

Hematological Parameter as Predictor Mortality in Acute Myocardial Infarction Patients

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Purpose: Acute myocardial infarction (AMI) is one of the leading causes of death in the world. Several hematological parameters are involved in AMI conditions and can be explored for their ability to predict in-hospital mortality. We evaluated hematological parameter value as predictors of in-hospital mortality in AMI patients.

Patients and Methods: Analytical observational study on AMI patients that admitted to Dr. Saiful Anwar Hospital, June–August 2021. Complete blood count was taken at the beginning of hospital admission. Patients with sepsis were excluded from the study. The research subjects were divided into two groups, survivor group and non-survivor group (in-hospital mortality). Hematological parameters as predictors of mortality were analyzed using the ROC curve and odds ratio.

Results: Among 44 study subjects, 19 (43.18%) patients were in the non-survivor group and 25 (56.82%) patients were in the survivor group. Hematological parameters that can be predictors of mortality include leukocytes (AUC = 0.744; $p = 0.006$), neutrophils (AUC = 0.729; $p = 0.010$), eosinophils (AUC = 0.696; $p = 0.028$), and eosinophils/leukocytes ratio (AUC = 0.772; $p = 0.012$). The cut-off value for leukocytes was 13,725/ μ L (OR: 9), neutrophils was 12,008/ μ L (OR: 8.14), eosinophils was 58.3/ μ L (OR: 4.06), and eosinophil/leukocyte ratio was 0.0025 (OR: 4.41) with sensitivity 63.25%, 52.6%, 78.9%, and 63.2%, respectively, and specificity 84%, 88%, 52%, and 72%, respectively.

Conclusion: Leukocyte, neutrophils, eosinophils count and eosinophil/leukocyte ratio can help predict in-hospital mortality of AMI patients.

Keywords: leukocytes, neutrophils, eosinophils, mortality, acute myocardial infarction

Introduction

Acute myocardial infarction (AMI) is the leading cause of death worldwide. One of the causes of AMI is the rupture of atherosclerotic plaques. An ongoing inflammatory process contributes to the initiation and development of the atherosclerotic process. Atherosclerotic plaques in blood vessels can cause thrombosis and cause the acute coronary syndrome. Acute coronary syndrome (ACS) consists of unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI).¹ The prognosis of AMI is still primarily poor, even though it is managed according to recommended therapy guidelines. Therefore, it is necessary to detect the risk of patient death as early as possible, which quick action to prevent it.^{2,3}

Inflammatory conditions in AMI are widely studied, and new research is being carried out in the field of biomarkers that are useful in patient's diagnosis and risk stratification. The results of previous studies found that in AMI, there was an increase in myeloid cell activity and an inflammatory process associated with the acute coronary syndrome, causing an increase in erythropoietin concentrations. The condition can be identified from hematological parameters in the peripheral blood. Research in experimental mice-induced myocardial infarction shows the sympathetic nervous system was active. Release of hematopoietic stem cells from the bone marrow can lead to further systemic stimulation of atherosclerotic plaques. Chronic inflammation at low levels plays a vital role in the initiation and development of atherosclerotic plaques, leading to plaque instability with thrombus formation.⁴

Hematological parameters have the potential to be studied as diagnostic and prognostic indicators in ACS because they are widely available, relatively inexpensive, and easy to perform in daily clinical practice. In determining diagnostic and prognostic value, hematological parameters were studied for several diseases, including coronary artery disease.⁴ Previous studies proved the predictive value of hematological parameters for mortality, cardiovascular complications, heart rhythm disturbances, and thrombosis in ACS, but in other studies, the results contradicted their predictions. Further studies on these hematological biomarkers are still needed, for example, leukocyte count significantly predicts mortality in the first 30 days to 6 months after acute MI.⁵

Faster and more accurate identification of high-risk patients will support improved management and follow-up of these patients, which is very useful in preventing the worsening of the condition of AMI patients. Previous studies have mainly focused on predicting long-term mortality (six months and one year) and complications in AMI patients.^{5,6} Still, few have investigated the role of these hematological parameters in predicting the risk of death in short-term AMI patients in the hospital.⁷

Patients and Methods

Research Design and Data Collection

This is a cohort study conducted on AMI patients treated at Dr. Saiful Anwar Hospital, from June to August 2021. All participants have provided informed consent in accordance with the Declaration of Helsinki. This research has approved by the Health Research Ethics Committee of Dr. Saiful Anwar Hospital with the number 400/117/K.3/302/2021.

