

# Which White Blood Cell Subtypes Predict Increased Cardiovascular Risk?

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<b>OBJECTIVES</b>	We sought to determine the predictive ability of total white blood cell (WBC) count and its subtypes for risk of death or myocardial infarction (MI).
<b>BACKGROUND</b>	An elevated WBC count has been associated with cardiovascular risk, but which leukocyte subtypes carry this risk is uncertain.
<b>METHODS</b>	Consecutive patients without acute MI who were assessed angiographically for coronary artery disease (CAD) and were followed up long-term were studied. The predictive ability for death/MI of quartile (Q) 4 versus Q1 total WBC, neutrophil (N), lymphocyte (L), and monocyte (M) counts and N/L ratio were assessed using Cox regressions.
<b>RESULTS</b>	A total of 3,227 patients was studied. Mean age was 63 years; 63% of patients were male, and 65% had CAD. In multivariable modeling entering standard risk factors, presentation, and CAD severity, the total WBC (hazard ratio [HR] 1.4, $p = 0.01$ ) and M (HR 1.3, $p < 0.02$ ) were weaker and N (HR 1.8, $p < 0.001$ ), L (HR 0.51, $p < 0.001$ ), and N/L ratio (HR 2.2, $p < 0.001$ ) were independent predictors of death/MI. When WBC variables were entered together, N/L ratio and M were retained as independent predictors. Risk associations persisted in analyses restricted to CAD patients or including acute MI patients.
<b>CONCLUSIONS</b>	Total WBC count is confirmed to be an independent predictor of death/MI in patients with or at high risk for CAD, but greater predictive ability is provided by high N (Q4 $>6.6 \times 10^3/\mu\text{l}$ ) or low L counts. The greatest risk prediction is given by the N/L ratio, with Q4 versus Q1 ( $>4.71$ versus $<1.96$ ) increasing the hazard 2.2-fold. These findings have important implications for CAD risk assessment. (J Am Coll Cardiol 2005;45:1638–43) © 2005 by the American College of Cardiology Foundation

Atherosclerosis is a multifactorial disease, with dyslipidemia, dysglycemia, smoking and other causes of endothelial injury, and genetic predisposition all contributing to pathogenesis (1,2). In recent years, it has been recognized that atherogenesis represents an active, inflammatory process rather than simply passive injury with infiltration of lipids (1,3,4). Leukocytes play a major role in these inflammatory processes (5), which may be either adaptive (reparative) or maladaptive, and acute or chronic. Mononuclear cells (monocyte/macrophages, T-lymphocytes) are prevalent and pathogenic within unstable coronary artery plaques (1–3). Neutrophils are intimately involved with adaptive infarct healing, but also may be pathogenic (e.g., as with leukocyte-platelet aggregate formation, and as a cause of reperfusion injury in the setting of acute coronary syndromes) (6–8).

The circulating white blood cell (WBC) count has been proposed as one of a few biomarkers of potential current utility for cardiovascular risk prediction (9). Of these proposed inflammatory markers, C-reactive protein (CRP) has been the most extensively studied and clinically applied to date; however, its value as a predictor of risk has recently

been questioned (10,11), and the need to develop and apply additional complementary inflammatory markers of risk is apparent. The WBC count provides an assessment of inflammatory status (5), but this inexpensive and universally obtained test result has not been fully explored or exploited for its predictive ability (9).

A number of observational epidemiologic studies over more than a decade have noted a relationship between WBC count and the risk of symptomatic or fatal coronary heart disease (CHD) (12–20). Further studies have linked an elevated leukocyte count to increased short- and longer-term risk for ischemic events and death in patients presenting with acute coronary syndromes (21–24). Despite these frequent associations of total WBC count with cardiovascular risk, controversy exists about the value of WBC count independent of smoking and gender and the at-risk populations to which it applies. Moreover, little has been published about the predictive ability of specific differential WBC counts to predict CHD risk.

The goal of this study was to further establish the predictive ability of total WBC count for CHD, independent of standard risk factors, and to explore the specific question of which leukocyte subtypes (compartments) carry this increased risk. The study was undertaken in a large cohort of consecutive patients with or at high risk for CHD who underwent coronary angiography and were subsequently followed up long-term.

