CARDIOVASCULAR MEDICINE

White blood cell count and long term mortality after non-ST elevation acute coronary syndrome treated with very early revascularisation

C Mueller, F-J Neumann, A P Perruchoud, H J Buettner

Heart 2003;89:389-392

See end of article for authors' affiliations

Correspondence to:
Dr C Mueller, Department
of Internal Medicine,
University Hospital,
Petersgraben 4, CH-4031
Basel, Switzerland;
chmueller@uhbs.ch

Accepted
1 November 2002

Objective: To evaluate the predictive value of white blood cell count (WBC) for short and long term mortality in patients with non-ST elevation acute coronary syndromes (NSTACS) treated with a very early invasive strategy.

Design: Prospective cohort study in 1391 consecutive patients with NSTACS undergoing very early revascularisation. Patients were stratified according to quartiles of WBC determined on admission.

Results: Kaplan-Meier survival analysis showed a cumulative three year survival of 93.8% in the first quartile of WBC ($< 6800/\text{mm}^3$), 94.4% in the second quartile ($6800\text{--}8000/\text{mm}^3$), 95.1% in the third quartile ($8000\text{--}10000/\text{mm}^3$), and 82.4% in the fourth quartile ($> 10000/\text{mm}^3$) at 36 months ($p < 0.001$ by log rank). Relative to patients in the three lower WBC quartiles, patients in the highest quartile were three times more likely to die during the hospitalisation (hazard ratio 3.2, 95% confidence interval (CI) 1.5 to 7.1; $p = 0.003$) and during long term follow up (hazard ratio 3.4, 95% CI 2.2 to 5.3; $p < 0.001$). By multivariate Cox regression analysis including baseline demographic, clinical, and angiographic covariables, WBC in the highest quartile remained a strong independent predictor of mortality (hazard ratio 3.3, 95% CI 1.9 to 5.6; $p < 0.001$).

Conclusions: WBC is a strong independent predictor of short and long term mortality after NSTACS treated with very early revascularisation.

The integral role of inflammation in stable and unstable coronary artery disease (CAD) has attained increasing recognition.¹ Increases in white blood cell count (WBC) have been associated with the development of CAD, with an increased event rate in stable CAD, and a higher 30 day mortality in the setting of an acute myocardial infarction (MI).²⁻⁷ The WBC is a very attractive marker for risk stratification, as it is inexpensive and routinely measured on admission.

Approximately 2-2.5 million patients worldwide are hospitalised for non-ST elevation acute coronary syndromes (NSTACS) each year, and NSTACS is the most common reason for admission to a coronary care unit. However, risk stratification is often particularly challenging in NSTACS. Very early coronary angiography and revascularisation have been proposed as a novel potentially superior management strategy in these patients.^{8,9}

We sought to determine whether very early revascularisation can ameliorate the negative prognostic impact of increased WBC in a large cohort of consecutive unselected patients.

METHODS

Patient population

From January 1996 to December 1999 consecutive patients admitted to our hospital (Herz-Zentrum Bad Krozingen) with NSTACS have been treated with a very early invasive strategy. Patients were eligible for inclusion in this study if they had unstable angina of Braunwald classes IIB and IIIB. Patients with persistent ST elevation, patients in whom angiography was not performed because of patient refusal ($n = 6$) or extremely severe concomitant disease ($n = 9$), and patients with no WBC determined on admission ($n = 59$) were excluded from the study.

The study was carried out according to the principles of the Declaration of Helsinki. Informed consent was obtained from all participating patients.

Very early revascularisation

Eligible patients with persistent chest pain underwent immediate coronary angiography. In patients who became asymptomatic with medical treatment, coronary angiography was performed within 24 hours of admission. Whenever possible, coronary stenting of the culprit lesion was performed immediately after angiography. Catheter revascularisation was the preferred treatment modality even in triple vessel disease. If percutaneous coronary intervention (PCI) was not suitable (unprotected left main disease or diffuse three vessel disease), patients in need of revascularisation were scheduled for urgent coronary artery bypass grafting (CABG).

Follow up

All patients were scheduled for outpatient visits at six months. In addition, patients were contacted by questionnaire in September 2000, nearly five years after enrolment of the first patient. For patients reporting cardiac symptoms, at least one clinical and electrocardiographic examination was performed in the outpatient clinic or by the referring physician. All information derived from contingent hospital readmission records or provided by the referring physician or by the outpatient clinic was reviewed and entered onto the computer database.

