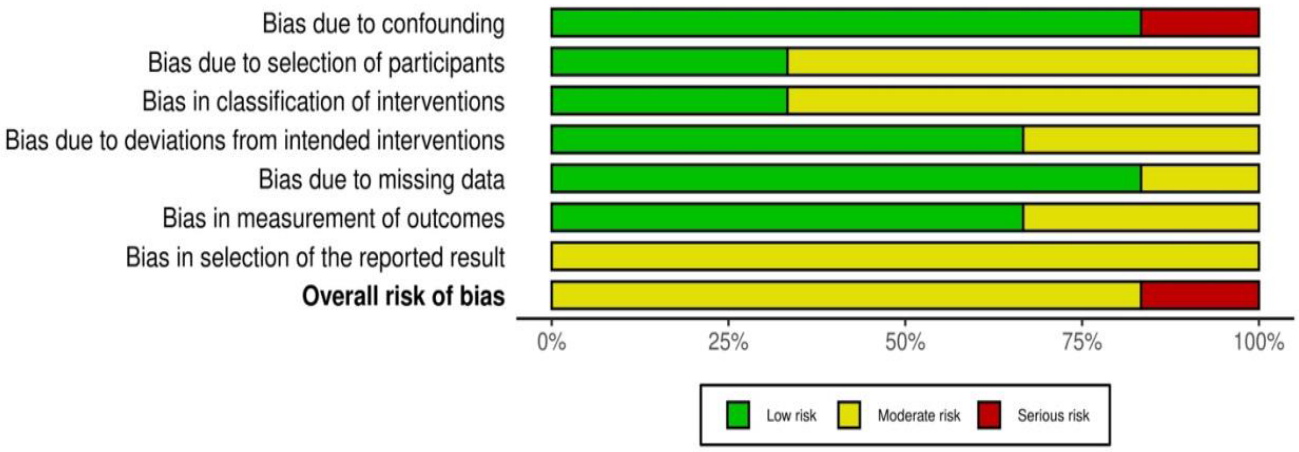

Figure 3: Bias risk assessment in research articles.[13]

Table 2: Inflammatory biomarkers conducted by research.[18-20,22-24]

Types of inspected biomarker	Percentages (%)	Reference study
Interleukin-1β	50	Xiang, Vedantam, Juengst
Interleukin-2	16.67	Vedantam
Interleukin-4	50	Xiang, Vedantam, Juengst
Interleukin-5	16.67	Juengst
Interleukin-6	100	Xiang, Vendatam, Juengst, Devoto, Tamar
Interleukin-7	16.67	Juengst
Interleukin-8	33.3	Xiang, Juengst
Interleukin-10	100	Xiang, Vendatam, Juengst, Devoto, Tamar
Interleukin-12p70	16.67	Vedantam
Interleukin-17a	16.67	Vendantam
Interferon β	33.3	Xiang, Vedantam
Tumor nekrosis α	100	Xiang, Vendatam, Juengst, Devoto, Tamar
sVCAM-1	16.67	Juengst
sICAM-1	16.67	Juengst
sFAS	16.67	Juengst
CCL2	16.67	Xiang
CXCL8	16.67	Xiang
Interleukin-12	33.3	Xiang, Juengst

The systematic study used 6 research articles that met the inclusion criteria, then after conducting a systematic review, there were four research articles that could not be meta-analyzed because of the inhomogeneous examination of proinflammatory depression biomarkers and different research designs. The meta-analysis research carried out 2 research studies. This is due to the fact that this study used the most studied inflammatory biomarkers, namely IL-6, IL-10 and TNF-a with a cross-sectional design.

This study obtained 6 research articles based on inclusion criteria and there were 459 individuals who participated and 161 individuals as controls. All studies that met the inclusion criteria were primary studies with 4 prospective cohort study designs and 2 cross-sectional designs. The study was conducted in the USA (4 studies), China (1 study), and England (1 study) with a time span of 2014-2020. The average age of the study sample was 16-70 years, although the distribution of the number of distributions was uneven according to the characteristics of the study.

