# Neutrophil-Lymphocyte Ratio: Prognostic Impact in Heart Surgery. Early Outcomes and Late Survival

Shuli Silberman, MD, Ulfat Abu-Yunis, BMedSci, Rachel Tauber, MPH, Linda Shavit, MD, Tal Grenader, MD, Daniel Fink, MD, Daniel Bitran, MD, and Ofer Merin, MD

Departments of Cardiac Surgery, Nephrology, and Oncology, Shaare Zedek Medical Center, Jerusalem, Israel



*Background.* **The neutrophil-lymphocyte ratio (NLR) is a recognized marker of inflammation associated with poor outcomes in various clinical situations. We analyzed the prognostic significance of preoperative elevated NLR in patients undergoing cardiac surgery.**

*Methods.* **We performed a retrospective review of 3,027 consecutive patients undergoing cardiac surgery. Receiver-operating-characteristic was used to determine the cutoff value for elevated NLR. Multivariate regression was used to determine the predictive value of preoperative NLR on clinical outcomes. Cox proportional hazards functions were used to determine predictors of late events. Late survival data to 16 years was obtained from the Ministry of Interior.**

*Results.* **The cutoff value for elevated NLR was 2.6. Patients with elevated NLR were older ($p < 0.0001$), had a higher incidence of cardiac comorbidity ($p < 0.0001$), and higher European System for Cardiac Operative Risk Evaluation score ($p < 0.0001$). An elevated NLR emerged as an independent predictor of operative mortality (hazard ratio [HR] 2.15, 95% confidence interval [CI]: 1.51 to 3.08, $p < 0.0001$); pleural effusion (HR 1.42, 95% CI: 1.13 to 1.80, $p = 0.003$); low output syndrome (HR 1.54, 95% CI: 1.23 to 1.93, $p = 0.0002$); prolonged ventilation (HR 1.49, 95% CI: 1.23 to 1.82, $p = 0.0001$); or composite outcomes (HR 1.61, 95% CI: 1.36 to 1.91, $p < 0.0001$). The NLR emerged as an independent predictor of late mortality (HR 1.19, 95% CI: 1.11 to 1.28; $p < 0.0001$).**

*Conclusions.* **Elevated NLR is associated with a higher incidence of adverse outcomes after cardiac surgery. It is a predictor of operative as well as late mortality. Further studies are warranted to determine whether prophylactic treatment with antiinflammatory agents can prevent such outcomes. It may be warranted to include the baseline NLR as another variable in risk stratification of patients about to undergo cardiac surgery.**

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In recent years, the neutrophil-to-lymphocyte ratio (NLR) has emerged as a sensitive inflammatory marker [1] associated with poor outcomes in a variety of clinical settings. Elevated NLR was found to be associated with adverse outcomes and reduced survival of patients presenting with a wide spectrum of coronary disease, including stable coronary artery disease [2], acute coronary syndrome [3], and myocardial infarction [4, 5]. Elevated NLR was also found to be associated with adverse outcomes and increased mortality among patients undergoing coronary intervention, including both percutaneous coronary intervention and coronary artery bypass graft surgery (CABG) [6–9].

In the present study, we sought to determine the short-term and long-term prognostic significance of elevated NLR in patients undergoing cardiac surgery in our department. The primary endpoint was survival. Secondary endpoints were low output syndrome, prolonged ventilation, and pleural effusion.

## Patients and Methods

### *Patients*

We performed a retrospective review of 4,063 consecutive patients who underwent cardiac surgery utilizing cardiopulmonary bypass between the years 2001 and 2016 and including CABG or valve surgery or mixed surgery. Excluded were patients without preoperative blood count containing absolute values of neutrophils and lymphocytes within 2 weeks before surgery and patients undergoing surgery for active endocarditis, leaving a total of 3,027. Normal values of neutrophils were between 1,400/μL and 6,500/μL and lymphocytes were between 1,200/μL and 3,400/μL. Our institutional laboratory participates in the United Kingdom Quality Assurance Scheme quality control program. For the purpose of comparing outcomes, patients with both normal neutrophil count as well as nonelevated NLR at baseline served

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Address correspondence to Dr Silberman, Department of Cardiothoracic Surgery, Shaare Zedek Medical Center, PO Box 3235, Jerusalem 91031, Israel; email: ssilberman@szmc.org.il.



