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CLINICAL INVESTIGATION

PRE-OPERATIVE NEUTROPHIL-LYMPHOCYTE RATIO AND OUTCOME FROM CORONARY ARTERY BYPASS GRAFTING

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ABSTRACT

Background. An elevated pre-operative white cell count (WCC) has been associated with a worse outcome following coronary artery bypass grafting **(**CABG). Leukocyte sub-types, and in particular the N/L ratio, may, however, convey superior prognostic information. We hypothesized that the N/L ratio would predict the outcome of patients undergoing surgical revascularization. The current study tests this hypothesis.

Methods. Baseline clinical details were obtained prospectively in 1,938 patients undergoing CABG. The differential leukocyte was measured 1 day before surgery and patients were followed-up 3.6 years later. The primary end-point was all-cause mortality.

Results. The pre-operative N/L ratio was a powerful univariable predictor of mortality (hazard ratio [HR] 1.13 per unit, $p<0.001$). In a backward conditional model, including all other study variables, it remained a strong predictor (HR 1.09 per unit, $p=0.004$). In a further model, including the European system for cardiac operative risk evaluation, the N/L ratio remained an independent predictor (HR 1.08 per unit, $p=0.008$). Likewise, it was an independent predictor of cardiovascular mortality and predicted death in the subgroup of patients with a normal WCC ($<10 \times 10^9$ per litre). This excess hazard was concentrated in patients with a N/L ratio in the upper quartile (>3.36).

Conclusion. An elevated N/L ratio is associated with a poorer survival after CABG. This prognostic utility is independent of other recognized risk factors.

Coronary artery bypass grafting (CABG) is associated with a small but significant incidence of morbidity and mortality. While methods of risk assessment, such as the European system for cardiac operative risk evaluation (EuroSCORE), are widely employed, there are limits to their predictive ability.[1] There remains, therefore, a need for additional methods of risk stratification, particularly if these are easily obtained and widely available.

The role of low-grade inflammation in the pathogenesis of atherosclerosis and its acute complications is well-recognized,[2] and several biological markers of inflammation predict cardiovascular risk.[3,4] One of the most readily available indices is the total leukocyte count. This foretells cardiovascular events in unselected adults,[5,6] in patients with stable angina,[7,8] and in the acute coronary syndromes.[9,10] The total white cell count (WCC) has also been recently found to predict mortality following CABG.[11-13] This may reflect an association with the severity and/or activity of atherosclerosis. It may also be due to direct cardiac and vascular injury initiated by leukocytes following myocardial ischemia.

The total leukocyte count does, however, have limitations – the link between leukocytosis and outcome is complex and non-linear,[14,15] not all studies reveal an independent association[16] and many have demonstrated confounding relationships with other risk factors such as smoking.[17] There is, therefore, interest in analysis of white cell subtypes. For example, much of the predictive power of the total leukocyte count is contained in the neutrophil component.[18-20] Likewise, a reduced lymphocyte count has also been

associated with poorer prognosis.[15,21,22] The predictive value of these indices has been combined by calculating the neutrophil/lymphocyte (N/L) ratio. This may be a more powerful predictor of cardiovascular risk than the total WCC or individual white cell subtypes.[23,24,25] However, the prognostic utility of the N/L ratio has not previously been evaluated in patients undergoing surgical revascularization. We hypothesized that, particularly given the relationship between leukocytes and the myocardial and vascular injury that follows ischemia, the N/L ratio would predict outcome in this setting.

METHODS

The study complies with the Declaration of Helsinki and ethical approval was granted by the local Research Ethics Committee. Between April 2000 and March 2004, 2,076 consecutive patients underwent CABG in our institution. Seventy-six patients who underwent emergency surgery and/or CABG within 1 week of acute myocardial infarction were excluded, as were 62 patients who had no pre-operative (<1 week before CABG) leukocyte count available. The study cohort comprised the remaining 1,938 subjects. Baseline clinical data, including Canadian Cardiovascular Society angina status, New York Heart Association functional class and the EuroSCORE, were collected prospectively.

