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Impact of preprocedural white blood cell count on long term mortality after percutaneous coronary intervention: insights from the EPIC, EPILOG, and EPISTENT trials

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Background: Raised inflammatory markers are associated with worse outcome after percutaneous coronary interventions (PCI). An increase in the white blood cell (WBC) count is a non-specific response to inflammation. We hypothesised that a raised baseline WBC count would be a predictor of mortality in patients undergoing PCI.

Methods: The association between preprocedural WBC count and long term mortality was studied in 7179 patients enrolled in the EPIC, EPILOG, and EPISTENT trials. The end points were the incidence of myocardial infarction at one year, and one and three year mortality.

Results: There were 188 deaths and 582 myocardial infarctions at one year. While WBC count was a strong predictor of death at one year, with every increase of 1 k/ μ l (1×10^6 /l) being associated with a hazard ratio (HR) of 1.109 (95% confidence interval (CI) 1.072 to 1.147, $p < 0.001$), there was no association with myocardial infarction at one year (HR 1.020, 95% CI 0.990 to 1.052, $p = 0.195$). There were a total of 406 deaths at three years with a strong association between WBC count and three year mortality (HR for every 1 k/ μ l increase 1.089, 95% CI 1.058 to 1.121, $p < 0.001$). WBC count remained a significant predictor of mortality after multivariable adjustment (HR for every 1 k/ μ l increase 1.100, 95% CI 1.069 to 1.131, $p < 0.001$). The association was significant across multiple subgroups, including diabetes, female sex, clinical presentation, and cigarette smoking.

Conclusion: A raised pre-procedural WBC count in patients undergoing PCI is associated with an increased risk of long term death. These results suggest a key role for inflammation in coronary artery disease.

Coronary atherosclerosis is increasingly viewed as an inflammatory process.^{1,2} Multiple studies have confirmed an association between various inflammatory markers and worse outcome in patients with coronary atherosclerosis.²⁻¹² Further, inflammatory processes have been shown to be integral in plaque formation, progression, and instability.^{13,14}

Leucocytes are major mediators of inflammation and have a key role in host defence to injury. Increases in white blood cell count have been associated with a worse outcome in the general population, in patients with stable coronary disease, in acute coronary syndromes, and in those with acute myocardial infarction.^{8-10,12,15-21} Recently, we have shown that white cell count is an independent predictor of long term mortality in patients undergoing percutaneous coronary intervention (PCI) in a single centre registry.²²

These intriguing findings must be interpreted with caution since they have not been validated in other populations. Further, the relation between an increased white cell count and the future risk of myocardial infarction has not been determined in this population. We sought to validate the relation between white cell count and three year mortality among the cohort of patients enrolled in three trials of PCI. Additionally, we sought to explore the relation between preprocedural white cell count and subsequent myocardial infarction and the relation between leucocyte subtypes and outcomes in a subset of this population.

METHODS

Data from three randomised controlled trials of platelet IIb/IIIa inhibition in patients undergoing PCI were pooled for this study. The EPIC (evaluation of 7E3 for the prevention of

ischemic complications) trial enrolled 2099 patients undergoing high risk angioplasty in the setting of acute evolving myocardial infarction, unstable angina, or high risk clinical or angiographic characteristics between November 1991 and November 1992.²³ Patients were randomly assigned to receive a placebo, a bolus of abciximab, or a bolus and infusion of abciximab. The majority (90%) of patients in EPIC underwent percutaneous transluminal coronary angioplasty (PTCA), with the remainder undergoing either directional coronary atherectomy or both PTCA and directional coronary atherectomy. No stents were implanted electively. The EPILOG (evaluation in PTCA to improve long-term outcome with abciximab GP IIb/IIIa blockade) study enrolled 2792 patients undergoing urgent or elective PCI between February 1995 and December 1995.²⁴ Patients were randomly assigned to receive placebo, abciximab, and low dose heparin, or abciximab and standard dose heparin. PTCA was performed in 95% (2648) of the patients with the remainder undergoing directional coronary atherectomy, rotational atherectomy, extraction atherectomy, or excimer laser ablation. The EPISTENT (evaluation of platelet IIb/IIIa inhibitor for stenting) enrolled 2399 patients undergoing PCI for elective or urgent indications between July 1996 and September 1997.²⁵ Patients were