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as the control group. Our Institutional Ethics Review Board approved this study and waived the need for individual patient consent. We compared outcomes between patients with baseline elevated NLR to those of patients with low NLR. Late survival data were obtained from the Ministry of Interior and is 93% complete.

### *Statistical Analysis*

Preoperative, operative, and early postoperative data were collected prospectively in our departmental database (Summit Medical, Europe). The data were imported and analyzed using JMP software (SAS Institute, Cary, NC). The cutoff value for elevated NLR was determined using receiver-operating characteristics. Continuous variables were compared using Student's $t$ test and presented as mean ± SD. Nominal and categoric values were compared using the $\chi^2$ likelihood ratio or Fisher's exact tests. Analysis of variance was used to determine the correlation between values of NLR and operative mortality. Multivariate logistic regression was used to identify predictors of outcomes. Univariate and multivariate Cox proportional hazards functions were used to determine predictors of late events. Variables evaluated as predictors of late events included patient age, preoperative symptoms of congestive heart failure, left ventricle dysfunction, baseline absolute lymphocyte and neutrophil count, baseline NLR, and the European System for Cardiac Operative Risk (EuroSCORE) [10]. Because the EuroSCORE is primarily a predictor of operative mortality, it was not included in the analysis of outcomes other than mortality.

### *Definitions*

Operative mortality was defined as death within 30 days of surgery or within the same hospitalization. Preoperative risk of mortality was calculated using the logistic EuroSCORE. Left ventricular function, degree of mitral regurgitation, and tricuspid regurgitation gradient were determined using transthoracic echocardiograms according to previously established methods [11]. Renal failure was determined if preoperative creatinine level was greater than 1.5 mg%. Acute kidney injury was determined if there was a twofold rise in baseline creatinine or creatinine value of greater than 2 mg/dL in a patient with normal baseline values. Low output syndrome was determined in patients requiring inotropic support, or by clinical assessment if there were indications of malperfusion (low urine output, acidosis, elevated lactate values). Infection includes one or more of the following: deep sternal wound infection, pneumonia, mediastinitis, and septicemia. Urinary tract infection and superficial wound infection were not included in the analysis. Prolonged ventilation was defined as ventilation 24 hours or longer after surgery. Pleural effusion was determined in cases with pleural effusion necessitating pleurocentesis.

## Results

Preoperative blood count was available for 3,027 patients (75%), and they comprise the cohort of this study. Preoperative blood count was unavailable for patients who underwent operation on an urgent basis, as well as patients whose blood tests were not recorded on our institutional database, such as patients from other institutions. The clinical profile of these patients was similar to the study cohort. These patients were therefore not included in our study. The cutoff value for elevated NLR was found to be 2.6. By univariate analysis, patients in the high NLR group had a higher incidence of comorbidity: left ventricular dysfunction ($p < 0.0001$), mitral regurgitation grade ≥2 ($p < 0.0001$), and elevated pulmonary pressure ($p < 0.0001$) as well as a higher EuroSCORE ($p < 0.0001$). More cases were performed on an urgent basis ($p < 0.0001$), and there was a higher incidence of postoperative adverse events: low output syndrome ($p < 0.0001$), prolonged ventilation ($p < 0.0001$), pleural effusion ($p < 0.0001$), and operative mortality ($p < 0.0001$). Baseline patient characteristics and operative data are shown in Table 1. Postoperative events are shown in Table 2.

Observed mortality was increased in the elevated NLR group compared with the nonelevated NLR group: 137 of 1,329 (10%) and 54 of 1,698 (3%), respectively ($p < 0.0001$). That was true also in patients with normal baseline neutrophil count (n = 2,459). Within this group, mortality

