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Relationship Between Baseline White Blood Cell Count and Degree of Coronary Artery Disease and Mortality in Patients With Acute Coronary Syndromes

A TACTICS-TIMI 18 Substudy

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OBJECTIVES This study was designed to determine the relationship between baseline white blood cell (WBC) count and angiographic and clinical outcomes in patients with unstable angina (UA)/non–ST-segment elevation myocardial infarction (NSTEMI) and to see if WBC count was a significant predictor of outcomes independent of other biomarkers.

BACKGROUND Inflammation has been shown to play a role in atherosclerosis and acute coronary syndromes.

METHODS We evaluated the relationship between baseline WBC count, other baseline variables and biomarkers, angiographic findings, and clinical outcomes in 2,208 patients in the Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction 18 (TACTICS-TIMI 18) trial.

RESULTS Higher baseline WBC counts were associated with lower Thrombolysis In Myocardial Infarction (TIMI) flow grades ($p = 0.0045$) and TIMI myocardial perfusion grades ($p = 0.03$) as well as a greater extent of coronary artery disease (CAD) ($p < 0.0001$). A higher baseline WBC count was predictive of higher six-month mortality, ranging from 1.5% to 3.6% to 5.1% for patients with low, intermediate, and high WBC counts, respectively ($p = 0.0017$). In a multivariable proportional hazards model, patients with a low C-reactive protein (CRP) but an elevated WBC remained at significantly higher risk of death at six months (hazard ratio [HR] 4.3, $p = 0.049$), and patients with a high CRP were at even higher risk (HR 8.6, $p = 0.004$).

CONCLUSIONS In patients with UA/NSTEMI, elevations in a simple, widely available blood test, the WBC count, were associated with impaired epicardial and myocardial perfusion, more extensive CAD, and higher six-month mortality. After adjustment for traditional risk factors and other biomarkers, assessment of two inflammatory markers, WBC count and CRP, can be used to stratify patients across an eightfold gradation of six-month mortality risk. (J Am Coll Cardiol 2002;40:1761–8) © 2002 by the American College of Cardiology Foundation

An association between white blood cell (WBC) count and cardiovascular disease was first noted more than a quarter of a century ago (1). It is now appreciated that inflammation plays a central role in atherosclerosis and acute coronary syndromes (ACS) (2). This has led to a renewed interest in the study of inflammatory markers, including C-reactive protein (CRP) and, more recently, WBC count, in ACS (3–6).

Previously, we have reported that in the setting of ST-segment elevation myocardial infarction (MI), elevations of the baseline WBC count were associated with worse angiographic findings as well as higher 30-day mortality (5). We hypothesized that the same would be true of unstable angina (UA)/non–ST-segment elevation MI (NSTEMI), and we also hypothesized that this would be independent of elevations of other inflammatory or myonecrosis markers. We evaluated these hypotheses in a large cohort of patients from the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)-Thrombolysis In Myocardial Infarction (TIMI) 18 trial (7).

METHODS

Patient population and clinical end points. The design and main results of TACTICS-TIMI 18 were reported previously (7). In brief, 2,220 patients with evidence of UA/NSTEMI within the prior 24 h were randomized to an early invasive or conservative strategy. The protocol was approved by the relevant institutional review boards, and written informed consent was obtained from all patients. The prespecified clinical end points were death, nonfatal MI, and rehospitalization for ACS; patients were followed for six months.

WBC count and other laboratory data. Per protocol, blood samples were obtained at baseline for WBC count, creatinine, cardiac troponin, and CRP. The WBC count

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Abbreviations and Acronyms

ACS	= acute coronary syndrome
CAD	= coronary artery disease
CRP	= C-reactive protein
HR	= hazard ratio
IL	= interleukin
MI	= myocardial infarction
NSTEMI	= non–ST-segment elevation myocardial infarction
OR	= odds ratio
TACTICS	= Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy
TFG	= Thrombolysis In Myocardial Infarction flow grade
TIMI	= Thrombolysis In Myocardial Infarction
TMPG	= Thrombolysis In Myocardial Infarction myocardial perfusion grade
UA	= unstable angina
WBC	= white blood cell

