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Prognostic value of the leuko-glycemic index in coronary chronic total occlusion patients

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ABSTRACT

Objectives: Inflammation parameters are related to the prevalence and mortality of coronary artery disease (CAD). We aimed to evaluate the prognostic value of the leuko-glycemic index (LGI) and determine mortality in patients with chronic coronary total occlusion (CTO).

Methods: A total of 546 patients were evaluated in the study. All-cause death was the primary endpoint. The leuko-glycemic index was calculated from the blood samples at admission and patients were divided into 3 groups according to their LGI levels. Kaplan-Meier survival curves were performed and logistic regression analyses was used for all multivariable analysis.

Results: The mean age of the study population was 63.1 ± 11.1 years and 70.3% were male. Median follow-up time 58.2 ± 22.4 months. The mortality rate was 33.6% in the high LGI group and significantly higher compared to the other group. In multivariable analysis, LGI (OR: 1.05, 95% CI: 1,0-1.2; $p = 0.02$) and age (OR: 1.07, 95% CI: 1.04-1.11; $p = 0.001$) were found as predictors of all-cause death.

Conclusions: The study revealed that high LGI is associated with all-cause death in CTO patients and LGI was a predictor of all-cause death.

Keywords: Leuko-glycemic index, coronary total occlusion, mortality, coronary artery disease

Coronary artery disease (CAD) is still the leading cause of mortality and morbidity all over the world [1]. Coronary total occlusion (CTO) is a complex coronary lesion, and it is a condition of 100% angiographic occlusion for 3 months or more [2]. It is detected in an average of 10-30% of coronary angiographies [3]. The presence of CTO has been associated with recurrent myocardial infarction, cardiogenic shock, heart failure, and sudden death [4-6]. Parameters or findings that predict clinical events in patients with CTO have always been the subject of research.

Identifying high-risk patients with CAD may help clinicians take preventive measures. Inflammatory markers, which are elevated in the primary response to ischemic heart disease, may be helpful in estimating the extent of ischemic damage [7]. It has been found in previous studies that inflammation parameters are

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closely related to the prevalence and mortality of CAD [7, 8]. Systemic immune-inflammation index, neutrophil-lymphocyte ratio, and other additional hematological parameters have been investigated in coronary artery patients with CTO and acute coronary syndrome patients and have been associated with adverse cardiac events [8-11].

The leuko-glycemic index (LGI) is an easy-to-calculate, noninvasive simple indicator of inflammation that includes parameters directly related to inflammation, such as glucose and leukocyte count. LGI is an inflammation parameter studied in patients with acute coronary syndrome and is associated with poor clinical outcomes and coronary artery prevalence [12-14]. There are no studies examining the relationship between LGI and mortality in CTO patients. Therefore, the study aims to investigate the relationship between LGI and mortality in CAD patients with CTO.

METHODS

Our study is a retrospective and observational study and includes patients with CTO in at least one vessel after CAG between 2014 and 2020. Angiograms were analyzed by the independent experienced operators. Chronic inflammatory disease, nonregulated diabetes mellitus, hemolytic disease, malignancy, and active infectious disease were excluded.

The electronic database of the hospitals was used to acquire the baseline characteristics and medical histories of the patients. After exclusions, a total of 546 patients enrolled in the study. The study protocol was approved by the ethics committee (Dicle University) with the date 04/03/2021 and number 181.

The laboratory parameters of the patients were obtained from blood samples taken at the admission. All-cause deaths were determined as the primary endpoint.

The leuko-glycemic index (mg/dl.mm3) was calculated by multiplying the fasting blood glucose (mg/dL) and leukocyte count (on admission) in mm3 divided by one thousand [7].

Statistical Analysis

The continuous variables were presented as mean ± standard deviation or median interquartile range (IQR) (25-75%). Normally distributed data were compared using one-way ANOVA, and non-normally distributed data were compared using the Kruskal-Wallis test. The categorical variables were examined using Fisher's exact test and are shown as the number of cases with percentages. The relationship between LGI and mortality was investigated using multivariate logistic regression analysis. The survival of groups was analyzed using Kaplan-Meier methods. A $p < 0.05$ was considered statistically significant.

RESULTS

A total of 546 patients were included in the study. The mean age of the study population was 63.1 ± 11.1 yearsand 70.3% were male. The patients were divided into 3 groups according to their LGI levels as follows: < 1082 (mg/dL.mm3) in group 1 (low), 1082-1688 (mg/dl.mm3) in group 2 (intermediate), and > 1688 (mg/dL.mm3) in group 3 (high). White blood count, platelet, CRP (c-reactive protein), triglyceride, and glucose levels were higher in patients in group 3 compared to other groups, while glomerular filtration rate (GFR) and ejection fraction (EF) were lower than other groups. Patients in group 3 had a higher prevalence of hypertension (HT), diabetes mellitus (DM), and all-cause mortality. The demographic and laboratory findings of the groups are shown in Table 1.