Two hundred and eight patients (10.7%) underwent other major operative procedures in addition to CABG. These included 191 valve replacement or repair procedures (145 aortic [1 with aortic root replacement], 43 mitral and 3 combined aortic and mitral). There were 9 left ventricular aneurysm resections, 3 thoracic aortic procedures (without

valve replacement), 2 atrial myxoma resections, 2 ventricular septal defect repairs and 1 pericardiectomy.

All analyses used the blood sample obtained immediately prior to surgery. Differential leukocyte count was obtained using an Advia 2120 Hematology System (Bayer HealthCare, Tarrytown, NY). This automated analyser exhibits an excellent correlation with manual cell counts and has co-efficients of variation of <2.5% for the total white cell count, <1.5% for the neutrophil count and <2.9% for the lymphocyte count.[26] The total WCC, neutrophil, lymphocyte and monocyte counts were recorded. In addition, the pre-operative N/L ratio was calculated.

Follow up

Patients were followed up using a vital events search by the General Register Office for Scotland. The primary end-point was all-cause mortality. Cause of death was defined as cardiac if this was listed as the primary cause or a contributory factor on the death certificate. The duration of hospitalization was also recorded.

Statistical analyses

Categorical data are summarized using absolute values (percentage). Normally distributed continuous data are presented as mean (standard deviation) or, where skewed, as median (interquartile range). Survival was described using the Kaplan-Meier method and comparison made using the log-rank statistic. Estimations of risk were performed using Cox regression. Backward conditional multivariable models of survival were

developed. One of these included all variables and a second included white cell indices plus the EuroSCORE. Retention in these models was set at a significance level of <0.05.

The hazard associated with different quartiles of N/L ratio was assessed using Cox regression, using either the lowest quartile as the reference or comparing the upper quartile with all others. Power calculations for the log-rank test were used as an approximate method to assess whether the Cox regression would have sufficient power to detect differences in hazard between the quartiles. In a comparison of two groups of 483 patients (the minimum number in each quartile) a hazard ratio of 2 could be detected with 95% power with a minimum of 100 events (deaths) in the two groups combined.

Comparisons of the clinical characteristics and the duration of post-operative hospital stay of patients with differing quartiles of N/L ratio were compared using the chi-squared test for trend (for categorical variables) and analysis of variance or the Jonckheere-Terpstra test (for normally and non-normally distributed continuous variables respectively). SPSS version 13.0 (SPSS Inc., Chicago, Illinois) was used for all analyses.

RESULTS

Patient population and outcome

The study cohort were predominantly male with a median age of 66 years (table I). The differential leukocyte count was measured a median of 1 (1-3) day before surgery. The median total WCC was 7.5 (6.4-8.9) x 10^9 per litre with a median N/L ratio of 2.43 (1.86-3.36). Two-hundred and twenty six patients (12%) had a WCC above 10 x 10^9 per litre. Vital status data were available for all patients. During a median of 3.6 (1.4-4.7) years follow-up 177 patients (9%) died, 154 from primarily or partly cardiovascular causes. Fifty deaths (28%) occurred within the first 30-days of surgery.

Univariable predictors of mortality

The total WCC was not predictive of mortality (table I). This remained the case even when the total WCC was divided in to categories (<6, 6.0-7.9, 8.0-9.9, 10.0-11.9 and >12 x 10^9 per litre) or quartiles (HR 1.01, p=0.86 and HR 0.79 for upper quartile *v* lowest quartile, p=0.29, respectively). A higher neutrophil count was associated with an increased risk of death, whereas a lower pre-operative lymphocyte count was a strong univariable predictor of mortality: as was the pre-operative N/L ratio (table I).

Multivariable predictors of mortality

The neutrophil and lymphocyte counts and the N/L ratio are mathematically related. The N/L ratio was a stronger univariable predictor of outcome (χ^2 27.4) than the neutrophil count (χ^2 3.2) or lymphocyte count (χ^2 18.4) and, in this cohort, when the N/L ratio was used its components provided no additional prognostic information. Therefore, the N/L

ratio was entered in all subsequent regression models. Likewise, cardiopulmonary bypass and cross-clamp times are closely related. The former was, however, the stronger predictor of outcome and, when this was available, cross-clamp time provided no incremental information regarding prognosis. Cardiopulmonary bypass time was, therefore, used in all multivariable models.

