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Neutrophil/lymphocyte ratio as a mortality predictor following coronary artery bypass graft surgery

Koroner arter baypas greft cerrahisi sonrası mortalite prediktörü olarak nötrofil/lenfosit oranı

Ertekin Utku Ünal,[1] Ahmet Barış Durukan,[2] Anıl Özen,[1] Emre Kubat,[1] Sinan Sabit Kocabeyoğlu,[1] Okan Yurdakök,[1] Elif Durukan,[3] Cemal Levent Birincioğlu[1]

[1]Department of Cardiovascular Surgery, Türkiye Yüksek İhtisas Training and Research Hospital, Ankara, Turkey
[2]Department of Cardiovascular Surgery, Medicana International Ankara Hospital, Ankara, Turkey
[3]Department of Public Health, Medical Faculty of Başkent University, Ankara, Turkey

Background: In this study, we aimed to investigate the newly introduced inflammatory biomarker, neutrophil/lymphocyte ratio, as a mortality predictor following coronary artery bypass graft (CABG) surgery.

Methods: Between December 2011 and April 2012, 210 consecutive patients who underwent isolated CABG surgery in our clinic were prospectively analyzed. The baseline characteristics of the patients and preoperative neutrophil/lymphocyte ratio were determined. The postoperative follow-up was 86.1±38.9 days. The primary endpoint was all-cause mortality.

Results: Eight patients (3.8%) died of whom four deaths occurred during the first 30 days of follow-up. Univariate analyses revealed a significant difference in the preoperative neutrophil/lymphocyte ratio between the groups in which mortality was seen and the group in which no mortality was observed (p=0.037). The Receiver operating characteristic (ROC) curve showed a threshold value of 2.81 for neutrophil/lymphocyte ratio (AUC=0.72, sensitivity: 75%, specificity: 67%). Logistic regression analysis of the variables with significant differences between two groups revealed that the neutrophil/lymphocyte ratio over its threshold value was an independent predictor for mortality (OR 6.47, 95% CI 1.18-35.38, p=0.031).

Conclusion: Neutrophil/lymphocyte ratio, which can be easily calculated, can be used as an independent factor in predicting early mortality following CABG surgery.

Key words: Coronary artery bypass grafting; lymphocyte; mortality; neutrophil.

Amaç: Bu çalışmada yeni geliştirilen bir enflamatuvar parametre olan nötrofil/lenfosit oranının koroner arter baypas greft (KABG) cerrahisi sonrası erken dönem mortalite prediktörü olarak etkisi araştırıldı.

Çalışma planı: Aralık 2011 - Nisan 2012 tarihleri arasında kliniğimizde izole KABG cerrahisi yapılan ardışık 210 hasta prospektif olarak incelendi. Hastaların başlangıç özellikleri ve ameliyat öncesi nötrofil/lenfosit oranları belirlendi. Ameliyat sonrası takip süresi 86.1±38.9 gün idi. Primer sonlanım noktası, tüm-nedenlere bağlı mortalite olarak belirlendi.

Bulgular: Dört hastada ameliyat sonrası ilk 30 günde olmak üzere, toplam sekiz hastada (%3.8) mortalite görüldü. Tek değişkenli analizlerde ameliyat öncesi nötrofil/lenfosit oranı, mortalite gelişen ve gelişmeyen gruplar arasında anlamlı derecede farklı olarak saptandı (p=0.037). Alıcı işlem karakteristikleri (ROC) eğrisinde nötrofil/lenfosit oranı için eşik değeri 2.81 olarak belirlendi (AUC=0.72, duyarlılık: %75, özgüllük: %67). İki grup arasında anlamlı farka sahip olan değişkenler ile yapılan lojistik regresyon analizinde ise, nötrofil/lenfosit oranı için eşik değerinin üzerinde olması mortalite için bağımsız bir prediktör olarak saptandı (OR 6.47, %95 CI 1.18-35.38, p=0.031).

Sonuç: Kolay bir şekilde hesaplanabilen nötrofil/lenfosit oranı KABG cerrahisi sonrası erken dönem mortaliteyi öngörmede bağımsız bir faktör olarak kullanılabilir.

