Journal of the American College of Cardiology
© 2001 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 38, No. 6, 2001
ISSN 0735-1097/01/$20.00
PII S0735-1097(01)01613-8

The Association Between White Blood Cell Count and Acute Myocardial Infarction Mortality in Patients ≥65 Years of Age: Findings From the Cooperative Cardiovascular Project

Hal V. Barron, MD, FACC,*† Steven D. Harr, MD,* Martha J. Radford, MD, FACC,‡§‖
Yongfei Wang, MS,‡ Harlan M. Krumholz, MD, FACC‡§‖¶

San Francisco, California; and New Haven and Middletown, Connecticut

OBJECTIVES The purpose of the study was to examine the association between white blood cell (WBC) count on admission and 30-day mortality in patients with acute myocardial infarction (AMI).

BACKGROUND Elevations in WBC count have been associated with the development of AMI and with long-term mortality in patients with coronary artery disease. However, the relationship between WBC count and prognosis following AMI is less clear.

METHODS Using the Cooperative Cardiovascular Project database, we evaluated 153,213 patients ≥65 years of age admitted with AMI.

RESULTS An increasing WBC count is associated with a significantly higher risk of in-hospital events, in-hospital mortality and 30-day mortality. Relative to those patients in the lowest quintile, patients in the highest quintile were three times more likely to die at 30 days (10.3% vs. 32.3%; $p < 0.001$). After adjustment for confounding factors, WBC count was found to be a strong independent predictor of 30-day mortality (odds ratio = 2.37; 95% confidence interval 2.25 to 2.49, $p = 0.0001$ for the highest quintile of WBC count).

CONCLUSIONS White blood cell count within 24 h of admission for an AMI is a strong and independent predictor of in-hospital and 30-day mortality as well as in-hospital clinical events. Although the mechanism of the association remains speculative, the results of this study have important clinical implications for risk-stratifying patients with AMI. (J Am Coll Cardiol 2001;38: 1654–61) © 2001 by the American College of Cardiology

Inflammation is thought to play a key role in the development of coronary artery disease as well as in the pathogenesis of coronary thrombosis (1). Elevations in white blood cell (WBC) count have been associated with development of coronary heart disease (2–9) as well as with long-term mortality in patients with known coronary artery disease (10–12). Krumholz et al. recently demonstrated (13) that WBC count was a strong independent predictor of mortality in acute myocardial infarction (AMI) as well. They analyzed data on 82,359 patients ≥65 years of age admitted with AMI to 2,401 hospitals and developed a model that predicted 30-day mortality (13). Of the 73 variables of candidate predictors examined, the seven most important variables were age, cardiac arrest, anterior or lateral location of myocardial infarction, systolic blood pressure, serum creatinine, congestive heart failure and WBC count. The purpose of the present analysis is to better characterize the relationship between the WBC count and 30-day mortality and specifically examine this association in many different subgroups. A greater understanding of this relationship could be helpful in risk stratifying patients with AMI, as WBC count is inexpensive and routinely measured on admission. Furthermore, such an association, if present, could lend epidemiologic support to the hypothesis that leukocytes are involved in myocardial damage following reperfusion therapy (6,14), as well as support the findings from an angiographic study in which an increased WBC count was associated with a hypercoagulable state (15).

Thus, the purpose of the present study was to explore the association between WBC count and 30-day mortality following AMI in a very large, geographically diverse cohort of patients ≥65 years of age. In addition, we sought to compare the impact of WBC count on 30-day mortality by age, gender, smoking status and use of reperfusion therapy.

From the *Departments of Epidemiology and Biostatistics and Medicine (Cardiology), University of California, San Francisco, San Francisco, California; †Department of Medical Affairs, Genentech Inc., South San Francisco, California; ‡Section of Cardiovascular Medicine, Department of Medicine, Yale University School of Medicine, New Haven, Connecticut; §Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, Connecticut; ‖Qualidigm, Middletown, Connecticut; and ¶Section of Health Policy and Administration, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut. The analyses upon which this publication is based were performed under Contract Number 500-96-P549, entitled "Utilization and Quality Control Peer Review Organization for the State of Connecticut," sponsored by the Health Care Financing Administration, Department of Health and Human Services. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products or organizations imply endorsement by the U.S. Government. The author assumes full responsibility for the accuracy and completeness of the ideas presented. This article is a direct result of the Health Care Quality Improvement Program initiated by the Health Care Financing Administration, which has encouraged identification of quality improvement projects derived from analysis of patterns of care, and therefore required no special funding on the part of this contractor. Ideas and contributions to the author concerning experience in engaging with issues presented are welcomed.