was determined by the laboratories at the local enrolling institutions and was treated both as a continuous variable and as a categorical variable, with low ($<6.65 \times 10^9$/l, <25th percentile), intermediate (6.65 to 10.11×10^9/l, 25th to 75th percentiles), and high ($>10.11 \times 10^9$/l, >75th percentile) levels. A serum creatinine above 1.5 mg/dl, also determined locally, was considered elevated. Both cardiac troponin T and CRP were assayed at the TIMI Biomarker Core Laboratory (Boston, Massachusetts). Cardiac troponin T was measured on the Elecsys 10/10 (Roche Diagnostics, Indianapolis, Indiana). We used a clinical cutpoint of 0.01 ng/ml based on prior work (8). Quantitative CRP determination was performed with the BN II Nephelometer (Dade-Behring, Deerfield, Illinois); the sensitivity of the assay is 0.01 mg/dl. We used a cutoff of 1.5 mg/dl, which corresponds to the 99th percentile value in healthy controls (3). B-type natriuretic peptide was measured using an established immunoassay (Biosite, San Diego, California).

Angiographic analyses. Local investigators recorded the extent and severity of coronary artery disease (CAD) in all patients undergoing angiography. To eliminate possible selection bias, analyses of the association between WBC count and extent of CAD were restricted to patients in the invasive arm (n = 983), in whom routine angiography was mandated per protocol. Patients who underwent a percutaneous coronary intervention (n = 538) were eligible for enrollment in the angiographic substudy, for which angiographic data were sent to the TIMI Angiographic Core Laboratory (Boston, Massachusetts) for analysis. Thrombolysis In Myocardial Infarction flow grade (TFG), corrected TIMI frame count, and Thrombolysis In Myocardial Infarction myocardial perfusion grade (TMPG) were assessed as previously defined (9–11).

Statistical analysis. Continuous variables were reported as medians with interquartile ranges. Wilcoxon rank-sum and Kruskal-Wallis tests were used for analysis of continuous variables. The chi-squared test or the chi-square test for linear trend was used for analysis of categorical variables. Cumulative survival curves were calculated using the Kaplan-Meier method. Multivariable-adjusted associations between WBC count and angiographic findings were evaluated using logistic regression models, and between inflammatory markers and six-month mortality using Cox proportional hazard models.

RESULTS

Baseline characteristics. Baseline WBC counts were available in 2,208 of the 2,220 patients in the TACTICS-TIMI 18 trial. The baseline WBC count ranged from 2.0 to 25.9 $\times 10^9$/l. The mean WBC count was $8.6 \pm 2.8 \times 10^9$/l, the median was 8.1×10^9/l, and the 25th and 75th percentiles were 6.65 and 10.11×10^9/l, respectively. Baseline characteristics that were associated with a higher WBC count included age <65 years, smoking, impaired renal function, no prior aspirin use or statin use, ST-segment deviation on the presenting electrocardiogram, an elevated cardiac troponin level, and an index diagnosis of NSTEMI (Tables 1 and 2). There was a stepwise association between degree of smoking and WBC count: median WBC count was 7.7×10^9/l in never-smokers, 7.9×10^9/l in former smokers, 8.1×10^9/l in <10 cigarette/day smokers, 9.2×10^9/l in 10 to 20 cigarette/day smokers, and 9.5×10^9/l in >20 cigarette/day smokers ($p < 0.0001$).

Relationship of WBC count to angiographic findings. There were no statistically significant differences in baseline characteristics between patients in the angiographic substudy (n = 538) and the overall trial cohort, including median baseline WBC count (8.2 vs. 8.1×10^9/l). However, among patients in the angiographic substudy, the baseline WBC count was higher in patients with worse culprit artery TFG: 8.1×10^9/l in patients with TFG 3; 8.3×10^9/l in patients with TFG 2, 8.4×10^9/l in patients with TFG 1; and 9.75×10^9/l in patients with TFG 0 ($p = 0.007$). When treated as a categorical variable, higher baseline WBC counts were associated with lower TFG, with TFG 3 present in 71% of patients with a low WBC count (<25th percentile), 68% of patients with an intermediate WBC count (25th to 75th percentiles), and 54% of patients with a high WBC count (>75th percentile) ($p = 0.0045$, chi-squared for trend) (Fig. 1A). Similarly, the median corrected TIMI frame count increased with increasing WBC count (30 frames in patients with a low WBC count, 32 frames in patients with an intermediate WBC count, and 41 frames in patients with a high WBC count; $p = 0.0006$). A higher proportion of patients had angiographically apparent thrombus with increasing WBC count (32% vs. 35% vs. 45%; $p = 0.04$, chi-square for trend). Elevated baseline WBC count was also associated with lower rates of optimal myocardial perfusion (TMPG 3) (50% vs. 35% vs. 35%; $p = 0.03$, chi-squared for trend). In multivariable analyses that adjusted for potential confound-