Anahtar sözcükler: Koroner arter baypas greftleme; lenfosit; mortalite; nötrofil.

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Correspondence: Ertekin Utku Ünal, M.D. Türkiye Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Kalp ve Damar Cerrahisi Kliniği, 06230 Sıhhiye, Ankara, Turkey.
Tel: +90 312 - 306 17 14 e-mail: utkuunal@gmail.com

Coronary artery bypass grafting (CABG) is the definitive surgical treatment for coronary artery disease (CAD). However, despite surgical advances, morbidity and mortality still occur.[1] In addition, determining the degree of risk prior to surgery has become more important. The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is a widely accepted and commonly used application for risk stratification in adult cardiac surgery.[2] Besides the concerns about its overestimation/underestimation, there has always been the desire to establish more reliable predictors and systems that can employ them.

The inflammatory process in the pathogenesis of atherosclerosis is a well-known entity.[3] There are vast numbers of reports in the literature about the biomarkers of inflammation and their association with cardiovascular risk.[4] The total white blood cell count (WCC) has been shown to be a predictor of mortality after CABG.[5,6] However, it has been demonstrated that measurements of specific subtypes of WCCs and their ratios have more predictive value than the WCC count alone.[7,8] The neutrophil-to-lymphocyte ratio (NLR) is such a measurement instrument, and it has been determined to be a potentially useful biopredictor of inflammation in cardiovascular diseases.[9]

The aim of this study was to evaluate the correlation between the NLR and in-hospital mortality along with major adverse cardiac events (MACE) after CABG surgery.

PATIENTS AND METHODS

Between December 2011 and April 2012, 262 consecutive patients underwent isolated CABG at our institution. A total of 52 patients who had either undergone redo CABG or off-pump CABG, experienced myocardial infarction (MI) within the previous week, or suffered from acute or chronic infections, known malignancies, or other hematological problems were excluded from the study. That left 210 patients (173 males, 37 females; mean age 60.7±10.3 years; range 33 to 84 years) were included in the study. This study complied with the Declaration of Helsinki, and ethical approval was granted by the local institutional review board. In addition, informed consent was obtained from all of the patients.

The baseline clinical data, New York Heart Association (NYHA functional class, cardiovascular risk factors, medical history, and the EuroSCORE II were obtained prospectively. Preoperative blood samples were used for the baseline data, and additional blood samples were also obtained at the postoperative first and second days. The total WBC analysis, including differential leukocyte count, was measured using the Sysmex SE 9500 automated flow counter (Roche Diagnostics, Mannheim, Germany). Furthermore, the total WCC along with the neutrophil and lymphocyte counts were recorded preoperatively, and the NLR was also calculated.

The primary end-point was all-cause in-hospital mortality following surgery. Postoperative mortality was defined as death any time after the surgery during the hospital stay, and MACE included events such as postoperative MI, reoperation due to hemodynamic instability, and early repeated revascularization. Postoperative MI was defined as the occurrence of a creatine kinase myocardial band (CK-MB) along with troponin I levels five times above the upper normal limits troponin I level above 15 ng/ml at postoperative day one and above 35 ng/ml at postoperative day two and/or new electrocardiographic changes.[10] Combined adverse events were defined as all-cause mortality, postoperative MI, reoperation, prolonged ventilation, prolonged intensive care unit (ICU) and hospital stay, and rehospitalization for any cardiac cause.

Statistical analyses

Normally distributed continuous variables were expressed as mean ± standard deviation (SD) or median values with an interquartile range if not normally distributed. Categorical variables were expressed as numbers and percentages. Demographic characteristics, perioperative variables, and calculated values were compared using an independent samples t-test or the Mann-Whitney U test for continuous variables and a chi-square test or Fisher's exact test for categorical variables. Correlations were assessed using Pearson's correlation test. Receiver-operating characteristic (ROC) curve analysis was used to determine the optimum cut-off levels of the preoperative NLR to predict mortality. The odds ratios (ORs) and 95% confidence intervals (CIs) were estimated with different logistic regression models that were created to determine independent predictors of mortality. A p value of <0.05 was considered to be statistically significant, and all statistical analyses were performed using the SPSS for Windows version 15.0 statistical software program (SPSS Inc., Chicago, IL, USA).

