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ORIGINAL RESEARCH

Predictive Utility of PLR and Platelet-to-LDL Ratio for in-Stent Restenosis Following Carotid Artery Stenting

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Background: Carotid artery stenting (CAS) has been widely used to remodel the vascular structure and restore the blood flow for preventing ischemic stroke. However, in-stent restenosis (ISR) after CAS is extremely associated with an increased risk of ischemic stroke recurrence.

Objective: The aim of this study was to explore potential predict biomarkers for ISR after CAS.

Methods: In this study, data from 221 patients with CAS, which was divided into no-ISR group and ISR group, and 145 healthy controls were retrospectively analyzed. The ratios of neutrophil, lymphocyte, monocyte, platelet, glucose (Glu), and triglyceride (TG) to lymphocyte, HDL, and LDL were analyzed, respectively. In addition, the ratios of SII, SIRI, and AISI were analyzed as the following formulas: SII = platelet × neutrophil-to-lymphocyte ratio, SIRI = monocyte × neutrophil-to-lymphocyte ratio, and AISI = neutrophil × platelet × monocyte-to-lymphocyte ratio. ROC curve analysis was performed to analyze the predict roles of PLR and platelet/LDL for ISR.

Results: The ratios of NLR, PLR, Glu/lymphocyte, TG/lymphocyte, NHR, PHR, Glu/HDL, TG/HDL, neutrophil/LDL, platelet/LDL, Glu/LDL, TG/LDL, and SII increased in patients with CAS, indicating the predict roles of these values in carotid artery stenosis. Most importantly, increased ratios of PLR and platelet/LDL before the first operation of CAS, but not the second operation, were found in ISR patients after CAS as compared with no-ISR group. ROC analysis showed a more effective role of PLR for predicting ISR. While PLR showed high specificity (96.95%), its modest sensitivity (35.29%) suggests the need for complementary biomarkers in clinical practice.

Conclusion: These results indicate that ratios of PLR and platelet/LDL before the first CAS operation can act as the predict biomarkers of ISR.

Plain Language Summary:

Type of Research: Single-center retrospective cohort study.

Key Findings: Increased ratios of PLR and platelet/LDL before the first operation of carotid artery stenting (CAS), but not the second operation, were found in in-stent restenosis (ISR) patients after CAS as compared with no-ISR group. ROC analysis showed the potential role of PLR for predicting ISR.

Take home Message: The ratios of PLR and platelet/LDL before the first CAS operation can act as the predict biomarkers of ISR.

Summary: In this retrospective study of 221 patients, ratios of PLR and platelet/LDL increased in the ISR patients before the first, but not the second, operation of CAS. The ratios of PLR and platelet/LDL before the first CAS operation can act as the predict biomarkers of ISR.

Keywords: carotid artery stenting, in-stent restenosis, PLR, platelet to LDL ratio, biomarker

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Introduction

Atherosclerotic stenosis of the carotid and vertebral arteries are well-documented risk factors for cerebral infarction.[1] Studies indicate that 7%–20% of all ischemic stroke are caused by carotid artery stenosis.[2] With the development of neuro-interventional devices, carotid artery stenting (CAS) has been widely used to remodel the vascular structure and restore the blood flow for preventing ischemic stroke, especially for patients with symptomatic carotid stenosis >50% or asymptomatic carotid stenosis >70%.[3–5]

Despite the advances in endovascular CAS, complications are still happened during these processes. In-stent restenosis (ISR), one of the major complications after stent insertion, is extremely associated with an increased risk of ischemic stroke recurrence after stenting[6,7] and is defined as the flow velocity thresholds for ≥50%.[8] The reported rates of ISR following CAS vary widely, ranging from 3.3% to 21% within follow-up periods from 6 months to 5 years after carotid artery stent placement.[9] This variation has also been attributed to the definition of stenosis severity (>50% vs >70%−80%) in different imaging modality, previously reported a high incidence from 23% to 32% for >50% carotid in-stent stenosis when applying the standard carotid duplex ultrasound.[10–12] Therefore, identifying sensitive biomarkers for ISR prediction will play a vital role in improving the long-term efficacy of CAS treatment.

Numerous studies have investigated ISR following coronary interventions or restenosis after carotid endarterectomy (CEA). While coronary ISR is primarily driven by smooth muscle cell proliferation in response to cyclic mechanical stress,[13] post-CEA restenosis may arise from myointimal hyperplasia (typically occurring within the first two years) or from recurrent or progressive atherosclerosis beyond this timeframe.[14,15] Interestingly, one study explored the use of carotid stents in coronary patients undergoing coronary artery bypass grafting (CABG), suggesting that performing elective CAS (e-CAS) prior to CABG may yield favorable early outcomes while minimizing the risk of myocardial infarction, provided the procedures are performed within a very narrow interval.[16] Unlike these mechanisms, ISR following CAS exhibits distinct pathophysiological and clinical characteristics. Specifically, CAS-related ISR primarily results from chronic foreign body reaction and neoatherosclerosis.[17] Following stent implantation, vascular smooth muscle cells (VSMCs) undergo a phenotypic switch from a differentiated, contractile phenotype in the medial layer to a dedifferentiated, synthetic state. The activated VSMCs translocate from the medial layer to the intima, where they undergo clonal expansion and excessive extracellular matrix (ECM) deposition. This process is exacerbated by sustained secretion of pro-inflammatory cytokines (eg, IL-6, TNF-α) that perpetuate a feed-forward loop of vascular inflammation and pathological remodeling, ultimately manifesting as clinically significant ISR.[18,19] This study specifically addresses CAS-related ISR, as its clinical management and prognostic implications require distinct considerations.

Although previous investigations have performed to identify the possible risk factors for ISR in clinical trials, including smoking, hypertension, diabetes mellitus, and hyperlipidemia,[20–23] the exact risk factors remain controversial. The inflammatory responses to implanted stents are the driving force and primary pathophysiology mechanism of ISR.[24] It has been confirmed that inflammation response is closely related to the pathophysiology mechanism of acute ischemic stroke.[25] The counts of white blood cell, especially neutrophils, monocytes, lymphocytes, and platelets, are the core element of systemic inflammation response. It has been confirmed that elevated levels of neutrophils and platelets together, along with reduced levels of lymphocytes, are associated with vascular disease.[26,27] Systemic inflammation plays a crucial role in the pathophysiology of carotid stenosis and can be assessed through the newly derived biomarkers like neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR).[28,29] The ratios of NLR, MLR, and PLR have been widely investigated as their convenience to obtain, which have been confirmed to be closely associated with neurological disease.[30–32] To date, limited studies have been focused on the roles of NLR and PLR in predicting restenosis after CAS. In addition, as novel indexes related to systematic inflammation, the systemic immune-inflammation index (SII), systemic immune response index (SIRI), and aggregate inflammation response index (AISI), which predicted poor outcomes in patients undergoing CAS,[33–35] were also investigated to evaluate their predict roles on ISR after CAS. Hence, we aim to investigate the relationship of these indices with ISR after CAS.

Lipid accumulation is another principal pathophysiology mechanism for ISR after stenting operation.[24] High-density lipoprotein (HDL) and low-density lipoprotein (LDL), the primary type of human serum lipid profile, have long been recognized as the risk factors of intracranial stenosis. Improvement of HDL or decrease of LDL were associated with the

decreased risk of ISR.[36] Given that HDL and LDL are directly involved in immuno-regulation by altering the membrane lipid contents of immune cells, the combined effects of HDL with WBC subsets have been explored to assess the inflammatory risk recent years, such as the ratios of neutrophil, lymphocyte, monocyte, platelet to HDL.[37,38] As a new biological marker, the ratio of neutrophil to HDL (NHR) can reflect the inflammation and lipid profile level, and it has been confirmed to be independently associated with acute myocardial infarction.[39] Furthermore, NHR has been demonstrated to be an independent predictor of coronary artery stenosis.[40] However, limited studies addressed the associations of peripheral blood cells with HDL or LDL to ISR following CAS.

Therefore, in this investigation, we retrospectively analyzed the circulating data of peripheral blood in patients with CAS, which were divided into non-ISR and ISR by imaging methods. We aimed to investigate the predictive effects of the ratios related to HDL, LDL, and peripheral blood cells on ISR in patients with CAS.

Materials and Methods

Research Ethics

This study was performed according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Jinan Central Hospital Affiliated to Shandong First Medical University (No. SZR2021-006-01) and The Second Hospital of Shandong University (No. KYLL-2021 (KJ)P-0300).

