

**ARTICLE INFO**

**AUTHOR'S AFFILIATIONS**

Internal Medicine  
 Department, Faculty of  
 Medicine Sultan Agung Islamic  
 University – Sultan Agung  
 Islamic Teaching Hospital,  
 Semarang Indonesia<sup>1</sup>  
 Research Assistant, Division of  
 Respiriology and Critical Illness,  
 Department of Internal Medicine  
 Faculty of Medicine Universitas  
 Indonesia – Cipto  
 Mangunkusumo General  
 Hospital, Jakarta, Indonesia<sup>2</sup>

**CORRESPONDING AUTHOR**

**Muhammad Rizki Triono**  
 Research Assistant Division of  
 Respiriology and Critical Illness,  
 Department of Internal  
 Medicine  
 Faculty of Medicine Universitas  
 Indonesia – Cipto  
 Mangunkusumo General  
 Hospital, Jakarta, Indonesia

**E-mail:**

[m.rizkitriono@gmail.com](mailto:m.rizkitriono@gmail.com)

**Article history**

Received 23-01-2024

Revised 26-01-2024

Accepted 22-03-2024

Available online

**Please cite this article in APA 7<sup>th</sup> edition style as:**

Abduh, M. S., Triono, M. R.,  
 Widyastuti, R. (2024). Role of  
 Anemia and Leukocytosis as  
 Severity Predictors of Coronary  
 Artery Disease Stenosis : A  
 Retrospective Cross-sectional  
 Study. *Jurnal Ilmiah Kedokteran  
 Wijaya kusuma*, 13(1), XX-XXX  
<https://doi.org/10.30742/jikw.v13i1.3555>

**Role of Anemia and Leukocytosis as Severity Predictors of Coronary Artery Disease Stenosis: A Retrospective Cross-sectional Study**

*M Saugi Abduh<sup>1</sup>, Muhammad Rizki Triono<sup>2\*</sup>, Retno Widyastuti<sup>1</sup>*

**Abstract**

**Background:** Anemia and leukocytosis were found to be associated with conditions that higher the risk for the formation of atherosclerotic plaque which will develop into cardiovascular disease. Basic laboratory parameters such as anemia and leukocytosis are not routinely used to assess Coronary Artery Disease (CAD) severity based on its stenosis. This study aimed to analyze the role of simple laboratory examiantion anemia and leukocytosis as predictors of the severity of stenosis in CAD. **Methods:** Cross-sectional approach was used in this study. Secondary data on CAD patients treated at Sultan Agung Islamic Hospital Semarang in 2022 were analyzed. Anemia and leukocytosis are the main risk factors analyzed in this study. Other risk factors such as gender, age, smoking status, hypertension and diabetes mellitus (DM) were also included in the analysis of this study. We performed bivariate analysis and multivariate analysis to see the relationship between these risk factors and the CAD stenosis severity. **Results:** Bivariate analysis with chi-square showed that anemia had a significant relationship with CAD severity ( $P<0.05$ ). Multivariate analysis between anemia and smoking status reported that anemia was the most significant risk factor for the CAD stenosis severity ( $P<0.05$ ). **Conclusion:** No association found between leukocytosis and CAD severity.

**Keywords:** anemia, severity, coronary artery disease, immunity, leukocytosis, stenosis

**Original Research Article**

**INTRODUCTION**

Coronary Artery Disease (CAD) is a condition of an imbalance between the need for blood and oxygen delivered to the myocardium, resulting in a lack of supply to the myocardium (Cassar et al., 2009). This imbalance is caused by plaque blocking blood flow in the coronary arteries, which ultimately causes dysregulation of the supply and demand of oxygen throughout the body (Shahjehan, 2022). This

plaque in CAD or what is known as "stenosis" causes narrowing of the heart arteries. This narrowing of the heart arteries plays an important role in determining the prognosis and appropriate management for CAD patients (Mirbolouk et al., 2020). The severity of stenosis in CAD can be influenced by several contributing factors. These factors are generally known and divided into non-modifiable risk factors and modifiable risk factors (Brown et al., 2023). Gender (males are more at risk), family history of CAD, advanced age, and race are among the non-modifiable risk factors. Modifiable factors include lack of physical activity, obesity, smoking, diabetes, high blood pressure, stress, and unhealthy food intake (Hajar, 2017).

