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The Relationship Between Mortality Markers and All-cause Mortality in Left Main Coronary Disease with Percutaneous Coronary Intervention

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ABSTRACT

Introduction: This study aimed to investigate the relationship between all-cause mortality and markers of hematological mortality in post-procedure follow-up of patients who underwent percutaneous coronary intervention (PCI) due to severe left main coronary artery (LMCA) disease.

Patients and Methods: Between January 2015 and August 2019, a retrospective cohort study was performed based on the data of 166 consecutive patients (43 females, 123 males) who were diagnosed with severe LMCA disease as a result of coronary angiography performed in our clinic. The study population was followed median 631.00 (270.75-1172.00) days, was divided into two groups as deceased (group 1, n= 42, 25.3%) and living (group 2, n= 124, 74.6%).

Results: Fasting blood glucose, blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), uric acid, C-reactive Protein (CRP)/Albumin ratio, leukocyte, neutrophil, erythrocyte distribution width percentage (RDW) values were found to be higher ($p< 0.05$) and triglyceride, total protein, albumin, hemoglobin, hematocrit values were lower in the deceased group ($p< 0.05$). In logistic regression analysis, statistical significance of all of these parameters disappeared.

Conclusion: Advanced age, presence of chronic renal failure (CRF), FBS, BUN, creatinine, AST, ALT, uric acid, CRP/Albumin ratio, leukocyte, and neutrophil height may be helpful in determining increased mortality risk after percutaneous LMCA interventions.

Key Words: Left main coronary artery; percutaneous coronary intervention; hematological mortality markers; all-cause death

Perkütan Koroner Girişim Yapılan Sol Ana Koroner Hastalığında Mortalite Belirteçleri ile Tüm Nedenlere Bağlı Ölüm Arasındaki İlişki

ÖZET

Giriş: Çalışmanın amacı, ciddi sol ana koroner arter (LMCA) hastalığı nedeniyle perkütan koroner girişim (PKG) uygulanan hastaların işlem sonrası takiplerinde, tüm nedenlere bağlı ölümle hematolojik mortalite belirteçleri arasındaki ilişkiyi araştırmaktır.

Hastalar ve Yöntem: Ocak 2015 ve Ağustos 2019 tarihleri arasında, kliniğimizde yapılan koroner anjiyografi neticesinde ciddi LMCA hastalığı tespit edilerek PKG uygulanan 166 ardışık hastanın (43 kadın, 123 erkek) verilerine dayanılarak retrospektif bir kohort çalışması yapıldı. Çalışma protokolüne uygun 166 hastadan oluşan çalışma popülasyonu ortanca 631.00 (271.00-1172.00) gün takip edilerek ölen (grup 1, n= 42, % 25.3) ve yaşayan (grup 2, n= 124, % 74.6) olmak üzere iki gruba ayrıldı.

Bulgular: Ölenlerde açlık kan şekeri (AKŞ), kan üre azotu (BUN), kreatinin, alanin aminotransferaz (ALT), aspartat aminotransferaz (AST), ürik asit, C-reaktif Protein (CRP)/Albumin oranı, lökosit, nötrofil, eritrosit dağılım genişlik yüzdesi (RDW) değerleri daha yüksek ($p< 0.05$); trigliserid, total protein, albumin, hemoglobin, hematokrit değerleri daha düşük bulundu ($p< 0.05$). Lojistik regresyon analizinde, bu parametrelerin tümünün istatistiki anlamlılığını kaybettiği görüldü.

Sonuç: Perkütan LMCA girişimleri sonrası artmış mortalite riskini belirlemede, ilerlemiş yaş varlığı, kronik böbrek yetersizliği (KBY) varlığı, AKŞ, BUN, kreatinin, AST, ALT, ürik asit, CRP/Albumin oranı, lökosit ve nötrofil yüksekliği yardımcı olabilir.

Anahtar Kelimeler: Sol ana koroner arter; perkütan koroner girişim; hemotolojik mortalite belirteçleri; tüm nedenlere bağlı ölüm

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INTRODUCTION

Left main coronary artery (LMCA) involvement is associated with increased mortality and morbidity in comparison to other localizations of the coronary arteries. Interventional treatment methods including percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABGO) are known to reduce mortality and morbidity rates[1,2]. Despite the increase in technological developments and experiences in interventional treatment applications, LMCA's early and late mortality rates after interventional treatment are still not at the desired level[3]. Early detection of markers associated with increased mortality will be important to reduce mortality in the follow-up and treatment of these patients.

