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Is Preoperative Eosinopenia an Independent Predictor of Early Mortality for Coronary Artery Bypass Surgery?

Ozge Korkmaz, Asisst Prof,[1] Hakki Kaya, Asisst Prof,[2] Osman Beton, Asisst Prof,[2] Ali Zorlu, Asisst Prof,[2] Sabahattin Göksel, Asisst Prof,[1] Muslim Gül, MD,[3] Ilker Ince, Asisst Prof,[4] Ocal Berkan, Prof,[1] Mehmet Birhan Yilmaz, Prof[2]

Departments of [1]Cardiovascular Surgery and [2]Cardiology, Cumhuriyet University School of Medicine, Sivas; [3]Clinic of Cardiovascular Surgery, Sivas State Hospital, Sivas; [4]Department of Cardiovascular Surgery, Gaziosmanpaşa University School of Medicine, Tokat, Turkey

ABSTRACT

Objective: Coronary artery bypass graft surgery in one of the most effective and widely used methods employed in the treatment of ischemic heart disease, but many factors to various degrees are directly associated with perioperative and postoperative problems. In this study, we evaluated the relationship between preoperative eosinophil count and postoperative mortality in patients who underwent coronary artery bypass graft operation.

Methods: A total of 241 patients (157 males, 84 females) who underwent isolated on-pump coronary artery bypass graft operation between 2011 and 2013 in two centers were evaluated retrospectively. The mean age of patients was 64 ± 11 years. After the mean 6.2 ± 0.8 month follow-up period, 36 (15%) of the 241 patients experienced cardiovascular death. Patients were classified into two groups as those who survived versus those who died.

Results: Eosinophil levels were lower among the patients who died compared to the patients who survived (0.8 [0-3.8] versus 1.7 [0-9.4] ×1000 cells/mm^3; $P < .001$). Optimal cut-off level of eosinophils for predicting mortality was determined as ≤1.6 ×1000 cells/mm^3, with a sensitivity of 85.7% and specificity of 51.0% (area under curve, 0.703; 95% CI, 0.641-0.760).

Conclusion: Eosinopenia was used as the predictor of mortality in pediatric and adult patients in the intensive care units. Eosinopenia after coronary artery bypass graft can be related to the endogenous stress hormones, and insufficiency of the existing cardiac status. Eosinophil levels can assist and facilitate risk stratification for patients with coronary artery bypass graft.

INTRODUCTION

Coronary artery disease (CAD) is the most common type of heart disease, and many factors are involved in the development and progression of atherosclerosis. After plaque formation, the disease may have a wide range of consequences from narrowing in the vessel wall and myocardial ischemia to infarction and sudden cardiac death. Coronary artery bypass graft (CABG) surgery in one of the most effective and widely used methods employed in the treatment of ischemic heart disease. CABG is a complex surgery involving significant operative risks, and many factors to various degrees are directly associated with perioperative and postoperative problems. In addition, patients currently undergoing an operation are not only low-risk patients as in previous years; surgery is performed both in high-risk cardiac and non-cardiac patients [Estafanous 1992]. As a result, postoperative morbidity and mortality is an important problem. Various scoring systems such as EuroSCORE, CABDEAL (creatinine, age, body mass index, diabetes, emergency surgery, abnormal ECG, lung disease), Cleveland Clinic, and various biomarkers including creatinine kinase-myocardial band (CK-MB) [Muehlschlegel 2009], troponin, high sensitive troponin (hs-TnT) [Wang 2013], and brain natriuretic peptide (BNP) [Schachner 2010] are used to predict prognosis during surgery, and there are many ongoing studies investigating new markers. The common goal of these markers is to predetermine these problems and take due precautions to minimize the risks.