RESULTS

The patient demographics, preoperative blood test results, and operative characteristics of patients are summarized in Table 1. Out of 210 patients, eight died during the hospital stay following surgery, and four more died during the first 30 days of follow-up.

Table 1. Preoperative and operative characteristics of patients versus overall mortality

Patient characteristics	All patients (n=210)	Mortality		
		No (n=202)	Yes (n=8)	*p*
Age (years) (mean±SD)	60.7±10.3	60.3±10.3	70.3±5.6	0.007*
Male, n (%)	173 (82.4)	168 (83.2)	5 (62.5)	0.149†
Hypertension, n (%)	131 (62.4)	125 (61.9)	6 (75.0)	0.713†
Hyperlipidemia, n (%)	114 (54.3)	111 (55.0)	3 (37.5)	0.474†
Diabetes mellitus, n (%)	74 (35.2)	72 (35.6)	2 (25.0)	0.715†
Ejection fraction	55 (50-60)	55 (50-60)	55 (40-55)	0.247‡
New York Heart Association I, n (%)	148 (70.5)	145 (71.8)	3 (37.5)	0.051†
New York Heart Association II-III, n (%)	62 (29.5)	57 (28.2)	5 (62.5)	
EuroSCORE	1.0 (0.7-1.5)	0.9 (0.7-1.5)	1.9 (1.1-2.6)	0.006‡
Preoperative blood results				
Renal function				
Creatinine (mg/dl)	1.01±0.56	1.01±0.66	1.03±0.35	0.951*
Estimated GFR (ml/min per 1.73 m^2)	93.2±34.3	93.9±34.5	76.0±24.1	0.150*
Hematological parameters				
Total white cell count (x10^9/L)	8.3±2.0	8.3±2.0	8.2±1.4	0.878*
Neutrophil count (x10^9/L)	5.3±1.7	5.2±1.7	5.6±1.6	0.532*
Lymphocyte count (x10^9/L)	2.2±0.7	2.2±0.7	1.6±0.4	0.035*
Neutrophil-to-lymphocyte ratio	2.72±1.36	2.68±1.33	3.67±1.69	0.043*
Operative data				
Cardiopulmonary bypass duration (minutes)	96 (70-120)	94 (70-120)	124 (102-145)	0.054‡
Cross-clamp time (minutes)	63 (46-80)	63 (45-79)	78 (60-88)	0.296‡
Number of bypass grafts	3 (3-4)	3 (2-4)	4 (3-4)	0.328‡

EuroSCORE: European System for Cardiac Operative Risk Evaluation; GFR: Glomerular filtration rate; Data is expressed as mean±SD for normally distributed data and median (interquartile range) for skewed data or as percentage for categorical variables; * Independent-samples t-test; † Fisher's exact test; ‡ Mann-Whitney U test.

The deaths occurred in predominantly male patients (not significant) who were notably older (p=0.007) and had greater preoperative risk scores (p=0.006). Neither the total WCC nor the neutrophil count was associated with mortality, but the reduced lymphocyte count (p=0.035) and increased NLR (p=0.043) were associated with an increased risk of death (Table 1). The cardiopulmonary bypass (CPB) duration was higher in the patients who died, but there was no significant correlation (p=0.054).

The ROC curves for the NLR were connected with mortality following CABG. The area under curve (AUC) for the preoperative NLR was 0.72 (95% CI 0.55- 0.88; p=0.038). Using a cut-off value of 2.81, the preoperative NLR predicted mortality with a sensitivity of 75% and specificity of 67%. When the study population was divided into two groups using a cut-off value of 2.81, the OR for patients with a NLR greater than 2.81 was calculated as 6.04 (95% CI 1.19-30.76; p=0.015; x^2=5.94). In addition, a higher NLR was associated with prolonged hospital stay (p=0.021). When the risk factors for CAD were evaluated, there were no significant differences the between the patients, except for those with hyperlipidemia (p=0.012) (Table 2). However, the EuroSCORE values of the patients were statistically significantly different among the groups (p=0.002).

