Blood Leukocyte Count on Admission Predicts Cardiovascular Events in Patients with Acute Non-ST Elevation Myocardial Infarction

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Abstract

We aim to test the hypothesis that blood leukocyte count adds prognostic information in patients with acute non–ST-elevation myocardial infarction (non-STEMI).

A total of 585 patients with acute non-STEMI (thrombolysis in myocardial infarction risk score ≥ 3) were enrolled in this cohort retrospective study. Blood leukocyte count was measured immediately after admission in the emergency department. The composite of death, reinfarction, urgent revascularization, and stroke during hospitalization were defined as the primary end point of the study.

The mean age of the patients was 61 $\pm$ 9.6 years and most of them were male (79%). Using multivariate Cox regression analysis involving seven variables (history of smoking, hypertension, heart rate $>$ 100 beats/minute, serum creatinine level $>$ 1.5 mg/dL, blood leukocyte count $>$ 11,000/μL, use of β-blocker, and use of angiotensin-converting enzyme inhibitor), leukocyte count $>$ 11,000/μL demonstrated to be a strong predictor of the primary end point (hazard ratio = 3.028; 95% confidence interval = 1.69–5.40, $p < 0.001$).

The high blood leukocyte count on admission is an independent predictor of cardiovascular events in patients with acute non-STEMI.

Keywords
- leukocyte count
- acute non-STEMI
- predictor
- cardiovascular event

Inflammation plays an important role in the course of atherosclerosis including acute plaque rupture leading to thrombosis, manifested as acute coronary syndrome (ACS).[1–3] The leukocyte is one of the inflammatory biomarkers,[4] and quantification of leukocyte density in blood is available in almost all the laboratories worldwide. Leukocytosis affects acute thrombosis by mechanisms involving inflammation, that will induce a hypercoagulability state and microvascular obstruction, leading to a more extensive of an infarction.[5]

Several studies have shown that leukocytosis is a predictor of cardiovascular events in healthy individuals,[6–8] and also in patients with a history of myocardial infarction,[9–11] but another study failed to find such an association.[12] Furthermore, as the clinical laboratories in most developing countries lack the routine assay of established inflammatory markers—such as interleukins and C-reactive protein (CRP)—a simple, reliable, inexpensive but accurate marker is needed to be measured routinely in the daily management of infarct patients to identify patients who are at an increased risk for subsequent cardiovascular events. Therefore, this study was designed to assess the predictive role of baseline leukocyte count on in-hospital cardiovascular events of patients with acute

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non–ST-segment elevation myocardial infarction (non-STEMI) in Jakarta, Indonesia. One should keep in mind that studies which assess the association between blood leukocyte count and cardiovascular events in developing countries are relatively scarce and that measurement of blood leucocyte count is available in nearly all hospitals in Indonesia.

Methods

Study Population

Data were collected from the Jakarta Acute Coronary Syndrome Registry database involving 585 patients admitted to the emergency department of the National Cardiovascular Center Harapan Kita, Jakarta, Indonesia. The inclusion criteria were all patients diagnosed with moderate to high risk acute non-STEMI (thrombolysis in myocardial infarction [TIMI] risk score ≥ 3) who were hospitalized between January 2008 and December 2010. Patients with known history of infection or systemic inflammation during the last 2 weeks before admission, patients with severe gout or rheumatic disease, patients with liver disease, or patients with hematologic disease at admission were excluded.

Diagnosis of acute non-STEMI was based on (1) typical chest discomfort in the preceding 48 hours, (2) the absence of ST-segment elevation, and (3) the presence of at least one of the following two criteria: (a) positive serum marker of myocardial necrosis, defined as troponin T values above the 99th percentile of a healthy reference population, and (b) electrocardiographic indices of ischemia consisting of transient ST-segment depression (≥ 0.05 mV) or T-wave inversion (≥ 0.1 mV) in two or more contiguous leads.