There is a large body of evidence to support the contribution of inflammation in the induction and progression of atherosclerosis and even thrombus formation on the ruptured plaque [Libby 2009]. There are studies in the literature that examined the relationship between biomarkers of inflammation and cardiovascular risk. There are also publications suggesting the use of preoperative total white blood cell (WBC) count and neutrophil/lymphocyte ratio as the predictor of mortality after CABG [Gibson 2007]. An eosinophil is a type of leukocyte found in the blood that comes from the myeloid series of cell development and is produced in the bone marrow. They account for 1-4% of all leukocytes in the blood. Their number increases in allergic, parasitic, and various immunologic disorders, while the number decreases in the acute phase of some infections, anaphylactic shock, after cortisol therapy, after stress and in Cushing's syndrome. In addition, eosinopenia has been shown to be a determinant of mortality in pediatric and adult patients in the intensive care units in recent studies [Kim 2013].

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Correspondence: Hakki Kaya, Assist Prof, Department of Cardiology, Cumhuriyet University School of Medicine, Sivas, Turkey; +903462581807; fax: +903462191268 (e-mail: drhakkikaya84@gmail.com).

In a literature search conducted by the authors of the present study, no study was found that evaluated the relationship between preoperative eosinophil count and postoperative mortality in patients who underwent CABG operation. The present study sought an answer for this question: is preoperative eosinophil count an independent predictor of mortality in patients undergoing CABG operation?

PATIENTS AND METHODS

Patient Population and Data Collection

This was a multicenter, cross-sectional and observational study. The data of the patients were collected from patient charts, perfusion, and intensive care unit follow-up cards. Mortality data were obtained from the patient data found on the patient charts and follow-up forms and patient control cards. In all patients, age, sex, diabetes mellitus (DM), hyperlipidemia, hypertension (HT), smoking history, left ventricular ejection fraction (LVEF), preoperative biochemical tests, hemogram parameters, thyroid hormones, and operative medications were evaluated. Blood samples were obtained from the antecubital vein using a sterile 21-gauge needle syringe without stasis within the 24 hours before the operation. Blood samples were drawn from each patient into EDTA tubes and were immediately transported to the laboratory department at room temperature. The assays were performed within 30 minutes of blood sampling. The eosinophil count was determined using an automated analyzer (Mindray BC-6800, Auto Hematology Analyzer, Mindray, Nanshan, Shenzhen, China).

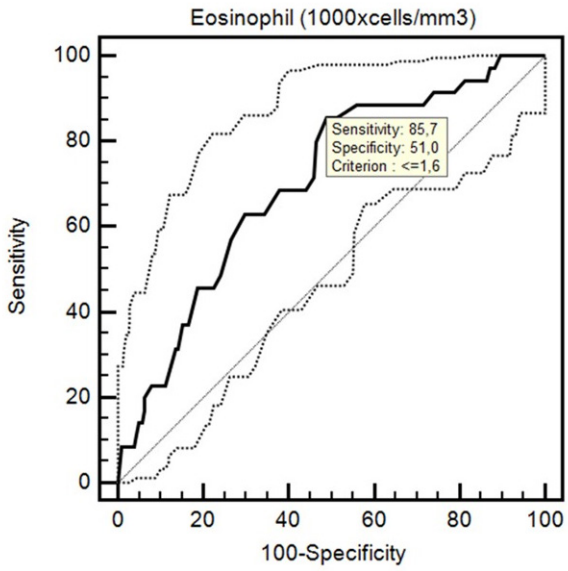
The patients with acute chronic infections, history of blood transfusion in the last six months, severe hepatic or renal insufficiency, chronic systemic inflammatory disease, those receiving systemic steroid therapy, and patients with a known malignancy or those with a hematological problem were excluded. As a result, a total of 241 patients (157 males, 84 females), who underwent isolated on-pump CABG operation between 2011 and 2013 in different centers and for whom study data were available, were retrospectively reviewed. The study was approved by the institutional ethics committee.