Study Population

We retrospectively analyzed patients who underwent CAS in the Central Hospital Affiliated to Shandong First Medical University from 2016 to 2023. Patients were selected according to the following criteria: (1) age >18 years; (2) in stent restenosis ≥50% was diagnosed by digital subtraction angiography (DSA), computed tomography angiography (CTA), and/or color doppler imaging. (3) Standardized Modality Selection: Primary diagnostic tool: All patients underwent Duplex Ultrasound (DUS) as the first-line imaging for ISR surveillance at 6 months, 1 year, and 2 years, respectively, after stenting, with stenosis ≥50% defined by peak systolic velocity (PSV) ≥125 cm/s and internal carotid artery (ICA)/common carotid artery (CCA) PSV ratio ≥2.0, per the Society of Radiologists in Ultrasound consensus criteria.[41] Confirmatory imaging: For cases with inconclusive DUS results or planned reintervention, CT Angiography (CTA) (n=48) or Digital Subtraction Angiography (DSA) (n=66) was performed. DSA served as the gold standard for borderline lesions (eg, PSV 120–150 cm/s). The primary endpoint of this study was the occurrence of restenosis during follow-up. (4) Modality-Specific Criteria: CTA: Stenosis was quantified using NASCET criteria (≥50% = diameter reduction relative to distal normal ICA).[42] DSA: Measured via automated edge-detection software (eg, QVA, Medis Medical Imaging). (5) Consistency Assurance: All imaging interpretations were independently reviewed by two vascular radiologists. Exclusion criteria: (1) Patients who had never undergone follow-up neuroimaging after stent insertion, or only received MRI without further brain imaging, were excluded; (2) had severe other disease, such as hepatic (Child-Pugh Class C) and renal insufficiency (eGFR < 30 mL/min/1.73m² by CKD-EPI equation), cardiac impairment (LVEF < 40% by echocardiography), severe inflammatory conditions (clinical diagnosis of autoimmune/rheumatic disease under immunosuppression), and malignant tumor.

About 221 CAS patients (ranging from 36 to 84 years old), including 179 males and 42 females, were analyzed for peripheral clinical characteristics. They were observed for two years after the first carotid artery stenting. These patients were subdivided into two groups (no-ISR group and ISR group) according to ISR progression. In the ISR group, the perioperative clinical characteristics of these patients were collected within 24 hours prior to both the initial (ISR-1) and the second operation (ISR-2). During the observation period, 16 patients were lost to follow-up due to various reasons. 145 age- and sex-matched healthy controls were collected and confirmed to have no cerebrovascular disease or other sever conditions in the physical Examination Department of The Second Hospital of Shandong University over the same period.

Clinical Data Collection

The basic information of each participant, including age, sex, history of smoking, alcohol, hypertension, and coronary artery disease (CAD), was recorded. Venous blood samples were collected before the CAS performance. Biochemical assays like high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride (TG),

glucose (Glu), and total cholesterol (TC) were performed on a Roche Cobas c502 analyzer following manufacturer protocols, while hematologic parameters like counts of leukocytes, neutrophiles, monocytes, lymphocytes, and platelets were measured using a Sysmex XN-9000 automated hematology analyzer. The peripheral characteristics of patients were measured in the clinical laboratory of the Central Hospital Affiliated to Shandong First Medical University, while the parameters of healthy controls were detected in the clinical laboratory of the Second hospital of Shandong University. Both laboratories are ISO 15189-accredited and followed identical Standard Operating Procedures (SOPs) for sample processing and analysis, as required by ISO 15189. Both labs participated in the National External Quality Assessment Program (EQA) organized by the National Center for Clinical Laboratories (NCCL), the China's highest authority for laboratory quality control. All reported parameters achieved inter-assay CVs <5% in NCCL EQA rounds, demonstrating excellent precision. Internal quality control (IQC) was performed per ISO 15189 requirements. In addition, to assess inter-laboratory variability, a subset of samples (n=30) was re-tested at the central lab, showing high correlation.

The NLR, MLR, PLR, LLR, NHR, LHR, MHR, PHR, SII, SIRI, and AISI were calculated using the following formulas: NLR = neutrophil ($\times 10^9$/L) to lymphocyte ($\times 10^9$/L) ratio, MLR = monocyte ($\times 10^9$/L) to lymphocyte ($\times 10^9$/L) ratio, PLR = platelet ($\times 10^9$/L) to lymphocyte ($\times 10^9$/L) ratio, LLR = LDL (mmol/L) to lymphocyte ($\times 10^9$/L) ratio, NHR = neutrophil ($\times 10^9$/L) to HDL (mmol/L) ratio, LHR = lymphocyte ($\times 10^9$/L) to HDL (mmol/L), MHR = monocyte ($\times 10^9$/L) to HDL (mmol/L) ratio, PHR = platelet ($\times 10^9$/L) to HDL (mmol/L), SII = platelet ($\times 10^9$/L) × neutrophil ($\times 10^9$/L)-to-lymphocyte ($\times 10^9$/L) ratio, SIRI = monocyte ($\times 10^9$/L) × neutrophil ($\times 10^9$/L)-to-lymphocyte ($\times 10^9$/L) ratio, and AISI = neutrophil ($\times 10^9$/L) × platelet ($\times 10^9$/L) × monocyte ($\times 10^9$/L)-to-lymphocyte ($\times 10^9$/L) ratio. In addition, the ratios of Glu (mmol/L) to lymphocyte ($\times 10^9$/L), TG (mmol/L) to lymphocyte ($\times 10^9$/L), LDL (mmol/L) to HDL (mmol/L), Glu (mmol/L) to HDL (mmol/L), TG (mmol/L) to HDL (mmol/L), neutrophil ($\times 10^9$/L) to LDL (mmol/L), lymphocyte ($\times 10^9$/L) to LDL (mmol/L), monocyte ($\times 10^9$/L) to LDL (mmol/L), platelet ($\times 10^9$/L) to LDL (mmol/L), Glu (mmol/L) to LDL (mmol/L), TG (mmol/L) to LDL (mmol/L) were also detected. All the ratios were calculated as the proportions of the absolute counts. The relationship between the coincidence of ISR after CAS and the ratios of PLR and platelet-to-LDL was evaluated. The clinical characteristics of healthy controls provided baseline reference values for comparative analyses with other study groups.

Statistical Analysis

Given the retrospective and exploratory nature of this study, our analyses aimed to generate hypotheses rather than confirm causal relationships. We examined a broad range of variables to identify potential associations, acknowledging the increased risk of Type I error due to multiple testing. All the data were analyzed using GraphPad Prism software (Version VIII, La Jolla, CA, USA) and presented as means ± standard error of the mean (SEM). Data normality was assessed using Shapiro–Wilk tests. Variables with $p<0.05$ were considered non-normally distributed and analyzed via Kruskal–Wallis test. Post-hoc analysis employed Tukey's HSD (ANOVA) or Dunn's test for comparisons between more than two groups. ROC curve analysis was used to analyze the optimum values of PLR and platelet/LDL for identifying ISR. The optimal cut-off value was determined by maximizing the Yoden index (sensitivity + specificity - 1). $p<0.05$ was considered the threshold for statistical significance.

Results

Clinical Characteristics and Laboratory Indicators of CAS Patients and Healthy Controls

About 221 CAS patients and 145 healthy controls were collected, and the characteristics of the peripheral blood were retrospectively analyzed. Among all the 221 CAS patients, 21 patients progressed with ISR. The rate of ISR following CAS was 9.5%. These patients were divided into two groups based on the diagnosis of ISR. The retrospective data from healthy controls and non-ISR patients, and the data before the first (ISR-1) and the second CAS operation (ISR-2) from ISR patients were initially collected and analyzed. The baseline demographic and clinical characteristics are shown in Table 1. No significant differences were found in the baseline characteristics, including gender, age, history of smoking, drinking, platelets, TC, and LDL. As risk factors of AIS, there was higher incidence of hypertension ($p<0.0001$) and coronary artery disease (CAD, $p=0.04$) in CAS patients than in healthy controls. In addition, increased levels of white

Table 1 Baseline and Clinical Characteristics of AIS Patients with CAS and Healthy Controls