Many factors, including chronic inflammation, play a role in the pathogenesis of atherosclerosis. It is suggested that all risk factors contribute to the pathogenesis by aggravating the underlying inflammatory process. Many studies show that many factors associated with inflammation, such as high levels of CRP, uric acid, RDW, CRP/Albumin, are closely associated with increased risk of cardiovascular mortality and morbidity[4-7]. Additionally, it is known that conditions such as advanced age, anemia, renal failure, systolic and diastolic heart failure are associated with increased cardiovascular mortality. In this study, we aimed to investigate the relationship between all-cause mortality and CRP, uric acid, RDW, and CRP/Albumin rate in patients undergoing interventional treatment with LMCA involvement.

PATIENTS and METHODS

This retropsective study included patients with LMCA lesions detected in coronary angiography performed in our university's hospital and who underwent a percutaneous coronary intervention with a SYNTAX score of < 32 between January 2015 and August 2019. Patients under the age of 18, with a history of the acute coronary syndrome, advanced kidney or liver failure, acute infection, severe chronic obstructive pulmonary disease, active cancer history, severe anemia, hematological disorder, and immunosuppressive drug use in the last month were excluded from the study. Data of the patients were obtained from the archive files and the hospital automation system. Demographic, echocardiographic, and laboratory data of all patients were recorded before the procedure. Then the time and causes of death of the patients were questioned and recorded from the Ministry of Health Death Report System.One hundred and sixty-six patients (43 females, 123 males) who met the criteria were included into the study.

Ethical Statement

The design of the study, prepared in accordance with the principles stated in the Helsinki Declaration, was approved by the local Clinical Research Ethics Committee.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test was used to determine normality of the distribution. Continuous variables were expressed as mean ± standard deviation or median (Q1-Q3), while categorical variables were expressed as percentages. For categorical variables, the differences between the groups were compared with the Chi-square test. According to the distribution, the differences between the groups for numerical parameters were compared with the Student t-test or the Mann-Whitney U test. Multivariate logistic regression analysis was used to determine independent predictors of mortality. $P< 0.05$ value was considered statistically significant.

RESULTS

From the study population consisting of 166 patients in accordance with the study protocol, two groups were formed: the deceased (group 1, n= 42) and the living (group 2, n= 124). Median follow-up time of the living was 631.00 (271.00-1172.00) days. However, it was found that the deceased died within a median of 8.50 (1.00-406.00) days (Table 1). The demographic characteristics of the participants are given in Table 1. Sex, risk factors and concomitant disease rates were similar between the groups ($p> 0.05$). Only the presence of chronic renal failure (CRF) and age were significantly higher in group 1.

Laboratory findings of the patients before the interventional procedure are given in Table 2. Total cholesterol, LDL cholesterol, HDL cholesterol, CRP, platelet count, mean platelet volume values were similar between the deceased and the living groups ($p> 0.05$). Fasting blood sugar (FBS), blood urea nitrogen (BUN), creatinine, AST, ALT, uric acid, CRP/Albumin rates, leukocyte, neutrophil, RDW values were higher ($p< 0.05$), triglyceride, total protein, albumin, hemoglobin, hematocrit values were lower ($p< 0.05$) in the deceased group.

Conventional echocardiographic data of the groups before the procedure are given in Table 3. There was no difference between the left ventricle wall thickness, left ventricle diameter, and left atrium diameter between the groups ($p> 0.05$). E/A ratio was significantly lower in group 1 ($p< 0.05$).

Distal region of the left main coronary arteries was most frequently affected, and there was no difference in stenosis localization between the two groups ($p= 0.981$). It was observed that the angle of stenosis ($p= 0.511$), the length of the applied stent ($p= 0.688$), and the diameter ($p= 0.500$) were similar between the two groups. Moreover, the rate of post-dilation after stent implantation was similar between the groups ($p= 0.372$) (Table 4).

In the multivariate logistic regression analysis, it was seen that the statistic significance of all parameters, which were found significantly different in the deceased group, were lost.