Table 1. Categorical Baseline Characteristics and WBC Count

Baseline Characteristic	Median WBC Count Among Patients		p Value
	With Characteristic	Without Characteristic	
Age ≥ 65 yrs	7.85 (6.5–9.6) (n = 954)	8.4 (6.8–10.3) (n = 1,253)	< 0.0001
Male	8.1 (6.7–10.0) (n = 1,457)	8.1 (6.6–10.3) (n = 751)	0.6
Hypertension	8.0 (6.6–9.8) (n = 1,462)	8.4 (6.7–10.6) (n = 746)	0.006
Diabetes	8.2 (6.6–10.0) (n = 611)	8.1 (6.7–10.1) (n = 1,597)	0.7
Hypercholesterolemia	8.0 (6.6–9.9) (n = 1,342)	8.3 (6.7–10.4) (n = 866)	0.008
Current smoker	9.1 (7.4–11.2) (n = 609)	7.8 (6.4–9.5) (n = 1,479)	< 0.0001
Elevated creatinine	8.5 (7.6–10.3) (n = 111)	8.1 (6.6–10.1) (n = 2,081)	0.064
Prior MI	7.9 (6.4–9.7) (n = 859)	8.3 (6.7–10.3) (n = 1,349)	0.0002
Prior aspirin	8.0 (6.6–9.8) (n = 1,470)	8.5 (6.8–10.7) (n = 738)	< 0.0001
Prior statin	7.8 (6.5–9.6) (n = 542)	8.25 (7.5–8.75) (n = 1,666)	0.0001
ST-segment deviation	8.6 (7.0–10.6) (n = 847)	7.9 (6.5–9.8) (n = 1,361)	< 0.0001
Elevated TnT	8.8 (7.2–10.7) (n = 995)	7.5 (6.2–9.1) (n = 842)	< 0.0001
Index NSTEMI	9.1 (7.3–11.1) (n = 823)	7.8 (6.4–9.4) (n = 1,385)	< 0.0001

White blood cell (WBC) count values are $\times 10^9$/l and are reported as medians, interquartile ranges, and number in each group.
MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; TnT = troponin T.

Table 2. Categorical Baseline Characteristics and WBC Count Category

Baseline Characteristic	WBC Count Category			p Value
	Low	Intermediate	High	
Age ≥ 65 yrs	48.6	44.4	35.3	< 0.0001
Male	65.4	67.2	64.0	0.6
Hypertension	66.5	69.4	59.4	0.014
Diabetes	29.4	27.6	26.2	0.24
Hypercholesterolemia	63.4	62.3	54.9	0.004
Current smoker	18.8	27.3	43.9	< 0.0001
Elevated creatinine	3.1	5.9	5.5	0.07
Prior MI	43.5	38.9	34.1	0.0016
Prior aspirin	69.9	68.9	58.3	< 0.0001
Prior statin	28.4	25.4	18.7	0.0002
ST-segment deviation	30.8	38.6	45.6	< 0.0001
Elevated TnT	36.8	54.7	70.9	< 0.0001
Index NSTEMI	24.1	36.0	53.4	< 0.0001

White blood cell (WBC) counts are categorized as low (< 6.65×10^9/l, < 25th percentile), intermediate (6.65 to 10.11×10^9/l, 25th to 75th percentiles), and high (> 10.11×10^9/l, > 75th percentile).
Abbreviations as in Table 1.

ers including age, gender, smoking status, index diagnosis, time to angiography, and culprit artery, a high WBC count was associated with a longer corrected TIMI frame count (p = 0.009) and a lower likelihood of achieving TFG 3 (odds ratio [OR] 0.55, p = 0.04) and TMPG 3 (OR 0.60, p = 0.09).