Types of traumatic brain injury in this study were divided into the categories of mild brain injury, moderate brain injury, and severe brain injury. Minor brain injury was assessed by GCS 13-15 in the studies conducted by Xiang and Vedantam with onset 24 hours post-TBI. Moderate brain injury and severe brain injury were assessed with an GCS of less than 12 in the studies conducted by Juengst (2014 and 2015 with a 24-hour onset of head injury. The studies conducted by Devoto et al and Tamar (2020) did not mention the type of brain injury. but the sample used was every individual who worked in the military who had a history of previous head injury with onset of 16 months and 13.09 years, respectively, before the study was conducted.[17-22]

Table 1: Characteristics of research studies.[18-20,22-24]

Article title	Researcher, year, country	No. of samples	TBI type	TBI onset	Depressed sample	Research design	Types of biomarkers	Measurement time	Depression diagnostic instrument	Outcome
Elevated C-reactive protein levels may be a predictor of persistent unfavorable symptoms in patients with mild traumatic brain injury: A preliminary study	Xiang, 2019, China	95	Mild	7 days	95	Cohort	IL-1 ß, IL-6, IL-12, IL-4, IL-10, CCL2 (MCP-1), chemokine CXC (CXCL8) IL-8, interferon-ß(IFN- ß); and TNF- α	Onset 7 days after TBI and re-measured at 1 month and 3 months	TMT A, digit span, digit symbol coding, fluency language	Serum levels of IL-1B, IL-6, and CCL2 were acutely elevated in patients with mild TBI compared with controls; CCL2 levels remained high for 3 months whereas IL-1B and IL-6 levels decreased 3 months post-injury. High CCL2 levels were associated with greater severity of post-concussion symptoms (which persisted in multiple test corrections); elevated IL-1ÿ was associated with poorer working memory in the acute phase (which failed to correct); and acutely high CCL2 levels predict higher information processing speed at 3 months post-injury (which failed to correct)
Early versus late profiles of inflammatory cytokines after mild TBI and their association with neuropsychological outcomes	Vedantam, 2019, England	104	Mild	24 hours	53	Cohort	IL-1 ß, IL 2, IL-4, IL-6, IL-10, IL12p70, IL-17, IFN ß, and TNF-α	24 hour onset continued 6 months later.	Verbal selective reminder test (VSRT), digit-symbol modality test (SDMT), Rivermead post-concussion symptoms questionnaire (RPCSQ), post-traumatic stress checklist-civil form (PCL-C),	Plasma IL-2 (p=0.01) and IL-6 (p=0.01) at twenty-four hours post-injury were significantly higher for patients with mild TBI compared to OI controls. High plasma IL-2 at twenty-four hours is associated with 1-week post-concussion more severe symptoms (p=0.001). At six months an increase in the plasma IL-10 is associated with depression scores (p=0.004) and more severe post-traumatic stress disorder (PTSD) symptoms (p=0.001). The plasma cytokine levels (within twenty-four hours as well as the six months after injury) significantly associated with the early and late post-concussion symptoms, PTSD, as well as the depression scores after mild TBI.

Continued.

Article title	Researcher, year, country	No. of samples	TBI type	TBI onset	Depressed sample	Research design	Types of biomarkers	Measurement time	Depression diagnostic instrument	Outcome
Acute inflammatory biomarker profiles predict depression risk following moderate to severe traumatic brain injury	Juengst, 2015, USA	50	Medium and severe	24 hours	34	Cohort	IL-1 ß, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, and TNF- α, sVCAM-1, sICAM-1, and sFAS.	24 hour onset then continued for the first 1 week post-TBI then continued at 6 months and 12 months	PHQ 9 and DSM IV	Serum cohort (n=50) didn't differ significantly from CSF cohort. Higher levels of acute CSF cytokine surface markers (sVCAM-1, sICAM-1, and sFAS) in inflammatory biomarker risk score (IBR) were associated with a 3,920-fold increase in likelihood of developing PTD at 6 months (95% CI: 1,163 -8,672). Having sICAM-1, sVCAM-1, or sFAS above 75th % had positive predictive value of 85.7%-PTD risk at 6 m. IBR scores including inflammatory biomarkers IL-7 and 8 showed trend association with 12-m PTD risk (OR=3.166, 95% CI: 0.936-10.708)
Inflammation relates to chronic behavioral and neurological symptoms in military personnel with traumatic brain injuries	Devoto, 2016, USA	63	Not explained for the type of TBI	16 months after injury	50 samples	Cross sectional	TNF- α, IL-6, and IL-10	Collected one time check	Check PTSD military version, symptoms of depression quick inventory, SF-36, WARCAT	Concentrations of IL-6 and TNF-α greater in TBI group compared to the control group. Of those with TBI, IL-6 and TNF- conc. greater in high PTSD group than in low PTSD group. No significant difference found in ratio IL-10/IL-6/IL 10 between those with low and high PTSD. Exploratory factor analysis carried out to describe latent structure of variables related to emotional and physical health (i.e., short form sub-components 36, etc.) and their association in TBI group with inflammatory cytokines. Four symptom profiles found, with 3rd component most associated with PTSD and high levels of depressive, inflammatory symptoms. Study shows comorbidity of TBI and PTSD associated with inflammation in military samples, emphasizing need for interventions to reduce risk associated with inflammation

Continued.