Manuscript received March 2, 2001; revised manuscript received July 16, 2001, accepted August 15, 2001.

Abbreviations and Acronyms

AMI	= acute myocardial infarction
CCP	= Cooperative Cardiovascular Project
CI	= confidence interval
CK	= creatine phosphokinase
ICD-9-CM	= International Classification of Diseases, 9th Revision, Clinical Modification
OR	= odds ratio
TIMI	= Thrombolysis In Myocardial Infarction
WBC	= white blood cell

METHODS

Data sources. THE COOPERATIVE CARDIOVASCULAR PROJECT (CCP) DATABASE. The CCP database has been described previously (16). In brief, it includes more than 200,000 patients hospitalized across the country with a principal discharge diagnosis of AMI (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] 410) in 1994 and 1995. Trained technicians abstracted predefined demographic, clinical and treatment variables from copies of the hospital records and entered them directly into a computer database using interactive software. For all CCP samples, >3,000 records were reabstracted, with overall variable agreement of 95%.

MEDICARE ENROLLMENT DATABASE. The Medicare Enrollment Database contains accurate records of the vital status of Medicare beneficiaries, but entries from the social security records include unverified dates of death that were recorded as the last day of the month when the exact date from a death certificate was unavailable. We eliminated cases with unverified dates of death from the mortality analysis if mortality could not be classified with certainty at the time of evaluation, as described in an earlier report (17). We found unverified dates of death for 325 patients in our sample (0.1% of such patients or 0.8% of deaths).

Study sample. The overall study sample was restricted to patients ≥65 years of age who had confirmed AMI, as previously reported (16), and who were not received in transfer from another institution (Table 1). To avoid counting patients more than once, we included only a patient's first confirmed AMI hospitalization in the CCP database.

Table 1. Study Logic (Inclusions and Exclusions)

Total sample	234,769
Exclusions*	
Age < 65 yrs	17,593 (7.5%)
AMI not confirmed	31,186 (13.3%)
Transfer in	34,409 (14.7%)
Repeat hospitalizations†	23,773 (10.6%)
WBC count unknown or out of range‡	12,893 (5.5%)
Terminal illness or metastatic cancer	4,617 (2.0%)
Unverified death	325 (0.1%)
Discharge date beyond study period	77 (0.0%)
Study sample	153,213

*Not mutually exclusive; †repeat hospitalizations occurred in 22,187 patients; ‡Range is (0.5 to 50) in thousands.

We also excluded patients with WBC count <500 mm^3 or >50,000 mm^3, patients whose WBC value was missing and patients with a terminal illness or metastatic cancer.

Study variables. The main outcome variable of the study was mortality within 30 days from admission. This information was ascertained from the Medicare Enrollment Database, which was derived from the Master Beneficiary Record from Social Security Administration data, a valid source of vital status (18). Other outcomes were in-hospital mortality and in-hospital events.

In our analysis, the cohort of patients was divided into five groups based on the quintiles of their admission WBC count. White blood cell count was defined as the first value documented in the medical record within 24 h of admission. If no WBC count was recorded, the closest value within 24 h before admission was used.

Missing observations exceeded 5% for the following candidate predictor variables: angina, time since chest pain started, evidence of heart failure or pulmonary edema on chest x-ray, location of AMI, ventricular tachycardia, height, weight, albumin, atrial fibrillation/flutter, heart block on electrocardiogram, left or right bundle branch block and paced rhythm. Values for continuous variables outside the following ranges were considered implausible and set to missing: respiratory rate >80 breaths/min, systolic blood pressure >300 mm Hg, diastolic blood pressure >150 mm Hg, serum urea nitrogen >200 mg/dl, creatinine >25 mg/dl, and albumin >20 mg/dl. Observations with missing values for myocardial infarction location and radiographic evidence of heart failure were set to null. Alternative methods for controlling missing values, such as including dummy variables indicating missing observations or restricting the analysis to observations without any missing values, did not substantially affect model estimates, calibration or our conclusions.

Statistical analysis. First, we sought to examine bivariate associations of patient clinical and demographic characteristics with WBC count quintiles, and then we described the impact of WBC count quintiles on outcomes. Continuous variables were dichotomized or categorized based on clinical significance as shown in the tables. Missing values were coded as characteristics not present. Statistical significance of associations was tested using the chi-square statistic.