Abbreviations: CK, creatine kinase; CRP, C reactive protein; EPIC, evaluation of 7E3 for the prevention of ischemic complications; EPILOG, evaluation in PTCA to improve long-term outcome with abciximab GP IIb/IIIa blockade; EPISTENT, evaluation of platelet IIb/IIIa inhibitor for stenting; HR, hazard ratio; PAMI, primary angioplasty in myocardial infarction; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary balloon angioplasty

Table 1 Baseline demographics of the cohort based on preprocedural white cell count

	Quintile 1 (n=1480)	Quintile 2 (n=1391)	Quintile 3 (n=1463)	Quintile 4 (n=1413)	Quintile 5 (n=1432)
White cell count					
Median (k/ μ l)	5.30	6.48	7.50	8.70	10.90
Range (k/ μ l)	1.90–5.90	5.91–6.91	6.93–8.00	8.01–9.50	9.51–46.22
Mean age (years)	61.66	60.58	60.02	58.89	57.36
BMI (mean)	27.85	28.35	28.91	29.10	29.04
Women (%)	25.95	25.09	26.79	26.75	29.54
White (%)	87.09	90.65	91.59	91.37	92.53
Prior MI	655 (44.50%)	661 (47.62%)	737 (50.44%)	799 (56.71%)	851 (59.68%)
Prior CABG	222 (15.01%)	201 (14.45%)	176 (12.03%)	136 (9.62%)	130 (9.08%)
Prior PCI	362 (24.54%)	332 (23.94%)	317 (21.76%)	266 (18.89%)	221 (15.51%)
History of CHF	81 (5.50%)	81 (5.84%)	82 (5.62%)	105 (7.46%)	119 (8.36%)
Current smoker or quit within 1 year	268 (18.38%)	363 (26.30%)	485 (33.68%)	591 (42.18%)	739 (51.86%)
History of hypertension	811 (54.80%)	738 (53.29%)	804 (55.30%)	797 (56.69%)	841 (58.89%)
History of diabetes	292 (19.74%)	278 (20.0%)	338 (23.13%)	328 (23.23%)	368 (25.72%)

BMI, body mass index; CABG, coronary artery bypass graft; CHF, congestive heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention.
k/ μ l = 1×10^6 /l.

randomly assigned to treatment with stent plus placebo with standard dose heparin, stent plus abciximab with low dose heparin, or balloon angioplasty plus abciximab with low dose heparin.

The study evaluated several end points. Mortality was defined as total mortality. Myocardial infarction was defined as new significant Q waves in two or more contiguous ECG leads or an increase in creatine kinase MB isoenzyme (CK-MB) concentration to more than three times the upper limit of normal within 24 hours of PCI. After PCI, the development of either new Q waves or a CK or a CK-MB concentration more than twice the upper limit of normal was required to diagnose myocardial infarction. All end points and angiographic data were centrally adjudicated. Vital status was ascertained for all patients at three years. While one year myocardial infarction incidence was available for all patients, patients in the EPIC trial were in addition followed up for myocardial infarction for three years. White cell differentials were available only for patients in the EPIC trial.

Statistical analysis

The relation between white cell count and outcome was explored using white cell as a continuous variable, with spline transformation, and by dividing the cohort into quintiles.

Differences in baseline characteristics between patients in groups were compared using the χ^2 and Fisher's exact tests for dichotomous variables, and analysis of variance and Wilcoxon rank sum tests for continuous variables. White cell quintiles were used for descriptive analysis and all outcome analysis was performed using white cell count as a continuous variable. Cox proportional hazards regression analysis was used to estimate the unadjusted and adjusted hazard ratios (HR) for three year mortality. Linear spline transformation was used for body mass index and blood pressure for multivariable modelling. The other variables used in the model were age, race, sex, heart rate, recent myocardial infarction, unstable angina, history of hypertension, prior revascularisation, prior myocardial infarction, history of peripheral vascular disease, pre-hospital medications, smoking status, and treatment with a platelet glycoprotein IIb/IIIa inhibitor. The interactions between various variables were explored and the significant interaction terms incorporated in to the model. The hazard of mortality associated with white cell count was also assessed across age and multiple prespecified subgroups known to affect white cell count: chronic renal insufficiency (defined as creatinine > 133 μ mol/l), sex, diabetes, clinical presentation, and smoking status.

