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ORIGINAL ARTICLES

High platelet to lymphocyte ratio as a risk factor for poor outcome in acute ischemic stroke patient

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Abstract

Background & Objective: Stroke is one of the leading causes of death and disability worldwide. The incidence of ischemic stroke in the anterior circulation is greater in the middle cerebral artery (MCA) distribution. A high level of platelet to lymphocyte ratio (PLR) has been widely studied as a predictor of poor outcomes in various conditions, such as cardiovascular disease and malignancy. However, the significance of PLR as a predictor of outcome in stroke patients, especially the ischemic type, are still uncertain. This study aimed to determine whether increased PLR was a risk factor for poor outcomes in acute ischemic stroke patients. *Methods:* This is a single-center case-control study. The data of acute ischemic stroke patients in MCA territory admitted from January 2019 to April 2020, who met the inclusion and exclusion criteria, were collected. The stroke outcome was defined by NIHSS upon discharge. The Control group was those with NIHSS <10 and Case group with NIHSS≥10 or death. The determinant of this study as a risk factor was PLR with a cut-off ratio of 148. *Results:* Ninety-three subjects with 47 cases (mean age 65.51±11.73) and 46 controls (mean age 57.78±11.39) were collected. In adjusted multivariate analysis, independent risk factor was high PLR (p=0.008) and high CRP (p=0.008). Meanwhile, in bivariate analysis, significant risk factors for poor outcome of acute ischemic stroke were high PLR (odds ratio [OR], 4.88; 95% confidence interval [CI], 2.02-11.73, p<0.01), elderly (OR, 4.02; 95% CI, 1.48-10.87, p=0.05), embolic stroke type (OR, 2.85; 95% CI, 1.21-6.76, p=0.01), and high CRP (OR, 5.13; 95% CI,2.09-12.57, p<0.01). *Conclusions:* High PLR is an independent risk factor for poor outcomes in acute MCA ischemic stroke.

Keywords: Acute ischemic stroke, middle cerebral artery, platelet to lymphocyte ratio

INTRODUCTION

Stroke is one of the leading causes of death and disability worldwide. The incidence of thrombus or embolic etiology related to ischemic stroke is commonly found in the anterior circulation of middle cerebral artery (MCA) distributions.[1,2] The role of the platelets and lymphocytes in stroke is known.; When an endothelial injury occurs, the platelets will undergo adhesions to close the damaged blood vessels.[3,4] Meanwhile, other studies have shown that the depletion of regulatory T lymphocytes (T-reg) will increase brain damage.[5]

High platelet to lymphocyte ratio (PLR) has been studied as a predictor of poor outcomes in various conditions, such as cardiovascular disease and malignancy.[6,7] However, investigation on high PLR as a predictor in ischemic stroke patients is still conflicting in reports.[8-11] Sha *et al*. identified three predictors of death within 6 months of stroke in Chinese patients that included Barthel index, PLR, and serum albumin.[8] This is consistent with report by Zhang *et al*. who found the PLR and neutrophil to lymphocyte ratio (NLR) being correlated with the NIHSS score of acute ischemic stroke patients.[9] However, Cao *et al*. found the 90-day mortality of patients with acute ischemic stroke was associated with platelet-to-neutrophil ration (PNR), platelet-to-white blood cell ratio (PWR), and neutrophil-to-lymphocyte

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ratio (NLR), while PLR was not.[10] Another study also found that PLR was significantly increased in patients with stroke compared to normal but PLR was negatively correlated with the Glasgow Outcome Scale (GOS).[11] In this study, we aim to investigate the PLR in acute ischemic stroke patients and its correlation with the outcome.

METHODS

This is a retrospective case-control study design to examine the risk factors for poor outcomes in the clinical course of stroke. The Case group is the acute ischemic stroke patient with poor outcomes (NIHSS on discharge ≥10 or died) whereas the Control group was patients with better outcomes (NIHSS on discharge <10). The risk factor's determinant of this study is the PLR.