The associations between WBC count quintiles and 30-day mortality from admission was evaluated using logistic regression models. Clinical characteristics previously reported to be associated with AMI mortality were included in the models. These characteristics included gender, age, race, medical history (hypertension, diabetes, smoking, dementia, AMI, heart failure, coronary bypass grafting, percutaneous transluminal coronary angioplasty, stroke, chronic obstructive pulmonary disease, peripheral vascular disease/claudication, angina/chest pain), admission characteristics (cardiac arrest, shock, hemorrhage, cardiomegaly, atrial fibrillation/flutter, ST elevation, left and right bundle

Table 2. Baseline Characteristics Among WBC Count Quintile (%)*

Characteristic (WBC count range)	Total	Quintile 1 (<7.5)	Quintile 2 (7.5–9.1)	Quintile 3 (9.1–10.9)	Quintile 4 (11.0–13.6)	Quintile 5 (>13.6)
Demographics						
Age ≥75 yrs	56%	56%	54%	54%	55%	59%
Gender: Female	49%	45%	47%	49%	50%	55%
Race: White	90%	86%	90%	91%	92%	92%
Medical history						
Congestive heart failure	21%	18%	18%	19%	22%	29%
Myocardial infarction	29%	31%	30%	29%	28%	28%
Diabetes mellitus	31%	25%	28%	30%	33%	38%
Hypertension	62%	61%	61%	62%	63%	63%
CVA/stroke	14%	12%	12%	13%	15%	18%
Angina/chest pain	45%	50%	48%	46%	45%	39%
Cigarette smoker	15%	10%	13%	16%	18%	18%
CABG surgery	13%	16%	15%	14%	12%	10%
PTCA	7%	8%	8%	7%	6%	5%
PVD/claudicating	10%	9%	9%	10%	11%	12%
COPD	20%	16%	17%	20%	22%	26%
Dementia/Alzheimer's disease	6%	5%	5%	5%	6%	9%
Clinical symptoms						
Cardiac arrest	4%	2%	2%	3%	4%	7%
Congestive heart failure	60%	52%	55%	58%	64%	74%
Angina ≥60 min after arrival	37%	39%	40%	40%	38%	27%
Temperature >100.4°F	2%	1%	1%	1%	2%	4%
Heart rate >100 beats/min	26%	16%	18%	22%	28%	43%
Respiratory rate >25 breaths/min	20%	11%	13%	16%	22%	37%
ECG characteristics						
ST elevation	29%	24%	28%	30%	32%	33%
LBBB	10%	8%	9%	9%	10%	14%
RBBB	12%	11%	12%	12%	13%	13%
Atrial fibrillation/flutter	21%	18%	19%	20%	23%	27%
Heart block, 2nd or 3rd	4%	3%	4%	4%	5%	6%
Location of MI						
Anterior	46%	42%	44%	46%	48%	51%
Lateral	29%	25%	27%	29%	31%	31%
Posterior	10%	9%	10%	10%	10%	9%
Inferior	47%	44%	46%	48%	48%	47%
Other	9%	9%	9%	9%	10%	9%
Laboratory data						
Albumin >3 g/dl	68%	68%	69%	68%	68%	65%
Creatinine > 2.25 or BUN > 40 mg/dl	10%	7%	7%	8%	11%	18%
Sodium < 130 mmol	3%	2%	2%	2%	3%	4%
Peak CK ≥ 1,260	25%	17%	21%	25%	29%	32%
Treatments						
Aspirin	79%	82%	83%	81%	79%	68%
ACE inhibitor	42%	37%	39%	42%	45%	49%
Reperfusion therapy: PTCA	11%	12%	12%	12%	10%	8%
Reperfusion therapy: TTx	22%	21%	23%	25%	24%	17%
Beta-blocker	49%	53%	53%	52%	49%	39%

*$p < 0.001$ for all variables listed.

ACE = angiotensin-converting enzyme; BUN = blood urea nitrogen; CABG = coronary artery bypass graft surgery; CK = creatine phosphokinase; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; ECG = electrocardiogram; LBBB = left bundle branch block; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; PVD = peripheral vascular disease; RBBB = right bundle branch block; TTx = thrombolytic therapy.

branch block, old AMI, heart block, systolic and diastolic blood pressure, heart rate, respiratory rate, creatinine, blood urea nitrogen, sodium, glucose, albumin), treatments administered (aspirin, angiotensin-converting enzyme inhibitor, beta-blocker, primary percutaneous transluminal coronary angioplasty, and thrombolytic therapy), and peak creatinine phosphokinase (CK) values. Factors other than WBC count that were independently associated with 30-day mortality were identified using a logistic regression model and stepwise selection method (entry significance level = 0.0005 and exit significance level = 0.0001). Subgroup analyses were also performed in men and women and in various age groups (65 to 74 years, 75 to 84 years and ≥85 years).