Table 1. Demographic features of the groups

	Group 1 (Deceased) n = 42	Group 2 (Living) n = 124	p
Age (years)	75.24 ± 9.95	69.52 ± 10.50	**0.002*[a]**
Sex, Female, n (%)	8 (19.0)	35 (28.2)	0.241[b]
HT, n (%)	28 (66.7)	100 (80.6)	**0.050*[b]**
DM, n (%)	21 (50.0)	45 (35.8)	0.103[b]
Hyperlipidemia, n (%)	29 (69.0)	99(79.8)	0.191[b]
Smoking, n (%)	9 (21.4)	30 (24.2)	0.323[b]
COPD, n (%)	8 (19.0)	18 (14.5)	0.593[b]
CRF, n (%)	18 (42.9)	10 (8.1)	**< 0.001*[b]**
Syntax score	26.79 ± 6.34	25.22 ± 5.94	0.148[a]
Life Time (Days) Median (Q1-Q3)	8.50 (1.00-405.75)	631.00 (270.75-1172.00)	**< 0.001*[b]**

HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic Obstructive Pulmonary Disease, CRF: Chronic Kidney Failure [a]; Independent sample t test, [b]; Chi-square test, * The difference is statistically significant.

Table 2. Laboratory findings of groups

	Group 1 (Deceased) n= 42	Group 2 (Living) n= 124	p
FBG, median (Q1-Q3)	147.00 (107.00-203.50)	115.00 (98.50-162.25)	**0.016*[a]**
BUN, median (Q1-Q3)	32.00 (20.75-58.50)	18.00 (15.00-23.00)	**0.001*[a]**
Creatinine, median (Q1-Q3)	1.33 (0.99-1.95)	0.90 (0.80-1.17)	**0.001*[a]**
AST, median (Q1-Q3)	29.50 (19.00-57.50)	21.00 (15.00-30.00)	**0.002***
ALT, median (Q1-Q3)	24.50 (16.00-45.48)	19.00 (15.00-27.00)	**0.034*[a]**
Total cholesterol, median (Q1-Q3)	165.00 (148.00-206.00)	183.50 (152.50-212.50)	0.112[a]
LDL cholesterol, median (Q1-Q3)	114.00 (90.00-135.00)	118.00 (94.25-147.75)	0.333[a]
HDL cholesterol, median (Q1-Q3)	36.00 (32.50-45.00)	38.00 (33.00-47.00)	0.403[a]
Triglyceride, median (Q1-Q3)	110.00 (86.50-145.00)	150.00 (105.25-202.50)	**0.001*[a]**
Total protein	63.36 ± 7.61	67.45 ± 7.31	**0.005*[b]**
Albumin	34.12 ± 7.62	38.89 ± 5.66	**< 0.001*[b]**
Uric acid	6.88 ± 2.11	5.31 ± 1.50	**< 0.001*[b]**
CRP, median (Q1-Q3)	9.10 (4.50-15.00)	6.00 (3.20-13.00)	0.054[a]
CRP/Albumin oranı	3.03 (1.28-4.79)	1.63 (0.91-3.65)	**0.008*[a]**
Hemoglobin	11.25 ± 1.56	12.54 ± 2.05	**< 0.001*[b]**
Hematocrit	34.62 ± 4.93	38.06 ± 5.69	**0.001*[b]**
Leukocyte, median (Q1-Q3)	11.00 (8.73-15.75)	8.05 (6.69-9.79)	**< 0.001*[a]**
Neutrophils	7.15 (4.88-12.27)	5.60 (4.21-7.19)	**0.002*[a]**
Platelet, median (Q1-Q3)	250.50 (204.00-339.50)	245.00 (193.25-300.50)	0.657[a]
RDW	16.00 ± 2.20	14.54 ± 1.68	**<0.001*[b]**
MPV	9.94 ± 1.67	9.92 ± 1.43	0.949[b]

FBG: Fasting Blood Glucose, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDL: Low density lipoprotein, HDL: High density lipoprotein CRP: C-reactive protein, RDW: Erythrocyte distribution width percentage, MPV: Mean platelet volume. [a]; Mann-Whitney U test, [b]; Independent sample t test, *; The difference is statistically significant.

Table 3. Echocardiographic findings of the groups

	Group 1 (Deceased) n= 42	Group 2 (Living) n= 124	p
LVDD	48.20 ± 3.12	47.84 ± 4.46	0.808[a]
IVSd (mm)	12.10 ± 1.66	11.90 ± 2.22	0.785[a]
PWd (mm)	11.10 ± 0.74	10.66 ± 1.69	0.419[a]
LA (mm)	40.30 ± 5.79	39.15 ± 6.25	0.584[a]
LVEF (%)	45.00 (35.00-55.00)	50.00 (40.00-55.00)	0.362[b]
E velosite (cm/sec)	50.00 (40.00-50.00)	50.00 (49.00-75.00)	0.061[b]
A velosite (cm/sec)	80.00 (65.00-90.00)	80.00 (70.00-90.00)	0.706[b]
E/A ratio	0.57 (0.56-0.65)	0.69 (0.61-0.84)	**0.037*[b]**

LVDD: Left ventricular diastolic diameter, IVS: Inter ventricular septum diastolic thickness, PWd: Posterior wall diastolic thickness, LVEF: Left ventricular ejection fraction, LA: Left atrium, E: Early diastolic velocity, A: Late diastolic velocity *Difference is statistically significant, Independent sample t test, [b]; Mann-Whitney U test, *; The difference is statistically significant.

