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Correlation of MLR with CRP and MPVPCR with LED in Traumatic Brain Injury

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Abstract

BACKGROUND: Traumatic brain injury (TBI) contributes greatly to high rates of death and disability globally. It may be divided into primary and secondary injuries. Primary head injuries occur at the moment of impact which causes mechanical loads and accelerations both linearly and rotationally, causing injury to the brain. After the primary brain injury, further biochemical and cellular processes occur that lead to secondary injury. Secondary insult in TBI may lead to several neuroinflammation processes that are reflected on laboratory markers. The monocyte-lymphocyte ratio and mean platelet volume-platelet count ratio (MPVPCR) theoretically have the potential to be used as neuroinflammation markers in TBI.

AIM: This study was conducted to assess the relationship between monocyte-lymphocyte ratio (MLR), MPVPCR with both C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) regarded as inflammation markers in relation to secondary brain injury.

METHODS: This study was a cross-sectional prospective analytic observational study conducted at the Sanglah hospital emergency department from February to May 2022. Patients diagnosed with TBI aged 18 years and over that were willing to be included in the study by consecutive sampling. Patients with a history of autoimmune disease, history of taking immunosuppressant drugs, and fractures of > 2 long bones were excluded and the presence of infection characterized by fever was excluded from the study. History taking and physical examination were done to obtain data regarding age, gender, mechanism of injury, Glasgow Coma Scale, fainting duration, and memory loss. The blood sample was taken at 24 h after trauma to obtain MLR, MPVPCR, CRP, and ESR results. Pearson correlation test was done to determine the correlation between MLR and MPVPCR with CRP and LED.

RESULTS: There are a total of 85 patients included in this study with the mean of age which is 36 ± 2.5 years old. Most of them are men (71.3%) with the mean of GCS on admission which is 12. Mean ± (SD) of the monocyte, lymphocyte, and platelet was 1.12 ± 0.82 × 10^3/μL, 1.83 ± 1.69 × 10^3/μL, and 259.34 ± 85.79 × 10^3/μL consecutively. MLR with CRP had a weak positive correlation and was statistically significant (r = 0.215; p = 0.045), as well as MPVPCR with ESR also had a weak positive correlation and was statistically significant (r = 0.276; p = 0.010). While both MLR with ESR and MPVPCR with CRP had no correlation.

CONCLUSION: MLR can be an option representing CRP in predicting the magnitude of inflammation in head injury and MPVPCR can be considered to be used as a predictor of thrombotic phenomena in TBI.

Introduction

Traumatic brain injury (TBI) contributes significantly to high rates of mortality and disability globally. Head injuries are caused by impact on the head, and the process can be divided into primary and secondary head injuries. Primary head injuries occur at the moment of impact, which causes mechanical loads and accelerations both linearly and rotationally, causing injury to the brain [1]. After a primary head injury, further biochemical and cellular processes can exacerbate the brain injury, called a secondary head injury. Secondary head injury includes excitotoxicity, mitochondrial dysfunction, oxidative stress, lipid peroxidation, and neuroinflammation, which may lead to axonal degeneration and apoptosis of brain cells [2], [3], [4]. These processes may be promoted and worsened by systemic inflammation after TBI [5]. TBI also causes cellular damage, which promotes surrounding cells to secrete cytokines and chemokines [6].

Systemic inflammation response can be reflected as an increase in inflammatory cells counts, such as neutrophils, monocytes, and lymphocytes, as well as an increase in inflammatory biomarkers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate [7], [8]. CRP is an acute inflammation biomarker used as a prognostic biomarker in TBI

patients, with increased CRP levels associated with worse outcomes [9], [10]. Erythrocyte sedimentation rate (ESR) is also increased in acute inflammation [11].

In recent studies, monocyte-lymphocyte ratio (MLR) and mean platelet volume-to-platelet count ratio (MPVPCR) have been used as prognostic biomarkers in the severity of systemic inflammation [12], [13], [14]. Furthermore, MLR is also associated with increased hematoma volume in cerebral contusion following TBI [15].

The MLR and MPVPCR theoretically have the potential to be used as markers of the severity of the secondary brain injury process that occurs in head injury cases. Since MLR and MPVPCR values can be obtained from a simple complete blood count (CBC) examination, the severity of the secondary brain injury process may be evaluated in a more accessible and affordable way [16]. Therefore, this study was conducted to assess the relationship between MLR and MPVPCR results with CRP and ESR results in head injury patients as markers of the severity of the inflammatory process and secondary brain injury following head injury.

