



Neutrophil-to-lymphocyte Ratio and Platelet-to-lymphocyte Ratio Correlations with C-reactive Protein and Erythrocyte Sedimentation Rate in Traumatic Brain Injury

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Abstract

BACKGROUND: Immune system and inflammatory response play an essential role in the development of secondary brain injury (SBI) after traumatic brain injury (TBI). An inflammatory biomarker that can reflect the SBI severity is needed to increase the effectivity of TBI management and prevent morbidity and mortality post-TBI. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which are more affordable than C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), theoretically have the potential to be used as a marker of the SBI severity. However, NLR and PLR in daily medical practice are not yet fully utilized.

AIM: The aim of the study was to correlate NLR and PLR with CRP and ESR as a marker of SBI severity post-TBI.

METHODS: This cross-sectional study was conducted at Sanglah Hospital Denpasar from January to April 2020. Patients diagnosed with TBI were included in this study by consecutive sampling. The blood samples were taken at 24-h post-TBI to obtain the NLR, PLR, CRP, and ESR results. Spearman's correlation test was conducted to determine the correlation between NLR and PLR with CRP and ESR.

RESULTS: Eighty-five patients were included in data analysis. Median \pm (interquartile range) of the NLR, PLR, CRP, and ESR were $7.60 \pm (6.83)$, $145.58 \pm (76.95)$, $60.83 \pm (66.3)$, and $12.50 \pm (13.85)$ consecutively. NLR and PLR had a significant positive correlation with CRP ($r = 0.472$, $**p < 0.01$; $r = 0.283$, $**p < 0.01$ consecutively). But, NLR and PLR were not correlated with ESR.

CONCLUSION: NLR and PLR can become a useful and more affordable marker for reflecting the SBI severity in acute TBI.

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Introduction

Traumatic brain injury (TBI) is a type of injury that becomes one of the leading causes of global morbidity, mortality, and socio-economic burden [1], [2], [3]. TBI caused by direct external mechanical force to the cranium and its intracranial components, causing disruption to the brain structure and function, which can be temporary or permanent [4]. There are two pathologic processes that occur in TBI [5]. The first is primary brain injury, which caused by mechanical force exposure to the brain tissue, causing axonal, glial cells, and vascular damages of the brain tissue [5], [6]. Those damaged brain cells then can initiate the second pathologic process in TBI by releasing various inflammatory factors and neurotransmitters that can initiate and develop the inflammatory cascade, thus causing neuroinflammation and aggravate the brain injury, which called secondary brain injury

(SBI) [6], [7], [8], [9], [10], [11], [12], [13], [14]. This SBI can lead to more severe morbidities such as motoric, cognitive, and psychological disturbances that can be suffered by the patients for the rest of their lives, or even death [6], [15], [16]. Thus, an inflammatory biomarker that can reflect the neuroinflammation and SBI severity post-TBI is needed to increase the effectivity of TBI patient management and prevent the morbidity and mortality caused by SBI post-TBI.

The levels of inflammatory reactions that occur in the body can be reflected from increased inflammatory cell count, such as neutrophils and platelets, or increased inflammatory biomarker levels, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [17], [18]. CRP and ESR are commonly used by medical practitioners to help them in monitoring the progression of inflammatory diseases. However, CRP and ESR are barely used in traumatic cases, especially in SBI post-TBI. In addition, CRP

and ESR examinations are not always available and affordable in every hospital, especially in rural areas.

On the other hand, recent studies showed that neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) could act as a promising inflammatory biomarker and very easy to be measured [18], [19], [20], [21], [22], [23]. NLR and PLR can be obtained from the complete blood count (CBC) examination, which is more routinely done compared to CRP and ESR in traumatic case management, especially TBI. The CBC examination also more available and affordable in every hospital, including in primary health care in rural areas [24]. The CBC examination is a simple laboratory test and can provide several important data at once about the markers that can be useful in daily medical practice. Thus, the CBC is recommended to be done before carrying out other laboratory tests that are more expensive and invasive [25], [26].

