Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1052129
J Health Sci Med 2022; 5(2): 652-658

Is the systemic immune-inflammation index a predictive marker of carotid artery stenosis?

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Cite this article as: Karacan Gölen M, Yılmaz Okuyan D. Is the systemic immune-inflammation index a predictive marker of carotid artery stenosis?. J Health Sci Med 2022; 5(2): 652-658.

ABSTRACT

Introduction: The relationship between inflammation and atherosclerosis and ischemic stroke was shown in studies, and we aimed to evaluate the relationship between the systemic immune-inflammation (SII) index and carotid artery stenosis (CAS) in our study.

Material and Method: Forty patients with CAS with acute cerebrovascular disease and sixty three patients without CAS with acute cerebrovascular disease were included in the study. Demographic characteristics, neutrophil/lymphocyte ratio (NLR), and the SII indexes of the patients were compared between the groups with and without CAS.

Results: There was a statistically significant difference between the groups in terms of NLR and SII index values ($p<0.05$). In the ROC analysis, the sensitivity of the SII index was 65% and the specificity was 84.1%, based on a cut-off value of ≥14.032, and the sensitivity and specificity of NLR were 65% and 82.5%, repectively, based on a cut-off value ≥4.701. In terms of prognosis, poor outcome (mRS 3-6) was detected in 22/40 (55%) in the group with CAS, and a statistically significant difference was found between the groups ($p<0.05$). When evaluated in terms of mortality, the 1-month mortality rate in the group with CAS was 20% (8/40), and 4.8% (3/63) in the group without CAS ($p<0.05$).

Conclusion: In our study, the SII index and NLR were thought to be markers associated with the presence of CAS in patients with symptomatic CAS, and higher NLR and SII index values were found to be associated with poor prognosis and mortality.

Keywords: Carotid artery stenosis, inflammation, systemic immune-inflammation index (SII), neutrophil/lymphocyte ratio (NLR)

INTRODUCTION

Approximately 11.8% of all deaths in the world are due to stroke, and stroke ranks second after coronary artery diseases in terms of causing mortality (1). Carotid artery stenosis is one of the most important risk factors for ischemic stroke and is responsible for approximately 30% of strokes. The degree of carotid artery stenosis is correlated with the development of ischemic stroke, and the risk of stroke increases with stenosis of 50% or more in symptomatic patients and 70% or more in asymptomatic patients. (2).

Atherosclerosis is the most important factor in the formation of carotid artery stenosis (3). It is thought that chronic inflammation on the endothelial surface contributes to the process of the formation of atherosclerosis, and the increased risk of stroke in chronic inflammatory diseases supports this hypothesis. When studies on pathogenesis are examined, the presence of macrophages and T lymphocytes has been shown at every stage of the atherosclerotic process. Oxidative stress and inflammation lead to plaque destabilization in atherosclerosis, leading to the development of the thrombotic process. The expression of intercellular adhesion molecules by the endothelium in the area of atherosclerosis and the presence of activated T lymphocytes and macrophages in endarterectomy preparations support the contribution of the acute inflammatory response to the process. The fact that mediators released from symptomatic plaques, unlike asymptomatic plaques, cause rupture explains the risk of ischemic stroke in symptomatic stenosis and the contribution of inflammation to the process (4-6). Many previous studies have shown the relationship of inflammatory markers, especially C-reactive protein (CRP) and fibrinogen, with stable and unstable angina pectoris, peripheral artery disease, and carotid artery stenosis (7-9).

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Received: 01.01.2022 **Accepted:** 25.02.2022

CRP is one of the preferred acute-phase proteins in the follow-up of inflammation with acute phase response, and a strong correlation has been found between high CRP levels and risk of stroke and cardiovascular disease (10,11). It is reported as a result of 12 observational studies that CRP levels increase the risk of ischemic stroke (12,13).

In light of new developments, new diagnostic approaches focusing on the content of plaques rather than the known effects of the clinical consequences of atherosclerosis such as lumen narrowing, have been brought to the agenda. Recently, the obtained systemic immune inflammation (SII) index, which is used in combination with neutrophil, lymphocyte, and platelet counts as an inflammation marker and is considered to predict prognosis, has come to the fore. In studies, the SII index as an inflammation marker has been shown to have a stronger predictive value in showing inflammation than known parameters such as white blood cell (WBC) counts, the neutrophil/lymphocyte ratio (NLR), and neutrophil and lymphocyte counts (14-16).