Assessment of the severity of CAD stenosis brings many benefits to the management of CAD patients. This evaluation is best conducted through an angiography examination to assess the extent of direct stenosis in the coronary arteries (Omidi et al., 2020). A simple assessment can reportedly be performed to evaluate the severity of the stenosis of this disease. Previous studies have found that simple tests such as lipid profiles (LDL, HDL, total cholesterol) have a role in assessing the severity of stenosis (Abduh & Triono, 2022). Other tests have also been reported to have a similar role. Simple blood tests such as hemoglobin (anemia) and leukocyte count (leukocytosis) are reported to predict the severity of CAD (Mirbolouk et al., 2020). This simple blood test has advantages compared to other blood parameter tests because it does not require fasting preparation before sampling.

The condition of a decrease in the number of red blood cells or concentration of hemoglobin (Hb) or hematocrit (HCT) is called anemia (Turner et al., 2022). Anemia is a risk factor that is independently reported as a risk factor for cardiovascular disease (CVD) (Goel et al., 2021). Anemia was also reported in previous studies to be associated with the severity of CAD. In someone who experiences anemia, there is a hyperactivation of immune system and increased inflammation state. This condition is strongly associated with increased susceptibility to the development of CVD and other poor prognoses (Lanser et al., 2021).

Increased systemic inflammation and immune system activity are one of the key mechanisms for the development of CAD severity (Dai et al., 2022). One simple marker of systemic inflammation is the number of leukocytes (Mirbolouk et al., 2020). Leukocytes are reported to have a vital function in the development of CAD (Moriya, 2019). Significant correlation between leukocyte count and the severity of CAD has been documented in the previous study (Kose et al., 2019).

Anemia and leukocytes as simple serological examinations are not routinely used as indicators to assess CAD stenosis severity in Indonesia. This study aimed to analyze anemia and leukocytosis as stenosis severity predictor in CAD patients.

## **MATERIALS AND METHODS**

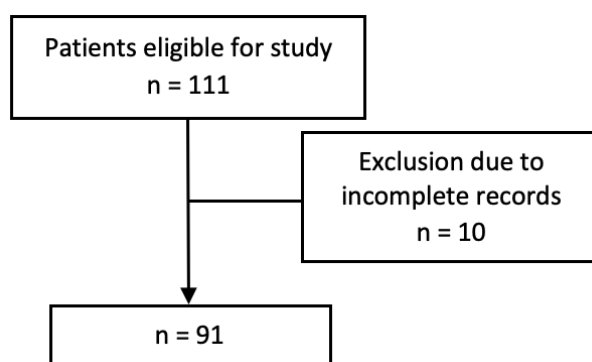
This study adopts an observational approach with a cross-sectional design. The dataset utilized and analyzed in this research was derived from secondary medical records of patients diagnosed with CAD who received treatment at Sultan Agung Islamic Hospital in Semarang and underwent coronary angiography during the year 2022. Inclusion criteria in this study included: the availability of hemoglobin levels data, leukocyte counts, body mass index (BMI), blood pressure, historical records of hypertension, historical data on diabetes mellitus, and the smoking status of the individuals involved.

The variables in this investigation were categorized into independent variables, specifically anemia and leukocytes, and the dependent variable, which is the severity of coronary artery disease (CAD) stenosis. Anemia was further divided into two groups: the anemia group (Hb <13 mg/dL) and the non-anemia group (Hb >13mg/dL). Leukocyte counts were classified into three groups: normal (3,500-11,000), leukopenia (<3,500), and leukocytosis (>11,000). The assessment of CAD stenosis severity was based on coronary angiography and categorized into non-significant CAD and significant CAD. Significant CAD was defined as the presence of >50% stenosis in the left main stem, >70% stenosis in the main coronary artery, or 30%-70% stenosis with a fractional flow reserve of  $\leq 0.9$  (Neglia et al., 2015). Additionally,

other variables scrutinized and analyzed in this study encompassed body mass index (BMI), gender, history of diabetes mellitus (DM) and hypertension, as well as smoking status. The data in this study was analyzed using the SPSS application. Bivariate analysis was carried out with the chi-square test. Variables that have a P value <0.25 are continued for multivariate testing to see variables that were significantly related to the dependent variable (CAD stenosis severity). A P value baseline of <0.05 was used in the multivariate test in this study which can be considered as statistically significant.

