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Original Article

Mean Platelet-Lymphocyte Volume Ratio as Predictors of Coronary Artery Severity in Chronic Coronary Syndrome

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Abstract

Background : The increase in platelet aggregation and inflammation play an essential role in atherosclerosis. Furthermore, the level of activity depends on their size, with larger platelets facilitating the thrombosis process. Severe Coronary Artery Disease (CAD) is associated with low lymphocyte count. It is also linked with Mean platelet volume [MPV], Platelet Lymphocyte Ratio [PLR], and Mean Platelet Volume to Lymphocyte Ratio [MPVLR]. This study aims to investigate MPV, PLR, and MPVLR as predictors of the severity of Coronary Artery Lesion in Chronic Coronary Syndrome (CCS) using the Gensini score.

Methods : This is a cross sectional study conducted in Dr. Kariadi General Hospital, involving a total sample of 68 respondents. Furthermore, CCS were evaluated before conducting coronary angiography. The study comprises of two group of patients divided according to their Gensini scores, namely mild and severe, for ≤ 20 and > 20, respectively. MPV, PLR, and MPVLR were then compared between the two groups.

Results : At a cut-off level of 3.4, MPVLR predicted the coronary artery severity with a sensitivity, specificity, positive predictive value (PPV), and negative predictive value of 80%, 50%, 82%, and 47% (area under the curve [AUC] 0.67; 95% confidence interval [CI], 0.52–0.82; p 0.029). Meanwhile, its value ≥3.4 has OR 1.55; 95% CI, 0.99–2.43; p 0.034.

Conclusion : This study conclude that MPVLR ≥3.4 can be used as a predictor of Coronary Artery Lesion Severity based on the Gensini score in CCS cases.

Keywords : Chronic Coronary Syndrome, Gensini Score, Mean Platelet Volume, Mean Platelet Volume to Lymphocyte Ratio, Platelet Lymphocyte Ratio

INTRODUCTION

The most leading cause of death in the world is cardiovascular disease suffered by 18.6 million people in 2019. Its primary significant contributor is Coronary Artery Disease (CAD), with 9.14 million mortality.[1] The 2016 report from the Heart Disease and Stroke Statistics Update stated that the number of people with CAD in the United States was 15.5 million which is 6.2% of the adult population, where 8.2 million had angina pectoris and 7.6 million experienced myocardial infarction.[2] According to Basic Health Research (Riskesdas), there is an increase in the prevalence of this disease in Indonesia from 0.9% in 2013 to 1.5% in 2018. Furthermore, the region with the highest incidence of 1.6% was the Central Java province.[3]

Chronic inflammation and thrombosis are crucial causes of atherosclerosis.[4,5] Furthermore, activated platelets express adhesion, coagulation, and inflammation mediators. This triggers the steady progression of plaque formation, thrombosis, and atherosclerosis. Low-Density Lipoprotein (LDL), when accumulated in its oxidized form, can stimulate a chronic inflammatory process characterized by the lymphocytes and monocytes migration to the tunica intima of blood vessels, resulting in atherosclerotic plaques.[4,5] The platelet activation and inflammatory markers, such as P-selectin, as well as interleukins and High Sensitivity C-Reactive Protein (hs-CRP), can assess the prognosis of the CAD severity.[6–8] However, their examination process is still expensive. The degree of severity depends on the number of coronary lesions and the stenosis intensity. These can be detected by coronary angiography as a gold standard examination.

Mean Platelet Volume (MPV) is the measurement of platelet activity. Larger platelets tend to have higher activity and are more pro-thrombotic than their small counterpart, which plays an essential role in atherosclerosis pathogenesis.[9–11] High MPV has increased platelet aggregation, thromboxane production, adhesion molecules expression, and β-thromboglobulin production. Furthermore, its higher values is experienced among patients with CAD risk factors such as hypercholesterolemia, diabetes mellitus, smoking, hypertension, atrial fibrillation, obesity, and cerebrovascular disease.[10,12–16] This was related to the prevalence of Acute Myocardial Infarction (AMI) as well as the Major Adverse Cardiac Events (MACE) prognosis. Additionally, MPV value can be used as a prognostic predictor of death in CAD and the severity of the coronary lesions.[16]

Examination of the Platelet Lymphocyte Ratio (PLR) describes the platelet aggregation and inflammation level in patients with coronary atherosclerosis. Its elevated levels are common in various heart problems, including unstable angina and coronary syndromes (acute or chronic), such as *ST-elevation myocardial infarction* (STEMI) and *Non-ST-elevation myocardial infarction* (NSTEMI). This is closely related to the prevalence of severe atherosclerosis, MACE, more frequent post-angiographic no-reflow events, and increased mortality risk from any cause.[13,17,18]

Mean Platelet Volume to Lymphocyte Ratio (MPVLR) has been used in several previous studies as a prognostic biomarker for various conditions, including malignancy, stroke, cystic fibrosis, pulmonary embolism, chronic obstructive pulmonary disease, and some cardiovascular disorders.[19–21] In existing studies, it shows a positive correlation with no reflow after percutaneous coronary angiography, poor angiography results, death from various causes within 30 days, and mortality due to myocardial infarction within 1 year.[19,20] Therefore, this study aims to determine the ability of MPV, PLR, and MPVLR values to predict coronary artery lesions severity in Chronic Coronary Syndrome (CCS) using the Gensini Score.

