

# Predicting the Severity of Coronary Artery Disease: Can the Leukocyte Glucose Index be Used?

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## ABSTRACT

**Objective:** To investigate the usability of leuko-glycemic index (LGI) at chronic coronary syndromes (CCS) class 1 for determining the extent and severity of coronary artery disease (CAD).

**Study Design:** An observational study.

**Place and Duration of Study:** Department of Cardiology, University of Pamukkale University Hospital, Turkey, between September 2021 and January 2022.

**Methodology:** One hundred and thirty-four patients, whose myocardial perfusion scintigraphy (MPS) was requested due to CCS class 1, and on whom a coronary angiogram (CAG) was performed due to evidence of ischemia, were analysed. Blood samples were taken from the patients during their hospitalisation before CAG. LGI was calculated as  $\text{mg/dl.mm}^3$  by multiplying both values and dividing by a thousand. The patients were analysed in two groups according to the critical stenosis and non-critical stenosis detected in the coronary arteries.

**Results:** The LGI was recorded as  $480 \text{ mg/dl.mm}^3$  (407-603) vs.  $572 \text{ mg/dl.mm}^3$  (433-877),  $p=0.006$ , and the Gensini score (6 (3-10) vs 40 (23-60),  $p<0.001$ ) was significantly higher in the critical CAD group. A significant relationship has detected the increase in LGI and the extensity and severity of CAD (Unadjusted; OR (95% CI); 1.003 (1.001 – 1.004)  $p=0.002$ , adjusted; OR (95% CI); 1.002 (1.001 – 1.004)  $p=0.004$ ).

**Conclusion:** A high LGI was a predictor of CAD severity among CCS class 1 patients and was found to correlate with the Gensini score. The use of this simple and inexpensive index, together with other non-invasive tests before CAG, may provide some knowledge about the severity of CAD.

**Key Words:** Coronary artery disease, Leukocyte glucose index, Myocardial perfusion scintigraphy.

**How to cite this article:** Kilic O, Buber I, Kahraman F. Predicting the Severity of Coronary Artery Disease: Can the Leukocyte Glucose Index be Used?. *J Coll Physicians Surg Pak* 2022; **32(12)**:1519-1523.

## INTRODUCTION

Myocardial ischemia has many causes. The most common cause is stable coronary artery disease (SCAD). In 2019, the European Society of Cardiology guidelines for chronic coronary syndrome (CCS) was published. In this guide, CCS 1 is used instead of the term SCAD.<sup>1</sup> According to this guideline, patients are divided into 5 groups. Patients with symptoms without known CAD are included in group 1. In this group of patients, an initial non-invasive diagnostic test is recommended at the clinical likelihood of CAD. While scores are defining the severity of CAD in acute coronary syndromes, they seem insufficient for CCS class 1.

Hyperglycemia can cause thrombosis and fibrinolysis, which lead to the formation of atherosclerotic plaques.<sup>2</sup> Leukocytes are very important in inflammatory diseases. Increased leukocyte levels are significantly associated with atherosclerosis and cardiovascular disease. Therefore, leukocyte levels have been used as an important indicator for assessing cardiovascular disease risk.<sup>3-5</sup> The leuko-glycemic index (LGI) is an easily calculated and non-invasive index that combines leukocyte count and blood glucose score. Previous studies have shown LGI to be a good clinical predictor of acute myocardial infarction and stroke.<sup>6-8</sup> This study aimed to investigate the usability of LGI at CCS class 1 for determining the extent and severity of CAD.

## METHODOLOGY

This study is a retrospective single-centre observational study, approved by the institutional review board and conducted according to the Declaration of Helsinki (Approval Number: 25.01.2022/02).