Beyond associations with the culprit artery, there was also a statistically significant correlation between baseline WBC count and the overall extent of a patient's CAD (stenosis ≥50%), with higher WBC counts associated with a greater burden of CAD (p < 0.0001, chi-squared for trend) (Fig. 1B). In a multivariable logistic regression model that adjusted for traditional CAD risk factors, a WBC count above the 25th percentile remained a significant predictor of multivessel disease (OR 1.4; p = 0.018). Among patients undergoing left ventriculography, there was a statistically significant but weak inverse association between WBC count and left ventricular ejection fraction (Spearman's rho = −0.08; p = 0.003).

Relationship of WBC count to clinical outcomes. The baseline WBC count was higher in patients who died within 30 days (p = 0.0016) and within six months (p = 0.0047) (Table 3). There was no association between WBC count and new or recurrent MI or rehospitalization for ACS, either at 30 days or at 6 months. When analyzed as a categorical variable, higher baseline WBC count was predictive of higher six-month mortality, ranging from 1.5% among patients with a low WBC count (<25th percentile) to 3.6% among patients with an intermediate WBC count (25th to 75th percentiles), to 5.1% among patients with a high WBC count (>75th percentile) (p = 0.0017, chi-squared for trend) (Fig. 2A). Similar trends were seen both in patients who had UA and in those who had NSTEMI. When stratified by baseline WBC count, event rates diverged over the first four weeks (p = 0.0028) and then remained roughly parallel (Fig. 2B).

There was no evidence for modification by WBC count of the effect of an early invasive strategy. The ORs for the composite end point for patients in the invasive versus conservative arms were similar for patients with low (OR 0.75), intermediate (OR 0.77), and high (OR 0.82) WBC counts, with nonsignificant heterogeneity (p = 0.9). We also examined the relationship between WBC count and revascularization, a post-randomization decision at the discretion of the treating physician. The six-month mortality rates across the WBC count categories were 0.6%, 3.3%, and 7.1% among patients who were not revascularized (p < 0.0001) and 2.6%, 3.9%, and 3.1% among patients who were (p = 0.76) revascularized.

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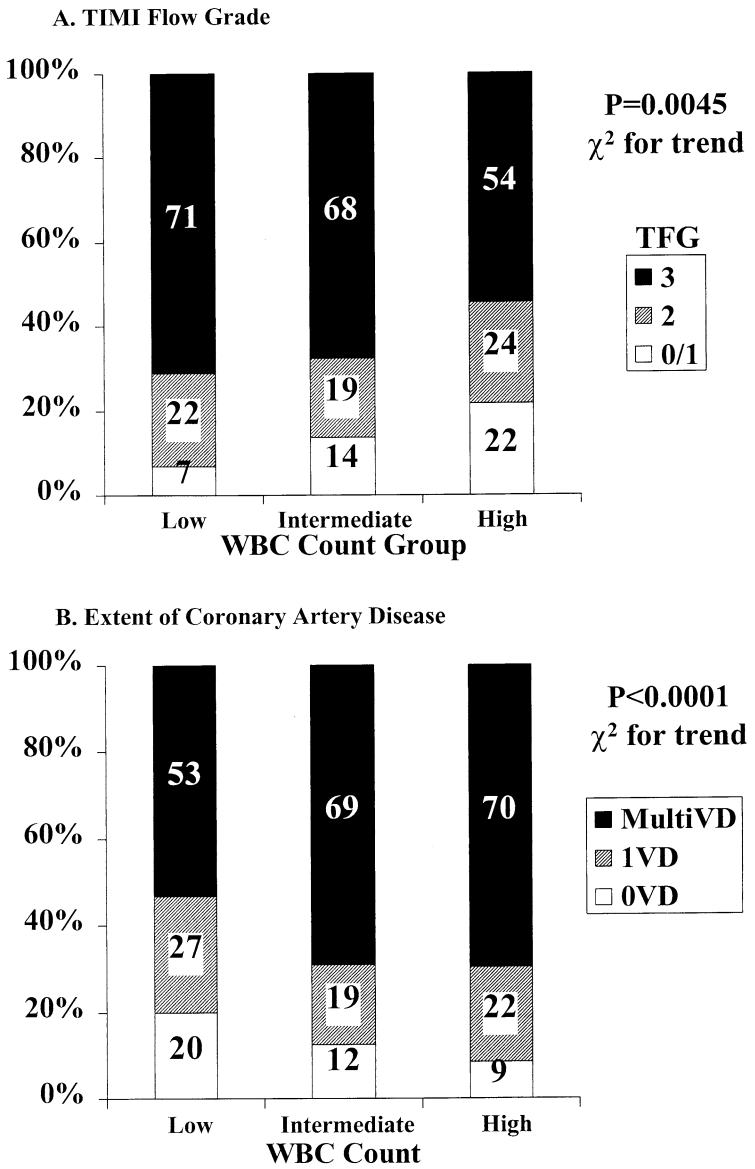

