INTERVENTIONAL CARDIOLOGY AND SURGERY

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


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/µl (1 × 10^9/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/µl 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/µl 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. Multiple studies have confirmed an association between various inflammatory markers and worse outcome in patients with coronary atherosclerosis. Further, inflammatory processes have been shown to be integral in plaque formation, progression, and instability.

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. 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.

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. 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. 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. 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.
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 \( \chi^2 \) 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 µmol/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 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/µl (1 × 10⁶/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/µl 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 1.010, 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/µl increase 1.100, 95% CI 1.069 to 1.131; \( p < 0.001 \)). Although a higher white cell count was

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

<table>
<thead>
<tr>
<th>Quintile</th>
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<th>Quartile</th>
<th>Quartile</th>
<th>Quartile</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cell</td>
<td>(n=1480)</td>
<td>(n=1391)</td>
<td>(n=1463)</td>
<td>(n=1413)</td>
<td>(n=1432)</td>
</tr>
<tr>
<td>Median (k/µl)</td>
<td>5.30</td>
<td>6.48</td>
<td>7.50</td>
<td>8.70</td>
<td>10.90</td>
</tr>
<tr>
<td>Range (k/µl)</td>
<td>1.90-5.90</td>
<td>5.91-6.91</td>
<td>6.93-8.00</td>
<td>8.01-9.50</td>
<td>9.51-46.22</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>61.66</td>
<td>60.58</td>
<td>60.02</td>
<td>58.89</td>
<td>57.36</td>
</tr>
<tr>
<td>BMI (Mean)</td>
<td>27.85</td>
<td>28.35</td>
<td>28.91</td>
<td>29.10</td>
<td>29.04</td>
</tr>
<tr>
<td>Women (%)</td>
<td>25.95</td>
<td>25.09</td>
<td>26.79</td>
<td>26.75</td>
<td>29.54</td>
</tr>
<tr>
<td>White (%)</td>
<td>87.09</td>
<td>90.65</td>
<td>91.59</td>
<td>91.37</td>
<td>92.53</td>
</tr>
<tr>
<td>Prior MI</td>
<td>655 (44.50%)</td>
<td>661 (47.62%)</td>
<td>737 (50.44%)</td>
<td>799 (56.71%)</td>
<td>851 (59.68%)</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>222 (15.01%)</td>
<td>201 (14.45%)</td>
<td>176 (12.03%)</td>
<td>136 (9.62%)</td>
<td>130 (9.08%)</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>362 (24.54%)</td>
<td>332 (23.94%)</td>
<td>317 (21.76%)</td>
<td>266 (18.89%)</td>
<td>221 (15.51%)</td>
</tr>
<tr>
<td>History of CHF</td>
<td>81 (5.50%)</td>
<td>81 (5.84%)</td>
<td>82 (5.62%)</td>
<td>105 (7.46%)</td>
<td>119 (8.36%)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>811 (54.80%)</td>
<td>738 (53.29%)</td>
<td>804 (55.30%)</td>
<td>797 (56.69%)</td>
<td>841 (58.89%)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>292 (19.74%)</td>
<td>278 (20.0%)</td>
<td>338 (23.13%)</td>
<td>328 (22.33%)</td>
<td>368 (25.72%)</td>
</tr>
</tbody>
</table>

BMI, body mass index; CABG, coronary artery bypass graft; CHF, congestive heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention.

V/µl = 1 × 10⁶/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 (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).

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). The increased risk is seen within the range of white cell count considered to be normal.

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

<table>
<thead>
<tr>
<th>Quintile 1 (n=1480)</th>
<th>Quintile 2 (n=1391)</th>
<th>Quintile 3 (n=1463)</th>
<th>Quintile 4 (n=1413)</th>
<th>Quintile 5 (n=1432)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three vessel disease</td>
<td>180 (12.16%)</td>
<td>139 (9.99%)</td>
<td>160 (10.94%)</td>
<td>139 (9.84%)</td>
</tr>
<tr>
<td>ACC/AHA worst lesion class type C*</td>
<td>256 (17.59%)</td>
<td>251 (18.42%)</td>
<td>232 (16.28%)</td>
<td>230 (16.65%)</td>
</tr>
<tr>
<td>ACC/AHA worst lesion class type B2*</td>
<td>811 (55.74%)</td>
<td>774 (56.79%)</td>
<td>831 (58.32%)</td>
<td>845 (61.19%)</td>
</tr>
<tr>
<td>ACC/AHA worst lesion class type B1*</td>
<td>223 (15.33%)</td>
<td>216 (15.85%)</td>
<td>230 (16.14%)</td>
<td>198 (14.34%)</td>
</tr>
<tr>
<td>ACC/AHA worst lesion class type A*</td>
<td>165 (11.34%)</td>
<td>122 (8.95%)</td>
<td>132 (9.26%)</td>
<td>108 (7.82%)</td>
</tr>
<tr>
<td>Major or minor bleeding*</td>
<td>168 (11.40%)</td>
<td>135 (9.73%)</td>
<td>148 (10.21%)</td>
<td>163 (11.95%)</td>
</tr>
<tr>
<td>Postprocedural CK-MB increase*</td>
<td>267 (18.30%)</td>
<td>276 (20.32%)</td>
<td>301 (20.92%)</td>
<td>284 (20.58%)</td>
</tr>
<tr>
<td>Postprocedural creatinine &gt;1.5 mg/dl*</td>
<td>85 (5.77%)</td>
<td>84 (6.07%)</td>
<td>89 (6.13%)</td>
<td>102 (7.27%)</td>
</tr>
</tbody>
</table>

*Complete data not available for all patients.

ACC, American College of Cardiology; AHA, American Hospital Association; CK, creatine kinase.
the normative aging study, a white cell count greater than
9 × 10^9/L was associated with a 1.8–2.5 times mortality hazard as
compared with a lower white cell count. In the Framingham
study, a similar association was described between baseline white
cell count and future development of cardiovascular disease. 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. 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. 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. In the acute myocardial infarction setting, an
association between increased white cell count and reduced myo-
cardial perfusion, poor epicardial flow, a greater thrombus burden,
and increased thromboresistance has been shown. Multiple
studies of acute myocardial infarction have reported increased
mortality in patients with higher white cell count. 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. In that
study a J shaped relation was shown between prepro-
edural 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 out-
come 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 previous
lymphocyte count and future development of cardiovascular disease.

It is tempting to ascribe the association between white cell
count and mortality to differences in baseline clinical charac-
teristics. 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.

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 long term mortality but does not prove or
support a causal relation.

Also, the white cell count is affected by medications and is
associated 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.


described. However, in the absence of postmortem data, and in
view of the known fallacies in ascribing cause of death to
cardiac or other causes, such an explanation can only be con-
sidered to be one of many plausible mechanisms. It is, however,
important to note that a recent study from the stent PAMI (pri-
mary 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.

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
related, a higher lymphocyte count being associated with a
better outcome, whereas all other subtypes were positively—
albeit non-significantly—associated. Since the leucocyte sub-
sets 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 surro-
gate of coronary inflammation than any of the traditional
leucocyte subsets. However, further research will probably iden-
tify 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 mark-
ers 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 preprocedur-
ally 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.

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Preprocedural white cell count and long term mortality
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