No study has been found in the literature evaluating the relationship between the presence of carotid artery stenosis (CAS) and the SII index. It has been shown that inflammation is associated with atherosclerosis and ischemic stroke in different studies. We aimed to evaluate the relationship between the SII index and CAS.

MATERIAL AND METHOD

The study was carried out with the permission of KTO Karatay University, Faculty of Medicine Non-pharmaceutical and Non-medical Device Researches Ethics Committee (Date: 15.10.2021, Decision No: 2021/019). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This was a single-center, retrospective study. Forty patients with CAS and sixty three patients without CAS who were followed up in our clinic with the diagnosis of acute cerebrovascular disease between January 2019 and January 2021 were included in the study, and ultrasound of carotid and vertebral arteries was performed to these patients. Patients with a diagnosis of COVID-19, those who were pregnant, and patients with cancer, autoimmune disease, history of hematologic disease, history of immunosuppressive use, carotid dissection secondary to trauma, infectious process, or findings of sepsis (e.g. pneumonia, urinary system infections, pancreatitis, cholangitis) were excluded from the study. Ultrasound of carotid and vertebral arteries was performed in the first 5 days after symptom onset. CAS was evaluated using high-resolution B-mode carotid and vertebral artery Doppler ultrasonography. Accordingly, symptomatic patients with stenosis of a rate of ≥50% in the internal carotid artery (ICA) were considered to have significant stenosis. Patients without stenosis in the ICA were included in the comparison group. Demographic characteristics, chronic diseases, laboratory parameters, neutrophil/lymphocyte ratio, and the SII indexes of the patients were compared between groups with and without CAS.

Among the laboratory markers, WBC, neutrophil, lymphocyte and platelet counts, CRP, high-density lipoprotein (HDL), low-density lipoprotein (LDL), D-dimer, troponin, activated partial thromboplastin time (aPTT), prothrombin time (PT), and were recorded. Calculations were made according to the following formulae: NLR = neutrophil count/ lymphocyte count and SII index = neutrophil count x platelet count / lymphocyte count.

Ischemic stroke types were classified according to the Trial of Org 10 172 in Acute Stroke Treatment (TOAST) classification (17). Modified Rankin scale (mRS) scores at admission and 1 month, and National Institute of Health Stroke Scale (NIHSS) scores at admission were recorded in all patients. mRS 0-2 was considered a good prognosis and 3-6 as a poor prognosis. In addition, 30-day mortality was evaluated in all patients.

Demographic data, risk factors, laboratory findings, clinical findings, prognosis, and mortality findings were compared between the two groups.

Statistical Analysis

The data obtained in this study were analyzed using the IBM SPSS Statistics Version 21 package program.

The Shapiro-Wilk test was used because of the number of patients in the groups while investigating the normal distribution of the variables. While interpreting the results, 0.05 was used as the significance level; it was stated that in the case of $p<0.05$, the variables did not show normal distribution, and in the case of $p>0.05$, the variables showed normal distribution.

While examining the differences between the groups, the Mann-Whitney U test was used because the variables did not show normal distribution.

The Chi-square test was used while examining the relationships between groups of nominal variables.

While interpreting the results, 0.05 was used as the significance level, and it was stated that there was a significant relationship in case of $p<0.05$, and there was no significant relationship in case of $p>0.05$.

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Receiver operating characteristics (ROC) curve analysis was performed to determine the diagnostic values of some numerical measurements. Discrimination of the model was graded according to the area under the ROC curve as follows: 0.5-0.6 = weak discrimination, 0.6-0.7 = poor discrimination, 0.7-0.8 = acceptable discrimination, 0.8-0.9 = good discrimination, 0.9- 1 = excellent discrimination

RESULTS

Demographic Features

Forty patients with CAS and sixty three patients without CAS were included in the study. In the group with CAS, 18/40 (45%) of the patients were female and 22/40 (55%) were male. In the group without CAS, 25/63 (39.7%) of the patients were female, and 38/63 (60.3%) were male. The mean age was 73.15 years in the group with CAS and was 69.04 years in the group without CAS. There was no statistically significant difference between the groups in terms of age and sex (**Table 1**)