Since only the EPIC study recorded preprocedural white blood cell differentials, the relation between different white

cell subtypes and long term mortality was assessed only in this subgroup using Cox proportional hazard regression.

All analyses were performed using the SAS system, version 6.12 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Of the 7290 patients enrolled in the three trials, a baseline preprocedural white blood cell count was available for 7179 patients. Table 1 describes the baseline characteristics of these patients divided into quintiles of white cell count. Patients with higher white cell counts were more likely to be younger and to have a higher body mass index; more of these patients were women and were current or recent smokers. These patients were also more likely to have had a prior myocardial infarction and a history of congestive heart failure, diabetes, or hypertension and were less likely to have had a prior surgical or percutaneous coronary revascularisation.

Table 2 describes certain key angiographic and procedural variables across white cell quintiles. Patients in the highest white cell quintile were more likely to have thrombotic lesions and had slightly fewer American College of Cardiology/American Heart Association type C lesions. Furthermore, they were more likely to have postprocedural increases in CK-MB concentration and to develop bleeding complications. No difference was seen with respect to final residual stenosis or complications such as distal embolisation, need for bailout stenting, abrupt vessel closure, new thrombus, side branch occlusion, stroke or intracranial bleeding, seven day target vessel revascularisation, or postprocedural renal failure across the white cell quintiles.

Over a follow up of three years there were 406 deaths among the 7179 patients. There was an almost linear relation between white cell count and three year mortality hazard (fig 1). Although white cell count was a strong predictor of death at one year (number of events 188, HR for every 1 k/ μ l (1×10^6 /l) increase 1.109, 95% confidence interval (CI) 1.072 to 1.147; $p < 0.001$) and at three years (HR for every 1 k/ μ l increase 1.089, 95% CI 1.058 to 1.121; $p < 0.001$), there was no association with myocardial infarction at one year (number of events 582, HR 1.020, 95% CI 0.990 to 1.052; $p = 0.195$). A similar lack of association was seen between myocardial infarction at three years and white cell count among the 2032 patients enrolled in the EPIC trial (number of events 243, HR 1.101, 95% CI 0.968 to 1.061; $p = 0.565$).

The association between white cell count and three year mortality remained highly significant after multivariable adjustment (HR for every 1 k/ μ l increase 1.100, 95% CI 1.069 to 1.131; $p < 0.001$). Although a higher white cell count was

Table 2 Angiographic findings and procedural outcome in the cohort based on preprocedural white count

	Quintile 1 (n=1480)	Quintile 2 (n=1391)	Quintile 3 (n=1463)	Quintile 4 (n=1413)	Quintile 5 (n=1432)
Three vessel disease	180 (12.16%)	139 (9.99%)	160 (10.94%)	139 (9.84%)	131 (9.15%)
ACC/AHA worst lesion class type C*	256 (17.59%)	251 (18.42%)	232 (16.28%)	230 (16.65%)	200 (14.36%)
ACC/AHA worst lesion class type B2*	811 (55.74%)	774 (56.79%)	831 (58.32%)	845 (61.19%)	864 (62.02%)
ACC/AHA worst lesion class type B1*	223 (15.33%)	216 (15.85%)	230 (16.14%)	198 (14.34%)	211 (15.15%)
ACC/AHA worst lesion class type A*	165 (11.34%)	122 (8.95%)	132 (9.26%)	108 (7.82%)	118 (8.47%)
Lesion thrombus*	196 (13.40%)	241 (17.57%)	231 (16.05%)	278 (20.01%)	346 (24.61%)
Major or minor bleeding*	168 (11.40%)	135 (9.73%)	148 (10.21%)	163 (11.59%)	217 (15.24%)
Postprocedural CK-MB increase*	267 (18.30%)	276 (20.32%)	301 (20.92%)	284 (20.58%)	376 (26.63%)
Postprocedural creatinine >1.5 mg/dl*	85 (5.77%)	84 (6.07%)	89 (6.13%)	102 (7.27%)	104 (7.31%)

*Complete data not available for all patients.

ACC, American College of Cardiology; AHA, American Hospital Association; CK, creatine kinase.

Figure 1 Pre-procedural white blood cell (WBC) count and three year mortality rate after percutaneous coronary intervention (PCI). 1 k/μl = 1×10^6 /l.