Article title	Researcher, year, country	No. of samples	TBI type	TBI onset	Depressed sample	Research design	Types of biomarkers	Measurement time	Depression diagnostic instrument	Outcome
Exploratory associations with tumor necrosis factor-a, dis-inhibition and suicidal endo-rsement after traumatic brain injury	Juengst, 2014, USA	74	Medium and severe	24 hours post-injury	27 samples with characteristics of 13 patients with onset of the first 6 months, and 14 patients with onset of 12 months	Cohort	TNF- α, IL-6, and IL-10	Collected 24-hour onset continued for the first 1 week then continued every 2 weeks for 6 months and 12 months	PHQ 9 and DSM IV	Participants with TBI had significantly higher serum CSF and TNFa levels than healthy controls ($p<0.05$). Acute and chronic serum TNFa was significantly associated with disinhibition at 6 months post-injury ($p=0.009$, $p=0.029$ respectively), and 6-month disinhibition was associated with suicidal support at 6 and 12 months ($p=0.045$, $p=0.033$ each) and disinhibition at 12 months post-injury ($p<0.001$).
High IL-6 in military personnel relates to multiple traumatic brain injuries and post-traumatic stress disorder	Tamar, 2020, USA	73	Not explained the type of TBI	13 years after injury	48 samples	Cross sectional	TNF- α, IL-6, and IL-10	Collected one time check	Posttraumatic stress disorder checklist - civilian version (PCL-C), combat exposure scale (CES), PHQ 9.	The primary outcomes were serum levels of inflammation-associated proteins TNF-, IL-6 and IL-10, history of TBI, and symptoms of PTSD. The mean IL-6 concentration significantly higher in the recurrent TBI group compared with those with 1-2 TBI or no history of TBI ($p=0.050$). In addition, for participants with a history of TBI, PTSD symptom severity, in particular, intrusion ($p=0.006$ and $p=0.007$) and avoidance ($p=0.034$ and 0.009), were significant predictors of higher IL-6 and IL. -10 concentrations each. These findings suggest that recurrent TBI along with high PTSD symptoms in military personnel and veterans is associated with chronic inflammation, and in particular elevated IL-6 concentrations. Examining changes in the inflammatory process can identify potential therapeutic targets for early intervention after TBI to prevent the development of neurologic deficits and disorders.

The risk assessment for bias in the six studies that counted as inclusion criteria was that they had a high risk of bias in the Vedantam study because the samples used were not followed according to the inclusion criteria and included samples with comorbidities such as infectious diseases into the inclusion criteria.[18] Other 5 studies had a moderate risk of bias due to small sample size.

The research quality assessment was evaluated using Gradepro software with a narrative format with overall analysis results on all selected research articles. The assessment of the risk of bias in the six outputs had a moderate risk because the research design had been carried out according to the inclusion criteria and the output assessment was evaluated with standardized objective tools, but the weakness was that the number of samples carried out by the study was still small, so we judged that the risk of bias is moderate.

META-ANALYSIS OF PROINFLAMMATORY BIOMARKERS OF DEPRESSION IN TBI

The meta-analysis in this study was drawn from 2 studies with a cross-sectional design. Both of these studies are correlation studies with the aim of finding the relationship between inflammatory biomarkers and depression in traumatic brain injury. This had been done by selection from inclusion criteria so that from the six research articles, two studies obtained that have the same examination of proinflammatory depression biomarkers, namely tumor necrosis alpha, interleukin-6, and interleukin-10. Diagnosis of depression in Devoto study used PCL-C (PTSD checklist-civilian) questionnaire tools, quick inventory of depressive symptomatology, and quality of life using the short from survey instrument-36 (SF-36) questionnaires. Study Tamar using PCL-C, PHQ-9, and combat exposure scale tools.

