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Original Article

Correlation Between Platelet Index, Neutrophil-Lymphocyte Ratio, and Mean Platelet-Volume Lymphocyte Ration with Lesion in Chronic Coronary Syndrome Based on SYNTAX Score

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ABSTRACT

Background: Platelet aggregation and inflammation have been associated with atherosclerosis, and inflammatory parameters such as mean platelet volume (MPV), platelet distribution width (PDW), neutrophil-lymphocyte ratio (NLR), and mean platelet-lymphocyte volume ratio (MPLVR) are often used. However, the relationship between these inflammatory parameters and the SYNTAX Score in CAD remains uncertain.
Objective: The purpose of this study was to investigate the relationship between angiographic SYNTAX score, NLR, and platelet parameters (MPV, PLR, MPLVR).
Material and Methods: We conducted a study involving patients undergoing elective coronary angiography from January 2023 to June 2023 at Dr. Saiful Anwar General Hospital, who were 18 years of age or older and had CAD. All participants willingly agreed to be part of the study. We collected complete routine blood counts and performed blood biochemistry assessments 24 hours before the coronary angiography procedure. Pearson's correlation was used to examine the relationship between the variables.
Result: A total of 366 individuals meeting the study's inclusion criteria were included. MPV, PLR, MPLVR, NLR, and PDW showed weak to negligible correlations with the SYNTAX Score, displaying correlation coefficients of 0.260, 0.190, 0.320, 0.470, and 0.290, respectively, all with p-values <0.001.
Conclusion: This study in individuals with coronary artery disease revealed a limited to negligible correlation between the SYNTAX Score and inflammatory parameters including MPV, PLR, MPLVR, NLR, and PDW.

1. Introduction

In 2019, coronary artery disease (CAD) emerged as a prominent cause of death, accounting for over 9.14 million fatalities worldwide. The prevalence of CAD in Indonesia increased from 0.9% in 2013 to 1.5% in 2018, as indicated by data from the national health survey Riset Kesehatan Dasar (Riskesdas).[1,2] The etiology of atherosclerosis is attributed to chronic inflammation.[3] Platelets are the primary mediators of plaque rupture and atherothrombosis. Numerous studies have demonstrated that platelets exert a significant influence on both the inflammatory process and the progression of atherosclerosis. [4,5]

The platelet index refers to a set of parameters obtained from standard blood testing. Measurements of mean platelet volume (MPV) and Platelet distribution width (PDW), indicating the width and depth of the platelet distribution, are useful indicators of platelet function.[6] Leukocytes, also known as white blood cells, serve as inflammatory markers and play a significant role in the processes of atherogenesis and thrombosis. An easily accessible inflammatory biomarker, the neutrophil-lymphocyte ratio (NLR), is commonly used for risk stratification in individuals with cardiovascular disease.[7]

The platelet-lymphocyte count ratio (PLR) can also predict coronary lesions in CAD patients. This ratio has advantages because it can reflect the condition of platelet aggregation and the inflammatory process during coronary atherosclerosis.[8] PLR is associated with slow flow after percutaneous coronary intervention (PCI) and a high incidence of rehospitalization and death following acute coronary syndrome (ACS).[9] This research investigated the platelet index, NLR, PLR, and mean platelet-lymphocyte volume ratio (MPLVR) in patients with chronic coronary syndrome (CCS) to gain a better understanding of the correlation with the SYNTAX score and lesion severity.

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2. Material and Methods

2.1. Study design and Participation

The cross-sectional study was conducted from January 2023 to June 2023 at Dr. Saiful Anwar General Hospital and received ethical clearance from the Health Research Ethics Committee.Inclusion criteria comprised patients aged 18 years or older diagnosed with chronic coronary syndrome, who had undergone coronary angiography and expressed willingness to participate. Exclusion criteria included individuals with acute coronary syndrome, prior cauterization, valvular heart disease, inconsistent dual antiplatelet treatment (DAPT) in the week leading up to the examination, evidence of various medical conditions, history of cerebrovascular accident (CVA), stage IV chronic kidney disease (CKD), hematological disorders, and pregnancy.