METHODS

1. Observational Study

The method used was observational analytic with a cross-sectional design conducted at Dr. Kariadi General Hospital, Semarang, from November 2021 to March 2022. The inclusion criteria are Chronic Coronary Syndrome (CCS) patients aged >18. Meanwhile, patients with Acute Coronary Syndrome (ACS), a history of coronary intervention, Coronary Artery Bypass Graft surgery (CABG), and heart valve disease, were excluded from the study subjects. It also applies to those with a history of liver cirrhosis, severe infection or sepsis, acute infection, tuberculosis, Chronic Obstructive Pulmonary Disease (COPD), Chronic Inflammatory Disease, Thromboembolic Disease, Autoimmune Disease, malignancy, chronic kidney disease (CKD) Stage IV- V, and NYHA (New York Heart Association) CHF (Congestive Heart Failure) class III-IV. Similarly, this study excluded patients with hematological disorders such as aplastic anemia, leukemia, thrombocytopenia, polycythemia vera, pregnancy, and incomplete data.

2. Laboratory Analysis

The independent variables such as MPV, PLR, and MPVLR, were examined with an automated hematology analyzer SYSMEX XN 1000 with the principle of laser flow cytometry. It was checked 20–30 minutes after the blood was drawn and treated with a citrate anticoagulant. The MPV variable with fL units, was obtained from the direct analysis results of the hematology analyzer machine. The PLR variable was measured using the following formula of Platelets (uL) / Number of lymphocytes (% lymphocytes x number of Leukocytes

(uL)). Meanwhile, MPVLR was calculated by dividing MPV (fL) with Number of lymphocytes (%lymphocytes x number of Leukocytes (uL)) with units (fl / (10^3/µL)).

3. Gensini score assessment

The dependent variable in this study is CCS which is assessed by the Gensini score and grouped into severe and mild, with > 20 and ≤20, respectively. The Gensini score is measured by multiplying each stenotic lesion severity degree with the multiplication factor for each lesion based on the location. Subsequently, the sum of all lesion severity scores was determined.

4. Statistical Analysis

Primary data was obtained from the results of the examination conducted at the Clinical Pathology Laboratory of Dr. Kariadi General Hospital. They were then analyzed using the IBM SPSS Statistics 25 Program. Furthermore, their distribution was tested using the Kolmogorov–Smirnov test to assess normality. The mean value and standard deviation (SD) was used to report the quantitative variables with normal distribution. Variables with non-normal distribution will be reported using the median value, while categorical variables will be presented as numbers and percentages. The Spearman test calculates the correlation coefficient of MPV value with PLR and MPVLR based on Gensini score. It is considered statistically significant when p<0.05. The cut-off point value was taken from the Receiver Operating Curve (ROC) analysis of the MPV, PLR, and MPVLR values for the CCS severity category. The results are presented in the form of a sensitivity value (true positive / (true positive + false negative) x 100%), specificity (true negative / (true negative + false positive), positive predictive value (true positive / (true positive + false positive) x 100%), and Negative Predictive Value (true negative / (false negative + true negative) x 100%). Risk estimation was also performed between the MPV, PLR, and MPVLR values. This study was approved by the Medical and Health Research Ethics Commission (MHREC) at Dr. Kariadi General Hospital with number 991/EC/KEPK-RSDK/2021.

RESULTS

There were 68 respondents in this study, which comprises of 48 men and 20 women. They have mean age of 58.47, with 36, 52, 21, 40, 14, and 21 people having comorbid obesity, hypertension, Diabetes Melitus (DM), dyslipidemia, smoking, and smoking history, respectively, as shown in Table 1.

The respondents were divided into 2 categories of 50 severe and 18 mild people. The severe Gensini group consist of 79.2% male, with an average age of 58.78. Furthermore, it is dominated by comorbidities of obesity, hypertension, DM, dyslipidemia, and smoking (p>0.05). It has lowere median platelet and mean absolute lymphocyte counts (249.5 vs. 303; p 0.02 and 2.4 vs. 2.73; p 0.068). Additionally, the MPVLR values were significantly higher (p 0.029), while MPV and PLR values were insignificantly higher (p>0.05), as presented in Table 2.

The mean age in the severe and mild Gensini groups are 58.78 and 57.61. However, there are 35 and 9 people, respectively, in the severe and mild Gensini group that are ≥55 years, as shown in Figures 1 and 2.

The Spearman test analysis shows a significant positive correlation between the MPV value and the CCS severity (R 0.271; P 0.025). There is also a significant negative correlation between the number of platelets and the CCS severity (R -0.304; P 0.012), as shown in Table 3.