One hundred and thirty-four patients, whose myocardial perfusion scintigraphy (MPS) was requested due to CCS class 1, and

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Received: July 01, 2022; Revised: October 18, 2022;

Accepted: November 11, 2022

DOI: <https://doi.org/10.29271/jcpsp.2022.12.1519>

on whom a coronary angiogram (CAG) was performed due to evidence of ischemia, were analysed. All the patients between September 2021 and January 2022 without exclusion criteria were analysed. Chronic inflammatory disease, previously diagnosed with CAD, thyroid disorders, hemolytic disease, malignancy, chronic lung diseases, liver diseases, rheumatic disease, chronic kidney failure and history of hemodialysis, non-regulated diabetes mellitus, and normal coronary arteries at CAG were excluded. Demographic data were obtained from the hospital registration system. The patients were evaluated with the Affiniti 50 echocardiography device before CAG. The left ventricular ejection fraction (LVEF) was calculated using the modified Simpson method. A resting blood pressure  $\geq 140/90$  mmHg in  $\geq 2$  measurements or taking antihypertensive medication was considered hypertensive (HT).<sup>9</sup> Patients with fasting blood glucose  $\geq 126$  mg/dl or postprandial blood glucose  $\geq 200$  mg/dl or glycated haemoglobin (HbA1c)  $\geq 6.5$  or taking anti-diabetic drugs were considered as diabetes mellitus (DM).<sup>10</sup> A low density lipoprotein cholesterol (LDL-C) level below the European Society of Cardiology Guideline threshold or patients who received an anti-lipidemic were considered to have dyslipidemia.<sup>11</sup>

Laboratory values of each patient were checked before CAG. Blood glucose was expressed as mg/dl and white blood cell count as the number of cells per mm<sup>3</sup>. LGL was calculated as mg/dl.mm<sup>3</sup> by multiplying both values and dividing by a thousand.<sup>12</sup>

Coronary angiography was performed via the femoral or radial artery, depending on the operator's experience. A routine Judkins catheter was used in the diagnostic CAG. The left main coronary artery (LMCA), left anterior descending (LAD), and left circumflex artery (LCX) were evaluated from the left caudal, right caudal, left cranial, right cranial, and antero-posterior cranio-caudal poses. The right coronary artery (RCA) was evaluated in the left anterior oblique and left cranial poses. According to the results of the CAG, stenosis of  $\geq 50\%$  for the LMCA and  $\geq 70\%$  for other epicardial vessels was considered to be obstructive-severe CAD. The patients were analysed in two groups according to the critical stenosis (81 patients) and non-critical stenosis (53 patients) detected in the coronary arteries. Patients without obstructive CAD were labelled group 1; patients with  $\geq 70\%$  stenosis in  $\geq 1$  epicardial vessel or  $\geq 50\%$  stenosis in LMCA were labelled group 2. The extent and severity of atherosclerosis in coronary arteries were calculated with the Gensini score. According to the degree of angiographic stenosis, 1 point for 1-25% stenosis, 2 points for 26-50% stenosis, 4 points for 51-75% stenosis, 8 points for 76-90% stenosis, 16 points for 91-99% stenosis, and 32 points were awarded for 100 total lesions. The calculated scores were multiplied by the coefficient defined for each segment of the coronary arteries. The Gensini score was calculated by summing the results. Segment and coefficients: 5 for the LMCA, 2.5 for the LAD artery proximal, 1 for the mid1.5, apical 1, diagonal 1 and 0.5 for the diagonal; 2: 2.5 for the LCx artery, 1 for the distal, 1 for the obtuse margin, and 1 for the posterior descending artery

(PDA); if left dominant, 0.5 for the posterolateral artery (PL): 1 for the RCA proximal, 1 for the mid1, distal 1 and PDA. A Gensini score between 1-20 was accepted as mild coronary atherosclerosis, and a score of  $>20$  was considered to be severe coronary atherosclerosis.<sup>13</sup>