*Table 1. Baseline Clinical Variables*

| Variables | NLR ≥2.6 | NLR <2.6 | $p$ Value |
|---|---|---|---|
| Number of patients | 1,329 (44) | 1,698 (56) | … |
| Male | 943 (71) | 1142 (67) | 0.03 |
| Age, years | 66 ± 11 | 63 ± 12 | <0.0001 |
| Hypertension | 962 (72) | 1176 (69) | 0.06 |
| Diabetes mellitus | 525 (39) | 660 (39) | 0.7 |
| Chronic lung disease | 162 (12) | 161 (9) | 0.02 |
| Renal failure | 251 (19) | 130 (8) | <0.0001 |
| Pulmonary hypertension | 686 (52) | 648 (38) | <0.0001 |
| Stroke | 120 (9) | 121 (7) | 0.05 |
| Peripheral vascular disease | 145 (11) | 138 (8) | 0.009 |
| Atrial fibrillation | 242 (18) | 202 (12) | <0.0001 |
| Congestive heart failure | 771 (58) | 824 (49) | 0.01 |
| EuroSCORE (logistic) | 12 ± 15 | 7 ± 9 | <0.0001 |
| Echocardiography | | | |
| Left ventricular dysfunction | 277 (21) | 245 (14) | <0.0001 |
| MR grade ≥2 | 620 (47) | 609 (36) | <0.0001 |
| TR gradient | 40 ± 21 | 34 ± 14 | <0.0001 |
| Operative data | | | |
| Pure CABG | 479 (36) | 813 (48) | <0.0001 |
| CABG + any valve | 284 (21) | 248 (15) | <0.0001 |
| MV procedure, ± other | 556 (42) | 509 (30) | <0.0001 |
| Urgent | 348 (26) | 336 (20) | <0.0001 |
| Reoperation | 139 (10) | 94 (5) | <0.0001 |
| Bypass time, minutes | 114 ± 54 | 103 ± 50 | <0.0001 |
| Ischemic time, minutes | 83 ± 42 | 76 ± 37 | <0.0001 |
| Need for inotropes | 372 (28) | 242 (14) | <0.0001 |

Values are n (%) or mean ± SD.

CABG = coronary artery bypass graft surgery; EuroSCORE = European System for Cardiac Operative Risk Evaluation; MR = mitral regurgitation; MV = mitral valve; NLR = neutrophil-lymphocyte ratio; TR = tricuspid regurgitation.

*Table 2. Postoperative Events*

| Variables | NLR ≥2.6 | NLR <2.6 | *p* Value |
|---|---|---|---|
| Number of patients | 1,329 (44) | 1,698 (56) | … |
| Perioperative MI | 13 (1) | 18 (1) | 0.8 |
| Low cardiac output | 259 (19) | 180 (11) | <0.0001 |
| Infection | 121 (9) | 79 (5) | <0.0001 |
| New stroke | 23 (2) | 14 (1) | 0.02 |
| Prolonged ventilation | 368 (28) | 265 (16) | <0.0001 |
| Acute kidney injury | 87 (7) | 58 (3) | <0.0001 |
| Dialysis | 23 (2) | 16 (1) | 0.06 |
| Atrial fibrillation | 335 (25) | 363 (21) | 0.01 |
| Pacemaker implantation | 37 (3) | 37 (2) | 0.3 |
| Pleurocentesis | 194 (15) | 157 (9) | <0.0001 |
| Mortality | 137 (10) | 54 (3) | <0.0001 |

Values are n (%).

MI = myocardial infarction; NLR = neutrophil- lymphocyte ratio.

was 78 of 844 (9%) and 51 of 1,615 (3%), respectively ($p = 0.0007$).

By multivariate analysis, elevated NLR emerged as a predictor of operative mortality ($p < 0.0001$). Operative mortality was in correlation with increasing values of NLR ($p < 0.0001$). Other predictors include the EuroSCORE ($p < 0.0001$) and female gender ($p < 0.0001$). In the presence of the EuroSCORE, age did not emerge as a predictor of operative mortality, although other components of the EuroSCORE such as congestive heart failure and left ventricular dysfunction did (Table 3).

Elevated NLR emerged as an independent predictor of other adverse outcomes, including low-output syndrome, prolonged ventilation, pleural effusion, or any one or more of the listed outcomes. In addition, elevated NLR emerged as an independent predictor of prolonged (more than 2 weeks) intensive care stay after surgery (hazard ratio 1.7, 95% confidence interval: 1.01 to 3.01, $p = 0.048$). Predictors of outcomes are shown in Table 3.