Echocardiographic examinations were performed using a Vivid 7 System (GE Medical System, Little Chalfont, UK) with 2.5-5 Mhz probes. The ejection fraction was calculated by employing the Modified Simpson method, while the left atrium (LA) size was examined according to the latest guidelines [Lang 2006]. The chamber sizes were also determined according to the latest guidelines [Lang 2006]. The LA size was measured at the endoventricular systole by M-mode linear dimension, obtained from the parasternal long axis view.

HT was defined as blood pressure 140/90 mmHg on more than two occasions during visit measurements or while receiving antihypertensive treatment. DM was defined as the use of anti-diabetic medication, or a fasting plasma glucose level 126 mg/dL (7.0 mmol/L). Patients who were smoking at the time of admission were considered as current smokers.

Surgical Technique

All study patients underwent cardiopulmonary bypass surgery using aortic-right atrial cannulation. Systemic mild hypothermia and intermittent anterograde and continuous retrograde blood cardioplegia was used for myocardial protection. Retrograde warm blood cardioplegia was performed in all patients before removal of aortic cross clamp. In all patients, revascularization of the left descending coronary artery was accomplished using the left internal mammarian artery. Distal anastomoses were performed using cross clamping and proximal anastomoses were performed using side clamp. The patients received positive inotropic support and intraaortic balloon pump was used, when required.



ROC curve of eosinophils for mortality.

Statistical Analysis

Parametric data were expressed as mean ± standard deviation or median (min-max), while categorical data were expressed as percentages. SPSS 14.0 (SPSS, Chicago, Illinois, USA) was used for statistical procedures. Independent parameters were compared using independent sample t test, while the Mann-Whitney U test with median and min-max was used in case there was no normal distribution. Categorical data were evaluated using the Pearson chi-square test. Correlation was evaluated using the Spearman correlation test. Receiver operator characteristic (ROC) curve analysis was performed to identify the optimal cutoff point of eosinophils (where sensitivity and specificity would be highest) for the prediction of mortality. Areas under the curve (AUC) were calculated to assess the accuracy of the tests. AUC comparisons were performed using the Z test. Variables determined to be statistically significant in univariate analysis, as well as other potential confounders, were used in a multivariate logistic regression model with forward stepwise method in order to determine the independent prognostic factors of cardiovascular mortality. A P value <.05 was considered statistically significant.

Table 1. Baseline Characteristics of Patients

	Patients Who Survived (n = 205)	Patients Who Died (n = 36)	*P*
Baseline characteristics			
Mean age, y	64 ± 11	66 ± 12	.118
Sex, M/F	134/71	23/13	1.000
Presence of hypertension, n (%)	173 (84)	23 (64)	.007
Presence of DM, n (%)	73 (36)	8 (22)	.168
COPD, n (%)	84 (41)	10 (28)	.189
Smoking, n (%)	81 (40)	8 (22)	.073
Preop beta-blocker usage, n (%)	154(75)	21(58)	.037
Preop RAAS inhibitors usage, n (%)	162 (79)	17(47)	<.001
Atrial fibrillation, n (%)	9(4)	2(6)	.671
Echocardiography			
LV ejection fraction, %	50 ± 11	46 ± 12	.066
Left atrial diameter, cm	3.7 ± 0.5	3.7 ± 0.5	.794
LV diastolic diameter, cm	4.7 ± 0.5	4.7 ± 0.3	.635
LV systolic diameter, cm	3.5 ± 0.6	3.3 ± 0.7	.529

Data are presented as the mean ± SD or median (min-max) where indicated. DM indicates diabetes mellitus; COPD, chronic obstructive pulmonary disease; RAAS, renin angiotensin aldosterone system; LV, left ventricle.
P < .05 is considered statistically significant.