Sampling was done with the consecutive sampling method. Patients admitted to the Cardiovascular Care Unit (CVCU) with a diagnosis of AMI based on clinical symptoms, electrocardiography, cardiac Troponin-I (cTnI) examination, and Creatinine Kinase-MB (CKMB) enzyme were inclusion criteria for this study's subject. Exclusion criteria for research subjects were patients with sepsis, kidney failure, and malignancy. Data collection on the patient's complete blood count, cTnI, and CKMB enzymes were carried out at the beginning of hospital admission. In addition, demographic data (age, gender), clinical data (diagnosis of AMI, comorbid of diabetes mellitus type 2), and outcome status or death in the hospital were recorded. The research subjects were divided into two groups, namely the group of survivor and non-survivor AMI patients while being treated at the hospital (Table 1).

Laboratory examinations were carried out at the Central Laboratory of the Dr. Saiful Anwar Hospital. Complete blood count was measured using a hematology autoanalyzer Sysmex XN2000. Hematological parameters recorded included hemoglobin (Hb), red cell distribution width (RDW), leukocytes, eosinophils, basophils, neutrophils, lymphocytes, monocytes, neutrophil-lymphocyte ratio (NLR), platelets, platelet distribution width (PDW), mean platelet volume (MPV), and the platelet-lymphocyte ratio (PLR). cTnI examination using the AIM Troponin-I Q Rapid Test was read quantitatively using the Easy reader. CKMB examination was determined using the Cobas e411.

Table 1 Characteristics of Research Subjects

Characteristic	Survivor (N = 25)	Non-Survivor (N = 19)	p
Age (Years)	57±9.5	58±11.1	0.864 [^]
Sex, N (%)			
Male	21 (84%)	16 (84.2%)	0.985 [°]
Female	4 (16%)	3 (15.8%)	
Comorbid of diabetes mellitus type 2, N (%)	9 (36%)	10 (52.6%)	0.270 [°]
cTn I (µg/L)	3.75 (1.60–11.75)	14.70 (11.00–28.20)	0.002 ^{##} *
CKMB (U/L)	63.50 (24.25–100.25)	179.0 (109.0–260.0)	0.001 ^{##} *

Notes: [^]Independent t-test, [°]Chi-Square Test, ^{##}Mann-Whitney test. *Significant if p < 0.05.

Statistical Analysis

The results are presented as mean $\pm$ SD, median (Q1-Q3) for continuous variables, and frequency and percentage for categorical variables. Comparison between groups was performed by independent *t*-test for data with normal distribution and Mann–Whitney test for data with non-normal distribution. For categorical data, comparative analysis was carried out with Chi-Square test.

We use ROC curve analysis and odds ratio analysis of hematological parameter data as a predictor of mortality in AMI patients. For each parameter, the optimal cut-off value is determined with the highest Youden's index. The statistical significance value is $p < 0.05$.

Results

In this study, 44 AMI patients met the study criteria, consisting of 25 (56.82%) survivor and 19 (43.18%) non-survivor AMI patients. All study subjects had elevated levels of the heart damage biomarkers cTnI and CKMB. The characteristics of the research subjects are listed in Table 1.

Comparison of Hematological Parameters of AMI Patients in the Survivor and Non-Survivor AMI Patient Groups

The results of the analysis of differences in hematological parameters between survivor and non-survivor AMI patient groups showed differences in the parameters of leukocytes, absolute eosinophils, absolute neutrophils, and the ratio of eosinophils/leukocytes. The difference in the value of each hematological parameter between the two groups can be seen in Table 2.

Hematologic Parameter as AMI Patients Mortality Predictor

Hematological parameters with significant differences in the survivor and non-survivor patient groups were analyzed for their ability to predict mortality in patients with AMI using the ROC curve. The comparison of the ROC curve results in the four parameters, namely leukocytes, neutrophils, eosinophils, and the ratio of eosinophils/leukocytes can be seen in Figure 1A and B. An increased number of leukocytes and neutrophils will increase the mortality rate, while the decreased number of eosinophils and a decreased eosinophil/leukocyte ratio will increase mortality.