Using the ROC chart, the study calculated the cut-off point for the most optimal MPV value as a predictor of the CCS severity. According to the analysis, the area under the curve was 63% (95% CI 4779) with p value of 0.094. Furthermore, the optimum MPV cut-off point was

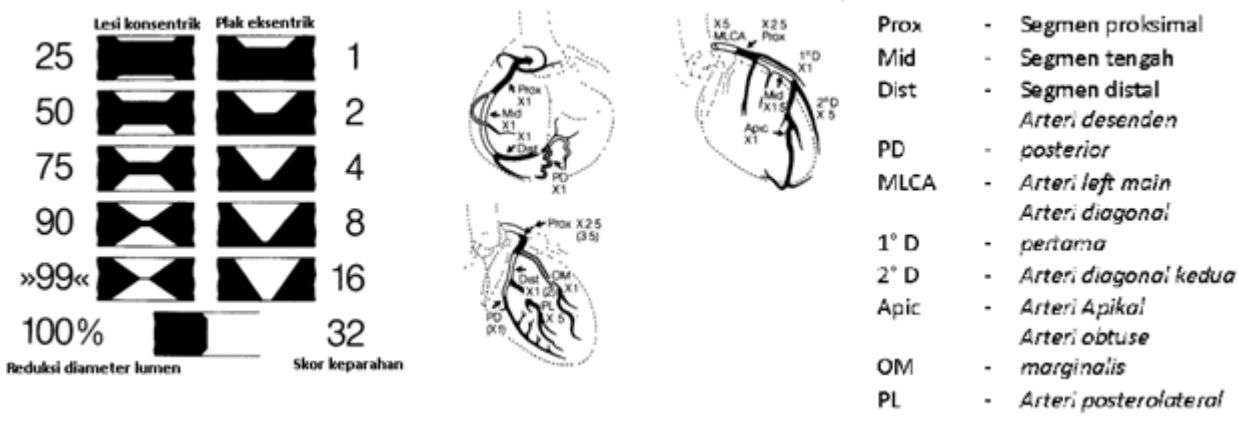

Figure 1. Gensini scoring system[21]

TABLE 1
Characteristics of study subjects

Variable		N (%)	Mean (SD)	Median	Minimum–Maximum
Gender	Male	48 (70.6)			
	Female	20 (29.4)			
Age			58.47 (7.106)		
Obesity		36 (44.1)			
Hypertension		52 (76.5)			
DM		21 (30.9)			
Dyslipidemia		40 (58.8)			
Smoking status	Smoking	14 (20.6)			
	No smoking	36 (52.9)			
	Have a smoking history	18 (26.5)			
Platelet count				262.000	(155.000–464.000)
MPV (fL)			9.997 (1.038)		
Absolute Lymphocyte Count (10^3/µL)			2487 (0.797)		
PLR				112.79	(54.13–282.93)
MPVLR (fl /(10^3/µL))			4.442 (1.513)		
Gensini Score					(2–190)

DM diabetes mellitus, MPV of mean platelet volume, PLR platelet count to lymphocyte count ratio, MPVLR mean platelet volume to lymphocyte count ratio.

TABLE 2
Characteristics of subjects according to Gensini score category

Characteristics		Severe Gensini (N 50)	Mild Gensini (N 18)	p
Gender, n (%)	Male	38 (79.2)	10 (20.8)	0.183
	Female	12 (60)	8 (40)	
Age, mean [SD]		58.78 [6.914]	57.61 [7.755]	0.495
BMI, N (%)	Obesity	21 (70)	9 (30)	0.757
	Not obese	29 (76.3)	9 (23.7)	
Hypertension, N (%)		36 (69.2)	16 (30.8)	0.261
Diabetes mellitus, N (%)		14 (66.7)	7 (33.3)	0.576
Dyslipidemia, N (%)		29 (72.5)	11 (27.5)	1
Smoking status, N (%)	Smoke	11 (78.6)	3 (21.4)	0.379
	Smoking history	15 (83.3)	3 (16.7)	
Platelet count (10^3/µL),		249.5	303	0.02
Median (minimum–maximum)		(155–464)	(186–407)	

TABLE 2. Continued

Characteristics	Severe Gensini (N 50)	Mild Gensini (N 18)	p
MPV (fL), Mean [SD]	10.11 [0.963]	9.69 [1.201]	0.09
Absolute Lymphocyte Count (10^3/µL), Mean [SD]	2.4 [0.813]	2.73 [0.719]	0.068
PLR, Mean [SD]	122.4 [45.73]	121.24 [48.18]	0.646
MPVLR (fl /(10^3/µL)), Mean [SD]	4.65 [1.49]	3.88 [1.44]	0.029

BMI body mass index, MPV mean platelet volume, PLR ratio of platelet count to lymphocyte count, MPVLR ratio of mean platelet volume to lymphocyte count