To ascertain the validity of elevated NLR as a predictor of mortality in a more homogenous subgroup, we performed a separate analysis in patients undergoing elective first-time isolated CABG. There were 1,183 patients. In the elevated NLR group and nonelevated NLR group, observed mortality was 11 (3%) and 8 (1%), respectively ($p = 0.04$). Elevated NLR was found to be an independent predictor of operative mortality ($p = 0.03$; Table 4).

### *White Blood Cell Subgroups*

Elevated NLR can occur in various white blood cell (WBC) subgroups: (1) elevated neutrophils; (2) reduced lymphocytes; and (3) normal neutrophils and normal lymphocyte count. By univariate analysis, elevated NLR emerged as an independent predictor of mortality in all WBC subgroups ($p < 0.0001$) in comparison with the control group. It was also found to be a predictor within each subgroup, with the exception of patients having low

*Table 3. Predictors of Outcomes by Multivariate Regression*

| Variable | HR | 95% CI | *p* Value |
|---|---|---|---|
| Mortality | | | |
| Elevated NLR | 2.15 | 1.51–3.08 | <0.0001 |
| Female | 2.3 | 1.63–3.26 | <0.0001 |
| CHF | 1.7 | 1.15–2.54 | 0.008 |
| LV dysfunction | 1.54 | 1.04–2.26 | 0.03 |
| Renal failure | 2.03 | 1.38–2.95 | 0.0003 |
| Atrial fibrillation | 1.5 | 1.02–2.18 | 0.04 |
| Logistic EuroSCORE | 1.05 | 1.03–1.06 | <0.0001 |
| Low output syndrome | | | |
| Elevated NLR | 1.54 | 1.23–1.93 | 0.0002 |
| Female | 1.35 | 1.06–1.72 | 0.02 |
| Age | 1.02 | 1.01–1.03 | 0.0002 |
| CHF | 2.7 | 2.08–3.52 | <0.0001 |
| LV dysfunction | 5.03 | 3.94–6.42 | <0.0001 |
| AKI | 1.41 | 1.05–1.88 | 0.02 |
| Atrial fibrillation | 1.84 | 1.39–2.41 | <0.0001 |
| Prolonged ventilation | | | |
| Elevated NLR | 1.49 | 1.23–1.82 | 0.0001 |
| Female | … | … | 0.08 |
| Age | 1.04 | 1.03–1.05 | <0.0001 |
| CHF | 2.12 | 1.71–2.62 | <0.0001 |
| LV dysfunction | 2.46 | 1.95–3.09 | <0.0001 |
| AKI | 2.20 | 1.67–2.8 | <0.0001 |
| Atrial fibrillation | 1.54 | 1.2–1.97 | 0.0006 |
| Pleural effusion | | | |
| Elevated NLR | 1.42 | 1.13–1.8 | 0.003 |
| Female | 1.34 | 1.05–1.71 | 0.02 |
| Age | 1.02 | 1.01–1.03 | <0.0001 |
| CHF | 1.48 | 1.16–1.91 | 0.002 |
| LV dysfunction | … | … | |
| AKI | 1.55 | 1.14–2.09 | 0.0004 |
| Atrial fibrillation | … | … | |
| Any outcome | | | |
| Elevated NLR | 1.61 | 1.36–1.91 | <0.0001 |
| Female | 1.44 | 1.2–1.73 | 0.0001 |
| Age | 1.03 | 1.02–1.04 | <0.0001 |
| CHF | 2.19 | 1.83–2.61 | <0.0001 |
| LV dysfunction | 2.99 | 2.41–3.72 | <0.0001 |
| AKI | 1.93 | 1.51–2.47 | <0.0001 |
| Atrial fibrillation | 1.81 | 1.44–2.8 | <0.0001 |
| Mortality in CABG patients | | | |
| Sex | 3.92 | 1.9–8.2 | 0.0003 |
| LV dysfunction | 3.9 | 1.5–6.4 | 0.002 |
| NLR | 3.03 | 1.4–6.8 | 0.005 |
| Plus valve surgery | 2.94 | 1.4–6.5 | 0.006 |

With the European System for Cardiac Operative Risk Evaluation (EuroSCORE), age did not emerge as a significant predictor of operative mortality. The EuroSCORE was not used in evaluating outcomes other than mortality.