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#### Abbreviations and Acronyms

AUC	= area under the curve
CAD	= coronary artery disease
CHD	= coronary heart disease
CI	= confidence interval
CK-MB	= creatine kinase-myocardial band
CRP	= C-reactive protein
HR	= hazard ratio
L	= leukocyte
M	= monocyte
MI	= myocardial infarction
N	= neutrophil
Q	= quartile
WBC	= white blood cell

## METHODS

**Study population.** Study patients were drawn from the cardiac catheterization registry of the Intermountain Heart Collaborative Study, a population of patients undergoing coronary arteriography at the LDS Hospital (Salt Lake City, Utah). Patients of unrestricted age and gender provided written informed consent for a blood draw at the time of angiography for use in confidential studies approved by the hospital's institutional review board. Clinical presentation included a stable pattern of chest pain or other clinical indication for coronary angiography (i.e., stable angina, positive stress test result, and so on) or an unstable pattern of chest pain (suggesting unstable angina). Patients with an acute myocardial infarction (MI) during the index hospitalization were excluded from the primary analysis but were included in a secondary analysis.

Of consecutive angiographically studied patients enrolled between 1994 and 2001, 3,227 were found to have blood tested at baseline (on admission, before angiography) for total and differential WBC count, did not present with acute MI (i.e., did not have creatine kinase-myocardial band [CK-MB] >6 mg/dl or CK-MB index >3%), survived hospitalization, had long-term follow-up, and were included in this study. Angiography was scheduled electively for patients with a stable pattern of symptoms (e.g., stable angina) and was scheduled urgently at hospital admission for those with unstable symptoms.

**Follow-up and patient outcomes.** Patients were followed up until death or until December 2001. Deaths were determined from electronic hospital records, State of Utah Health Department records, and national Social Security Administration death records. Patients not listed as deceased in any registry were considered to be alive. Incident MI (after the index hospitalization) was identified by searching the Intermountain Health Care electronic medical records database. In patients with a discharge diagnosis of MI (International Classification of Diseases-9th Revision code), confirmation was further made by identifying a CK-MB >6 mg/dl or a CK-MB index >3% (troponin was

not routinely measured in patients entered in the early years of the database).

**Study variables.** Total WBC count and peripheral differential leukocyte count were assessed using standard Coulter counter techniques (Coulter Gen'S Hematology Analyzer, Beckman Coulter Corp, Hialeah, Florida). The intra-assay coefficient of variation for WBC was 2.5%, and the standard errors of neutrophil (N), lymphocyte (L), and monocyte (M) counts were 3.0%, 2.7%, and 2.7%, respectively. The N, L, and M counts were prospective variables of interest, and the N/L ratio was tested post hoc.

**Other variables examined.** Risk factors, historical items, and physical findings were determined from the physician's report on the demographics page of the LDS Hospital's standard angiographic report form. Study variables other than WBC included age, gender, diabetes, hypertension, hyperlipidemia, smoking, family history of early coronary artery disease (CAD), and number of severely diseased coronary vessels (i.e., zero, one, two, or three coronary arteries with  $\geq 70\%$  stenosis as determined at angiography by the patient's physician). Diabetes was determined by physician report and was based on a fasting blood sugar level  $\geq 126$  mg/dl or use of an antidiabetes medication. Hypertension was physician-reported for systolic blood pressure  $\geq 140$  mm Hg, diastolic blood pressure  $\geq 90$  mm Hg, or use of anti hypertensive agents. Hyperlipidemia was physician-reported for total cholesterol  $\geq 200$  mg/dl, low-density lipoprotein level  $\geq 130$  mg/dl, or use of cholesterol-lowering medication. Family history was self-reported when a first-order relative had suffered cardiovascular death, MI, or coronary revascularization before age 65. Smoking included active or previous (>10 pack-years) tobacco use. Clinical presentation included stable angina (exertional symptoms only, including a positive stress test result) or unstable angina (progressive symptoms or symptoms at rest). Left ventricular ejection fraction was measured only among 74% of patients, by ventriculography or echocardiogram, and was included in the secondary analysis as a categorical variable for >40%,  $\leq 40\%$ , or missing.