**RESULTS**

This research took all CAD patients treated at Sultan Agung Islamic Hospital in Semarang in 2022. There were 111 CAD patients who underwent coronary angiography and could potentially be included in the study. In the end there were 91 patients included in this study, as shown in Figure 1.



**Figure 1.** Flow-chart of subject selection in this study

Baseline characteristics and results of bivariate analysis in this study are shown in Table 1. As reported in Table 1, of the total 111 patients, the majority of subjects were men with a total of 61 patients (67%) compared to women with 30 patients (33%). Based on the results of the hemoglobin examination, 28 patients were anemic (30%) and 63 patients were not anemic (70%). From the results of leukocyte count examination, there were 3 patients (3.2%) with leukocytosis, 2 patients (2.1%) with leukopenia and 86 patients with normal leukocytes (94%).

**Table 1.** Baseline characteristic and results of bivariate analysis

Variable	CAD				P	OR
	Significant		Non-significant			
	n=61	%	n=30	%		
Gender						
Men	44	(72.1)	18	(60.0)	0.253	1.725
Women	17	(27.9)	12	(40.0)		
Anemia						
Anemia	26	(42.6)	2	(6.7)	0.000*	10.400
No	35	(57.4)	28	(93.3)		
Leukocytes						
Leukocytosis	1	(1.6)	2	(6.7)	1.000	0.656
Leukopenia	2	(3.3)	0	(0.0)		
Normal	58	(95.1)	28	(93.3)		
Nutritional status						
Underweight	3	(4.9)	0	(0.0)	0.908	1.159
Overweight	25	(41.0)	10	(33.3)		
Obese	10	(16.4)	10	(33.3)		

Normal	23	(37.7)	10	(33.3)		
Diabetes						
Yes	16	(26.2)	5	(16.7)	0.309	1.778
No	45	(73.8)	25	(83.3)		
Hypertension						
Yes	1	(1.6)	2	(6.7)	1.000	0.656
No	2	(3.3)	0	(0.0)		
Smoking						
Yes	30	(49.2)	10	(34.5)	0.190	1.839
No	31	(50.8)	19	(65.5)		

CAD, Coronary Artery Disease; P, P-value; OR, Odd Ratio

According to the findings of this research, 23% of the patients had diabetes mellitus (DM), totaling 21 individuals. Hypertension was observed in 58% of the patients, comprising 53 individuals. Smoking status, identified as another risk factor for coronary artery disease (CAD), was present in 43.7% of the subjects, with 40 patients having a history of smoking. Additionally, nutritional status emerged as a risk factor, with 21.9% (20 patients) classified as obese and 42% (35 patients) classified as overweight in this study.

In this study, the degree of stenosis of the disease was grouped based on the percentage of stenosis. The stenosis percentage of CAD patients was classified into significant and nonsignificant stenosis. Upon analyzing the severity of stenosis in CAD patients treated at Sultan Agung Islamic Hospital in 2022, our findings indicated that a majority, constituting 68%, presented with significant stenosis, while the remaining 32% exhibited non-significant stenosis.

As reported in Table 1, the results of the bivariate analysis showed a relationship between the independent variables used for data collection in this study and the dependent variable, namely the severity of stenosis. The primary goal is to pinpoint which variable is most closely linked to the severity of CAD stenosis. Among all the characters and variables analyzed in this study, including conditions related to anemia and leukocytes, only anemia exhibited a noteworthy association with the degree of stenosis ( $P < 0.05$ ). This underscores a meaningful correlation between anemia and the categorization of stenosis into significant and non-significant. The bivariate analysis findings for the remaining variables indicate P values surpassing 0.05. A total of 26 (92%) of the 28 anemia patients had a significant degree of stenosis, while 56% of patients who were not anemic had a significant degree of stenosis. The Odds Ratio (OR) for the association between anemia and the severity of CAD is 10.4, signifying that an individual with anemia is 10.4 times more likely to have significant CAD compared to an individual without anemia.