2.2. Coronary Artery Lesion Assessment

Coronary angiography is a valuable tool for evaluating the extent of coronary lesions in both clinical and research contexts. The SYNTAX score, a widely recognized scoring system, is commonly used for this purpose. Developed to assess coronary vessels, the SYNTAX score considers the number, location, complexity, and functional impact of obstructive lesions angiographically. A higher SYNTAX score indicates a more complex lesion, making treatment more challenging. Two independent interventional cardiologists analyzed the SYNTAX score, and kappa evaluation was employed to measure the disparity between their readings.

2.3. Hematologic Parameters Assessment

Blood samples were obtained intravenously for routine examination 24 hours before elective angiography procedures. The assessed components included MPV (fl), PDW (%), PLR, MPVLR, and NLR. The blood samples were collected from the patients after providing detailed explanations and obtaining informed consent. Samples were examined using a hematology automated analyzer immediately after collection, with the addition of EDTA as an anticoagulant. All blood sample analyses were conducted at the central laboratory of Dr. Saiful Anwar General Hospital. The results of the blood sample examination were collected and analyzed independently by the researcher, ensuring a systematic assessment of hematologic parameters while adhering to ethical standards and maintaining accuracy in the analysis.

2.4. Statistical analysis

The normality of the data was assessed using the Kolmogorov-Smirnov test. The relationship between the variables was analyzed using Pearson's correlation. The diagnostic utility of the factors was evaluated through a Receiver Operating Characteristic (ROC) curve. SPSS for Windows version 23.0 will be utilized for the analysis of the test scores.

Table 1 Comparison of Baseline Characteristics according to SYNTAX Score

Variable	Total	SYNTAX		
	N / mean ±sd	< 23, N: 148	≥ 23, N: 218	P
Male Sex	301	118(80.4%)	183(84.4%)	0.330
Age	53.6±18.7	51.3±18.6	55.9±18.7	0.310
Smoker	192	81(54.7%)	111(50.9%)	0.470
Hypertension	225	88(59.5%)	137(63.3%)	0.520
Diabetes Mellitus	101	44(29.7%)	57(26.1%)	0.200
Chronic Kidney Disease	12	5(4.9%)	7(2.3%)	0.320
Dyslipidemia	10	1(0.7%)	9(3.7%)	0.140
Peripheral Artery Disease	3	3(2.0%)	0.0%	0.120
Body Mass Index	24.7±4.5	28.4 ± 3.8	28.9 ± 28.3	0.120
Aspilet	46	17(4.7%)	29(7.9%)	0.120
Clopidogrel	17	5(1.4%)	12(5.5%)	0.110
Ticaglerol	6	6(1.6%)	0.0%	0.130
Aspilet+ Clopidogrel	238	97(26.0%)	141(38.6%)	0.210
Aspilet+ Ticaglerol	59	19(5.2%)	35(9.6%)	0.140
Angiotensin-converting enzyme inhibitor / Angiotensin II Receptor Blockers	190	60(40.4%)	130(59.6%)	0.970
Beta-blocker	190	60(40.1%)	130(59.9%)	0.146
Statin	190	60(40.8 %)	130(59.2 %)	0.970
LM Artery	115	33(9.0 %)	82 (20.5%)	0.005
LAD Artery	313	109(29.8%)	204(55.8%)	<0.001
LCx Artery	251	81(22.1%)	170 (46.4%)	0.002
RCA	268	86(23.4%)	182(73.2%)	<0.001
Trombocyte	254.4±5.4	252.3±5.2	255.4±5.5	0.660
Lymphocyte	2.6±0.5	2.9±0.5	2.49±0.5	<0.001
MPV (fl)	9.8±0.7	9.4±0.4	10.04±0.7	<0.001
Platelet Lymphocyte Ratio	99.5±27.5	91.1±24.2	105±28.2	<0.001
Mean Platelet Volume Lymphocyte Ratio	3.9±0.9	3.4±0.5	4.2±0.9	<0.001
PDW (%)	15.3±2.1	14.5±1.7	15.9±2.0	<0.001
NLR	3.7±1.0	2.9±0.6	4.3±0.8	<0.001