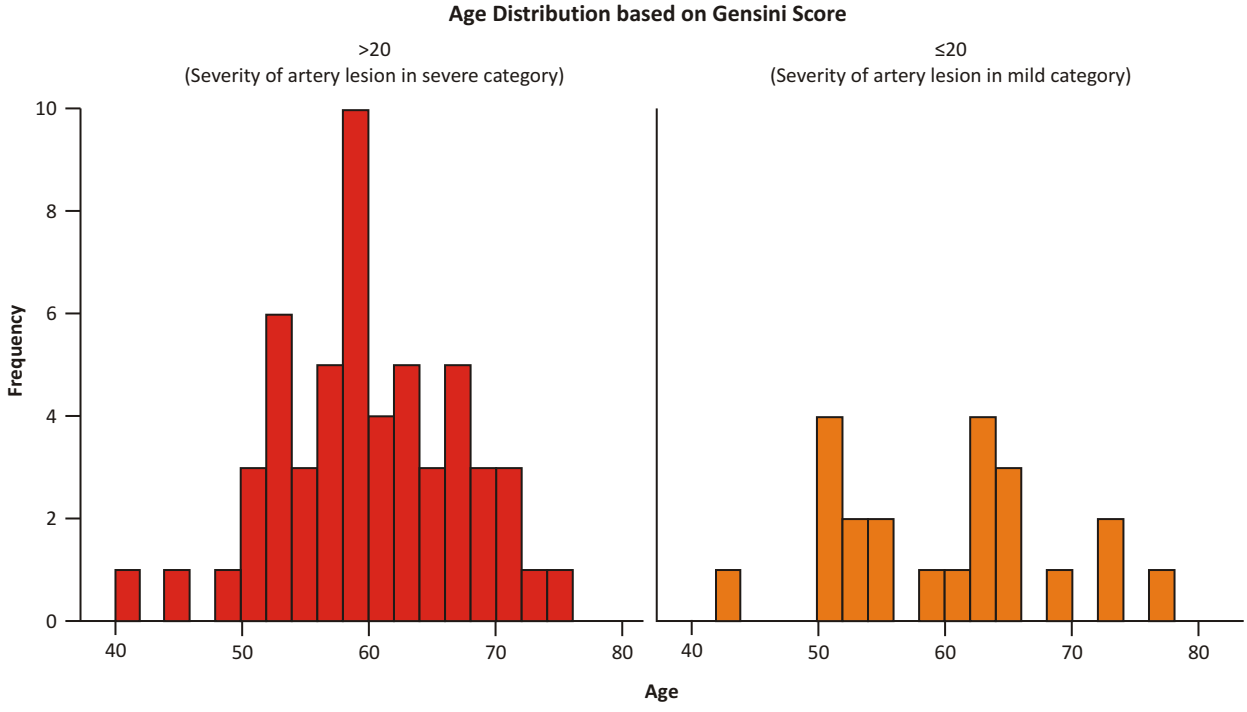

Figure 2. Graph of age comparison by Gensini score category

9.75 fl with sensitivity, specificity, PPV, and NPV of 60% sensitivity, 61%, 81%, and 35%, respectively (OR 1.26; 95% CI 0.93–1.70; p 0.205), as presented in Figure 3.

The PLR value has an insignificant negative correlation with the CCS severity (r -0.057; p 0.645). However, no significant relationship was observed between the PLR value and the CCS severity. The hypothesis showed that no further statistical tests were conducted.

The MPVLR value has an insignificant positive correlation with the CCS severity (r 0.217; p 0.076). Furthermore, there is a significant difference between the MPVLR values of the severe and mild groups.

Using the ROC chart, the cut-off point for the MPVLR value to be used as a predictor of the CCS severity was calculated. A statistically significant ROC value of 67% (95% CI 5282) was obtained for the MPVLR score (p 0.029). Subsequently, the optimum value was 3.4 with sensitivity, specificity, PPV, and NPV of 80%, 50%, 82%, and 47% (OR 1.55; 95% CI 0.99-2.43; p 0.034).

DISCUSSION

Based on characteristics data, it was discovered that the severe Gensini group was dominated by males at 79.2% with a mean age of 58.78. Its MPV, PLR, and MPVLR values were higher than those in the mild Gensini group (MPV 10.11 vs. 9.69; PLR 122.4 vs. 121.24; MPVLR 4.65 vs. 3.88). Finally, it also exhibit a lower absolute lymphocyte count.

A low lymphocyte count was also shown in previous studies in patients with ACS and stable

