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Original Article

Association of systemic inflammatory index and HbA1c with in-stent restenosis in arteriosclerosis obliterans patients after stenting: a propensity score-matched analysis

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Abstract: Objective: To analyze the association between systemic immune-inflammation index (SII), glycated hemoglobin (HbA1c) levels and the risk of in-stent restenosis (ISR) in patients with arteriosclerosis obliterans (ASO) after stent implantation. Methods: A retrospective study was conducted on ASO patients (n=129) who underwent stent implantation at the Affiliated Hospital of Guilin Medical University between January 2021 and December 2023. Patients were categorized into ISR (n=71) and non-ISR (n=86) groups based on ISR status at 1-year follow-up. Propensity score matching (PSM, 1:1) was used to balance baseline characteristics. Logistic regression and restricted cubic spline (RCS) models were used to evaluate the SII-ISR relationship. An external validation cohort comprising 72 ASO patients from the same center, recruited between January 2024 and December 2024, was used to verify the generalizability of the established predictive model. Results: After PSM, the ISR group exhibited significantly higher HbA1c and SII levels compared to the non-ISR group ($P < 0.05$). Multivariate logistic regression showed that elevated HbA1c and SII were independently associated with increased ISR risk ($P < 0.05$). RCS models revealed linear dose-response relationships between SII ($P_{total\ trend}$=0.037, $P_{nonlinear}$=0.427), HbA1c ($P_{total\ trend}$=0.023, $P_{nonlinear}$=0.099), and ISR risk. The combination of SII and HbA1c enhanced model predictive performance (AUC=0.705, 95% CI: 0.599-0.811) with good calibration. External validation confirmed the model's predictive ability, with an AUC of 0.718 (95% CI: 0.594-0.841). Conclusion: Both HbA1c and SII are correlated with ISR risk in ASO patients, and the risk increases with higher levels of these markers. A predictive model integrating SII and HbA1c had good performance and generalizability, facilitating early identification of high-risk ISR patients.

Keywords: Arteriosclerosis obliterans, in-stent restenosis, system inflammation index, propensity score matching, correlation

Introduction

Arteriosclerosis obliterans (ASO) is characterized by lower extremity symptoms such as paresthesia (pain, cold, numbness, rest pain), intermittent claudication, and skin lesions (ulcers, gangrene) caused by arterial stenosis or occlusion due to arterial intimal thickening or atherosclerosis. ASO affects primarily middle-aged and elderly people, with a prevalence of up to 20% in people over 60 years old [1, 2]. If not treated in a timely and effective manner, it may lead to adverse consequences such as amputation, significantly compromising the prognosis [3]. At present, stent implantation is a widely used treatment of ASO, with advantages of minimally invasive operation, low procedural risk, and high safety. However, in-stent restenosis (ISR) remains a common postoperative complication, with an incidence ranging from 30% to 50% [4]. ISR not only increases patient morbidity and economic burden but also may lead to treatment failure, highlighting the significance of investigating its mechanism and risk factors.

The pathophysiology of ISR is complex, mainly involving vascular endothelial injury, local

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inflammatory responses, atherosclerotic plaque formation, and long-term maladaptive vascular remodeling [5, 6]. Accumulating evidence indicates that inflammatory response plays an important role in ISR development [7]. Among various inflammatory markers, the systemic immune-inflammation index (SII), calculated as platelet count × neutrophil count/lymphocyte count, comprehensively reflects both thrombotic and inflammatory status [8]. Compared to traditional inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), SII integrates three peripheral blood cell types and is considered a more stable and comprehensive indicator of systemic inflammation. Previous studies have also shown that regular monitoring of serum inflammatory markers may help predict ISR occurrence after coronary stent implantation in a timely manner [9], and SII has been shown to closely related to ISR in ASO patients [10]. However, prior research failed to control for confounding factors, resulting in baseline imbalances and deviation from predicting outcomes. Propensity score matching (PSM) is a method to adjust confounding factors by matching patients with similar propensity scores (PS), thereby offsetting the interference of uneven distribution on study outcomes [11].

In this study, we employed PSM to investigate the association between SII and ISR in ASO patients undergoing stent implantation. Additionally, we constructed a nomogram combining SII and HbA1c, evaluated dose-response relationships using restricted cubic spline (RCS) analysis, and validated the model's generalizability in an independent external cohort. Clinically, a validated predictive model based on routine blood markers (SII and HbA1c) may facilitate early identification of high-risk ISR patients and guide more intensive postoperative management.