We collected the data from all acute ischemic stroke patients who were registered in admitted to the Sanglah General Hospital from January 2019 - April 2020 who met the inclusion and exclusion criteria. The inclusion criteria were: Stroke onset ≤ 24 hours, age of 40-80 years, MCA territory of ischemic stroke patients who have been confirmed by neurological clinical examination and CT scan of the head with NIHSS score at discharge (NIHSS score ≥10 or death for case group and NIHSS score <10 for the control group). The exclusion criteria were: a). patients with a previous history of stroke, confirmed by history and head CT scan; b). patient with a history of infection, using anti-inflammatory drugs, acute coronary heart disease, malignancy, autoimmune disease, history of surgery, or history of trauma; c). patient with chronic illness of other organs such as lungs, liver, or kidney; d). patient who received recombinant tissue plasminogen activator (r-TPA). Non-modified (age, gender, ethnicity) and modifiable (hypertension, dyslipidemia, diabetes mellitus, smoking status, alcohol consumption) risk factors, and subgroups analysis of ischemic stroke etiology i.e. thrombus and embolic, were assessed based on history, physical examination, and investigations.

The laboratory and imaging records were performed and relevant information collected. This study was approved by the Coordinating Ethics Committee of Universitas Udayana/ Sanglah Hospital with ethical clearance number: 1185/UN14.2.2.VII.14/LT/2020.

We used descriptive analysis to describe the basic characteristics of study subjects in each group. Bivariate analysis was performed for unpaired categorical comparative testing using the Chi-Square test with statistical significance determined based on the p-value. It is considered significant if $p < 0.05$, and the degree of association are by the Odds Ratio (OR) value. We analyzed the multivariate category using logistic regression, the variables included in the multivariate analysis are the same variable in the bivariate analysis which had a p-value <0.25.

RESULTS

This study involved 93 acute ischemic stroke patients. Subjects were divided into two groups, 47 acute ischemic stroke patients with NIHSS on discharge ≥10 or death (Cases) and 46 acute ischemic stroke patients with NIHSS at discharge <10 (Control). The mean age of Cases was 65.51±11.73 years, men accounted for 57.4 % while the mean age of Controls was 57.78±11.39 years, men accounted for 52.2%. The basic characteristics of study subjects based on the NIHSS upon discharged are shown in Table 1.

We investigated the association of PLR as the poor outcome predictor of acute ischemic stroke using NIHSS score, *Receiver Operating Characteristic* (ROC) value, and *Area Under the Curve* (AUC) value. The ROC curve in Figure 1 shows that the value of the PLR is above 50% of the line which is reliable for diagnosis. The AUC value obtained from the ROC method was 86.4% (95% CI 0.79 - 0.94, p = 0.001). The AUC value of 86.4% indicated sufficient diagnostic power statistically.

From the analysis of the ROC curve, a list of specificity and sensitivity figures was obtained using the optimal cut-off point. The results of the intersection showed 148 with 80.9% sensitivity and 79.6% specificity. (Figure 2) The patients was divided into a high-PLR group (≥ 148) and low PLR (<148) group.

Relationship between PLR and other acute ischemic stroke risk factors

There was a significant relationship between increased PLR with increased CRP (OR 4.54; 95% CI 1.87-10.97; p = 0.001) and dyslipidemia (OR = 2.71; 95% CI = 1, 14-6.49; p = 0.023).