The first model included all variables shown in table I except EuroSCORE - which is a composite that includes several of these parameters and is widely used to predict peri-operative risk, but has also been demonstrated to be a useful predictor of long-term outcome.[27-29] The independent predictors of mortality in this model are shown in table II. In a further model, including the pre-operative total WCC, the pre-operative monocyte count, the pre-operative N/L ratio and EuroSCORE, the only independent predictors of outcome were the N/L ratio (HR 1.08 per unit, 95% CI 1.02-1.15, p=0.008) and the EuroSCORE (HR 1.25 per unit, 95% CI 1.19-1.32, p<0.001).

Secondary analyses

Cardiovascular mortality

When only cardiovascular death was considered an end-point, the N/L ratio remained a univariable predictor (HR 1.12 per unit, 95% CI 1.06-1.18, p<0.001), as did the pre-operative lymphocyte (HR 0.57 per $1x10^9$ per litre, 95% CI 0.44-0.75, p<0.001) and monocyte (HR 1.59 per $1x10^9$ per litre, 95% CI 1.16-2.17, p=0.004) counts. In contrast, neither the total WCC (HR 0.97 per $1x10^9$ per litre, 95% CI 0.91-1.04, p=0.44) or

neutrophil count (HR 1.03 per $1x10^9$ per litre, 95% CI 0.94-1.13, p=0.49) predicted cardiovascular mortality.

In a multivariable model, including all variables shown in table I except EuroSCORE the N/L ratio remained an independent predictor of cardiovascular death (HR 1.11 per unit, 95% CI 1.03-1.19, p=0.01), as did the pre-operative monocyte count (HR 1.49 per $1x10^9$ per litre, 95% CI 1.08-2.05, p=0.02). The other independent predictors of cardiac death were time on cardiopulmonary bypass (HR 1.04 per 10 minutes, p<0.001), estimated glomerular filtration rate (HR 0.97 per mL/min per $1.73m^2$, p<0.001), requirement for a major cardiac surgical procedure in addition to CABG (HR 1.99, p=0.003), ejection fraction <50% (HR 1.91, p=0.001) and diabetes mellitus (HR 1.65, P=0.02). In a model including the pre-operative total WCC, the pre-operative monocyte count, the pre-operative N/L ratio and EuroSCORE, the only independent predictors of cardiovascular death were the N/L ratio (HR 1.08 per unit, 95% CI 1.00-1.16, p=0.046) and the EuroSCORE (HR 1.28 per unit, 95% CI 1.21-1.35, p<0.001).

Patients with normal white cell count only

In patients with a normal total WCC (≤10 x 10^9 per litre, n=1,712) the N/L ratio remained a powerful univariable predictor of all-cause mortality (HR 1.18 per unit, 95% CI 1.11-1.26, p<0.001). The pre-operative lymphocyte count also remained a strong predictor (HR 0.51 per $1x10^9$ per litre, 95% CI 0.38-0.68, P<0.001), but neither the total WCC or any other leukocyte subsets were predictive of death in this subgroup.

In multivariable models, similar to those described above, N/L ratio remained an independent predictor of outcome (HR 1.15 per unit, 95% CI 1.07-1.24, p<0.001 in a model including all other variables and HR 1.14 per unit, 95% CI 1.06-1.23, p=0.001 in a model including total WCC, monocyte count and EuroSCORE).

