PLATELET TO LYMPHOCYTE RATIO ELEVATION AS A PREDICTOR FACTOR OF DEGREE OF HEAD INJURY

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Abstract: The inflammatory process of head injury was characterised by the release of pro-inflammatory and inflammatory mediators. This process could be assessed using mediators such as platelet-lymphocyte ratio (PLR) and leukocytes. This study aims to determine the association between PLR and leukocytes in assessing the degree of head injury through the Glasgow coma scale (GCS). This study was an observational analytic study using the medical record of brain-injured patients who visited the Emergency Department of Ulin Hospital from May to November 2017. 59 samples met the criteria in this study. The results of multiple linear regression test in this study found that PLR and leucocyte affected GCS ($p = 0.009$). The leukocyte value was significantly more associated to GCS ($p = 0.008$) than PLR value ($p = 0.146$). The value of leukocyte R was 0.1224, and R PLR was 0.0401. Based on these results, it can be concluded that leukocytes had a better role in predicting the degree of head injury than PLR.

Keywords: platelet-lymphocyte-ratio (PLR), head injury, inflammatory mediator

INTRODUCTION

Head injury is an injury that can cause scalp injuries, skull fractures, tearing of the lining of the brain, intracerebral and extracerebral blood vessel damage, and damage to brain tissue. The most common cause of head injury is traffic accidents, both pedestrians and motorists. Because of this, a person may experience a critical condition, severe disability, and death.

In 2003, as many as 1,565,000 patients had a brain injury in the United States, consisted of 1,224,000 outpatients in the emergency unit, 290,000 inpatients, and 51,000 died. In Europe (Denmark), approximately 363 per one million people had moderate to severe head injury every year, which more than a third of them require rehabilitation.[2] The head injury case at Cipto Mangunkusumo Hospital Jakarta in 2005 reached 772 cases, while Pirngadi Hospital Medan found 1095 cases from 2002-2003.[3] Based on a survey at Surgery Department of Ulin Hospital Banjarmasin in January - August 2017, head injury was still the highest case of neurosurgery in the emergency department.

In head injury, there will be an inflammatory process characterised by the release of pro-inflammatory and inflammatory mediators. This inflammatory process can be assessed using several values such as Neutrophil Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR) and Red Cell Distribution Width (RDW) that can be obtained through routine blood tests as soon as the patient arrives at the ER.[4] PLR is one of the marker used to determine the prognosis of various diseases. Durmus et al. 's study at Silifke State Hospital, Turkey in 2015 reported that PLR and NLR elevated in patients with heart failure.[5] Other studies such as Wu G et al. on 2015 in China showed that the higher the PLR, the worse the prognosis of non- small cell pulmonary carcinoma.[6] PLR assessment to the degree of head injury has not been widely studied. One of the studies of Acar E in Turkey in 2015 reported that NLR, PLR and Troponin T could be used as a parameter for post-injury brain abnormalities as evidenced by CT Scan.[4]

Therefore, this study examined the relationship between PLR obtained from routine blood test with the degree of head injury assessed by Glasgow Coma Scale (GCS). In this study, the relationship between leukocytes with GCS was also evaluated because leukocytes were the previous inflammatory markers. Based on this result, hopefully, PLR can be used to assess the degree of a patient's head injury. Also, PLR becomes an affordable test in all hospitals including Ulin Hospital.

RESEARCH METHODS

This study was an observational analytic study. The subjects were single head-injured patients who received treatment at the Emergency Department of Ulin Hospital Banjarmasin from May to November 2017.

Samples were selected by time restriction method. Sampling technique used nonprobability method followed by purposive sampling method. Inclusion criteria were single head injury, adult (> 18 years old, according to WHO), assessable GCS, and treated in the emergency department Ulin Hospital Banjarmasin. Exclusion criteria were multiple injuries, childhood age, and specific conditions before the damage that caused GCS was challenging to assess.