TIMI risk score[13] was calculated as the sum of each of the following variables of which its presence contributes one point to the total score: age 65 years or older, at least three risk factors for coronary artery disease, prior coronary stenosis of $\geq 50\%$, ST-segment deviation on electrocardiogram at presentation, at least two anginal events in the prior 24 hours, use of aspirin in the preceding week, and elevated cardiac marker levels in serum. Moderate- and high-risk patients are defined as having TIMI scores of 3 to 4 and 5 to 7, respectively. To investigate a homogenous study population, only moderate-to-high-risk patients (TIMI risk score ≥ 3) were included in the study.

Laboratory Determination

Immediately after admission, venous blood samples were taken in tubes containing ethylenediaminetetraacetic acid (EDTA). One blood sample was used to measure the blood leukocyte count using flow cytometry (Sysmex Corporation, Kobe, Japan). Plasma sample of cardiac troponin T was assayed using a chemiluminescence immunoassay (Roche Diagnostics Corporation, Indianapolis, IN), and creatine kinase-MB activity was measured using an immuno-inhibition assay (Roche Diagnostics Corporation).

Study End Point

Primary end point of the study is major adverse cardiovascular event (MACE) defined as the composite of death, reinfarction, urgent revascularization, and stroke during hospitalization, as judged by an independent clinical event committee of which the members were blinded to the laboratory results.

Statistical Methods

Continuous variables are presented as mean values $\pm$ standard deviation (SD) or median (range) if not fitting a normal distribution. Categorical variables were expressed as percentages or proportions. Cut-off value for blood leukocyte count was determined using the receiver operator characteristic (ROC) test, based on a specificity of 70% and a sensitivity of 50%. A leukocyte count of 11,000/μL was chosen as the cut-off point. The specificity measured was the highest value, and concordant with this, Cannon and colleagues[10] used a leukocyte count of $>$ 10,000/μL as a cut-off point. Normally distributed variables were compared by Student *t*-test, skewed distribution data were compared by Mann–Whitney U-test, and categorical variables were compared by Pearson chi-square test. Univariate and multivariate Cox regression analyses were performed to identify whether a variable is a predictor of cardiovascular events. Variables with p value < 0.25 in univariate analysis were entered in the multivariate analysis. To detect a reduction in MACE by at least 16% MACE difference, each group should contain at least 85 patients at a study power of 80% and a probability of 5%. A p value < 0.05 was considered as statistically significant. All computations were performed using a statistical package (SPSS version 13.0, SPSS Inc., Chicago, IL).

Results

Most of the patients were men (79%) and the mean age was 61 $\pm$ 9.6 years. The mean blood leukocyte count at admission was 10,382 $\pm$ 4,007/μL. On admission, patients with a leukocyte count $>$ 11,000/μL had a higher heart rate ($p < 0.001$), a higher creatine kinase-MB level on admission ($p < 0.001$), and a higher creatinine level ($p = 0.014$) than patients with a leukocyte count $\leq$ 11,000/μL. There are no treatment differences between the two groups (►**Table 1**).

During the hospitalization period, MACE occurred in 52 patients (9%). Incidence of MACE was significantly higher in patients with leukocyte count $>$ 11,000/μL than in patients with leukocyte count $\leq$ 11,000/μL (16 vs. 5%, $p < 0.001$).

In univariate analysis, patients with leukocyte count $>$ 11,000/μL had a higher risk of MACE than patients with leukocyte count $\leq$ 11,000/μL (hazard ratio = 3.17, 95% confidence interval [CI], 1.81 to 5.57; $p < 0.001$), and in multivariate analysis, the hazard ratio was 3.028 (95% CI 1.69 to 5.40, $p < 0.001$) (►**Tables 2** and **3**).

Discussion

In this study involving 585 patients with acute non-STEMI, we found a strong relationship between leukocyte count on admission and incidence of MACE during hospitalization. This is the first study evaluating the predictive role of leukocyte count on MACE in moderate-to-high-risk non-STEMI patients in Jakarta, Indonesia.

