



A Novel Marker Triglyceride Glucose Index in Predicting the Development of No-reflow in Acute Coronary Syndrome without ST-segment Elevation

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Abstract

Aim: The triglyceride-glucose (TyG) index is a new marker that predicts adverse clinical outcomes in coronary artery disease. We aimed to investigate the relationship between the TyG index and the no-reflow phenomenon after percutaneous coronary intervention (PCI) to saphenous vein grafts (SVGs) in patients with non ST-elevation acute coronary syndrome (NSTEMI-ACS).

Methods: In this retrospective study, 289 patients diagnosed with NSTEMI-ACS who underwent PCI for SVG obstruction were included. Patients were divided into 2 groups according to the development of a no-reflow phenomenon in the infarct-related artery after PCI: group 1 normal reflow group (n=209) and group 2 (n=80) no-reflow group. The groups were then compared according to the TyG index.

Results: The TyG index ($p<0.001$) was significantly higher in the no-reflow group. Univariate and multivariate logistic regression identified that congestive heart failure ($p<0.001$), degenerated SVG ($p=0.002$), intraluminal thrombus ($p<0.001$), and TyG index ($p<0.001$) were independent no-reflow predictors. In the receiver operating characteristic curve analysis, the TyG index with an optimum threshold value of 0.82 detected the development of no-reflow with 70% sensitivity and 83.7% specificity.

Conclusion: The TyG index, a simple measurable laboratory variable, is an independent predictor of no-reflow development in NSTEMI-ACS patients undergoing PCI for SVG occlusion.

Keywords: Coronary artery disease, triglyceride-glucose index, no-reflow phenomenon

Introduction

In coronary artery bypass graft (CABG) surgery, saphenous vein grafts (SVGs) are often used when the arteries aren't good enough for bypass grafting or when there are multiple vessel lesions. However, SVG tends to degenerate over time, and the patency rate drops to 41% after 10 years (1). Failure of the SVG in the early period (up to 18 months) is mainly due to inflammation, endothelial damage, platelet aggregation, a reduction in nitric oxide production, and intraluminal foam cell deposition due to mechanical trauma (2). Late graft failure (after 18 months) occurs because of an atherosclerotic occlusive plaque that

develops with the progression of intimal hyperplasia (3). For treating SVG disease, redo-CABG or percutaneous coronary intervention (PCI) treatment options are available. Percutaneous coronary intervention to the bypassed native artery should be attempted first, and if this is not possible, PCI of the SVG should be considered (4). Since redo surgery is associated with high mortality rates, it should be considered only in patients who cannot be treated with PCI (5). Percutaneous coronary intervention of SVG lesions, accounting for approximately 5-10% of all PCIs, results in a higher complication rate and worse clinical outcomes than native artery interventions. The intervention has significant limitations, such as distal embolization in the acute phase,

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lack of reflow, high restenosis rate in the follow-up, and progression of SVG disease (6). The phenomenon of no-reflow, occurring in 3.4-18.5% of SVG PCIs (4), is associated with high early and late major adverse cardiac events (MACE) and mortality rates (7). Although it is thought to be caused by no-reflow, microembolization, microvascular spasm, endothelial dysfunction, increased oxidant production, and reperfusion injury, the reasons for its development are still controversial (8). Unfortunately, a widely accepted risk classification method that can predict the no-reflow outcome is not yet available. However, because the prevention of no-reflow development is the best strategy to minimize its negative consequences, it is vital to identify modifiable factors associated with no-reflow development.

The triglyceride-glucose (TyG) index is a simple index calculated from fasting blood sugar and triglyceride (TG) levels. It has been shown that the TyG index is an independent risk factor for cardiovascular disease and can predict MACE (9,10). In addition, studies have shown that elevated blood glucose values (11) and high triglyceride levels (12) increase the risk of no-reflow development in patients with acute coronary syndrome (ACS) undergoing PCI. However, the relationship between the TyG index and no-reflow development is unknown. Because the prognosis of the no-reflow phenomenon in SVG PCIs is poor, parameters that can predict this situation are vital. Therefore, in this study, we investigated the relationship between TyG index values and the development of the no-reflow phenomenon after PCI of SVGs in patients with non-ST-segment elevation ACS (NSTEMI-ACS).