All the data were analysed using SPSS version 22.0 (SPSS, Inc., Chicago, Illinois). Continuous variables were expressed as mean  $\pm$  standard deviation. Before the non-parametric test, the authors examined the normality of the variables with the Shapiro-Wilks test. For abnormally distributed continuous variables, the non-parametric Mann-Whitney U test was used. Categorical variables were expressed as percentages and numbers. The Chi-square test was used for categorical variables. Logistic regression analysis was used to find the association between LGL and CAD severity. The odds ratio (OR) and confidence interval (CI) were calculated with the noncritical CAD serving as a reference. The first, the unadjusted model, included only LGL for the prediction of CAD severity. In the adjusted model, the authors included age, HT, and DM for multivariate logistic regression analysis. The ROC curve was used to determine the cut-off for the P wave duration change. A p-value of  $<0.05$  was considered statistically significant.

**Table I: Baseline clinical, demographic and laboratory characteristics of the study.**

	Noncritical stenosis (n=53)	Critical stenosis (n=81)	p-value
Age, years	57 (50-61)	60 (53-68)	0.019
Gender, male (%)	24 (45.28)	48 (59.25)	0.140
HT, n (%)	25 (47.2)	55 (67.9)	0.020
DM, n (%)	19 (35.8)	51 (63)	0.003
HL	1 (1.9)	8 (9.9)	0.087
LVEF	60 (55-60)	60 (55-60)	0.153
Platelet	246,6 $\pm$ 50.2	230,5 $\pm$ 65.7	0.069
Hemoglobin	14.3 (12.6-15.7)	14.2 (13-15)	0.537
Urea	29 (24-33)	31 (24-42)	0.076
Creatinine	0,96 $\pm$ 0.2	1,0 $\pm$ 0.2	0.210
GFR, ml/min	81,2 $\pm$ 10.9	77,0 $\pm$ 18.8	0.117
Sodium	140 (138-141)	139 (137-140)	0.124
Potassium	4.1 (3.9-4.4)	4.3 (4-4.5)	0.067
CRP	4.5 (3.6-8.9)	5.6 (4.2-7.7)	0.263
ALT	19 (13-26.5)	20 (14-27.5)	0.600
AST	18 (16-26)	23 (18-31)	0.072
Total cholesterol	188,7 $\pm$ 39.4	180,7 $\pm$ 46.1	0.372
Triglyceride	139 (118-188)	138 (96-191)	0.667
LDL	114 (96-137)	112 (79-141)	0.285
HDL	44.3 $\pm$ 1.2	42.4 $\pm$ 1.3	0.345
LGI	480 (407-603)	572 (433-877)	0.006
Gensini score	6 (3-10)	40 (23-60)	$<0.001$

HT: Hypertension, DM: Diabetes Mellitus, HL: Hyperlipidemia, LVEF: Left ventricular ejection fraction, GFR: Glomerular Filtration Rate, CRP: C-reactive Protein, ALT: Alanine aminotransferase AST: Aspartate Aminotransferase, LDL: Low density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol LGL: Leukocyte Glucose Index, Risk factors adjusted by age, HT and DM. CAD: Coronary artery disease, CI: Confidence interval, DM: Diabetes mellitus, HT: Hypertension. Continuous variables were summarised as mean  $\pm$  SD and categorical variables were summarised as count and percentages. For abnormally distributed continuous variables, the non-parametric Mann-Whitney U test was used.