Furthermore, there was a strong correlation between CPB duration, aortic cross-clamp time (r=0.869; p<0.001), and number of bypass grafts (r=0.663; p<0.001). The NLR, a measured value, and was related to the neutrophil and lymphocyte counts. Therefore, the NLR and CPB duration were entered into the subsequent multivariate regression models. The EuroSCORE was included in the regression model since it is used to comprehensively evaluate preoperative data. In the logistic regression model, which included the preoperative total WCC, the preoperative NLR, EuroSCORE, and CPB duration, the only independent predictors of mortality were the NLR (OR 1.59 per unit; 95% CI 1.02-2.45; p=0.036) and the CPB duration (OR 1.25 per 10 min; 95% CI 1.01-1.56; p=0.041) (Table 3).

In a subgroup of the patients with a normal WCC (≤9.7 x10^9/L, n=172), the preoperative NLR cut-off value of 2.81 remained a strong univariate

Table 2. Patient characteristics and outcomes with regard to the neutrophil-to-lymphocyte ratio

	Neutrophil-to-lymphocyte ratio										
	≤2.81 (n=137)					>2.81 (n=73)					
	n	%	Mean±SD	Median	Range	n	%	Mean±SD	Median	Range	*p*
Patient characteristics											
Age (years)			59.8±9.7					62.3±11.3			0.093*
Male	113	82.5				60	82.2				0.958†
Hypertension	85	62.0				46	63.0				0.890†
Diabetes mellitus	46	33.6				28	38.4				0.490†
Hyperlipidemia	83	60.6				31	41.5				0.012†
Ejection fraction				55	50-60				55	45-58	0.095‡
EuroSCORE				0.8	0.6-1.4				1.1	0.8-1.8	0.002‡
Outcome following surgery											
Mortality	2	1.5				6	8.2				0.022ϕ
Adverse events	24	17.5				16	21.9				0.439†
Postoperative MI	14	10.2				9	12.3				0.641†
Major adverse cardiac event	14	10.2				14	19.2				0.069†
Prolonged ventilation (>24 hr)	8	5.8				7	9.6				0.315†
Need for inotropes	13	9.5				12	16.4				0.139†
Need for IABP	5	3.6				5	6.8				0.322ϕ
Prolonged ICU stay (>2 days)	19	13.9				15	20.5				0.211†
Prolonged hospital stay (>7 days)	24	17.5				23	31.5				0.021†

SD: Standard deviation; EuroSCORE: European System for Cardiac Operative Risk Evaluation; MI: Myocardial infarction; IABP: Intraaortic balloon pump; ICU: Intensive care unit; Data is expressed as mean ± SD for normally distributed data and median (interquartile range) for skewed data or as a percentage for categorical variables; * Independent-samples t-test; † Chi-square test, ϕ Fisher's exact test, ‡ Mann-Whitney U test.

independent predictor of mortality (OR 6.84; 95% CI 1.33-35.07; p=0.021). In similar multivariate models, the preoperative NLR >2.81 was associated with a six-fold increase in the risk of mortality (OR 6.29; 95% CI 1.01-39.19; p=0.049) in a model that included the total WCC, EuroSCORE, and CPB duration.

DISCUSSION

The most commonly used applied risk score for the evaluation of cardiac operative mortality is the EuroSCORE,[2,11,12] which was first established in 1999 based on 15,000 adult patient records.[13] In 2002, the EuroSCORE II was developed.[14] The main purpose of employing the EuroSCORE is to evaluate the quality of cardiac surgical care,[13] but in the years following the establishment of the EuroSCORE system, major concerns were published regarding the insufficiency of its estimates and its lack of progression.[15] Additionally, another scoring system was designed by the Society of Thoracic Surgeons (STS) and published in 2007.[16] In contrast to the EuroSCORE, the required data entry for the STS is more detailed. There are reports that indicate that the STS score is superior to the EuroSCORE system for special subgroups of cardiac surgery patients.[17-19] However, since the EuroSCORE system is the risk scoring method that is primarily used in our institution, it was used in this study.