Figure 2 Hazard for three year death in pre-specified subgroups. 1 k/μl = 1×10^6 /l.

associated with a higher incidence of postprocedural CK-MB rise, incorporating CK-MB increase in the multivariable model did not affect the strength of the association (HR 1.103, 95% CI 1.072 to 1.135; $p < 0.001$). A significant interaction was noted between smoking status and white cell count, and the association between long term mortality and white cell count was attenuated in smokers (fig 2). No interaction was noted between white cell count and abciximab assignment. Furthermore, the association between white cell count and mortality remained consistent across all the other prespecified subgroups (fig 2).

The association of various leucocyte subtypes was explored in the subset of patients enrolled in the EPIC study for whom this information was available at baseline (fig 3). The total white cell count remained the best predictor of three year death (HR for every 1 k/μl increase 1.099, 95% CI 1.059 to 1.140; $p < 0.001$). While an increased neutrophil count was also associated with an increased risk of long term mortality

Figure 3 Three year mortality hazard in EPIC based on pre-procedural white blood cell (WBC) subtypes. 1 k/μl = 1×10^6 /l.

(HR 1.003, 95% CI 1.000 to 1.005; $p = 0.017$) a higher lymphocyte count seemed to impart a protective effect (HR 0.977, 95% CI 0.959 to 0.994; $p = 0.008$). There was no significant relation between three year mortality and monocyte, eosinophil, or basophil count.

DISCUSSION

In this study of patients enrolled in three large, controlled, systematically evaluated clinical trials, we found the preprocedural white cell count to be an independent and strong predictor of mortality after PCI. Each rise in white cell count of 1 k/μl (1×10^6 /l) was associated with an almost 10% increase in three year mortality. This association was consistent across most subgroups. Finally, the increased risk is seen within the range of white cell count considered to be normal.

It has been recently recognised that inflammation has a central role in the pathophysiology of coronary artery disease. Multiple studies have described an association between increased inflammatory markers and outcome in various patient populations. Chew and associates found that increased C reactive protein (CRP) was associated with a heightened risk of death or myocardial infarction after PCI with an event rate of 14.2% among patients in the highest quartile compared with 3.9% in the lowest quartile ($p = 0.004$).⁶ Similarly, in 121 patients undergoing PTCA, clinical restenosis defined as the recurrence or worsening of ischaemic symptoms (typical angina, myocardial infarction, or death) or ischaemia at exercise testing (≥ 1 mm ST segment depression) developed at one year in 63% of patients with high CRP concentrations and in 27% of those with normal CRP concentrations ($p < 0.001$).⁷

White cell count is a universally available marker of inflammation that is obtained in virtually all patients undergoing PCI. Previous studies have described an association between an increased white cell count and worse outcome in populations at varying baseline risk of coronary morbidity and mortality. In

the normative aging study, a white cell count greater than $9 \times 10^6/l$ was associated with a 1.8–2.5 times mortality hazard as compared with a lower white cell count.⁸ In the Framingham study, a similar association was described between baseline white cell count and future development of cardiovascular disease.¹⁶ Similarly, in the Caerphilly and Speedwell studies, the odds of incident ischaemic events over 10 years was 2.84 in patients in the highest white cell quintile.²⁶ In a meta-analysis of 19 studies, the risk ratio of coronary heart disease among patients in the third white cell tertile was 1.5 (95% CI 1.4 to 1.6) compared with those in the lowest tertile.⁹ Furthermore, an association between increased white cell count and all cause mortality (relative risk 1.25, 95% CI 1.17 to 1.35) and coronary mortality (relative risk 1.32, 95% CI 1.15 to 1.51) was described by Weijenberg and colleagues among a cohort of elderly Dutch patients in the Zutphen study.²¹ In the acute myocardial infarction setting, an association between increased white cell count and reduced myocardial perfusion, poor epicardial flow, a greater thrombus burden, and increased thromboresistance has been shown.⁴ Multiple studies of acute myocardial infarction have reported increased mortality in patients with higher white cell count.^{4 18 19}

We have previously described a strong and independent association between preprocedural white cell count and long term mortality in a cohort of patients undergoing PCI.²² In that study a J shaped relation was shown between preprocedural white cell count and mortality with both a high and low white cell count portending a worse outcome. Compared with the second quintile, the patients with highest white cell count had a two and half times excess mortality, whereas those with the lowest white cell count had almost twofold excess mortality after adjusting for multiple predictors of outcome after PCI.