NLR and PLR have the potential to be used as a marker of the SBI severity post-TBI [18], [19], [20], [21], [22], [23], [24], [27], [28], [29], [30], [31], [32], [33]. Nevertheless, the TBI patients NLR and PLR results in daily medical practice are not yet completely utilized. Therefore, this study was conducted to correlate the NLR and PLR results with the CRP and ESR results of TBI patients as the marker of the inflammatory process and SBI severity post-TBI. It is hoped that NLR and PLR can become a useful and more affordable marker for predicting the severity of inflammatory processes and SBI post-TBI. Thus, more effective SBI monitoring to alert and prevent the clinical deterioration, morbidities, and mortality of TBI patients can be done.

Methods

This cross-sectional study was conducted at Sanglah Hospital Denpasar from January to April 2020 to correlate the NLR and PLR results with the CRP and ESR results of TBI patients as the marker of the inflammatory process and SBI severity post-TBI. This study has been approved and permitted by the Ethical Committee of Fakultas Kedokteran Universitas Udayana – Sanglah Hospital Denpasar and the Clinical Research Unit of Sanglah Hospital Denpasar. This study used all of the TBI patient's medical record that hospitalized in Sanglah Hospital Denpasar from January to April 2020 and used the consecutive sampling technique for the patient selection. The inclusion criteria were: (1) Diagnosed with TBI; and (2) aged 18 to 65 years old. The patients with: (1) History of autoimmune diseases such as systemic lupus erythematosus, multiple sclerosis, myasthenia gravis, and Guillain–Barre syndrome; (2) history of routine immunosuppressant drugs consumption, such as dexamethasone and

methylprednisolone; and (3) multiple bone fractures on the extremities that accompanied the TBI were excluded from the study.

Variables obtained from the TBI patient's medical record were age, sex, mechanism of injury, Glasgow coma scale (GCS) on admission, unconscious duration after TBI, history of memory loss after TBI, and the laboratory results of NLR, PLR, CRP, and ESR at 24-h post-TBI. The 5cc of TBI patient's blood sample was obtained at 24-h post-TBI. Then, the 3cc of the blood sample was inserted into the ethylenediaminetetraacetic acid anticoagulant tube (purple) for CBC and ESR laboratory examination, and the other 2cc of the blood sample was inserted into the coagulant separating gel tube (yellow) for CRP laboratory examination.

The CBC was measured through the flow cytometry method using the CELL-DYN Ruby tool manufactured by Abbott Laboratories, Illinois – USA. Then, the NLR and PLR were calculated by dividing the neutrophils count (for NLR) and platelets count (for PLR) with the lymphocytes count that obtained from the TBI patient's CBC result. The CRP was measured through the immunoturbidimetry method using the CRP Latex Cobas 601 tool manufactured by Roche Diagnostics, Mannheim – Germany. The ESR was measured using the Caretium XC-A30 ESR Analyzer tool manufactured by Caretium Medical Instruments Co Ltd, Shenzhen – China.

The collected data were analyzed using the SPSS Statistics 23 application. A descriptive analysis test was done to obtain the result of the characteristics of TBI patients involved in this study. Then, the results were described with mean \pm standard deviation (SD) or median \pm interquartile range (IQR) and frequency. The Kolmogorov–Smirnov test was done to obtain the normality of the data distribution. Finally, the nonparametric Spearman's rho correlation test was done to obtain the correlation between the NLR and PLR with the CRP and ESR in TBI patients. The values of the correlation between these variables were stated in the correlation coefficient (r) and p -value. A significant correlation is achieved if $*p < 0.05$ in the data analysis result.