Table 4. Processed lesion, applied stent and procedure features

	Group 1 (Deceased) n= 42	Group 2 (Living) n= 124	p
Affected part of the left main coronary artery			
Osteal, n (%)	11(26.2%)	34 (27.4%)	
Body, n (%)	10 (23.8%)	28 (22.6%)	0.981
Distal, n (%)	21 (50%)	62 (50%)	
Degree of stenosis, (%)	79.1 ± 13.9	75.9 ± 13.9	0.511
Stent length, (mm)	22.4 ± 6.7	21.9 ± 7.8	0.688
Stent width, (mm)	3.19 ± 0.51	3.27 ± 0.51	0.500
Post dilation presence, n (%)	17 (40.5%)	62 (50%)	0.372

DISCUSSION

In our study, the relationship between BUN, AST, leukocyte, uric acid, age, chronic renal failure, and CRP / Albumin rate and mortality was shown after PCI in patients with LMCA involvement.

The narrowing of the vessel lumen by 50% or more is defined as LMCA stenosis. It is seen in 3-10% of all patients undergoing coronary angiography[8]. In many clinical studies, it has been found that interventional treatment methods have a lower mortality rate compared to LMCA with reduced ventricular function and/or optimal medical treatment alone in three-vessel coronary artery disease[9]. Therefore, interventional treatment is preferred along with the optimal medical treatment in LMCA involvement. SYNTAX scoring system evaluating angiographic features of the coronary vessels provides useful data on the choice of interventional treatment method[10]. Both methods can be applied in patients whose SYNTAX score is not significantly increased. In a clinical study, 3-year mortality was similar in LMCA patients with a SYNTAX score of < 33 and in PCI and CABGO patients[11]. 2018 European Society of Cardiology - European Society of Cardiac and Thoracic Surgery revascularization guideline recommends class IA for patients with LMCA involvement and low SYNTAX score (< 22), class IIA for patients with moderate SYNTAX score (22-32), and class IIIB for patients with high SYNTAX score (> 32) and CABGO was given class IA recommendation regardless of the SYNTAX score[12]. The aim of our study was to investigate the relationship of PCI with long-term mortality markers in general, regardless of the interventional method preferred in severe LMCA stenosis.

Critical LMCA involvement in coronary artery disease is a condition that maintains high mortality despite the developments in interventional treatment methods. In the EXCEL study, which includes participants with the LMCA disease, there was no significant difference between PCI and CABGO in the 5th year in terms of the composite outcome of death, stroke, or myocardial infarction in patients with low or moderate anatomical difficulties. In the fifth year data, all causes of death were determined as 9.9% in the CABGO subsection and 13% in the PCI subsection[13]. Therefore, it is important to be

able to identify the clinical markers predicting high mortality early in order to distinguish those who will undergo aggressive risk modification.

We found that demographic characteristics of the patients are significantly associated with increased mortality from advanced age and chronic renal failure from classical risk factors such as age, sex, hypertension, diabetes mellitus, hyperlipidemia, smoking, peripheral vascular disease, and renal failure. We found in the laboratory tests that BUN and creatinine levels were also associated with increased mortality. Moreover, high level of AST, ALT that we detected in the deceased group may be related to liver damage due to liver congestion as a result of systolic and/or diastolic heart failure, which may be associated with increased mortality.

It is known that diabetes mellitus is a disease associated with increased cardiovascular mortality and morbidity. In our study, although there is no significant relationship between the frequency of diabetes mellitus and mortality, it was found that it may be related to increased mortality with increased blood sugar level. These results suggest that effective regulation of blood sugar in LMCA patients undergoing PCI, and efficient and rapid approaches to correcting renal function in patients with chronic renal failure, may be effective in decreasing mortality.

In our study, in the evaluation of conventional transthoracic echocardiographic data performed on the participants, there was no significant structural difference between the deceased group and the living group that might be associated with mortality. However, we found that the E/A ratio we used as an indicator of diastolic function was significantly suppressed in the deceased group. However, in the multivariate analysis, the suppression of the E/A ratio lost its significance.