In multivariate regression analysis, age (odds ratio (OR): 1.07, 95% CI: 1.04-1.11; $p = 0.001$) and LGI (OR: 1.05, 95% CI: 1,0-1.2; $p = 0.02$) were found as independent factors for all-cause mortality. The multivariate regression analysis is given in Table 2.

The log-rank test was used to quantify the significance of the differences between the Kaplan-Meier curves, and it revealed that group 3 had a greater incidence of all-cause death. (Fig. 1).

DISCUSSION

In this study, we found that high LGI was associated with all-cause mortality in CTO patients. In the multivariate analysis, we showed that LGI and age were independent predictors of all-cause mortality. The relationship of CTO with some inflammatory parameters has been studied before, but the relationship between LGI and CTO is examined for the first time.

There is a long-known relationship between CAD

Table 1. Baseline demographic and laboratory parameters of groups

	Tertile 1 (n = 276)	Tertile 2 (n = 134)	Tertile 3 (N =136)	*p* value
Age (years)	62.3 ± 10.9	63.3 ± 11.1	63.5 ± 11.3	0.73
Male, n (%)	215 (77.8)	95 (70.8)	81 (59.5)	**0.001**
HT, n (%)	75 (27.2)	49 (36.6)	70 (51.4	**0.001**
DM, n (%)	25 (9.1)	36 (26.9)	50 (36.7)	**0.001**
Smoking, n (%)	76 (27.5)	43 (32.1)	31(22.8)	0.23
CKD, n (%)	13 (4.7)	6 (4.5)	12 (8.8)	0.18
All-cause death, n (%)	55 (19.9)	30 (23.4)	46 (33.8)	**0.007**
MI, n (%)	90 (32.6)	42 (31.3)	49 (36)	0.69
Follow-up period (months)	58 ± 23.2	57 ± 23.7	59 ± 24.5	0.1
EF (%)	50.6 ± 10.4	49.2 ± 11.4	46.4 ± 11.1	**0.003**
WBC count ($\times 10^3/\mu L$)	7.8 ± 1.8	10.3 ± 2.4	11.9 ± 3.6	**< 0.001**
Hemoglobin (g/dL)	13.6 ± 1.8	13.7 ± 1.7	13.3 ± 2.1	0.15
Platelets ($\times 10^3/\mu L$)	236.3 ± 78.5	269.7 ± 84.9	272.8 ± 91.3	**< 0.001**
Glucose (mg/dL)	102 ± 21.6	136.7 ± 36.8	220 ± 87.3	**< 0.001**
Albumin (g/dL)	3.6 ± 0.43	3.5 ± 0.52	3.5 ± 0.49	0.08
GFR ($mL/min/1.73m^2$)	86.5 ± 23.8	86.1 ± 24.3	76.6 ± 24.3	**< 0.001**
LDL (mg/dL)	106.3 ± 38.8	106.5 ± 40.2	106.8 ± 44.2	0.98
Triglyceride (mg/dL)	160 ± 79.6	182.6 ± 88.3	205.5 ± 120.2	**0.001**
Total cholesterol (mg/dL)	177.6 ± 47.7	180.5 ± 47.3	185.7 ± 52.7	0.27
CRP (mg/L)	1.4 ± 0.7	2.7 ± 1.1	4.9 ± 1.5	**< 0.001**
LGI ($mg/dL.mm^3$)	783.9 ± 182.3	1343.5 ± 168.2	2775.3 ± 980.2	**< 0.001**
SYNTAX score	15.3 ± 6.3	15.8 ± 5.9	17.9 ± 5.5	**0.03**

Data are shown as mean ± standard deviation or number (percent). HT = hypertension, DM = diabetes mellitus, MI = myocardial infarction, CKD = chronic kidney disease, EF = ejection fraction, WBC = white blood cell, GFR = glomerular filtration rate, LDL = low density lipoprotein, CRP = C-reactive protein, LGI = leuko-glycemic index, SYTNAX = Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery

and inflammation [15, 16]. It has been found in many previous studies that the indicators of inflammation in the blood are high in patients with stable CAD and acute coronary syndrome [17, 18]. An increase in inflammatory markers is associated with free oxygen radical release, coagulation cascade activation, an increase in platelet aggregation and an increase in infarct size [19]. One of the main indicators of inflammation in the blood is the leukocyte count. It has been found that a high leukocyte count is closely associated with cardiogenic shock, heart failure, and in-hospital mortality in acute coronary syndrome patients [20, 21].

The inflammatory process affects glucose metabolism through some mediators and also increases the blood glucose level in acute states independent of DM. Inflammation and hyperglycemia accelerate the atherosclerotic process with an additive effect [22]. As a result of the HORIZONS-AMI study, it was determined that a high glucose level at admission was associated with 1-month and 3-year mortality [23]. In addition, it has been shown in previous studies that a high blood glucose level is associated with no reflow and adverse cardiac events [24].