Table 1. Evaluation of the relationship between sex and age of the groups

	Groups				Total		p value
	CAS ≥50% (n=40)		Control (n=63)				
	n	%	n	%	n	%	
Sex							
Female	18	45	25	39.7	43	41.7	
Male	22	55	38	60.3	60	58.3	
Total	40	100	63	100	103	100	0.594
Age	**n**	**Mean**	**SD**	**Median**	**Min**	**Max**	
CAS ≥50%	40	73.15	12.98	75	37	93	
No CAS	63	69.04	11.35	70	38	92	
Total	80	70.64	12.11	71	37	93	0.072

SD: Standard Deviation. n: number of patients. p<0.05 Chi-square test was used for statistical analysis. Mann-Whitney U test was used for statistical analysis.

When the demographic data characteristics of the patients were examined, no statistically significant difference was found between the groups in terms of smoking, hypertension, diabetes mellitus, hyperlipidemia, and atrial fibrillation (**Table 2**).

In the group with CAS, according to the NIHHS score, 3/40 (7.5%) had mild stroke, 16/40 (40%) had moderate stroke, and 21/40 (52.5%) had severe stroke. In group without CAS 18/63 (28.6%) had mild stroke, 29/63 (46%) had moderate stroke, and 16/63 (25.4%) had severe stroke.

When evaluated in terms of prognosis, poor outcomes (mRS 3-6) were found in 22/40 (55%) of the patients in the group with CAS, whereas it was found in 13/63 (20.6%) of the patients in the group without CAS. A statistically significant difference was found between the groups in terms of prognosis (p<0.05).

When evaluated in terms of mortality, the 1-month mortality rate was 20% (8/40) in the group with CAS, whereas it was 4.8% (3/63) in the group without CAS. Mortality was found to be statistically and significantly higher in the group with CAS (p<0.05) (**Table 2**).

According to the TOAST classification, the most common etiologic factor was large-artery atherosclerosis in 39/40 (97.5%) patients in the group with CAS. The most common etiologic factor was cardioembolism in 19/63 (30.2%) patients in the group without CAS (**Table 2**).

Table 2. Demographic and clinical features

	CAS ≥50% (n=40)	Control (n=63)	p value
	n (%)	n (%)	
Smoking			
Yes	6 (15%)	9 (14.3%)	0.920
No	34 (85%)	54 (85.7%)	
Hypertension			
Yes	21 (52.5%)	40 (63.5%)	0.269
No	19 (47.5%)	23 (36.5%)	
Diabetes mellitus			
Yes	13 (32.5%)	25 (39.7%)	0.462
No	27 (%67.5)	38 (60.3%)	
Hyperlipidemia			
Yes	13 (32.5%)	27 (42.9%)	0.293
No	27 (67.5%)	36 (57.1%)	
Prior ischemic stroke			
Yes	5 (12.5%)	6 (9.5%)	0.634
No	35 (87.5%)	57 (90.5%)	
Atrial fibrillation			
Yes	11 (27.5%)	26 (41.3%)	0.156
No	29 (72.5%)	37 (58.7%)	
Mortality			
Yes	8 (20%)	3 (4.8%)	0.015
No	32 (80%)	60 (95.2%)	
NIHSS			
Mild	3 (7.5%)	18 (28.6%)	
Modatere	16 (40%)	29 (46%)	0.005
Severe	21 (52.5%)	16 (25.4%)	
TOAST			
Large-artery atherosclerosis	39 (97.5%)	13 (20.69%)	
Cardioembolism	1 (2.5%)	19 (30.2%)	
Small-vessel occlusion	0 (0%)	13 (20.6%)	<0.001
Stroke of other determined etiology	0 (0%)	2 (3.2%)	
Stroke of undetermined etiology	0 (0%)	16 (25.4%)	
MRS			
Good (MRS 0-2)	18 (45%)	50 (79.4%)	<0.001
Poor (MRS 3-6)	22 (55%)	13 (20.6%)	

n: number of patients, Chi-square test was used for statistical analysis. p<0.05 shows a statistical difference. TOAST: Trial of Org 10172 in acute stroke. NIHSS: National Institutes of Health Stroke Scale.MRS: Modified Rankin Scale

Laboratory findings

When laboratory parameters were compared between the two groups, there was a statistically significant difference in terms of WBC and monocyte counts, CRP, D-dimer, troponin, PT, aPTT, LDH, and HDL.