Variables	Healthy Control	No-ISR	ISR-1	ISR-2	P value
	n=145	n=200	n=21	n=17	
Gender (male, %)	90 (62.06)	133 (66.50)	16 (76.19)	13 (76.47)	0.39
Age (years)	65.17±0.59	66.21±0.54	67.95±1.61	68.41±1.87	0.06
Smoking (n, %)	65 (44.83)	98 (49)	10 (47.62)	8 (47.06)	0.75
Alcohol (n, %)	60 (41.38)	87 (43.5)	9 (42.86)	8 (47.06)	0.93
Hypertension (n, %)	45 (31.03)	132 (66)	15 (71.43)	13 (76.47)	<0.0001
CAD (n, %)	32 (22.07)	69 (34.5)	7 (33.33)	6 (35.29)	0.04
WBC, 10^9/L	5.91±0.08	7.33±0.19	6.73±0.22	5.56±0.35	<0.0001
Neutrophile, 10^9/L	3.25±0.06	4.82±0.18	4.22±0.33	3.21±0.22	<0.0001
Lymphocyte, 10^9/L	2.08±0.04	1.83±0.05	1.62±0.15	1.79±0.18	<0.0001
Monocyte, 10^9/L	0.43±0.01	0.49±0.02	0.43±0.06	0.37±0.04	0.0016
Platelet, 10^9/L	226.1±4.01	219.7±3.92	226.9±11.61	221.3±14.79	0.43
Glucose, mmol/L	5.11±0.04	6.81±0.19	5.85±0.23	6.24±0.41	<0.0001
TC, mmol/L	4.80±0.05	4.04±0.08	3.58±0.24	3.63±0.15	<0.0001
TG, mmol/L	0.95±0.03	1.44±0.07	1.30±0.13	1.26±0.14	<0.0001
HDL, mmol/L	1.43±0.02	1.08±0.02	1.16±0.06	1.23±0.05	<0.0001
LDL, mmol/L	2.41±0.05	2.39±0.07	2.15±0.19	2.09±0.17	0.08

Abbreviations: CAD, coronary artery disease; WBC, white blood cells; TC, total cholesterol; TG, Triglycerides; HDL, high-density lipoprotein; LDL, low density lipoprotein.

blood cells (WBC, p<0.0001), neutrophils (p<0.0001), monocytes (p=0.0016), glucose (p<0.0001), and triglyceride (TG, p<0.0001) were found in the CAS patients than that in healthy controls. In contrast, lower levels of lymphocytes (p<0.0001) and high-density lipoprotein (HDL, p<0.0001) were found in CAS patients than in healthy controls.

Biomarkers of in-Stent Restenosis in CAS Patients

We next determined the predictors of ISR in CAS patients. We initially analyzed the ratios of neutrophil, monocyte, platelet, glucose, TG, and LDL to lymphocyte, respectively. As shown in Figure 1, we found higher NLR (Figure 1A, p<0.0001), MLR (Figure 1B, p<0.0001), and PLR (Figure 1C, p<0.0001) in the no-ISR group and ISR-1 group than that in healthy controls. Interestingly, we found elevated PLR in the ISR-1 group as compared with that in the no-ISR group (Figure 1C, p=0.03). However, no significant difference of PLR was found between the ISR-2 group and the no-ISR group. There is no significant difference in the LLR in the four groups (Figure 1D, p=0.43). In addition, increased ratios of Glu/lymphocyte (Figure 1E, p<0.0001) and TG/lymphocyte (Figure 1F, p<0.0001) were found in the no-ISR group and ISR-1 group than that in healthy controls. These results suggest that PLR in the first detection may be the potential predictor of ISR in CAS patients.

Next, we analyzed the ratios of blood index to HDL. We found increased NHR in the no-ISR group and ISR-1 group, but not ISR-2 group, as compared with healthy control group (Figure 2A, p<0.0001). Among the four groups, elevated LHR (Figure 2B, p=0.04) and MHR (Figure 2C, p<0.0001) were only found in the no-ISR group as compared with healthy control group. In addition, PHR increased in both the no-ISR group (Figure 2D, p<0.0001) and the ISR-1 group (Figure 2D, p=0.03), but not in the ISR-2 group. The higher ratio of LDL/HDL (LHR) was only observed in the no-ISR group as compared with healthy control group (Figure 2E, p=0.01). Moreover, the ratios of Glu/HDL and TG/HDL were

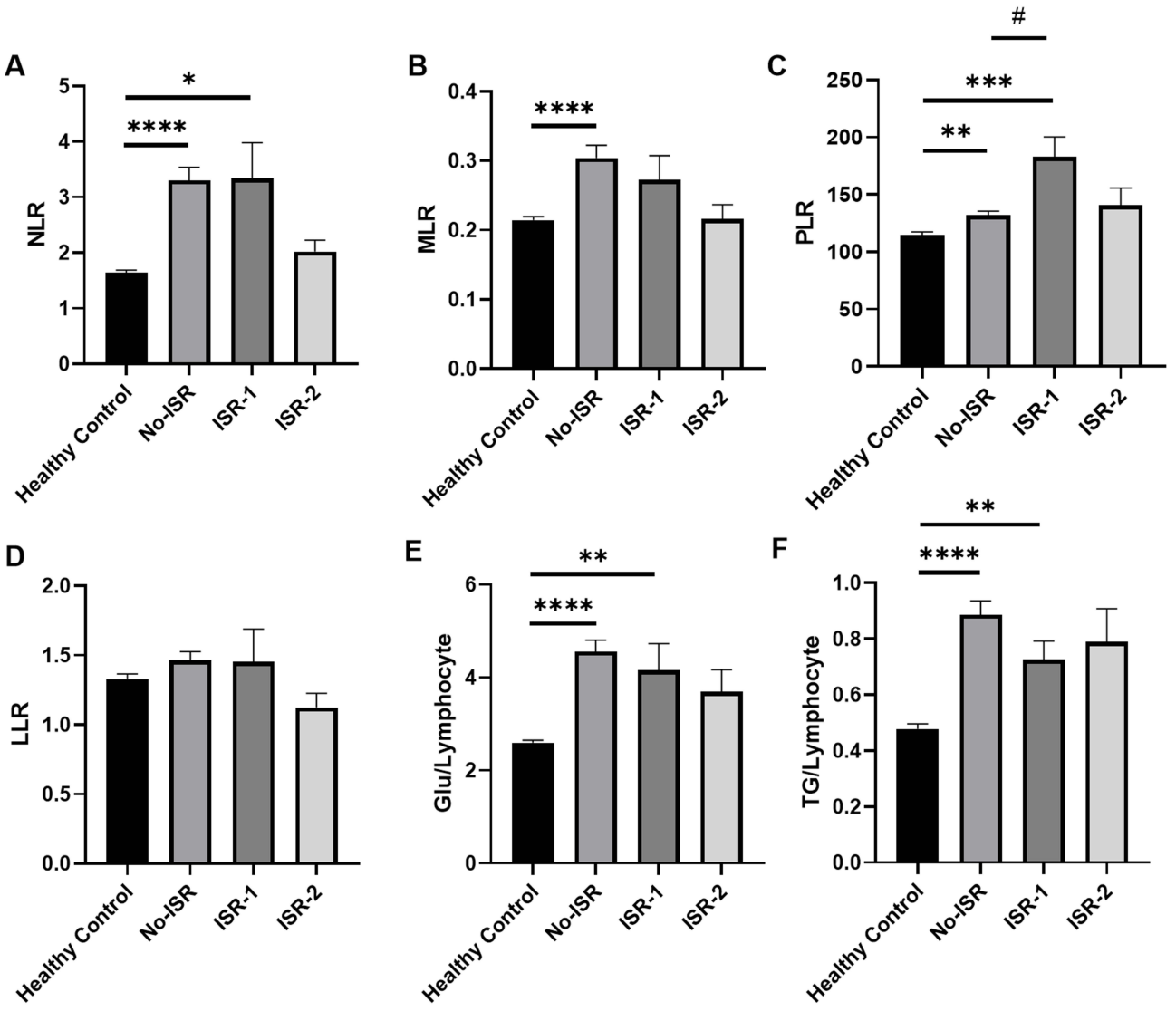

Figure 1 The NLR (**A**), MLR (**B**), PLR (**C**), LLR (**D**), Glu/lymphocyte ratio (**E**), and TG/lymphocyte ratio (**F**) in healthy control group, no-ISR group, ISR-1 group, and ISR-2 group. (*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 vs healthy control group; #p<0.05 vs no-ISR group).

also detected, and we found significantly higher ratios in the no-ISR group (Glu/HDL: Figure 2F, p<0.0001; TG/HDL: Figure 2G, p<0.0001), ISR-1 group (Glu/HDL: Figure 2F, p=0.0003; TG/HDL: Figure 2G, p=0.03), and ISR-2 group (Glu/HDL: Figure 2F, p=0.001; TG/HDL: Figure 2G, p=0.04) than that in the healthy control group. These results indicate that the increased ratios of blood index to HDL in the first onset of CAS are associated with the progression of carotid artery stenosis.

