Blood leukocyte count on admission predicts cardiovascular events in patients with acute non ST-elevation myocardial infarction

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Submitted

Abstract

Background

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

Methods

A total of 585 patients with acute non-STEMI (TIMI 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, re-infarction, urgent revascularization and stroke during hospitalization was defined as the primary end-point of the study.

Results

The mean age of the patients was 61 ± 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 beta-blocker and use of ACE inhibitor), leukocyte count >11,000 /μL demonstrated to be a strong predictor of the primary end-point (HR=3.028; 95% CI=1.69–5.40, p<0.001).

Conclusion

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

Keywords: leukocyte, acute non-STEMI, predictor.

Introduction

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 laboratories worldwide. Leukocytosis affects acute thrombosis by mechanisms involving inflammation that will induce a hypercoagulability state and microvascular obstruction, leading to a more extensive infarction [5].

Many studies have shown that leukocytosis is a predictor of cardiovascular events in healthy individuals [6-8], and in patients with a history of myocardial infarction [9-11], but another study failed to find such an association [12]. Studies that observe an association between blood leukocyte count and cardiovascular events in the developing countries are scarce. As the clinical laboratories in most developing countries lack the routine assay of established inflammatory markers, such as interleukins and C-reactive protein (CRP), these laboratories need a simple, reliable, inexpensive but accurate marker is to be measured routinely in daily management of infarct patients to identify patients who are at increased risk for subsequent cardiovascular events.

This study was designed to observe the predictive role of baseline leukocyte count on in-hospital cardiovascular events in patients with acute non ST-segment elevation myocardial infarction (non-STEMI).

Methods

Study population

Data was 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 (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 two weeks before admission, or 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 preceeding 48 hours, (2) the absence of ST-segment elevation, and (3) the presence of at least one of the following 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 3 risk factors for coronary artery disease, prior coronary stenosis of ≥50%, ST-segment deviation on electrocardiogram at presentation, at least two anginal events in the prior 24 hours, use of acetylsalicylic acid in the preceeding week, and elevated cardiac marker levels in serum. Moderate and high-risk patients are defined when having TIMI score of 3-4 and 5-7, 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 EDTA. One blood sample was used to measure the blood leukocyte count using flow cytometry (Sysmex Corporation, Kobe, Japan). In plasma samples cardiac troponin T was assayed using a chemiluminescence immunoassay (Roche Diagnostics Corporation, Indianapolis, IN, USA), 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, re-infarction, urgent revascularization, and stroke during hospitalization, as judged by an independent clinical event committee of which the members were blinded to the laboratory results. This study has been approved by the local institutional review committee and all patients have given written informed consent.

Statistical methods

Continuous variables are presented as mean values ± standard deviation (SD) or median (range) if not fitting a normal distribution. Categorical variables were expressed as percentages or proportions. The 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. Normally distributed variables were compared by Student's *t*-test, skewed distribution data by Mann-Whitney *U*-test and categorical variables by Pearson's 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 of MACE by at least 16%, 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, USA).

Results

Most patients were men (79%) and the mean age was 61 ± 9.6 years. The mean leukocyte count was 10,382 ± 4,007 /μL. On admission, patients with a leukocyte count >11,000 /μL had higher heart rate (p<0.001), a higher CK-MB level on admission (p<0.001) and a higher creatinine level (p=0.014) than patients with a leukocyte count ≤11,000 /μL (Table 1).

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

Table 1. Demographic and clinical characteristics including baseline blood chemistry of patients with acute non-STEMI 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 (years)	61 ± 9.6	61.3 ± 9.6	60.0 ± 9.4	0.223
Male gender	462 (79%)	306 (77%)	156 (82%)	0.102
Systolic blood pressure (mmHg)	142.5 ± 29	143.3 ± 29	140.9 ± 28	0.383
Heart rate (beats/minute)	90 ± 23.8	87 ± 23	97 ± 24	<0.001
Prior myocardial infarction	97 (16%)	66 (17%)	31 (16%)	0.947
Risk factor profile				
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 (days)	8.77 ± 7.14	8.82 ± 6.7	8.68 ± 7.8	0.501
Coronary angiography	221 (38%)	161 (40%)	60 (32%)	0.042
PCI	79 (13%)	54 (13%)	25 (13%)	0.262
CABG	29 (5%)	22 (5%)	7 (3%)	0.696
Medication at enrollment				
ACE Inhibitor	313 (53%)	205 (51%)	108 (57%)	0.188
Beta-blocker	373 (64%)	273 (68%)	100 (53%)	<0.001
MACE	52 (9%)	21 (5%)	31 (16%)	<0.001

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

In univariate analysis, patients with leukocyte count >11,000 /µL had an increased cardiovascular events compared to patients with leukocyte count ≤11,000 /µL (hazard ratio=3.17, 95% CI=1.81-5.57, p<0.001), and in multivariate analysis, the hazard ratio was 3.028 (95% CI=1.69–5.40, p< 0.001) (Tables 2 and 3).

Table 2. Univariate predictors of cardiovascular events.

Variables	HR (95% CI)	P Value
Age (>65 years)	0.913 (0.50 – 1.63)	0.759
Male gender	1.085 (0.54 – 2.17)	0.818
History of MI	0.915 (0.42 – 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 mmHg	0.853 (0.26 – 2.78)	0.792
Heart rate >100 beats/minute	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

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

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/minute	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 beta-blocker	0.775 (0.43 – 1.37)	0.384
Use of ACE inhibitor	0.575 (0.32 – 1.02)	0.058

ACE= angiotensin converting enzyme, HR= hazard ratio, CI= confidence interval.

Discussion

In this study involving 585 patients with acute non-STEMI we found a strong relationship between leukocyte count on admission and incidence of cardiovascular events during hospitalization. This result is consistent with a study from 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.

Several mechanisms explain how leukocytosis affects coronary heart disease through multiple pathologic mechanisms that mediate inflammation: (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) leukocytes may induce increased expression of Tissue Factor on monocytes [14]. It is hypothesized that these mechanisms may cause activation of intrinsic and extrinsic pathways of the coagulation system [15], leading to thrombus formation [16] and infarct expansion [5]. The prognostic value of inflammatory markers is observed accross 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. Firstly, patients with a leukocyte count >11,000 /μL may have larger infarct size as shown by higher initial CK-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. Secondly, heart rate on admission was higher in patients with a leukocyte count >11,000 /μL ($p<0.001$) than in the patients with low leukocyte count, and in patients with acute myocardial infarction heart rate on admission is an established risk factor [18]. Thirdly, the baseline creatinine level was significantly higher in the patients with a leukocyte count >11,000 /μL than in the patients with low leukocyte count, and the GRACE study has demonstrated that elevated creatinine levels are a risk factor for developing cardiac events [18]. After adjustment of all those variables and other variables such as history of smoking, hypertension, use of beta-blocker and use of ACE inhibitor, a leukocyte count >11,000 /μL proved to be a strong predictor of in-hospital cardiovascular events. Thus, for patients with acute non-STEMI having 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 [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 bed side 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 the present study should be considered. The design of the study was a retrospective analysis and data was collected from an existing registry. Furthermore, the assay of additional inflammatory markers such as CRP is lacking which would have strengthened the role of the leukocyte count in the present study.

Conclusion

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

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