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Original Article

Correlation between Mean Platelet Volume, Fibrinogen and D-dimer with NIHSS Score

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Abstract

Introduction: Stroke is a clinical syndrome that develops rapidly due to focal or global brain disorders with symptoms last for >24 hours and potentially cause death. Due to the consideration that this Mean Platelet Volume (MPV) marker is not invasive, easy to do and is in line with the pathogenesis of stroke, researchers are interested in carrying out this research. And hopefully this research can provide information for the world of education and health about changes in MPV, fibrinogen and D-dimer in ischemic stroke patients. So it can be taken as consideration in the early management of ischemic stroke patients.

Subject and Methods: This research was an observational study with a cross-sectional design at Haji Adam Malik General Hospital from October to November 2023. The research subjects were stroke patients who were treated in emergency room and met inclusion criteria. This research was to study about correlation of MPV, fibrinogen, and D-dimer with NIHSS scores of ischemic stroke patients. The method used in this research is the Pearson correlation test where data was normally distributed. All statistical tests with a p value < 0.05 were considered significant.

Results: The mean MPV was 10.4 ± 1.6, while the mean NIHSS value was 19.9 ± 8.7, and there was a statistically significant correlation between the MPV value and the NIHSS score ($p<0.05$). The mean fibrinogen was 421.9 ± 109.3, while mean NIHSS value was 19.9 ± 8.7, and there was a statistically significant correlation between fibrinogen values and NIHSS scores ($p<0.001$). The mean D-Dimer was 8.0 ± 11.3, while the mean NIHSS value was 19.9 ± 8.7, and showed a statistically significant correlation between D-Dimer value and NIHSS score ($p<0.05$). The r value of MPV, fibrinogen, and D-dimer on NIHSS score was 0.494; 0.495; and 0.504. The regression coefficient for MPV variable is 0.093, therefore MPV variable influence on NIHSS variable is positive.

Conclusion: There is a strong correlation between D-dimer and the NIHSS score, and a moderate correlation between MPV and fibrinogen with NIHSS score.

Keywords: Mean Platelet Volume (MPV), fibrinogen, D-dimer, NIHSS

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I. Introduction

According to the World Health Organization (WHO), stroke is a clinical syndrome that develops rapidly due to focal or global brain disorders with symptoms that last for >24 hours and can cause death without any other clear cause other than vascular abnormalities. There are approximately 5.5 million deaths caused by cerebrovascular disease worldwide. Globally, 2.7 million people died caused by ischemic stroke and 2.8 million people died caused by hemorrhagic stroke. The stroke prevalence in Indonesia has increased to 10.9% in 2018 from 7% in 2013. Based on doctors' diagnoses in Indonesian residents aged ≥ 15 years, the stroke prevalence in 2018 was 10.9%, which was estimated to reach 2,120,362 people.[1,2] The inflammatory process in ischemic stroke involves endothelial activation, destruction of blood-brain

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barrier, accumulation of oxidants, inflammatory mediators, neurotoxins and massive leukocyte and platelet cells infiltration. The association of inflammatory processes with stroke increases the incidence of mortality and disability. The role of inflammatory markers is quite large in assessing course of ischemic stroke, one of which is mean platelet volume (MPV).[3,4]

Mean platelet volume (MPV) is mean volume of platelets in circulation which describes state of platelet stimulation and production.[5,6] Endothelial activation, destruction of blood-brain barrier, accumulation of oxidants, inflammatory mediators, neurotoxins and massive leukocytes and platelets infiltration in stroke have all been associated with greater platelet aggregation in response to adenosine diphosphate (ADP) and collagen, leading to a presumed MPV values increase. associated with the severity of ischemic stroke and hemorrhagic stroke.[7] The D-dimer value is a prognostic parameter that is generally used in ischemic stroke event. D-dimer is a product of fibrin degradation that occurs after thrombus formation. In several studies, baseline D-dimer values were used to predict early neurological deterioration (END) occurrence. High D-dimer levels indicate excessive activation of coagulation and fibrinolytic systems. In these conditions, additional thrombus can form easily, allowing stroke recurrence through various mechanisms such as embolism, in situ thrombosis, and atherogenic plaque instability. High D-dimer levels can indicate a large and severe stroke. D-dimer has been shown to positively correlate with infarct volume and severity of neurological deficits.[8]