Note: significant difference p<0.05, LM Artery: Right Coronary Artery, Left Main Artery, Left Anterior Descending Artery, Left Circumflex Artery, and Left Main Artery, fl : femtoliters, SYNTAX: Percutaneous Coronary Intervention Using Taxus and Its Relation to Cardiac Surgery

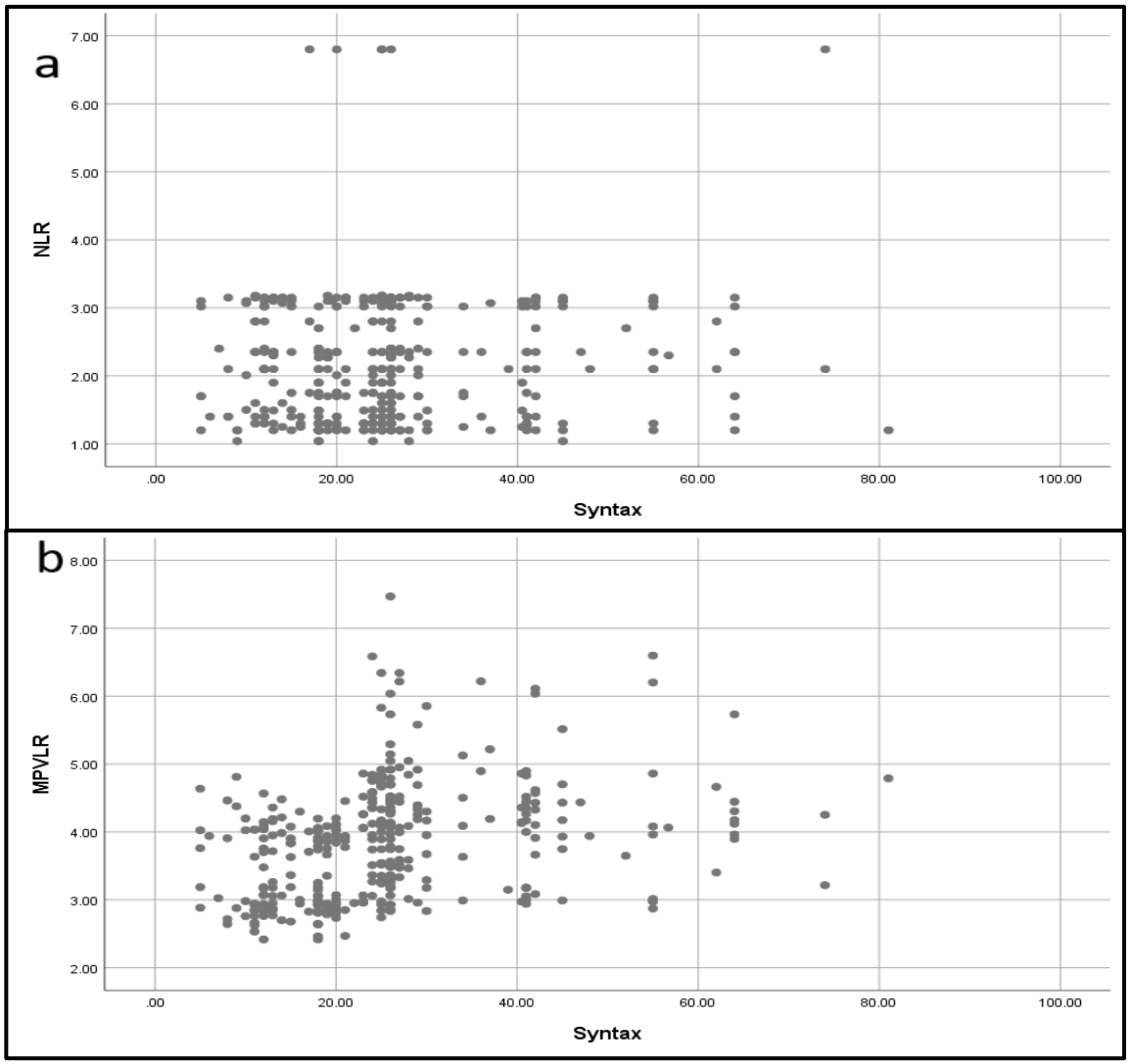

Figure 1. Correlation between SYNTAX score, NLR and MPVLR, (a).neutrophil-lymphocyte ratio (NLR) ($p < 0.001$, $r = 0.470$), (b) mean platelet volume lymphocyte ratio (MPVLR)($p<0.001$, $r= 0.320$); SYNTAX : Heart surgery and taxus-assisted percutaneous coronary intervention work well together