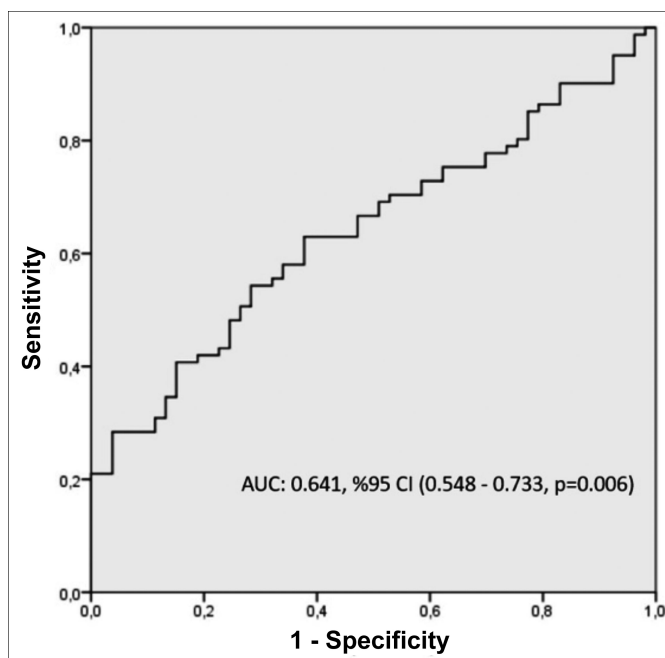
## RESULTS

One hundred and thirty-four patients were analysed. Seventy-two patients were male (53.2%) and 62 patients were female (46.8%). The age ranges were recorded as 57 (50-61) vs. 60 (53-68),  $p=0.019$  (Table I). The present rate of HT was recorded as  $n=25$  (47.17%) vs.  $n=55$  (67.90%),  $p=0.020$  and the DM as

n=19 (35.8%) vs n=51 (63%),  $p=0.003$  (Table I). The LGI was recorded as 480 mg/dl.mm<sup>3</sup> (407-603) vs 572 mg/dl.mm<sup>3</sup> (433-877),  $p=0.006$ , and the Gensini score (6 (3-10) vs 40 (23-60),  $p<0.001$ ) was significantly higher in the critical CAD group (Table I). The relationship between the LGI and the severity of CAD was evaluated using logistic regression analysis. A significant relationship has detected the increase in LGI and the extensity and severity of CAD. Unadjusted logistic regression analysis showed that the increase in LGI was associated with the extent and severity of CAD (OR (95% CI); 1.003 (1.001 - 1.004)  $p=0.002$ , Table II). After adjusting the model for confounding factors (age, HT, and DM), multivariate logistic regression analysis showed that the increase in LGI was still associated with the extent and severity of CAD (OR (95% CI); 1.002 (1.001 - 1.004)  $p=0.004$ , Table II). The ROC curve of the LGI to estimate the severity of CAD is shown in Figure 1. The LGI AUC value was 0.641 (95% CI: 0.548-0.733,  $p=0.006$ , Figure 1). The cut-off value for LGI was 543.81, with a sensitivity of 54.3% and a specificity of 71.7%.

**Table II: Logistic regression analysis regarding correlations between severity of CAD and leuko-glycemic index.**

Variables	Odds ratio (95% CI)	p-value
Leuko-glycemic index		
Unadjusted	1.003 (1.001 - 1.004)	0.002
Adjusted	1.002 (1.001 - 1.004)	0.004



**Figure 1: Receiver operating characteristics curve of leuko-glycemic index for predicting CAD severity.**

## DISCUSSION

This study showed that increased LGI was associated with more extended and severe CAD in patients who underwent CAG for CCS class 1. The LGI is an index calculated with the formula blood sugar x white blood cell/1000 (mg/dl.mm<sup>3</sup>).<sup>12</sup> It was first defined by Castro *et al.*, who used it in their study in 2010 to determine the prognostic value in patients presenting with

acute myocardial infarction (AMI).<sup>12</sup> According to this study, when the LGI was >1600 mg/dl.mm<sup>3</sup>, it was related with increased in-hospital complications. Prado *et al.* also showed that a high LGI value is a predictor of in-hospital, as is Killip 3-4 in patients presenting with AMI.<sup>6</sup> Similarly, Leon Aliz *et al.* and Rodriguez-Jimenez *et al.* found that an increased LGI was associated with increased in-hospital mortality.<sup>7,14</sup> Caldas *et al.* and Alvarez *et al.* showed that the LGI is a predictive marker for mortality at ischemic stroke.<sup>8,15</sup> This study showed that LGI was a useful marker for the CAD severity among CCS group 1 patients.