Figure 1. Thrombolysis In Myocardial Infarction (TIMI) flow grade (TFG) **(A)** and extent of coronary artery disease **(B)** in relation to baseline white blood cell (WBC) count, categorized as low (<25th percentile), intermediate (25th to 75th percentiles), and high (>75th percentile). MultiVD = multivessel disease; 1VD = single vessel disease; 0VD = no significant disease.

WBC count and CRP. Baseline WBC count and CRP level were available in 1,840 patients. Although the correlation between WBC count and CRP was statistically significant ($p < 0.001$), the strength of the correlation was weak (Spearman's rho = 0.3). As an elevated WBC count may be a marker of inflammation similar to CRP, we further explored the relationship among WBC count, CRP, and clinical outcomes. Patients were stratified by baseline CRP level using a previously established cutoff of 1.5 mg/dl (Table 4) (3). Among the 1,421 patients (77%) who had a CRP level ≤1.5 mg/dl, WBC count remained a predictor of six-month mortality. Patients with a low WBC count (<25th percentile) had a six-month mortality of 0.8%, whereas patients with an intermediate or high WBC count (>25th percentile) had a six-month mortality of 2% to 3% ($p = 0.055$). In contrast, among the 419 patients (23%) who had an elevated CRP level (>1.5 mg/dl), six-month mortality was relatively high (5% to 7%) and was not statistically different among the WBC count groups ($p = 0.7$).

Therefore, patients were categorized into three groups according to their combined WBC and CRP status: 1) low WBC count (<25th percentile) plus low CRP level (≤1.5 mg/dl); 2) high WBC count (>25th percentile) plus low CRP level; and 3) any WBC count plus high CRP level (>1.5 mg/dl). Using these two markers allowed us to risk stratify patients across an approximate eightfold graded increase in six-month mortality (Fig. 3). Patients with both a low WBC count plus a low CRP level (n = 397) had a very low mortality rate (0.8%), patients with an elevated WBC count but a low CRP level (n = 1,021) had an

Table 3. Clinical Outcomes and WBC Count

End Point	WBC Count		p Value
	Outcome Present	Outcome Absent	
30 Days			
Death	9.1 (7.8–12.0) (n = 43)	8.1 (6.6–10.0) (n = 2,171)	0.0016
MI	8.1 (6.9–9.9) (n = 98)	8.1 (6.6–10.1) (n = 2,116)	0.76
Rehospitalization for ACS	8.2 (6.9–9.7) (n = 99)	8.1 (6.6–10.1) (n = 2,115)	0.99
6 Months			
Death	8.75 (7.6–10.95) (n = 76)	8.1 (6.6–10.0) (n = 2,138)	0.0047
MI	8.1 (6.9–10.1) (n = 128)	8.1 (6.6–10.1) (n = 2,086)	0.56
Rehospitalization for ACS	8.0 (6.8–9.6) (n = 274)	8.2 (6.6–10.2) (n = 1,940)	0.44

White blood cell (WBC) count values are $\times 10^9$/l and are reported as medians, interquartile ranges, and number in each group.
ACS = acute coronary syndrome; MI = myocardial infarction.

intermediate mortality rate (2.7%), and patients with any WBC count plus an elevated CRP level (n = 420) had a high mortality rate (6.2%) ($p < 0.0001$ by chi-square).

Multivariable analyses. In a Cox proportional hazards model that controlled for all potential confounders of the effect of the inflammatory markers on outcome (including age, gender, cardiac risk factors, prior MI, creatinine, prior aspirin and statin use, ST-segment deviation, troponin level, index diagnosis, and B-type natriuretic peptide level), patients with a low CRP but an elevated WBC remained at significantly higher risk of death at six months (hazard ratio [HR] 4.3, $p = 0.049$), and patients with a high CRP were at even higher risk (HR 8.6, $p = 0.004$).