3. Result

3.1. Baseline Characteristics

There were a total of 366 individuals who met the inclusion criteria for the study. Information was collected from the medical records and cardiac angiography results of Dr. Saiful Anwar General Hospital. No statistically significant differences were observed between the groups in terms of age, gender, body mass index, history of hypertension, smoking, diabetes mellitus, or therapy with coronary heart disease drugs (all $P > 0.05$). However, the majority of the study participants were older men. Angiographic parameters, including lesions in the left main (LM), left anterior descending (LAD), left circumflex (LCx), and right coronary arteries (RCA), were compared among SYNTAX score groups. Higher SYNTAX scores were associated with statistically significantly more complex lesions. The inflammatory indices, including thrombocyte, lymphocyte, MPV, PLR, MPVLR, PDW, and NLR, were significantly higher in the high SYNTAX group ($p < 0.001$). The patients' initial states are presented in Table 1.

3.2. Correlation of Inflammation Parameters and Coronary Lesion Severity

From the Pearson correlation test, we identified a weak correlation between NLR and the SYNTAX score ($r=0.470$; $p <0.001$). Similarly, a weak correlation was observed between MPVLR and the SYNTAX score ($r=0.320$, $P<0.001$) (Figure 1b). There was a negligible positive correlation between MPV and the SYNTAX score ($r=0.260$; $p<0.001$) as well as between PLR and the SYNTAX score ($r=0.190$; $p<0.001$). The summary of correlation values is presented in Table 2.

Table 2 Correlation of MPV variables, lymphocyte thrombosis ratio, NLR, and lymphocyte platelet volume ratio with SYNTAX score

Variable	P	R
MPV (fl)	<0.001	0.260
Lymphocyte ($10^3/mm^3$)	<0.001	0.280
Thrombocyte ($10^3/mm^3$)	0.799	0.013
Thrombocyte Lymphocyte Ratio	<0.001	0.190
Mean Platelet Volume Lymphocyte Ratio	<0.001	0.320
PDW (%)	<0.001	0.290
NLR	<0.001	0.470

Note: PDW: Platelet Distribution width, NLR: Neutrophil Lymphocyte Ratio, fl : femtoliters

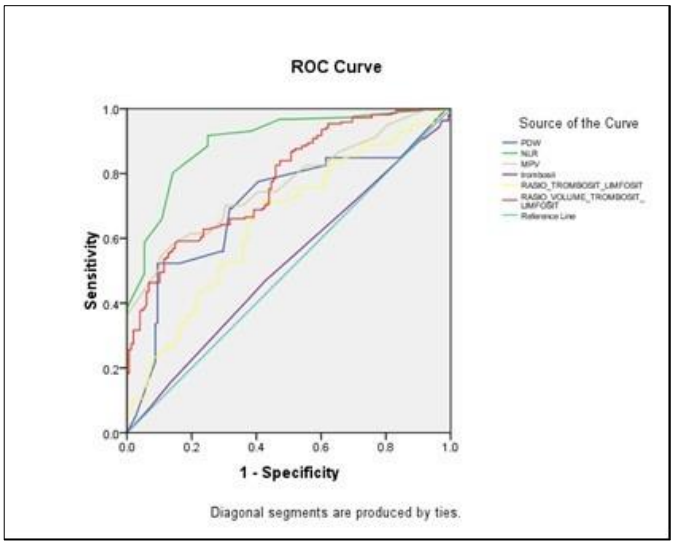

Figure 2 ROC Value. Cut-off values for predicting the severity of coronary artery disease.
AUC of MPV:0.780 (95% CI 71 – 81, p<0.001); AUC of PLR 0.650 (95% CI 59 – 78, p<0.001); AUC of MPLVR: 0.780 (95% CI 73 – 82, p<0.001); AUC of PDW: 0.700 (95% CI 61 – 75,p<0.001); AUC of NLR: 0.890 (95% CI 86 – 93, p<0.001); PDW: Platelet Distribution width, NLR: Neutrophil Lymphocyte Ratio, MPV: Mean Platelet Volume