The patient data was taken from the medical record, including patient identification, routine blood test (leukocytes, platelets, lymphocytes), GCS score, and final diagnosis. PLR is a proportion of platelet counts against lymphocytes,

whereas GCS score is obtained from examination of the eye, verbal and motor responses to stimuli. GCS score according to CDC and ATLS are 3 to 15 where the lower the GCS score, the worse the condition of the patient.

After the data was retrieved and sorted, then it was recorded in PASW Statistics 18 for Multiple Linear Regression test. If the classical assumption test (multicollinearity, autocorrelation, heteroscedasticity, and normality) and feasibility test (F test and t-test) are fulfilled then data is interpreted. This study is conducted with value $\alpha = 0.05$.

Ethical approval was obtained from the research ethics committee of the Faculty of Medicine, Universitas Lambung Mangkurat (FK ULM). Research permission to use medical record data was also approved by Ulin Hospital Banjarmasin Director via Research and Development Department.

RESULTS AND DISCUSSION

In this study we found 59 samples meeting the criteria, consisting of 46 male patients and 13 female patients as shown in table 1.

Table 1. Distribution of the patients by age and degree of head injury

	Male	Female	Total
Number of patients	46 (77.95%)	13 (22.1%)	59
Mean age (year)	43	39	40
Severe head injury (GCS 3-8)	11 (18.64 %)	3 (5.08 %)	14 (23.72%)
Moderate head injury (GCS 9-13)	25 (42.37%)	2 (3.38%)	27 (45.76%)
Mild head injury (GCS 14-15)	10 (16.94%)	8 (13.55%)	18 (30.50 %)

The youngest patient was 18 years old, and the oldest was 77 years old, with mean productive age was 43 years old in a male patient and 39 years old in a female patient. Most male patients came with a mild head injury of 42.37%, while female patients came with a mild head injury of 13.35%. Overall the most patients came with moderate head injury (45.76%), and the least suffered from severe head injury (23.72%). Head injury in this productive age will undoubtedly affect the productivity and quality of life of patients. Multiple linear regression test was conducted to determine the association between PLR and leukocytes to GCS.

Before the test, the classical assumption test was conducted to determine whether there were multicollinearity, heteroscedasticity and normality. The multicollinearity test was seen from the Durbin Watson (DW) value with the sample number 59, the number of independent variables 2, and the alpha 0.05. The DW value in this study was 2.068 (table 2), and the value was between dU (down upper) and 4 - dU so this study showed no autocorrelation. The heteroscedasticity test and normality test were performed by looking at the pattern of the point on the scatterplot and P-P plots. In this study, the point distribution on the scatterplot did not form a particular pattern, and the distribution of dots approaching or meeting in a straight line (diagonal) on P-P plot so it can be concluded that the data were normally distributed and no heteroscedasticity.

Table 2. Multiple linear regression test results of PLR and Leukocytes to GCS

Independent Variable	VIF	Durbin Watson	Anova (sig)	Coefficients			R Square
				sig	B	Std.Error	
PLR	1.003	2.068	0.009	0.146	-0.1	0.094	0.155
Leukocyte	1.003	2.068	0.009	0.008	-0.259	0.007	0.155

Table 2 showed that there was an association between leukocytes and PLR to GCS with p = 0.009 (P value <0.05). It was a negative association (Leukocytes = -0.259; PLR = -0.10), which meant that the higher the leukocyte and PLR, the lower the GCS. The effect of PLR and leukocyte was 15.5% seen from the value of R^2 = 0.155. The results of this study were in accordance with the theory which stated that post-trauma inflammatory response would happen after a head injury, especially those affecting the brain. This post-traumatic inflammatory response was one of the conditions that might cause tissue damage. The ongoing inflammatory process would cause harm to blood vessel structures followed by disruption of the blood-brain barrier and brain edema.[7]

Inflammation triggered by activation of microglia and lymphocytes following the onset of trauma also played a significant role. An open blood-brain barrier in the event of trauma would close approximately 60 minutes after the injury. During the process of opening the blood-brain barrier, the microglia cell body would have hypertrophy, elongation and branching which then produced MHC antigens class I and II. This MHC was recognised by lymphocytes in the regional lymph nodes and ultimately activated lymphocytes in the central nervous system circulation. This suggested that microglia and lymphocytes played an essential role in inducing and maintaining an immune response in the event of a head injury.[8-9]