Table 1 Demographic and clinical characteristics including baseline blood chemistry of patients with acute non–ST-elevation myocardial infarction divided into two groups having blood leukocyte count > 11,000/μL and ≤ 11,000/μL

Variables	All patients ($N = 585$)	Leukocyte count ≤ 11,000/μL ($N = 397$)	Leukocyte count > 11,000/μL ($N = 188$)	*p*-Value
Age (y)	61 ± 9.6	61.3 ± 9.6	60.0 ± 9.4	0.223
Male gender, *N* (%)	462 (79%)	306 (77%)	156 (82%)	0.102
Systolic blood pressure (mm Hg)	142.5 ± 29	143.3 ± 29	140.9 ± 28	0.383
Heart rate (beats/min)	90 ± 23.8	87 ± 23	97 ± 24	< 0.001
Prior myocardial infarction	97 (16%)	66 (17%)	31 (16%)	0.947
Risk factor profile, *N* (%)				
Family history	148 (25%)	106 (27%)	42 (22%)	0.231
Smoker	141 (24%)	89 (22%)	52 (27%)	0.230
Hypertension	423 (72%)	287 (72%)	136 (72%)	0.990
Diabetes mellitus	220 (38%)	141 (35%)	79 (42%)	0.104
Dyslipidemia	277 (47%)	192 (48%)	85 (45%)	0.529
Lipid profile				
Total cholesterol (mg/dL)	188 ± 50	190 ± 49	184 ± 50	0.313
LDL-cholesterol (mg/dL)	123 ± 42	124.3 ± 42	120 ± 42	0.420
HDL-cholesterol (mg/dL)	37.8 ± 12	38.2 ± 12	36.8 ± 11	0.235
Triglyceride (mg/dL)	142 ± 91	146 ± 93	133 ± 86	0.060
CK-MB (U/L)	25 (3–523)	23 (4–324)	32 (3–523)	< 0.001
Troponin T > 0.03 μg/L	512 (88.6)	342 (86)	170 (90)	0.142
Creatinine (mg/dL)	1.4 ± 0.9	1.38 ± 0.9	1.52 ± 1.1	0.014
Length of stay (d)	8.77 ± 7.14	8.82 ± 6.7	8.68 ± 7.8	0.501
Coronary angiography, *N* (%)	221 (38%)	161 (40%)	60 (32%)	0.042
PCI, *N* (%)	79 (13%)	54 (13%)	25 (13%)	0.262
CABG, *N* (%)	29 (5%)	22 (5%)	7 (3%)	0.696
Medication at enrollment, *N* (%)				
ACE inhibitor	313 (53%)	205 (51%)	108 (57%)	0.188
Beta-blocker	373 (64%)	273 (68%)	100 (53%)	< 0.001
MACE, *N* (%)	52 (9%)	21 (5%)	31 (16%)	< 0.001

Abbreviations: ACE, angiotensin-converting enzyme; CABG, coronary artery bypass grafting; CK-MB, creatine kinase-MB; MACE, major adverse cardiac event; PCI, percutaneous coronary intervention.
Continuous data presented as mean ± standard deviation or median (range) and categorical variables as number and percentages.

The result of this study is consistent with a study by Cannon and colleagues[10] who showed that patients with acute myocardial infarction or high risk unstable angina pectoris with a leukocyte count > 10,000/μL had a high mortality rate. Barron et al[9] also showed that acute myocardial infarction patients with a white blood cell count in the highest quintile (> 13,600/μL) had a higher 30-day mortality rate than patients with a leukocyte count in the lower quintiles.

Several mechanisms may explain how leukocytosis increases MACE in ACS patients: (1) Leukocytes may cause endothelial cell injury by proteolytic and oxidative damage, (2) leukocytes may plug the microvasculature, (3) leukocytes may induce hypercoagulability,[5] and (4) activated monocytes have increased expressions of tissue factor.[14] It is hypothesized that these mechanisms may lead to activation of the extrinsic pathway of the coagulation system,[15] thrombus formation,[16] and promote infarct expansion.[5] The prognostic value of inflammatory markers is observed across a wide clinical spectrum of atherosclerotic diseases.[17]

In this study, the higher MACE rate in patients with a leukocyte count > 11,000/μL could be explained by several reasons. First, patients with a leukocyte count > 11,000/μL may have a larger infarct size as shown by higher initial creatine kinase-MB level in the group with high leukocyte count than in the group with low leukocyte count (32 vs. 23 U/L, $p < 0.001$), and deserves further investigation. Second, the heart rate on admission was higher in patients with a leukocyte count

