



Original Article

Leukocytosis as The Short-Term Predictor of Mortality in Acute Coronary Syndrome Patients Undergoing Percutaneous Coronary Intervention

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ABSTRACT

Background : In daily clinical practice, the leukocyte count is the most common and simple inflammation parameter. However, its role in predicting the clinical outcomes and prognosis of patients with acute coronary syndrome (ACS) is still conflicting.

Objectives : This study aimed to assess the role of leukocytosis as the predictor of mortality in ACS patients undergoing percutaneous coronary intervention (PCI).

Methods : This single-centre retrospective cohort study used the STEMI registry data in Saiful Anwar General Hospital, Malang, Indonesia, from January to July 2019. The predictor was the leukocyte count during hospital admission, and the outcome was the 30-day mortality following PCI procedure. The receiver-operating characteristic (ROC) curve was used to determine leukocyte count cut-off point, sensitivity, and specificity.

Results: The best leukocyte count cut-off value was 12300/ μ L, with the area under the curve (AUC) of 0.702 (95% CI 0.575 - 0.83), the sensitivity of 71.4%, and specificity of 61.3%. Leukocytosis increased the risk of 30-day mortality (74.5% vs 42.4%; OR = 3.958; 95% CI = 1.518-10.25; $p = 0.014$). Survival rate within 30-day after PCI was lowered in the leukocytosis group (the Log-Rank $p = 0.002$). The difference became apparent after day five post-PCI.

Conclusion: Leukocytosis during hospital admission is associated with increased mortality in ACS patients undergoing PCI. Leucocytosis may be considered as the prominent predictor of mortality within 30 days after PCI in this population.

1. Introduction

Inflammation plays a significant role in atherosclerosis disease.^{1,2} The inflammatory cascade may serve as a promoter and initiator in the evolution of atherosclerosis. Inflammation also contributes to promoting fibrous cap rupture, leading to acute thrombosis and acute arterial occlusion. If this circumstance occurs in the coronary arteries, this condition may lead to the development of ACS.^{3,4} Increased inflammatory markers, such as C-reactive protein, serum amyloid receptor A, interleukin-6, and interleukin-1, had been studied to be associated with poor clinical outcomes in ACS patients.^{1,2,5-7} However, those inflammatory markers are not widely available because of their high cost and time-consuming examination process. Therefore, their utilization is very restricted. In daily clinical practice, leukocyte count is the most common and simple inflammation parameter. Moreover, the role of leukocyte to predict the clinical outcomes and the prognosis of ACS patients had been investigated by several studies.^{1,2} Increased leukocyte count is associated with poor clinical outcomes, including a larger infarct area, decreased left ventricular function, and increased long-term mortality in ACS patients.^{8,1,9,10}

In ST-elevation myocardial infarction (STEMI), the correlation between leukocyte count at hospital admission and mortality had been reported for more than 50 years. However, inconsistent findings were observed across the studies.¹ Moreover, several scores dedicated to predicting the mortality of ACS patients, such as the thrombolysis in myocardial infarction (TIMI) risk score and global registry of acute coronary events (GRACE) score, do not include the leukocytosis as the predictor of mortality.¹¹⁻¹³ Our current study, therefore, aimed to assess the role of leukocytosis as the predictor of mortality in ACS patients undergoing PCI.

2. Method

2.1 Study population, exposure, and outcome

This single-centre retrospective cohort study used the STEMI registry data in Saiful Anwar General Hospital, Malang, Indonesia, from January to July 2019. Our study was registered and approved by the local Ethical Committee of Saiful Anwar General Hospital and

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conformed with the principles outlined in the Declaration of Helsinki. During the study period, we successfully collected data from 242 ACS patients. We included all ACS patient undergoing PCI as the revascularization strategy. Exclusion criteria included: (1) unavailability of leukocyte count data during the hospital admission; (2) incomplete data; (3) infection/sepsis; (4) malignancy; and/or (5) patients who lost to follow up.

The predictor covariate was the levels of leucocytes during hospital admission. The cut-off point of the leukocyte count was determined using the ROC curve. Subsequently, the patients were divided into two groups following the cut-off point. The outcome of this study was the 30-day mortality following PCI procedure. We also performed a subgroup analysis to determine another variable that contributes to predict the mortality of ACS patients treated with PCI.