Methods

This study was a cross-sectional prospective analytic observational study conducted at the Surgical Triage at Sanglah Hospital Denpasar from February to May 2022. The inclusion criteria were: (1) Patients diagnosed with TBI; (2) Aged 18 years and over; and (3) willing to be included in the study. Patients with: (1) a history of autoimmune disease; (2) a history of taking immunosuppressant drugs; (3) fractures of two long bones or more; and (4) infection characterized by fever and leukocytosis were excluded from the study.

Data on age, gender, mechanism of injury, Glasgow Coma Scale (GCS), duration of fainting, and memory loss were obtained through history taking and physical examination during admission. Five ccs of the patient's blood sample were taken 24 h after TBI to get MLR, MPVPCR, CRP, and ESR results. Then, three ccs of the blood sample were inserted into a tube containing EDTA for CBC and ESR examination. The other two ccs of the blood sample were inserted into the coagulant separating gel tube 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. MLR was calculated by dividing the monocyte count by the lymphocyte count obtained from the TBI patient's CBC result. MPVPCR was calculated by dividing the mean platelet volume (MPV) by the platelet count obtained from the TBI patient's CBC result. The CRP was measured through the immunoturbidimetry method using the CRPLX 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 27 application. A descriptive analysis test was done to define the characteristics of TBI patients involved in this study. A normality test using the Kolmogorov–Smirnov test was done to define the normality of data distribution. Pearson correlation test was conducted to determine the correlation between MLR and MPVPCR with CRP and LED. The correlation values between these variables were stated in a correlation coefficient (r) and p-value. P-value < 0.05 is considered significant correlation.

Results

Based on the sampling criteria, we identified 87 patients within the time frame. Moreover, most of the samples were male (71.3%), with a mean age is 36.15 ± 18.03. All of the trauma was caused by a road traffic accident. From the severity of the TBI, 10 (11.49%) samples were categorized as severe TBI, 27 (31.04%) samples with moderate TBI, and 50 (57.47%) samples with mild TBI (Table 1). Based on Head CT imaging (Table 2), we found 4 (4.59%) samples with a skull fracture, 22 (25.29%) samples with epidural hematoma, 22 (25.29%) samples with subdural hematoma, 10 (11.49%) samples with intracerebral hematoma, 7 (8.05%) samples with a cerebral contusion, and 9 (10.34) samples with subarachnoid hemorrhage.

Table 1: Characteristics of the samples

Variable	Frequency (%)
Age (years old) (mean±SD)	36 ± (29.5)
Sex	
Men	62 (71.3)
Women	25 (28.7)
Mechanism of injury	
Traffic accident	87 (100)
TBI severity	
Mild	50 (57.47)
Moderate	27 (31.04)
Severe	10 (11.49)

SD: Standard deviation, TBI: Traumatic brain injury.

Table 2: Radiographic characteristic

Variable	Frequency (%)
Skull fracture	4 (4.59)
Epidural hematoma	22 (25.29)
Subdural hematoma	22 (25.29)
Cerebral contusion	10 (11.49)
Intracerebral hematoma	7 (8.05)
Subarachnoid hemorrhage	9 (10.34)

The laboratory markers result were summarized in Table 3. The mean monocyte count of all the patients was 1.12 ± 0.82 × 10^3/μL, with the minimum and maximum monocyte count being 0.23 × 10^3/μL and 6.50 × 10^3/μL consecutively. The severe TBI group had the highest trend in monocyte count

(1.47 ± 0.93 × 10^3/μL), followed by the mild TBI group (1.09 ± 0.94 × 10^3/μL) and moderate TBI (1.03 ± 0.44 10^3/μL) (Figure 1).

Table 3: Laboratory markers, mean-lymphocyte ratio, and mean platelet volume-platelet count ratio results