DISCUSSION

In the present study in more than 2,000 patients with UA/NSTEMI, we observed strong relationships among baseline WBC count, angiographic findings, and mortality, which extend our previous observations in patients with ST-segment elevation myocardial infarction and UA/NSTEMI (5,6). Moreover, after adjustment for traditional risk factors including troponin and ST-segment deviation, simultaneous use of two inflammatory markers, WBC count and CRP, allowed risk stratification of patients with UA/NSTEMI across a eightfold gradation of six-month mortality.

More than 25 years ago, Friedman et al. (1) observed that an increased WBC count was associated with an increased risk of developing an MI, and Schlant et al. (12) observed that an elevated WBC count was a predictor of mortality post-MI. More recently, we have demonstrated that in the setting of STEMI, an elevated WBC count was associated with reduced epicardial and myocardial perfusion and worse clinical outcomes (5). We have also found that an elevated WBC count was associated with increased short-term and long-term mortality in the full spectrum of ACS (6). The present study offers several important insights.

The role of inflammation in the development of CAD and in plaque destabilization is becoming increasingly well recognized (13). An inflammatory response is often found at the site of plaque rupture (14), and even subtle elevations in CRP predict a higher rate of MI in otherwise healthy persons (15). In support of this relationship between inflammation and CAD is our observation that the extent of CAD found at angiography was related to the WBC count, even after adjusting for traditional risk factors.

There is some evidence to suggest that inflammation and the WBC itself may directly contribute to coronary thrombosis, impaired perfusion, and reperfusion injury (16). Interleukin (IL)-6, IL-8, and CD40 ligand have been shown to upregulate monocyte tissue factor expression, thereby facilitating the initiation of the extrinsic pathway of the coagulation cascade (17). Mac-1 (CD11b-CD18), which is found on the surface of leukocytes, can directly serve as a procoagulant by catalyzing the conversion of factor X to factor Xa (18). Because of their large size and relatively high cytoplasmic viscosity, leukocytes may directly cause capillary plugging, especially in the setting of low flow and ischemia (19). Platelet-leukocyte aggregation, mediated by Mac-1, may also lead to thrombus formation and reduced perfusion (20). Lastly, leukocytes may contribute to reperfusion injury via the effects of oxygen-free radicals and complement activation (21). Our data support these potential pathobiologic processes, as patients with higher WBC counts had worse epicardial and myocardial perfusion and were more likely to have angiographically apparent thrombus. Thus, WBC count may be both a marker of a heightened inflammatory state and more extensive atherosclerotic disease burden and a direct contributor to coronary artery thrombosis and microvascular injury in the setting of plaque rupture.

We found that an elevated baseline WBC count was associated with a higher mortality rate, both at 30 days and at 6 months. In contrast, there was no association between WBC count and either MI or rehospitalization for ACS. These observations are in agreement not only with our prior studies of WBC count (5,6), but also with studies of other inflammatory markers, such as CRP and IL-6, elevations of which appear to primarily predict death rather than recurrent ischemic events (22–24). The basis for this remains unknown, but the early divergence of the cumulative mortality curves suggests that patients with an elevated WBC count have a higher risk of death from the index event. This early hazard may be related to the worse epicardial and myocardial perfusion that we observed in these patients. Another possibility is that WBC elevation is not a cause but rather a consequence of acute MI and that the degree of