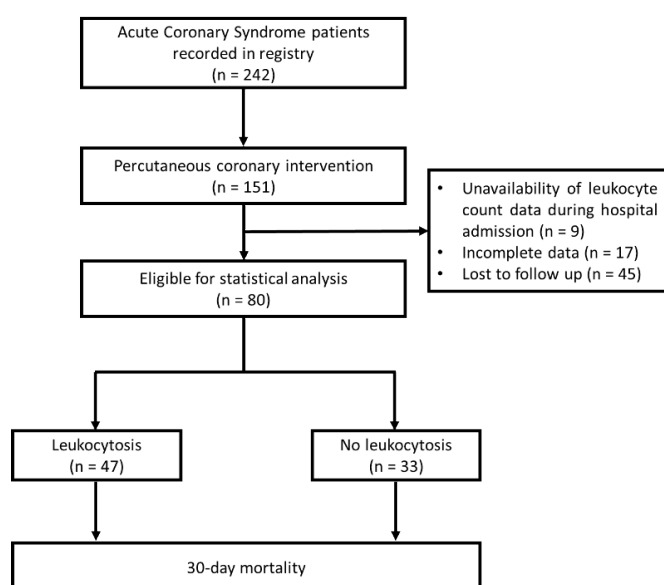


Figure 1. A flowchart of patients selection in our study

2.2. Statistical Analysis

The categorical data were presented in frequency (%), while numerical data were presented in mean and standard deviation (SD). The comparison between both groups was evaluated using the chi-square test or Fisher's exact test for categorical data. While for the continuous data, we used the Mann Whitney test because our data were not normally distributed. The cut-off point of the leukocyte count was determined using the ROC curve. We also conducted a bivariate analysis test to assess the important predictor for mortality in ACS patients undergoing PCI. The survival analysis using the Kaplan-Meier curve was performed to analyze the 30-day mortality after PCI. All data processing and analysis were done using Statistical Package for Social Science (SPSS version 25.0) from IBM. A p-value of < 0.05 was considered statistically significant.

3. Results

3.1. Baseline Characteristics

Among 242 patients, we excluded a total of 162 patients because they did not conform to the eligibility criteria. Finally, we included a total of 80 patients in our analysis. Figure 1 shows the flowchart of patients selection in our current study. We conducted the analysis using the ROC curve to determine the cut-off point of leukocyte levels. The best leukocyte count cut-off value was 12300/ μ L, with the area AUC of 0.702 (95% CI 0.575 - 0.83), the sensitivity of

71.4%, and specificity of 61.3%. Patients with leukocyte count $\geq 12330/\mu$ L were classified as the leukocytosis group, while patients with leukocyte count $<12330/\mu$ L were categorized as a non-leukocytosis group. The ROC analysis is shown in figure 2. Baseline characteristics of both groups were not significant, suggesting that the data were distributed homogeneously in both groups. However, the number of patients with diabetes mellitus (DM) was lower in the leukocytosis group (12.8% vs. 42.4%; $p = 0.003$). The baseline characteristics of the study participants are summarized in Table 1.

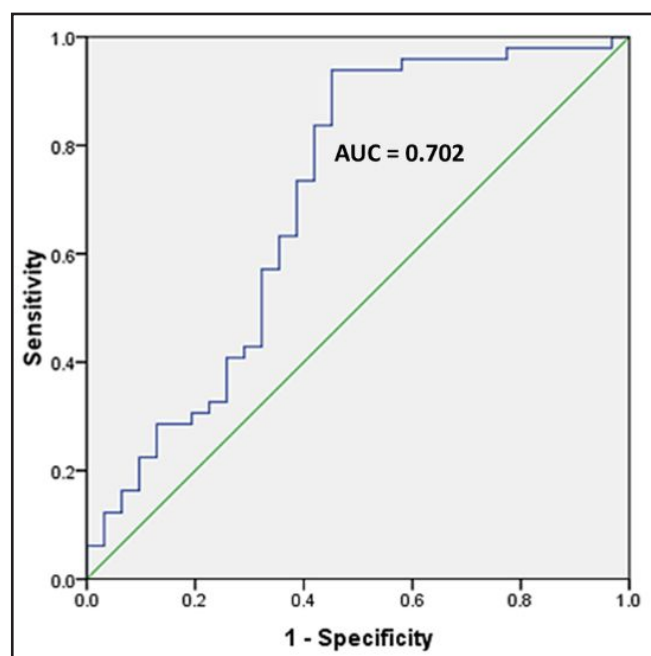


Figure 2. The receiver-operating characteristic (ROC) curve to determine the cut-off point of the leukocyte count.