Materials and Methods

Study Population

This was a single-center, observational, and retrospective study. We included 408 consecutive patients who underwent PCI due to SVG disease with a diagnosis of NSTEMI-ACS at our center between April 2016 and July 2019.

Patients with cardiogenic shock (n=21), stent restenosis and thrombosis (n=23), ST-segment elevation myocardial infarction (STEMI; n=36), and percutaneous transluminal balloon angioplasty alone (n=39) were excluded (Figure 1). The diagnosis of NSTEMI-ACS was made according to the current guidelines of the European Society of Cardiology (13). Coronary blood flow was defined according to the thrombolysis in myocardial infarction (TIMI) flow degree. Blood flow below TIMI flow 3 was defined as no reflow in the absence of dissection, vasospasm, or stenosis. The Clinical Research Ethics Committee of the University of Health Sciences Turkey, Mehmet Akif Ersoy Thoracic and

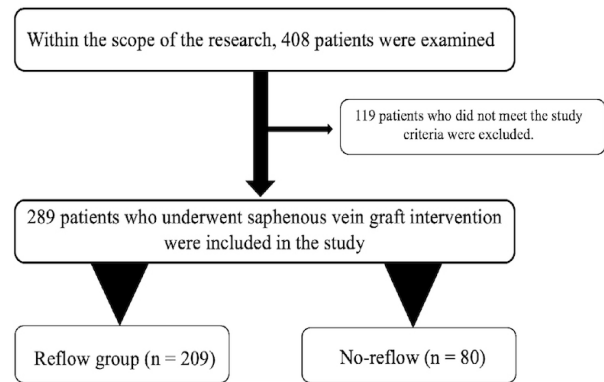


Figure 1. Flow chart of patients included in the study

Cardiovascular Surgery Training and Research Hospital approved the protocol for this study in accordance with the Declaration of Helsinki and good clinical practice (approval no.: 2023.02-10, date: 21.02.2023). Because the study had a retrospective design, informed consent was not obtained from the patients.

Patient Characteristics

Laboratory, clinical, and demographic data were obtained from hospital records. Complete blood count, serum creatinine, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), TG, and serum electrolyte levels were evaluated using the Friedewald equation. Blood samples were collected during hospitalization in the emergency room. The TyG index was calculated as fasting TG mg/dL and fasting glucose mg/dL/2 (14). In addition, echocardiographic imaging was performed on all patients during their hospitalization in the coronary intensive care unit immediately after PCI. The patients were examined using an echocardiography device (GE Vingmed Ultrasound AS, Horten, Norway) with a 3.2 MHz adult probe. Left ventricular ejection fraction, left ventricular end-systolic diameter, left ventricular end-diastolic diameter, left ventricular posterior wall thickness, and interventricular septum thickness were measured according to the guidelines of the American Society of Echocardiography (15).

Coronary Angiographic Evaluation

Coronary angiography was performed on each patient from the femoral or radial artery using the Judkins technique. All PCIs were performed using 6F or 7F guide catheters. After the diagnosis of NSTEMI-ACS was made according to the recommended guidelines, adequate antiaggregant and anticoagulant drug therapy was administered to all patients (16). The primary operator

decides on the stent length, diameter, and pre- and post-dilatation. The use of drugs such as intracoronary tirofiban, nitroprusside, and adenosine is at the discretion of the operator. Coronary blood flow was analyzed according to the degree of TIMI flow. Thrombolysis in myocardial infarction flow grades were defined as follows: grade 0, no antegrade flow beyond the lesion; grade 1, weak distal antegrade flow leading to incomplete filling of the artery; grade 2, slow antegrade flow despite complete opacification of the entire coronary bed; and grade 3, mean opacification rate of the entire coronary bed (17). Patients were divided into 2 groups according to post-intervention TIMI flow grade: group 1 included patients with TIMI flow grade 3, and group 2 included patients with TIMI flow grades 0 to 2. Digital media were used for quantitative analysis and documentation of coronary angiograms (Dicom viewer; Med-Com GmbH, Darmstadt, Turkey). Two expert interventional cardiologists, unaware of all the clinical data, analyzed the digital angiograms, and in case of disagreement, a consensus decision was made. Interobserver variability in the coronary angiographic evaluation of no-reflow was 5%.