Odds ratios (OR) and 95% confidence intervals (CI) were calculated using logistic regression models with and without adjusting for confounding effects. All these analyses were done by using PC-SAS 6.12 software 1989 to 1996 (SAS Institute Inc., Cary, North Carolina).

Table 3. Outcomes in WBC Count Groups

WBC	Range	Total No.	In-Hospital Event* No. (%)†	In-Hospital Death No. (%)†	Death at 30 Days No. (%)†
Quintile 1	(0.6–7.5)	30,639	19,032 (62.12)	2,346 (7.66)	3,148 (10.27)
Quintile 2	(7.5–9.1)	31,267	19,748 (63.16)	2,981 (9.53)	3,947 (12.62)
Quintile 3	(9.1–10.9)	30,388	19,664 (64.71)	3,796 (12.49)	4,894 (16.11)
Quintile 4	(11.0–13.6)	30,154	20,759 (68.84)	4,944 (16.40)	6,230 (20.66)
Quintile 5	(13.6–49.8)	30,765	23,573 (76.63)	8,436 (27.26)	9,943 (32.32)
Total	(0.6–49.8)	15,213	102,777 (67.08)	22,453 (14.65)	28,162 (18.38)

*Events included evidence of bradycardia, shock or heart failure during the index admission; †there were significant differences among quintiles and increasing trend among quintiles.
WBC = white blood cell.

RESULTS

There were a total of 153,213 patients included in this analysis. Table 1 reports the development of the study sample. Table 2 describes the baseline, demographic and clinical characteristics of the cohort, divided into quintiles, as a function of their WBC count. Patients in the highest quintile were older, more likely women and in general had more cardiac risk factors and more comorbidities than patients did in the lowest quintile.

The overall in-hospital mortality and 30-day mortality rates were 14.7% and 18.4% respectively. There was a significantly higher risk of in-hospital events, in-hospital mortality and 30-day mortality with increasing WBC count (Table 3). Relative to patients in the lowest quintile, patients in the highest quintile were three times more likely to die at 30 days (10.3% vs. 32.3%; $p < 0.001$). Approximately one-third of the patients had an elevated WBC count (defined as >12 mm^3) on admission (Table 4). These patients were more than twice as likely to die as those patients with a normal WBC count (defined as 6 to 12) and almost three times as likely as those with a low WBC count (defined as <6). The increased mortality in patients with higher WBC counts was seen in all subgroups examined (Table 5 and Fig. 1).

A multivariate model was developed to identify all the predictors of 30-day mortality. All variables in Table 2 were included in the logistic regression analysis and entered in a stepwise method. After adjustment for these factors, WBC count was found to be a strong independent predictor of 30-day mortality (Tables 6 and 7). Relative to those patients in the lowest quintile, there was a 2.4-fold increase in the odds of death in patients in the highest quintile (OR = 2.37; 95% CI 2.25 to 2.49, $p = 0.0001$). This effect did not differ in men versus women or in patients aged <75 years compared with those aged >75 years (Tables 6 and 7).

Table 4. Outcomes in WBC Groups

WBC	Total No.	In-Hospital Death (%)*	Died in 30 Days (%)*
<6	10,209	786 (7.70)	1,022 (10.01)
6–12	96,637	10,449 (10.81)	13,656 (14.13)
>12	46,367	11,218 (24.19)	13,484 (29.08)
Total	153,213	22,453 (14.65)	28,162 (18.38)

*$p < 0.001$.
WBC = white blood cell.

DISCUSSION

In the present study we observed a strong independent association between increasing WBC count and 30-day mortality. This effect was present in both men and women, was observed in all age groups and was seen in patients who received reperfusion therapy as well as those who did not. Patients with a WBC count in the highest quintile had a 30-day mortality rate that was >3 times higher than that of patients with a WBC count in the lowest quintile.

In 1974, Friedman et al. (2) first described the association between WBC count and coronary heart disease. These investigators found that an increased WBC count increased the risk of developing a first AMI. Numerous other studies subsequently confirmed this observation (3–9). Schlant et al. (11) were the first to document an elevation in WBC count as a predictor of all-cause mortality in patients who survived an AMI. Others also confirmed these findings (10,12). In none of the above studies, however, was the short-term prognostic importance of the WBC count measured during the acute phase of the AMI assessed.