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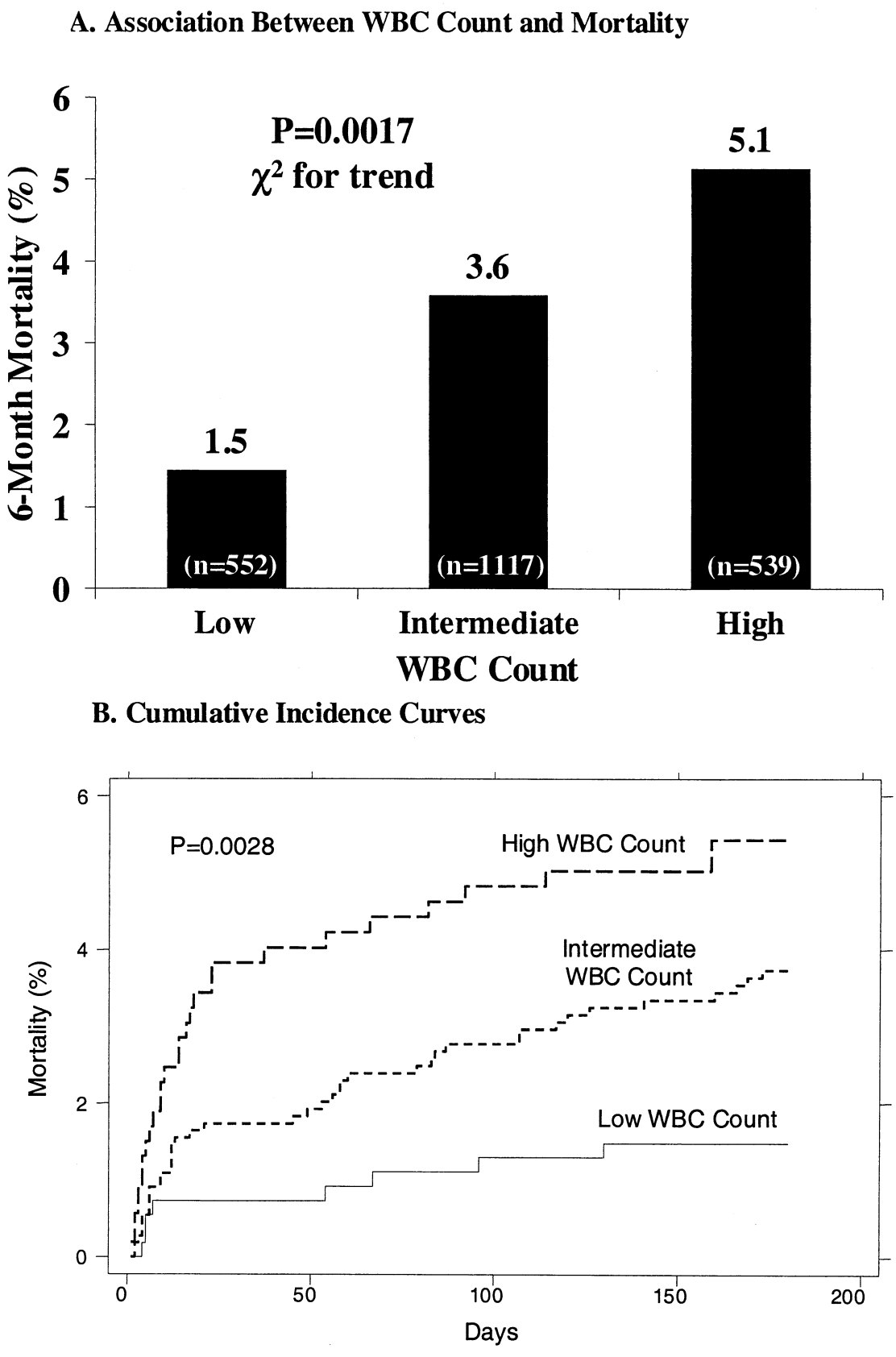

Figure 2. Mortality at six months **(A)** and cumulative mortality incidence curves **(B)** in relation to baseline white blood cell (WBC) count, categorized as low (<25th percentile), intermediate (25th to 75th percentiles), and high (>75th percentile).

Table 4. WBC Count, CRP, and 6-Month Mortality

CRP Level	Mortality Rate by 6 Months WBC Percentile <25th ($<6.65 \times 10^9$/l)	25th to 75th (6.65 to 10.11×10^9/l)	>75th ($>10.11 \times 10^9$/l)	p Value
CRP ≤1.5 mg/dl	0.8 (3/397)	2.9 (22/748)	2.2 (6/276)	0.055
CRP >1.5 mg/dl	7.1 (4/56)	5.1 (10/195)	7.1 12/168)	0.7

White blood cell (WBC) count values are $\times 10^9$/l.
CRP = C-reactive protein.

elevation reflects the severity of the infarct. This hypothesis was not supported by our data, in which there were only weak correlations between WBC count and both troponin level and left ventricular ejection fraction. Moreover, the association between WBC count and outcome was observed even after adjusting for troponin level and index diagnosis.