The mean neutrophil count was statistically significantly higher in the group with CAS (7.86±2.54 x103/μL) compared with the group without CAS (6.14±2.4 x103/μL) (p<0.05). The mean lymphocyte count was statistically significantly lower in the group with CAS (1.58±0.7 x103/μL) compared with the group without CAS (2.4±0.94 x103/μL) (p<0.05).

The mean value of platelet count was statistically significantly higher in the group with CAS (293.82±65.66 x103/μL) compared with the group without CAS (239.82±68.45 x103/μL). (p<0.05) (**Table 3**).

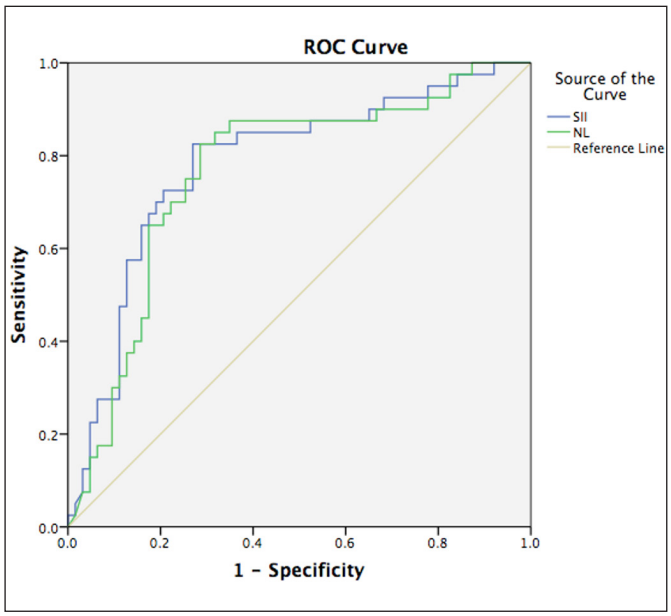

Figure 1. The ROC analysis curve

There was a statistically significant difference between the groups in terms of NLR and SII index (p<0.05) (**Table 4**).

ROC analysis was performed for the SII index and NLR. For the SII index, the sensitivity was 65% and specificity was 84.1% based on the cut-off value ≥14.032, and the sensitivity was 65% and specificity was 82.5% based on the NLR cut-off value ≥4.701. Details of the ROC analysis are given in **Table 5** and **Figure 1**.

Table 3. Comparison of Laboratory Parameters Between Groups with and without CAS

	CAS ≥50% (n=40)	Control (n=63)	
	Mean ± SD (min-max) (median)	Mean ± SD (min-max) (median)	p value
White Blood Cell, ×10³/μL	10.3±2.95 (5.88-16) (10.8)	9.63±2.99 (4.8-18.8) (8.9)	0.267
Neutrophil, ×10³/μL	7.86±2.54 (3.7-13.6) (7.15)	6.4±2.4 (2.7-13.3) (5.7)	0.001
Lymphocyte, ×10³/μL	1.58±0.7 (0.34-2.97) (13.6)	2.4±0.94 (0.34-3.9) (2.5)	<0.001
Monocyte, ×10³/μL	0.71±0.46 (0.2-3.2) (0.67)	0.72±0.34 (0.2-2.8) (0.7)	0.571
Platelet, ×10³/μL	293.82±65.66 (169-402) (299)	239.82±68.45 (3.18-396) (238)	<0.001
C reactive protein (CRP) mg/L	21.28±29.52 (1.7-108) (7.45)	11.69±24.66 (0.6-190) (5.28)	0.080
D-Dimer, ng/mL	2.45±2.49 (0.1-11.1) (1.8)	2.85±2.63 (0.1-12.1) (2)	0.405
Troponin, ng/mL	21.19±37.49 (2-229) (8.45)	35.38±137.43 (0.1-850) (6.8)	0.097
Prothrombin time (PT) s	12.65±3.68 (8.88-31.2) (11.8)	12.46±4.1 (8.58-38.9) (12)	0.743
Activated Partial thromboplastin time (aPTT) s	26.92±5.67 (19.3-42.3) (26.45)	26.93±7.54 (16.5-55.4) (26.5)	0.636
Lactate dehydrogenase (LDL) U/L	122.15±44.25 (13-263) (124)	139.3±62.4 (13-400) (124)	0.285
High density lipoprotein (HDL) U/L	39.53±11.03 (11-61)(41)	42.76±11.53 (1-72) (43)	0.116