The platelet to lymphocyte ratio and other factors related to acute ischemic stroke outcomes (Table 1)

The PLR as the independent variable and the acute ischemic stroke outcome as the dependent variable were assessed using bivariate analysis. The statistical test we used was *Chi-Square*

Table 1: Descriptive, bivariate, and multivariate analysis

Variables	Case (n=47)	Control (n=46)	Chi-square test		Logistic regression test	
			OR (CI 95%)	p-value	OR (CI 95%)	p-value
Gender						
Male	27 (57,4%)	24 (52,2%)	1.24	0.26		
Female	20 (42,6%)	22(47,8%)	(0.55-2.80)			
Age band (years), Mean (Standard Deviation)	65,51 (±11,73)	57,78 (±11,39)				
Elderly (>55 years old)	40 (85,1%)	27 (58,7%)	4.02	**0.05**		
Younger age (<55 years old)	7 (14,9%)	19(41,3%)	(1.48-10.87)			
Tribes						
Balinese	33 (70,2%)	33 (71,7%)	0.93	0.87		
Non-Balinese (Indonesian)	14 (29,8%)	13 (28,3%)	(0.38-2.3)			
Stroke onset (hours), mean (min-max)	8 (1-24)	6 (1-24)				
Stroke type						
Emboli	34 (72,3%)	22 (47,8%)	2.85	**0.016**		
Thrombus	13 (27,7%)	24 (52,2%)	(1.21-6.76)			
Hypertension						
Yes	39 (83%)	31 (67,4%)	2.36	0.082		
No	8 (17%)	15 (32,6%)	(0.89-6.3)			
Dyslipidemia						
Yes	28 (59,6%)	30 (65,2%)	0.79	0.574		
No	19 (40,4%)	16 (34,8%)	(0.34-1.82)			
Diabetes Mellitus						
Yes	17 (36,2%)	15 (32,6%)	1.17	0.718		
No	30 (63,8%)	31 (67,4%)	(0.50-2.76)			
Smoking						
Yes	15 (31,9%)	8 (17,4%)	2.23	0.105		
No	32 (68,1%)	38 (82,6%)	(0.84-5.93)			
Alcohol						
Yes	3 (6,4%)	4 (8,7%)	0.72	0.673		
No	44 (93,6%)	42 (91,3%)	(0.16-3.39)			
CRP (mg/L), Mean (min-max)	10 (0,41-348,98)	3 (0,3-33,59)				
High	29 (61,7%)	11 (23,9%)	5.13	**0.001**	4.5	**0.008**
Low	18 (38,3%)	35 (76,1%)	(2.09-12.57)		(1.49-13.58)	
Platelet (10^3/uL), Mean (Standard deviation)	245,85 (±85,94)	255,94 (±89,74)				
Lymphocyte (10^3/uL), Mean (min-max)	1,24 (0,53-2,92)	2,28 (0,88-4,46)				
PLR, Mean (min-max)	188,46 (71-400)	108,29 (35,28-245,20)				
High (≥148)	32 (68,1%)	14 (30,4%)	4,88	**0,001**	4.121	**0.009**
Low (<148)	15 (31,9%)	32 (69,6%)	(2,02-11,73)		(1.42-11.90)	
MPV (fL), Mean (min-max)	7,3 (4,48-11,31)	6,8 (5,30-14,39)				