All independent variables representing coronary artery disease (CAD) risk factors, identified through bivariate analysis, underwent multivariate logistic regression analysis to identify the most dominant variable associated with the severity of CAD stenosis. Variables eligible for inclusion in the multivariate analysis were those with  $P$ -values  $< 0.25$  in the bivariate analysis, namely anemia ( $P = 0.000$ ) and smoking status ( $P = 0.190$ ). The results of the logistic regression multivariate analysis are presented in Table 2.

**Table 2.** Results of the multivariate analysis

Variables	P Value	Exp(B)	95% CI	
			Lower	Upper
Anemia	<b>0.002</b>	12.005	2.536	56.829
Smoking	0.069	2.517	0.930	6.811

The multivariate logistic regression analysis presented in Table 2 revealed that anemia is the variable most strongly associated with CAD stenosis severity ( $P = 0.002$ ). This notable correlation is

emphasized by the Exp value (B) or Odds Ratio (OR) value, which is calculated at 12.005. Consequently, an individual with anemia is at a significantly higher risk, specifically 12.005 times, of experiencing significant CAD in comparison to an individual without anemia.

## DISCUSSION

The findings of this research indicate that anemia is the most strongly correlated predictor of stenosis severity in patients with coronary artery disease (CAD). These results align with earlier studies by Lanser et al., which also reported an association between anemia and the progressive severity of CAD (Lanser et al., 2021). Findings in other studies also found a link between anemia and heart disease such as heart failure (Gan et al., 2023). The complex pathophysiological mechanisms underlying anemia in cardiovascular disease and CAD involve a multitude of factors. Anemia initiates immediate hemodynamic shifts, influencing blood viscosity, arterial dilation, vascular resistance, and stroke volume (Metivier et al., 2000). These hemodynamic changes caused by anemia disrupt the arterial wall and lead to the development of left ventricular hypertrophy, subsequently contributing to irreversible alterations and the initiation of congestive heart failure (Mozos, 2015). Beyond hemodynamic effects, anemia is linked to non-hemodynamic alterations, including compromised erythropoietin production, which plays a role in the context of CAD (Rymer & Jennifer, 2017). Anemia's contribution to the advancement of CAD is associated with its crucial role as a mechanism in inflammatory processes. Previous studies have suggested that individuals experiencing anemia exhibit immune system hyperactivation and heightened inflammatory states, marked by increased levels of inflammatory cytokines (IL-12 and IL-6), both of which are correlated with CAD severity (Lanser et al., 2021).

The results of this research suggested that there were no notable connection between an elevated white blood cell count and the extent of stenosis in patients with CAD ( $P > 0.05$ ). In line with previous studies, this observation corresponds to the varied findings reported in different research regarding the relationship between leukocytes and the severity of coronary artery disease. Some reports proposed that an increased white blood cell count serves as a predictor of cardiovascular events, while others have not identified a clear association (Dharma et al., 2015). Other findings documented total leukocytes and leukocyte count as prognostic markers in CAD patients (Yan et al., 2020). The count of leukocytes serves as a crucial factor in predicting and initiating cardiovascular disease, functioning as a biomarker that is both cost-effective and easily measurable (Madjid et al., 2004). Previous studies have established an association between an elevated leukocyte count and heightened severity of CAD (Rana et al., 2007). The number of leukocytes is associated with both the extent of stenosis in coronary arteries and the size of the infarct in individuals undergoing acute myocardial infarction (Yan et al., 2020). Previous research reported that the number of leukocytes correlated with the severity and progression of infarct heart disease (Ferrari et al., 2016). The discrepancies in findings regarding the link between leukocytes and CAD severity might arise from unaccounted factors in this study that have the potential to impact leukocyte levels (Stoner et al., 2013). The differences in results may also stem from variations in demographics and characteristics of subjects among various studies. In the current investigation, 86 patients (94%) demonstrated leukocyte levels within the normal range.

Our study possesses few limitations, including its observational cross-sectional design. Additionally, the analysis did not encompass other potential risk factors such as a history of physical activity and familial predisposition. We also did not include specificity and sensitivity test. Many studies have reported the relationship between physical activity and coronary heart disease (Vooturi et al., 2023). Therefore, further studies with a better cohort prospective approach need to be carried out to see the role of anemia and leukocytes on the severity of CAD. The study's patient pool was exclusively drawn from a single hospital center in Central Java, resulting in a relatively small study population.