Inflammation is the process underlying atherosclerosis process which can be identified using fibrinogen. Patients with ischemic stroke had significantly increased mean fibrinogen values (> 4mg/dl). A significant correlation between fibrinogen levels and presence of ischemic lesions on brain CT was observed: patients with fibrinogen levels > 3.41 mg/dl showed a 3.29-fold increased risk of ischemic lesions.[9] Neurological deficits, such as in ischemic stroke, often lead to disability, and impaired quality of life. Therefore, stroke outcome can be assessed both from presence of functional or structural disorders of the body (impairment), activity (disability), and participation (handicap) which suffered by the patient. The National Institutes of Health Stroke Scale (NIHSS) is an instrument used to measure the level of functional impairment or neurological deficit (impairment) due to an ischemic stroke.[10] Based on the considerations above, researchers were interested in conducting research related to MPV in stroke because this marker is not invasive, easy to do and in line with stroke pathogenesis. Researchers wish that MPV can become an alternative marker for long-term monitoring and prognosis of ischemic stroke patients.

II. Material and Methods

This research was an observational study with a cross-sectional data collection method to assess the correlation between Mean Platelet Volume (MPV), fibrinogen and D-dimer with NIHSS score of stroke patients in the emergency room at Haji Adam Malik General Hospital from October to November 2023. The research subjects were stroke patients who were treated in an emergency room and met the inclusion criteria. Sampling was carried out consecutively with a minimum sample size of 30 samples for each group. The study was accessible to people between the ages of 18 and 65 and have been recognized with an ischaemic stroke consistent with the countrywide Institute of health Stroke Scale (NIHSS). Patients with malignant diseases, autoimmune illnesses, extreme infections, liver illnesses, platelet transfusions, hematological illnesses, and hemorrhagic strokes were not allowed to participate.

Research procedure

The families of research subjects were given an explanation about research purpose and benefits, then the research subjects were given an explanation to fill out a letter of approval to take part in this research or informed consent. An examination with NIHSS score was carried out on ischemic stroke patients who were treated in the emergency room within <12 hours. MPV, Fibrinogen and D-dimer examination was carried

out in ischemic stroke patients.

Statistical Analysis

Data analysis was carried out using SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) software for Windows. An overview of research subjects characteristics is presented in tabulated form. Correlation of MPV, fibrinogen, D-dimer WITH NIHSS scores of ischemic in stroke patients used the Pearson correlation test where data was normally distributed. If the data was not normally distributed, Spearman rank test was used. All statistical tests with a p value < 0.05 were considered significant. And a simple linear regression test was also carried out to assess MPV variable as a predictor of ischemic stroke severity.

III. Result

This research aimed to assess correlation between Mean Platelet Volume (MPV), fibrinogen and D-dimer with NIHSS score in stroke patients. The research subjects who met the inclusion and exclusion criteria totaling 30 people with total dropouts was 6 people. In table 1, it was found that majority research subjects were men as many as 21 people (70%) compared to 9 women (30%). Mean age in this research was 55.9 ± 7.9, Mean body mass index (BMI) was 22.1 ± 2.8 and mean GCS was 10.5 ± 3.6. In this research, it was found that 20 people (66.7%) smoking while 10 people (33.3%) did not smoke. There were 25 people with diabetes (83.35%) while 5 people (16.7%) without diabetes. There were 27 people with hypertension (90%) while there were 3 people without hypertension (10%). Mean MPV value was 10.4 ±1.6, while mean NIHSS value was 19.9 ± 8.7. Mean fibrinogen value was 421.9 ± 109.3. Mean D-dimer value was 8.0 ± 11.3. Based on table 2, mean MPV value with moderate NIHSS score was 9.3 ± 1.1, while mean MPV value with severe NIHSS score was 11.4 ± 1.4. The comparison between MPV value and NIHSS score was statistically significant with a p value <0.001. Mean fibrinogen value with moderate NIHSS score was 364.3 ± 121.9, while mean fibrinogen value with severe NIHSS score was 476.9 ± 69.7. The comparison between fibrinogen value and NIHSS score was statistically significant with a p value <0.009. The mean D-dimer value with moderate NIHSS score was 2.0 ± 1.9, while mean D-dimer value with severe NIHSS score was 14.6 ± 13.8. The