SD: Standard Deviation, n: number of patients. Mann-Whitney U test was used for statistical analysis. P<0.05 shows the statistical difference.

Table 4. Comparison of Neutrophil/Lymphocyte ratio and SII index between groups

	n	Mean	SS	Medyan	Min	Max	p-value
Neutrophil/Lymphocyte							<0.001
CAS ≥50%	40	6.61	5.9	5.17	1.58	36.47	
Control	63	3.84	5.03	2.19	0.9	36.47	
Total	80	4.92	5.53	3.27	0.9	36.47	
SII index							<0.001
CAS ≥50	40	2021.14	1786.12	1712.02	267.44	10102.35	
Control	63	940.29	1224.07	535.38	14.92	8169.41	
Total	80	1360.04	1552.66	770.92	14.92	10102.35	

SD: Standard Deviation, n: number of patients, Mann-Whitney U test was used for statistical analysis. p<0.05 shows a statistical difference. SII: Systemic immune inflammation index.

Table 5. ROC curve analysis results for significant laboratory variables.

	AUC	SD	p-value	95% CI		Cut-off	Sensitivity	Specificity
				Lower	Upper			
SII index	0.782	0.48	<0.001	0.688	0.877	≥14.032	65	84.1
NLR	0.765	0.50	<0.001	0.668	0.862	≥4.701	65	82.5

SD: Standard Deviation, AUC: Area Under the Curve. ROC analysis was used for statistical analysis. SII index: Systemic immune inflammation index. NL: Neutrophil/Lymphocyte.

DISCUSSION

The SII index is a marker that has recently been investigated concerning prognosis and the inflammatory process. In our study, a statistically significant increase was found between symptomatic CAS, the SII index, and NLR when patients with and without CAS as the etiologic factor followed up during the cerebrovascular disease process were compared.

Studies evaluating the relationship between the SII index and related CAS concluded that the SII index was a parameter that could predict severe obstruction hemodynamically and was a predictor of major cardiac risk events that might develop in patients with coronary artery disease (18,19). We could not find a similar study in the literature, so, based on this hypothesis, we evaluated patients with acute ischemic stroke with symptomatic CAS, and we thought that CAS was associated with the SII index and NLR.

When ischemic cerebrovascular disease develops, neutrophil levels increase and lymphocyte levels decrease in case of acute stress, and this situation has been found to be associated with the severity of ischemia. Lymphopenia develops due to the apoptosis of lymphocytes under the influence of physiologic stress during the inflammation process (16). In addition, an increase in the neutrophil count causes atherosclerosis by causing plaque rupture, reperfusion damage, and plaque remodeling, which plays a critical role in the development of CAS. Increased neutrophil levels increase platelet levels and cause platelet aggregation. In addition, neutrophils also stimulate thrombogenesis by affecting tissue factors. Thus, besides the increase in neutrophils, the correlated increase in platelets leads to inflammation and thrombosis. Activated platelets cause the rupture of thrombus formation from atherosclerotic plaques and increase the risk of rupture by activating the release of proteolytic enzymes and myeloperoxidase-like oxidation enzymes in activated neutrophils. Ultimately, ruptured plaque formation leads to ischemic stroke. An increase in neutrophil levels in the histopathologic examinations of ruptured plaques that cause ischemic stroke or stenosis supports this situation. Nasr et al. (20) reported that the development of cerebral ischemia secondary to symptomatic CAS was associated with neutrophil levels. In our study, when the laboratory parameters of the groups with and without CAS were compared, the increase in neutrophil and platelet levels and a decrease in lymphocyte levels were considered statistically significant. The SII index, which evaluates all these neutrophil, lymphocyte, and platelet levels together, has been shown to be more valuable in predicting prognosis compared with other inflammatory markers (16).