**Statistical considerations.** Patient demographic characteristics are presented as means and standard deviations for continuous variables and as proportions (percentages) for categorical variables. Simple two-group comparisons used chi-square for categorical and *t*-test statistics for continuous variables. Because WBC and differential counts were non-normally distributed, these variables are presented as geometric mean with 25th and 75th percentile ranks and are further categorized into quartiles for the primary analyses. Natural logarithmic transformation was found to normalize the distributions. All statistical comparisons of WBC and differential counts used natural logarithmic-transformed WBC variables. Time-to-event analyses were performed using univariable and multivariable (forced entry or backward stepwise conditional) Cox regression analysis. Conditional entry into the regression model was based on the status of a variable as a confounder of the WBC variables,

**Table 1.** Baseline Characteristics (Proportions [%], Averages [Mean ± SD], or Medians)

Characteristic	Overall (N = 3,227)	No Event (N = 2,749)	Event (N = 478)	p Value
Age (yrs)	63 ± 14	61 ± 14	69 ± 13	<0.001
Gender (male)	63%	63%	63%	0.97
Hypertension	50%	50%	49%	0.62
Hyperlipidemia	42%	44%	33%	<0.001
Diabetes	17%	16%	21%	0.001
Smoking	17%	18%	16%	0.36
Family history	31%	32%	24%	<0.001
Unstable angina	29%	31%	21%	<0.001
Diseased vessels				
0	35%	36%	31%	
1	23%	23%	26%	
2	18%	18%	19%	
3	23%	22%	24%	0.06

\*Statistical comparisons are from 2 degrees of freedom analysis of variance or 2 to 6 degrees of freedom Pearson chi square tests.

and its removal was based on the criterion of  $p > 0.15$  for the covariate, whereas forced entry was used for variables that were independently significant or had a confounding effect (association of covariate with WBC variable and >10% change in regression coefficient). Because of multicollinearity, WBC count and its subcompartments were entered in different models. Colinearity diagnostics were also assessed between subcompartments. The primary end point was the first occurrence of MI or death after hospital discharge. Nominal significance was taken as a two-tailed  $p$  value  $\leq 0.05$ .

## RESULTS

**Study population.** The study population consisted of 3,227 angiographically studied high-risk patients (Table 1). The mean age of the patients was 63 years; 63% were male, 50% were hypertensive, 42% were hyperlipidemic, 17% were smokers, and 17% were diabetic; CAD was found to be present in 65%.

**Baseline WBC counts.** Total and differential subtype WBC counts were nonnormally distributed. Baseline values are presented as geometric means with 25th and 75th percentile ranks and as quartiles in Table 2.

**Univariable prediction of death/MI.** A total of 478 (14.8%) patients died (N = 294), had a nonfatal MI event (N = 219), or both by the time of the last follow-up, which averaged 3.5 years (Table 1). In univariable analysis, an increased hazard ratio (HR) of death/MI was associated

with the fourth (vs. first) quartile (Q) total WBC (HR = 1.4,  $p < 0.01$ ), N (HR = 2.1,  $p < 0.001$ ), and M counts (HR = 1.4,  $p < 0.01$ ); reduced risk with L count (HR = 0.41,  $p < 0.001$ ); and increased risk with N/L ratio (HR = 2.7,  $p < 0.001$ ) (Fig. 1). Similarly, for absolute counts (natural log-transformed), an increased HR of death/MI was found for total WBC (HR = 1.42/ln unit,  $p = 0.004$ ), N (HR = 1.69/ln unit,  $p < 0.001$ ), and M (trend) (HR = 1.2/ln unit,  $p = 0.053$ ); reduced risk with L count (HR = 0.59/ln unit,  $p < 0.001$ ); and increased risk with N/L ratio (HR = 1.49/ln unit,  $p < 0.001$ ).