Table 2 Univariate predictors of cardiovascular events

Variables	HR (95% CI)	*p*-Value
Age (> 65 y)	0.913 (0.50–1.63)	0.759
Male gender	1.085 (0.54–2.17)	0.818
History of MI	0.915 (042–1.96)	0.820
Risk factor profile		
Family history	0.774 (0.39–1.51)	0.453
Diabetes mellitus	1.240 (0.70–2.17)	0.453
Hypertension	0.701 (0.39–1.24)	0.227*
Dyslipidemia	1.089 (0.61–1.93)	0.772
Smoker	0.749 (0.51–1.08)	0.130*
Systolic blood pressure < 100 mm Hg	0.853 (0.26–2.78)	0.792
Heart rate > 100 beats/min	1.425 (0.80–2.54)	0.229*
Lipid profile		
Total cholesterol > 200 mg/dL	1.202 (0.57–2.51)	0.625
HDL-cholesterol < 40 mg/dL	0.780 (0.37–1.61)	0.501
LDL-cholesterol > 130 mg/dL	1.210 (0.58–2.51)	0.609
Triglyceride > 150 mg/dL	0.883 (0.37–2.10)	0.779
Creatinine > 1.5 mg/dL	1.958 (1.10–3.47)	0.022*
Leukocyte count > 11,000/μL	3.178 (1.81–5.57)	< 0.001
Medication at enrollment		
Beta-blocker	0.676 (0.38–1.17)	0.167*
ACE inhibitor	0.638 (0.36–1.11)	0.116*

Abbreviations: ACE, angiotensin-converting enzyme; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.
*Variables with *p* value < 0.25 were entered into multivariate Cox regression analysis.

Table 3 Multivariate predictors of cardiovascular events

Variables	HR (95% CI)	*p*-Value
History of smoking	0.727 (0.49–1.06)	0.101
Hypertension	0.410 (0.15–1.09)	0.076
Heart rate > 100 beats/min	1.803 (0.71–4.56)	0.214
Creatinine > 1.5 mg/dL	1.642 (0.90–2.97)	0.102
Leukocyte count > 11,000/μL	3.028 (1.69–5.40)	< 0.001
Use of β-blocker	0.775 (0.43–1.37)	0.384
Use of ACE inhibitor	0.575 (0.32–1.02)	0.058

Abbreviations: ACE, angiotensin-converting enzyme; CI, confidence interval; HR, hazard ratio.

> 11,000/μL ($p < 0.001$) than in patients with low leukocyte count, and heart rate on admission is also known as a risk factor in patients with acute myocardial infarction.[18] Third, the baseline creatinine level was higher in patients with a leukocyte count > 11,000/μL ($p = 0.014$) than in patients with low leukocyte count, and elevated creatinine levels are a risk factor for developing cardiac events as described in the GRACE (Global Registry of Acute Coronary Events) risk score.[18] After adjustment of all those variables and other variables—such as history of smoking, hypertension, use of β-blocker, and use of angiotensin-converting enzyme inhibitor—a leukocyte count > 11,000/μL was a strong predictor of in-hospital cardiovascular events ($p < 0.001$).

This study demonstrates that there is a relationship between a high leukocyte count and incidence of MACE. Thus, for patients with acute non-STEMI, who have a blood leukocyte count > 11,000/μL, aggressive treatment seems clearly indicated. In Jakarta, Indonesia, the group of patients with acute non-STEMI is larger than the group of patients with STEMI, and since our data cover the majority of ACS

patients referred from other hospitals, the reported data are considered representative for all non-STEMI patients in Jakarta, Indonesia.[19] As the measurement of leukocyte count is cheap, rapid, and available in almost every laboratory worldwide, the leukocyte count might be used as an additional marker for immediate bedside risk stratification of patients with non ST-elevation ACS, and particularly in rural areas where other established markers, such as interleukin-6, interleukin-1β, and CRP, are not available.

Study Limitation

Several limitations of this study should be considered. The design of the study was a retrospective analysis and data were collected from an existing registry. Furthermore, the assay of additional inflammatory markers, such as CRP, is lacking which would have strengthened the role of leukocyte count in this study.