3.3. Diagnostic Performance of Inflammation Parameters in Predicting Coronary Lesion Severity

In this study, ROC analysis was conducted for MPV, revealing an area under the curve (AUC) of 0.765 (95% CI 71-81). The most effective cut-off MPV value for predicting a high SYNTAX Score was 9.460 fl, with a sensitivity of 74% and specificity of 60%. For PLR, ROC analysis indicated an AUC of 0.650 (95% CI 59-78, p<0.001), with an optimal cut-off point of 93.6, resulting in a sensitivity of 82% and specificity of 51%. MPVLR, in ROC analysis, showed an AUC of 0.780 (95% CI 73-82, p<0.001), with a sensitivity of 84% and specificity of 62%. The optimal cut-off value for predicting a high SYNTAX Score was 3.35. PDW had an AUC of 0.700 (95% CI 61-75, p<0.001) in ROC analysis, with a sensitivity of 69% and specificity of 68%. The optimal cut-off value for predicting a high SYNTAX Score was 14.85. For NLR, ROC analysis revealed an AUC of 0.890 (95% CI 86-93, p<0.001), and a cutoff value of 3.350 (sensitivity 88%, specificity 75%) was optimal for predicting a high SYNTAX Score. Figure 2 displays the ROC values.

4. Discussion

Our study investigated the correlation between inflammation parameters, including MPV, PDW, PLR, NLR, and MPVLR, with the severity of lesions in patients with CAD using the SYNTAX score. We obtained different results compared to several previous studies. The study found only weak to insignificant connections between MPV, PLR, MPVLR, NLR, PDW, and the SYNTAX Score. Previous research suggests that the Syntax score is more closely aligned with the decisions made by the cardiac team compared to the Gensini scores.[12]

Atherosclerosis is a chronic inflammatory disorder triggered by multiple factors. Endothelial dysfunction contributes to the progression of atherosclerosis, a condition characterized by various processes such as inflammation, cell migration, proliferation, tissue damage, and plaque accumulation. Atherosclerosis is a multifaceted process that entails the intricate interplay between blood cells, namely platelets and monocytes, and plasma components, culminating in the emergence of the disease.[13] Platelets play a substantial role in both the initial and final phases of atherosclerosis, contributing to events such as endothelial dysfunction and the rupture of vulnerable plaques. Large platelets, characterized by more granules and mitochondria, exhibit a greater ability to release inflammatory mediators and express more membrane receptors. As a result, they are more atherogenic compared to smaller platelets.[14] The accumulation of lipids triggers diverse immune responses involving T and B cells, neutrophils, granulocytes, and dendritic cells (DC). This process leads to cellular activation, monocyte transformation, and differentiation into foam cells, among other events.[15] Risk factors for multivessel disease comprise diabetes mellitus, dyslipidemia, arterial hypertension, a family history of CAD, male gender, advanced age, chronic renal failure, and a previous manifestation of atherosclerosis.[16]

Platelet function has been observed to positively correlate with the average size of platelets, measured by MPV. PDW is used to gauge the range of platelet sizes, with higher PDW readings indicating increased generation of more mature reticulated platelets. Elevated platelet indices, such as MPV and PDW, are associated with an increased risk of coronary artery disease and/or myocardial infarction. During the initial phases of lesions, leukocytes migrate toward the intimal layer of the artery. However, in advanced phases, particularly in cases with a significant amount of lipids, angiogenesis occurs, originating from arterial blood vessels around the base of the lipid core—where plaque rupture most commonly occurs. Pro-atherogenic mediators include factors linked to the Th1 immune response, involving the synthesis of IFN-γ and cytokines triggering its release, such as IL-12 and IL-18. IFN-γ can induce increased metalloproteinase (MMP) expression, decreased interstitial collagen creation, and inhibition of vascular smooth muscle cell proliferation, potentially leading to thinning of the fibrous cap.[17]