Table 3. The mean of PLR and leukocytes / WBC based on GCS

	Mild Head Injury	Moderate Head Injury	Severe Head Injury
PLR	178.88	145.89	162.55
Leukocyte / WBC	17.31 x 10^3 /ul	15.38 x 10^3 /ul	13.97 x 10^3 /ul

Leukocytes had a significantly higher association with GCS than PLR as shown in Table 2 (P = 0.008; P <0.05). The mean leukocyte in patients with severe head injury (GCS 3-8) was 17.31 x 103 thousand / ul while in patients with mild head injury (GCS 14-15) was 13.97 x 103 thousand / ul (table 3). This showed the higher the leukocyte value, the lower the GCS value. It will affect the patient's prognosis.

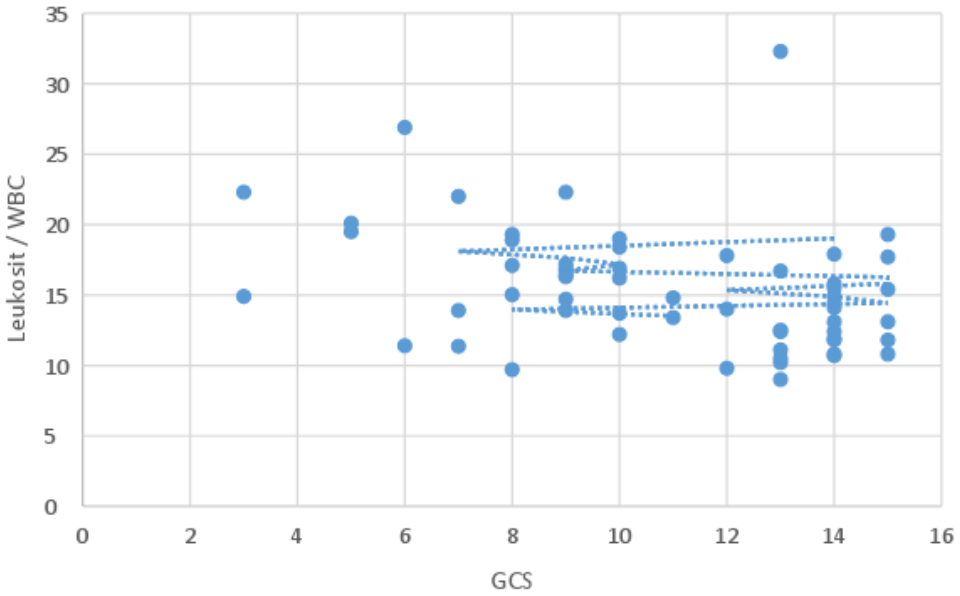

Figure 1. Correlation between leukocytes and GCS

The correlation of leukocytes to GCS was also shown in figure 3 with an R^2 value of 12.24. This result was in accordance with Gurkanlar et al., in Turkey Hospital where the leukocyte affected GCS and length of hospitalisation. High leukocytes (23.74 x 106 / l) were associated with a higher degree of injury and longer admission, while lower leukocyte (11.3 x 106 / l) had a good prognosis.[9]

Brain injury that occurs in head injury will cause an increase in catecholamines. Catecholamines are responsible for releasing neutrophils as an inflammatory response. Brain oedema that occurs after a head injury may be an inflammatory response induced by cytokine production in the brain and increased leukocyte adhesion as a result of increased vascular permeability and leukocyte activation.[10]

Another mechanism that causes leukocytes associated with head injury, especially brain damage is the rupture of small blood vessels followed by occlusion due to vasoconstriction and platelet aggregation in the blood vessels. Leukocytes have smaller ability than erythrocytes in changing its shape so that larger pressure difference is required to pass through small capillaries. The presence of occlusion and decreased cerebral perfusion pressure (CPP) that occur in brain injury will lead to trapped leucocytes and form complexes in the vascular endothelium. This leucocyte-formed complex is not readily biodegradable even though CPP returns to normal and this complex will release some cytotoxic which in turn increases the interaction of endothelial leukocytes.[4,11] Based on this theory, the more blood vessels that rupture in the event of head injury, the higher leukocytes are formed.