End points and statistical analysis

The prespecified primary end point was death from any cause. Secondary end points were non-fatal MI and a combined end

Abbreviations: CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; CRP, C reactive protein; MI, myocardial infarction; NSTACS, non-ST elevation acute coronary syndromes; OPUS, orbofiban in patients with unstable coronary syndromes; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; WBC, white blood cell count

Table 1 Baseline patient and procedural characteristics according to the quartile of white blood cell count on admission

	1st quartile <6800/mm ³ (n=363)	2nd quartile 6800–8000/mm ³ (n=341)	3rd quartile 8100–10000/mm ³ (n=328)	4th quartile >10000/mm ³ (n=359)	p Value*
Age (years)	66 (10)	66 (10)	64 (11)	63 (12)	0.001
Female sex (%)	29	28	33	26	0.331
Prior myocardial infarction (%)	32	33	30	36	0.488
Prior coronary bypass grafting (%)	15	14	15	11	0.264
Prior coronary angioplasty (%)	25	25	18	21	0.048
Diabetes (%)	18	20	21	21	0.843
Hypercholesterolaemia (%)	70	68	71	66	0.644
Hypertension (%)	61	65	65	64	0.762
Smoking (%)	22	27	28	40	0.001
Angina pectoris at rest >48 hours (%)	23	16	15	11	0.001
Angina pectoris at rest <48 hours (%)	71	72	69	64	0.129
Non-Q myocardial infarction (%)	6	12	16	25	0.001
Mechanical CPR (%)	0.8	0.9	0.3	3.3	0.002
Defibrillation (only) (%)	0.8	1.5	0.9	3.6	0.013
Cardiogenic shock (%)	0.5	0.3	0.6	2.2	0.030
New ST depression at entry (%)	7	11	12	14	0.026
New T wave inversion	29	28	30	29	0.899
Troponin T ≥0.1 µg/l (%)	46	54	54	68	0.001
Serum creatinine (µmol/l)	83 (76)	80 (48)	85 (77)	82 (42)	0.765
Platelet count (×10 ³ /µl)	209 (58)	229 (66)	238 (71)	263 (91)	0.001
Coronary vessels with ≥50% stenosis (%)					0.451
0	15	14	14	11	
1	24	28	22	27	
2	20	23	25	24	
3	42	35	39	39	
Percutaneous coronary intervention (%)	55	53	59	57	0.395
Proportion with stent	81	76	82	79	0.587
Proportion with abciximab	8	11	12	15	0.267
Coronary artery bypass grafting (%)	13	14	15	15	0.754
Medical treatment (%)	33	33	25	27	0.118

Data are mean (SD) or percentages.

*Between group comparison.

CPR, cardiopulmonary resuscitation.

point of death or non-fatal MI. MI was defined as typical chest pain at rest followed by an increase in creatine kinase (and creatine kinase MB fraction beyond twice the upper limit of normal and five times the upper limit of normal after CABG) or new Q waves on the ECG. The statistical analyses were performed using the SPSS/PC (version 11.0, SPSS Inc, Chicago, Illinois, USA) software package. Cox proportional hazards regression analysis was used as the appropriate method throughout. Backward-stepwise multivariate Cox regression analysis was performed to identify independent predictors of death. All baseline, demographic, clinical, and angiographic variables were entered into the model. The cumulative survival curves were constructed with the use of the Kaplan-Meier method.

RESULTS

Patient demographics and cardiovascular risk profile

WBC was determined on admission in 1391 consecutive patients. The median WBC was 8000/mm³. Table 1 describes the baseline, demographic, clinical, angiographic, and procedural characteristics of the cohort, divided into quartiles, as a function of their WBC. Patients in the highest quartile were younger, were more often smokers, and more often had established high risk features present than patients in the other quartiles. In particular, patients in the fourth quartile (WBC > 10 000/mm³; of note, 10 000/mm³ is the upper limit of normal in our laboratory) more often had undergone mechanical cardiopulmonary resuscitation or defibrillation, were in cardiogenic shock, had ST segment depression of at least 1 mm, had increased troponin T concentrations, and more often developed non-Q MI. In addition, the platelet count was higher in these patients. In contrast, there was no significant difference in the angiographic extent of CAD between the

WBC quartiles, nor were there differences in the primary revascularisation procedure applied. About 70% of patients actually underwent revascularisation and the PCI to CABG ratio was 4:1, without significant differences between the WBC quartiles.

Clinical outcome

There were 83 deaths and 59 non-fatal MIs during a median follow up of 17 months. The majority of deaths were from cardiac causes. In-hospital mortality and mortality during follow up (table 2) were significantly higher in the highest WBC quartile. Relative to patients in the other three quartiles, patients in the highest quartile were more than three times more likely to die during the hospitalisation (hazard ratio 3.2, $p = 0.003$) and during follow up (hazard ratio 3.4, $p < 0.001$). The incidence of non-fatal MI during follow up was similar across all WBC quartiles.