Table 1. Research Subjects Characteristics

Characteristics	Total
Gender, n/%	
Male	21 (70%)
Female	9 (30%)
Age, mean±SD	55.9±7.9
BMI , mean±SD	22.1±2.8
GCS, mean±SD	10.5±3.6
Smoking, n/%	
Yes	20 (66.7%)
No	10 (33.3%)
Diabetes, n/%	
Yes	25 (83.3%)
No	5 (16.7%)
Hypertension n/%	
Yes	27 (90%)
No	3 (10%)
MPV	10.4±1.6
Fibrinogen	421.9±109.3
D-dimer	8.0±11.3

Table 2. Correlation of MPV, Fibrinogen, and D-dimer Values with NIHSS Scores

No	Variables	NIHSS		P Value
		Moderate	Severe	
1	Mean Platelet Volume	9.3±1.1	11.4±1.4	0.001*
2	Fibrinogen	364.3±121.9	476.9±69.7	0.009*
3	D-dimer	2.0±1.9	14.6±13.8	0.001*

* Mann Whitney Test

Table 3. Correlation between MPV Values and Fibrinogen

Variable	Mean Platelet Volume	Fibrinogen	P. Value
Mean±SD	10.4±1.6	421.9±109.3	0.139

* Spearman Test

comparison between D-dimer value and NIHSS score was statistically significant with a p value <0.001. Based on table 3, mean fibrinogen value was 421.9 ± 109.3, while mean MPV value was 10.4 ± 1.6. These results showed that correlation between MPV value and Fibrinogen was not statistically significant with a p value <0.139. Based on table 4, mean MPV value was 10.4 ± 1.6, while mean D-dimer value was 8.0 ± 11.3. The correlation between MPV and D-dimer values obtained statistically significant results with a p value <0.001. Based on table 5, the significance level was <0.005. which means that regression can be used to predict MPV variables or in other words there was an influence of NIHSS variables on MPV variables. The table above also explains correlation/correlation value (R), which was 0.494. From this output, the coefficient of determination (R square) was 0.244, which means that the influence of MPV variable on NIHSS variable was 24.4%. The table above also explains that the constant value was 8.573. The MPV variable regression coefficient was 0.093 which means that for every 1% increase in NIHSS value, the MPV value will increase by 0.093. The regression coefficient was positive therefore direction MPV variable influence on NIHSS variable was positive.

Table 4. Correlation between MPV Values and D-dimer

Variable	Mean Platelet Volume	D-dimer	P. Value
Mean±SD	10.4±1.6	8.0±11.3	0.001*

* Spearman Test

Table 5. MPV as a Predictor of Ischemic Stroke Severity

Variable	Mean±SD	P. Value	R value	R Square value	Regression coefficient (ß) constant	Regression coefficient (ß) NIHSS value
MPV	10.4±1.6					
NIHSS value	19.9±8.7	0.005*	0.494	0.244	8.573	0.093

Simple Linear Regression Test

IV. Discussions

In this research, a significant correlation was found between MPV value and NIHSS score with a significance level with p value <0.005. Meanwhile, the influence of MPV variable on NIHSS variable was 24.4%, and it was also found that regression coefficient for the MPV variable was 0.093, indicating that for every 1% increasement of NIHSS value, the MPV value will be increased by 0.093. The regression coefficient is positive therefore the influence of MPV variable on NIHSS variable was positive. MPV and platelet count are related to stroke severity and have a high predictive value for distinguishing between severe and mild ischemic stroke. Thus, we can use MPV and platelet count as prognostic markers in acute ischemic stroke.[11] This research is also in accordance with some research which states that MPV value has a significant correlation with NIHSS score. MPV value appears to be higher in ischemic stroke with an increase in NIHSS score above 11.[12] Compared to smaller platelets, increased MPV is assumed to be linked to a stronger thrombogenic potential. Larger platelets are more prone to form thrombi because they are denser, aggregate with collagen

more quickly, express more glycoprotein Ib and IIb/IIIa receptors, and contain larger quantities of thromboxane A2. The average MPV value found in this investigation was 10.4 ± 1.6, exceeding the standard MPV range of 7.5–11.5. MPV is a marker of platelet feature and is related to indicators of platelet interest such as aggregation and launch of thromboxane A2, platelet factor four, and thromboglobulin beta. Platelet size is determined by the time of platelet formation and destruction. Small platelets have denser and more potent granules and are greater thrombogenic than massive platelets. expanded MPV, as a marker of expanded platelet aggregation capability, slows blood float to target mind tissue and reduces perfusion, thereby growing the danger of infarction, in particular in ischemic stroke.[13,14]