Variable	Mean±SD
Monocyte count	
Mild TBI	1.09 ± (0.94) × 103/μL
Moderate TBI	1.03 ± (0.44) × 103/μL
Severe TBI	1.47 ± (0.93) × 103/μL
Lymphocyte count	
Mild TBI	1.48 ± (1.13) × 103/μL
Moderate TBI	2.33 ± (2.06) × 103/μL
Severe TBI	2.24 ± (2.55) × 103/μL
Platelet count	
Mild TBI	260.50 ± (69.66) × 103/μL
Moderate TBI	261.41 ± (80.72) × 103/μL
Severe TBI	248.10 ± (157.89) × 103/μL
MLR	
Mild TBI	0.30 ± (0.39)
Moderate TBI	0.51 ± (0.64)
Severe TBI	0.73 ± (1.13)
MPVPCR	
Mild TBI	4.11 ± (1.17)
Moderate TBI	4.36 ± (1.85)
Severe TBI	7.78 ± (11.04)
CRP	
Mild TBI	17.11 ± (24.36) mg/L
Moderate TBI	24.43 ± (35.98) mg/L
Severe TBI	20.84 ± (14.97) mg/L
ESR	
Mild TBI	14.00 ± (20.48) mm/h
Moderate TBI	19.48 ± (25.74) mm/h
Severe TBI	24.90 ± (41.30) mm/h

SD: Standard deviation, TBI: Traumatic brain injury, MLR: Mean-lymphocyte ratio, MPVPCR: Mean platelet volume-platelet count ratio, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate.

The mean lymphocyte count of all the patients was 1.83 ± 1.69 × 10^3/μL, with the minimum and maximum monocyte count 0.33 × 10^3/μL and 8.12 × 10^3/μL consecutively. The average lymphocyte count was lowest in the mild TBI group with a mean of 1.48 ±1.13 × 103/L, followed by severe TBI and moderate TBI with a mean lymphocyte count of 2.24 ± 2.55 × 10^3/μL and 2.33 ± 2.06 × 10^3/μL consecutively (Figure 2).

Table 4: Pearson correlation for each variables

	CRP	ESR
MLR		
Correlation coefficient (r)	0.215**	−0.044
P	0.045	0.683
MPVPCR		
Correlation coefficient (r)	0.173	0.276**
P	0.109	0.010
CRP		
Correlation coefficient (r)		0.244**
P		0.023

**Significant correlation found in p < 0.05. (Two-tailed). CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, MLR: Mean-lymphocyte ratio, MPVPCR: Mean platelet volume-platelet count ratio.

The mean platelet count in this study is 259.34 ± 85.79 × 10^3/μL, with the minimum value being 26.00 × 10^3/μL and the maximum value being 629.00 × 10^3/μL. The lowest level of platelet count was found in the severe TBI group with a mean of 248.10 ± 157.89 × 10^3/μL, followed by mild TBI and moderate TBI with a mean of 260.50 ± 69.66 × 10^3/μL and 261.41 ± 80.72 × 10^3/μL consecutively (Figure 3). Furthermore, the minimum MPV value in this study is 8.50 × 10^3/μL, and the maximum MPV is 13.80 × 10^3/μL, with a mean MPV value being 10.02 ± 0.97 × 10^3/μL. This study found a median of MPVPCR is 3.97 ± 1.95. After transforming the data, we found that the severe TBI group had the highest value with a mean of 7.78 ± 11.04, followed by moderate TBI with a mean of 4.6 ± 1.86 and mild TBI with a mean of 4.11 ± 1.17.

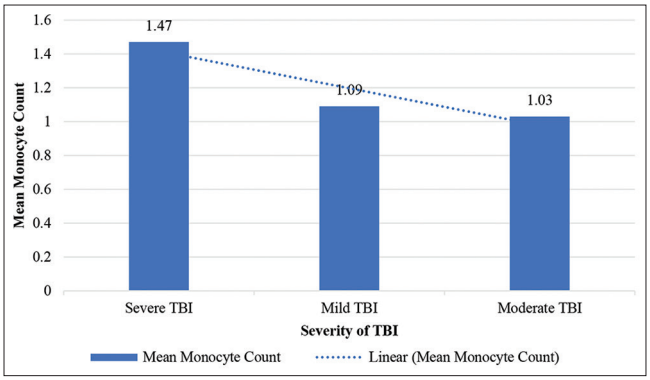

Figure 1: Mean monocyte count based on TBI severity

The mean MLR in this study is 0.41 ± 0.61, with minimum MLR values of 0.03 and a maximum value of 3.62. After transforming the data, we found that mild TBI had the highest MLR value (mean 0.73 ± 1.13) compared to moderate TBI (mean 0.51 ± 0.64) and severe TBI (mean 0.30 ± 0.39).