Our findings of increasing long term mortality with a rising white cell count in the current study are consistent with the previous findings. The lack of a J shaped curve in the current study may suggest that a higher mortality in patients with low white cell count was unique to the population in our previous study. Low white cell count may be a marker of poor general health in some patients. Since registry populations include all patients that undergo PCI at an institution whereas clinical trials select a somewhat healthier subset for enrolment, the comparison between the two studies may not be valid.

Our current data thus confirm and extend the previously described association between increased mortality hazard and a high white cell count in PCI and other populations. Leucocytes are the key mediators of inflammatory processes and have an important role in the development of atherosclerotic lesions and response to PCI. PCI is associated with leucocyte activation, increased expression of adhesion molecules, and formation of platelet-leucocyte complexes.^{27–29} Further, the activated state of different white cell subtypes directly affects the early and late term response of the vessel wall to PTCA with some subtypes being pro-restenosis and others anti-restenosis.³⁰

It is tempting to ascribe the association between white cell count and mortality to differences in baseline clinical characteristics. The association remained strong after adjusting for such variables, as well as with postprocedural CK-MB rise. We were able to show an association between white cell count in all prespecified subgroups except for smokers. While such an association can be expected in patients undergoing PCI for acute coronary syndromes, the strength of this association in patients undergoing PCI for more elective indications suggests that such a relation is likely to be extant.

Our study could not define an association between myocardial infarction and white blood cell count. Since the major cause of death in patients with coronary artery disease is myocardial infarction, such a finding is hard to explain. It is conceivable that a majority of these deaths were sudden and possibly arrhythmogenic in origin.³¹ Indeed, such an association between sudden cardiac death and CRP has been recently

described.³² However, in the absence of postmortem data, and in view of the known fallacies in ascribing cause of death to cardiac or other causes,³³ such an explanation can only be considered to be one of many plausible mechanisms. It is, however, important to note that a recent study from the stent PAMI (primary angioplasty in myocardial infarction) investigators found a strong relation between baseline white cell count and risk of myocardial infarction at one year. The lack of a similar finding in our study may relate to the different patient populations; the stent PAMI trial enrolled patients with ST elevation myocardial infarction, whereas our study cohort covered a wider spectrum of coronary artery disease patients.³⁴

The availability of differential white cell count in EPIC allowed us to study the relative association of different cell types with outcome. The total white cell count was the best correlate of outcome, whereas all the individual subtypes were more weakly related. Further, the lymphocyte count was inversely correlated, a higher lymphocyte count being associated with a better outcome, whereas all other subtypes were positively—albeit non-significantly—associated. Since the leucocyte subsets have varying roles in coronary atherosclerosis, with some having a pro-atherosclerosis and others an anti-atherosclerosis function, the total white cell count is likely to be a better surrogate of coronary inflammation than any of the traditional leucocyte subsets. However, further research will probably identify unique subsets of leucocyte in the peripheral blood that will reflect the inflammatory activity in the vascular bed better than the currently available techniques.

Limitations

Our study is a retrospective analysis of prospectively collected data and is thus susceptible to the limitations inherent in such studies. We did not have access to other inflammatory markers such as CRP and interleukin 6. The role of white cell count as a marker of outcome after PCI needs to be explored after adjusting for the additive risk associated with increased CRP. Only a single value of white cell count obtained preprocedurally was available. It would be interesting to evaluate the association between outcome and change in white cell count immediately and late after PCI. Furthermore, it must be emphasised that our study shows an association between white cell count and long term mortality but does not prove or support a causal relation.

Also, the white cell count is affected by medications and is correlated with various measures of haemostatic function such as fibrinogen, haematocrit, plasma viscosity, factors VII and VIII, and von Willebrand factor. We were unable to adjust for these and other variables in our analysis, as they were not routinely obtained in the study population.

Conclusion

White cell count, an inexpensive and routinely available marker of inflammation, is strongly and independently associated with long term mortality after PCI. Our study provides further evidence to support the role of inflammation in general, and white cells in particular, in coronary artery disease. Further studies are warranted to study the interaction between white cell count and commonly used therapeutic agents, and to delineate the potential role of white cell count in clinical decision making in patients undergoing PCI.

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