Prognostic Usefulness of White Blood Cell Count on Admission and One-Year Outcome in Patients With Non–ST-Segment Elevation Acute Chest Pain

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The present study investigated the usefulness of white blood cell (WBC) count for prognostic evaluation in a nonselected series of consecutive patients who presented to the emergency department with non–ST-segment elevation acute chest pain with or without increased troponin.

Methods and Results

The study group consisted of 1,461 consecutive patients (from January 15, 2001 to November 31, 2004) who presented to the emergency department with chest pain. In total, 1,461 patients who presented to the emergency department with non–ST-segment elevation chest pain were studied by clinical history, electrocardiography, serial troponin I determination, and leukocyte count on admission. End points were 1-year mortality and major events (mortality or infarction). Overall patient distribution by quartiles of leukocyte count showed increased mortality (6%, 7%, 6%, and 17%, \( p = 0.0001 \)) and major events (13%, 13%, 15%, and 24%, \( p = 0.0001 \)) in the fourth quartile. After adjustment for other risk factors, the fourth quartile cut-off value (>10,000 cells/ml) predicted mortality (hazard ratio 2.0, 95% confidence interval 1.4 to 2.8, \( p = 0.0001 \)) but not major events (\( p = 0.07 \)). When analysis was performed to assess troponin status, in the subgroup with increased troponin (\( n = 634 \), 16% mortality), a leukocyte count >10,000 cells/ml was related to mortality (hazard ratio 2.2, 95% confidence interval 1.5 to 3.4, \( p = 0.0001 \)). However, in the subgroup with normal troponin levels (\( n = 827 \), 4.2% mortality), there were no differences in mortality between patients with or without a leukocyte count >10,000 cells/ml (4.4% vs 4.2%, \( p = 0.8 \)), with survival curves showing a tight overlap (\( p = 0.9 \)). Further, in the subgroup with normal troponin levels, leukocyte count was not significantly different between patients with or without ST depression (7.969 ± 2.171 vs 8.108 ± 2.356 cells/ml, \( p = 0.6 \)) and was not associated with mortality in patients with ST depression (\( p = 0.7 \)). In conclusion, leukocyte count on admission is predictive of mortality in patients with chest pain and non–ST-segment elevation myocardial infarction. However, in the absence of myocardial necrosis, leukocyte count lacks prognostic value.

All patients were evaluated by a chest pain unit protocol implemented in our institution and evaluation comprised clinical history, electrocardiogram, serial troponin I determination, and early exercise testing in a low-risk subgroup (no ischemic changes on electrocardiogram and normal troponin levels) with an ability to exercise.\textsuperscript{1–3} Electrocardiograms were evaluated for ST-segment depression (≥1 mm at 80 ms from the J point) and T-wave inversion (≥1 mm) in ≥2 contiguous leads. Troponin I was determined in the emergency department on arrival, at 6 hours (in patients arriving within the first 2 hours from pain onset), and 8 and 12 hours after pain onset. Troponin I was determined with an Immulite assay (Diagnostic Products Corp., Los Angeles, California). According to the manufacturer’s instructions, troponin I increase was defined as ≥1 ng/ml. The troponin I assay was tested in our laboratory, and the coefficient of variation was <10%. Coefficients of variation were obtained at 2 levels: 1 within the normal range and the other above the normal range.

In total, 1,210 patients were hospitalized and 251 were discharged early (all patients with a negative exercise test result and those with an inconclusive result according to the supervising physician). During hospital admission, 675 patients underwent cardiac catheterization. Indication for invasive study was left to the discretion of the attending physician.
physician. Percutaneous coronary intervention was performed in 270 patients and coronary surgery in 117.

Patients were followed for 1 year. Complete follow-up was achieved in 98% of patients. The end point was all-cause mortality and major events defined by death or non-fatal acute myocardial infarction (AMI). AMI was defined as a new episode of chest pain with increased troponin I. In case of a new episode of chest pain after hospital admission and previously increased troponin I, reinfarction was defined as creatine kinase-MB mass increase. In case of an eventual reinfarction, creatine kinase-MB mass was routinely assessed in all patients with increased troponin I, with an upper limit of normal of 5 ng/ml. Creatine kinase-MB mass was determined immunologically with an Immulite assay.