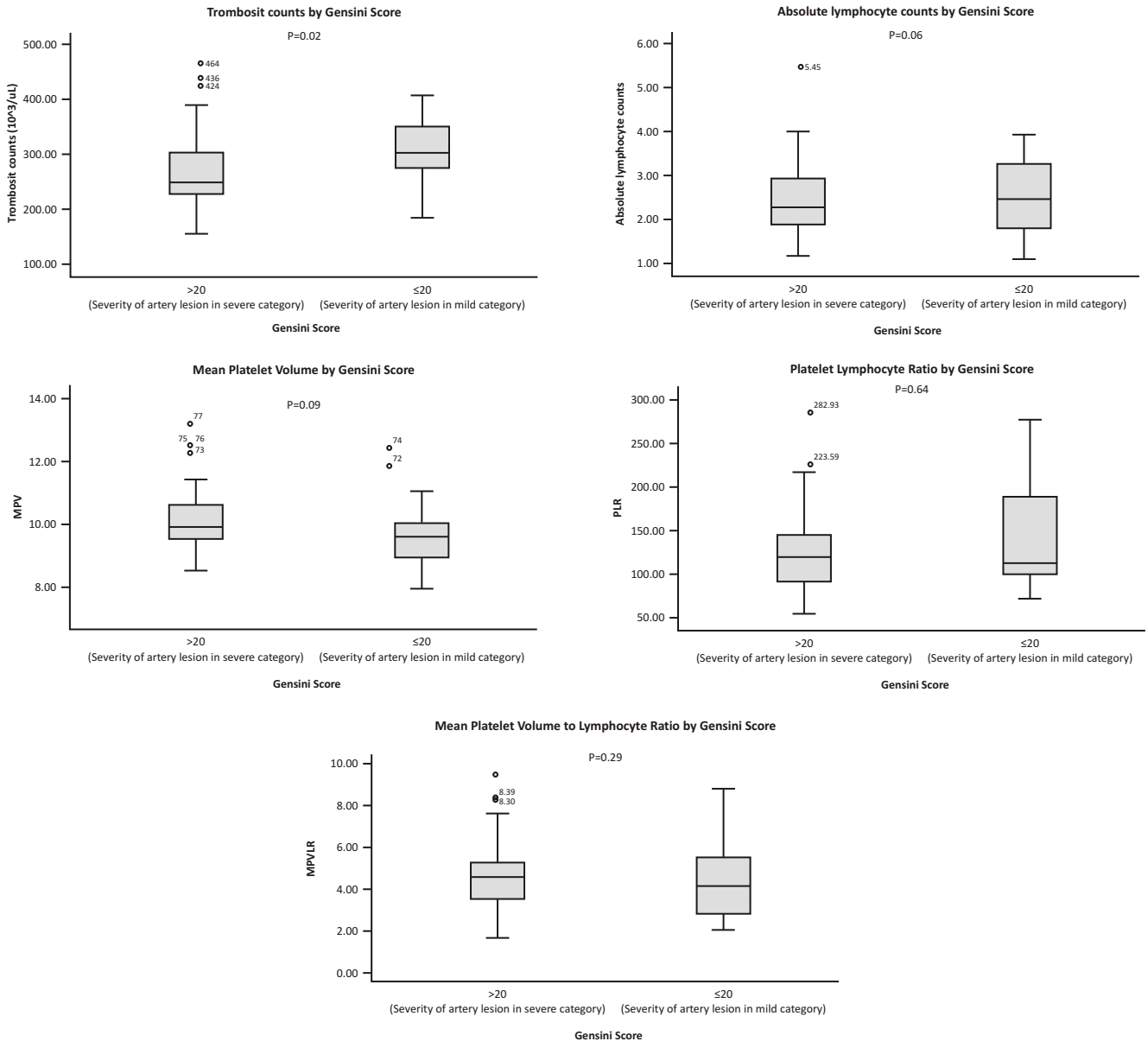

Figure 3. Graph of variable platelet count, absolute lymphocyte count (ALC), MPV, PLR, and MPVLR values according to the Gensini score category

CHD.[13,17,22,23] This is because the inflammatory process plays an essential role in atherosclerosis, from initiation to thrombosis. Furthermore, the low lymphocyte count was due to increased steroid levels associated with physiological stress, increased inflammatory response, and elevated lymphocyte apoptosis.[13,24]

In this study, the platelet count of the severe Gensini group was significantly lower than its mild counterpart ($p<0.05$). Spearman test showed a negative correlation between the number of platelets and the Gensini score (r - 0.304; p 0.012). This result is inconsistent with previous studies on stable CHD patients, in which the severe group had higher mean platelet counts and mean age (63–64 years) than its mild counterpart.[13,22,23] The decrease in platelet count in the severe Gensini group could be due to the predominance of 35 subjects aged ≥55. Furthermore, it is generally relatively stable at 25–59 years, reduced significantly 10x103/µL at 60–69 years, and decreased 20×103/µL at the age > 69 years.[25]

There is a significant positive correlation between the MPV value and the CCS severity, namely r 0.271 ($p<0.05$). This follows previous studies in which the MPV value correlated significantly with the Gensini score in CHD patients undergoing elective angiography.[12,16,26] It is because large platelets store more granules and mitochondria per unit volume, have a greater capacity to secrete inflammatory mediators, and express more receptors per unit membrane area, hence, they are more

TABLE 3
Spearman correlation between age, platelet count, absolute lymphocyte count, MPV, PLR, MPVLR values, and Gensini score

Parameter	R	P
Age	0.089	0.469
Platelet count (10^3/µL)	-0.304	0.012*
Absolute Lymphocyte Count (10^3/µL)	-0.140	0.256
MPV (fL)	0.271	0.025*
RLR	-0.057	0.645
MPVLR (fl /(10^3/µL))	0.217	0.076