**Results of multivariable analysis.** In multivariable modeling, entering an individual WBC variable, standard risk factors, presentation, and CAD severity, WBC (HR = 1.4,  $p = 0.01$ ) and M (HR = 1.3,  $p < 0.02$ ) were weaker and N (HR = 1.8,  $p < 0.001$ ), L (HR = 0.51,  $p < 0.001$ ), and N/L ratio (HR = 2.2,  $p < 0.001$ ) were stronger independent predictors of death/MI (Fig. 1). When WBC variables were entered together, N/L ratio and M were retained as independent predictors, together with age, diabetes, presentation, CAD severity, and family history (Table 3). Adjustment for ejection fraction caused only a minor change in effect size for N/L ratio (HR = 2.1,  $p < 0.001$ ) and none for M (HR = 1.4,  $p = 0.01$ ). When further adjustment was made for treatment factors by forced entry of interventional treatment (none, percutaneous coronary intervention, bypass surgery) and medical therapy (statin, beta-blocker, converting enzyme inhibitor), no diminution in the multivariable prediction by N/L ratio (HR = 2.4, 95% CI 1.8 to 3.2,  $p < 0.001$ ) or monocyte count (HR = 1.4, 95% CI 1.1 to 1.7,  $p = 0.01$ ) was observed.

The N/L ratio strongly predicted death alone or MI alone as outcome variables. The multivariable HR for death of the N/L ratio was 3.0 (95% CI 2.1 to 4.3,  $p < 0.001$ ). The Q4/1 N/L ratio also predicted an increased relative risk of incident MI alone, 1.6 (95% CI 1.1 to 2.4,  $p = 0.026$ ).

**Additional analyses and incremental risk.** Risk associations of WBC subtypes also were assessed in a more restricted population limited to patients with significant angiographic CAD ( $\geq 70\%$  stenosis, N = 2,292) as well as an expanded population that included patients in the angiographic database with a diagnosis of acute MI (N = 4,625). Risk associations persisted in both of these analyses (Table 4). In an additional analysis, the N/L ratio also predicted increased risk among high-risk patients free from occlusive angiographic CAD (Table 4).

To address the question of incremental predictive ability of WBC parameters, the area under the curve (AUC) for risk using the standard independent risk factors (Table 3) was first calculated: the AUC was 0.675. When the total WBC count was added to this multivariable predictive model, the AUC increased modestly to 0.689. When the N/L ratio and M quartiles were substituted for total WBC count, the AUC increased notably to 0.718 ( $p < 0.001$ ). This AUC increment (0.038) compares favorably to that obtained with high-

**Table 2.** Baseline White Blood Cell Counts

White Blood Cells/ $10^3/\mu\text{l}$	Geometric Mean (25th, 50th, 75th Percentiles)
Total white blood cell count	7.82 (6.2, 7.6, 9.4)
Neutrophils	5.15 (3.8, 5.0, 6.6)
Monocytes	0.55 (0.4, 0.6, 0.7)
Lymphocytes	1.56 (1.2, 1.7, 2.2)
Neutrophil/lymphocyte ratio	3.29 (1.96, 2.87, 4.71)

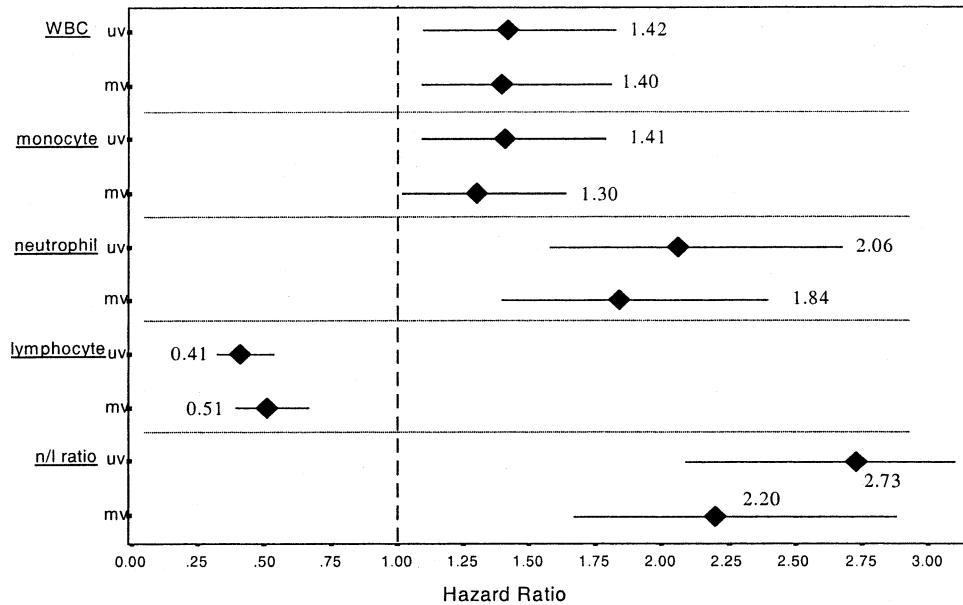


Figure 1. Univariate (uv) and multivariate (mv) analysis of quartile 4 versus 1 white blood cell (WBC) subtypes. N/L = neutrophil/leukocyte.