Quartiles of neutrophil/lymphocyte ratio

The excess risk was observed in patients with N/L ratios in the upper quartile (table III and figure 1). In univariable analysis, the hazard associated with a N/L ratio in the highest quartile (*v* all others) was 2.09, 95% CI 1.54-2.84, p<0.001. In backward conditional multivariable models, firstly including all variables shown in table II and then the EuroSCORE, pre-operative WCC and monocyte count, the independent hazard associated with a N/L ratio in the upper quartile was 1.72, 95% CI 1.25-2.36, p=0.001 and 1.53, 95% CI 1.13-2.13, p=0.008, respectively. A relationship between the quartile of N/L ratio and length of post-operative hospitalization was also observed (p<0.001). Patients with higher N/L ratios tended to be older, have poorer renal function and a higher EuroSCORE (table IV). They were also more likely to require re-intubation following surgery and had a tendency towards higher cardiac troponin I levels at 24 hours following surgery.

DISCUSSION

The current data demonstrate that in patients undergoing CABG the N/L ratio conveys powerful prognostic information that is independent of other conventional clinical risk factors. Patients with N/L ratios in the upper quartile are at particularly high risk.

Total white cell count

Prior data have suggested that an elevated leukocyte count is associated with a worse cardiovascular outcome in a variety of settings.[17] It has also been reported to predict increased mortality following CABG.[11-13] A relationship between pre-operative total WCC and mortality was not observed in the current cohort. The explanation for this is not clear. Our cohort is an unselected consecutive population similar to others in which the total leukocyte count has proved to be prognostic. Likewise, the mean, median and distribution of the WCC are almost identical to those reported in comparable studies.[11-13] Two of these[12,13] included emergency and peri-infarct cases. However, Bagger and colleagues demonstrated a persisting relationship of WCC in sub-group analysis, when emergency and post-infarct cases were excluded.[11]

There is evidence of a biphasic, or J-shaped, relationship between total WCC and mortality following myocardial infarction[30] and percutaneous coronary intervention.[31] This might diminish the overall predictive value of the WCC. However, in the current cohort we found no evidence of such a relationship - possibly reflecting the selected population that undergoes CABG.

The absence of any relationship between total WCC and survival may relate to the effects of medication. The Long-term Intervention with Pravastatin in Ischemic Disease study showed that the WCC predicted cardiovascular mortality over 6 years in patients randomized to placebo, but not in those receiving pravastatin.[32] We do not have accurate details of statin use in the current population, but in a similar cohort of patients

undergoing all forms of cardiac surgery in our institution, post operative statin use was 78%,[33] rising to 87% in patients undergoing CABG (unpublished data).

Leukocyte subtypes

Despite the absence of an association between total WCC and outcome in this cohort, we found lymphocyte and monocyte counts to be significant univariable predictors, with the neutrophil count demonstrating a trend towards significance. The improved survival associated with a higher lymphocyte count was particularly striking. This has previously been observed in patients with stable coronary artery disease,[22] those undergoing 'high-risk' angioplasty[14] and those with heart failure.[21,34]

More recently, it has been demonstrated that increased prognostic information could obtained by deriving the N/L ratio. In a cohort of 3,227 patients undergoing coronary angiography, the N/L ratio was a powerful predictor of mortality - and was independent and superior to individual leukocyte subtypes.[23] After adjustment for other factors, patients with a N/L ratio in the upper quartile had a 3 times higher hazard of death during follow-up than those in the lowest quartile.[23] Likewise, in 1,046 patients undergoing percutaneous coronary intervention, the pre-procedural N/L ratio, but not the total WCC, was an independent predictor of all-cause death.[24] This was, however, a selected population, from which <25% of eligible patients had a differential leukocyte available - raising the possibility that unidentified clinical factors may have introduced bias.

Potential mechanisms

Both an elevated neutrophil count and a depressed lymphocyte count are associated with a worse outcome. It seems likely that the ability to integrate these two facets of the differential WCC underpins the particular prognostic utility of the N/L ratio. A higher ratio was associated with several major determinants of cardiovascular outcome. However, the observed increased hazard is independent of such factors. Analysis of the survival curves demonstrates that the excess mortality is concentrated in patients with the highest ratio. The curves separate immediately and continue to diverge – suggesting an increased risk both in the early post-operative period and in the longer term.