Kaplan-Meier survival analysis showed a significantly reduced survival in patients in the highest WBC quartile (fig 1). At 36 months, cumulative survival was 93.8% in the first quartile, 94.4% in the second quartile, 95.1% in the third quartile, and 82.4% in the fourth quartile ($p < 0.001$ by log rank). The increased mortality in patients with increased WBC was consistently seen in all subgroups studied: women, men, patients older or younger than 75 years of age, smokers, non-smokers, and troponin positive and troponin negative patients. In addition, the predictive value of WBC was similar in patients receiving revascularisation (PCI hazard ratio 2.7, 95% confidence interval (CI) 1.4 to 5.2; CABG hazard ratio 3.7, 95% CI 1.8 to 7.7) and those not receiving revascularisation (hazard ratio 4.3, 95% CI 1.6 to 11.0).

Together with quartiles of WBC, all baseline, demographic, clinical, and angiographic variables shown in table 1 were entered in a backward stepwise multivariate Cox regression

Table 2 Association between white blood cell count (WBC) on admission and outcome

	1st quartile <6800/mm ³ (n=363)	2nd quartile 6800–8000/mm ³ (n=341)	3rd quartile 8100–10000/mm ³ (n=328)	4th quartile >10000/mm ³ (n=357)	Hazard ratio (95% CI)*	p Value*
In-hospital						
Death	4 (1.1%)	5 (1.5%)	3 (0.9%)	14 (3.9%)	3.24 (1.48 to 7.10)	0.003
Non-fatal MI	8 (2.2%)	12 (3.5%)	10 (3.1%)	8 (2.2%)	0.83 (0.36 to 1.93)	0.670
Total follow up						
Death	14 (3.9%)	13 (3.8%)	13 (4.0%)	42 (11.8%)	3.40 (2.19 to 5.25)	<0.001
Non-fatal MI	11 (3.0%)	22 (6.5%)	13 (4.0%)	13 (3.6%)	0.95 (0.50 to 1.81)	0.870
Combined end point of death or non-fatal MI	24 (6.6%)	34 (10.0%)	25 (7.6%)	53 (14.9%)	2.14 (1.50 to 3.06)	<0.001

*For patients with WBC >10000/mm³ compared with patients with WBC ≤10000/mm³.
CI, confidence interval; MI, myocardial infarction.

Figure 1 Cumulative survival in relation to white blood cell count (per mm³) on admission.**Table 3** Independent predictors of long term mortality in multivariate analysis

	Odds ratio (95% CI)	p Value
WBC >10 000/mm ³	3.29 (1.94 to 5.58)	<0.001
Cardiogenic shock	3.77 (1.47 to 9.66)	0.006
Troponin T ≥0.1 µg/l	2.60 (1.34 to 5.04)	0.005
Coronaries with ≥50% stenosis	1.78 (1.27 to 2.50)*	0.001
Serum creatinine	1.38 (1.20 to 1.59)*	<0.001
Age	1.09 (1.05 to 1.12)*	<0.001
Platelet count	1.003 (1.001 to 1.005)*	0.002
Male sex	1.96 (1.02 to 3.70)	0.044
New T wave inversion	0.48 (0.25 to 0.93)	0.029

*For an increase in age of one year, platelet count of 10³/µl, serum creatinine of 1 mg/dl (88.4 µmol/l), and one coronary with ≥50% stenosis.

analysis. After adjustment for these factors, a WBC in the highest quartile was found to be a strong independent predictor of long term mortality (table 3). Relative to patients in the other three quartiles, there was 3.3-fold increase in the risk of death in patients in the highest quartile (hazard ratio 3.3, $p < 0.001$). Other independent predictors of mortality were cardiogenic shock, troponin T concentration ≥ 0.1 µg/l, number of coronaries with at least 50% stenosis, serum creatinine concentration, age, platelet count, male sex, and T wave inversion. The predictive value of WBC remained unchanged if troponin T was entered into the model as a continuous rather than a binary variable. In that model, the hazard ratio for the highest WBC quartile was 3.7 (95% CI 2.2 to 6.1). In addition, WBC remained an independent predictor of death after adjustment for C reactive protein (CRP) in the subgroup of patients where CRP was determined on admission. The hazard ratio for the highest WBC quartile was 2.3 (95% CI 1.1 to 4.3) and the hazard ratio for CRP > 10 mg/l was 3.8 (95% CI 2.1 to 6.8) in that model. Therefore, WBC was synergistic with CRP.