In this study, we have obtained several different findings compared to prior investigations. Our analysis revealed a weak correlation between NLR and MPVLR investigations. The NLR value exhibited the strongest correlation, with scores of (r= 0.470; p<0.001). Additionally, the AUC was 0.890 (95% CI 86 - 93, p<0.001). These findings align with a study conducted by Chen et al. in 2014, which showed a limited correlation between NLR and the severity of CAD lesions assessed by the Gensini score. The investigation revealed that the NLR exhibited the highest area under the curve (AUC= 0.63, 95%CI: 0.59-0.67, p = 0.000), with an optimal cut-off value of 2.04 (sensitivity: 62.1%, specificity: 54.8%). The MPVLR study reveals a weak link. According to the study conducted by Limantoro et al. in 2022, there is a limited connection between the MPVLR value and the degree of coronary artery disease, as determined by the Gensini score (p=0.076; r=0.217).[18] The MPVLR value of 3.4 exhibited a sensitivity of 80%, specificity of 50%, positive predictive value (PPV) of 82%, and negative predictive value (NPV) of 47%.[18] A key discovery from the study conducted by Kurtul et al. in 2017 is the robust association between the assessment of MPVLR and the occurrence of no-reflow [19]. According to our research, there was minimal association between CAD and MPV, PDW, or PLR levels. The presence of reticulated platelets in circulation and megakaryocyte ploidy have both demonstrated correlations with MPV.[24] Moreover, it has been demonstrated that MPV and thrombopoietin levels are positively correlated in CAD patients. Despite its correlation with the degree and complexity of CAD, a higher platelet volume may not always result in greater platelet reactivity. Larger platelets may function as precursors to mature platelets, which could contribute to lower aggregation. Research has indicated a connection between platelet enlargement and other variables that may be predictive of outcomes, including obesity, diabetes, cancer, smoking, and high blood pressure. However, besides platelet volume, these risk factors can primarily influence the degree of coronary artery disease and clinical outcomes. Würtz et al. showed a significant association between platelet aggregation and platelet count in patients diagnosed with CAD, even in those with normal platelet levels, which supports our findings.[25] In individuals with coronary heart disease, Aliberti et al. demonstrated a significant correlation between fibrinogen and platelet count.[26] Two main factors that contribute to the development and pathophysiology of cardiovascular disease are fibrinogen and platelets. Atherosclerosis, a chronic inflammatory condition, may be indicated by a high platelet count. However, more information is needed to understand the connection between platelet count and the onset of atherosclerosis or subclinical atherosclerosis.[14]

This study had some limitations. First, due to the cross-sectional nature of the study, it was unable to establish whether the variables were associated at all. Prospective studies with larger sample sizes would have been preferable to gain a better understanding of the relationship between MPV, PDW, NLR, PLR, and MPVLR and the severity of arterial coronary lesions as measured by the SYNTAX score in patients with CAD. Second, to prevent confounding variables, patients with blood coagulation disorders, cancers, and other chronic diseases had to be appropriately excluded; however, these patients were only screened by regular laboratory work, physical examinations, and anamnesis. Third, more participants were required to ensure that the study's findings accurately represented the entire population of CAD patients.

5. Conclusion

This study found a negligible to weak correlation between the SYNTAX Score and inflammatory markers, including MPV, platelet-lymphocyte ratio, and lymphocyte-thrombocyte volume ratio, in patients with coronary artery disease. This suggests that inflammatory markers may not be very informative in assessing the extent of CAD in this particular cohort. Further research is needed to explore the potential utility of these indicators in other patient groups.

6. Declaration

6.1 Ethics Approval and Consent to participate

The study involved human subjects, necessitating adherence to ethical guidelines. Ethical review had been conducted and approval obtained through Certificate of Ethical Eligibility No. 400/185/K.3/302/2023 from the Health Research Ethics Committee at Dr. Saiful Anwar Malang.