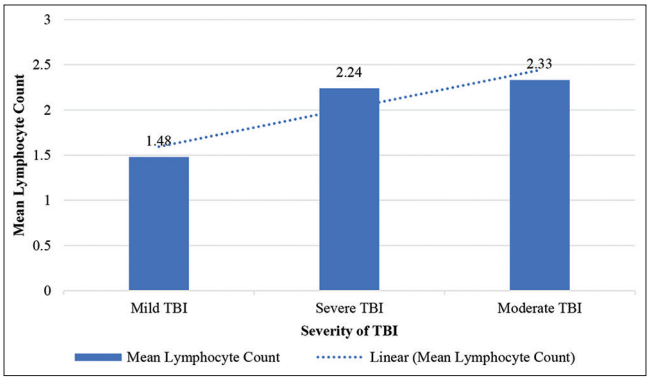

Figure 2: Mean lymphocyte count based on TBI severity

Mean CRP is 19.81 ± 27.64 mg/L with minimum CRP value is 1.00 mg/L and maximum is 169.10 mg/L. After transforming the data, we found that the moderate TBI group had the highest CRP value with a mean of 24.43 ± 35.98 mg/L, followed by severe TBI with a mean of 20.84 ± 14.97 mg/L and mild TBI with a mean of 17.11 ± 24.36 mg/L.

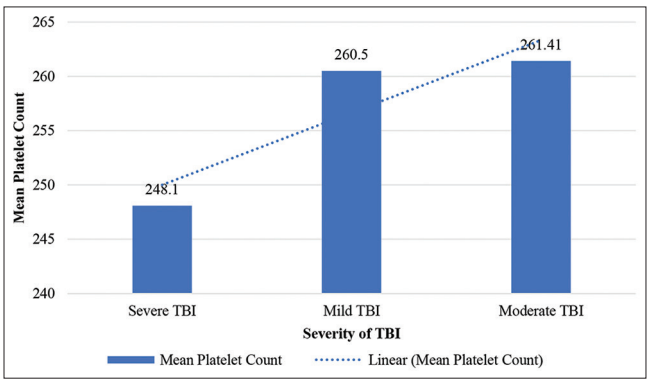

Figure 3: Mean platelet count based on TBI severity

Mean ESR is 16.95 ± 25.14 mm/h with a minimum value of 2 mm/h and maximum ESR values of 137 mm/h. After transforming the data, we found that the severe TBI group had the highest mean ESR of 24.90 ± 41.30 mm/h, followed by moderate TBI with a mean of 19.48 ± 25.74 mm/h and mild TBI with a mean of 14.00 ± 20.48 mm/h.

Correlation between MLR, MPVPCR, CRP, and LED

Based on statistical results (Table 4), we found that MLR and CRP had a weak positive correlation with r = 0.215, and it is statistically significant (p = 0.045). Analysis for MPVPCR and CRP also had a weak positive correlation with r = 0.276 and was statistically significant (p = 0.010). Furthermore, correlation between MPVPCR and CRP, MLR and ESR had no correlation with is r = 0.73 (p = 0.109) and −0.044 (p = 0.683) consecutively. Finally, based on *Pearson* statistical analysis, we found that CRP and ESR had a weak positive correlation with r = 0.244, which is statistically significant (p = 0.023).

Discussion

This study found that the mean age group for TBI cases is 36.15 ± 18.03. This study had similar results compared to previous research that previously mentioned the mean age of TBI cases is 32–41 years of age, and TBI is a significant cause of morbidity and mortality worldwide for individuals under 45 years of age. Based on gender, 62 (62.81%) of our samples are men, and 25 (27.5%) are women. This result is supported by several previous studies, which found that men's proportion was more significant than women's in cases of TBI. The high incidence of TBI in males may be due to the tendency for men to be more dominant in carrying out high-risk activities, work risks, and serious injuries. As from a previous study, TBI is mainly caused by traffic accidents that may be related to gender disparities [12].

The neuroinflammation process will lead to disruption, brain edema, activation of several chemotactic factors, and accumulation of leukocytes (monocyte and neutrophil) that invade BBB and produce proinflammatory cytokine that further disrupts BBB integration [17]. Hypoxia condition is commonly found in patients with TBI; this correlated with monocyte proliferation and angiogenesis to oxygen delivery to the cell through the HIF-2a factor [18].

The acute phase of TBI is related to the body's inflammation response. Monocyte accumulation surrounding the damaged tissue, especially in the first 3 days after trauma [19], [20], may lead to neurotropic or neurotoxic effects. This response assisted in neuronal cell regeneration, but on the other side, overactivity of monocyte may lead to further tissue damage [21].