Statistical Analysis

Statistical analysis was performed using the SPSS Version 26.0 program (SPSS Inc., Chicago, Illinois, USA). Whether the variables indicate a normal dispersion. Normally dispersion numerical variables were described as mean \pm standard deviation (SD), non-normally dispersion numerical variables as median (interquartile range), and categorical variables were described as a percentage (%). Receiver operating characteristic (ROC) curve and Youden index [maximum (sensitivity + selectivity -1)] were used to identify the predictive value of the TyG index value that best detects no-reflow development. Statistical analysis of numerical variables between independent groups was performed using the Student's t-test or Mann-Whitney U test. Analysis of categorical variables such as reflow and no-reflow was performed using the chi-square or Fisher's exact test. Pearson's or Spearman's study evaluated the correlation between the TyG index and other numerical variables. Multivariate logistic regression analysis was performed to identify independent predictors of no-reflow. If the area under the ROC curve was above 0.5 and the p-value was <0.05 , it was considered statistically significant.

Results

This study evaluated 289 consecutive patients who underwent PCI with the diagnosed NSTEMI-ACS of SVGs. Of these 289 patients, 48 (16.6%) were female, and the mean age was 63.5 ± 9.2 years. The study patients were

divided into two groups based on TIMI flow grade after PCI. The regular reflow group comprised 209 patients, and the no-reflow group included 80 patients. The baseline demographic, clinical, and laboratory characteristics of the patients are shown in Table 1. The mean (SD) age was 62.6 (8.6) years in group 1 and 66.1 (10.2) years in group 2 ($p=0.004$). Additionally, the number of patients with diabetes ($p<0.001$), history of stroke ($p<0.001$), previous MI ($p=0.035$), atrial fibrillation ($p=0.031$), chronic kidney disease ($p=0.007$), WBC ($p<0.001$), platelets ($p<0.001$), neutrophils ($p<0.001$), lymphocytes ($p<0.001$), and CHF ($p<0.001$) were higher in group 2 than in group 1. The mean (SD) ejection fraction was lower in group 2 ($p<0.001$), whereas the TyG index was higher in group 2 ($p<0.001$) (Figure 2). There was no significant difference in terms of gender, hypertension, dyslipidemia, smoking, peripheral arterial disease, previous PCI, COPD, serum creatinine, total cholesterol, LDL-C, and HDL-C between the groups.

Coronary angiography findings and procedural characteristics of the entire study group are shown in Table 2. Preinterventional TIMI flow grade 0 ($p<0.001$) and grade 3 ($p<0.001$), degenerated SVG ($p<0.001$), thrombus ($p<0.001$), and glycoprotein IIb/IIIa receptor antagonist use ($p<0.001$) were higher in group 2, whereas the number of patients implanted with drug-eluting stents ($p=0.041$) was larger in group 1. The stent diameter ($p=0.004$) was larger in group 2.

The results of univariate and multivariate regression analyses for selected preprocedural and procedural variables in the prediction of the no-reflow phenomenon are presented in Table 3. The TyG index ($p<0.001$), congestive HF ($p<0.001$) degenerated SVG ($p=0.001$), and intraluminal thrombus ($p<0.001$), were found to be independent predictors of the no-reflow phenomenon in multivariate logistic regression analysis.

To determine the cut-off value for the TyG index that best detects the presence of the no-reflow phenomenon, the ROC curve was drawn (Figure 3), and the cut-off value was determined as 5.15 using the Youden index (area under the curve: 0.821, 95% confidence interval: 0.769-0.873, $p<0.001$). This cut-off value could detect no-reflow with 70% sensitivity and 83.7% specificity. In addition, a positive predictive value of 62.2%, a negative predictive value of 87.9%, and an accuracy rate of 79.9% were detected.

Discussion

The main findings of this study are summarized below:

1. A higher TyG index is an independent risk factor for the no-reflow phenomenon in saphenous venous grafts in patients with acute coronary syndrome.