To further detect the potential roles of lipids in the progression of artery stenosis, we further detected the ratios of blood index to LDL. Although no difference was found in the serum levels of LDL among all the groups, increased ratios of neutrophil to LDL were found in both the no-ISR group (Figure 3A, p<0.0001) and ISR-1 group (Figure 3A, p<0.0001) as compared with healthy control group. No significant difference was found in the ratio of lymphocyte to LDL among the four groups (Figure 3B, p=0.40). Elevated ratio of monocyte to LDL was found in the no-ISR group (Figure 3C, p<0.0001). In addition, increased ratios of platelet to LDL in the no-ISR group were observed in both the no-ISR group (Figure 3D, p=0.01) and ISR-1 group (Figure 3D, p<0.0001). To our surprise, we found higher ratio of platelet to LDL in the ISR-1 group than that in no-ISR group (Figure 3D, p=0.01), suggesting the potential role of this ratio as a predictive biomarker of ISR in the CAS patients. Moreover, the ratios of Glu/LDL and TG/LDL were further observed.

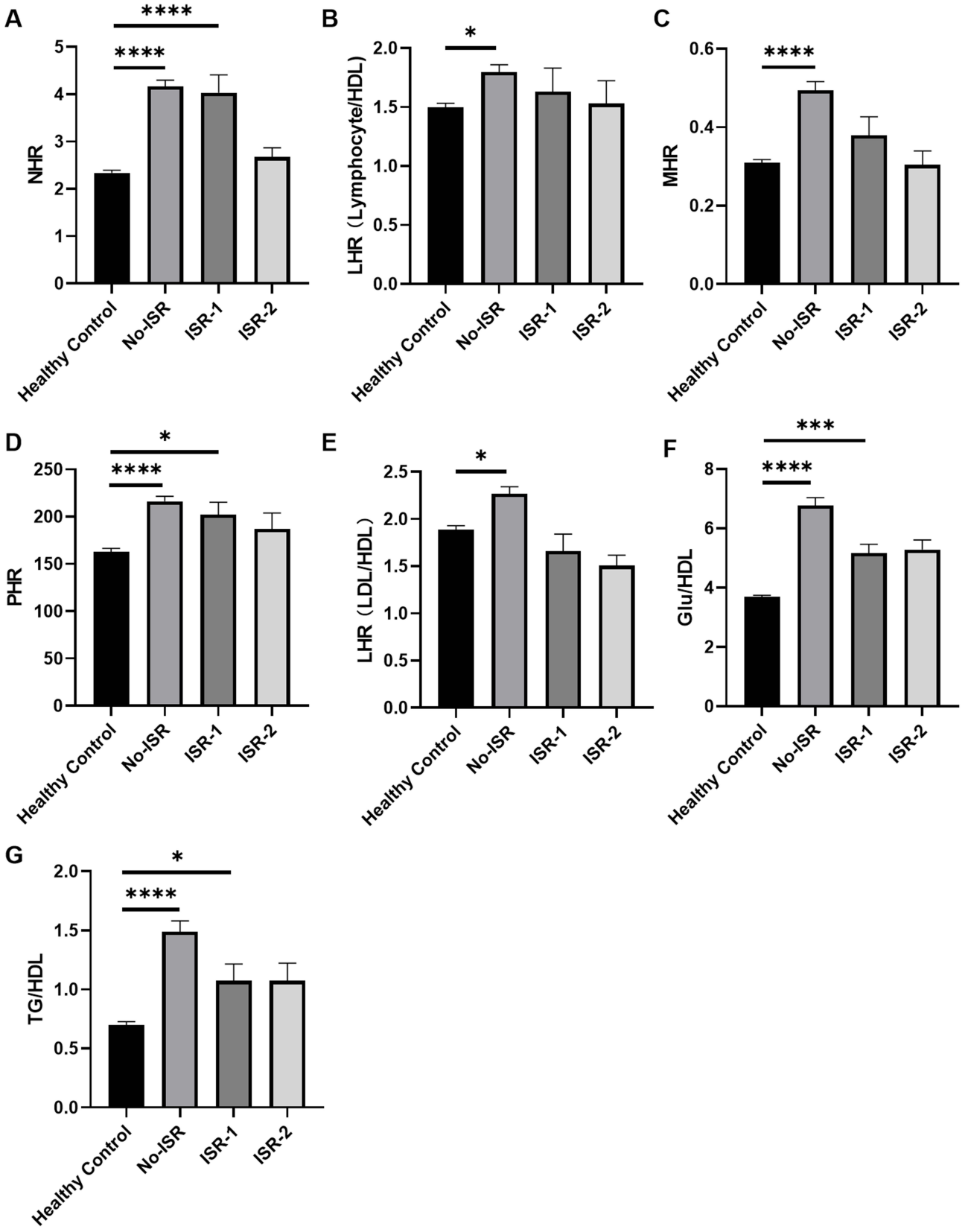

Figure 2 The NHR (**A**), LHR (lymphocyte/HDL) (**B**), MHR (**C**), PHR (**D**), LHR (LDL/HDL) (**E**), Glu/HDL ratio (**F**), and TG/HDL ratio (**G**) in healthy control group, no-ISR group, ISR-1 group, and ISR-2 group. (*p<0.05, ***p<0.001, ****p<0.0001 vs healthy control group).

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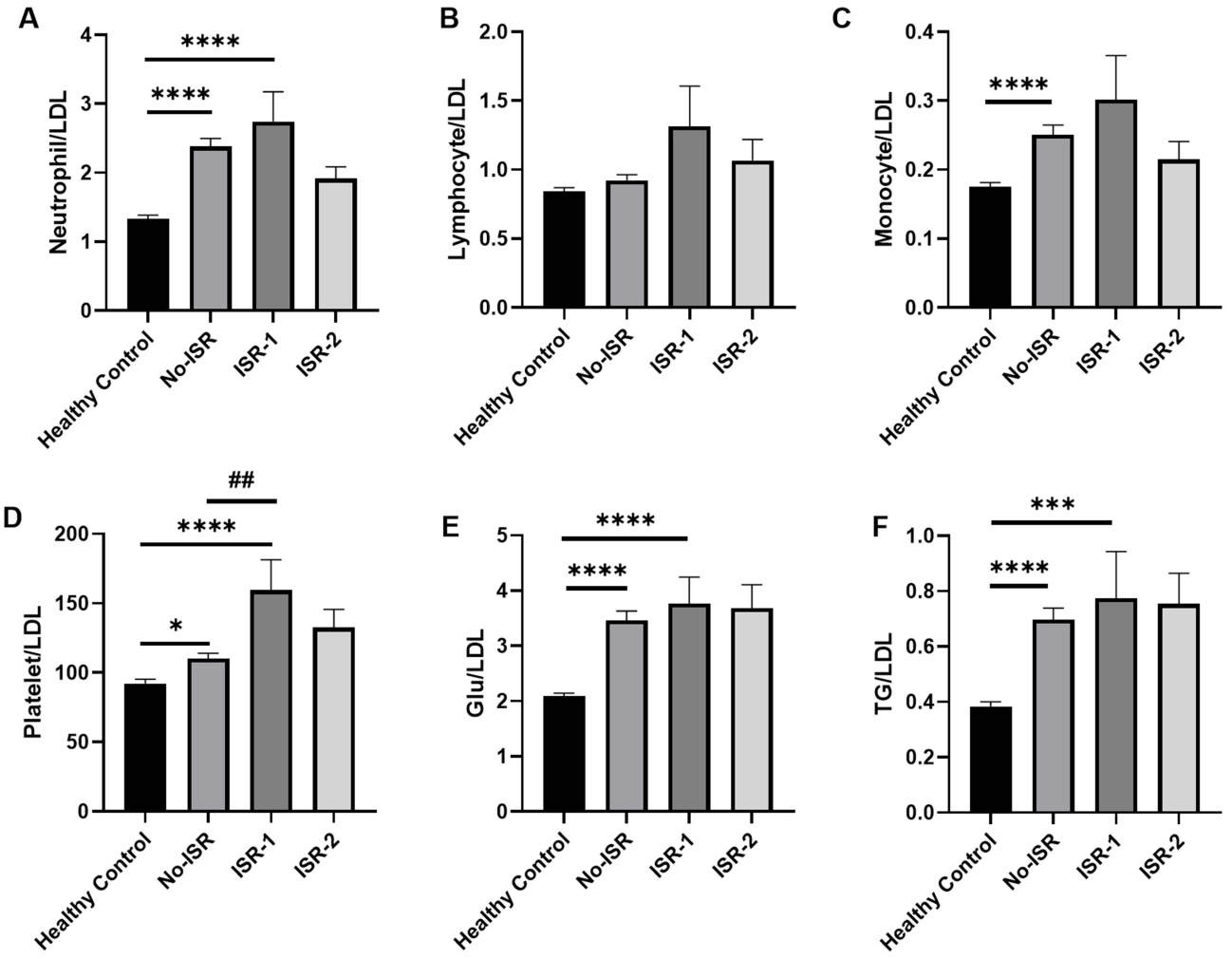

Figure 3 The ratios of neutrophil/LDL (**A**), lymphocyte/LDL (**B**), monocyte/LDL (**C**), platelet/LDL (**D**), Glu/LDL (**E**), and TG/LDL (**F**) in healthy control group, no-ISR group, ISR-1 group, and ISR-2 group. (*p<0.05, ***p<0.001, ****p<0.0001 vs healthy control group; ##p<0.05 vs no-ISR group).