AKI = acute kidney injury; CABG = coronary artery bypass graft surgery; CHF = congestive heart failure; CI = confidence interval; HR = hazard ratio; LV = left ventricle; NLR = neutrophil-lymphocyte ratio.

*Table 4. Predictors of Operative Mortality for Isolated Coronary Artery Bypass Graft Surgery Patients (n = 1,183)*

| Variable | HR | 95% CI | p Value |
|---|---|---|---|
| Elevated NLR | 4.9 | 1.2–23 | 0.03 |
| Log EuroSCORE | 1.1 | 1.03–1.11 | 0.0001 |
| Renal failure | 5.2 | 1.8–14.2 | 0.001 |

CI = confidence interval; EuroSCORE = European System for Cardiac Operative Risk Evaluation; HR = hazard ratio; NLR = neutrophil-lymphocyte ratio.

baseline lymphocyte count in whom it did not reach statistical significance, possibly owing to the small number of patient in this group. However, in the group with low lymphocytes, as a whole, mortality was significantly higher in comparison with the control group ($p < 0.0001$). By definition, both elevated neutrophils and reduced lymphocyte count denote an elevated NLR. Operative mortality was especially high in this group ($p < 0.0001$). Results for the various WBC subgroups, comparisons within the subgroups, and comparison with the control group are shown in Table 5.

### *Late Survival*

Of the 2,836 patients discharged, follow-up for survival to 16 years was available for 2,622 (93%). Kaplan-Meier estimates of survival are shown in Figure 1. By Cox multivariate regression, predictors of late mortality were age ($p < 0.0001$), sex ($p < 0.0001$), reduced left ventricle function ($p < 0.0001$), mitral regurgitation ($p = 0.01$), congestive heart failure ($p < 0.0001$), atrial fibrillation ($p = 0.006$), pulmonary hypertension ($p = 0.001$), renal failure ($p < 0.0001$), and elevated NLR ($p < 0.0001$; Table 6). To verify that operative mortality was not the determining factor for the difference in long-term survival, we performed a separate analysis of survival for patients who survived surgery. Elevated NLR still emerged as a predictor of late mortality ($p = 0.0003$). Kaplan-Meier estimates of survival for isolated CABG patients show reduced survival for patients with elevated NLR ($p < 0.0001$; Fig 2). That remained also after correcting for operative mortality ($p = 0.002$).

In summary, patients with abnormal values of WBC subtypes had increased mortality as well as increased incidence of adverse events. In all groups, including those with WBC subtypes within normal range, elevated NLR emerged as a predictor of mortality, both short term and long term. Mortality was especially high among patients having both elevated neutrophil and low lymphocyte count.

## Comment

Elevated WBC count and WBC subtypes represent an inflammatory process that has been associated with increased risk in coronary artery disease patients. Neutrophilia is associated with atherosclerotic plaque disruption and hypercoagulability [12]. Neutrophils play an important role in the acute inflammatory response to tissue injury and are associated with reperfusion injury [13, 14]. The negative prognostic implications of an elevated neutrophil count have been documented [15]. Studies by Cooper and associates [16] and Gurm and associates [17] demonstrated a significant association between altered WBC subtypes, namely, elevated neutrophil count as well as reduced lymphocyte count, with cardiac death. More recent studies found the ratio of neutrophils to lymphocytes to be a yet more sensitive predictor of adverse outcomes in coronary patients [2, 9, 15, 18].

In patients with coronary artery disease, raised neutrophil counts and reduced lymphocyte counts have been shown to be markers of worse outcomes in patients with stable coronary disease [2] as well as acute coronary events and ischemic stroke [3, 5, 15]. The NLR has been found to be a predictor of late mortality after percutaneous coronary intervention [18]; and the NLR significantly improves the Framingham risk score in predicting coronary artery disease–related mortality [19].