MPV of mean platelet volume, PLR ratio of platelet count to lymphocyte count, MPVLR mean ratio of platelet volume to lymphocyte count,
*P < .05 was considered statistically significant

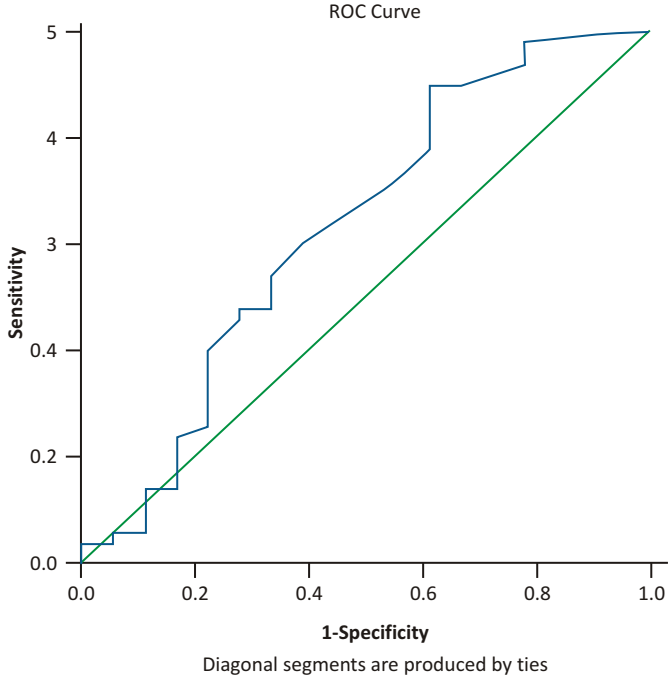

Figure 4. Graph of ROC between the MPV value and the severe Gensini score

atherogenic.[12,13,16,26] In contrast to previous cohort studies on diabetic patients undergoing coronary angiography, it was discovered that the MPV value was significantly related to age, inversely proportional to the platelet count, and was not related to P-selectin as a marker of platelet reactivity in CHD patients.[27]

The MPV value of 9.75 fl has a sensitivity, specificity, PPV, and NPV of 60%, 61%, 81%, and 35%. Despite having a good level of sensitivity and specificity, statistically based on the p-value and 95% CI, the variable cannot predict coronary syndrome severity (OR 1.26; 95% CI 0.93-1.70; p 0.205). Furthermore, other studies have shown different results; namely, the MPV value can be used as a predictor of the coronary complex lesions incidence in stable angina.[26]

In this study, the PLR values were negatively correlated with the CCS severity but not significant (r -0.057; p>0.05). It was previously reported that the PLR value was positively correlated and significantly different from the CCS severity.[13,22,23] The difference in this study was that there were 35 subjects aged ≥55 in the severe Gensini group compared to the 9 in its mild counterpart, accounting for 79% vs. 21%.

Trakarnwijitr *et al*. stated that there was a significant relationship between high PLR values ≥146.7 and an increased incidence of CAD (stenosis ≥50%) in patients aged ≥55.27 In CAD patients, P-selectin levels decreased at age >65 and increased at <55. They are

TABLE 4
Diagnostic test of MPV value as a predictor of CCS severity

	Severe Gensini	Mild Gensini	Total
MPV ≥9.75	30	7	37
MPV <9.75	20	11	31
Total	50	18	68

Sensitivity 60%, Specificity 61%, PPV 81% , NPV 35%

TABLE 5
Diagnostic test of MPVLR value as a predictor of CCS severity

	Severe Gensini	Mild Gensini	Total
MPVLR ≥3.4	40	9	49
MPVLR <3.4	10	9	19
Total	50	18	68

Sensitivity 80%, Specificity 50 %, PPV 82 %, NPV 47

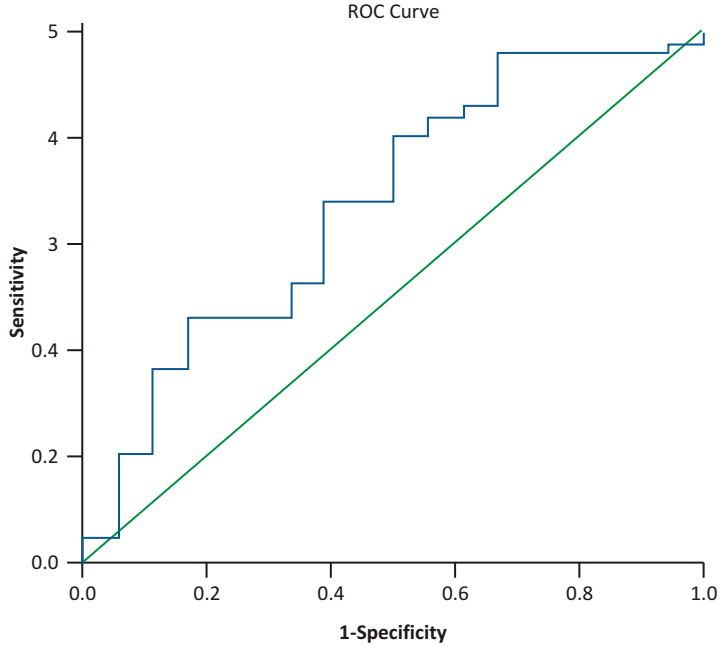

Figure 5. Graph of ROC between MPVLR values and severe Gensini scores

known to be positively correlated with the Gensini score and increase according to the number of coronary lesions involved.[28] Furthermore, P-selectin levels are known to be positively correlated with platelet counts.[29] The PLR values in this study were unrelated to the CCS severity. However, previous report stated that it is an independent predictor with OR 1.043; KI 1.036-1.049).[22]