Results

A total of 85 samples were met the sampling criteria, and their data were obtained in this study. The sample characteristics are shown in Table 1. The minimum and maximum age obtained from this study were 18-year-old and 64-year-old consecutively, with mean \pm (SD) 38.89 \pm (15.27)-year-old and median \pm (IQR) 39 \pm (29.5)-year-old. Moreover, the TBI cases in this study were dominated by the 20–29-year-old age group (Figure 1). In this study, men (77.6%) were more

Table 1: The characteristics of TBI patients

Variable	Frequency (%) / mean \pm (SD) / median \pm (IQR)
Age (years old)	39 \pm (29.5)
Sex	
Men	66 (77.6)
Women	19 (22.4)
Mechanism of injury	
Traffic accident	72 (84.7)
Fall	12 (14.1)
Assault	1 (1.2)
GCS on admission	12 \pm (5)
Head injury severity	
Severe	10 (11.8)
Moderate	39 (45.9)
Mild	36 (42.3)
Unconscious duration	
>24-h	15 (17.6)
30-min to 24-h	30 (35.3)
<30 min	40 (47.1)
Memory loss	
Yes	19 (22.4)
No	66 (77.6)
Neutrophils count	10.84 \pm (3.87)
Neutrophilia	
Yes	69 (81.2)
No	16 (18.8)
Lymphocytes count	1.33 \pm (0.98)
Lymphopenia	
Yes	24 (28.2)
No	61 (71.8)
Platelets count	203.75 \pm (60.70)
Thrombocytopenia	
Yes	19 (22.4)
No	66 (77.6)
NLR	7.60 \pm (6.83)
PLR	145.58 \pm (76.95)
CRP	60.83 \pm (66.3)
ESR	12.50 \pm (13.85)

SD: Standard deviation, IQR: Interquartile range, GCS: Glasgow coma scale, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate. Mean \pm (SD): Neutrophils count, platelet count, Median \pm (IQR): Age, GCS on admission, lymphocytes count, NLR, PLR, CRP, ESR.

dominant to had TBI compared to women (22.4%). Traffic accident (84.7%) was the leading cause of TBI, followed by fall (14.1%) and assault (1.2%) consecutively.

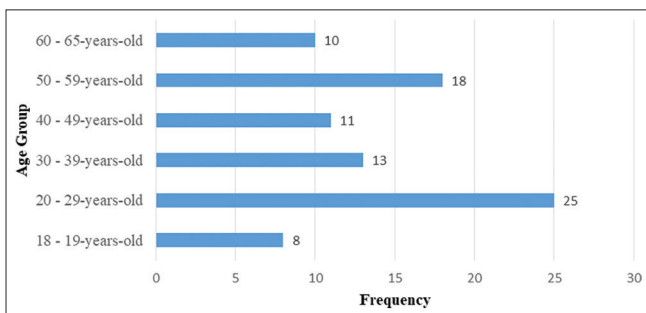


Figure 1: Bar chart of the traumatic brain injury cases age group frequency

The minimum and maximum GCS on admission score obtained from this study were three and 15 consecutively, with mean \pm (SD) 11.45 \pm (3.45), and median \pm (IQR) 12 \pm (5). The proportion of samples who had a severe, moderate, and mild head injury were 11.8%, 45.9%, and 42.3% consecutively. Based on the unconscious duration, as many as 47.1%, 35.3%, and 17.6% of the samples had unconscious duration for <30-min, 30-min to 24-h, and >24-h consecutively. As many as 22.4% of the samples had a history of memory loss after TBI, while the other 77.6% of the samples had no history of memory loss after TBI.

The minimum and maximum neutrophils count obtained from this study were $3.82 \times 10^3/\mu\text{L}$ and 20.40

$\times 10^3/\mu\text{L}$ consecutively, with mean \pm (SD) $10.84 \pm (3.87) \times 10^3/\mu\text{L}$, and median \pm (IQR) $10.36 \pm (5.02) \times 10^3/\mu\text{L}$. As many as 81.2% of the TBI patients had neutrophilia (neutrophils count $>7.5 \times 10^3/\mu\text{L}$), while the other 18.8% were within the normal range. The minimum and maximum lymphocytes count obtained from this study were $0.48 \times 10^3/\mu\text{L}$ and $3.74 \times 10^3/\mu\text{L}$ consecutively, with mean \pm (SD) $1.49 \pm (0.65) \times 10^3/\mu\text{L}$ and median \pm (IQR) $1.33 \pm (0.98) \times 10^3/\mu\text{L}$. There were only 28.2% of the TBI patients who had lymphopenia (lymphocytes count $<1 \times 10^3/\mu\text{L}$), while the other 71.8% were within the normal range. The minimum and maximum platelets count obtained from this study were $92.30 \times 10^3/\mu\text{L}$ and $330.10 \times 10^3/\mu\text{L}$, with mean \pm (SD) $203.75 \pm (60.70) \times 10^3/\mu\text{L}$, and median \pm (IQR) $202 \pm (86.2) \times 10^3/\mu\text{L}$. As many as 22.4% of the TBI patients had thrombocytopenia (platelets count $<150 \times 10^3/\mu\text{L}$), while the other 77.6% were within the normal range.