Gibson and colleagues [9] examined the impact of elevated NLR in patients undergoing coronary artery

*Table 5. Mortality in White Cell Population Subgroups, Univariate Analysis*

| Variable | n | Mortality | p Value Within Group | p Value Compared With Controls |
|---|---|---|---|---|
| Normal neutrophils | 2,459 | 129 (5) | | |
| NLR >2.6 | 844 (34) | 78 (9) | <0.0001 | … |
| NLR <2.6[a] | 529 (65) | 22 (4) | … | … |
| Elevated neutrophils | 568 | 62 (11) | … | <0.0001 |
| NLR >2.6 | 485 (85) | 59 (12) | 0.01 | <0.0001 |
| NLR <2.6 | 83 (15) | 3 (4) | … | 0.8 |
| Low lymphocytes | 433 | 70 (16) | … | <0.0001 |
| NLR >2.6 | 385 (89) | 65 (17) | 0.2 | <0.0001 |
| NLR <2.6 | 48 (11) | 5 (10) | … | … |
| High neutrophils + low lymphocytes | 92 | 22 (24) | … | <0.0001 |

[a] Controls are patients with neutrophil-lymphocyte ratio (NLR) less than 2.6 and normal baseline neutrophil count.

Values are n (%).

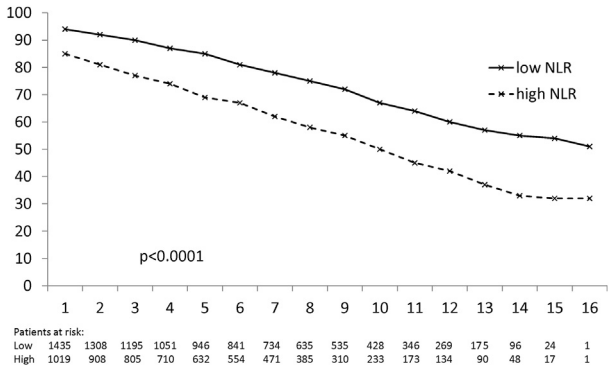


*Fig 1. Long-term survival of patients with elevated neutrophil-lymphocyte ratio (broken line) compared with patients with nonelevated neutrophil-lymphocyte ratio (solid line). NLR = neutrophil-lymphocyte ratio.*

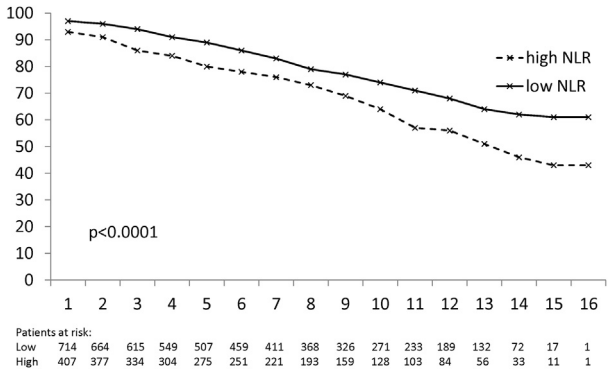


*Fig 2. Long-term survival of isolated coronary artery bypass graft surgery patients with elevated neutrophil-lymphocyte ratio (broken line) compared with patients with nonelevated neutrophil-lymphocyte ratio (solid line). NLR = neutrophil-lymphocyte ratio.*

surgery. Their study included patients undergoing concomitant procedures as well as prior coronary surgery with follow-up to 4 years. In their study, elevated NLR was found to be a predictor of operative as well as postoperative mortality. In a separate analysis including preoperative total WBC, monocyte count, and NLR as well as the EuroSCORE, they found that the WBC in itself did not emerge as a predictor of mortality, but rather the ratio of neutrophils to lymphocytes. Our study examined the effect of elevated NLR within the various combinations of WBC values; in all, NLR emerged as a predictor of operative mortality.

Most studies to date report on outcomes of patients with coronary artery disease. There is a paucity of reports on outcomes of patients with valvular disease. Condado and associates [20] showed increased occurrence of 30-day adverse outcomes in patients with elevated NLR undergoing transcatheter aortic valve implantation. Gursoy and colleagues [21] showed an association between elevated NLR and mitral prosthetic valve thrombosis. Although the suggested mechanism connecting elevated NLR to coronary disease is through inflammatory pathways, no such mechanism has been suggested for valve disease. Habib and associates [22] showed that an elevated NLR was a predictor of short-term mortality as well as survival at 3 years after aortic valve replacement. To date, publications in the cardiac literature are almost exclusively reports of NLR and its relationship to outcomes. We could not find any studies in the English literature that shed light on mechanism or on background variables that are represented by elevated NLR, and possibly are the cause of outcomes. Consequently, we could not find any report on modulation of the inflammatory process to reduce the negative prognostic the effect of high NLR.