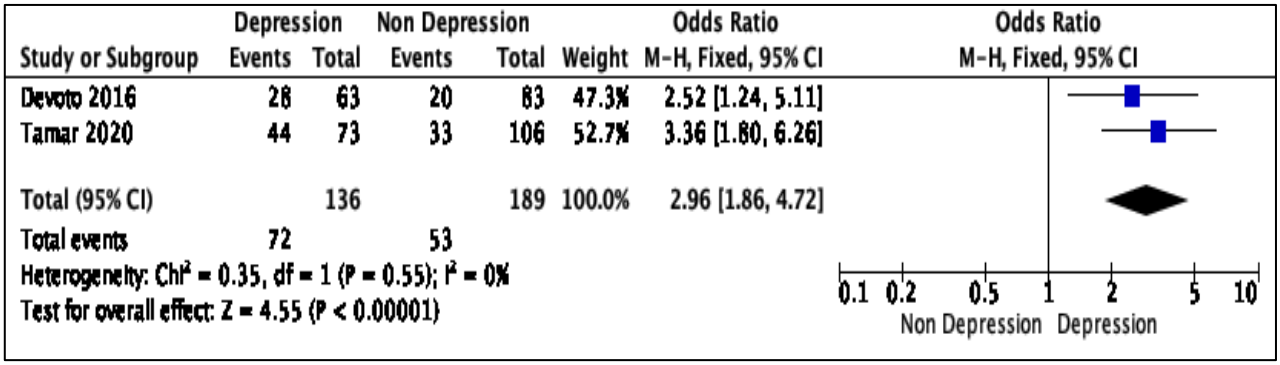

Figure 4: Forest plot results of meta-analysis of interleukin 6 proinflammatory biomarkers in recurrent TBI and post-TBI depression.[16,25]

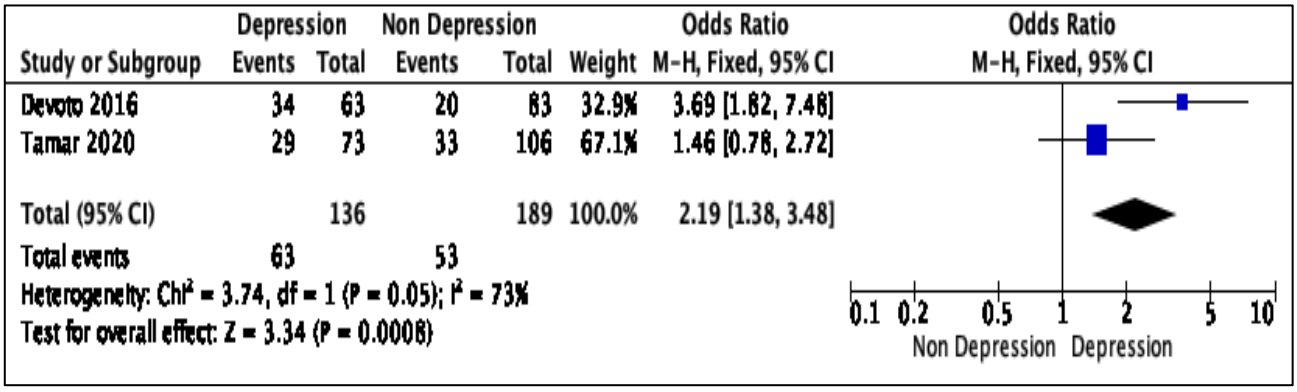

Figure 5: Forest plot results of meta-analysis of interleukin 6 proinflammatory biomarkers in non-recurrent TBI and post-TBI depression.[16,25]

The Devoto et al study showed that there was a 2.52-fold effect between the IL-6 biomarker on depression in cases of severe PTSD.[19] The number of samples who experienced depression were seven individuals. The value of IL-6 concentration increased significantly in cases of TBI with severe PTSD with the average value of IL-6 concentration in high PTSD was 4.08 pg/mL while in mild PTSD it was 1.94 pg/mL. Tamar's study (2020) showed that there was a 3.36-fold effect between the IL-6 biomarker on recurrent TBI and in this study, the number of samples experiencing depression was 36 participants. The value of IL-6 concentration was significantly increased in cases of recurrent TBI compared to non-recurrent TBI. Repeated TBI had an IL-6 concentration value of 2.65 pg/mL and non-repeated TBI was 1.58 pg/mL. When the meta-analysis was performed, the odds ratio was 2.96 with $p<0.00001$ which had a significant

relationship between IL 6 and depression in traumatic brain injury, in this case, in cases of severe PTSD and repeated TBI, number of participants who experienced depression was 36. Individuals in the Tamar study and in the Devoto study were found to be depressed. Both studies homogeneous and there was no heterogeneity.