Angiographic features such as the degree of coronary stenosis, its localization, the length and diameter of the stent used, and the technique of the interventional procedure are factors associated with clinical outcome. It is known that long stent length and short stent diameter are associated with poor clinical outcome. However, in our study, no relation was found between death due to all causes and the localization of the lesion in the left main coronary vessel, the degree of stenosis of the lesion, the length and diameter of the stent used, and the post-dilation procedure applied after stent implantation. This may have been due to the small volume of the study.

In our study, hemoglobin and hematocrit values from laboratory findings were lower in the deceased group. Anemia has been shown to be associated with increased cardiovascular and all-cause mortality in various cardiovascular diseases[14,15]. Additionally, several studies in which the study population consisted of patients with stable coronary artery disease have shown that persistent or beginning anemia could be a predictor of cardiovascular and all-cause mortality[16]. Therefore, treatments for the correction of anemia in patients with LMCA involvement and accompanying anemia may contribute to a reduction in mortality in the long term.

Increasing evidence in recent years has shown that inflammation is a major mechanism in the etiopathogenesis of atherosclerosis[17,18]. In many studies, inflammatory markers such as leukocyte, neutrophil, RDW, C-reactive protein (CRP), uric acid (UA), Albumin, CRP/Albumin ratio have been associated with increased cardiovascular mortality[4-7]. In our study, we investigated the relationship between inflammation and mortality in the treatment of LMCA with PCI using these markers.

Serum UA level is a parameter that has a close relation with inflammation and atherosclerosis[19]. It has been reported that increased level of UA, which is the final product of purine metabolism, may have a protective effect from oxidative damage. Although its mechanism cannot be fully explained, increased levels of UA are thought to provide some advantages by protecting against oxidative damage[20]. It has also been shown to be a marker associated with cardiovascular mortality[6,21]. In our study, we found that UA level and leukocyte and neutrophil levels, which are hematological parameters, were significantly higher in the deceased group. These elevations at subclinical levels may reflect the relationship between increased mortality and inflammation.

In recent years, high level of erythrocyte distribution width (RDW) has been associated with an increased cardiovascular risk and has been suggested as a new marker of mortality[4,22]. RDW is a semi-quantitative measure of erythrocyte anisocytosis. Elevated RDW value is an indicator of increased heterogeneity in erythrocyte cell size. In our study, we determined that the RDW level, which is one of the hematological parameters, was higher in the deceased group. However, statistical significance did not persist in the multivariate analyzes. One of the indicators of iron deficiency anemia is considered to be RDW. For this reason, anemia may have played a confusing role as it was significantly higher in the deceased group in our study.

Albumin and CRP are laboratory parameters associated with systemic inflammation and atherosclerosis. The inflammation level of CRP, which is one of the acute phase proteins, increases in the case of inflammation. Albumin, on the other hand, is a negative acute-phase protein that responds to an increase in inflammation with a reduced blood level. Hypoalbuminemia and increased CRP have been shown to be associated with increased mortality in cardiovascular diseases[23,24]. In our study, although CRP values were similar among the groups, albumin levels were significantly lower in the deceased group. Hypoalbuminemia may be the result of the combined effects of inflammation and inadequate protein and calorie intake in

patients with chronic diseases such as chronic renal failure. In our study, higher chronic kidney failure rate and increased inflammatory status in the deceased group may have been related to low albumin levels. In recent years, it has been reported that CRP/Albumin ratio can predict coronary artery disease severity better than CRP or albumin alone[25]. It has also been suggested that the CRP/Albumin ratio may be a marker of mortality in CAD[24]. In our study, although total protein, albumin was significantly lower in the deceased group, CRP/Albumin ratio was significantly higher, and none predicted mortality. This may have been due to the small volume of the study.

Limitations

The retrospective design and the small volume of the study can be considered as the main limitations. Additionally, the effect of the invasive method on mortality may have been reduced since all participants had low (< 22) and moderate (22-32) SYNTAX scores.

CONCLUSION

In conclusion, advanced age, CRF presence, blood sugar, BUN, creatinine, transaminases, uric acid, CRP / Albumin ratio, leukocyte, and neutrophil levels may be helpful in determining the mortality risk after PCI in patients with severe LMCA involvement. Moreover, total protein, albumin, hemoglobin, hematocrit, and mitral E/A in echocardiography may also be a guide.

Ethics Committee Approval: The approval for this study was obtained from Sütçü İmam University, School of Medicine Ethics Committee (Decision no: 2019/20-07 Date: 30.07.2020).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

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