P-selectin is a granular membrane protein secreted by α-granules in platelets. It roll and stick platelets to endothelial cells' surface and is activated in atherosclerosis. Therefore, it can be used as a marker of platelet activation.[28,29] The PLR values in this study were not related to the CCS severity. However, previous studies stated that PLR is an independent predictor with an OR of 1.043; KI 1.036–1.049).[22]

The correlation between the MPVLR value and the Gensini score was insignificant (p 0.076; r 0.217). A statistically significant difference in MPVLR values was found (p 0.029) when comparing the heavy and mild CCS groups. Studies on the relationship between the value

and the degree of CCS severity measured using the Gensini score have never been conducted. Previous reports also stated that patients with poor coronary circulation would have higher MPVLR values ($p < 0.001$) than coronary collateral circulation in those with stable angina pectoris/CCS.[19] Coronary collateral circulation is affected by several factors, such as the duration and severity of coronary stenosis, endothelial dysfunction, hypertension, DM, dyslipidemia, and smoking.[30] Finally, laboratory indicators such as platelet count (282.1 vs. 261.7), lymphocyte count (1.8 vs. 2), PLR value (156.8 vs. 132.1), and mean platelet volume (MPV) also differ significantly between stable angina patients with poor and good coronary collateral circulation (8.3 vs. 8).[31–33]

The MPVLR value of 3.4 has a sensitivity, specificity, PPV, and NPV of 80%, 50%, 82%, and 47%. Patients with values ≥ 3.4 were 1.55 times at risk (95% CI 0.99-2.43; p 0.034) of experiencing complex coronary lesion events. The disadvantage of this study is that it has limited sample and was conducted in one place, hence, the data obtained is less diverse. Furthermore, there is no molecular explanation regarding the relationship between variables with future prognosis. As a result, further studies is needed with a larger population and conducted in many places to deepen the understanding of the mechanism. It also makes the MPVLR value a predictor that can be applied in daily.

CONCLUSION

MPVLR can be used as a predictor of the severity of Chronic Coronary Syndrome. Its value of 3.4 has a sensitivity, specificity, PPV, and NPV of 80%, 50%, 82%, and 47% for complex coronary lesions in CCS patients. Furthermore, MPVLR value ≥ 3.4 has been shown to reperesent a 1.55 times greater risk of complex coronary lesions.