The Devoto et al study showed that there was a 3.69-fold effect between the IL-6 biomarker on depression in cases of mild PTSD. Tamar's study (2020) showed an OR value of 1.46 and touched the graph number 1, meaning that there was no significant relationship between IL 6 to depression in non-recurrent TBI cases. The number of samples who experienced depression in non-repetitive brain injury was 12 participants. At the time of meta-analysis, the OR was 2.19 with 95% CI in the range 1.38-3.48 with p=0.00008 which had a significant relationship between IL-6 and depression in traumatic brain injury. The Tamar study showed that there were 12 samples of depressed patients and Devoto's study showed that there were depressed patients in mild PTSD cases. Both studies showed a high heterogeneity of 73%.[19]

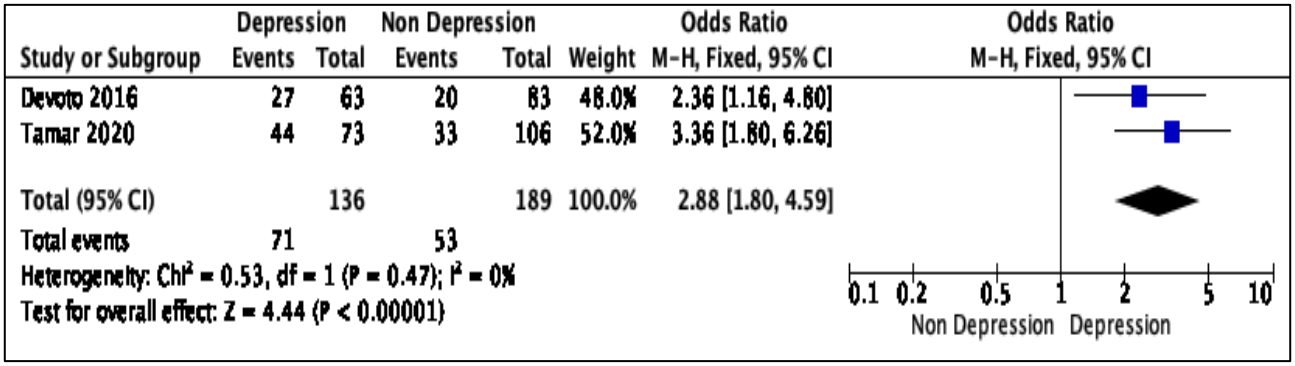

Figure 6: Forest plot results of meta-analysis of TNF-α proinflammatory biomarkers in recurrent TBI and post-TBI depression.[16,25]

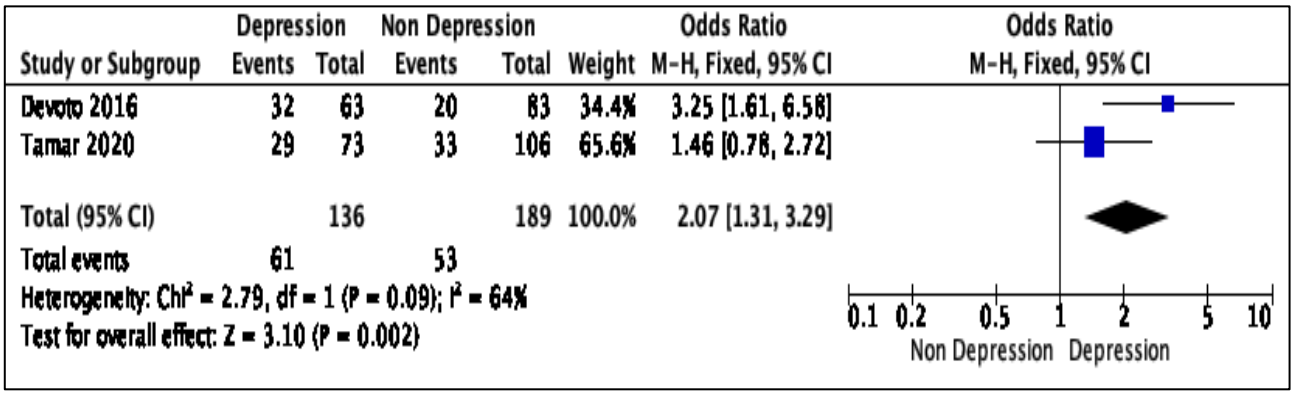

Figure 7: Forest plot results of meta-analysis of TNF- α proinflammatory biomarkers in non-recurrent TBI and post-TBI depression.[16,25]