DISCUSSION

This large study of 1391 consecutive patients with NSTACS treated with a very early invasive strategy confirmed WBC as a strong independent predictor of long term mortality and thereby extends this important finding to the most contemporary revascularisation strategy. In addition, this study has three novel findings. Firstly, the increase in risk seemed to be confined to patients in the highest WBC quartile. Long term survival was similar in patients in the first, second, and third quartiles of WBC. Secondly, WBC $> 10\,000/\text{mm}^3$ remained a significant predictor of death even after adjustment for CRP in the subgroup of patients who had CRP determined on admission.¹⁰ Thirdly, there was no association between WBC and the angiographic severity of CAD. The incidence of multi-vessel disease was very similar in all four quartiles of WBC (58–64%). This finding is supported by recent data from Maekawa and colleagues¹¹ and provides further evidence that angiographic appearance alone is a poor guide to future adverse cardiac events.

Our results encourage the use of WBC as a powerful and inexpensive parameter for the risk stratification of patients with NSTACS. This analysis has four particular strengths. Firstly, it is derived from a prospective study of consecutive unselected patients rather than a randomised trial. This eliminates selection bias and eases the extrapolation of findings into clinical practice. Secondly, it includes long term follow up. Thirdly, a uniform revascularisation strategy was applied in all patients. Fourthly, the extent of CAD was quantified in all patients and included in the multivariate analysis as a potential confounder.

Previous epidemiological studies exploring the association between WBC and outcome in general included patients with acute MI receiving either no or thrombolytic reperfusion. Using the Cooperative Cardiovascular Project database, Krumholz and colleagues⁴ and Barron and associates⁷ established WBC as an independent predictor of 30 day mortality in a very large series of patients hospitalised for an acute MI in 1994 and 1995. The odds ratio for the highest quintile in WBC was 2.4. Evaluating data from 975 patients in the TIMI (thrombolysis in myocardial infarction) 10A and 10B trials, Barron and colleagues⁵ obtained strong evidence that increases in WBC are associated with a resistance to thrombolysis as shown by lower rates of coronary patency at both 60 and 90 minutes after the administration of thrombolytics, as well as an increased thrombus burden in patients with a patent infarct related artery. In addition, an increase in WBC was associated with impaired microvascular perfusion as shown by a reduction in myocardial perfusion grade. Leucocyte mediated microvascular impairment may therefore have been of particular importance in our study, where epicardial flow was successfully restored by PCI or CABG in the majority of patients.^{5 12–17}

Cannon and colleagues⁶ evaluated data from the large OPUS (orbofiban in patients with unstable coronary syndromes)

trial including patients with acute MI or high risk unstable angina pectoris within 72 hours from the onset of their acute coronary syndrome. Thirty day and 10 month mortality were significantly increased in patients with a WBC > 10 000/mm³. The adjusted relative risk for 10 month mortality was 1.9. Our study and the study by Cannon and colleagues⁶ are complementary, as they document the strong association between WBC and mortality for different treatment strategies for NSTACS. WBC seems to be a powerful predictor of long term mortality with a primarily conservative medical treatment with oral glycoprotein IIb/IIIa inhibition and an early invasive strategy. The prognostic importance of an increased WBC seems to be even higher with the early invasive strategy (adjusted relative risk 3.3). Interestingly, in both studies WBC did not correlate with the incidence of non-fatal MI during follow up.

Our study was not designed to clarify whether WBC is causally linked to increased mortality or is a marker of the severity of the initial insult. Nevertheless, several hypotheses have been proposed for the mechanisms responsible for the association between WBC and adverse outcome. These include a leucocyte mediated hypercoagulable state, leucocyte mediated endothelial dysfunction, microvascular plugging and no reflow, and myocyte necrosis mediated through proinflammatory cytokines.^{5 12-17}

Conclusion

WBC is a strong independent predictor of long term mortality in NSTACS treated with very early revascularisation. Regardless of whether the association between WBC and long term mortality reflects a fundamental pathophysiological process or is a marker of the severity of the ischaemic episode, the results of this study have important clinical implications. Increased WBC is a simple non-specific marker of inflammation. With its universal availability, it may serve as an inexpensive new tool for risk stratification in NSTACS.

Authors' affiliations

*C Mueller, F-J Neumann, H J Buettner, Herz-Zentrum Bad Krozingen, Bad Krozingen, Germany

A P Perruchoud, University Hospital Basel, Department of Internal Medicine, Basel, Switzerland

*Also the University Hospital Basel

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