Multiple properties of leukocytes may contribute to peri-operative myocardial damage and, thus, a worse outcome. Neutrophil infiltration is associated with secondary damage following myocardial ischemia and is implicated in reperfusion injury - through both direct toxic effects on the myocardium and vascular endothelium, and leukocyte plugging in the microvasculature[15,17] In support of this, the use of a neutrophil and platelet depleted reperfusate has been associated with a reduction in post-operative myocardial damage.[35] Increased neutrophil counts are also associated with increased blood viscosity and hypercoagulability.[17] Likewise, cardiopulmonary bypass itself is associated with neutrophil activation,[36] which may accentuate the effects of elevated pre-operative levels.

The longer-term excess risk associated with an elevated N/L ratio may, in part, reflect the consequences of increased peri-operative myocardial injury. Certainly, peri-operative myocardial damage is associated with long-term adverse outcome.[33] It is likely that it also

due to other mechanisms. Atherosclerosis is an inflammatory process,[2] and elevation of the N/L ratio may reflect a chronic background inflammatory state. Although neutrophils play a limited role in atherogenesis they have a major role in the disruption of atherosclerotic plaques – and, thereby, influence their progression and the risk of acute complications.[15,17,19,23,37] Meanwhile, although lymphocytes are also involved in the development and progression of atherosclerosis,[2] peripheral lymphopenia predicts a poorer outcome in patients with stable coronary heart disease.[22] The reasons for this are not fully understood. The most widely accepted explanation, however, is that a reduced lymphocyte count reflects a physiological stress.[15,22] Thus, lymphopenia may serve as a surrogate marker for the general health of an individual rather than reflecting a protective role of lymphocytes *per se*. It appears, therefore, that the N/L ratio integrates several parameters that will determine both the early and later outcome from CABG.

Study strengths and limitations

This study comprised a large cohort of consecutive patients undergoing non-urgent CABG in a regional cardiothoracic centre. The results are, therefore, representative of stable patients undergoing surgical revascularization. The use of all-cause mortality as a primary end-point provides an objective measure of outcome. However, no data were obtained regarding other important morbidities such as peri-operative myocardial infarction or stroke. Data are also lacking regarding pre and post-operative medication, which may have influenced the outcome of patients, and possibly the N/L ratio itself.

The use of a single blood sample does not allow assessment of the stability of the N/L ratio in an individual over time and there is some diurnal variation in the differential leukocyte count, depending on glucocorticoid levels. Finally, some patients with minor sepsis may have been included in the study. Patients were, however, undergoing elective surgery that would be re-scheduled if acute infection were suspected clinically. Likewise, subgroup analysis of only patients with a normal WCC demonstrates similar results.

Despite these limitations the current data demonstrate a clear relationship between pre-operative N/L ratio and survival after CABG, with patients in the highest quartile at greatest risk. Importantly, this prognostic utility is independent of other well-recognized individual risk factors and the EuroSCORE. The N/L ratio, which is easily calculated and readily available, may, therefore, assist the risk-stratification of patients undergoing surgical revascularization. It remains unclear whether elevation of the N/L ratio directly contributes to the observed poorer outcome and further work is required to clarify the underlying mechanisms.

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Table I. Clinical characteristics of study cohort and univariable relationship to mortality.