Table 2. Laboratory Findings of Patients

	Patients Who Survived (n = 205)	Patients Who Died (n = 36)	*P*
Hemoglobin, g/dL	13.6 ± 2.3	12.5 ± 2.3	.008
Hematocrit, %	40 ± 6	38 ± 7	.017
Mean corpuscular volume	86 ± 6	87 ± 5	.389
Platelet count, $\times 10^3$	265 ± 82	228 ± 89	.014
White blood cell, 1000 x cells/mm^3	8 (4-91)	10 (5-25)	.070
Mean platelet volume, fL	8 (6-17)	8 (6-12)	.681
Red cell distribution width, %	13.6 (11-24)	14 (11-17)	.794
Eosinophil count ($\times$1000 cells/mm^3)	1.7 (0-9.4)	0.8 (0-3.8)	<.001
Basophil count ($\times$1000 cells/mm^3)	0.3 (0-3.8)	0.2 (0-1.3)	.026
Fasting blood glucose, mg/dL	113 (65-393)	120 (79-358)	.297
Blood urea nitrogen, mg/dL	18 (4-51)	17 (7-78)	.627
Creatinine, mg/dL	0.9 (0.5-8.4)	1.1 (0.5-8.3)	.030
Alanine aminotransferase, IU/L	20 (5-121)	27 (6-634)	.286
Aspartat aminotransferase, IU/L	25 (10-765)	27 (12-797)	.226
Creatinine kinase-myocardial band	12 (8-164)	14 (2-118)	.045
Sodium, mmol/L	138 ± 3	138 ± 5	.805
Potassium, mmol/L	4.2 (3.1-5.6)	4.1 (3.3-5.2)	.328
Thyroid stimulating hormone	1 (0-9)	0.8 (0-3)	.220
T3	2.4 ± 0.6	2.3 ± 0.6	.326
T4	1.2 ± 0.3	1.1 ± 0.1	.653
Total cholesterol, mg/dL	170 (87-321)	175 (94-243)	.686
Low-density lipoprotein cholesterol, mg/dL	109 (32-235)	106 (67-200)	.771
High-density lipoprotein cholesterol, mg/dL	33 (15-73)	35 (18-54)	.148
Triglycerides, mg/dL	115 (28-693)	101 (22-281)	.031

Data are presentation as the mean ± SD or median (min-max) where indicated.
P < .05 is considered statistically significant.

RESULTS

The mean age of patients was 64 ± 11 years, while 65% of the patients were male and 35% were female. After the mean 6.2 ± 0.8 month follow-up period, 36 (15%) of the 241 patients experienced cardiovascular death. Patients were classified into two groups as those who survived versus those who died. Eosinophil levels were lower among the patients who died compared to the patients who survived (0.8 [0-3.8] versus 1.7 [0-9.4] $\times$1000 cells/mm^3; *P* < .001). Among the patients who died, hemoglobin, hematocrit, platelet counts, and triglyceride levels were lower, while white blood cell, creatinine, and CK-MB levels were higher. In addition, HT, smoking, preoperative beta-blocker use and renin angiotensin aldosterone system (RAAS) inhibitor use were more frequent among the patients who died compared to those who survived (Tables 1 and 2).

Eosinophil levels were negatively correlated with age, aspartate aminotransferase, and WBC, while being positively correlated with basophil, platelet counts, and triglyceride (Table 3).

In the multivariate cox regression model with forward stepwise method, eosinophil (OR = 0.548; 95% CI, 0.332-0.904; *P* = .019), absence of HT (OR = 4.740; 95% CI, 1.563-14.374; *P* = .006), and the lack of preoperative RAAS inhibitor use (OR = 3.086; 95% CI, 1.025-9.290; *P* = .045) were associated with an increased risk of death, following adjustment for variables determined to be statistically significant in univariate analysis and correlated with eosinophil level (Table 4).

Optimal cutoff level of eosinophils for predicting mortality was determined as 1.6 $\times$1000 cells/mm^3, with a sensitivity of 85.7% and specificity of 51.0% (AUC, 0.703; 95% CI, 0.641-0.760) (Figure).