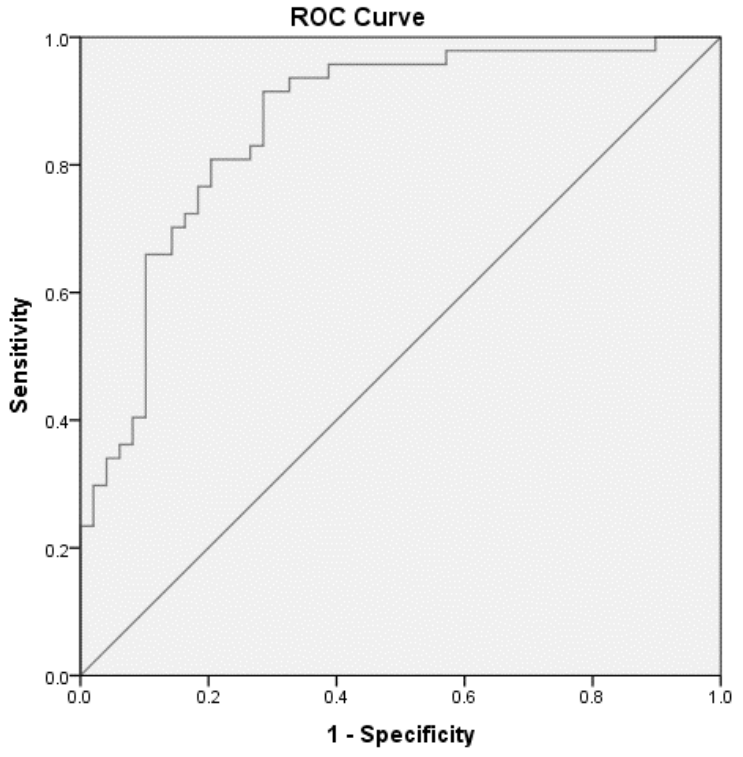

Figure 1: ROC - PLR results on treatment outcome for acute ischemic stroke

with *continuity correction* to obtain the value of *odds ratio* (OR) with a 95% CI. The level of significance of this study was determined with a probability value (p) <0.05. The Case group was dominated with high PLR whereas Controls group with low PLR. We also found other factors that was associated with the outcomes of acute ischemic stroke patients, i.e., high level of serum C-Reactive Protein (CRP), embolic stroke, and being elderly.

Independent risk factors of poor outcome in acute ischemic stroke patients

To determine the variables as the independent risk factors for poor outcomes in acute ischemic stroke

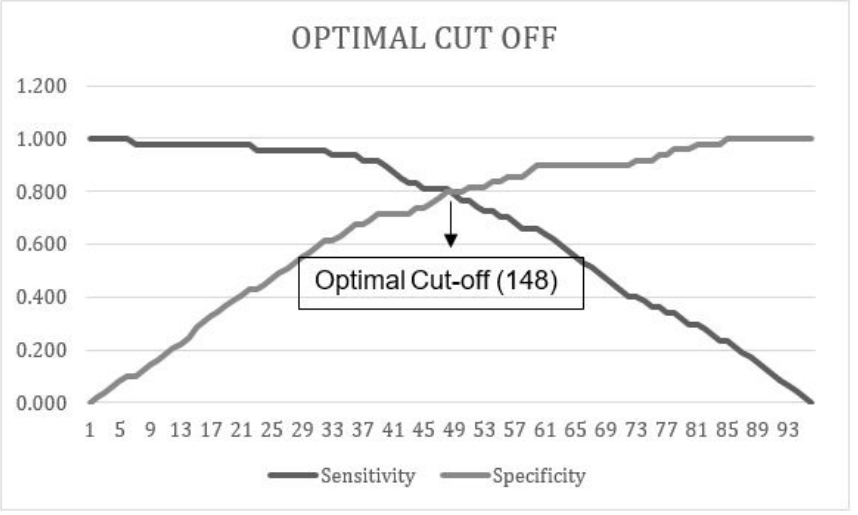

Figure 2: Optimal cut-off from PLR variable

patients, a multivariate analysis was performed using logistic regression methods. The variables included in the multivariate analysis were those that were obtained in the bivariate analysis with a value of $p<0.25$.

Based on the results of multivariate analysis, we found that the independent risk factors for the poor outcome of acute ischemic stroke patients were PLR (adjusted OR = 4.121; 95% CI = 1.42-11.90; p = 0.009) and high levels of CRP (*adjusted* OR = 4.5 ; CI 95% = 1.49-13.58; p = 0.008).