Table 2 Hematological Parameter Comparison Between Survivor and Non-Survivor Patient Groups

Parameter	Survivor	Non-Survivor	p
Hb (g/dL)	13.5 $\pm$ 2.05	14.1 $\pm$ 2.83	0.367 [^]
Leukocyte (/ μ L)	11,194 $\pm$ 3,234	15,096 $\pm$ 5,371	0.009 ^{^*}
Thrombocyte (/ μ L)	255,960 $\pm$ 7,966	275,000 $\pm$ 6,221	0.394 [^]
RDW (%)	13.2 (12.6–13.8)	13.4 (12.2–15.7)	0.537 ^{^#}
PDW (fL)	11.5 (10.2–12.4)	11.4 (10.6–12.4)	0.892 ^{^#}
MPV (fL)	10.24 $\pm$ 0.78	10.25 $\pm$ 0.92	0.965 [^]
PLR (%)	26.56 $\pm$ 6.20	26.67 $\pm$ 7.29	0.960 [^]
Absolute Eosinophil (/ μ L)	58.55 (17.71–147.67)	33.09 (0–58.11)	0.020 ^{^#*}
Absolute Basophil (/ μ L)	30.80 (15.51–38.17)	33.09 (22.31–51.24)	0.308 ^{^#}
Absolute Neutrophil (/ μ L)	8,475 $\pm$ 3,073	11,940 $\pm$ 5,062	0.010 ^{^*}
Absolute Lymphocyte (/ μ L)	1,555 (1,170–2,271)	1,586 (1,133–2,766)	0.687 ^{^#}
Absolute Monocyte (/ μ L)	697 (509–1050)	962 (682–1414)	0.072 ^{^#}
Absolute NLR	5.23 (3.65–8.35)	8.60 (3.59–10.19)	0.420 ^{^#}
Eosinophil/Leucocyte Ratio	0.005 (0.001–0.018)	0.002 (0.000–0.005)	0.012 ^{^#*}

Notes: [^]Independent *t*-test, ^{^#}Mann–Whitney test. ^{^*}Significant if $p < 0.05$.

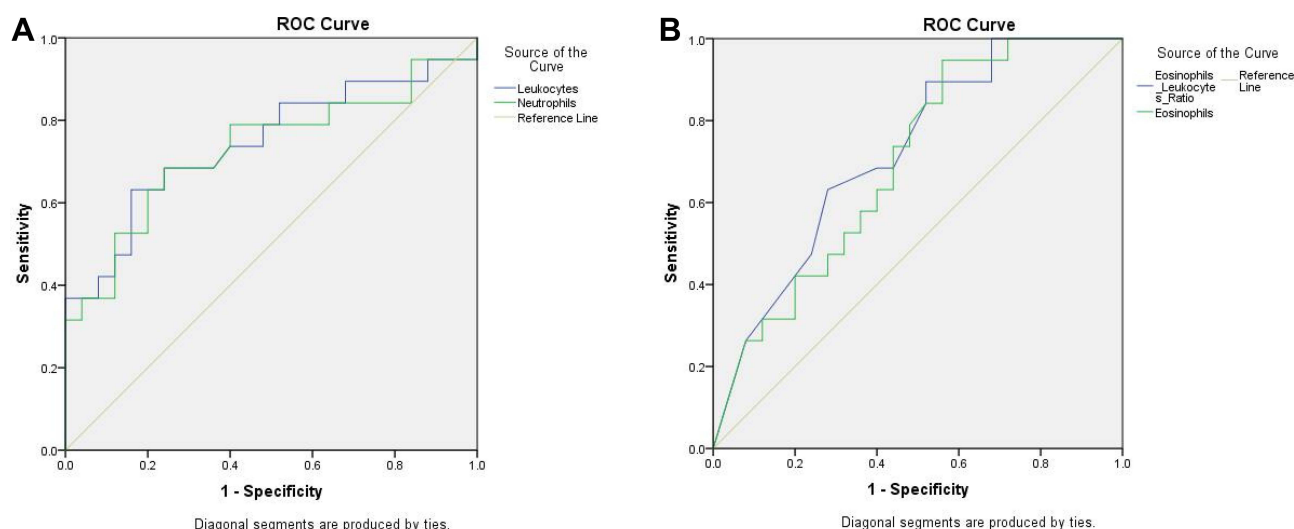


Figure 1 Comparison of ROC curves of hematological parameters. (Remarks: **(A)** comparison of the ROC curve of leukocytes and neutrophils in mortality of AMI patients, **(B)** comparison of the ROC curve of eosinophils and the ratio of eosinophils/leukocytes in mortality of AMI patients).

From the ROC curve analysis, the discriminatory power of each parameter is seen from the area under the curve (AUC) value and its significance value. The analysis showed that the parameters of the number of leukocytes, neutrophils, eosinophils, and the ratio of eosinophils/leukocytes had good and significant AUC values. The AUC value, significance, and cut-off value with the highest Youden's index of each parameter are shown in Table 3.