## CONCLUSION

Our study found a notable relationship between anemia and CAD stenosis severity. Anemia has been reported as one of the risk factor to CAD severity. We found that leukocytosis was not associated with

CAD stenosis severity. Anemia condition has a role in predicting the severity of CAD stenosis. Further stronger research are needed to validate this relationship between anemia and the severity of CAD stenosis.

### **CONFLICT OF INTEREST**

All authors have no any conflict of interest.

### **ACKNOWLEDGEMENTS**

Thank you to *Lembaga Penelitian dan Pengabdian Masyarakat Universitas Islam Sultan Agung* (LPPM UNISSULA) which has funded this research.

### **REFERENCES**

- Abduh, M. S., & Triono, M. R. (2022). Analisis Profil Lipid sebagai Prediktor Keparahan Stenosis Coronary Artery Disease yang Dinilai Menggunakan Gensini Score. *Jurnal Wiyata: Penelitian Sains Dan Kesehatan*, 9(2), 79–87. <https://doi.org/10.56710/WIYATA.V9I2.603>
- Brown, J., Gerhardt, T., & Kwon, E. (2023). Risk Factors for Coronary Artery Disease. *StatPearls Publishing LLC*.
- Cassar, A., Holmes, D. R., Rihal, C. S., & Gersh, B. J. (2009). Chronic Coronary Artery Disease: Diagnosis and Management. *Mayo Clinic Proceedings*, 84(12), 1130. <https://doi.org/10.4065/MCP.2009.0391>
- Dai, X., Kong, T., & Zhang, X. (2022). Relationship between Increased Systemic Immune-Inflammation Index and Coronary Slow Flow Phenomenon. *BMC Cardiovascular Disorders*, 8(22), 362. <https://doi.org/10.1186/s12872-022-02798-0>
- Dharma, S., Hapsari, R., & Siswanto, B. (2015). Blood Leukocyte Count on Admission Predicts Cardiovascular Events in Patients with Acute Non-ST Elevation Myocardial Infarction. *Int J Angiol*, 2, 127–132. <https://doi.org/10.1055/s-0035-1544178>
- Ferrari, J. P., Lueneberg, M. E., Silva, R. L. da, Fattah, T., Gottschall, C. A. M., & Moreira, D. M. (2016). Correlation between Leukocyte Count and Infarct Size in ST Segment Elevation Myocardial Infarction. *Archives of Medical Sciences. Atherosclerotic Diseases*, 1(1), e44. <https://doi.org/10.5114/AMSAD.2016.60759>
- Gan, T., Hu, J., Liu, W., Li, C., Xu, Q., Wang, Y., Lu, S., Aledan, A. K. O., Wang, Y., & Wang, Z. (2023). Causal Association Between Anemia and Cardiovascular Disease: A 2-Sample Bidirectional Mendelian Randomization Study. *Journal of the American Heart Association*, 12(12), 29689. <https://doi.org/10.1161/JAHA.123.029689>
- Goel, H., Hirsch, J. R., Deswal, A., & Hassan, S. A. (2021). Anemia in Cardiovascular Disease: Marker of Disease Severity or Disease-modifying Therapeutic Target? *Current Atherosclerosis Reports*, 23(10). <https://doi.org/10.1007/s11883-021-00960-1>
- Hajar, R. (2017). Risk Factors for Coronary Artery Disease: Historical Perspectives. *Heart Views Journal*, 3(18), 109–114. [https://doi.org/10.4103/HEARTVIEWS.HEARTVIEWS\\_106\\_17](https://doi.org/10.4103/HEARTVIEWS.HEARTVIEWS_106_17)
- Kose, N., Akin, F., & Ergun, G. (2019). The Association Between the Lymphocyte-to-Monocyte Ratio and Coronary Artery Disease Severity in Patients with Stable Coronary Artery Disease. *Eur Rev Med Pharmacol Sci*. [https://doi.org/10.26355/eurrev\\_201903\\_17406](https://doi.org/10.26355/eurrev_201903_17406)
- Lanser, L., Fuchs, D., & Shcarnagl, H. (2021). Anemia of Chronic Disease in Patients with Cardiovascular Disease. *Front Cardiovascular Medicine*. <https://doi.org/10.3389/fcvm.2021.666638>
- Madjid, M., Awan, I., Willerson, J. T., & Casscells, S. W. (2004). Leukocyte Count and Coronary Heart Disease: Implications for Risk Assessment. *Journal of the American College of Cardiology*, 44(10), 1945–1956. <https://doi.org/10.1016/J.JACC.2004.07.056>
- Metivier, F., Marchais, S. J., Guerin, A. P., Pannier, B., & London, G. M. (2000). Pathophysiology of Anaemia: Focus on the Heart and Blood Vessels. *Nephrology, Dialysis, Transplantation: Official*