Characteristic	All patients (n=1,938)	ALL-CAUSE MORTALITY			
		Alive (n=1,761)	Died (n=177)	Hazard ratio (95% CI)	P value
Age, years	65 ±9	65 ±9	69 ±9	1.06 (1.04-1.08)*	<0.001
Risk factors and medical history					
Male	1,499 (77%)	1,366 (78%)	133 (75%)	0.85 (0.61-1.20)	0.36
Current smoker	197 (10%)	180 (10%)	17 (10%)	0.95 (0.58-1.57)	0.86
Diabetes	297 (15%)	261 (15%)	36 (20%)	1.54 (1.07-2.22)	0.02
Hypertension	1,170 (60%)	1,064 (60%)	105 (59%)	1.07 (0.79-1.44)	0.67
Prior PCI	161 (8%)	149 (8%)	12 (7%)	0.86 (0.48-1.55)	0.62
Prior CABG	41 (2%)	35 (2%)	6 (3%)	1.56 (0.69-3.53)	0.28
Previous MI	953 (49%)	859 (49%)	94 (53%)	1.12 (0.83-1.50)	0.46
Estimated LVEF <50%†	662 (34%)	575 (33%)	87 (49%)	1.87 (1.40-2.52)	<0.001
CCS angina status‡					
0 to II	872 (45%)	794 (45%)	78 (45%)		
III or IV	1,060 (55%)	963 (55%)	97 (55%)	0.88 (0.65-1.19)	0.40
NYHA functional class#					
I or II	841 (47%)	774 (47%	67 (41%)		
III or IV	966 (53%)	868 (53%)	98 (59%)	1.07 (0.78-1.46)	0.68
EuroSCORE	4 (2-6)	4 (2-6)	6 (4-8)	1.27 (1.21-1.33)	<0.001
Renal function					
Creatinine (mg/dL)	1.21 ±0.43	1.20 ±0.37	1.38 ±0.79	1.49 (1.29-1.73)§	<0.001
Estimated GFR (mL/min/1.73m^2)	63.9 ±14.4	64.4 ±14.0	58.6 ±17.8	0.97 (0.96-0.98)‖	<0.001
Differential leukocyte count					
Total white cell count (x 10^9 per litre)	7.5 (6.4-8.9)	7.5 (6.4-8.9)	7.5 (6.2-8.7)	0.99 (0.94-1.05)	0.83
Neutrophil count (x 10^9 per litre)	4.7 (3.7-5.8)	4.7 (3.7-5.8)	4.9 (3.8-6.0)	1.07 (0.99-1.16)	0.07
Monocyte count (x 10^9 per litre)	0.4 (0.3-0.5)	0.4 (0.3-0.5)	0.4 (0.3-0.5)	1.58 (1.15-2.16)	0.005
Lymphocyte count (x 10^9 per litre)	1.9 (1.5-2.4)	1.9 (1.5-2.4)	1.6 (1.3-2.2)	0.59 (0.46-0.75)	<0.001
Neutrophil/lymphocyte ratio	2.43 (1.86-3.36)	2.39 (1.84-3.27)	2.79 (2.00-4.22)	1.13 (1.08-1.18)	<0.001
Peri-operative data					

Pre-operative intra-aortic balloon	74 (4%)	67 (4%)	7 (4%)	1.58 (0.74-3.38)	0.24
Additional major cardiac procedure**	208 (11%)	167 (9%)	41 (23%)	1.72 (1.45-2.05)	<0.001
Number of bypass grafts	2.57 ±0.83	2.58 ±0.83	2.46 ±0.89	0.82 (0.68-0.98)	0.03
Internal mammary artery used	1298 (67%)	1212 (69%)	86 (49%)	0.48 (0.36-0.65)	<0.001
Off pump procedure	219 (11%)	207 (12%)	12 (7%)	0.73 (0.40-1.31)	0.28
Bypass time (minutes)	79 (59-97)	78 (59-96)	87 (67-123)	1.04 (1.03-1.04)††	<0.001
Cross clamp time (minutes)	43 (32-53)	43 (32-53)	46 (36-74)	1.07 (1.05-1.09)††	<0.001

PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting, MI = myocardial infarction, LVEF = left ventricular ejection fraction, CCS = Canadian Cardiovascular Society, NYHA = New York Heart Association, GFR = glomerular filtration rate.

* Hazard ratio per year, § Hazard ratio per mg/dL, ‖ Hazard ratio per mL/min/1.73m^2, †† Hazard ratio per 10 minutes

† LVEF was not defined in 13 cases, ‡ CCS status was not accurately recorded in 6 patients, # NYHA functional class was not accurately recorded in 131 patients. Percentages refer to patients with data available. ** see text for details.

To convert creatinine values to micromols per liter multiply by 88.4.

Table II. Multivariable predictors of mortality.