DISCUSSION

This case-control study showed that poor outcome after ischemic stroke was associated with high PLR. The results were consistent with other studies. Sung *et al*. suggested that PLR is increased in acute ischemic stroke patients with NIHSS ≥6 compared to acute ischemic stroke patients with NIHSS ≤6 (PLR cut-off value 128) with a sensitivity of 50% and a specificity of 81%; PLR was said to be a good predictor of a poor outcome in an ischemic stroke patient.[12] Altintas *et al*. showed that PLR value >145 increased the risk of death 4 to 5 times. The mortality rate was significantly higher in patients with PLR >145 when compared with PLR <145 (24.6 vs. 5.3%, p = .023).[13] Other studies also found that PLR was positively correlated with poor outcomes in acute ischemic stroke patients.[8,9] These investigations show a similar result as our study, that showed high PLR (≥148) significantly increased the risk of a poor outcome in acute ischemic stroke patients when compared to patients with low PLR (OR = 4.88; 95% CI = 2.02-11.73; p= 0.001).

There were studies that showed a high levels of PLR are a predictor of mortality in patients with cardiovascular disease.[14] Xu *et al*. showed that high PLR levels at admission can be used as a risk factor (95% CI 1.854-11.029, p= 0.001) for outcome of severity in ischemic stroke patients with OR 4.522.[15] Soylu *et al*. concluded that high PLR levels are an independent variable for stroke with an *adjusted* OR of 1.012 (95% CI 1.001-1.024, p= 0.031) so that it can be used as a simple and easily measured marker to predict the incidence of ischemic stroke.[16]

Platelets have an important role in atherosclerotic formation, especially in plaque and fibrin web formation as a result of unstable unruptured plaque. Platelets also release inflammatory mediators such as chemokine and cytokines.[15] Lymphocytes have an important role from the subtype of the leukocyte family that plays a role in an inflammatory process. Previous studies have shown the presence of immune system dysfunction after cerebral ischemia. Cerebral ischemia can induce lymphocyte apoptosis. Secondary lymphatic organs such as the spleen and thymus also experience atrophy after cerebral ischemia. Thus, cerebral ischemia induces a large and rapid lymphocyte apoptosis process in lymphoid organs and peripheral blood.[17] This appears 6-12 hours after cerebral ischemia which cause a decrease in blood lymphocytes.[18] High PLR levels reflect micro-thrombus formation, which increases the risk of stroke and is associated with poor outcomes in ischemic stroke patients.[19]

The subjects of this study were acute ischemic stroke patients with MCA territory involvement based on the known epidemiological data.[20-22] Acute ischemic stroke patients in the Case group were dominated by the elderly (85.1%). This study showed that the elderly patients had a significantly worse outcomes with acute ischemic stroke (OR 4.02; CI 95% 1.48-10.87; p = 0.005). This study used an elderly age limit> 55 years. In a 2015 study, patients age> 75 years were at risk of poor outcome in acute ischemic stroke (OR = 2.29; 95% CI 1.48-3.55; p = 0.001).[23] Another study in 2014 also found that old age is an independent risk factor for stroke severity (*adjusted* OR 2.98, 95% CI 1.75-5.06; p = 0.001).[24]

The embolic type of ischemic stroke also dominated the Case group (72.3%) and the rest were thrombus type (27.7%). Bivariate analysis with *Chi-Square* test showed that patients with acute ischemic stroke with an embolic type had a 2.85 times increased risk of experiencing a bad outcome compared to patients with acute ischemic stroke with a thrombus type (OR = 2.85; 95% CI = 1.21 -6.76; p = 0.016). Results on 1,915 stroke patients in the ASTRAL study showed that the proportion of severity strokes was greater in the cardioembolic type 49.3%, compared to the thrombus type 12.5%.[25] In the study, Bill *et al*. found by a multivariate analysis that cardioembolic stroke were significantly associated with the severity of stroke (OR = 1.74; p<0.01). This may be related to a wider distribution of cerebral vascular occlusion in embolic-type strokes, leading to more severe neurological deficits and worse treatment outcomes.[25,26]