REFERENCES

1. Roth G, Mensah G, Johnson C. Global Burden of Cardiovascular Diseases and Risk Factors. J Am Coll Cardiol. 2020;76:2982–30.
2. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, *et al*. ESC guidelines on the management of stable coronary artery disease. Eur Heart J. 2013;34(38):2949–3003.
3. Kementerian Kesehatan RI [Internet]. Hasil Utama Rikesdas 2018. Jakarta; 2018.
4. Andersson J, Libby P, Hansson GK. Adaptive immunity and atherosclerosis. Clin Immunol. 2010;134(1):33–46.
5. Chatterjee M, Gawaz M. Platelets in Atherosclerosis. Platelets Thromb Non-Thrombotic Disord Pathophysiol Pharmacol Ther an Updat. 2017 Mar;993–1013.
6. Kodiatte TA, Manikyam UK, Rao SB, Jagadish TM, Reddy M, Lingaiah HKM, *et al*. Mean Platelet Volume in Type 2 Diabetes Mellitus. J Lab Physicians. 2012 Jan;4(1):5.
7. Taleb S. L'inflammation dans l'athérosclérose. Arch Cardiovasc Dis. 2016;109(12):708–15.
8. Madjid M, Fatemi O. Components of the Complete Blood Count as Risk Predictors for Coronary Heart Disease: In-Depth Review and Update. Texas Hear Inst J. 2013;40(1):17.
9. Kaushansky K. Megakaryocytes and Platelets. USA: Lippincott Williams and Wilkins; 2004.
10. 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 Apr;1–14.
11. Handtke S, Thiele T. Large and small platelets(When) do they differ? J Thromb Haemost. 2020 Jun;18(6):1256–67.
12. Sansanayudh, N., Anothaisintawee, T., Muntham, D., McEvoy, M., Attia, J., & Thakkinstian A. Mean platelet volume and coronary artery disease: a systematic review and meta-analysis. Int J Cardiol. 2014 Aug;175(3):433–40.
13. Uysal HB, Dağlı B, Akgüllü C, Avcil M, Zencir C, Ayhan M, *et al*. Blood count parameters can predict the severity of coronary artery disease. Korean J Intern Med. 2016;31(6):1093–100.
14. Murat SN, Duran M, Kalay N, Gunebakmaz O, Akpek M, Doger C, *et al*. Relation Between Mean Platelet Volume and Severity of Atherosclerosis in Patients With Acute Coronary Syndromes. 2012 Feb;64(2):131–6.
15. Bodí V, Sanchis J, Núñez J, Rumiz E, Mainar L, López-Lereu MP, *et al*. Post-Reperfusion Lymphopenia and Microvascular Obstruction in ST-Segment Elevation Acute Myocardial Infarction. Rev Española Cardiol (English Ed). 2009 Oct;62(10):1109–17.
16. Chu S, Becker R, Berger P, Bhatt D, Eikelboom J, Konkle B, *et al*. Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. J Thromb Haemost. 2010 Jan;8(1):148–56.
17. Qiu Z, Jiang Y, Jiang X, Yang R, Wu Y, Xu Y, *et al*. Relationship Between Platelet to Lymphocyte Ratio and Stable Coronary Artery Disease: Meta-Analysis of Observational Studies. 2020 Jul;71(10):909–15.
18. Wahyuni I, Wijaya I, Sukrisman L, Nasution S, Rumende C. Diagnostic Accuracy of Platelet/Lymphocyte Ratio for Screening Complex Coronary Lesion in Different Age Group of Patients with Acute Coronary Syndrome - PubMed. Acta Med Indones. 2018.p. 50(3):185–192.
19. Ornek E, Kurtul A. Relationship of mean platelet volume to lymphocyte ratio and coronary collateral circulation in patients with stable angina pectoris. Coron Artery Dis. 2017;28(6):492–7.
20. Hudzik B, Szkodziński J, Lekston A, Gierlotka M, Poloński L, Gąsior M. Mean platelet volume-to-lymphocyte ratio: a novel marker of poor short- and long-term prognosis in patients with diabetes mellitus and acute myocardial infarction. J Diabetes Complications. 2016 Aug;30(6):1097–102.
21. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol. 1983;51(3):606
22. Akboga M, Canpolat U, Yayla C, Ozcan F, Ozeke O, Topaloglu S, *et al*. Association of Platelet to Lymphocyte Ratio With Inflammation and Severity of Coronary Atherosclerosis in Patients With Stable Coronary Artery Disease. Angiology. 2016 Jan;67(1):89–95
23. Yüksel M, Yıldız A, Oylumlu M, Akyüz A, Aydın M, Kaya H, *et al*. The association between platelet/lymphocyte ratio and coronary artery disease severity. Anadolu Kardiyol Derg. 2015;15(8):640–7
24. Hotchkiss RS KI. The pathophysiology and treatment of sepsis. N Engl J Med. 2003;348(2):138
25. Le Blanc J LM. Platelet Function in Aging. Front Cardiovasc Med. 2019
26. Lin Y, Chen X, Xu X. Utility of mean platelet volume to predict the prevalence of coronary artery disease on coronary angiography in patients with stable angina. Coron Artery Dis. 2019;30(8):615–20

27. Trakarnwijitr, I., Li, B., Adams, H., Layland, J., Garlick, J., & Wilson A. Age modulates the relationship between platelet-to-lymphocyte ratio and coronary artery disease. Int J Cardiol. 2017 Dec;248:349–54
28. De Luca G, Verdoia M, Cassetti E, Schaffer A, Di Giovine G, Bertoni A, Di Vito C, Sampietro S, Aimaretti G, Bellomo G, Marino P SFNAS (NAS) group. Mean platelet volume is not associated with platelet reactivity and the extent of coronary artery disease in diabetic patients. Blood Coagul Fibrinolysis. 2013;Sep;24(6)
29. Barbaux SC, Blankenberg S, Rupprecht HJ, Francomme C, Bickel C, Hafner G, Nicaud V, Meyer J, Cambien F TL. Association between P-selectin gene polymorphisms and soluble P-selectin levels and their relation to coronary artery disease. Arter Thromb Vasc Biol. 21(10):166
30. Song C, Wu G, Chang S BL. Plasma P-selectin level is associated with severity of coronary heart disease in Chinese Han population. J Int Med Res. 2020;48(6):3000
31. Werner GS, Ferrari M, Heinke S, Kuethe F, Surber R, Richartz BM FH. Angiographic assessment of collateral connections in comparison with invasively determined collateral function in chronic coronary occlusions. Circulation. 2003;Apr 22;107
32. Açar G, Kalkan ME, Avci A, Alizade E, Tabakci MM, Toprak C, *et al*. The Relation of Platelet-Lymphocyte Ratio and Coronary Collateral Circulation in Patients With Stable Angina Pectoris and Chronic Total Occlusion. Clin Appl Thromb. 2015;21(5):462–8
33. Akın F, Ayça B, Çelik Ö, Şahin C. Predictors of poor coronary collateral development in patients with stable coronary artery disease: Neutrophil-to-lymphocyte ratio and platelets. Anadolu Kardiyol Derg. 2015;15(3):218–23