6.2. Consent for publication

Not applicable.

6.3 Availibility of data and materials

Data used in our study were presented in the main text.

6.4 Competing interests

Not applicable.

6.5 Funding Source

Not applicable.

6.6 Authors contributions

Idea/concept: ZF. Design: CTT. Control/supervision: CTT, MZA, NK. Data collection/processing: ZF. Analysis/interpretation: ZF. Literature review: ZF, CTT. Writing the article: ZF. Critical review: CTT, MZA, NK. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

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References

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2022 Update: A Report from the American Heart Association. *Circulation*. 2022;145(8):E153-E639. doi:10.1161/CIR.0000000000001052

2. Maharani A, Sujarwoto, Praveen D, Oceandy D, Tampubolon G, Patel A. Cardiovascular disease risk factor prevalence and estimated 10-year cardiovascular risk scores in Indonesia: The SMARThealth Extend study. *PLoS One*. 2019;14(4). doi:10.1371/journal.pone.0215219

3. Kong P, Cui ZY, Huang XF, Zhang DD, Guo RJ, Han M. Inflammation and atherosclerosis: signaling pathways and therapeutic intervention. *Signal Transduct Target Ther*. 2022;7(1). doi:10.1038/s41392-022-00955-7

4. Von Hundelshausen P, Weber C. Platelets as immune cells: Bridging inflammation and cardiovascular disease. *Circ Res*. 2007;100(1):27-40. doi:10.1161/01.RES.0000252802.25497.b7

5. Wang L, Tang C. Targeting platelet in atherosclerosis plaque formation: Current knowledge and future perspectives. *Int J Mol Sci*. 2020;21(24):1-23. doi:10.3390/ijms21249760

6. Varastehravan H, Naghedi A, Nough H, Pourmirafzali H. The relationship between severity of coronary artery disease and mean platelet volume. *Cardiometry*. 2019;c(14):57-63. doi:10.12710/cardiometry.2019.14.5763

7. Sharma K, Patel AK, Shah KH, Konat A. Is Neutrophil-to-Lymphocyte Ratio a Predictor of Coronary Artery Disease in Western Indians? *Int J Inflam*. 2017;2017. doi:10.1155/2017/4136126

8. Wada H, Dohi T, Miyauchi K, et al. Mean platelet volume and long-term cardiovascular outcomes in patients with stable coronary artery disease. *Atherosclerosis*. 2018;277:108-112. doi:10.1016/j.atherosclerosis.2018.08.048

9. Wada H, Dohi T, Miyauchi K, et al. Mean platelet volume and long-term cardiovascular outcomes in patients with stable coronary artery disease. *Atherosclerosis*. 2018;277:108-112. doi:10.1016/j.atherosclerosis.2018.08.048

10. Shahian DM, O'brien SM, Sheng S, et al. Health Services and Outcomes Research Predictors of Long-Term Survival After Coronary Artery Bypass Grafting Surgery Results From the Society of Thoracic Surgeons Adult Cardiac Surgery Database (The ASCERT Study). Published online 2012. doi:10.1161/CIRCULATIONAHA

11. Zhang J, Jiang T, Hou Y, et al. Five-year outcomes comparing percutaneous coronary intervention with drug-eluting stents versus coronary artery bypass grafting in patients with left main coronary artery disease: A systematic review and meta-analysis. *Atherosclerosis*. 2020;308:50-56. doi:10.1016/j.atherosclerosis.2020.06.024

12. Boyraz B, Peker T. Comparison of SYNTAX and Gensini Scores in the Decision of Surgery or Percutaneous Revascularization in Patients With Multivessel Coronary Artery Disease. *Cureus*. Published online February 22, 2022. doi:10.7759/cureus.22482

13. Aukrust P, Halvorsen B, Ueland T, et al. Activated platelets and atherosclerosis. *Expert Rev Cardiovasc Ther*. 2010;8(9):1297-1307. doi:10.1586/erc.10.92