Each parameter was then classified according to the cut-off point and analyzed using a 2×2 table (Table 4). The number of leukocytes above 13,725/ μ L has a sensitivity of 63.25% and a specificity of 84%, with an odds ratio (OR) of 9. The number of neutrophils above 12,008/ μ L has a sensitivity of 52.6% and a specificity of 88%, with an OR value of 8.14. The number of eosinophils below 58.3/ μ L gave a sensitivity value of 78.9% and specificity of 52%, with an OR value of 4.06. The ratio of the number of eosinophils/leukocytes below 0.002 has a sensitivity of 63.2% and a specificity of 72%, with an OR value of 4.41 to the increased risk of mortality in AMI patients.

Discussion

Leukocytes have a role in the destabilization of atherosclerotic plaques in AMI patients. In this study, the number of leukocytes and neutrophils in AMI patients on admission to the hospital was associated with mortality during hospitalization. These results follow previous studies by Babes et al, which showed a correlation between the number of leukocytes and neutrophils at the time of initial hospital admission with mortality in patients with ACS, especially NSTEMI.⁷

The leukocyte profile has been widely sought for its association with clinical outcomes in patients with AMI. Another research shows that increased leukocyte was associated risk factor for death during the first 30 days to 6 months in

Table 3 Discriminatory Power of AUC Analysis of Hematological Parameters on Mortality of AMI Patients

Parameter	AUC	p	95% CI	Cut-Off Value	Youden's Index
Leukocyte	0.744	0.006*	0.588–0.900	13,725/ μ L	0.409
Eosinophil	0.696	0.028*	0.542–0.850	58.3/ μ L	0.406
Neutrophil	0.729	0.010*	0.569–0.890	12,008/ μ L	0.472
Eosinophil/Leukocyte Ratio	0.772	0.012*	0.573–0.871	0.002	0.352

Note: *Significant if $p < 0.05$.

Table 4 2 × 2 Table's Analysis of Each Parameter

Parameter	Cut-Off	Survivor (n = 25)	Non-Survivor (n = 19)	OR	p
Leukocytes	≥13,725/μL	4 (16%)	12 (63.2%)	9	p=0.001
	<13,725/μL	21 (84%)	7 (36.8%)		
Neutrophils	≥12,008/μL	3 (12%)	10 (52.6%)	8.14	p=0.003
	<12,008/μL	22 (88%)	9 (47.4%)		
Eosinophils	≤58.3/μL	12 (48%)	15 (78.9%)	4.06	p=0.037
	>58.3/μL	13 (52%)	4 (21.1%)		
Eosinophils/Leukocytes Ratio	≤0.0025	7 (28%)	12 (63.2%)	4.41	p=0.020
	>0.0025	18 (72%)	7 (36.8%)		

patients with unstable chest pain and NSTEMI.⁵ In the study by Barron et al that evaluated data from 975 patients in the Thrombolysis in Myocardial Infarction (TIMI) 10A and 10B trials, elevated leukocytes were shown to correlate with a high mortality rate in patients with AMI.⁸ Leukocytosis was associated with an increased heart disease mortality rate. Study by Cannon et al used the data from 7651 patients in a trial of Orbofiban therapy in AMI patients. They followed-up the outcome at 14 and 30 days and every 3 months, with a complete blood count performed at baseline (the time of enrollment). In that study, leukocytes >10,000/μL were associated with increased mortality at 30 days and ten months.⁹ Study by Ozturk et al evaluated the CBC parameters among the patients who suffered death or survived from ACS and showed that leukocytes >11,700/μL predicting mortality had a sensitivity of 70% and a specificity of 76%.¹⁰ According to existing experimental research data, there is a linear relationship between the size of necrotic tissue, the number of leukocytes, and the systemic response. Study by Adam et al shows that the larger the infarct size, the greater the leukocyte response. Larger infarcts are more likely to cause complications, including heart failure and death. Thus, infarct size can be reflected in the blood cell count and has relevance as a potential prognostic predictor.¹¹