The Devoto et al study showed that there was a 2.36-fold effect between TNF-α biomarkers on depression in cases of mild PTSD after traumatic brain injury.[19] The value of TNF-α concentration increased significantly in severe PTSD compared to mild PTSD, namely the average value of TNF-α concentration in high PTSD was 2.36 pg/mL. Tamar's study showed an OR value of 3.36 and did not touch the graph number 1, which means it had a significant relationship between TNF-α on depression in recurrent TBI cases with the number of samples experiencing depression was 36 samples. The value of TNF-α concentration increased significantly in repeated TBI compared to non-recurrent TBI, namely 5.26 pg/mL in repeated TBI and 5.08 pg/mL in non-repetitive TBI. This shows that, in cases of repeated TBI, it can cause depression, as seen in the results of a significantly increased TNF-α biomarker in repeated TBI compared to repeated TBI. Although in non-recurrent TBI there was an increase in the TNF-α biomarker, it was not significant in the case of recurrent TBI. When meta-analysis was performed, the OR value was 2.88 with 95% CI in the range 1.80-4.59 with p<0.00001 which had a significant relationship between TNF-α and depression in traumatic brain injury, in this case, severe PTSD and recurrent TBI. Both of these studies showed homogeneous results and did not have heterogeneity.

The Devoto et al study shows the OR value of 3.25 and did not touch the graph number 1 which means that there was a 3.25-fold effect between the TNF-α biomarker on depression in cases of mild PTSD. Tamar's study showed an OR value of 1.46 and touched the graph number 1,

which means that there was no significant relationship between TNF-α and depression in non-recurrent TBI cases. When meta-analysis was performed, the OR was 2.07 with 95% CI in the range 1.31-3.29 with p=0.002 which had a significant relationship between TNF-α and depression in traumatic brain injury. These two studies had a high heterogeneity of 64%.

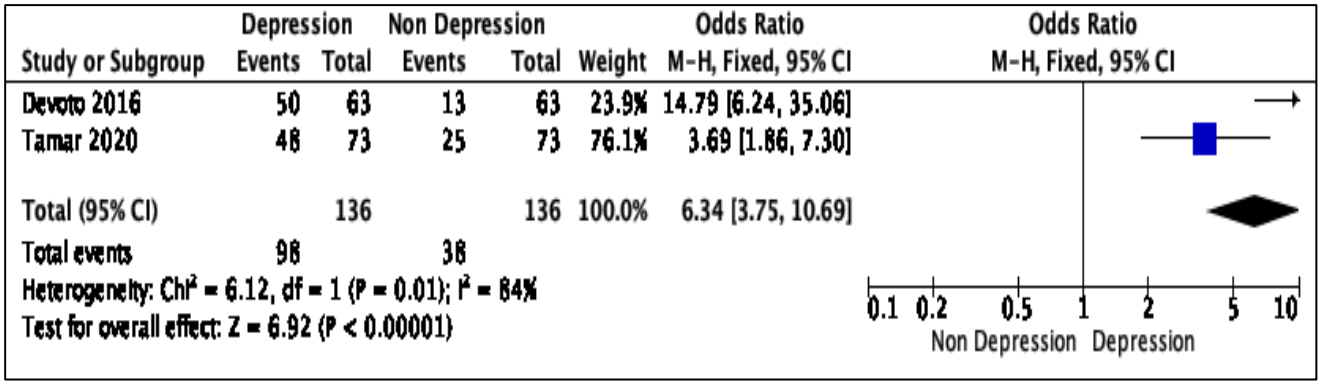

Figure 8. Forest plot results of meta-analysis of interleukin-10 inflammatory biomarkers and post-TBI depression.[16,25]