Acute embolic strokes are often associated with a larger brain infarction and lymphopenia, whilst lymphopenia is a marker of decreased immune response and can lead to more severe brain damage and a higher risk of stroke-related infections. A high level of PLR is associated with

thrombus formation in the endothelium of blood vessels.[18] A high level of PLR is commonly found in acute ischemic stroke patients with carotid artery stenosis which is a large blood vessel and is also a frequent source of embolism to intracranial blood vessels.[16]

We also found that the median CRP level was higher in the Case group at 10 mg / L compared to the Control group at 3 mg / L. There are more cases of acute ischemic stroke with high CRP in the case group of 61.7%. Bivariate analysis with *Chi-Square test* showed that acute ischemic stroke patients with high CRP has significantly increased the risk of having a poor outcome of 5.13 times more compared to acute ischemic stroke patients with normal CRP (OR = 5.13; 95% CI = 2.09 - 12.57; p = 0.001). A study conducted by den Hertog *et al*. in 2009 evaluated the CRP levels in the first 12 hours since the stroke onset, they found that CRP levels value ≥ 7 increased the risk of poor outcome in patients with ischemic stroke (OR 1.6; 95% CI 1.1-2.4) or even death (OR 1.7; 95% CI 1.0-2.9).[27] Darmawan's study showed that high CRP levels in patients with acute ischemic stroke with onset ≤72 hours has significantly increased the risk of 3.65 times to experience a poor outcome compared to patients with acute ischemic stroke with normal CRP (RR = 3.65; CI 95% = 1, 65-8.07; p = 0.005).[28]

In stroke patients, there is an increase of pro-inflammatory cytokines, including CRP in both peripheral blood and cerebrospinal fluid, the increase in CRP correlates with clinical symptoms of a stroke. It has been reported that a higher CRP titer is found in stroke patients with more severe neurological deficits.[29]

Based on our results of multivariate analysis, the independent risk factors of the poor outcome for acute ischemic stroke patients were a high level of PLR and CRP. Acute ischemic stroke patients with high PLR had a 4.12 times greater risk of experiencing poor outcomes compared to the patients with low PLR (adjusted OR = 4.12; 95% CI = 1.42-11.90; p = 0.009). Acute ischemic stroke patients with high CRP had a 4.5 times greater risk of experiencing a poor outcome compared to patients with normal CRP (*adjusted* OR = 4.5; 95% CI = 1.49-13.58; p = 0.008).

In this study, it was found that patients with high PLR had a 4.54 times greater risk of increasing CRP (OR 4.54; 95% CI 1.87-10.97; p = 0.001). This was also found in the study of Idil Soylu *et al,* which stated that the results of PLR correlated with the CRP. Patients with high PLR also have an elevated serum CRP. Platelets play an important role in atherosclerotic formations; by contributing to plaque formation and fibrin net formation as a result of *unstable unruptured* plaque. In addition, platelets will also release inflammatory mediators such as chemokines and cytokines.[15] Lymphocytes have an important role from the subtypes of the leukocyte family that play a role in an inflammatory process.[16] Likewise, CRP is a marker of increased pro-inflammatory cytokines.[29]

Patients with ischemic stroke with high PLR had a 2.71 times risk of having dyslipidemia as the risk factors (OR = 2.71; 95% CI = 1.14-6.49; p = 0.023), this may have a relationship with PLR levels. which is highly correlated with the formation of micro-thrombus and atherosclerotic plaque both intra-cranial and extra-cranial.[19,29]

The limitations of the study were first, several risks (infarct volume and uric acid levels) of this study could not be rated because of limited funding and investigatory facilities. As a consequence of the retrospective study, some data was incomplete, and hard to get specific definitions (example: uncontrolled or controlled hypertension) that might lead to misinterpretation. Aside from that, we only evaluated a single PLR measurement after the first stroke incidence, so the prior high PLR could not be excluded.

In conclusion, high PLR and CRP are independent risk factors for adverse outcomes during treatment in acute ischemic stroke patients with MCA territory.