Table 1. The baseline demographic, clinical, and laboratory data of the study patients

Variables	Normal reflow (n=209)	No reflow (n=80)	p-value
Male sex, n (%)	177 (80.4)	64 (80)	0.338
Age, year, mean (SD)	62.6±8.6	66.1±10.2	0.004
Hypertension, n (%)	156 (74.6)	68 (85)	0.059
Diabetes, n (%)	79 (37.8)	48 (60)	0.001
Dyslipidemia, n (%)	112 (53.6)	47 (58.8)	0.430
Current smoking status, n (%)	48 (23)	26 (32.5)	0.097
PAD, n (%)	40 (19.1)	23 (28.7)	0.077
History of stroke/TIA, n (%)	9 (4.3)	18 (22.8)	<0.001
Previous MI, n (%)	99 (47.4)	49 (61.3)	0.035
Previous PCI, n (%)	74 (35.4)	37 (46.3)	0.090
COPD, n (%)	28 (13.4)	8 (10)	0.434
Congestive HF, n (%)	41 (19.6)	49 (61.3)	<0.001
EF, %	51.5±9.2	42.3±11	<0.001
Atrial fibrillation, n (%)	18 (8.6)	14 (17.5)	0.031
CKD, n (%)	46 (22)	30 (37.5)	0.007
Serum creatinine, mg/dL, median (IQR)	1 (0.8-1.2)	1 (0.8-1.3)	0.062
Fasting blood glucose, mg/dL, median (IQR)	105 (91-139.5)	179 (112.3-281)	0.001
Hemoglobin, g/dL, median (IQR)	13.7 (12.2-15)	12.8 (11-14)	0.001
Total cholesterol, mg/dL, mean (SD)	186±55	187.9±55.3	0.459
LDL cholesterol, mg/dL, mean (SD)	115±46.2	115±47.6	0.994
HDL cholesterol, mg/dL, mean (SD)	39.6±8.7	38.6±10.7	0.412
Triglycerides, mg/dL, median (IQR)	132 (105-189.5)	219.5 (165-314.5)	<0.001
White blood cells, 10 ⁶ /L, mean (SD)	8±2.2	9.6±2.4	<0.001
Platelets x 10 ⁹ /mm ³ , mean (SD)	227.4±64.3	354.5±125.1	<0.001
Neutrophils, 10 ⁹ /L, median (IQR)	4.6 (3.8-5.5)	7.5 (6.1-9.7)	<0.001
Lymphocyte, 10 ⁹ /L, mean (SD)	2.3±0.7	1.8±1.2	<0.001
TyG index, mean (SD)	4.86±0.3	5.3±0.4	<0.001

Data are presented as percentage, mean ± standard deviation or median (interquartile range)
 AF: Atrial fibrillation, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, EF: Ejection fraction, HDL: High-density lipoprotein, HF: Heart failure, LDL: Low-density lipoprotein, MI: Myocardial infarction, PAD: Peripheral artery disease, PCI: Percutaneous coronary intervention, TyG: Triglyceride-glucose, TIA: Transient ischemic attack, IQR: Interquartile range, SD: Standard deviation

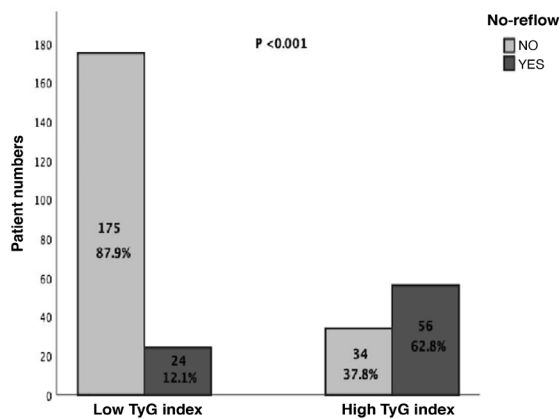


Figure 2. No-reflow development was higher in the high TyG index group than in the low TyG index group [56 (62.8%) vs 24 (12.1%); p<0.001]
 TyG: Triglyceride-glucose

2. The other independent risk factors for the no-reflow phenomenon in saphenous venous grafts are congestive heart failure, intraluminal thrombus, and degenerated SVGs.

The no-reflow phenomenon is a result of endothelial dysfunction that occurs after the revascularization of epicardial coronary arteries. The main immunopathological mechanisms include capillary edema with the contribution of leukocytes and inflammation-related mediators and distal coronary embolism after percutaneous intervention. It is commonly observed in patients with acute coronary syndrome (18). Percutaneous coronary interventions, which are performed on saphenous venous grafts, carry a high risk in terms of the coronary no-reflow phenomenon and restenosis (19). Many factors have been identified that predict the no-reflow phenomenon; however, additional markers are required (11).