In our study, when we compared the patients with and without CAS as the etiologic factor followed up during the cerebrovascular disease process, a statistically significant correlation was found with NLR, as well as the SII index, in patients with symptomatic CAS.

Supporting the results of our study, another study evaluated NLR in patients with CAS and it was reported that the NLR was increased in these patients, showing the risk of rupture in non-calcified carotid artery plaques (21). It has been shown in previous studies that NLR is a marker of poor prognosis in ischemic stroke (22). In our study, similarly, mortality was found to be statistically significantly higher in patients with symptomatic CAS.

In a review that evaluated the findings of 18 studies examining the prognostic value of NLR and PLR in patients with CAS, NLR was found to be associated with carotid intima-media thickness, carotid plaques, carotid stenosis, symptomatic stenosis, post-stenting re-stenosis, and cognitive dysfunction after CAS. It has been emphasized that NLR has prognostic value in evaluating the progression of atherosclerosis in subclinical atherosclerosis and carotid artery disease and that it can be used in patient management and individual treatment (23).

We found a study in which the clinical benefit and utility of the SII index were evaluated in 165 patients who underwent intravenous thrombolytic therapy for acute cerebrovascular disease when we look at the studies in which the SII index and NLR were evaluated together. For NLR, ROC-AUC was 0.86, sensitivity was 71.3%, and specificity was 65.7%. For the SII index, ROC-AUC was 0.802, sensitivity was 58.7%, and specificity was 72.7%. As a result, it was concluded that the SII index and NLR provided moderate benefit in predicting the risk of bleeding that might occur following thrombolytic therapy (24). Similarly, it was emphasized that the SII index was a marker that predicted hemorrhagic transformation in patients who had a stroke due to large artery atherosclerosis of anterior circulation (25). In our study, in the ROC analysis of patients with symptomatic CAS, the sensitivity of the SII index was 65% and the specificity was 84.1% based on the cut-off value ≥14.032. The sensitivity of NLR was found to be 65% and specificity 82.5%, based on the cut-off value ≥4.701.

To evaluate the prognostic role of the SII index and NLR in patients with acute ischemic stroke, in another study involving 277 patients, the mRS scores of the patients were recorded at the 1st, 3rd, 6th, and 12th months. Multivariate analysis revealed that the initial NLR had a prognostic role at 3 months after ischemic stroke (26). Considering the relationship between the SII index and disease severity in patients with acute ischemic stroke,

it was reported that the SII index was an independent risk factor in showing the severity of stroke in a study of 362 patients (27). In our study, mortality was higher in the patient group with symptomatic CAS than in the other group without CAS. In addition, in the group with symptomatic CAS, the rate of poor outcomes according to mRS was higher in the 1-month follow-up.

In addition to the relationship of the SII index with atherosclerotic and inflammatory processes, its relationship with prognosis has been mentioned in various studies. In the first of these, 270 patients who had sinus vein thrombosis were followed up for an average of 22 (range, 6-66) months, and the prognostic value of the SII index was examined. It was reported to be a potential predictor of poor prognosis (28). The SII index was used for the first time as a marker to evaluate the relationship between cancer and inflammation, and it was found as a predictor of poor prognosis in solid tumors such as hepatocellular carcinoma and colorectal cancer (29-31).

Given that our study was a retrospective study, we could not make a long-term follow-up and evaluate the prognosis, which was one of the limitations of our study. Other limitations of our study were that it was a single-center study and that the number of patients was low. We think that our findings will be supported by prospective multicenter studies with a larger patient samples on the effectiveness of the SII index by comparing it with other inflammatory markers.

CONCLUSION

In our study, the SII index and NLR were thought to be markers associated with the presence of symptomatic CAS, and high NLR and SII indexes were found to be associated with poor prognosis and mortality. We think that prospective randomised controlled studies with a larger number of patients evaluating the relationship of the SII index to acute ischemic stroke and CAS are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of KTO Karatay University, Faculty of Medicine Non-pharmaceutical and Non-medical Device Researches Ethics Committee (Date: 15.10.2021, Decision No: 2021/019).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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