Characteristic	Hazard ratio	95% CI	Wald χ^2	P value
Time on bypass (per 10 minutes)	1.04	1.03-1.05	34.8	<0.001
Age (per year)	1.04	1.02-1.06	16.2	<0.001
LV ejection fraction <50%	1.76	1.30-2.37	13.7	<0.001
Creatinine (mg/dL)	1.38	1.15-1.65	12.2	<0.001
Neutrophil/lymphocyte ratio	1.09	1.03-1.16	8.3	0.004
Additional major cardiac procedure	1.64	1.12-2.40	6.4	0.004

CI = confidence interval, LV = left ventricular

Table III. Outcomes according to the neutrophil/lymphocyte ratio (by quartile).

Characteristic	Quartile 1 0.12-1.85 n=483	Quartile 2 1.86-2.42 n=486	Quartile 3 2.43-3.35 n=483	Quartile 4 3.36-28.50 n=486
All-cause mortality, n (%)	37 (8%)	34 (7%)	33 (7%)	73 (15%)
Unadjusted HR (95% CI)	1	0.89 (0.56-1.42)	0.89 (0.56-1.43)	2.06 (1.39-3.06) ∗
HR adjusted for EuroSCORE (95% CI)	1	0.81 (0.51-1.30)	0.77 (0.48-1.23)	1.42 (0.95-2.15)†
Cardiovascular mortality, n (%)	30 (6%)	30 (6%)	31 (6%)	63 (13%)
Unadjusted HR (95% CI)	1	0.97 (0.59-1.61)	1.03 (0.63-1.71)	2.19 (1.42-3.39) ∗
HR adjusted for EuroSCORE (95% CI)	1	0.88 (0.53-1.47)	0.88 (0.53-1.46)	1.46 (0.93-2.29)‡
Post-operative hospital stay (days)	9 (7-11)	9 (7-11)	9 (7-12)	10 (8-13)

CI = confidence interval, HR = hazard ratio

∗ p<0.001 quartile 4 *v* quartile 1, † p=0.09 quartile 4 *v* quartile 1, ‡ p=0.10 quartile 4 *v* quartile 1.

Table IV. Baseline characteristics and early post-operative complications according to neutrophil/lymphocyte ratio (by quartile).

Characteristic / complication	Quartile 1 0.12-1.85 n=483	Quartile 2 1.86-2.42 n=486	Quartile 3 2.43-3.35 n=483	Quartile 4 3.36-28.50 n=486	P value
Age (years)	63 ±9	64 ±9	66 ±9	68 ±9	<0.001
Male	371 (77%)	377 (78%)	362 (75%)	389 (80%)	0.40
Creatinine (mg/dL)	1.14 ±0.20	1.17 ±0.23	1.23 ±0.48	1.30 ±0.63	<0.001
Estimated GFR (mL/min/1.73m^2)	66.9 ±12.6	65.0 ±13.3	62.6 ±15.0	60.9 ±16.0	<0.001
Hypertension	281 (58%)	281 (58%)	308 (64%)	300 (62%)	0.10
Diabetes mellitus	72 (15%)	64 (13%)	75 (16%)	86 (18%)	0.15
Smoker	57 (12%)	54 (11%)	50 (10%)	36 (7%)	0.02
Previous MI	244 (51%)	227 (47%)	219 (45%)	263 (54%)	0.35
Estimated LVEF <50%*	163 (34%)	149 (31%)	159 (33%)	191 (40%)	0.04
CCS status III or IV†	255 (53%)	270 (56%)	272 (57%)	263 (54%)	0.66
NYHA class III or IV‡	230 (51%)	242 (53%)	240 (53%)	254 (56%)	0.16
EuroSCORE	3 (2-5)	3 (2-5)	4 (2-6)	5 (3-7)	<0.001
Post-operative re-intubation	3 (1%)	6 (1%)	15 (3%)	19 (4%)	<0.001
New post-operative dialysis	1 (<1%)	4 (1%)	2 (<1%)	7 (1%)	0.06
Post-operative septicemia#	6 (1%)	8 (2%)	4 (1%)	11 (2%)	0.38
Post-operative chest infection#	44 (9%)	41 (8%)	44 (10%)	61 (13%)	0.08

Post-operative atrial dysrhythmia[#]	99 (20%)	83 (17%)	99 (20%)	120 (25%)	0.07
Cardiac troponin I at 24 h (ng/mL)	4.27 (2.15-8.77)	4.02 (2.18-8.91)	4.28 (2.26-9.19)	5.06 (2.54-11.40)	0.01

Data are expressed as mean (standard deviation) if normally distributed, median (interquartile range) if skewed or number (percentage) of patients if categorical.