Meanwhile, it was found that MPV has wide variability. Therefore, currently MPV doesn't have a role in making a diagnosis or determining disease prognosis. The wide variability of MPV is likely due to platelet count, gender, age, and ethnicity, as well as the very poor standardization of methodology used for MPV measurement, making it impossible to decide whether a patient is normal or otherwise. The large number of physiological variables that influence platelet size and poor standardization of MPV measurements mean that small differences in parameters identified by clinical studies in various conditions cannot be used for clinical purposes.[15] Platelets in blood circulation were in the form of thin discs. Rapid morphological changes, possibly related to blood clotting and occur when platelets are removed from the body. Blood platelet morphology has been studied under various conditions by fixing platelets, observing by microscope, and classifying them according to their shapes. It has been found that most platelets retain their original shape in citrated or oxalated blood stored at 37^{o}C.[16]

Technological developments have made it possible to obtain repeatable and trouble-free data on platelet length and distribution; yet, the scientific interpretation of this data remains dubious. The lack of laboratory uniformity is one of the main barriers to these measures' medicinal relevance. Although many laboratory variables, such as temperature, garage time, anticoagulant, and dimension methodology, are known to affect platelet volume, there is no established way to measure MPV. The majority of researchers record platelet volume within a few hours following venipuncture; nevertheless, there is no standard approach employed, and some studies are difficult to be interpreted because of missing information regarding laboratory procedures. In order to standardize platelet quantity size strategies, doctors should collaborate with laboratories if they wish to employ platelet parameters. The duration for platelet evaluation should be established since such measurements must be made on EDTA samples to guarantee significant scientific utility. Any further confusing factor in the interpretation of MPV is the common variable in platelet number as measured by platelet depend, indicating that the laboratory should provide an ordinary range adjusted for the platelet count of the affected individual. Notwithstanding problems with laboratory standards, studies have demonstrated that normal people's platelet counts remain rather stable throughout time.

Consequently, any extreme departure from the norm must be considered abnormal and cannot be considered a gradual alteration in physiology. When evaluating compromised platelet production, a physician can make use of platelet quantity. Additionally, it helps to differentiate between thrombocytopenia's hyperdestructive and hypoproductive causes and screens for conditions marked by increased platelet consumption. Research on the connection between platelets and atherosclerosis is ongoing; studies have shown that myocardial infarction and stroke are associated with changes in platelet markers. The relationship between platelet size, reactivity, and thrombus formation was highlighted by a recent large study that revealed MPV as an independent risk factor for coronary ischemia events in patients with myocardial infarction. Although the association between platelet markers and heart disease has not been investigated prospectively to date, platelet markers may have broad clinical utility and be used to treat heart disease in individuals at risk

for atherosclerotic disease if they can predict ischemic events in large prospective studies. It has therapeutic potential.[17]

In this research, a significant correlation was found between fibrinogen values and NIHSS scores. This research is in accordance with some research which stated that fibrinogen values have a significant correlation with NIHSS score. In this research, a correlation was found between fibrinogen levels at hospital admission and severity of symptoms as assessed by NIHSS score of stroke patients in first 6 hours after stroke onset.[18] Of the 31 patients in the high fibrinogen group, 16 (57.4%) were extreme (29.6%), 11 were mild (20.4%) and 4 were moderate (7.4%). Regarding the association between NIHSS assessment and plasma fibrinogen concentration on day 14 after initiation, increased fibrinogen concentration was associated with 2 (3.7%) severe, 22 (40.7%) moderate and 7 (13.0%) mild cases.[2] Fibrinogen is a marker of tissue inflammation in the acute phase, namely levels increase in response to tissue damage and inflammation. Fibrinogen as an acute phase protein is strongly associated with atherosclerosis and cardiovascular risk factors. The mean fibrinogen value obtained in this research was 421.9 ± 109.3, which is above normal fibrinogen value (200–400mg/dl). High fibrinogen levels are an independent risk factor related to histological composition of atherosclerotic plaque formation which predisposes to rupture and cause thrombosis. A significant role for fibrinogen is found in the viscosity of plasma and whole blood. Moreover, it is connected to platelet aggregation, primary hemostasis, and the relationship between endothelial cells and leukemia. Its higher levels are linked to atherosclerosis, which can cause ischemic strokes.[2,19]

