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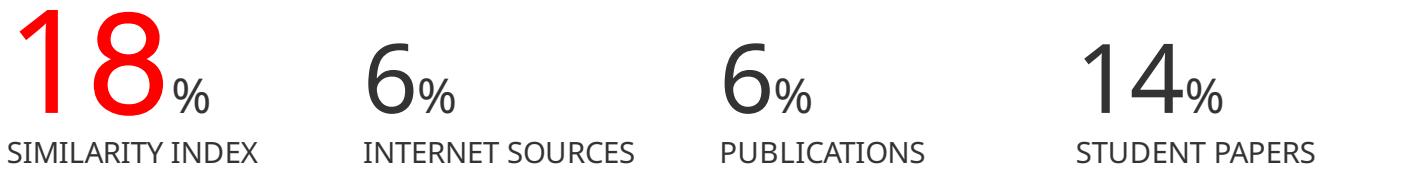
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Role of Anemia and Leukocytosis as Severity Predictors of Coronary Artery Disease Stenosis : A Retrospective Cross-sectional Study

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ABSTRACT

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. 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. 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 ($P<0.05$).

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. 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). Simple blood tests such as hemoglobin (anemia) and leukocyte count (leukocytosis) are reported to predict the severity of CAD (Mirbolouk et al., 2020).

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 ≤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. Data with a P value < 0.25 were followed by multivariate analysis with a logistic regression test to see variables that were significantly related to the dependent variable (CAD stenosis severity). Variables in multivariate analysis that have a P value <0.05 were considered 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.

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%).

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, we utilized classifications of significant and non-significant to assess the degree of stenosis in patients with coronary artery disease (CAD). 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.

Table 1 displayed the bivariate analysis undertaken to explore the connection between the independent variables gathered in this study and the severity of coronary artery disease (CAD) stenosis. The primary goal is to pinpoint which variable is most closely linked to the severity of CAD stenosis. Among all the variables scrutinized, including conditions related to anemia and leukocytes, only anemia exhibited a noteworthy association with the severity of CAD 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. Table 1 showed that 42.6% of patients with anemia display significant CAD, while 93.3% of those without anemia also lack significant (non-significant) CAD. 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.

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). 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. 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. 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 findings of this study indicate the absence of a significant correlation between leukocytosis and the severity of stenosis in CAD patients ($P>0.05$). Consistent with earlier research, this observation aligns with the divergent conclusions reached across different studies regarding the link between leukocytes and CAD severity. Some studies have suggested that leukocytosis acts as a predictor of cardiovascular events, while others have failed to identify such an 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. Previous studies have established an association between an elevated leukocyte count and heightened severity of CAD (Rana et al., 2007). The leukocyte count is linked to both the severity of stenosis in coronary arteries and the magnitude of infarct size in individuals experiencing acute myocardial infarction (Yan et al., 2020). 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. 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. 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.