Conclusion

The high blood leukocyte count on admission is an independent predictor of MACE during hospitalization of patients with acute non-STEMI.

Conflict of Interest
No conflict of interest.

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Note
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References

1 Kinlay S, Selwyn AP, Libby P, Ganz P. Inflammation, the endothelium, and the acute coronary syndromes. J Cardiovasc Pharmacol 1998;32(Suppl 3):S62–S66
2 Libby P. Molecular bases of the acute coronary syndromes. Circulation 1995;91(11):2844–2850
3 Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol 2009;54(23): 2129–2138
4 Khuseyinova N, Koenig W. Biomarkers of outcome from cardiovascular disease. Curr Opin Crit Care 2006;12(5):412–419
5 Madjid M, Awan I, Willerson JT, Casscells SW. Leukocyte count and coronary heart disease: implications for risk assessment. J Am Coll Cardiol 2004;44(10):1945–1956
6 Brown DW, Giles WH, Croft JB. White blood cell count: an independent predictor of coronary heart disease mortality among a national cohort. J Clin Epidemiol 2001;54(3):316–322
7 Lee CD, Folsom AR, Nieto FJ, Chambless LE, Shahar E, Wolfe DA. White blood cell count and incidence of coronary heart disease and ischemic stroke and mortality from cardiovascular disease in African-American and White men and women: atherosclerosis risk in communities study. Am J Epidemiol 2001;154(8):758–764
8 Takeda Y, Suzuki S, Fukutomi T, et al. Elevated white blood cell count as a risk factor of coronary artery disease: inconsistency between forms of the disease. Jpn Heart J 2003;44(2):201–211
9 Barron HV, Harr SD, Radford MJ, Wang Y, Krumholz HM. The association between white blood cell count and acute myocardial infarction mortality in patients > or = 65 years of age: findings from the cooperative cardiovascular project. J Am Coll Cardiol 2001;38(6):1654–1661
10 Cannon CP, McCabe CH, Wilcox RG, Bentley JH, Braunwald E, the OPUS-TIMI 16 Investigators. Association of white blood cell count with increased mortality in acute myocardial infarction and unstable angina pectoris. OPUS-TIMI 16 Investigators. Am J Cardiol 2001;87(5):636–639, A10
11 Mueller C, Neumann FJ, Perruchoud AP, Buettner HJ. White blood cell count and long term mortality after non-ST elevation acute coronary syndrome treated with very early revascularisation. Heart 2003;89(4):389–392
12 Byrne CE, Fitzgerald A, Cannon CP, Fitzgerald DJ, Shields DC. Elevated white cell count in acute coronary syndromes: relationship to variants in inflammatory and thrombotic genes. BMC Med Genet 2004;5:13
13 Antman EM, Cohen M, Bernink PJLM, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000;284(7):835–842
14 Neumann FJ, Ott I, Marx N, et al. Effect of human recombinant interleukin-6 and interleukin-8 on monocyte procoagulant activity. Arterioscler Thromb Vasc Biol 1997;17(12):3399–3405
15 Bovill EG, Bild DE, Heiss G, et al. White blood cell counts in persons aged 65 years or more from the Cardiovascular Health Study. Correlations with baseline clinical and demographic characteristics. Am J Epidemiol 1996;143(11):1107–1115
16 de Gaetano G, Cerletti C, Evangelista V. Recent advances in platelet-polymorphonuclear leukocyte interaction. Haemostasis 1999; 29(1):41–49
17 Morange PE, Simon C, Alessi MC, et al; PRIME Study Group. Endothelial cell markers and the risk of coronary heart disease: the Prospective Epidemiological Study of Myocardial Infarction (PRIME) study. Circulation 2004;109(11):1343–1348
18 Granger CB, Goldberg RJ, Dabbous O, et al; For the Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med 2003;163(19):2345–2353
19 Dharma S, Juzar DA, Firdaus I, Soerianata S, Wardeh AJ, Jukema JW. Acute myocardial infarction system of care in the third world. Neth Heart J 2012;20(6):254–259