Increased ratios of Glu/LDL and TG/LDL were found in both the no-ISR group (Glu/LDL: Figure 3E, p<0.0001; TG/LDL: Figure 3F, p<0.0001) and the ISR-1 group (Glu/LDL: Figure 3E, p<0.0001; TG/LDL: Figure 3F, p=0.0002) relative to those in healthy control group.

Next, we further detected the ratios of SII, SIRI, and AISI, which are new inflammatory biomarkers. As shown in Figure 4, the ratios of SII increased in the no-ISR group as compared with the healthy controls (Figure 4A, p<0.0001). In addition, elevated SII ratios were also found in the ISR-1 group (Figure 4A, p=0.02). In addition, increased ratios of SIRI (Figure 4B, p<0.0001) and AISI (Figure 4C, p<0.0001) were also observed in the no-ISR group as compared with healthy controls. No significant difference was found in these ratios in the ISR-2 group as compared with the control group.

ROC Curve Analysis of the Predictors for in-Stent Restenosis in CAS Patients

As the increased ratios of platelet to lymphocyte and LDL, we further want to evaluate the ability of the two ratios to identify ISR by using the ROC curve analysis. As shown in Figure 5, the AUC for ratio of platelet to lymphocyte (PLR) was 0.71 (95% confidence interval: 0.5896–0.8317, p=0.004), the cutoff value was 11.59, and the sensitivity and specificity was 35.29% and 96.95%, respectively. For the ratio of platelet to LDL (Figure 5), the AUC was 0.71 (95% confidence interval: 0.6154–0.8046, p=0.0032), the cutoff value was 4, and the sensitivity and specificity was 22.22% and 90.33%, respectively. Additionally, the Youden index (sensitivity + specificity - 1) for PLR (35.29% + 96.95% - 1 = 32.24%) was higher than that for the platelet-to-LDL ratio (22.22% + 90.33% - 1 = 12.55%), indicating a better overall balance between sensitivity and specificity for PLR

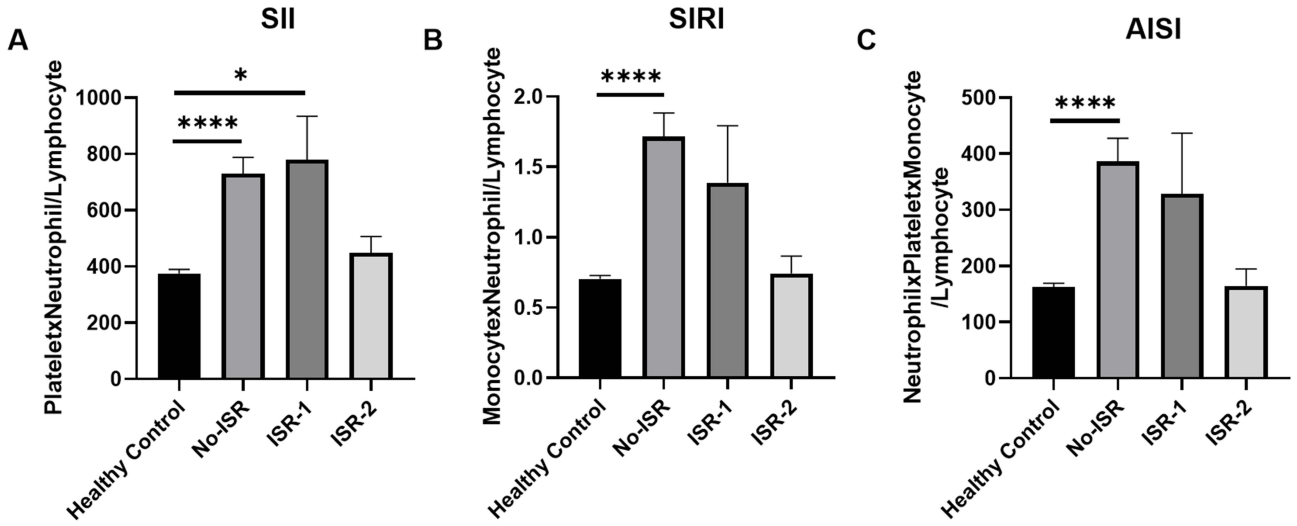

Figure 4 The SII (**A**), SIRI (**B**), and AISI (**C**) in healthy control group, no-ISR group, ISR-1 group, and ISR-2 group. (*p<0.05, ****p<0.0001 vs healthy control group).

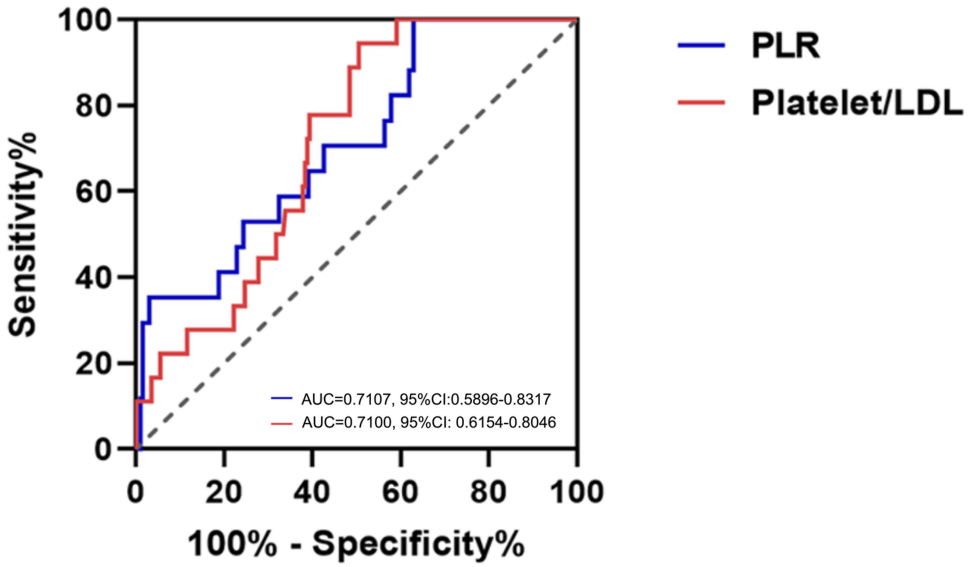

Figure 5 ROC curve analyses of PLR and platelet to LDL ratio.

when using the optimal cut-off values determined by maximizing the Youden index. Consequently, the ratio of PLR holds greater utility as a predictive biomarker for the ISR after CAS.

Discussion

In this study, we investigated the predictors of ISR in patients who underwent CAS operation. We found that multiple factors were associated with carotid artery stenosis, such as NLR, PLR, glucose/lymphocyte, TG/lymphocyte, NHR, PHR, GLU/HDL, TG/HDL, neutrophil/LDL, platelet/LDL, Glu/LDL, TG/LDL, and SII. Among all the indicators, PLR and platelet/LDL were associated with ISR in patients underwent CAS. We also found the predict roles of PLR and platelet/LDL before the first but not the second CAS operation in the ISR. ROC curve analysis further proved that PLR was more effective for predicting ISR.

The pathological mechanism of ISR development has been well investigated after coronary artery stenting, and vascular inflammation plays pivotal role.[43] Balloon inflation and stent placement during the endovascular treatment trigger the disruption and abrasion of endothelial cells, which lead to adhesion of thrombocytes, neutrophiles and monocytes.