Variables	Normal reflow (n=209)	No reflow (n=80)	p-value
Time elapsed from surgery to angiography, y, mean (SD)	10.4±4.9	11.4±4.8	0.133
Narrowed saphenous vein graft to			
Left anterior descending artery, n (%)	12 (5.8)	7 (8.8)	0.832
Diagonal artery, n (%)	23 (11.1)	8 (10)	
Circumflex artery, n (%)	88 (42.5)	34 (42.5)	
Right coronary artery, n (%)	84 (40.6)	31 (38.8)	
TIMI flow grade before the intervention			
0, n (%)	21 (10)	22 (27.5)	<0.001
1, n (%)	15 (7.2)	8 (10)	
2, n (%)	55 (26.3)	28 (35)	
3, n (%)	118 (56.5)	22 (27.5)	
TIMI flow grade following the intervention			
0, n (%)	0 (0)	9 (11.3)	<0.001
1, n (%)	0 (0)	23 (28.7)	
2, n (%)	0 (0)	48 (60)	
3, n (%)	209 (100)	0 (0)	
Procedural data			
Degenerated saphenous vein graft, n (%)	45 (21.5)	51 (63.7)	<0.001
Intraluminal thrombus, n (%)	41 (19.6)	54 (68.4)	<0.001
Focal lesion, n (%)	154 (74)	39 (48.8)	<0.001
Drug-eluting stent, n (%)	121 (59)	32 (45.1)	0.041
Stent diameter, mm, mean (SD)	3.2±0.5	3.4±0.6	0.004
Stent length, mm, mean (SD)	24.2±12.2	25.6±13.9	0.413
Predilatation, n (%)	72 (34.4)	37 (46.3)	0.064
Postdilatation, n (%)	51 (24.4)	13 (16.3)	0.135
Glycoprotein IIb / IIIa inhibitor use, n (%)	34 (16.3)	40 (50)	<0.001
Antiplatelets			
Clopidogrel, n (%)	185 (88.5)	74 (92.5)	0.589
Ticagrelor, n (%)	19 (9.1)	5 (6.3)	
Prasugrel, n (%)	5 (2.4)	1 (1.3)	
Additional variables			
Distal protection device use, n (%)	8 (3.8)	3 (3.8)	0.975
Thrombectomy, n (%)	3 (1.4)	4 (5)	0.078
Data are presented as number (percentage) unless otherwise indicated TIMI: Thrombolysis in Myocardial Infarction, SD: Standard deviation			

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.044 (1.014-1.076)	0.004	1.033 (0.987-1.081)	0.157
History of stroke/TIA	6.557 (2.803-15.341)	<0.001	3.117 (0.939-10.354)	0.063
Congestive HF	6.477 (3.682-11.392)	<0.001	4.728 (2.139-10.450)	<0.001
CKD	2.126 (1.216-3.717)	0.008	1.080 (0.471-2.476)	0.856
TyG index	12.01 (6.571-21.949)	<0.001	13.449 (5.823-31.06)	<0.001
Degenerated saphenous vein graft	6.409 (3.651-11.250)	<0.001	4.284 (1.804-10.169)	0.001
Intraluminal thrombus	8.852 (4.934-15.875)	<0.001	5.569 (2.534-12.241)	<0.001
Focal lesion	0.334 (0.195-0.571)	<0.001	1.041 (0.434-2.498)	0.929
TyG: Triglyceride-glucose, CKD: Chronic kidney disease, HF: Heart failure, TIA: Transient ischemic attack, CI: Confidence interval, OR: Odds ratio; others, see Table 1 and Table 2				