Materials and methods

Information of participants

A total of 185 patients with ASO who underwent stent implantation at the Affiliated Hospital of Guilin Medical University between January 2021 and December 2023 were initially screened. After excluding 28 patients who met the exclusion criteria, 157 patients were retrospectively included in the study. Based on the presence of ISR at 1-year follow-up, patients were divided into a non-ISR group (n=86) and an ISR group (n=71).

Inclusion criteria: (1) Diagnosis of ASO according to established diagnostic criteria [12], confirmed by CT angiography (CTA), and eligible for stent implantation; first-time stent implantation; (2) In-stent stenosis ≥ 70% on imaging examination; (3) Stent implantation completed by the same team using stents from the same manufacturer; (4) Complete clinical and laboratory data.

Exclusion criteria: (1) Intolerance to stent implantation; (2) Non-adherence to medications; (3) History of lower limb surgery; (4) Congenital diseases, autoimmune diseases, metabolic defects, or coagulation abnormalities; (5) Significant organ dysfunction; (6) Local or systemic infection.

To adjust for baseline confounders, 1:1 nearest neighbor PSM was performed using age, sex, BMI, coronary heart disease, diabetes, hypertension, hyperlipidemia, history of chronic renal insufficiency, smoking, alcohol consumption, number of diseased vessels, lesion length, and complete occlusion as covariates. The caliper value was set at 0.02, resulting in 48 matched pairs in the non-ISR group (n=48) and the ISR group (n=48). The patient screening flowchart is shown in **Figure 1**. In addition, an external validation cohort was established, comprising 72 ASO patients who underwent stent implantation at the same center between January 2024 and December 2024. The inclusion and exclusion criteria were identical to those of the ISR and non-ISR groups.

Treatment decisions, including the choice of stent implantation, were made by a multidisciplinary team comprising vascular surgeons and interventional radiologists, based on clinical guidelines and each patient characteristics (e.g., lesion length, degree of stenosis, and overall health status). Before the procedure, all patients or their legal guardians were fully informed of the benefits and risks of each treatment option, including conservative treatment, bypass surgery, and endovascular therapy.

This study was approved by the Ethics Committee of the Affiliated Hospital of Guilin Medical University (Ethics Review No: 2023ZQ-

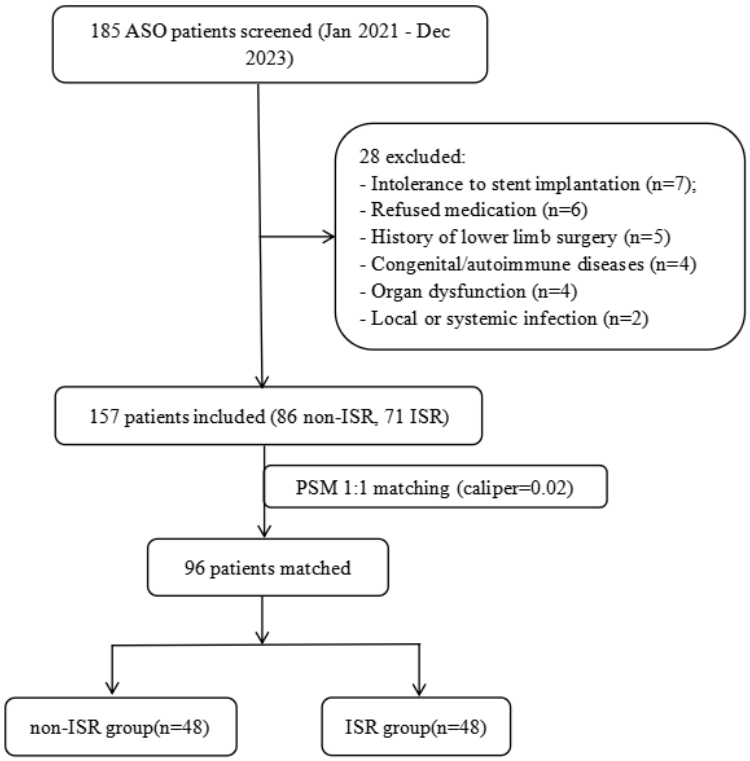

Figure 1. Patient screening flowchart.

NJSLL-01). Given the retrospective and de-identified nature of this study, the requirement for written informed consent was waived by the ethics committee.

Data extraction

Clinical data were extracted from electronic medical records, including age, sex, body mass index (BMI), medical history (coronary heart disease, diabetes mellitus, hypertension, hyperlipidemia, chronic renal insufficiency), smoking status, alcohol consumption, number of affected vascular branches, lesion length, and presence of complete occlusion. Laboratory indicators included white blood cell count (WBC), neutrophil count, platelet count, lymphocyte count, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total bilirubin, albumin, serum creatinine, uric acid, glomerular filtration rate (GFR), fasting blood glucose (FBG), and glycated hemoglobin A1c (HbA1c). Additionally, derived inflammatory indices were calculated: NLR, PLR, SII, and neutrophil-to-HDL cholesterol ratio (NHR). All laboratory tests were measured within 24 hours before stent implantation. All data were independently extracted by two researchers and cross-validated to ensure accuracy. Any discrepancies were resolved by discussion or consultation with a third researcher.