In this research, a significant correlation was found between D-dimer value and NIHSS score. This research is in accordance with previous research which stated that D-dimer value has a significant correlation with NIHSS score, it was found that 87 patients experienced increased D-dimer levels, 42.53% were reported to have suffered a severe stroke with NIHSS score of 21-42 followed by 29.88% with moderate to severe stroke with an NIHSS score of 16–20, and 25.28 % had a score in the range 5–15, namely a medium score. In this study, NIHSS score was higher in patients who had increased D-dimer levels.[20] Increasing plasma D-dimer levels at hospital admission were significantly associated with poor outcomes in ischemic stroke patients. This suggests a potential role of plasma D-dimer levels as a predictive marker for short-term adverse outcomes in ischemic stroke patients.[19] In ischemic stroke patients, higher D-dimer levels within 24 hours of stroke onset were associated with recurrence and 30th day mortality, as well as poor functional outcomes on 30th and 90th days. However, more research is needed to clarify this issue.[20]

D-dimer is a protein that is formed when blood clots break down. Blood clots themselves form when there is an injury, or a certain inflammatory process in the body. D-dimer is also a degradation product of the most specific and minor fibrinolysis process found in blood circulation. The mean D-dimer value obtained in this research was 8.0 ± 11.3, which is above normal D-dimer value (0-0.4 µg/mL). Elevated D-dimer can be a sign that there is a certain blood disorder or inflammation in the body. Plasma D-dimer levels increase during blood thrombosis and fibrin degradation, therefore plasma D-dimer can be a biomarker of hemostatic disorders and thrombosis. Increased plasma D-dimer levels are reported to be a determinant of stroke development, infarct volume and stroke incidence in cases of acute ischemic stroke.[20] Without serial measurements of circulating D-dimer levels, D-dimer test results cannot produce data regarding how long blood clot formation after D-dimer levels increase or how long D-dimer levels remain elevated in the circulation. A number of different commercial D-dimer assays are available, therefore results cannot necessarily be generalized to all assays. Additionally, D-dimer levels are rarely elevated in healthy individuals, and also elevated in many diseases and physiological conditions associated with thrombosis and thrombolysis. Patients may have had extensive vascular disease before stroke onset therefore possibility

that plasma D-dimer increases under other pathologic conditions cannot be ruled out.[19] Basically, ischemic stroke process begins with a blood vessel being blocked by a thrombus or embolism which causes brain cells to experience metabolic disorders, because they do not receive a supply of blood, oxygen and energy. If this process continues, brain tissue ischemia will occur, causing temporary or permanent damage, called infarction. The local metabolic changes mentioned above cause a continuous change cycle leading to increased neuronal damage and cell death. stimulates further cell damage, leading to local biochemical changes, which in turn cause more nerve damage. This process can be illustrated by increasing NIHSS scores.[7]

The National Institutes of Health Stroke Scale (NIHSS) is a systematic assessment tool that quantifies the neurological impairment associated with stroke. It is used to evaluate stroke patients, determine appropriate treatment, predict clinical outcome, initial prognosis and complications, and identify necessary interventions in addition to assessing the extent of neurological impairment. It is employed to forecast the result, ascertain the first prognosis, identify problems, and identify required treatments. The NIHSS evaluates verbal, motor, sensory, conscious, visible, visual field, extraocular, coordination, overlook, and language function. It is also frequently used to gauge the severity of ischemic stroke. The final ratings vary from 0 (no impairment) to the best rating; the degree of neurological deficit is classified as moderate (1–4), mild (five–14), intense (15–20), and truly severe (21 or more points) based on the NIHSS rating. The mean NIHSS score on this examination was 19.9 ± 8.7, which served as the standard assessment score for stroke cases. The additional severe the stroke, the higher the patient's NIHSS score.[6]