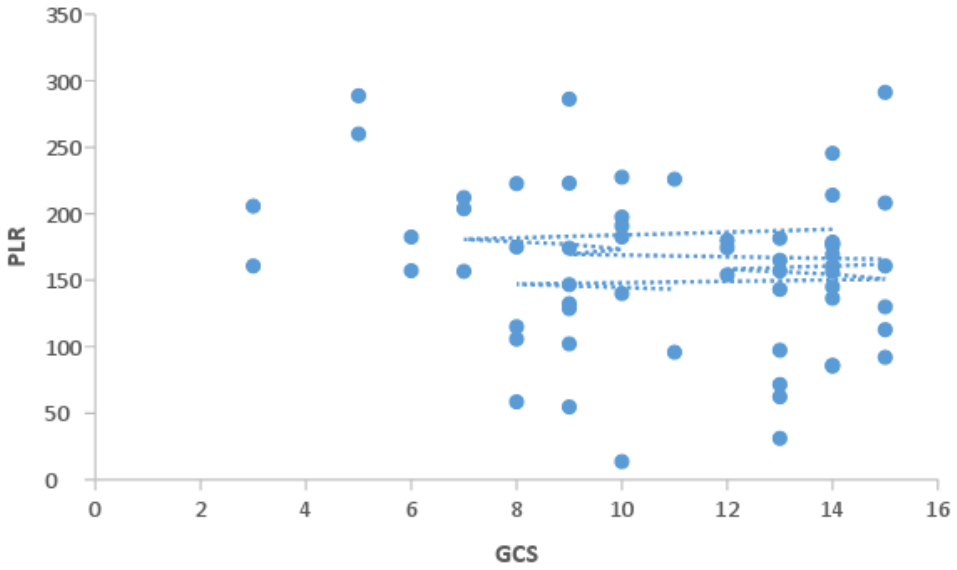

Figure 2. The correlation between PLR and GCS

PLR value in this study was not statistically significant with p = 0.146 (p> 0.05). The mean PLR in severe head injury was 178.88 (table 3). Figure 2 showed that the higher the PLR, the smaller the GCS, even though the effect was very small (R^2 = 0.040). The result of this study was similar to Acar E et al. It showed that PLR was a significant marker to predict the presence or absence of CT Scan abnormalities in patients with head injury. The mean PLR in head-injured patients who had brain abnormalities was 179.47, but PLR was not a significant marker to assess the improvement of patients who had or had not surgery. PLR was also not a significant marker for comparing patients with normal CT scans, intracranial haemorrhage, or skull fracture.[4]

PLR has been widely used as a marker to predict the prognosis of chronic diseases such as cardiovascular disease, malignancy, diabetes mellitus, and preeclampsia, whereas the role of PLR against acute inflammation has not been widely studied. PLR combines platelet aggregation pathways and inflammatory pathways although their pathophysiology is not yet known. Lymphocytopenia is often found in chronic inflammation due to increased apoptosis of lymphocyte cells. Besides, leukocytes production in the bone marrow causes increased neutrophils and decreased lymphocytes in response to tissue stress. Platelets may increase in the event of inflammation and bleeding, which will stimulate the release of inflammatory mediators such as cytokines. Cytokines will further increase platelet production. In chronic inflammation, there is also an increase in platelet production by megakaryocyte cells in the bone marrow. Increased platelets and decreased lymphocytes will eventually increase PLR.[5,6,12,13]