sensitivity CRP (i.e., 0.015 in the Monitoring Cardiovascular Disease [MONICA] study) (25).

**DISCUSSION**

**Summary of study findings.** The primary findings of this study are that a simple, relatively inexpensive, almost universally obtained test (the WBC count with differential) contains important risk information that is not only significant on its own but also is incremental to standard clinical cardiovascular risk factors. Further, the study found that greater predictive ability is contained within the WBC differential than is represented by the total WBC count alone. The incremental improvement in risk prediction achieved with the WBC differential was similar to or greater than that reported for the widely used inflammatory marker high-sensitivity CRP (25).

The predictive value of the WBC count has been reported in other populations (12-20), but the optimization of risk prediction by use of the WBC differential is a unique contribution of this study. We found that a relatively high N count, a relatively low L count, and, more modestly, an elevated M count account for WBC count risk. An elevated

N/L ratio, explored post hoc, proved to be the most powerful single WBC count predictor, with Q4 ratios (>4.7, or about 5 or more, for convenience) elevating risk three-fold, compared with Q1 ratios (<2). The results were robust: for even higher-risk populations consisting entirely of patients with angiographic CAD, or for our full angiographically studied population, including patients with acute MI, the Q4 N/L ratio remained strongly predictive. A substantial proportion of this WBC-subtype-related risk persisted in multivariable analyses. Given the routine acquisition of WBC counts, it also can be argued that other markers of inflammation should be adjusted for WBC risk information, rather than vice versa, when assessing incremental predictive ability.

**Literature comparisons.** A number of epidemiologic observational studies have reported an association between elevated WBC counts and symptomatic or fatal CHD (12-20). Additional studies in patients presenting with acute coronary syndromes have linked elevated leukocyte count to increased short-term and longer-term risk for fatal and nonfatal ischemic events (21-24). Despite this, not every study has found this association to be independent of other risk factors, such as smoking and gender (15,26). Furthermore, few have investigated which differential subtype carries this risk (16,26-28). A French study found an increased monocyte count to carry increased risk, whereas a British and two Asian studies reported that high N counts predicted greater risk (16,26,27). The WBC differential added to CK-MB determination in diagnosing acute MI in one study (29).

These studies were primarily in subjects at primary CHD risk. Studies of differential WBC risk in higher-risk, non-infarct, primary and secondary CHD risk cohorts, and in patients evaluated and treated in a contemporary U.S. health

Table 3. Multivariable Model for Death/Myocardial Infarction

Variables	Hazard Ratio (95% CI)	p Value
Neutrophil/lymphocyte ratio (Q4 vs. Q1)	2.2 (1.7-2.9)	<0.001
Monocytes (Q4 vs. Q1)	1.4 (1.1-1.6)	0.007
Age (per decade)	1.4 (1.3-1.5)	<0.001
Diabetes	1.5 (1.2-1.8)	<0.001
Coronary artery disease severity (per number of diseased vessels)	1.2 (1.1-1.4)	0.001
Unstable angina	0.77 (0.62-0.95)	0.01
Family history	0.83 (0.68-1.03)	0.09

CI = confidence interval; Q = quartile.

**Table 4.** Univariable Results for Neutrophil/Lymphocyte Ratio (Q4 vs. Q1) in Primary and Three Secondary Interest Populations

Population	# D-MI/Total N	Hazard Ratio (95% Confidence Interval)	p Value
All patients, except acute MI	478/3227	2.7 (2.1-3.6)	<0.001
No CAD patients	96/935	3.3 (1.8-5.9)	<0.001
CAD patients, no acute MI	382/2292	2.5 (1.9-3.4)	<0.001
All patients, including MI	769/4625	2.0 (1.7-2.5)	<0.001

CAD = coronary artery disease; D = death; MI = myocardial infarction; Q = quartile.

care system have not been reported to our knowledge. Our study addressed this gap and found that N count, and especially N/L ratio, predicted increased risk.