The IL-10 biomarker in these two studies showed a significant relationship to the proinflammatory biomarker of depression in TBI because it did not cut the number 1. IL-10 is one type of anti-inflammatory biomarker. When performed meta-analysis showed significant or significant results of proinflammatory biomarkers of depression in traumatic brain injury. The Devoto et al study which examined the IL-10 biomarker showed the OR value was 14.79 with a total of 50 samples experiencing depression, namely a combination of severe PTSD and mild PTSD, because there was no significant difference in increasing the IL-10 biomarker value. This value indicated that IL-10 had a 14.79-fold effect on depression in TBI. While the Tamar Study (2020) was not different from the Devoto et al study that showed a significant relationship to the proinflammatory biomarker of depression in TBI with an OR value of 3.69 and 48 individuals as the number of samples experiencing depression, that is a combination of samples experiencing repeated TBI and TBI not repeated that did not have a significant difference to the increase in IL-10.[19]

When a meta-analysis was carried out, it had a significant relationship with proinflammatory biomarkers of depression in TBI with an OR value of 6.34 which indicated that IL-10 had a 6.34-fold effect on depression in TBI. However, these two studies on the IL-10 biomarker had a fairly high heterogeneity with a value of 84%. The total value of effect size in these two studies on IL-10 biomarker was p<0.00001 so it had a significant relationship with IL-10 biomarker on depression in TBI.

DISCUSSION

Traumatic brain injury can lead to complications of cognitive and neuropsychiatric dysfunction that are directly related to inflammatory process. One of the long-term complications that can arise from TBI is depression which has an impact on quality of life of each individual. Cytokine elevations can be seen in populations experiencing post-TBI depression. Levels of inflammatory cytokine biomarkers may increase hours, days, after injury and may rise above physiological levels in months to years' post-TBI. Higher cytokines are associated with severity of head injury which can have adverse impact on cognitive function and neuropsychiatric disorders.

This research is secondary research that has included 6 observational studies for systematic study. A systematic review of this study involved 459 individuals and found that there was an association between inflammatory biomarkers of depression in traumatic brain injury compared with controls. This study shows that depression occurs in the traumatic process although depression can also occur in the non-traumatic process. The inflammatory response to TBI is triggered by brain tissue damage and involves activation of microglia, astrocytes, and peripheral inflammation. Elevated inflammatory biomarkers were elevated at 3 months post-TBI and suggest that low-grade systemic inflammation persists even in mild cases of TBI.

This meta-analysis was conducted in two cross-sectional studies with the inflammatory markers TNF-α, IL-6, and IL-10. Proinflammatory biomarkers TNF-α and IL-6 had a correlation with depression in traumatic brain injury. Research conducted by Devoto et al used a sample of 63 military officers who had a history of previous TBI with onset 16 months ago.[19] The 50 people experienced symptoms of PTSD which included symptoms of depression. The 28 people had mild PTSD and 22 people had severe PTSD. It showed that IL-6 and TNF-α concentrations were greater in severe PTSD group. The research conducted by Tamar was conducted on research samples that had a history of TBI since 13.09 years ago. The number of samples experiencing non-recurrent TBI was 29 individuals and number of samples experiencing recurrent TBI 44 individuals. A history of sustained TBI

associated with high inflammation in military personnel with comorbid PTSD and, to lesser extent, depression and comorbidity. Recurrent TBI had significantly more depressive symptoms than non-recurrent TBI.

The biomarkers IL-6 and IL-10 were significantly positively correlated with impaired PCL as well as with symptom of avoidance. Elevations of IL-6 and IL-10 were not significantly associated with mood. In addition, the age factor also affected the increase in biomarkers, especially at an older age. Meanwhile, TNF was not significantly associated with any of the PCL symptom groups. While the results of the meta-analysis showed an association between proinflammatory biomarkers of depression and traumatic brain injury. Repeated TBI was associated with an increase in inflammatory cytokines, especially an increase in IL-6 compared to non-recurrent TBI or no history of TBI. This study showed that PTSD symptoms are associated with higher levels of IL-6. Inflammatory activity was associated with a greater risk for PTSD symptoms. Higher IL-6 and IL-10 concentrations were associated with increased PCL and symptom of avoidance. These findings indicated that the inflammatory activity of IL-6 and IL-10 is associated with severity of PTSD symptoms, suggesting that there is a specific impact of inflammation experienced and can be used as a diagnosis in someone with a history of exposure or brain injury. Symptoms of PTSD include symptoms of depression so that it can be used as an association between depression and traumatic brain injury.