*Table 6. Predictors of Late Mortality*

| Variable | HR | 95% CI | *p* Value |
|---|---|---|---|
| Elevated NLR | 1.19 | 1.11–1.28 | <0.0001 |
| Age | 1.04 | 1.03–1.05 | <0.0001 |
| Female | 1.11 | 1.04–1.19 | 0.003 |
| Diabetes mellitus | 1.25 | 1.16–1.33 | <0.0001 |
| Atrial fibrillation | 1.36 | 1.04–1.23 | 0.006 |
| CHF | 1.22 | 1.12–1.31 | <0.0001 |
| LV dysfunction | 1.19 | 1.10–1.28 | <0.0001 |
| Mitral regurgitation | 1.10 | 1.02–1.19 | 0.01 |
| Renal failure | 1.42 | 1.33–1.56 | <0.0001 |
| Pulmonary hypertension | 1.14 | 1.05–1.22 | 0.001 |

CHF = congestive heart failure; CI = confidence interval; HR = hazard ratio; LV = left ventricle; NLR = neutrophil-lymphocyte ratio.

In our study, we found that elevated NLR was associated with (1) more severe baseline morbidity, and (2) more postoperative adverse events, independent of other baseline characteristics. High neutrophil count and low lymphocyte count are both associated with higher risk of mortality. There is a third group, in which both neutrophils and lymphocytes are within normal range, but the ratio between the two is elevated. That exposes patients at a "latent" risk. Along with known risk factors, NLR still emerged as an independent predictor of poor outcomes.

The purpose of our present study was to better establish any relationship between elevated NLR values and operative outcomes in a heterogenous patient population undergoing cardiac surgery. We believe this adequately represents patients referred for cardiac surgery in the present era. To our knowledge, ours is the largest series reported in the English literature, and the first to report a correlation between elevated NLR and very long term survival after open heart surgery.

Although the association of elevated neutrophils and coronary artery disease has been previously established, our data show that an elevated ratio of neutrophils to lymphocytes in itself has prognostic significance, also in the presence of a normal neutrophil count. To our knowledge, this has not been previously described. Even after discharge from surgery, patients with elevated baseline NLR are at a higher ongoing risk of reduced survival than patients with nonelevated NLR. This is independent of the fact that these patients suffer from more extensive comorbidity.

Our present study cannot offer insight into the question of mechanism. We can only reiterate the potential mechanisms suggested by Gibson and colleagues [9], namely, the association between neutrophils and ischemic injury. Neither can we answer the question of whether prophylactic treatment with antiinflammatory agents can temper any adverse events; these are topics for future investigation. With more advanced nonsurgical solutions becoming available, patients referred for heart surgery are sicker than in the past and pose a higher surgical risk. Current risk scores may not offer accurate enough estimates of outcomes. Our data, as well as those of others cited from the literature, support including baseline NLR values in the estimation of operative risk.

### *Study Limitations*

There are a number of limitations to our study. It is retrospective, and well-established inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein are not universally available. Therefore, we do not have a complete inflammatory profile for all patients. Our inclusion criteria required preoperative complete blood cell count in proximity to surgery, and those values are missing for 1,036 patients, either because of urgency or because laboratory results came from outside our institution, or laboratory results were beyond 2 weeks before surgery. However, the profile of these patients is similar to those of patients with available complete blood count and the study cohort is substantial, so we believe that would not have changed outcomes.

### *Conclusion*

Elevated NLR values are associated with a higher incidence of adverse outcomes after heart surgery. They represent an inflammatory process, and emerged as an independent predictor of adverse events also in the presence of other known risk factors. A prospective study is warranted to better define the prognostic significance of NLR values, and try to determine whether prophylactic treatment with antiinflammatory agents can temper poor outcomes, both short term and long term. It may be warranted to include the NLR in the preoperative risk assessment score.