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These cells further release vasoactive, thrombogenic, lymphocytic, and mitogen substances, which lead to ISR by vascular remodeling, thrombosis, and inflammation.[44] Many studies have focused on the biomarkers for ISR in cerebrovascular disease regarding their predictive value for progressive arterial disease, including routine blood biomarkers of inflammation and platelet aggregation. However, current predictive indicators are rarely applicable in clinical practice due to the individual differences and numerous influencing factors. Furthermore, limited studies have investigated biomarkers associated with ISR after CAS. Therefore, newly and easily accessible biomarkers for ISR after CAS need to be identified, which is highly significant.

As the indicators of systemic inflammation, NLR and PLR play crucial roles in the pathophysiology of carotid stenosis.[45] Although study has confirmed the important roles of NLR and PLR in predicting restenosis after carotid artery stenosis,[34] they did not distinguish the ISR caused by CAS from carotid endarterectomy (CEA). In our study, we found increased PLR but not NLR in the ISR-1 group as compared with non-ISR group, indicating the more important role of platelet aggregation in progression of ISR. It has been shown that there is a relationship between PLR and severity of CAS. Higher PLR are associated with increased all-cause mortality in patients with CAS.[26] Despite it has been proved that PLR is a useful test for predicting the postoperative restenosis after carotid endarterectomy,[46] few studies have focused on the predict role of PLR in CAS restenosis. Here, we found increased PLR in the initial test, but not in the second test when restenosis happened. These results suggest that PLR can specifically predict whether patients with carotid artery stenosis will experience restenosis after stenting.

Dyslipidemia is one of the important risk factors for artery stenosis. As the crucial components of lipid metabolism, the changes of HDL play essential roles in the pathophysiological process of artery stenosis.[47] HDL is associated with the incidence and functional outcome of stenosis by involving in anti-oxidation, anti-inflammation, antithrombosis, and the improvement of vascular endothelial function.[48] Therefore, many studies have focused on the predict roles of HDL-associated indicators in cerebrovascular disease. It has been confirmed that ratios of neutrophil to HDL (NHR) and monocyte to HDL (MHR) are potential ischemic stroke prognostic biomarkers.[49] In addition, TG/HDL level has been proved to be associated with post-stroke cognitive impairment.[50] Consistent with the previous research, we also found increased ratios of NHR, MHR and TG/HDL in the no-ISR group, which provided preliminary evidence for the associations between HDL-related inflammatory indices and carotid artery stenosis. However, different from previous study,[51] we did not demonstrate significant associations between LHR and MHR in the ISR group. The potential reason for the inconsistent findings is the differences of HDL-related inflammation in various models of stenosis.

As another primary pathophysiology mechanism of dyslipidemia, LDL dysfunction also plays an important role in the occurrence and progression of atherosclerosis-associated disease, such as carotid artery stenosis.[52] Oxidized LDL (oxLDL) has been identified as a key player in endothelial dysfunction by promoting inflammation and the recruitment of monocytes into the arterial wall, which are essential to the formation of atherosclerotic plaques.[53] Recent studies have highlighted the role of LDL in triggering a cascade of inflammatory responses in the arterial wall, which contributes to the formation of stenosis.[54] However, no changes of LDL have been observed in patients after CAS in our research. The observed limitations were primarily due to the modest sample size of the study population. To further explore the predict roles of LDL to carotid artery stenosis, we reanalyzed LDL by combining with the inflammation-related white blood cells and hematological parameters. Increased ratios of neutrophil, monocyte, glucose, and TG to LDL in patients with CAS, indicated the potential predict roles of them in the carotid artery stenosis.

Interestingly, we found increased ratio of platelet to LDL at the first but not the second onset of CAS in the ISR group. Together with the ascending ratio of PLR, these results further confirmed the role of platelets in CAS restenosis. Studies have demonstrated that there was a relationship between mortality and high baseline platelet counts in patients with acute coronary syndrome.[55] These high counts indicate the instability of plaque and are associated with stent thrombosis.[56] Although it has been confirmed that LDL is associated with carotid artery stenosis, there is no evidence regarding the role of LDL by combining with platelets. Previous study has indicated that LDL was the strongest predictor for most parameters of platelet reactivity.[57] Therefore, it can provide a clearer understanding of their roles in carotid artery stenosis by combining the analysis of LDL and platelets. Our study further confirmed that the ratios of platelet to LDL were more specific than the single level of serum hematologic parameters for predicting ISR. Although previous studies have reported correlations between PLT (platelet count) or LDL levels and coronary artery disease,[58,59] the major

cause of pathophysiological coronary ISR is vascular smooth muscle cell (VSMC) migration and proliferation in response to stent-induced arterial injury.[60] The distinct pathophysiology of carotid ISR (lipid-thrombosis dominance) provides a theoretical foundation for the application of the platelet-to-LDL ratio.[61,62] To our knowledge, this is the first study showing the predict role of platelet/LDL ratio to the restenosis after CAS.

Current ISR surveillance primarily relies on scheduled clinical follow-up, symptom assessment, and medical imaging, including computed tomography (CT), MRI, and digital DSA.[63] However, most of the examinations above require radiation exposure and are not feasible for patients with special circumstances, such as those with a pacemaker or emotional instability. In addition, frequent clinic visits and invasive procedures create significant burden for patients, which limits widespread or repeated application, especially in asymptomatic patients. Most importantly, these treatments take a long time and can easily delay the optimal treatment time. As the unique changes of ratios of PLR and platelet/LDL in the ISR group after CAS, our study will provide important assistance for the prediction of ISR after CAS.

While biomarkers hold promise for predicting ISR in carotid artery stenting, current research was limited by small sample sizes, short follow-up periods, population heterogeneity, and other confounding factors. This was primarily due to the low incidence of the condition and the inherent challenges of obtaining complete follow-up data in a single-center setting. Additionally, the outcomes of CAS could be influenced by aggressive medical treatment, including LDL-lowering strategies, such as statins, and anti-platelet agents.[64,65] As rightly noted, newer therapeutic approaches like rivaroxaban could also affect the prognosis of cerebrovascular disease.[66,67] However, all patients in our cohort received guideline-directed medical therapy (GDMT), and the current study specifically examined the predicted value of preprocedural parameters for ISR. These limitations may restrict the statistical power and generalizability of our findings. Moreover, the high specificity but low sensitivity of both PLR and platelet/LDL ratio in ROC analysis limits their utility as standalone rule-out tools. Clinical adoption would require integration with other diagnostic parameters to improve overall accuracy. Future studies should aim to address these limitations by conducting larger, well-designed, multicenter studies with standardized methodologies and comprehensive control of confounding variables to further clarify their prognostic and therapeutic roles. This will help to identify robust and clinically useful biomarkers for ISR after CAS.

Conclusion

In this study, we retrospectively analyzed the data in patients who underwent CAS in one cohort. We found increased ratios of NLR, PLR, Glu/lymphocyte, TG/lymphocyte, NHR, PHR, Glu/HDL, TG/HDL, neutrophil/LDL, platelet/LDL, Glu/LDL, TG/LDL, and SII in patients with carotid artery stenosis, indicating the predictive roles of these values in carotid artery stenosis. Most importantly, we found increased ratios of PLR and platelet/LDL before the first operation of CAS, but not the second operation for the restenosis after CAS, which further substantiate the association between ISR and platelet activation-induced inflammatory cascades coupled with dysregulated lipid metabolism. The negative results at the second timepoint may be attributed to the limited sample size, which could have led to insufficient statistical power to detect significant associations. In addition, their low sensitivity precludes use as independent predictive tools. Future studies should investigate whether combining these markers with clinical factors or imaging parameters can improve risk stratification.

Data Sharing Statement

Data are available upon request from the corresponding author.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Informed Consent

Informed consent was obtained from all subjects involved in the study.

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Disclosure

The authors declare no conflicts of interest in this work.