The purpose of employing risk stratification systems and biopredictors is to estimate adverse events prior to surgery. Besides the EuroSCORE systems, new markers have also been announced. The total leukocyte count was one of the first biopredictors that was speculated to be related to mortality. Bagger et al.[5] in their huge series of 2,058 patients identified preoperative increased WCC as a predictor of mortality within 30 days following

Table 3. Multivariate predictors of mortality

Variable	OR	95% CI	*p*
Total white cell count (x10^9/L)	0.82	0.52-1.28	0.380
Preoperative neutrophil-to-lymphocyte ratio	1.59	1.03-2.45	0.036
EuroSCORE	1.05	0.85-1.28	0.665
Bypass duration (per 10 minutes)	1.25	1.01-1.56	0.041

EuroSCORE: European System for Cardiac Operative Risk Evaluation.

CABG surgery. Furthermore, in a series of 3,024 patients, Newall et al.[6] documented the relationship between preoperative WCC and perioperative myocardial damage along with one-year mortality and found that WCC was a short-term prognostic marker. However, it is known that the leukocyte count is a nonspecific marker and that it increases due to a variety of events. Therefore, its reliability as a stand-alone marker is suspicious, despite the results of these large series. Unlike these findings, Gibson et al.,[9] a supporter of specific cell count and ratio analysis, in their series of 1,938 patients revealed no relationship between WCC and mortality. In addition, we also believe that more specific subtypes and ratios should be considered, and without any bias of opinion, we determined that mortality was not associated with WCC in our study.

With a tendency toward finding more specific markers, studies on the determination of specific cell types and the measurement of ratios has gained popularity. The relationship between cardiovascular diseases and decreased neutrophil counts was defined long ago,[20] and the connection between the worst-case prognosis of lymphopenia and lymphocytosis, which has a longer survival rate, was also previously documented.[9,21] In our study, we did not discover increased mortality with decreased neutrophil counts, but we did document increased mortality with decreased lymphocyte counts.

Besides these biomarkers, the NLR has more recently come to the forefront. It provides an indicator of inflammatory status that combines neutrophilia and lymphopenia, which are associated with the worst cardiovascular prognoses.[22] We also know that neutrophils produce a variety of inflammatory mediators and reactive oxygen species (ROS) within the myocardium during CPB.[23] In large series, the possible relationship between the NLR and mortality following CABG surgery has been studied in detail. Gibson et al.[9] who were pioneers in this field, demonstrated that the preoperative NLR inferred from differential WCC was prognostic for survival after CABG, but it was independent of well-recognized individual risk factors and the EuroSCORE. Its predictive role in acute coronary syndrome (ACS) has also been documented.[24] In our study, the increased NLR (cut-off: 2.81) in conjunction with the decreased lymphocyte counts predicted mortality. The hospital stay was also longer in patients with an NLR above 2.81, but this may have be related to the longer stay of the patients who died. Moreover, the EuroSCORE values were higher in the patients with an NLR over 2.81, but we did not document their predictive role in MACE or combined adverse events.

We believe that more than a simple causation should exist with regard to the predictive role of the NLR. Therefore, in the logistic regression model, we documented that the NLR is predictive independent of other risk factors, including the EuroSCORE, and this was consistent with the findings in other studies.[9,24,25]

One of the major limitations of our study was that it was comprised of a relatively low number of cases from a single center. Furthermore, there was a lack of long-term data. The short-term follow-up that we conducted may not be reliable enough to make such a definitive conclusion. Another important limitation was the inclusion of patients with elevated leukocyte counts without any demonstrable cause. To overcome this, we performed a subgroup analysis of the patients with normal WCCs, and this verified that an NLR above 2.81 was an independent predictor of mortality with an OR of 6.29.

In conclusion, we believe that the NLR is a very practical and easily measured parameter that can be derived from simple laboratory measurements related to defining mortality following CABG. It is independent of well-known risk factors, including the EuroSCORE system, which is still the most valid tool for assessing operative mortality.

Declaration of conflicting interests

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