Neutrophils can cause plaque rupture by releasing proteolytic enzymes, superoxide radicals, and arachidonic acid derivatives and aggravating inflammatory conditions. It has long been recognized that myocardial damage is followed by neutrophilia, in which neutrophils are initially in the infarct area with vigorous infiltration for 1 to 3 days, then the infarct repair process and fibrosis formation. In addition, it was also shown that an increase in intrinsic reparative processes after AMI could be obtained using intracoronary transfer from bone marrow autologous, which are rich in hematopoietic and mesenchymal precursor cells. On the other hand, neutrophilia may also represent a flawed adaptation process in AMI, as circulating leukocyte–platelet aggregates may contribute to vascular occlusion and expansion of the infarcted area.¹² The absolute peripheral neutrophil count may be a marker of the severity of myocardial inflammation attributable to ischemic injury or of the severity of the inflammation of the coronary arterial tree. Increased neutrophil count may also, in part, be explained by a lower probability of successful reperfusion or impaired microvascular perfusion.¹³ Research that proves the role of neutrophils as a predictor of mortality in short-term AMI patients is still limited. Previous studies have shown the role of neutrophils as a predictor of mortality and complications in long-term AMI patients.¹⁴

Eosinophils are important cells involved in the inflammatory response during acute myocardial infarction. Many thrombotic events have been observed in patients with eosinophil-associated disorders. Previous studies have confirmed that eosinophils enter coronary artery thrombi. Eosinophils in peripheral blood are significantly reduced in myocardial infarction, and a decrease in eosinophils indicates a significantly increased risk of heart disease events.¹⁵ In this study, the number of eosinophils tended to be lower in the non-survivor than in survivor group. These results align with Ye et al's research, which showed a decrease in the percentage of eosinophil counts had high sensitivity but low specificity for the presence of complications within 30 days after AMI, including death.¹⁶

At least three mechanisms might explain the reduction in ELR in patients presenting with STEMI: eosinophil adherence to coronary thrombi, eosinophil aggregation at the site of inflammation, and increased cortisol concentrations. Eosinophils may aggregate to form coronary thrombi in STEMI, but their numbers are reduced in the peripheral circulation. Circulating eosinophil's activity on the endothelium is mediated primarily by P-selectin. In patients with acute MI, P-selectin concentrations are higher in the infarcted coronary artery than in the circulation.¹⁷ Eosinophils play a crucial role in the initiation of thrombosis, with platelets adhering to the injured intravascular wall.¹⁸ Tissue factor is released upon degranulation of the eosinophils and is crucial in the initiation of blood coagulation.¹⁹ The half-life of eosinophils in vivo ranges between 8 and 18 h.²⁰ Therefore, within 24-h after the onset of STEMI, the peripheral counts of eosinophils may remain low due to the aggregation of eosinophils within thrombi until the cells are fully released from the bone marrow into the peripheral circulation to recover their original concentrations.⁶

The second possible mechanism is the migration of peripheral eosinophils to the site of inflammation. In acute, non-infectious inflammatory stimulation, a reduction in eosinophil counts has been observed, which persisted for several days. Since the rupture of atherosclerotic plaques in STEMI is associated with inflammation, some of the eosinophils might adhere to the intravascular plaques and thrombi. The infiltration of eosinophils into the infarcted myocardium occurs during the acute phase of MI.⁶

A further mechanism that may support the decrease in eosinophils is due to increased cortisol levels. Acute stress response to STEMI can make increase in the cortisol concentration, which might lower the peripheral eosinophil counts. It was proven that in patients presenting with MI, high cortisol concentrations have been associated with poor prognosis.²¹

The ratio of eosinophils to leukocytes has been proven to predict clinical outcomes in patients who have undergone primary percutaneous coronary intervention (PCI).⁶ However, no studies report the ratio of eosinophils to leukocytes as a predictor of short-term mortality in AMI patients. It is uncertain whether the eosinophil/leukocyte ratio predicts short-term mortality in AMI patients. It is also uncertain whether the eosinophil/leukocyte ratio is a better predictor of mortality than other hematological parameters. This study showed that the median eosinophil/leukocyte ratio was lower in the dead group than in the living group. Our specificity value of eosinophil/leukocyte ratio was higher than the specificity of eosinophils alone as a predictor of mortality in hospitalized AMI patients. Our research is still limited to the small population size and did not differentiate AMI into STEMI and NSTEMI group. In the future, a multi-centre study with a larger size number or a population-based study can be performed to provide a better result.

Conclusion

Hematological parameters are widely available and routinely performed in patients with AMI and have the potential to be prognostic indicators. The number of leukocytes, neutrophils, eosinophils, and the ratio of eosinophils/leukocytes in the blood measured at the beginning of hospital admission can predict mortality in AMI patients. Further research, for instance, on larger cohorts, is still needed to apply these hematological parameters clinically.

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Disclosure

The authors report no conflicts of interest in this work.

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