DISCLOSURE

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REFERENCES

1. Glushakova OY, Glushakov AV, Miller ER, Valadka AB, Hayes RL. Biomarkers for acute diagnosis and management of stroke in neurointensive care units. *Brain Circ* 2016; 2(1):28. Doi: 10.4103/2394-8108.178546.
2. Ropper AH, Samuels MA, Klein J. Adams and Victor's principles of neurology. 2014.
3. Franks ZG, Campbell RA, Weyrich AS, Rondina MT. Platelet-leukocyte interactions link inflammatory and thromboembolic events in ischemic stroke. *Ann N Y Acad Sci* 2010; 1207:11-7. Doi:10.1111/j.1749-6632.2010.05733.x
4. Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? *Curr Pharm Des* 2011;17 (1): 47-58. Doi: 10.2174/138161211795049804.
5. Liesz A, Suri-Payer E, Veltkamp C, *et al*. Regulatory

T cells are key cerebroprotective immunomodulators in acute experimental stroke. *Nat Med* 2009; 15(2): 192-9. Doi: 10.1038/nm.1927.
6. Ying HQ, Deng QW, He BS, *et al*. The prognostic value of preoperative NLR, d-NLR, PLR, and LMR for predicting clinical outcome in surgical colorectal cancer patients. *Med Oncol Northwood Lond Engl* 2014; 31(12): 305. Doi: 10.1007/s12032-014-0305-0.
7. Azab B, Shah N, Akerman M, McGinn JT. Value of platelet/lymphocyte ratio as a predictor of all-cause mortality after non-ST-elevation myocardial infarction. *J Thromb Thrombolysis* 2012; 34(3): 326-34. Doi: 10.1007/s11239-012-0718-6.
8. Sha L, Xu T, Ge X, Shi L, Zhang J, Gui H. Predictors of death within 6 months of stroke onset: A model with Barthel Index, platelet/lymphocyte ratio and serum albumin. *Nurs Open* 2020: 00:1-13. Doi: 10.1002/nop2.754.
9. Zhang Y, Jiang L, Yang P, Zhang Y. Comparison of lymphocyte count, neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in predicting the severity and the clinical outcomes of acute cerebral infarction patients. *Clin Lab* 2019: 65(7). Doi: 10.7754/Clin.Lab.2019.190102.
10. Cao X, Zhu Q, Xia X, *et al*. The correlation between novel peripheral blood cell ratios and 90-day mortality in patients with acute ischemic stroke. *PLoS One* 2020: 15(8):e0238312. Doi: 10.1371/journal.pone.0238312.
11. Zhang Y, Yang P, Wang J. Peripheral blood platelet to lymphocyte ratio as potential diagnostic and prognostic markers of acute cerebral infarction and its clinical significance. *Clin Lab* 2019;65(4). Doi: 10.7754/Clin.Lab.2018.180912.
12. Sung PH, Chen KH, Lin HS, Chu CH, Chiang JY, Yip HK. The Correlation between severity of neurological impairment and left ventricular function in patients after acute ischemic stroke. *J Clin Med* 2019;8(2). Doi: 10.3390/jcm8020190.
13. Altintas O, Altintas MO, Tasal A, Kucukdagli OT, Asil T. The relationship of platelet-to-lymphocyte ratio with clinical outcome and final infarct core in acute ischemic stroke patients who have undergone endovascular therapy. *Neurol Res* 2016: 38(9): 759-65. Doi: 10.1080/01616412.2016.1215030.
14. Sun XP, Li J, Zhu WW, *et al*. Impact of platelet-to-lymphocyte ratio in clinical outcomes in patients with ST-segment elevation myocardial infarction. *Angiology* 2017; 68(4): 346-53. Doi: 10.1177/0003319716657258.