Current CCS guidelines recommend CAD diagnosis through coronary computer tomography (CCT) for patients with suspected CAD.<sup>1</sup> Although the reliability and efficiency of the new methods are acceptable, MPS is still the most preferred non-invasive test due to its cost-effectiveness and ease of application.<sup>16</sup> In addition, CCT does not provide a hemodynamic answer if a fractional flow reserve is not available. Although MPS shows partial differences according to different techniques and application centres, it has 90% sensitivity and specificity at the same level.<sup>17,18</sup> There are significant difficulties and limitations in detecting coronary ischemia in MPS performed with single-photon emission computerised tomography because patient incompatibility, high heart rate, image artifacts, and significant false-positive results reduce the diagnostic accuracy in detecting the presence of obstructive CAD.<sup>19,20</sup> In this study, CAG was performed on 224 patients. The rate of occlusive CAD was 60.4% (134 patients). Considering these reasons, obtaining new data that can increase the sensitivity and specificity of non-invasive tests has great importance.

Logistic regression analysis revealed that LGI is strongly associated with CAD severity. But ROC analysis showed that LGI estimation is weak (AUC: 0.641). It has high specificity but low sensitivity. So, the authors should comment on these results carefully and need further studies to support these findings. As expected, the severity of CAD increased with age and the incidence of HT and DM was higher among these patients. LGI in the logistic regression analysis. It was observed that age is an independent predictor of CAD severity and is prevalent independent of DM and HT. This result may show us, especially among older patients, that LGI may be a more beneficial marker for the prediction of CAD severity.

The Gensini scoring system was developed by Gensini *et al.*<sup>13</sup> Points are given according to the location and severity of the stenosis. The stenosis severity coefficient for each lesion is multiplied by the values determined according to the location of the lesion. The Gensini score is obtained by summing the values found.<sup>21</sup> As the prevalence and severity of CAD increase, the Gensini score increases.<sup>22</sup> In a study comparing atherosclerosis predictors and angiographic scoring systems, when both the prevalence of CAD and its relationship with atherosclerotic predictors were examined, a positive correlation was found in both the Gensini score and the syntax score.<sup>23</sup> In the study by Amin *et al.*, a significant positive correlation was found between

the duration of DM and the Gensini score, and this correlation was shown to be stronger in elderly and male patients.<sup>24</sup> In the present study, the authors found the mean Gensini score to be 40 in the group with obstructive CAD and six in the group with non-obstructive CAD. When the relationship between the Gensini score and LGI was examined, a positive correlation was found. The correlation of LGI with proven scores such as the Gensini score can increase its reliability in use.

There are some limitations to the generalisation of this study's results. It is a retrospective, cross-sectional and single-centre study. Considering the number of patients and their data, the results cannot be generalised.

Although LGI was found as a predictor of CAD severity, its sensitivity is low. So, further and larger studies are needed. Finally, the study design does not provide with prognostic knowledge.

## CONCLUSION

A high LGI was a predictor of CAD severity among CCS class 1 patients and was found to correlate with the Gensini score. The use of this simple and inexpensive index, together with other non-invasive tests before CAG, may provide some knowledge about the severity of CAD. Prospective studies are needed to clarify the LGI and CAD severity prognostic relationship in terms of future cardiovascular events.

## ETHICAL APPROVAL:

This study was approved by the Pamukkale University ethics committee (Approval Number: 25.01.2022/02).

## PATIENTS' CONSENT:

Written informed consent were obtained from all patients.

## COMPETING INTEREST:

The authors declared no competing interest.

## AUTHORS' CONTRIBUTION:

OK: Research design and manuscript writing.

IB: Data collection.

FK: Statistical analysis and manuscript writing.

All the authors have approved the final version of the manuscript to be published.

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