The meta-analysis of non-recurrent TBI and mild PTSD cases had high heterogeneity in the biomarkers of IL-6, TNF-a, and IL-10. These two studies carried out the examination of inflammatory biomarkers with different onset even though the types of biomarkers used were the same. The Devoto et al study had a history of traumatic brain injury of 16 months while the Tamar study had a history of 13.09 years of traumatic brain injury. In addition, the method of diagnosing depression in the two studies was different. These two studies had a similar sample of a military soldier. This is the reason why these two studies had a high heterogeneity value.

Chronic activation of the immune system in chronic TBI provides a possible relationship with inflammation-related comorbidities related to TBI. It can cause chronic inflammation which leads other complications, one of which is depression. The consequences of chronic inflammation on neuronal function can result in nerve loss and can contribute to the long-term maintenance of behavioural symptoms. Chronic inflammation can increase the permeability of the blood brain barrier, increasing the risk of decreased mood and cognitive function as well as neurodegenerative processes.[19,20,26]

There is evidence that overactivity of inflammatory cytokines such as IL-6 and TNF-α in the central nervous system leads to overactivation of microglia, destruction of uninjured neurons and overall loss of neurons. Excessive activation of central inflammation contributed to neuronal changes associated with altered functioning of neuroendocrine system that compromises nerve health. Significantly higher TNF-α concentrations are associated with lower hippocampal volumes suggesting association between inflammation and neuronal damage.[27-29]

A study conducted by Nishuty showed that patients who are depressed will have an increase in the inflammatory biomarker IL-6 compared to CRP and also in cases of depressed patients who are resistant to antidepressant drugs showing the same thing. Nishuty's research in cases of depression showed an increase in IL-6 concentration of 2.94 pg/mL. A study conducted by Miranda et al showed that the level of IL-6 increased in cases of depression with an average of 1.75 pg/mL compared to normal subjects with an average value of 0.2 pg/mL. Studies conducted by Tao showed that level of IL-6 increased in cases of depression with an average value of 2.06 ng/L. Several of these studies had the same correlation with this study that patients with depression would experience IL-6 biomarker concentration values. A meta-analysis study conducted by Dowlati et al stated that depressed subjects will increase the concentration of IL-6 with an average value of 1.23-2.33 pg/mL while in TNF-α there will be an increase in concentration with an average value of 3.97 pg/mL with a range of values 2.24-5.71 pg/mL. A study conducted by Lindqvist stated that the concentration of IL-6 biomarker increased in the depression group with an average value of 0.35 pg/mL and an increase in the concentration of the biomarker TNF-α with an average value of 2.75 pg/mL.[26,29-31]

Both of these studies showed the same concentration of IL-,6, TNF-α, and IL-10 values in depressed patients with traumatic brain injury. The increase in the concentration of these biomarkers is related to the HPA-axis which is activated by the inflammatory response system, thus will then affect corticotroropin and adrenocorticotropic hormones, thereby increasing the turnover of catecholamines and serotonin. On the other hand, in response to immune activation, pro-inflammatory cytokines is produced by T cells, NK cells and macrophages to regulate the inflammatory response system. This is what causes an increase in concentration of depressive inflammatory biomarkers in traumatic brain injury.[30,32,33] Differences in inflammatory biomarker concentrations could be due to the different onset of TBI in 2 studies and sampling techniques. Tamar's study took serum that processed within 90 min of blood collecting process, frozen at -80°C, and stored until analyzed using an immunosorbent assay. Devoto study took serum into ethylenediaminetetraacetic acid tubes and frozen at -80°C with average sample collection time of 1 hour 54 min.[19]

CONCLUSION

Inflammatory biomarkers TNF-α, IL-6, and IL-10 have a significant relationship in depressed patients with TBI, especially in cases of recurrent TBI and high PTSD with

depression compared to cases of non-recurrent TBI and low PTSD with depression. Concentrations of TNF-α and IL-6 biomarkers are significantly increased in recurrent TBI and high PTSD with depression. IL-10 biomarker does not have significant difference in recurrent and non-recurrent TBI and high and low PTSD with depression.

ACKNOWLEDGEMENTS

Authors would like thank to department of neurology especially in neurobehavior division, Sam Ratulangi university, Manado, North Sulawesi, Indonesia for facilitating this research.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Ate A, Wariki W, Warouw F, Pertiwi JM. Systematic review and meta-analysis of biomarker proinflammation of depression in traumatic brain injury. Int J Res Med Sci 2023;11:289-301.