DISCUSSION

To the best of our knowledge, this study is the first in the literature to investigate the predictive value of eosinophil

Table 3. Spearman Correlation Coefficients for Eosinophils

	Eosinophils	*P*
Age, y	-0.135	.037
Aspartat aminotransferase, IU/L	-0.185	.004
White blood cell, ×1000 cells/mm^3	-0.208	.001
Basophil count, ×1000 cells/mm^3	0.543	<.001
Platelet count, ×103	0.137	.034
Triglycerides, mg/dL	0.143	.036

P < .05 is considered statistically significant.

Table 4. Multivariate Logistic Regression Analysis for In-Hospital Mortality

	P	OR (95% CI)
Absence of hypertension	.006	4.740 (1.563-14.374)
Eosinophil count	.019	0.548 (0.332-0.904)
Preop RAAS inhibitors not used	.045	3.086 (1.025-9.290)

P < .05 is considered statistically significant. All the variables from Table 1 were examined and only those with *P* < 0.1 (presence of hypertension, smoking, preop beta-blocker usage, preop renin angiotensin aldosterone system (RAAS) inhibitor usage, left ventricle ejection fraction, hemoglobin, hematocrit, platelet count, white blood cell, eosinophils, basophils, creatinine, creatinine kinase-myocardial band, and triglycerides) and correlated with eosinophil count (age and aspartat aminotransferase) were enrolled into a multivariate logistic regression model with forward stepwise method.

levels for mortality after CABG in patients with CAD. In this study, we demonstrated that eosinophil levels decreased significantly among patients who died after CABG. Among the patients who died, hemoglobin, hematocrit, platelet counts, and triglyceride levels were lower, while WBC, creatinine, and CK-MB levels were higher. In addition, HT, smoking, preoperative beta-blocker use and RAAS inhibitor use were more frequent among the patients who died compared to the patients who survived. Furthermore, eosinophil levels were negatively correlated with age, aspartate aminotransferase, and WBC, while being positively correlated with basophil, platelet counts, and triglyceride. However, after evaluating these parameters, we determined that lower eosinophil levels were strongly associated with increased mortality in the period following CABG.

In today's practice of cardiovascular surgery, the targets for morbidity and mortality have been met in low-risk patient groups. Therefore, predicting which patients have high mortality risk in the preoperative period and taking necessary precautions to minimize the existing risks have become the major objectives. There are many studies demonstrating that high-risk patients benefit more from surgery [European Study Group 1982]. Although mortality rate after cardiovascular operations including CABG has decreased over years, there has been a relative increase in the risk of mortality in the last decade associated with a higher number of elderly high-risk patients undergoing operation [Finks 2011; Ivanov 1998].

Many studies have been conducted to determine preoperative and postoperative variables that could affect the outcomes in patients undergoing CABG operation. In recent years, preoperative prediction of prognosis before open heart surgery using risk scoring methods plays an important role in operation decision given by the patient and surgical team. In addition to prediction of mortality, foreseeing perioperative and postoperative complication and taking preventive measures improves functional capacity in the long term and increases life expectancy. Many studies have been performed to develop risk scores, or to identify risk factors for patients undergoing CABG or cardiac surgery in general. Parsonnet, Pons and EuroSCORE only predict mortality [Ivanov 1998; Wouters 2002], while Cleveland Clinic, Ontario Province, French, and Society of Thoracic Surgeons scoring systems have been developed to predict both mortality and morbidity [Heijmans 2003]. Cabdeal, New York State, Northern New England, Magovern, Toronto, Toronto (modified), UK national score, and Veterans Affairs risk scoring systems were designed to predict mortality in the early period in patients undergoing CABG [Nilsson 2006]. When risk-scoring systems are compared to each other, Cleveland Clinic and EuroSCORE appear to be more prominent in preoperative risk assessment. However, scoring systems must be simple, accurate, validated, up-to-date, and cheap in order to gain acceptance. At the same time, risk factors that are regarded as criteria must be objective, attainable, and resistant to distortion. Due to all these reasons, developing an ideal risk scoring system is considerably difficulty and laborious [Hannan 2006].