14. Turk U, Tengiz I, Ozpelit E, et al. The relationship between platelet indices and clinical features of coronary artery disease. *Kardiol Pol*. 2013;71(11):1129-1134. doi:10.5603/KP.2013.0293

15. Nording HM, Seizer P, Langer HF. Platelets in inflammation and atherogenesis. *Front Immunol*. 2015;6(MAR). doi:10.3389/fimmu.2015.00098

16. Manchanda J, Potekar RM, Badiger S, Tiwari A. *The Study of Platelet Indices in Acute Coronary Syndromes.*; 2014. www.pacificejournals.com/apalm

17. Li W, Xie X, Wei D, et al. *Oncotarget 93771 Www.Impactjournals.Com/Oncotarget Baseline Platelet Parameters for Predicting Early Platelet Response and Clinical Outcomes in Patients with Non-Cardioembolic Ischemic Stroke Treated with Clopidogrel*. Vol 8.; 2017. www.impactjournals.com/oncotarget/

18. Limantoro C, Fitria I, Suharti C, Nugroho T. Mean Platelet Lymphocyte Volume Ratio as Predictors of Coronary Artery Severity in Chronic Coronary Syndrome. MedHosp 2023 vol 10(1) :16-25. https://doi.org/10.36408/mhjcm.v10i1.813

19. Kurtul A, Acikgoz SK. Usefulness of Mean Platelet Volume-to-Lymphocyte Ratio for Predicting Angiographic No-Reflow and Short-Term Prognosis After Primary Percutaneous Coronary Intervention in Patients With ST-Segment Elevation Myocardial Infarction. *American Journal of Cardiology*. 2017;120(4):534-541. doi:10.1016/j.amjcard.2017.05.020

20. Tzur I, Barchel D, Izhakian S, et al. Platelet distribution width: a novel prognostic marker in an internal medicine ward. *J Community Hosp Intern Med Perspect*. 2019;9(6):464-470. doi:10.1080/20009666.2019.1688095

21. Peng YF, Cao L, Zeng YH, et al. Platelet to lymphocyte ratio and neutrophil to lymphocyte ratio in patients with rheumatoid arthritis. *Open Medicine (Poland)*. 2015;10(1):249-253. doi:10.1515/med-2015-0037

22. Wu J, Mao W, Li X. Mean Platelet Volume/Lymphocyte Ratio as a Prognostic Indicator for HBV-Related Decompensated Cirrhosis. *Gastroenterol Res Pract*. 2020;2020. doi:10.1155/2020/4107219

23. Demirin H, Ozhan H, Ucgun T, et al. Normal range of mean platelet volume in healthy subjects: Insight from a large epidemiologic study. *Thromb Res*. 2011;128(4):358-360. doi:10.1016/j.thromres.2011.05.007

24. Smith NM, Pathansali R, Bath PMW. Altered megakaryocyte-platelet-haemostatic axis in patients with acute stroke. Published online 2002. doi:10.1080/095371001201

25. Würtz M, Hvas AM, Kristensen SD, Grove EL. Platelet aggregation is dependent on platelet count in patients with coronary artery disease. *Thromb Res*. 2012;129(1):56-61. doi:10.1016/j.thromres.2011.08.019

26. Aliberti G, Proietta M, Pulignano I, Del Porto F, Tammeo A, Trappolini M. Association between fibrinogen plasma levels and platelet counts in an outpatient population and in patients with coronary heart disease. *Blood Coagulation and Fibrinolysis*. 2010;21(3):216-220. doi:10.1097/MBC.0b013e32833449c9

27. Akbas EM, Gungor A, Ozcicek A, Akbas N, Askin S, Polat M. Vitamin D and inflammation: Evaluation with neutrophilto-lymphocyte ratio and platelet-to-lymphocyte ratio. *Archives of Medical Science*. 2016;12(4):721-727. doi:10.5114/aoms.2015.50625

28. Verdoia M, Nardin M, Rolla R, et al. Association of lower vitamin D levels with inflammation and leucocytes parameters in patients with and without diabetes mellitus undergoing coronary angiography. *Eur J Clin Invest*. 2021;51(4). doi:10.1111/eci.13439