References

1. Kim BJ, Kwon JY, Jung JM, et al. Association between silent embolic cerebral infarction and continuous increase of P2Y12 reaction units after neurovascular stenting. *J Neurosurg*. 2014;121(4):891–898. doi:10.3171/2014.6.JNS132448
2. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50(12):e344–e418. doi:10.1161/STR.0000000000000211
3. Zheng L, Li J, Liu H, et al. perioperative blood pressure control in carotid artery stenosis patients with carotid angioplasty stenting: a retrospective analysis of 173 cases. *Front Neurol*. 2020;11:567623. doi:10.3389/fneur.2020.567623
4. Markus HS, Harshfield EL, Compter A, et al. Stenting for symptomatic vertebral artery stenosis: a preplanned pooled individual patient data analysis. *Lancet Neurol*. 2019;18(7):666–673. doi:10.1016/S1474-4422(19)30149-8
5. Drazyk AM, Markus HS. Recent advances in the management of symptomatic vertebral artery stenosis. *Curr Opin Neurol*. 2018;31(1):1–7. doi:10.1097/WCO.0000000000000515
6. Jin M, Fu X, Wei Y, Du B, Xu XT, Jiang WJ. Higher risk of recurrent ischemic events in patients with intracranial in-stent restenosis. *Stroke*. 2013;44(11):2990–2994. doi:10.1161/STROKEAHA.113.001824
7. Bonati LH, Gregson J, Dobson J, et al. Restenosis and risk of stroke after stenting or endarterectomy for symptomatic carotid stenosis in the International Carotid Stenting Study (ICSS): secondary analysis of a randomised trial. *Lancet Neurol*. 2018;17(7):587–596. doi:10.1016/S1474-4422(18)30195-9
8. Szegedi I, Potvorszki F, Meszaros ZR, Daniel C, Csiba L, Olah L. Role of carotid duplex in the assessment of carotid artery restenosis after endarterectomy or stenting. *Front Neurol*. 2023;14:1226220. doi:10.3389/fneur.2023.1226220
9. Derdeyn CP, Fiorella D, Lynn MJ, et al. Nonprocedural symptomatic infarction and in-stent restenosis after intracranial angioplasty and stenting in the SAMMPRis trial (stenting and aggressive medical management for the prevention of recurrent stroke in intracranial stenosis). *Stroke*. 2017;48(6):1501–1506. doi:10.1161/STROKEAHA.116.014537
10. AbuRahma AF, AbuRahma ZT, Scott G, et al. The incidence of carotid in-stent stenosis is underestimated >/=50% or >/=80% and its clinical implications. *J Vasc Surg*. 2019;69(6):1807–1814. doi:10.1016/j.jvs.2018.08.185
11. Chen JH, Wu MH, Luo CB, et al. Long-term imaging follow-up to evaluate restenosis in patients with carotid stenosis after angioplasty and stenting. *J Chin Med Assoc*. 2021;84(1):87–94. doi:10.1097/JCMA.0000000000000405
12. Mihaly Z, Vertes M, Entz L, Dosa E. Treatment and predictors of recurrent internal carotid artery in-stent restenosis. *Vasc Endovascular Surg*. 2021;55(4):374–381. doi:10.1177/1538574421993716
13. Grebe A, Hoss F, Latz E. NLRP3 Inflammasome and the IL-1 Pathway in Atherosclerosis. *Circ Res*. 2018;122(12):1722–1740. doi:10.1161/CIRCRESAHA.118.311362
14. Zhou F, Hua Y, Ji X, Jia L. A systemic review into carotid plaque features as predictors of restenosis after carotid endarterectomy. *J Vasc Surg*. 2021;73(6):2179–2188e2174. doi:10.1016/j.jvs.2020.10.084
15. Chang H, Rockman CB, Veith FJ, et al. Outcomes of transfemoral carotid artery stenting and transcarotid artery revascularization for restenosis after prior ipsilateral carotid endarterectomy. *J Vasc Surg*. 2022;75(2):561–571e563. doi:10.1016/j.jvs.2021.07.245
16. Nardi P, Altieri C, Pisano C, et al. Early-staged carotid artery stenting prior to coronary artery bypass grafting: analysis of the early and mid-term results in comparison with a consecutive cohort of isolated coronary artery surgery patients. *J Clin Med*. 2024;13(2):480. doi:10.3390/jcm13020480
17. Otsuka F, Byrne RA, Yahagi K, et al. Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment. *Eur Heart J*. 2015;36(32):2147–2159. doi:10.1093/eurheartj/ehv205
18. Maguire EM, Xiao Q, Xu Q. Differentiation and application of induced pluripotent stem cell-derived vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol*. 2017;37(11):2026–2037. doi:10.1161/ATVBAHA.117.309196
19. Kumar A, Lindner V. Remodeling with neointima formation in the mouse carotid artery after cessation of blood flow. *Arterioscler Thromb Vasc Biol*. 1997;17(10):2238–2244. doi:10.1161/01.ATV.17.10.2238
20. Singh AD, Singal AK, Mian A, et al. Recurrent drug-eluting stent in-stent restenosis: a state-of-the-art review of pathophysiology, diagnosis, and management. *Cardiovasc Revasc Med*. 2020;21(9):1157–1163. doi:10.1016/j.carrev.2020.01.005
21. Megaly M, Alani F, Cheng CI, Ragina N. Risk factors for the development of carotid artery in-stent restenosis: multivariable analysis. *Cardiovasc Revasc Med*. 2021;24:65–69. doi:10.1016/j.carrev.2020.09.005
22. Loch A, Bewersdorf JP, Veeriah RS. Early and aggressive ISR with a polymer- and carrier-free drug-coated stent system. *Indian Heart J*. 2017;69(5):651–654. doi:10.1016/j.ihj.2017.03.002
23. Lee SP, Shin DH, Park KW, et al. Angiographic patterns of restenosis after percutaneous intervention of chronic total occlusive lesions with drug-eluting stents. *Int J Cardiol*. 2012;156(2):180–185. doi:10.1016/j.ijcard.2010.10.138