Furman et al. (19) examined the association between WBC count and mortality using data from the Worcester Heart Attack Study. Consistent with the findings from the present study, these investigators found that WBC count was significantly associated with in-hospital survival. Relative to those patients with the lowest WBC count, patients in the highest quintile of WBC count had 71% greater odds of dying from their AMI (OR = 1.71, 95% CI = 1.14 to 2.58). More recently, Barron et al. (15) examined the association between WBC count and angiographic findings in the Thrombolysis In Myocardial Infarction (TIMI) 10A and TIMI 10B data set. They found that patients with a closed infarct-related artery at 60 and 90 min had a higher WBC count than patients with an open artery. Furthermore, angiographically apparent thrombus was associated with a higher WBC count. The present study extends these observations in a much larger and less selective data set and clarifies that the response is graded and that there are no interactions between age and gender.

Table 5. Thirty-Day Mortality in Patients With AMI by WBC Count Quintile (%)

Subgroup	Quintile 1 (<7.5)	Quintile 2 (7.5–9.1)	Quintile 3 (9.1–10.9)	Quintile 4 (11.0–13.6)	Quintile 5 (>13.6)
Age ≥ 75 yrs	13%	17%	21%	26%	38%
Race: white	10%	12%	16%	21%	33%
Diabetes mellitus	11%	14%	17%	22%	33%
Cigarette smoker	9%	10%	12%	15%	24%
Prior stroke	14%	17%	22%	27%	39%
Angina/chest pain	9%	12%	15%	19%	30%
Prior MI	11%	13%	17%	22%	31%
Congestive heart failure	17%	20%	24%	27%	35%
PVD/claudicating	14%	16%	20%	23%	33%
Hypertension	10%	12%	16%	20%	30%
COPD	12%	14%	16%	20%	30%
CABG surgery	10%	12%	15%	21%	32%
PTCA	7%	9%	11%	13%	24%
Angina ≥ 60 min after arrival	9%	12%	14%	19%	28%
Temperature >100.4°F	18%	19%	20%	23%	34%
Albumin > 3 g/dl	9%	11%	15%	19%	29%
Creatinine > 2.5 mg/dl or BUN > 40 mg/dl	28%	29%	35%	38%	49%
ST elevation	13%	14%	18%	22%	35%
LBBB	18%	20%	24%	30%	38%
RBBB	16%	19%	24%	33%	44%
Aspirin	8%	10%	12%	16%	23%
ACE inhibitor	11%	13%	16%	19%	25%
Beta-blocker	7%	9%	12%	15%	23%

$p < 0.001$ for all variables listed.
AMI = acute myocardial infarction; other abbreviations as in Table 2.

The role of neutrophils in animal models of ischemia-reperfusion. The data from the current study as well as those from the study by Barron et al. (15) are consistent with the fact that WBCs may in some way be linked to the cause of the increased mortality (i.e., WBCs are in the causal pathway). In animal models of ischemia-reperfusion, neutrophils appear to lead to infarct expansion (20). In a canine model of AMI, neutrophil depletion was associated with a marked reduction in infarct size (21). The mechanism by which neutrophils cause this damage is unclear. Engler et al. (14) and others have documented that reperfusion following prolonged ischemia leads to progressive leukocyte capillary plugging and the "no reflow" phenomenon. This plugging likely results in part from neutrophils binding to the ischemic endothelium via the leukocyte integrin CD11b/CD18 (Mac-1) receptor (22). Three animal studies have demonstrated that treatment with an antibody to the CD18 receptor on neutrophils reduces infarct size (23–25). Furthermore, a receptor knockout experiment in rodents also suggested a role for neutrophils in increasing infarct size (26).

Another mechanism by which WBCs could cause increased mortality is by inducing a hypercoagulable state. We have recently reported that an increased WBC count was associated with lower rates of coronary patency and increased thrombus burden in patients with AMI treated with

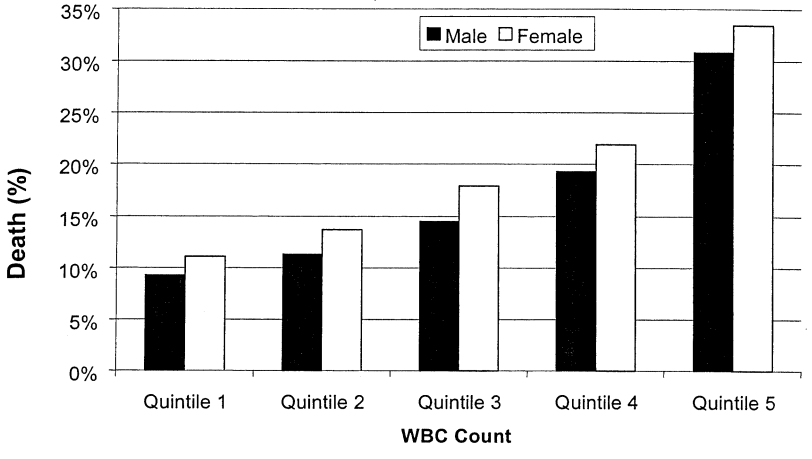

Figure 1. Thirty-day mortality rate by white blood cell (WBC) count quintiles and genders.