The NIHSS provides a rapid and reliable assessment of the severity of an acute stroke; nevertheless, it is not suitable for mirroring useful exchange as a measure of post-treatment progress, particularly when it comes to the routine monitoring of patients with low NIHSS scores. The NIHSS has its advantages, but it is not always appropriate as a daily gauge of development or as a tool for determining overall outcomes and whether or not patients are improving and, how the advancing processes are. These usual results are consistent with those seen in trials run by the National Institute of Neurological Disorders and Stroke (NINDS), where patient outcomes were better from the beginning of treatment compared to 24 hours later and at discharge based only on NIHSS criteria. More likely, the sensitivity increased throughout follow-up because a few healthy brain regions help the patient to recover little by little. Up to certain critical factors, any metric can be utilized, regardless of sensitivity, to detect reorganization. The NIHSS has a very high sensitivity when posterior flow characteristics and the proper hemisphere are not accurately visualized.

However, when comparing patients with lesions in the posterior move and right hemisphere to those with left hemisphere stroke, there was no difference in the NIHSS's sensitivity to measure population improvement. However, the NIHSS rating at admission determines the sensitivity of the scale, with patients who have an NIHSS rating of eight or above more likely to demonstrate a discernible improvement. This will replicate the truth that patients with better stroke rates have a higher chance of recuperating, however sufferers with decreased ranks need to totally recover to meet the necessities. It addition it means that the NIHSS is generally touchy sufficient to come across adjustments in patients with big artery blockage and high NIHSS ratings upon admission. However it is unhelpful in sufferers with little perforating infarcts and low ratings. Unfortunately, despite their low scores, people who have had a "mild stroke" (NIHSS < five) continue to experience significant difficulties with their social reintegration, were able to return to work, and had interpersonal interactions. The effect of lowering criteria for determining scientific development is assessed in light of the requirement for a change in NIHSS rating of four points or more to be considered a major practical shift. The inter-rater variability of the NIHSS is a problem when utilizing a lower cut-off price, and doing so may also increase the percentage of

false-fine adjustments in the check. This makes determining the appropriate threshold becoming difficult and it is entirely dependent on personal qualities. Because of the non-linearity of the NIHSS, intentional damage must be taken into account in addition to medical breakthroughs. This presents extra challenges. Patients with encephalopathy may not exhibit significant degeneration if the alternative rate is between 18 and 20, whereas recently diagnosed paraplegics exhibit significant degeneration if the alternative rate is between one and several. This highlights the need of using the examiner's judgment in addition to the numerical data.[1]

V. Conclusion

MPV, fibrinogen, and D-dimer had a significant effect on NIHSS score. There is a strong correlation between D-dimer value and NIHSS score, and a moderate correlation between MPV and fibrinogen with NIHSS score.

References

1. Farooque U, Lohano AK, Kumar A, Karimi S, Yasmin F, Bollampally VC, et al. Validity of National Institutes of Health Stroke Scale for severity of stroke to predict mortality among patients presenting with symptoms of stroke. Cureus. 2020;12(9): 1–11. Doi:10.7759/cureus.10255.

2. Akbar M, Arif M, Kaelan C, Karman, Muis A, Seweng A. Hubungan Kadar Fibrinogen Plasma dengan Luaran Klinis Strok Iskemik Akut. Program Studi Biomedik Program Pascasarjana Universitas Hasanuddin Makassar. 2013. Available in: https://core.ac.uk/works/17375678.

3. Murphy SJX, Werring DJ. Stroke: causes and clinical features. Medicine (Abingdon). 2020;48(9): 561–66. Doi:10.1016/j.mpmed.2020.06.002.

4. Thayabaranathan T, Kim J, Cadilhac DA, Thrift AG, Donnan GA, Howard G, et al. Global stroke statistics. Int J Stroke. 2022;17(9):946–56. Doi: 10.1177/17474930221123175.

5. Chang JC. Stroke classification: critical role of unusually large von Willebrand factor multimers and tissue factor on clinical phenotypes based on novel "two-path unifying theory" of hemostasis. Clinical Apply Thromb Hemost. 2020;26:1-23. Doi:10.1177/1076029620913634.