Abbreviations as in Table I

[*] LVEF was not defined in 13 patients, [†] CCS angina status was not accurately recorded in 6 patients, [‡] NYHA functional class was not accurately recorded in 131 patients. Percentages refer to patients with data available. [#] clinically apparent.

FIGURE LEGEND

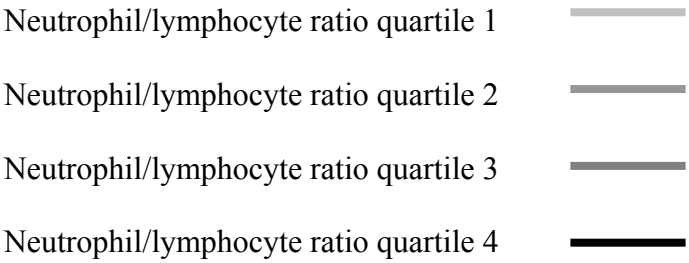
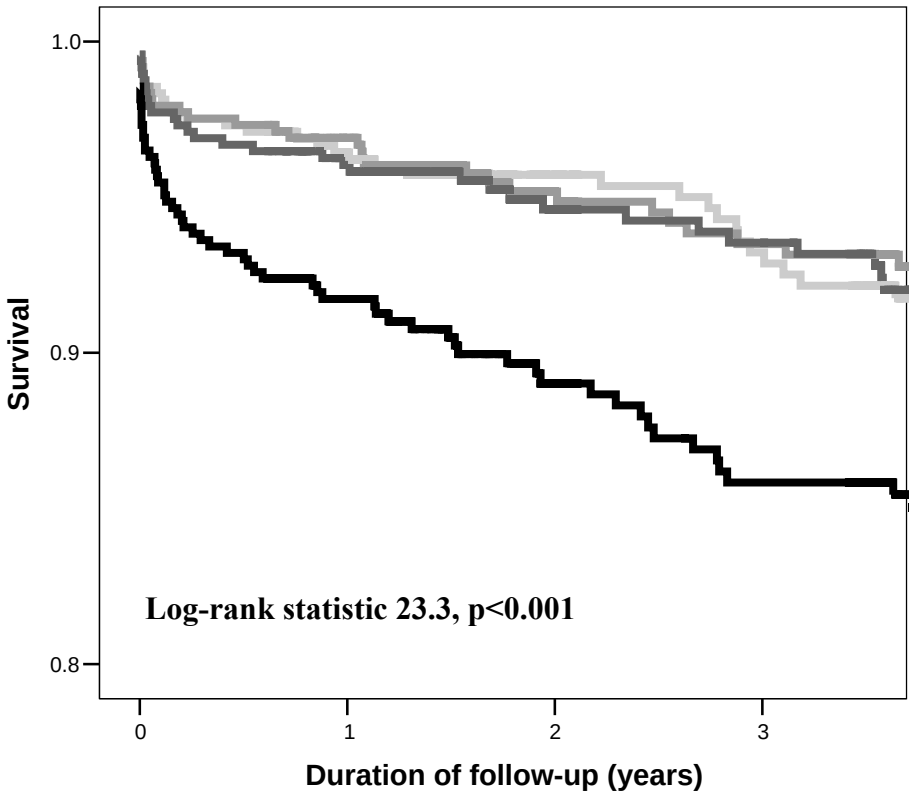


Figure 1. Relationship between quartiles of neutrophil/lymphocyte ratio and all-cause mortality.



Number at risk	**Q1**	**483**	**422**	**287**	**262**
	Q2	**486**	**441**	**291**	**275**
	Q3	**483**	**432**	**279**	**263**
	Q4	**486**	**406**	**264**	**242**