Table 6. Association Between WBC Count Quintile and 30-Day Mortality by Age and Gender

	Death		Unadjusted			Adjusted*		
	n	%	OR	95% CI	p Value	OR	95% CI	p Value
Overall								
Quintile 1	3,148	10.27	1.000			1.000		
Quintile 2	3,947	12.62	1.262	(1.200–1.326)	0.0001	1.217	(1.154–1.284)	0.0001
Quintile 3	4,894	16.11	1.676	(1.598–1.759)	0.0001	1.477	(1.402–1.556)	0.0001
Quintile 4	6,230	20.66	2.274	(2.171–2.382)	0.0001	1.751	(1.664–1.842)	0.0001
Quintile 5	9,943	32.32	4.170	(3.991–4.357)	0.0001	2.369	(2.253–2.490)	0.0001
Men								
Quintile 1	1,554	9.25	1.000			1.000		
Quintile 2	1,878	11.29	1.249	(1.163–1.341)	0.0001	1.192	(1.104–1.286)	0.0001
Quintile 3	2,259	14.44	1.657	(1.547–1.775)	0.0001	1.413	(1.312–1.522)	0.0001
Quintile 4	2,889	19.30	2.347	(2.197–2.507)	0.0001	1.732	(1.610–1.863)	0.0001
Quintile 5	4,305	30.89	4.388	(4.118–4.675)	0.0001	2.358	(2.193–2.535)	0.0001
Women								
Quintile 1	1,594	11.52	1.000			1.000		
Quintile 2	2,069	14.14	1.265	(1.179–1.356)	0.0001	1.244	(1.154–1.341)	0.0001
Quintile 3	2,635	17.87	1.670	(1.562–1.786)	0.0001	1.534	(1.427–1.650)	0.0001
Quintile 4	3,341	22.01	2.166	(2.031–2.311)	0.0001	1.766	(1.645–1.897)	0.0001
Quintile 5	5,638	33.50	3.868	(3.638–4.112)	0.0001	2.386	(2.226–2.558)	0.0001
Age <75 yrs								
Quintile 1	855	6.29	1.000			1.000		
Quintile 2	1,100	7.71	1.245	(1.135–1.366)	0.0001	1.183	(1.072–1.306)	0.0008
Quintile 3	1,406	10.04	1.664	(1.523–1.818)	0.0001	1.403	(1.275–1.543)	0.0001
Quintile 4	1,881	13.71	2.369	(2.177–2.578)	0.0001	1.724	(1.572–1.891)	0.0001
Quintile 5	3,061	24.44	4.821	(4.449–5.225)	0.0001	2.394	(2.186–2.622)	0.0001
Age ≥75 yrs								
Quintile 1	2,293	13.46	1.000			1.000		
Quintile 2	2,847	16.75	1.294	(1.219–1.373)	0.0001	1.236	(1.160–1.317)	0.0001
Quintile 3	3,488	21.28	1.739	(1.641–1.842)	0.0001	1.522	(1.430–1.619)	0.0001
Quintile 4	4,349	26.46	2.314	(2.188–2.447)	0.0001	1.781	(1.675–1.893)	0.0001
Quintile 5	6,882	68.82	3.896	(3.695–4.109)	0.0001	2.369	(2.231–2.516)	0.0001

*Adjusted by the confounding risk factors.
CI = confidence interval; OR = odds ratio; WBC = white blood cell.

thrombolytics (15). It has been hypothesized that this hypercoagulable state may be mediated by an increased expression of tissue factor on leukocytes in the setting of AMI (27). Finally, it is possible that leukocytes release proinflammatory cytokines that cause myocyte dysfunction and necrosis (15).