## References

1. Pearson T, Mensah G, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice. A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499–511.
2. Papa A, Emdin M, Passino C, Michelassi C, Battaglia D, Cocci F. Predictive value of elevated neutrophil-lymphocyte ratio on cardiac mortality in patients with stable coronary artery disease. Clin Chim Acta 2008;395:27–31.
3. Tamhane UU, Aneja S, Montgomery D, Rogers EK, Eagle KA, Gurm HS. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol 2008;102:653–7.
4. Azab B, Zaher M, Weiserbs KF, et al. Usefulness of neutrophil to lymphocyte ratio in predicting short- and long-term mortality after non-ST-elevation myocardial infarction. Am J Cardiol 2010;106:470–6.
5. Nunez J, Nunez E, Bodi V, et al. Usefulness of the neutrophil to lymphocyte ratio in predicting long-term mortality in ST segment elevation myocardial infarction. Am J Cardiol 2008;101:747–52.
6. Verdoia M, Schaffer A, Barbieri L, et al. Impact of neutrophil to lymphocyte ratio on periprocedural myocardial infarction in patients undergoing non-urgent percutaneous coronary revascularization. Neth Heart J 2016;24:462–74.
7. Akpek M, Kaya MG, Lam YY, et al. Relation of neutrophil/lymphocyte ratio to coronary flow to in-hospital major adverse cardiac events in patients with ST-elevated myocardial infarction undergoing primary coronary intervention. Am J Cardiol 2012;110:621–7.
8. Park JJ, Jang HJ, Oh IY, et al. Prognostic value of neutrophil to lymphocyte ratio in patients presenting with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Am J Cardiol 2013;111:636–42.
9. Gibson P, Croal BL, Cuthbertson BH, et al. Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. Am Heart J 2007;154:995–1002.
10. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European System for Cardiac Operative Risk Evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16:9–13.
11. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.
12. Madjid M, Awan I, Willerson JT, Casscells SW. Leukocyte count and coronary heart disease: implications for risk assessment. J Am Coll Cardiol 2004;44:1945–56.
13. Horne BD, Anderson JL, John JM, et al. Which white blood cell types predict increased cardiovascular risk? J Am Coll Cardiol 2005;45:1638–43.
14. Segel GB, Halterman MW, Lichtman MA. The paradox of the neutrophil's role in tissue injury. J Leukoc Biol 2011;89:359–72.
15. Guasti L, Dentali F, Castiglioni L, et al. Neutrophils and clinical outcomes in patients with acute coronary syndromes and/or cardiac revascularization. A systematic review on more than 34,000 subjects. Thromb Haemost 2011;106:591–9.
16. Cooper HA, Exner DV, Waclawiw MA, Domanski MJ. White blood cell count and mortality in patients with ischemic and nonischemic left ventricular systolic dysfunction (an analysis of the Studies of Left Ventricular Dysfunction [SOLVD]). Am J Cardiol 1999;84:252–7.
17. Gurm HS, Bhatt DL, Lincoff AM, et al. Impact of preprocedural white blood cell count on long term mortality after percutaneous coronary intervention: insights from the EPIC, EPILOG, and EPISTENT trials. Heart 2003;89:1200–4.
18. Duffy BK, Gurm HS, Rajagopal V, Gupta R, Ellis SG, Bhatt DL. Usefulness of an elevated neutrophil to lymphocyte ratio in predicting long-term mortality after percutaneous coronary intervention. Am J Cardiol 2006;97:993–6.
19. Shah N, Parikh V, Patel N, et al. Neutrophil lymphocyte ratio significantly improves the Framingham risk score in prediction of coronary artery disease mortality: insights from the National Health and Nutrition Examination Survey-III. Int J Cardiol 2014;171:390–7.
20. Condado JF, Junpaparp P, Binongo JN, et al. Neutrophil-lymphocyte ration (NLR) and platelet-lymphocyte ratio (PLR) can risk stratify patients in transcatheter aortic-valve replacement (TAVR). Int J Cardiol 2016;223:444–9.
21. Gursoy MO, Karakoyun S, Kalcik M, et al. Usefulness of novel hematologic inflammatory parameters to predict prosthetic mitral valve thrombosis. Am J Cardiol 2014;113:860–4.
22. Habib M, Thawabi M, Hawatmeh A, Habib J, ElKhalili W, Shamoon F, Zaher M. Value of neutrophil to lymphocyte ratio as a predictor of mortality in patients undergoing aortic valve replacement [Abstract]. J Am Coll Cardiol 2015:65.