Since LGI includes leukocyte count and glucose level, it can be an inflammation parameter that can help predict prognosis in cases of acute cardiac events

Table 2. Univariable and multivariable regression analysis for determine the predictor of all-cause mortality

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age	1.06 (1.04-1.09)	**0.001**	1.07 (1.04-1.11)	**0.001**
Gender	0.87 (0.68-1.34)	0.53		
HT	0.58 (0.34-0.77)	**0.001**	0.68 (0.36-1.30)	0.25
DM	0.66 (0.43-1.03)	0.058		
HL	0.92 (0.29-2.91)	0.89		
CKD	0.27 (0.12-0.56)	**0.001**	0.72 (0.2-2.28)	0.61
Smoking	0.99 (0.64-1.55)	0.95		
CRP	1.11 (1.02-1.22)	**0.008**	1.05 (0.96-1.14)	0.29
LGI	1.04(1.0-1.1)	**0.01**	1.05 (1.0-1.2)	**0.02**
SYNTAX score	0.98 (0.95-1.2)	0.40		

HT = hypertension, DM = diabetes mellitus, CKD = chronic kidney disease, CRP = C-reactive protein, LGI = leuko-glycemic index, SYTNAX = Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery

or stable coronary artery disease. It has been found that high LGI is closely associated with short and long-term prognosis and 1-year mortality in patients with acute myocardial infarction [13, 14]. CTO is a complex CAD, and the presence of CTO is associated with poor cardiovascular events. The relationship between CTO and inflammation parameters has been the subject of research before. In a study, it was found that a high leukocyte count at admission was associated with high cardiovascular risk in CTO patients [11]. Demir *et al*. found that the systemic immune-inflammatory index, which consists of many blood parameters, is closely associated with an increased risk of all-cause death in CTO patients [25]. In our study, similar to these studies, we found higher leukocyte count, CRP, and all-cause mortality in the high LGI group, and we

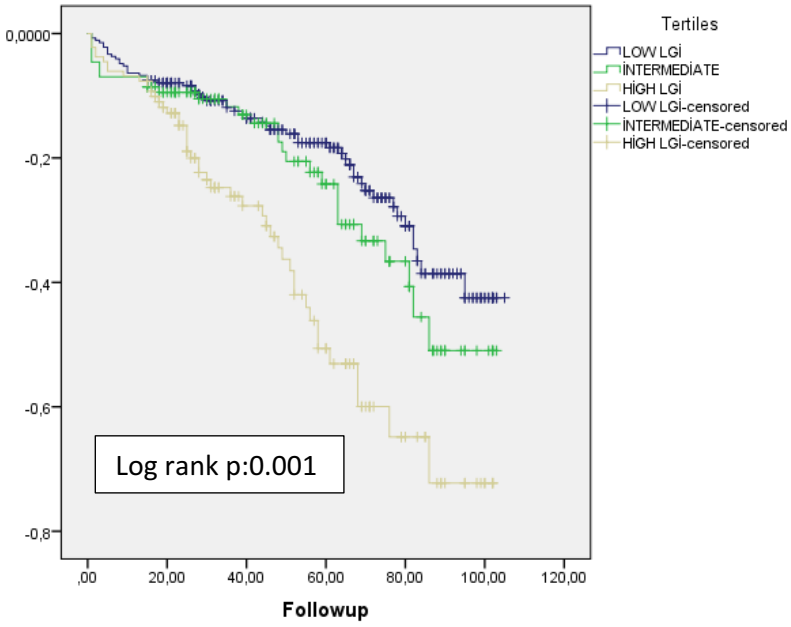

Fig. 1. Kaplan-Meier analysis of groups according to the survival.

also determined that LGI is an independent predictor of mortality.

Studies have shown that hyperglycemia is associated with poor cardiovascular events and a poor prognosis in CTO patients [26, 27]. Song *et al*. found that triglyceride-glucose index and stress hyperglycemia were associated with a poor prognosis in CTO patients [27]. In our study, triglyceride and glucose levels were found to be higher in the high LGI group compared to the other groups. In addition, mortality was higher in the high LGI group compared to the other groups.

Limitations

First of all, its retrospective nature and relatively small number of patients are important limitations. For the blood parameters used for LGI, values were taken at the time of admission to the hospital, and averaging the values during hospitalization or follow-up may affect the results. Evaluation of previously known inflammation parameters and comparison with LGI would have reinforced the effectiveness of our study. Multicenter studies with a higher proportion of patients are needed for risk assessment in CTO patients.

CONCLUSION

In this study, we determined for the first time that high LGI is associated with mortality in CTO patients. We also found that LGI was an independent predictor of all-cause death. This simple, noninvasive parameter can help identify high-risk CTO patients and help them be treated more effectively and followed up more closely.

Authors' Contribution

Study Conception: TP, MÖ, BB, SFA, MD, BA; Study Design: MÖ, BA; Supervision: SFA; Materials: TP, SFA; Data Collection and/or Processing: MÖ, SFA, MD; Statistical Analysis and/or Data Interpretation: BA, BB, TP; Literature Review: TP, BA; Writer: TP, BA; Manuscript Preparation:TP, SFA and Critical Review: BB

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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