It is possible that the associations between WBC count and mortality are simply confounded by some unmeasured covariate that reflects the severity of the initial insult. Although we did not directly measure the amount of myocardium at risk or the final infarct size, we did collect information as to whether the patient developed ST segment elevation, the infarct location, the symptom duration, the use of reperfusion therapy, baseline hemodynamic measures and whether the patient developed congestive heart failure. Although there was a weak correlation between WBC count and peak CK ($r = 0.12$), the association between WBC count and death was independent of this and other indirect markers of myocardium at risk and final infarct size. Thus, even though the association between WBC count and mortality may be partly explained by the association with larger infarcts, the present study clearly demonstrates that the WBC count on admission adds important additional information to risk-stratify patients following AMI. One other potential confounding factor is underlying infection. Several findings from this study suggest that this was not the case. First, 96% of the patients in the highest quintile of WBC count did not have an elevated temperature recorded on admission. Furthermore, when we excluded patients who were thought to have pneumonia on admission or who developed pneumonia during their hospitalization, our findings remained identical. Also, because we observed that increasing WBC count was associated with the development of other adverse events such as congestive heart failure, we believe that this is an unlikely explanation for the observed association.

Study limitations. There are several important limitations to the study. First, it is not possible to determine if the WBC count is a risk factor for adverse outcomes or a marker. Second, although we did measure peak CK levels, we did not directly measure several other potentially important indicators of the severity of the AMI, such as infarct size, the degree of ST segment elevation resolution or coronary artery patency. Lastly, our database did not contain information regarding the WBC count differential, which may have contributed important additional information.

Table 7. Association Between WBC Group and 30-Day Mortality by Age and Gender

	Death		Unadjusted			Adjusted*		
	n	%	OR	95% CI	p Value	OR	95% CI	p Value
Overall								
WBC < 6	1,022	10.22	1.000			1.000		
WBC 6–12	13,656	14.13	1.479	(1.383–1.582)	0.0001	1.407	(1.308–1.512)	0.0001
WBC > 12	13,484	29.08	3.686	(3.445–3.944)	0.0001	2.323	(2.157–2.501)	0.0001
Male								
WBC < 6	538	9.71	1.000			1.000		
WBC 6–12	6,426	12.63	1.344	(1.225–1.474)	0.0001	1.235	(1.117–1.365)	0.0001
WBC > 12	5,921	27.45	3.518	(3.203–3.864)	0.0001	2.076	(1.872–2302)	0.0001
Female								
WBC < 6	484	10.37	1.000			1.000		
WBC 6–12	7,230	15.80	1.623	(1.472–1.789)	0.0001	1.604	(1.444–1.781)	0.0001
WBC > 12	7,563	30.50	3.794	(3.440–4.184)	0.0001	2.608	(2.344–2.902)	0.0001
Age <75 yrs								
WBC < 6	285	6.47	1.000			1.000		
WBC 6–12	3,887	8.80	1.396	(1.232–1.581)	0.0001	1.248	(1.092–1.427)	0.0011
WBC > 12	4,131	21.17	3.884	(3.428–4.401)	0.0001	2.127	(1.856–2.438)	0.0001
Age ≥75 yrs								
WBC < 6	737	12.70	1.000			1.000		
WBC 6–12	9,769	18.62	1.572	(1.451–1.704)	0.0001	1.485	(1.363–1.617)	0.0001
WBC > 12	9,353	34.83	3.673	(3.386–3.984)	0.0001	2.423	(2.218–2.646)	0.0001

*Adjusted by the risk factors listed in the reference.
CI = confidence interval; OR = odds ratio; WBC = white blood cell.

CONCLUSIONS

In patients with AMI, the WBC count measured within 24 h of admission is a strong and independent predictor of in-hospital and 30-day mortality as well as in-hospital clinical events. Although the association is robust, the mechanism responsible for the association remains speculative. However, regardless of whether the association between WBC counts and mortality is confounded by an unmeasured covariate or whether it reflects some fundamental pathophysiologic process, the results of this study have important clinical implications for risk stratifying patients with AMI.

Reprint requests and correspondence: Dr. Harlan M. Krumholz, 333 Cedar Street, P.O. Box 208025, New Haven, Connecticut 06520-8025.