The minimum and maximum NLR obtained from this study were 1.87 and 33.44, with mean \pm (SD) $9.21 \pm (6.42)$, and median \pm (IQR) $7.60 \pm (6.83)$. The minimum and maximum PLR obtained from this study were 54.22 and 366.03, with mean \pm (SD) $153.77 \pm (62.57)$, and median \pm (IQR) $145.58 \pm (76.95)$. The minimum and maximum CRP obtained from this study were 3.54 mg/L and 271.90 mg/L, with mean \pm (SD) $73.79 \pm (52.34)$ mg/L and median \pm (IQR) $60.83 \pm (66.3)$ mg/L. As many as 97.6% of the TBI patients had elevated CRP levels (CRP >5 mg/L), while the other 2.4% were within the normal range. The minimum and maximum ESR obtained from this study were 1.6 mm/h and 84.3 mm/h, with mean \pm (SD) $16.76 \pm (14.42)$ mm/h, and median \pm (IQR) $12.50 \pm (13.85)$ mm/h. As many as 28.2% of the TBI patients had elevated ESR levels (ESR >20 mm/h), while the other 71.8% were within the normal range.

The Kolmogorov–Smirnov test results are shown in Table 2. The results of the NLR, PLR, CRP, and ESR variables were $*p < 0.05$, which means that the data were not normally distributed. Thus, the correlation test used is the nonparametric Spearman's rho correlation test. The nonparametric Spearman's rho correlation test results are shown in Table 3. NLR

Table 2: The NLR, PLR, CRP, and ESR variable's Kolmogorov–Smirnov test results

Variable	Sig. (p-value)
NLR	0.001
PLR	0.036
CRP	0.010
ESR	0.000

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

Table 3: The nonparametric Spearman's rho correlation test results

Variable	CRP	ESR
NLR		
r	0.472**	0.047
p-value	0.000	0.668
PLR		
r	0.283**	0.069
p-value	0.009	0.533

**Correlation is significant at the 0.01 level (2-tailed), r: Correlation coefficient, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate.

and PLR had a significant positive correlation with CRP ($r = 0.472$, $**p < 0.01$; and $r = 0.283$, $**p < 0.01$ consecutively) in TBI patients. While NLR and PLR were not correlated with ESR ($r = 0.047$, $p > 0.05$; and $r = 0.069$, $p > 0.05$ consecutively) in TBI patients.

Discussion

Samples characteristics

Based on the age variable, the result of this study had supported several previous studies, which found that the average age of the TBI patients was 32–41-year-old, and TBI is one of the leading cause of morbidity and mortality in individuals under 45-year-old [2], [34], [35]. The result of this study also supported the previous study, which found that TBI patients in the 21–30-year-old age group had the largest number of TBI cases compared to other age groups [36].

This study found that men were more likely to had a TBI compared to women. It supported several previous studies, which found that men had a bigger proportion compared to women in experiencing TBI, reaching 77–88% of TBI cases [29], [30], [34], [35], [36], [37]. The high incidence of TBI in men can be due to the fact that men are more dominant in doing high-risk activities, experiencing work-related accidents, and experiencing assault-related injuries compared to women [38].