15. Badimon L, Padro T, Vilahur G. Atherosclerosis, platelets and thrombosis in acute ischaemic heart diseases. *Eur J Acute Cardiovasc Care* 2012; 1(1): 60-74. Doi: 10.1177/2048872612441582.
16. Soylu AI, Cortcu SA, Uzunkaya F, *et al*. The correlation of the platelet-to-lymphocyte ratio with the severity of stenosis and stroke in patients with carotid arterial disease. *Vascular* 2016: 25(3): 299-306. Doi: 10.1177/1708538116673770.
17. Grotta JC, Albers GW, Broderick JP, *et al*. Stroke pathophysiology, diagnosis, and management. *Stroke Pathophysiol Diagn Manag* [Internet]. 2015 [cited 2021 Jan 18], p. 695-8. Available from: https://eprint.ncl.ac.uk/249619
18. Meisel C, Schwab JM, Prass K, Meisel A, Dirnarl U. Central nervous system injury-induced immune deficiency syndrome. *Nat Rev Neurosci* 2005; 6(10): 775-86. Doi: 10.1038/nrn1765.
19. Altintas O, Tasal A, Niftaliyev E, Kucukdagli OT, Asil T. Association of platelet-to-lymphocyte ratio with silent brain infarcts in patients with paroxysmal atrial fibrillation. *Neurol Res* 2016; 38(9): 753-8. Doi: 10.1080/01616412.2016.1210357.
20. Ng YS, Stein J, Ning M, Black-Schaffer RM. Comparison of clinical characteristics and functional outcomes of ischemic stroke in different vascular territories. *Stroke* 2007; 38(8): 2309-14. Doi: 10.1161/STROKEAHA.106.475483.
21. Brainin M, Heiss D. Textbook of stroke medicine. Cambridge University Press; 2019, 475: 102-4.
22. Markus H, Pereira A, Cloud G. Stroke Medicine (Oxford Specialist Handbooks in Neurology) [Internet]. Stroke Medicine. Oxford University Press; 2010, 8-9 [cited 2021 Jan 18]. Available from: https://oxfordmedicine.com/view/10.1093/med/9780199218776.001.0001/med-9780199218776
23. Manabe Y, Morihara R, Matsuzono K, *et al*. Estimation of the Presence of Small Dense Lipoprotein Cholesterol in Acute Ischemic Stroke. *Neurol Int* 2015; 7(1): 15-8. Doi: 10.4081/ni.2015.5973.
24. Corso G, Bottacchi E, Tosi P, *et al*. Outcome predictors in first-ever ischemic stroke patients: A population-based study. *Int Sch Res Not* [Internet]. 2014 Dec 25 [cited 2021 Jan 18]: 2014. Available from: https://www.ncbi.nlm.nih.fov/pmc.articles/PMC4897223/. Doi: 10.1155/2014/904647.
25. Bill O, Zufferey P, Faouzi M, Michel P. Severe stroke: patients profile and predictors of favorable outcomes. *J Thromb Haemost JTH* 2013: 11(1): 92-9. Doi: 10.1111/jth.12066.
26. Caplan LR. Caplan's Stroke. Cambridge University Press: 2016, 651.
27. den Hertog HM, van Rossum JA, van der Worp HB, *et al*. C-reactive protein in the very early phase of acute ischemic stroke: association with poor outcome and death. *J Neurol* 2009: 256(12):2003-8. Doi: 10.1007/s00415-009-5228-x.
28. Darmawan O, Adnyana O, Purwana TE, Tini K, Budiarsa IGN, Dewi AAAPL. High Neutrophil lymphocyte ratio as predictor of poor outcome in patients with acute ischemic stroke in Sanglah General Hospital Denpasar. *J Neurol Sci* 2017: 381:983. Doi: 10.1016/j.jns.2017.08.2769.
29. Wincbeck K, Poppert H, Etgen T, Conrad B, Sander D. Prognostic relevance of early serial C-reactive protein measurements after first ischemic stroke. *Stroke* 2002: 22(10): 2459-64. Doi: 10.1161/01.str.0000029828.51413.82.