REFERENCES

1. Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999;340:115–26.
2. Friedman GD, Klatsky AL, Siegelaub AB. Leukocyte count and myocardial infarction: correction. N Engl J Med 1974;291:1361.
3. Prentice RL, Szatrowski TP, Fujikura T, Kato H, Mason MW, Hamilton HH. Leukocyte counts and coronary heart disease in a Japanese cohort. Am J Epidemiol 1982;116:496–509.
4. Zalokar JB, Richard JL, Claude JR. Leukocyte count, smoking, and myocardial infarction. N Engl J Med 1981;304:465–8.
5. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 1998;279:1477–82.
6. Ernst E, Hammerschmidt DE, Bagge U, Matrai A, Dormandy JA. Leukocytes and the risk of ischemic diseases. JAMA 1987;257:2318–24.
7. Grimm RH, Jr, Neaton JD, Ludwig W. Prognostic importance of the white blood cell count for coronary, cancer, and all-cause mortality. JAMA 1985;254:1932–7.
8. Yarnell JW, Baker IA, Sweetnam PM, et al. Fibrinogen, viscosity, and white blood cell count are major risk factors for ischemic heart disease. The Caerphilly and Speedwell collaborative heart disease studies. Circulation 1991;83:836–44.
9. 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;143:1107–15.
10. Lowe GD, Machado SG, Krol WF, Barton BA, Forbes CD. White blood cell count and haematocrit as predictors of coronary recurrence after myocardial infarction. Thromb Haemost 1985;54:700–3.
11. Schlant RC, Forman S, Stamler J, Canner PL. The natural history of coronary heart disease: prognostic factors after recovery from myocardial infarction in 2789 men. The 5-year findings of the coronary drug project. Circulation 1982;66:401–14.
12. Burr ML, Holliday RM, Fehily AM, Whitehead PJ. Hematological prognostic indices after myocardial infarction: from the Diet And Reinfarction Trial (DART). Eur Heart J 1992;13:166–70.
13. Krumholz HM, Chen J, Wang Y, Radford MJ, Chen YT, Marciniak TA. Comparing AMI mortality among hospitals in patients 65 years of age and older: evaluating methods of risk adjustment. Circulation 1999;99:2986–92.
14. Engler RL, Schmid-Schonbein GW, Pavelec RS. Leukocyte capillary plugging in myocardial ischemia and reperfusion in the dog. Am J Pathol 1983;111:98–111.
15. Barron HV, Cannon CP, Murphy SA, Braunwald E, Gibson CM. Association between white blood cell count, epicardial blood flow, myocardial perfusion and clinical outcomes in the setting of acute myocardial infarction. Circulation 2000;102:2329–34.
16. Marciniak TA, Ellerbeck EF, Radford MJ, et al. Improving the quality of care for Medicare patients with acute myocardial infarction: results from the Cooperative Cardiovascular Project. JAMA 1998;279:1351–7.
17. Normand ST, Glickman ME, Sharma RG, McNeil BJ. Using admission characteristics to predict short-term mortality from myocardial infarction in elderly patients. Results from the Cooperative Cardiovascular Project. JAMA 1996;275:1322–8.
18. Fleming C, Fisher ES, Chang CH, Bubolz TA, Malenka DJ. Studying outcomes and hospital utilization in the elderly. The advan-

tages of a merged data base for Medicare and Veterans Affairs hospitals. Med Care 1992;30:377–91.
19. Furman MI, Becker RC, Yarzebski J, Savegeau J, Gore JM, Goldberg RJ. Effect of elevated leukocyte count on in-hospital mortality following acute myocardial infarction. Am J Cardiol 1996;78:945–8.
20. Lucchesi BR, Werns SW, Fantone JC. The role of the neutrophil and free radicals in ischemic myocardial injury. J Mol Cell Cardiol 1989;21:1241–51.
21. Jolly SR, Kane WJ, Hook BG, Abrams GD, Kunkel SL, Lucchesi BR. Reduction of myocardial infarct size by neutrophil depletion: effect of duration of occlusion. Am Heart J 1986;112:682–90.
22. Horwitz LD, Kaufman D, Kong Y. An antibody to leukocyte integrins attenuates coronary vascular injury due to ischemia and reperfusion in dogs. Am J Physiol 1997;272:H618–24.
23. Arai M, Lefer DJ, So T, DiPaula A, Aversano T, Becker LC. An anti-CD18 antibody limits infarct size and preserves left ventricular function in dogs with ischemia and 48-hour reperfusion. J Am Coll Cardiol 1996;27:1278–85.
24. Aversano T, Zhou W, Nedelman M, Nakada M, Weisman H. A chimeric IgG4 monoclonal antibody directed against CD18 reduces infarct size in a primate model of myocardial ischemia and reperfusion. J Am Coll Cardiol 1995;25:781–8.
25. Simpson PJ, Todd RF 3rd, Fantone JC, Mickelson JK, Griffin JD, Lucchesi BR. Reduction of experimental canine myocardial reperfusion injury by a monoclonal antibody (anti-Mo1, anti-CD11b) that inhibits leukocyte adhesion. J Clin Invest 1988;81:624–9.
26. Palazzo AJ, Jones SP, Girod WG, Anderson DC, Granger DN, Lefer DJ. Myocardial ischemia-reperfusion injury in CD18- and ICAM-1-deficient mice. Am J Physiol 1998;275:H2300–7.
27. 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;17:3399–405.