In contrast to the recent report with IL-6 in Fragmin during Instability in Coronary Artery Disease (FRISC II) study (24), and the observations regarding WBC count and nonrandomized revascularization in Platelet Glycoprotein IIB/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) (25), we did not find an interaction between inflammatory marker status and the benefits of an invasive strategy. Our results are in keeping with data from CRP substudies from both the FRISC II trial (26) and the TACTICS-TIMI 18 trial (27). The attenuated relationship between WBC count and mortality in patients who underwent revascularization is intriguing and may be related to the higher thrombotic burden and hence importance of coronary interventions in patients with an elevated WBC count. This hypothesis, and the hypothesis offered by others that revascularization might itself exert an anti-inflammatory effect, would need to be prospectively tested in trials with randomized revascularization and serial measurements of inflammatory markers.

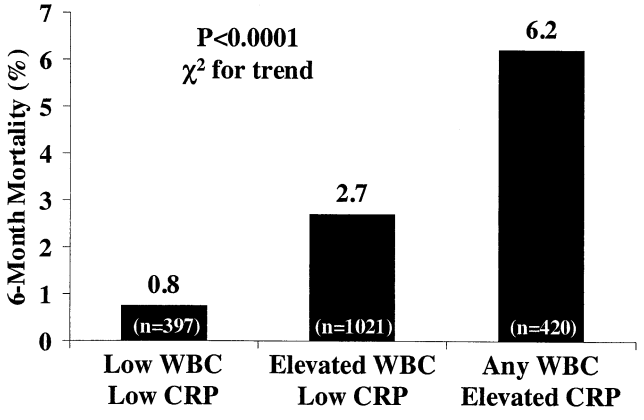

Figure 3. Mortality at six months in relation to both baseline white blood cell (WBC) count and C-reactive protein (CRP) level, categorized as low WBC count (<25th percentile) plus low CRP level (≤1.5 mg/dl), high WBC count (>25th percentile) plus low CRP level, and any WBC count plus high CRP level (>1.5 mg/dl).

An important advantage of the WBC count as a predictor of angiographic and clinical outcomes is its ubiquity. A WBC count is available in every hospital and, as part of the complete blood count, is it almost universally assayed in all patients presenting with ACS. The value for the 75th percentile of WBC count in our study was 10.1×10^9/l, which is close to the upper limit of normal for many laboratories. Patients above this threshold had more than three times the probability of having an occluded infarct-related artery and more than three times the probability of dying. As vascular-specific anti-inflammatory and antileukocyte therapies are developed (15,28,29), an elevated WBC count may help identify patients who would benefit the most from these interventions.

We and others have shown that elevation of another inflammatory marker, CRP, is also a powerful predictor of recurrent events in patients with ACS (3,4,22,27). To our knowledge, this is the first study to look at both CRP and WBC counts in such patients. We found that patients with an elevated CRP level had a relatively high risk of dying at six months (5% to 7%) that was similar across WBC count strata. In contrast, among patients with a low CRP, six-month mortality was related to baseline WBC count: patients had a very low mortality rate (0.8%) if they had a low WBC count (<25th percentile) and intermediate mortality rates (2.2% to 2.9%) if they had higher WBC counts (>25th percentile). Thus, at centers that routinely use CRP for risk stratification in ACS, baseline WBC count can be used to substratify mortality risk among patients with a low CRP level and identify patients with very low versus intermediate six-month mortality. The relationship between inflammatory marker status and mortality persisted even after adjustment for potential confounders including age, gender, cardiac risk factors, prior MI, creatinine, prior aspirin and statin use, ST-segment deviation, troponin level, index diagnosis, and B-type natriuretic peptide level.

There are several limitations to the present study. As an observational investigation, it can only identify associations and not causality. We did not collect information on WBC differential, which may be important. Although collection of WBC counts was a prespecified part of the analysis plan, the relationship between WBC count and CRP must be considered exploratory.

CONCLUSIONS

In patients with UA/NSTEMI, elevations in a simple, widely available blood test, the WBC count, were associated with impaired epicardial and myocardial perfusion, more extensive CAD, and higher six-month mortality rates. Even after adjusting for traditional risk factors including ST-segment deviation and troponin, assessment of two inflammatory markers, WBC count and CRP, can be used to stratify patients across a eightfold gradation of six-month mortality risk.

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