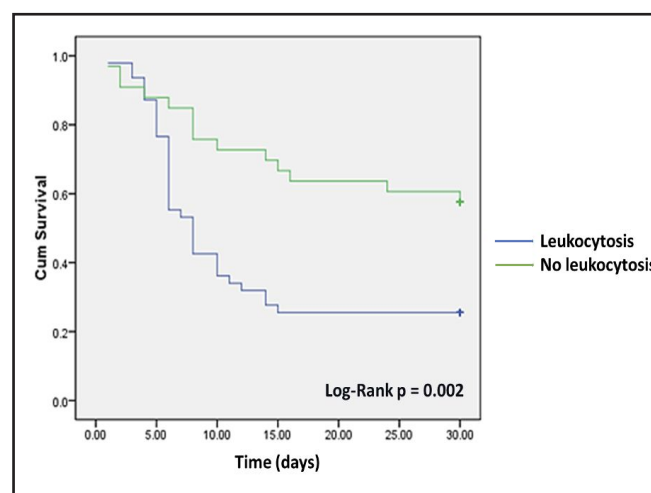


Figure 3. Kaplan Meier survival curves for 30-day mortality. Leukocyte count cut-off value = 2300/ μ L; AUC = 0.702; sensitivity = 71.4%; specificity = 61.3%. AUC = area under the curve.

4. Outcomes

We conducted the bivariate analysis test to identify the impact of several comorbid conditions such as diabetes mellitus, hypertension, smoking habit, and hypertension in 30-day mortality. The results of the bivariate analysis test revealed that leukocytosis increased the risk of 30-day mortality of ACS patients who treated with PCI (74.5% vs 42.4%; OR = 3.958; 95% CI = 1.518-10.25; $p = 0.014$).

In comparison, the other comorbid factors did not show a significant contribution to the 30-day mortality rate in this population. Bivariate analysis for several comorbidities and their impact on 30-day mortality are summarized in Table 2. Survival analysis using the Kaplan-Meier

curve revealed that the survival rate within 30-day after PCI was lowered in the leukocytosis group with the Log-Rank $p = 0.002$. The difference became apparent after day five post-PCI. The Kaplan-Meier curve analysis for 30-day mortality is outlined in Figure 3.

Table 1. Baseline characteristics of the patients.

Charateristics	Leukocytosis (n=47)	No Leukocytosis (n=47)	P-Value
Male	38 (80.9)	26 (78.8)	0.820
Age (years)	56.2 $\pm$ 11.4	58.4 $\pm$ 12.3	0.423
Diabetes mellitus	6 (12.8)	14 (42.4)	0.003
Hypertension	22 (46.8)	18 (54.5)	0.496
Smoking	30 (63.8)	20 (60.6)	0.769
Length of stay (Days)	6.04 $\pm$ 2.89	5.24 $\pm$ 2.77	0.220

Note, data were presented in n(%) or mean $\pm$ SD

Table 2. The summary of our cumulative analyses regarding several comorbidities and their impact on 30-day motality

Variables	Non-survivor (n = 49)	Survivor (n = 31)	OR	95% CI	p
Diabetes mellitus (%)	9 (45)	11 (55)	2.444	0.871 – 6.858	0.145
Hypertension (%)	23 (57.5)	17 (42.5)	1.373	0.556 – 3.385	0.646
Smoking (%)	30 (60)	20 (40)	1.152	0.408 – 3.249	0.953
Leukocytosis (%)	35 (74.5)	12 (25.5)	3.958	1.528 – 10.256	0.008

Note, data were presented in n(%); OR, Odd Ratio; CI, Confidence Interval

5. Discussion

Our study revealed that leukocytosis is associated with a higher risk of 30-day mortality in ACS patients undergoing PCI. To the best of our knowledge, our study was the first study evaluating the role of leukocyte count during hospital admission to predict 30-day mortality in Malang, Indonesia. Our present findings were consistent with some previous studies. A study from Cannon et al. in ACS patients revealed that the levels leukocytes of more than 11000/ μ L were associated with a higher mortality rate during the 10-month follow-up period.¹⁴ In patients with myocardial infarction, the study from Barron et al. revealed that the levels of leukocytes within 24 hours of admission > 13600/ μ L were correlated with the higher risk of in-hospital mortality, in-hospital clinical events, and 30-day mortality.¹⁵ In Non-ST Elevation Myocardial Infarction (NSTEMI), a study from Dharma et al. revealed that the levels of leukocytes > 11000/ μ L at hospital admission were the independent predictor for major adverse cardiovascular events (MACEs).¹⁶ However, a study from Dragu et al. which analyzed the subsets of leukocytes revealed that increased neutrophil count significantly correlated with the higher mortality rate in myocardial infarction patients.¹⁷ Data from GRACE also demonstrated that leukocytes levels were the significant predictor for heart failure and in-hospital mortality in unstable angina, NSTEMI, and STEMI.¹⁸ Our current findings supported several earlier studies. However, it should be noted that not all patients received PCI as the revascularization strategy in the previous studies.¹⁴⁻¹⁸ A study from Palmerini et al. revealed that leukocytosis at the baseline was associated with a higher 12-month mortality rate in STEMI patients undergoing primary PCI.¹