Dogan M et al. in Saudi Arabia showed that PLR> 160 had a poor prognosis in metastatic gastric cancer patients who had received first-line chemotherapy. Cetin M et al. reported that PLR> 128 was a strong predictor of risk of death, cardiac arrest, and infarct miocard in unstable angina and NSTEMI patients who would undergo PCI. Other studies have reported that PLR values correlated with target organ damage and peripheral vascular disease such as critical limb ischemic.[14-17]

Pickles E et al. recommended other parameters such as mean volume platelet (MVP), a neutrophil-lymphocyte ratio (NLR), and troponin T as a predictor marker of abnormality in the brain that will affect GCS and can be used to assess patient outcomes.[4]

CONCLUSION

Our study showed that PLR and leukocytes generally affected GCS in patients with head injury. Leukocytes were more important in predicting GCS (R^2 = 0.1224; P = 0.008) than PLR. PLR was not very significant in predicting GCS (P = 0.146). Further studies should be conducted with more samples and include other inflammatory markers such as NLR and MVP.

REFERENCES

1. Soertidewi L. Penatalaksanaan kedaruratan cedera kranioserebral. CDK 2012; 39(5): 327-331
2. Fildes J, Meredith JW, dkk. ATLS Student Course Manual 8thEd. USA : American College of Surgeons, 2008.
3. Zamzami NM, Fuadi I, Nawawi AM. Angka kejadian dan outcome cedera otak di RS. Hasan Sadikin Bandung tahun 2008-2010. JNI. 2013; 2(2): 89-94
4. Acar E, Demir A, *et al.* Evaluation of hematological markers in minor head trauma in the emergency room. Eur J Trauma Emerg Surg 2015;
5. Durmus E, *et al.* Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are predictors of heart failure. Arq Bras Cardiol 2015; 105(6): 606-613
6. Wu G, Yao Y, *et al.* Combination of platelet to lymphocyte ratio and neutrophil to lymphocyte ratio is a useful prognostic factor in advanced non-small cell lung cancer patients. Thoracic Cancer 2015; 6(3): 275-287
7. Dalbayrak S, et al. Early and delayed CT findings in patients with mild-to-moderate head trauma. Turk Neurosurg 2011; 21(4): 591-8.
8. Czigner A, et al. Kinetics of the cellular immune response following closed head injury. Acta Neurochir 2007; 149(3): 281-9.
9. Gurkanlar D, et al. Predictive value of leukocytosis in head trauma. Turkish Neurosurgery 2009; 19(3): 211-215
10. Juurlink BH. Introduction : the role of inflammation in mediating damage following stroke and neurotrauma. Brain Phatol 2000, 10: 93-94.
11. Harlan J.M. Leukocyte – endhotelial interactions. Blood 1985; 65(3): 513.
12. Aktar F, Tekin R. Mean platelet volume, neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in determining the diagnosis or outcome in children with snakebite. Arch Argent Pediatr 2017; 115(6): 576-587.
13. Erzat T, et al. Platelet-to-lymphocyte ratio : a new inflammatory marker for the diagnosis of preterm premature rupture of membranes. J Tur Ger Gynecol Assoc 2017; 18(3): 122-126
14. Dogan M, et al. The relationship between platelet – lymphocyte ratio, neutrophil – lymphocyte ratio, and survival in metastatic gastric cancer on first line modified docetaxel and cisplatinum plus 5 flurourasil regimen : a single institute experience. Saudi J Gastroenterol 2015; 21(5): 320-324.
15. Kyoung Im Cho, et al. Combined Usefulness of the Platelet-to-Lymphocyte Ratio and the Neutrophil-to-Lymphocyte Ratio in Predicting the Long-Term Adverse Events in Patients Who Have Undergone Percutaneous Coronary Intervention with a Drug-Eluting Stent. PLoS One 2015; 10(7)

16. Seyis S, et al. Relationship between platelet to lymphocyte ratio and coronary angiography timing in patients with NSTEMI. Biomedical Research 2017; 28(20): 8963-8968.

17. Gary T, et al. Platelet-to-lymphocyte ratio : a novel marker for critical limb ischemia in peripheral arterial occlusive disease patients. PLoS One 2013; 8(7)