AMI was defined as creatine kinase-MB mass increase. In case of an and previously increased troponin I, reinfarction was defined of cardiac origin. During follow-up, 133 patients died (9%) and 236 (16%) had a major event. In 104 patients (7%), death was considered of cardiac origin.

Table 1 lists characteristics of the patient population. During follow-up, 133 patients died (9%) and 236 (16%) had a major event. In 104 patients (7%), death was considered of cardiac origin.

Distribution by quartiles of WBC count in the entire population (<6,800, 6,801 to 8,200, 8,201 to 10,000, and >10,000 cells/ml) shows a higher rate of mortality (6%, 7%, 6%, and 17%, p = 0.0001) in the fourth quartile.

Analysis was carried out in the entire population and separately in subgroups with increased troponin I (non-ST-segment elevation AMI subgroup) and normal troponin levels (non-ST-segment elevation chest pain subgroup). In addition, patients with normal troponin levels were categorized according to whether or not they had ST-segment depression on electrocardiograms as a marker of ischemic changes.

Calculations were performed with SPSS 9.0 (SPSS, Inc., Chicago, Illinois).

Table 1 lists characteristics of the patient population. During follow-up, 133 patients died (9%) and 236 (16%) had a major event. In 104 patients (7%), death was considered of cardiac origin.

Table 2 presents results of univariate and multivariate analyses for mortality. Cox regression analysis identified older age (per-year HR 1.07, 95% CI 1.05 to 1.09, p = 0.0001), Killip’s class >I at admission (HR 3.5, 95% CI 2.4 to 5.0, p = 0.0001), diabetes mellitus (HR 2.0, 95% CI 0.05 to 3.4, p = 0.0001), ST-segment depression (HR 1.4, 95% CI 1.1 to 2.1, p = 0.04), increased troponin (HR 1.5, 95% CI 1.1 to 2.4, p = 0.04), and WBC count >10,000 cells/ml (HR 2.0, 95% CI 1.4 to 2.8, p = 0.0001) as independent predictors. When analyzing only cardiac death, a WBC count >10,000 cells/ml was also related (HR 2.0, 95% CI 1.3 to 2.9, p = 0.0001).
Table 3 presents results of univariate and multivariate analyses for major events. In Cox’s regression analysis, independent predictors were older age (per-year HR 1.04, 95% CI 1.03 to 1.06, p = 0.0001), Killip’s class >I at admission (HR 2.8, 95% CI 2.1 to 3.8, p = 0.0001), diabetes mellitus (HR 1.8, 95% CI 1.4 to 2.3, p = 0.0001), previous AMI (HR 1.5, 95% CI 1.2 to 2.0, p = 0.003), ST-segment depression (HR 1.5, 95% CI 1.1 to 2.0, p = 0.004), and increased troponin (HR 1.8, 95% CI 1.3 to 2.4, p = 0.01). However, a WBC count >10,000 cells/ml was not an independent predictor (p = 0.07).

The subgroup with increased troponin consisted of 634 patients. During follow-up, 98 patients (16%) died. WBC count was higher in patients who died (1,1185 ± 3,689 vs 9,070 ± 2,639 cells/ml, p = 0.0001). Likewise, patients with a WBC count >10,000 cells/ml showed higher mortality (26% vs 10%, p = 0.0001), and Kaplan-Meier curves showed an increased mortality associated with a WBC count >10,000 cells/ml (p = 0.0001; Figure 2). By multivariate analysis, a WBC count >10,000 cells/ml was an independent predictor of mortality (HR 2.2, 95% CI 1.5 to 3.4, p = 0.0001), in addition to patient age (per-year HR 1.07, 95% CI 1.05 to 1.1, p = 0.0001), Killip’s class >I (HR 3.3, 95% CI 2.2 to 5.1, p = 0.0001), diabetes mellitus (HR 1.7, 95% CI 1.2 to 2.6, p = 0.007), and previous AMI (HR 1.6, 95% CI 1.1 to 2.5, p = 0.02).