**Mechanistic considerations.** It has been long known that myocardial injury (acute MI) is followed by neutrophilia, the early appearance of neutrophils within the infarct zone with heavy infiltration by 1 to 3 days, followed by infarct healing and replacement fibrosis. Recent human trials using intracoronary transfer of autologous bone marrow, rich in hematopoietic and mesenchymal precursor cells, have suggested a benefit after MI (30,31) and have postulated to represent augmentation of intrinsic reparative processes. Acute MI was excluded in our primary analysis, but neutrophilia also could mark an augmented, more chronic adaptive response to ischemia (e.g., vasculogenesis). Neutrophilia also might indicate maladaptive processes: circulating leukocyte-platelet aggregates appear in acute coronary syndromes and might facilitate vascular plugging and infarct extension (6,7,21,32). Reperfusion injury (8), occurring spontaneously or after reperfusion therapy, has been postulated to be leukocyte mediated, and trials of inhibitors of leukocyte adhesion and transmigration have been undertaken, albeit without clinical success to date (33,34).

That the cardiovascular risk of elevated WBC counts is carried by increased circulating neutrophil counts and decreased total mononuclear cell counts (lymphocytes plus monocytes) is not intuitively obvious. Indeed, atherosclerotic plaque is characterized by infiltrates of monocytes/macrophages and lymphocytes, which have transmigrated from the vascular space into subendothelial layers of large and medium-sized arteries (3,4,35,36). If circulating WBC fractions were to maintain equilibrium with plaque fractions, then a parallel increase in absolute or proportionate mononuclear cell counts at the expense of a polymorphonuclear cell count could be postulated. However, this is not what was observed: we found that relative neutrophilia together with lymphopenia was associated with increased cardiovascular risk.

These observations support evidence that neutrophils are involved in ischemic cardiovascular disease, particularly its acute phases. Increased expression of neutrophil and monocyte adhesion molecules and other markers (e.g., CD11b/CD18) of polymorphonuclear and monocyte activation in the peripheral blood has been described in patients with acute coronary syndromes and ischemic heart disease (37,38). Recently, neutrophil invasion of atherosclerotic

plaque has been directly visualized in an animal model (39) and has been shown in the culprit clinical plaques in patients with acute coronary syndromes (40). Neutrophils can facilitate plaque disruption by releasing superoxide radicals, proteolytic enzymes, and arachidonic acid metabolites. In addition, together with platelets, they can aggregate when stimulated, contribute to the plugging of microvessels, and promote myocardial ischemia/infarction (6,7,21,24,32).

**Study limitations.** This study was prospective in patient enrollment and follow-up but was observational in nature and subject to limitations, including selection bias and uncorrected confounding. A small proportion of incident MIs, i.e., those treated outside of the Intermountain Health Care system, might have been missed, leading to an underestimate of MI risk. A mechanistic explanation for our findings is not provided by our observational data and must be explored separately. The study entailed an angiographic population, and results might differ in some respects for other coronary-risk-prone populations; replication of these results in independent populations is encouraged. An association does not prove causality; hence, a pathological role for elevated WBC in CHD and acute coronary syndromes has not been shown.

**Conclusions and implications.** Total WBC count was found to be an independent predictor of death/MI in a large, prospectively followed cohort of patients with a high risk of incident coronary events, but greater predictive value was provided by high N (Q4  $>6.6 \times 10^3/\mu\text{L}$ ) or low L counts. Optimal risk prediction was given by the N/L ratio, with Q4 versus Q1 ( $>4.71$  vs.  $<1.96$ ) ratio, increasing hazard by 2.2-fold. These findings provide important insights into CAD prognosis and pathogenesis using a routinely measured set of data. If validated, the finding of an abnormal (Q4) value for the WBC differential (e.g., N count or N/L ratio) might prompt more aggressive risk factor evaluation and therapy for patients with CAD, similar to the modification of risk assessment and treatment currently recommended for the finding of an elevated high-sensitivity CRP value (9).

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