Recently, MLR was one of the inflammation markers and proved helpful in predicting the severity and prognosis of coronary heart disease and tuberculosis. It reflects the balance between innate and adaptive immunity. In TBI cases, MLR may be used as a predictor factor of inflammation and cerebral contusion expansion.

As one of its derivatives, macrophages will produce several neuroprotective factors (IGF-1, BDNF, GDF15, and VEGF). These factors will trigger tissue regeneration and remodeling. Over and under expression of macrophages have adverse effects that may further damage brain tissue and disrupt edema resolution, respectively [22], [23]. Peripheral macrophage positively affects blood-brain barrier restoration as it correlates with microglia activity [24].

Consumptive coagulopathy in TBI may relate to platelet overconsumption. One of the essential proteins for coagulation is tissue factor, abundantly found in brain vasculature, and released after TBI. This cascade may contribute to disseminated intravascular coagulation commonly found in patients with severe TBI. This may explain the finding in this study and previous studies that lower platelet counts are correlated to TBI severity [11].

Platelet volume is inversely correlated with platelet count. Immature platelets have a larger size and volume reflected in increasing MPVPCR value [25]. Platelet volume is also related to chronic inflammation. A lower PC value in severe TBI compared to mild and moderate TBI is related to coagulopathy in more severe neuroinflammation [26], [27].

CRP synthesized by hepatocytes is used to identify and evaluate neuroinflammation related to secondary brain injury and may elevate due to infection, inflammation, stress response, tissue necrosis, trauma, and neoplasm [28]. This study supports several previous studies that showed elevated CRP levels in patients with TBI [11], [29], [30]. Elevated CRP levels started 24 h after the onset and peaked in 36–50 h. High CRP levels also correlate with TBI severity, bad prognosis, and mortality in patients with TBI [10].

In this study, we found that MLR and CRP have a positive correlation in patients with TBI and are statistically significant (r = 0.215, p = 0.045). Upregulation of monocyte may be due to microglia activation after TBI and acute inflammatory response in a patient with TBI [31], [32], [33]. Escalation of monocyte leads to upregulation of proinflammatory cytokine, then activates hepatocyte to synthesize CRP [29]. Neuronal damage will further increase IL-6 production that is affected in CRP synthesized by hepatocytes.

Positive correlation also found between ESR and CRP that statistically significant (r = 0.244, p = 0.023). The upregulation of CRP may explain this finding by hepatocytes in the acute neuroinflammatory phase, followed by other proinflammatory cytokines (IL-6, IL-1b, and TNF-α). These processes may also affect ESR in blood in a patient with TBI, especially in the acute phase [34].

Platelet volume reflects its activity as a larger volume found in newly synthesized platelet. Meanwhile, the platelet count in the inflammatory process was

reduced. Lower platelet count is related to poor clinical outcomes and mortality. Furthermore, ESR levels increase within 24–48 h after trauma, then slowly back to normal within a few weeks [25], [35]. According to these theories, we also found that MPVPCR and ESR have a weak positive correlation in patients with TBI, which is statistically significant (r = 0.276, p = 0.010).

MPVPCR was used as a prothrombotic indicator rather than an inflammatory indicator. Platelets may be classified as an immune factor due to their ability to recognize pathogens and attract other immune cells, such as neutrophils, macrophages, and lymphocytes, to the inflamed area [36], [37]. Conversely, CRP is specific to expressing acute inflammatory process [32]. In the early phase of the neuroinflammatory process, there is an increase in platelet count as a reaction to increasing in thrombopoietin in the blood that will lead to thrombocytosis. This phenomenon can lead to excessive consumption of platelets, causing a decrease in platelets and megakaryocytes, which were initially high due to the inflammatory process. In line with this theory, we found that MPVPCR has no correlation with CRP in patients with TBI (r = 0.173, p = 0.109).

Furthermore, this study found no correlation between MLR and ESR in TBI patient (r = −0.044, p = 0.683). This may be explained that MLR reflects neuroinflammatory process. This elevation may be seen in the acute phase of TBI (first 72 h). As opposed to MLR, ESR count is not related to any acute neuroinflammatory process [11], [32].

Conclusion

This study concludes that we have MLR-CRP, MPVPCR-ESR have weak positive correlation in patient with TBI. MLR may reflect CRP in correlation with neuroinflammatory process. Meanwhile, MPVPCR may be used as thrombosis indicator in TBI patients. Further study for serial MLR and MPVPCR may conduct to evaluate its precision for neuroinflammatory and thrombosis process in TBI.

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