This study found that traffic accident was the leading mechanism of injury that could cause TBI, followed by fall and assault consecutively. It supported several previous studies which also found that traffic accident was the highest mechanism of injury that could cause TBI, then followed by fall and other causes, such as assault [29], [34], [35], [36]. Therefore, young adult men must be more vigilant in carrying out high-risk activities to prevent TBI. Moreover, preventive measures such as providing education about safety riding and increasing awareness in driving can also be useful to prevent TBI due to traffic accidents.

This study found that there was an elevated mean neutrophils count in TBI patients, and most of the TBI patients had neutrophilia (neutrophils count $>7.5 \times 10^3/\mu\text{L}$). These results supported several previous studies, which also found that there was increased neutrophils count in TBI patients [28], [30]. Neutrophils can be modulated by various endogenous factors such as granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage-CSF (GM-CSF) [39], as well as external stimuli, such as stress and trauma, including TBI [40], [41]. Neutrophils can be activated by several cytokines, such as tumor necrosis factor- α (TNF- α), interleukin (IL) IL-1 β , IL-6, GM-CSF, C-X-C chemokine ligand (CXCL) CXCL1-5, and CXCL8-10 that released

by damaged glial cells after TBI [7], [8], [9], [14]. These activated neutrophils can initiate the inflammatory cascade and develop neuroinflammation, thus increased brain tissue damage and SBI post-TBI [2], [6].

This study found that the mean lymphocytes count in TBI patients was within the normal range and only 28.2% of them who had lymphopenia (lymphocytes count $<1 \times 10^3/\mu\text{L}$). These results could happen because the CBC examination in this study was carried out on the 1st-day post-TBI. The most significant decrease in lymphocytes count usually occurs on the 3rd-day post-TBI, and then it will return to the normal range on the 7–14th-day post-TBI [42], [43]. The decreased lymphocytes count in TBI patients can occur due to increased release of cortisol hormone by the adrenal glands in response to TBI stress [42], [44], [45].

Cortisol can reduce the lymphocytes count by suppressing lymphocyte's mobility and migration, thereby inhibiting the lymphocytes release into the circulation [45]. The higher the stress level or TBI severity, the higher the cortisol level, so the lower the lymphocytes count. Conversely, a higher lymphocytes count represents a more precise immune response and a more stable inflammatory pathway [44], [46]. The result of this study supported the previous study, which found that the plasma cortisol level did not change significantly on the 1st-day post-TBI, so they did not have a significant impact on the lymphocytes count [43]. The low number of samples who had lymphopenia in this study could also be due to only 11.8% of the samples that had a severe head injury, where the most significant reduction in lymphocytes count occurred in the group of patients with severe head injury [42], [43].

This study found that the mean platelets count in TBI patients was within the normal range, and none of them had thrombocytosis. Some of TBI patients had thrombocytopenia instead. These results supported several previous studies, which also found that the platelet count of TBI patients was still within the normal range [47], [48]. The decreased platelets count in TBI patients can occur due to the increased platelet consumption (consumption coagulopathy), where the coagulation system will be activated when the blood passes through the injured brain tissue post-TBI [47]. The brain vasculature has large deposits of tissue factor (TF), which play an important role in inducing the central nervous system and systemic coagulopathy post-TBI [49], [50]. TF is an essential initiator protein of the coagulation cascade and present in endothelial cells and leukocytes. TF will be released into the blood circulation after an injury to the brain vasculature [50].

This study found that there was an elevated mean CRP level in TBI patients, and most of the TBI patients had elevated CRP levels (CRP >5 mg/L). These results supported several previous studies, which also found that there were increased CRP levels in most of the TBI patients [51], [52], [53], [54]. This could occur because CRP is an acute-phase reactant that can be used to

identify and monitor the neuroinflammatory processes in SBI post-TBI [53], [55]. The increase in CRP levels is commensurate with the increase in inflammatory mediators (cytokines) produced by cells that actively participate in the neuroinflammatory processes post-TBI, such as IL-1, IL-6, TNF- α , and transforming growth factor- β [56]. The benefit of CRP over other non-specific inflammatory markers (such as ESR) is its ability to respond rapidly to inflammatory processes in the body [55]. Therefore, CRP can be useful in the assessment of severity, metabolic response, prediction of clinical outcomes, and monitoring of response in TBI patients [53].