24. Pelliccia F, Zimarino M, Niccoli G, et al. In-stent restenosis after percutaneous coronary intervention: emerging knowledge on biological pathways. *Eur Heart J Open*. 2023;3(5):oead083. doi:10.1093/ehjopen/oead083
25. Malekmohammad K, Bezsonov EE, Rafieian-Kopaei M. Role of lipid accumulation and inflammation in atherosclerosis: focus on molecular and cellular mechanisms. *Front Cardiovasc Med*. 2021;8:707529. doi:10.3389/fcvm.2021.707529
26. Tek M, Cetin MS, Diker E, Celebi S, Amasyali B, Berkalp B. Platelet to lymphocyte ratio predicts all-cause mortality in patients with carotid arterial disease. *Rom J Intern Med*. 2019;57(2):159–165. doi:10.2478/rjim-2018-0040
27. Stojkovic Lalosevic M, Pavlovic Markovic A, Stankovic S, et al. Combined diagnostic efficacy of Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Mean Platelet Volume (MPV) as biomarkers of systemic inflammation in the diagnosis of colorectal cancer. *Dis Markers*. 2019;2019:6036979. doi:10.1155/2019/6036979
28. Serra R, Ielapi N, Barbetta A, Andreucci M, de Franciscis S. Novel biomarkers for cardiovascular risk. *Biomarker Med*. 2018;12(9):1015–1024. doi:10.2217/bmm-2018-0056
29. Warimwe GM, Murungi LM, Kamuyu G, et al. The ratio of monocytes to lymphocytes in peripheral blood correlates with increased susceptibility to clinical malaria in Kenyan children. *PLoS One*. 2013;8(2):e57320. doi:10.1371/journal.pone.0057320
30. Clare J, Ganly J, Bursill CA, Sumer H, Kingshott P, de Haan JB. The mechanisms of restenosis and relevance to next generation stent design. *Biomolecules*. 2022;12(3):430. doi:10.3390/biom12030430
31. Niccoli G, Montone RA, Ferrante G, Crea F. The evolving role of inflammatory biomarkers in risk assessment after stent implantation. *J Am Coll Cardiol*. 2010;56(22):1783–1793. doi:10.1016/j.jacc.2010.06.045
32. Bao X, Zhou G, Xu W, Liu X, Ye Z, Jiang F. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio: novel markers for the diagnosis and prognosis in patients with restenosis following CAS. *Biomarker Med*. 2020;14(4):271–282. doi:10.2217/bmm-2019-0155
33. Keskin M, Ocal L, Cersit S, et al. The predictive role of a novel risk index in patients undergoing carotid artery stenting: systemic immune-inflammation index. *J Stroke Cerebrovasc Dis*. 2021;30(9):105955. doi:10.1016/j.jstrokecerebrovasdis.2021.105955
34. Scalise E, Costa D, Bolboaca SD, et al. The role of inflammation biomarkers in carotid artery stenosis procedures. *Ann Vasc Surg*. 2025;110(Pt A):34–46. doi:10.1016/j.avsg.2024.08.009
35. Song Y, Zhao Y, Shu Y, et al. Combination model of neutrophil to high-density lipoprotein ratio and system inflammation response index is more valuable for predicting peripheral arterial disease in type 2 diabetic patients: a cross-sectional study. *Front Endocrinol*. 2023;14:1100453. doi:10.3389/fendo.2023.1100453
36. Ryu JC, Bae JH, Ha SH, et al. Association between lipid profile changes and risk of in-stent restenosis in ischemic stroke patients with intracranial stenosis: a retrospective cohort study. *PLoS One*. 2023;18(5):e0284749. doi:10.1371/journal.pone.0284749
37. Catapano AL, Pirillo A, Bonacina F, Norata GD. HDL in innate and adaptive immunity. *Cardiovasc Res*. 2014;103(3):372–383. doi:10.1093/cvr/cvu150
38. Li L, Chen Y, Shi C. Nintedanib ameliorates oxidized low-density lipoprotein -induced inflammation and cellular senescence in vascular endothelial cells. *Bioengineered*. 2022;13(3):6196–6207. doi:10.1080/21655979.2022.2036913
39. Huang JB, Chen YS, Ji HY, et al. Neutrophil to high-density lipoprotein ratio has a superior prognostic value in elderly patients with acute myocardial infarction: a comparison study. *Lipids Health Dis*. 2020;19(1):59. doi:10.1186/s12944-020-01238-2
40. Kou T, Luo H, Yin L. Relationship between neutrophils to HDL-C ratio and severity of coronary stenosis. *BMC Cardiovasc Disord*. 2021;21(1):127. doi:10.1186/s12872-020-01771-z
41. Grant EG, Benson CB, Moneta GL, et al. Carotid artery stenosis: grayscale and Doppler ultrasound diagnosis--Society of Radiologists in Ultrasound consensus conference. *Ultrasound Q*. 2003;19(4):190–198. doi:10.1097/00013644-200312000-00005
42. North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. *Stroke*. 1991;22(6):711–720. doi:10.1161/01.STR.22.6.711
43. Buffon A, Liuzzo G, Biasucci LM, et al. Preprocedural serum levels of C-reactive protein predict early complications and late restenosis after coronary angioplasty. *J Am Coll Cardiol*. 1999;34(5):1512–1521. doi:10.1016/S0735-1097(99)00348-4
44. Weintraub WS. The pathophysiology and burden of restenosis. *Am J Cardiol*. 2007;100(5A):3K–9K. doi:10.1016/j.amjcard.2007.06.002
45. Serrano CV Jr, de Mattos FR, Pitta FG, et al. Association between neutrophil-lymphocyte and platelet-lymphocyte ratios and coronary artery calcification score among asymptomatic patients: data from a cross-sectional study. *Mediators Inflamm*. 2019;2019:6513847. doi:10.1155/2019/6513847
46. Goncalves VA, Geiger MA, Sarti DA, Guillaumon AT. Association between platelet lymphocyte ratio and neutrophil lymphocyte ratio and clinical outcomes following carotid endarterectomy. *J Vasc Bras*. 2023;22:e20220122. doi:10.1590/1677-5449.202201222
47. Senat A, Ilker Yon M, Yuce G, Deniz O, Erel O. High-density lipoprotein dysfunction in carotid artery stenosis. *Vasa*. 2023;52(5):342–348. doi:10.1024/0301-1526/a001082
48. Alkahtani R. Molecular mechanisms underlying some major common risk factors of stroke. *Heliyon*. 2022;8(8):e10218. doi:10.1016/j.heliyon.2022.e10218
49. Gkantzios A, Tsiptsios D, Karapepera V, et al. Monocyte to HDL and neutrophil to hdl ratios as potential ischemic stroke prognostic biomarkers. *Neurol Int*. 2023;15(1):301–317. doi:10.3390/neurolint15010019
50. Cheng Y, Zhu H, Chen J, et al. Serum TG/HDL-C level at the acute phase of ischemic stroke is associated with post-stroke cognitive impairment. *Neurol Sci*. 2022;43(10):5977–5984. doi:10.1007/s10072-022-06267-6
51. Guo X, Shen R, Lu P, Ma L. Predictive values of novel high-density lipoprotein-related inflammatory indices in in-stent restenosis among patients undergoing elective percutaneous coronary intervention. *Exp Ther Med*. 2024;27(2):62. doi:10.3892/etm.2023.12350
52. Liu Z, Deng C, Zhao R, et al. Association of LDL-C level with neoatherosclerosis and plaque vulnerability in patients with late restenosis: an optical coherence tomography study. *Int J Cardiovasc Imaging*. 2023;39(12):2609–2619. doi:10.1007/s10554-023-02956-1
53. Liang X, Li P, Xie W, et al. febuxostat protects human aortic valve endothelial cells from oxidized low-density lipoprotein-induced injury and monocyte attachment. *J Cardiovasc Pharmacol*. 2022;80(6):861–868. doi:10.1097/FJC.0000000000001326
54. Waksman R, Merdler I, Case BC, Waksman O, Porto I. Targeting inflammation in atherosclerosis: overview, strategy and directions. *EuroIntervention*. 2024;20(1):32–44. doi:10.4244/EIJ-D-23-00606
55. Azab B, Shah N, Akerman M, McGinn JT Jr. Value of platelet/lymphocyte ratio as a predictor of all-cause mortality after non-ST-elevation myocardial infarction. *J Thromb Thrombolysis*. 2012;34(3):326–334. doi:10.1007/s11239-012-0718-6

56. Dangas GD, Caixeta A, Mehran R, et al. Frequency and predictors of stent thrombosis after percutaneous coronary intervention in acute myocardial infarction. *Circulation*. 2011;123(16):1745–1756. doi:10.1161/CIRCULATIONAHA.110.981688
57. Barale C, Frascaroli C, Senkeev R, Cavalot F, Russo I. Simvastatin effects on inflammation and platelet activation markers in hypercholesterolemia. *Biomed Res Int*. 2018;6508709. doi:10.1155/2018/6508709
58. Wei K, Yu L, Li J, et al. Platelet-derived exosomes regulate endothelial cell inflammation and M1 macrophage polarization in coronary artery thrombosis via modulating miR-34a-5p expression. *Sci Rep*. 2024;14(1):17429. doi:10.1038/s41598-024-67654-x
59. Mohammed HSE, Kamal MM, ElBadre HM, et al. Lectin-Like OLR1 3'UTR rs1050286 gene polymorphism and plasma Oxidized-LDL in coronary artery disease and their relation to cardiovascular risk and outcomes. *Rep Biochem Mol Biol*. 2022;10(4):537–553. doi:10.52547/rbmb.10.4.537
60. Lyon CA, Wadey KS, George SJ. Soluble N-cadherin: a novel inhibitor of VSMC proliferation and intimal thickening. *Vascul Pharmacol*. 2016;78:53–62. doi:10.1016/j.vph.2015.11.040
61. Wei S, Wang H, Zhang G, et al. Platelet IkappaB kinase-beta deficiency increases mouse arterial neointima formation via delayed glycoprotein Ibalpha shedding. *Arterioscler Thromb Vasc Biol*. 2013;33(2):241–248. doi:10.1161/ATVBAHA.112.300781
62. Hao F, Zhang F, Wu DD, et al. Lysophosphatidic acid-induced vascular neointimal formation in mouse carotid arteries is mediated by the matricellular protein CCN1/Cyr61. *Am J Physiol Cell Physiol*. 2016;311(6):C975–C984. doi:10.1152/ajpcell.00227.2016
63. Shen J, Li X, Li Y, Wu B. Comparative accuracy of CT perfusion in diagnosing acute ischemic stroke: a systematic review of 27 trials. *PLoS One*. 2017;12(5):e0176622. doi:10.1371/journal.pone.0176622
64. Whayne TF Jr. Assessment of carotid artery stenosis and the use of statins. *Int J Angiol*. 2015;24(3):173–178. doi:10.1055/s-0035-1554910
65. Derdeyn CP, Chimowitz MI, Lynn MJ, et al. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. *Lancet*. 2014;383(9914):333–341. doi:10.1016/S0140-6736(13)62038-3
66. Troisi N, Bertagna G, Berchiolli R, Group RCS. RIvaroxaban and VAscular Surgery (RIVAS): insights from a multicenter, worldwide web-based survey. *Int Angiol*. 2024;43(2):306–308. doi:10.23736/S0392-9590.24.05146-0
67. Toni D, Carolei A, Caso V, et al. Use of rivaroxaban in patients with stroke. *Neurol Sci*. 2017;38(5):745–754. doi:10.1007/s10072-017-2855-3