Many biomarkers are used as the predictor of mortality in coronary artery bypass graft surgery, and Hannan et al reported alkaline phosphatase, alanine aminotransferase (ALT), and prothrombin time as independent predictors in CABG [Hannan 2015]. In the ensuing studies, elevated BNP, troponin T, C-reactive protein (CRP), creatinine kinase (CK), and CK-MB levels before the operation were suggested to indicate high mortality after CABG surgery. In addition, elevated BNP levels were suggested to be of use as the predictor of mortality in the presence of myocardial infarction, cardiogenic shock, and pulmonary embolism [Preeshagul 2013].

Inflammation is a key process in the induction, development, and progression of atherosclerosis. The studies well-document elevation of serum acute phase proteins with the progression of atherosclerosis and other conditions associated with atherosclerosis such as coronary artery disease and myocardial infarction [Ridker 2000; Garlanda 2005]. Various studies showed that WBC count and subunits reflected inflammation and had a prognostic value in cardiovascular disorders [Guasti 2011]. Total leukocyte count is the first parameter that was implicated as a predictor of mortality. In

a large series of 2,058 patients, Bagger et al emphasized that an increase in the white blood cell count in the preoperative period predicted mortality occurring within the first 30 days after CABG operation. However, some studies did not report any relationship between WBC count and mortality [Gibson 2007]. In an attempt to determine more specific markers, studies evaluating the subtypes of WBC and their proportions to each other have gained an increasing popularity. The relationship between the decrease in neutrophil count and cardiovascular diseases has been previously established, and in addition, previous reports documented a relationship between the presence of lymphopenia/lymphocytosis and prognosis [Gibson 2007]. In addition to these biomarkers, neutrophil/lymphocyte ratio has attracted a recent interest. An increased neutrophil count accompanied by lymphopenia indicates extremely poor cardiovascular prognosis, and a direct relationship with mortality after CABG surgery has been established [Gibson 2010].

There has been a recent interest in eosinophilia and many studies have been conducted on this subject. This recent interest owes to evidence supporting the modulation of eosinophil function to correct tissue damage and deliver an effective therapy in diseases such as asthma. Eosinopenia occurs in the acute period of the events (shock, advanced pyogenic infections, trauma, surgery). Glucocorticoids and adrenalin were found to decrease eosinophil count, and beta-blockers were found to limit eosinopenia produced by adrenalin. The mechanisms which lead to eosinopenia under these circumstances are not fully understood; however, it is known that eosinopenia is often related to acute inflammation or stress [Wardlaw 1994]. In addition, eosinopenia is used as a biomarker for infections, and recently, it was used as the predictor of mortality in pediatric and adult patients in the intensive care units. Eosinopenia occurring in these patients is considered to be associated with an increase in glucocorticoid and epinephrine levels caused by acute stress [Levinson 2011]. Acute phase reactants, in addition to inflammatory cytokines such as tumor necrosis factor, have been implicated in decreased eosinophil count [Bass 1980]. Based on these theories, eosinopenia can be linked to two basic factors in patients who died after CABG surgery. The first factor is the stress related to the operation and an associated release of stress hormones, particularly glucocorticoids and endogenous epinephrine. The second factor can be insufficiency of the existing cardiac status that potentiates the effect of first factor and generates endogenous adrenergic response.

Limitations

The BNP analysis method was not available at our laboratory, and was therefore not included in the study. The primary hypothesis of the present study was the existence of a relationship between eosinophil levels and mortality after CABG. The correlation of eosinophils with other inflammatory markers such as CRP could not be evaluated, while cytokines were not included in the study due to their high costs.

We believe that the measurement of eosinophil levels can assist and facilitate risk stratification for patients with CABG. However, further detailed clinical investigations are required to account for this relationship.

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