This study found that the mean ESR levels in TBI patients were within the normal range, and only 28.2% of them had elevated ESR levels (ESR >20 mm/h). These results could occur because the ESR examinations were carried out on the 1st-day post-TBI, where the ESR levels did not change rapidly at the beginning of the inflammatory process and would return to normal range in a longer time than other acute phase reactants [57]. This is also supported by previous research on TBI cases, which found that the results of ESR examination performed at 1-year follow-up post-TBI were significantly increased, compared to the control group, with mean ESR levels 24.6 ± 3.7 mm/h and 11.7 ± 2.6 mm/h for TBI group and control group consecutively [58].

Correlation of NLR and PLR with CRP and ESR in TBI patients

This study found that NLR and PLR were positively correlated with CRP in TBI patients. This could occur because the neuron and glial cells damaged by TBI can release various inflammatory cytokines and neurotransmitters, such as IL-1 β , TNF- α , IL-6, CXCL1-5, CXCL8-10, and GM-CSF to induce the inflammatory cascade response and develop neuroinflammation. These inflammatory cytokines can cause neutrophils and platelets activation, increase thrombopoiesis, and increase the CRP levels [6], [8], [9], [11], [56], [59], [60].

NLR is a reflection of inflammatory response levels (neutrophils) and immune status (lymphocytes), which indicates an increased release of inflammatory cytokines when its levels were increased [19], [20]. Neutrophils are recruited into the injury site within 1-h post-TBI and can release inflammatory cytokines that can exacerbate SBI and induce neuronal death [61], [62]. The increased neutrophils count can increase the blood-brain barrier (BBB) damage, brain tissue damage, and neuronal death, which results in increased inflammatory reactions and worsens the brain tissue damage [63]. Platelets also play an active role in the inflammatory process [18]. Platelets can induce the release of inflammatory cytokines and interact with various cells, including neutrophils, T-lymphocytes, and macrophages, which will have an impact on the

initiation and exacerbation of neuroinflammation and SBI [22], [32], [33]. The increase of NLR and PLR levels indicate increased cellular damage, BBB damages, neuroinflammation process, and cerebral edema, thus reflecting a more severe SBI post-TBI [64]. Furthermore, CRP levels are doubled every 8-h and peak within 36–50-h after the onset of TBI [65]. Since the NLR, PLR, and CRP are increased rapidly post-TBI so that the NLR and PLR results on the 1st-day post-TBI can have a positive correlation with CRP results on the 1st-day post-TBI in TBI patients.

This study found that NLR and PLR were not correlated with ESR in TBI patients. This could occur because the CBC and ESR examinations were carried out on the 1st-day post-TBI, where the ESR levels do not change rapidly at the beginning of the inflammatory process and return to normal range in a longer time than other acute phase reactants, while NLR levels can increase rapidly post-TBI, and PLR levels also have not increased significantly [2], [22], [42], [43], [57], [61], [62]. ESR begins to increase within 24–48-h after the onset of inflammation (slower than CRP), then gradually decreases after the inflammation subsides. Therefore, ESR is considered as a better marker for clinical monitoring over the course of the disease over time and for chronic inflammatory diseases [65], [66]. Maybe it would be better if the blood examinations were carried out on the 3rd-day post-TBI to assess the correlation between NLR and PLR with ESR in TBI patients, where the ESR levels had already begun to increase, and the lymphocytes count would experience a more significant decrease so that it could affect the PLR results in TBI patients [22], [42], [43].

Conclusion

This research proved that NLR and PLR were positively correlated with CRP in TBI patients, but NLR and PLR were not correlated with ESR in TBI patients. Therefore, the NLR and PLR can be considered as a useful and more affordable marker of acute inflammation to assess the severity of neuroinflammation and SBI post-TBI in daily medical practice. Thus, a more effective SBI monitoring using the NLR and PLR to alert and prevent the clinical deterioration, morbidities, and mortality of TBI patients can be done.

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