6. Su Z, Ye Y, Shen C, Qiu S, Sun Y, Hu S, et al. Pathophysiology of ischemic stroke: noncoding RNA role in oxidative stress. Oxid Med Cell Longev. 2022:1-12. Doi:10.1155/2022/5815843

7. Setyopranoto I, Bayuangga HF, Panggabean AS, Alifaningdyah S, Lazuardi L, Dewi FST, et al. Prevalence of stroke and associated risk factors in Sleman District of Yogyakarta Special Region, Indonesia. Stroke Res Treat. 2019: 1–8. Doi:10.1155/2019/2642458.

8. Nam KW, Kwon HM, Lee YS. Clinical significance of D-dimer levels during acute period in ischemic stroke. Thrombosis J. 2023;21:55. Doi: https://doi.org/10.1186/s12959-023-00496-1.

9. Patil S, Rossi R, Jabrah D, Doyle K. Detection, diagnosis and treatment of acute ischemic stroke: current and future perspectives. Front Med Technol. 2022;4:748949 Doi:10.3389/fmedt.2022.748949

10. Ghahremanfard F, Asghari N, Ghorbani R, Samaei A, Ghomi H, Tamadon M. The Relationship between mean platelet volume and severity of acute ischemic brain stroke. Neurosciences. 2013;18(2): 147–51. Available in: https://pubmed.ncbi.nlm.nih.gov/23545613/.

11. Antonio M, Puddu GM, Cenni A, Silvestri MG, Giuzio R, Rosati M, et al. Mean platelet volume (MPV) increase during acute non-lacunar ischemic strokes. Thromb Res. 2019;123(4): 587–91. Doi:10.1016/j.

thromres.2008.03.025.

12. Korniluk A, Koper-Lenkiewicz OM, Kamińska J, Kemona H, Dymicka-Piekarska V. Mean Platelet Volume (MPV): new perspectives for an old marker in the course and prognosis of inflammatory conditions. Mediators Inflamm. 2019, 1–14. Doi:10.1155/2019/9213074.

13. Koupenova M, Kehrel BE, Corkrey HA, Freedman JE. Thrombosis and platelets: an update. Eur Heart J. 2017; 38(11):785–91. Doi: https://doi.org/10.1093/eurheartj/ehw550

14. Demirin H, Ozhan H, Ucgun T, Celer A, Bulur S, Cil H, et al. Normal range of mean platelet volume in healthy subjects: Insight from a large epidemiologic study. Thromb Res. 2011; 128(4): 358–60. Doi: 10.1016/j.thromres.2011.05.007

15. Margraf A, Zarbock A. Platelets in inflammation and resolution. J Immunol. 2019; 203(9): 2357–367. Doi: https://doi.org/10.4049/jimmunol.1900899.

16. Xie D, Xiang W, Weng Y, Li J, Xu L, Zhang X, et al. Platelet volume indices for the prognosis of acute ischemic stroke patients with intravenous thrombolysis. Int J Neurosci. 2019;129(4): 344-49. Doi: https://doi.org/10.1080/00207454.2018.1536054.

17. Pikija S, Trkulja V, Mutzenbach JS, Mccoy MR, Ganger P, Sellner J. Fibrinogen consumption is related to intracranial clot burden in acute ischemic stroke: a retrospective hyperdense artery study. J transl Med. 2016;14(1): 250. Doi: 10.1186/s12967-016-1006-6.

18. Peycheva M, Deneva T, Zahariev Z. The role of fibrinogen in acute ischaemic stroke. Neurol Neurochir Pol. 2021; 55(1): 74–80. Doi:10.5603/PJNNS.a2020.0094

19. Goyal P, Sharma P, Sharma A. Assessment of D-dimer levels in stroke patients. J. Cardiovasc Dis Res 2023;14(1):3783–787. Available in: https://jcdronline.org/admin/Uploads/Files/63f5d9c2176f88.48022900.pdf.

20. Zhang J, Liu L, Tao J, Song Y, Fan Y, Gou M, et al. Prognostic role of early D-dimer level in patients with acute ischemic stroke. Plos One. 2019; 14(2): e0211458. Doi: https://doi.org/10.1371/journal.pone.0211458.