In total, 827 patients had normal troponin levels after serial determination. WBC count was lower in this subgroup than in the subgroup with increased troponin (8,090 ± 2,332 vs 9,070 ± 2,639 cells/ml, p = 0.0001). During follow-up, 35 patients (4.2%) died. There were no differences in mortality between patients with or without a WBC count >10,000 cells/ml (4.4% vs 4.2%, p = 0.8), with Kaplan-Meier curves showing a tight overlap (p = 0.9; Figure 2). As a continuous variable, WBC count was also unrelated to mortality (8,017 ± 3,195 vs 8,093 ± 2,289 cells/ml, p = 0.8).

In the subgroup with normal troponin levels, a subanalysis was performed in patients with ST-segment depression on the admission electrocardiogram as a marker of ischemic changes. No differences were observed in WBC count be-
between patients with (n = 106) or without (n = 721) ST-segment depression (7.969 ± 2.171 vs 8.108 ± 2.356 cells/ml, p = 0.6). In the subgroup with ST depression and normal troponin levels, 10 patients (9.4%) died. There were no differences in WBC count between patients who died or survived (8.210 ± 2.817 vs 7.944 ± 2.110 cells/ml, p = 0.7). When considering in the normal troponin population those patients with ST-segment depression or T-wave inversion, there were no differences in WBC count between patients with (8,052 ± 2,312 cells/ml, n = 183) and those without (8,101 ± 2,340 cells/ml, n = 644, p = 0.8) changes on the electrocardiogram.

**Discussion**

The main finding of the present study is that WBC count on admission contributes to prognostic assessment of non–ST-segment elevation acute chest pain in the subset of patients with AMI. However, in the absence of myocardial necrosis, WBC count lacks prognostic value.

Several studies have demonstrated that increased inflammatory markers predict a poor outcome in acute coronary syndromes. As an inflammation marker, this association has also been observed for WBC count. The prognostic role of WBC count was first evaluated in ST-segment elevation AMI. In this setting, a high WBC count was associated with short-term mortality and heart failure and with long-term mortality. Likewise, WBC count has been related to mortality in non–ST-segment elevation acute coronary syndromes. These data are in line with our finding that a high WBC count independently predicts 1-year mortality in patients who present to the emergency department with non–ST-segment elevation acute chest pain, in addition to clinical variables (age, diabetes, Killip’s class >1), ST-segment depression, and increased troponin I. However, the prognostic value of WBC count was confined to mortality and to the subgroup of patients with AMI as defined by increased troponin. In a recent study in a cohort of patients with chronic heart disease, the association between WBC count and infarct-free survival was eliminated after adjustment for coronary risk factors, but, as in our study, the association with total mortality persisted.

Our results and those of others indicate that WBC count is increased to a greater extent in the presence of myocardial necrosis. A critical issue is whether the prognostic value persists despite the smaller increase in WBC count in the subset of patients without necrosis. According to our data, WBC count did not predict outcome in the absence of increased troponin, even in patients with ischemic changes on electrocardiography. Other series of patients admitted to the hospital because of unstable angina have shown discordant results. Lloyd-Jones et al and Zouridakis et al found no independent association between WBC count and adverse outcome. In a subset of the Ortofiban in Patients with Unstable Coronary Syndromes-Thrombolysis In Myocardial Infarction (OPUS-TIMI) 16 trial, WBC count was strongly related to 30-day and 10-month mortalities in patients with AMI, but in the subgroup with unstable angina, the relation was not significant at 30 days and only borderline significant at 10 months. In this trial, blood samples for WBC determination were not obtained on admission but on enrollment (average 40 hours after onset of acute coronary syndrome), and troponin values were not widely used to distinguish unstable angina from AMI. In the Global Registry of Acute Coronary Events (GRACE) registry, which included the entire spectrum of acute coronary syndromes, WBC count predicted in-hospital mortality in the unstable angina subgroup. Two characteristics differentiate the multicenter GRACE registry from our study. First, troponin values were not universally used for the diagnosis of AMI; hence, some diagnoses of unstable angina could have corresponded to AMI according to the new definition. Second, follow-up was limited to the in-hospital phase. In the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, WBC count predicted mortality at 6 months in patients with normal creatine kinase levels, but troponin values were not used as necrosis markers.