*Publication of the European Dialysis and Transplant Association - European Renal Association, 15 Suppl 3(SUPPL. 3), 14–18. <https://doi.org/10.1093/OXFORDJOURNALS.NDT.A027970>*

Mirbolouk, F., Baharvand, F., Salari, A., Shakiba, M., Moayerifar, M., & Gholipour, M. (2020). Serum Parameters and Severity of Coronary Artery Disease in Patients with Acute Coronary Syndrome. *Immunopathologia Persa, 6*(1), 1–7. <https://doi.org/10.15171/ipp.2020.12>

Moriya, J. (2019). Critical Roles of Inflammation in Atherosclerosis. *Journal of Cardiology. <https://doi.org/10.1016/j.jjcc.2018.05.010>*

Mozos, I. (2015). Mechanisms Linking Red Blood Cell Disorders and Cardiovascular Diseases. *BioMed Research International, 2015. <https://doi.org/10.1155/2015/682054>*

Neglia, D., Rovai, D., Caselli, C., & Pietila, M. (2015). Detection of Significant Coronary Artery Disease by Noninvasive Anatomical and Functional Imaging. *Circ Cardiovasc Imaging, 3. <https://doi.org/10.1161/CIRCIMAGING.114.002179>*

Omid, N., Sadeghian, S., Salarifar, M., Jalali, A., Abbasi, S. H., Yavari, N., Ghorashi, S. M., Alidoosti, M., & Poorhosseini, H. (2020). Relationship between the Severity of Coronary Artery Disease and Cardiovascular Risk Factors in Acute Coronary Syndrome: Based on Tehran Heart Center’s Data Registry. *The Journal of Tehran University Heart Center, 15*(4), 165. <https://doi.org/10.18502/JTHC.V15I4.5942>

Rana, J., Boekholdt, S., & Ridker, P. (2007). Differential Leucocyte Count and the Risk of Future Coronary Artery Disease in Healthy Men and Women. *J Intern Med, 6. <https://doi.org/10.1111/j.1365-2796.2007.01864>*

Rymer, & Jennifer, A. (2017). Anemia and Coronary Artery Disease: Pathophysiology, Prognosis, and Treatment. *Coronary Artery Disease, 2*(29), 161–167. <https://doi.org/10.1097>

Shahjehan, R. D. (2022). *Coronary Artery Disease*. StatPearls [Internet].

Stoner, L., Lucero, A. A., Palmer, B. R., Jones, L. M., Young, J. M., & Faulkner, J. (2013). Inflammatory Biomarkers for Predicting Cardiovascular Disease. *Clinical Biochemistry, 46*(15), 1353–1371. <https://doi.org/10.1016/J.CLINBIOCHEM.2013.05.070>

Turner, J., Parsi, M., & Badireddy, M. (2022). Anemia. *StatPearls [Internet] Ncbi, 1*.

Vooturi, S., Anil, P., & Monica, Y. (2023). Effects of Exercise Training and Physical Activity in Patients with Coronary Artery Disease. <https://doi.org/10.1177/26324636231158460>, 4(2), 98–100. <https://doi.org/10.1177/26324636231158460>

Yan, X., Jin, J., & Zhang, M. (2020). Differential Leukocyte Counts and Cardiovascular Mortality in Very Old Patients with Acute Myocardial Infarction: a Chinese Cohort Study. *BMC Cardiovasc Disord, 20. <https://doi.org/10.1186/s12872-020-01743-3>*