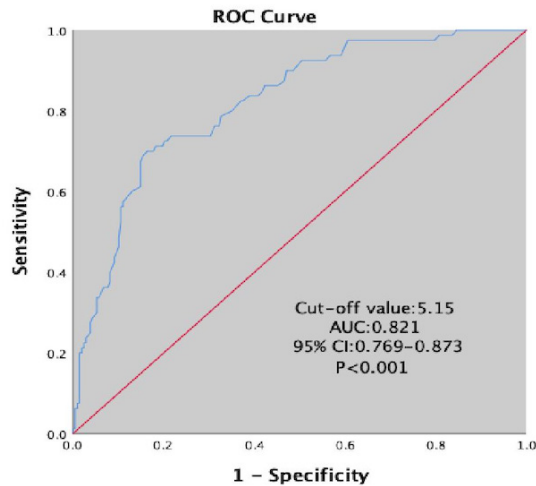


Figure 3. Receiver operating characteristics curve analysis showing the TyG index cut-off value of 5.15 that predicted no-reflow phenomenon with with 70% sensitivity and 83.7% specificity

TyG: Triglyceride-glucose, ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval

The TyG index, calculated as a parameter derived from fasting blood glucose and TG levels, is a new laboratory marker. High levels of TyG ratio are considered a worse setting in various clinical syndromes, namely diabetes and metabolic syndrome (20,21). Triglyceride-glucose index is associated with high arterial pulse wave velocity, even in patients without diabetes (22). Furthermore, hospitalized diabetic patients with high TyG index levels have more frequent cardiovascular complications than patients who are not diabetic (23). As a result, the TyG index can be used as a screening tool for, in particular, the worsening clinical setting for cardiovascular disease, irrespective of diabetes.

The TyG index is a composite indicator composed of TG and is a good marker of insulin resistance (24). In addition, insulin resistance is a marker of oxidative stress and inflammation (25). The conclusion to be drawn from this connection is the close relationship between the TYG index and inflammation, which is of critical importance for the no-reflow phenomenon. There are studies showing the relationship between the TyG index and stent restenosis, especially in acute coronary syndrome patients (26). In addition to inflammation, the TyG index is an indicator of insulin resistance and a predictor of the no-reflow phenomenon. Metabolic syndrome increases the development of no-reflow in patients with STEMI. Considering the relationship between the TyG index and metabolic syndrome, this correlation with no-reflow is not surprising.

Other parameters are associated with the no-reflow phenomenon in our study. Several studies have shown that congestive heart failure is related to the

no-reflow phenomenon. Consistent with previous reports, multivariate analysis in our study showed that congestive heart failure was independently associated with the no-reflow phenomenon (27). Similar to previous findings, our study also showed that the presence of intraluminal thrombus and degenerated SVGs could independently predict the no-reflow phenomenon before SVG intervention (28). Previous studies also reported a relationship between advanced age and the no-reflow phenomenon (29). Consistently, in our study, it was determined that the patients who developed no-reflow were older; however, in multivariate analysis, age was not among the factors predicting the no-reflow phenomenon.

Study Limitations

This study had several limitations. First, this was a retrospective study conducted with a relatively limited number of patients. Second, the baseline thrombus burden, an important determinant of the no-reflow phenomenon, was not evaluated in our study. Third, our current study included only patients with ACS, which may introduce selection bias and limit the generalizability of our findings to patients with chronic coronary syndromes. Finally, because fasting insulin was not routinely measured in our center, this study fails to compare the role of the Homeostasis Model Assessment of Insulin Resistance and TyG index in the setting of the no-reflow phenomenon. Despite these limitations, to the best of our knowledge, this study is the first to elucidate the relationship between the absence of reflow phenomena in venous grafts and the TyG index.

Conclusion

A simple measurable laboratory variable was related to a more frequent no-reflow phenomenon in patients with non-STEMI undergoing SVG PCI. In addition, the TyG index was an independent predictor of the no-reflow phenomenon in our study population. Triglyceride-glucose index levels higher than 5.15 have been shown to be effective in predicting the no-reflow phenomenon in such patient groups. It is a simple and non-invasive method that can be performed on either diabetic or non-diabetic patients.

Ethics

Ethics Committee Approval: The Clinical Research Ethics Committee of the University of Health Sciences Turkey, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital approved the protocol for this study in accordance with the Declaration of Helsinki and good clinical practice (approval no.: 2023.02-10, date: 21.02.2023).

Informed Consent: Because the study had a retrospective design, informed consent was not obtained from the patients.

Authorship Contributions

Concept: M.A., M.K., Design: M.A., M.K., Data Collection or Processing: M.K., Analysis or Interpretation: M.A., Literature Search: M.K., Writing: M.A.

Conflict of Interest: No conflicts of interest were declared by the authors.

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