In our study, we needed to assess the performance of leukocyte count during hospital admission as the predictor of 30-day mortality in ACS patients undergoing PCI. Our study demonstrated that leukocyte count ≥ 12330 / μ L was the predictor of 30-day mortality following PCI with sensitivity and specificity of 71.4% and 61.3%, respectively. Our findings were not much different with the result of the study from Dharma et al. They demonstrated that the leukocyte

levels >11000/ μ L had sensitivity and specificity of 50% and 70%, respectively to predict MACE in NSTEMI patients.¹⁶ Combining leukocyte levels and other complete blood count parameters may provide the better specificity and sensitivity. The study from Park et al. in patients with STEMI undergoing primary PCI revealed that the neutrophil to lymphocyte ratio (NLR) ≥ 5.44 had sensitivity and specificity of 72% and 68%, respectively, to predict mortality.¹⁹ A study from Çiçek et al. showed that leukocyte to mean platelet volume ratio ≥ 1653.47 was the best predictor of poor outcome in STEMI patients with the sensitivity and specificity were 75.4% and 87.3%, respectively.²⁰

Some pathophysiological mechanisms may explain the role of leukocytosis in increasing mortality in ACS. There are several mechanisms in which leukocytosis impairs myocardial blood flow. First, the white blood cells may lead to endothelial damage through the oxidation and its proteolytic enzyme.²¹ Second, a high level of leukocyte-platelet aggregates may cause microvascular plugging.²² Third, the white blood cells may release proinflammatory mediators or cytokines. These mediators may affect all thrombus formation stages, such as platelet activation, platelet aggregation, and coagulation cascade activation.²³ Fourth, at the tissue level, monocyte activation lead to extrinsic pathway activation, thrombus formation, and finally, infarct area broadening.^{21,24} In myocardial infarction patients who developed cardiogenic shock or acute heart failure, cytokines such as tumor necrosis factor- α , interleukin-6, and interleukin-8 level are increased.^{25,26} This systemic inflammation condition may lead to massive peripheral vasodilatation because of the release of nitric oxide synthase and peroxynitrite. The high level of nitric oxide synthase, peroxynitrite release, and proinflammatory cytokines in the bloodstream cause ventricular dysfunction because of their cardiotoxic properties. The decrease in cardiac output and systemic vascular resistance will lead to impaired tissue perfusion, which in turn will lead to multiple organ dysfunction syndrome and death.^{27,28}

Our study provided preliminary data regarding the role of

leukocytosis as a strong predictor of mortality in ACS patients undergoing PCI in our Hospital. However, our study had several limitations. First, our study was a retrospective study with small sample size and a short follow-up period. Second, we did not perform post-PCI angiographic analyzes such as complete revascularization and TIMI flow because data were not available. Third, we did not have data on baseline patient characteristics regarding hemodynamic disturbances as reflected by the Killip class, door to wire crossing time, and the presence of comorbidities in more detail. Fourth, we also did not have laboratory and echocardiographic examination data from the patients. A study with a better methodology and a larger sample size is still needed to confirm leukocytosis performance at hospital admission as a predictor of mortality in ACS patients undergoing PCI.

6. Conclusion

Our findings reveal that leukocytosis during hospital admission is associated with increased risk of mortality in ACS patients undergoing PCI. Leucocytosis is a significant predictor of mortality within 30 days after PCI in our population. Therefore we expected that, in the near future, the leukocytes levels are further investigated, and may be considered as the pivotal point in the scoring system to predict the risk of mortality among ACS patients undergoing PCI.

7. Declarations

7.1. Ethics Approval and Consent to participate

This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involve in the study.

7.2. Consent for publication

Not applicable.

7.3. Availability of data and materials

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

7.4. Competing interests

Not applicable.

7.5. Funding source

Not applicable.

7.6. Authors contributions

Idea/concept: SA. Design: SA, KAN, MRF. Control/supervision: SA. Data collection/processing: SA, KAN, MRF. Extraction/Analysis/interpretation: SA, KAN, MRF. Literature review: SA, KAN, MRF. Writing the article: SA, KAN, MRF. Critical review: SA. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

7.7. Acknowledgements

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