Outcome measures

The primary outcome was ISR within 1 year after stent implantation. Patients were followed for up to 1 year after operation, with follow-up time ending in December 2024. The end point of the study was the end of the follow-up time or the occurrence of ISR. Outpatient follow-up was scheduled every 3-6 months, including lower limb Color Doppler ultrasonography. Patients with suspected ischemia underwent CT angiography of the lower limbs. ISR was defined as ≥ 50% luminal stenosis within 5 mm proximal or distal to the stent or within the stent itself. Patients developing ISR during follow-up period were included in the ISR group, and those without ISR were included in the non-ISR group.

Secondary outcomes included the association between HbA1c and ISR, and predictive performance of the nomogram incorporating SII and HbA1c, and its external validation.

Statistical analysis

Statistical analyses were performed using SPSS 29.0. Propensity score matching was performed on the baseline data of patients according to a 1:1 ratio, and the caliper value was set to 0.02.

Categorical variables were expressed as n (%), and compared using the χ^2 test. Continuous variables conforming to normal distribution and homogeneous variance were expressed as mean ± standard deviation (SD), and compared using the independent-samples t-test. Non-normally distributed data were expressed as median and interquartile range [M (P_{25}, P_{75})], and compared using the rank sum test.

Table 1. Comparison of baseline clinical data between non-ISR group and ISR group before PSM

Item	non-ISR group (n=86)	ISR group (n=71)	$t/Z/\chi^2$	*P*
Age (years)	69.20±11.77	68.62±9.35	0.335	0.738
Sex [male/female, n (%)]	69/17	65/6	3.984	0.046
BMI (kg/m^2)	22.32±3.01	23.20±3.34	1.740	0.084
Coronary heart disease [n (%)]	13 (15.17)	13 (17.31)	0.278	0.592
Diabetes [n (%)]	23 (26.74)	27 (38.03)	2.282	0.131
Hypertension [n (%)]	58 (67.44)	51 (71.83)	0.353	0.552
Hyperlipidemia [n (%)]	13 (15.12)	17 (23.94)	0.257	0.109
History of chronic renal insufficiency [n (%)]	13 (15.12)	12 (16.90)	0.093	0.761
Smoking [n (%)]	43 (50.00)	43 (60.56)	1.752	0.186
Drinking [n (%)]	27 (31.40)	31 (43.66)	2.512	0.113
Number of diseased vessels (branches)	1 (1, 1)	1 (1, 2)	1.911	0.056
Lesion length (cm)	16 (8, 24)	22 (13, 32)	2.787	0.005
Total occlusion [n (%)]	68 (79.07)	62 (87.32)	1.861	0.173
White blood cell count (×10^9/L)	8.17±2.71	7.58±2.10	1.481	1.141
Neutrophil count (×10^9/L)	4.77±1.34	5.04±1.57	1.164	0.246
Platelet count (×10^9/L)	268.80±61.34	282.41±69.79	1.297	0.197
Lymphocyte count (×10^9/L)	1.93±0.72	1.79±0.56	1.414	0.159
TC (mmol/L)	4.21±1.27	4.28±1.17	0.332	0.740
TG (mmol/L)	1.70±1.37	1.68±1.18	0.079	0.937
HDL-C (mmol/L)	1.05±0.32	1.02±0.25	0.739	0.461
LDL-C (mmol/L)	2.90±1.02	3.02±0.98	0.734	0.464
Total bilirubin (μmol/L)	8.04±3.86	9.03±4.52	1.478	0.142
Albumin (g/L)	37.75±5.04	37.40±5.84	0.402	0.688
Serum creatinine (μmol/L)	83.48 (67.50, 112.50)	78.44 (66.00, 96.00)	0.933	0.351
Blood uric acid (μmol/L)	379.51±89.49	365.32±100.87	0.934	0.352
Glomerular filtration rate (mL/min)	50.85±20.57	53.77±23.82	0.806	0.422
FBG (mmol/L)	6.41±2.62	6.39±2.24	0.066	0.947
HbA1c (%)	5.77±1.05	6.46±1.02	4.158	< 0.001
NLR	2.27 (1.86, 3.60)	2.71 (2.08, 3.53)	1702	0.089
PLR	134.16 (110.75, 191.43)	157.31 (126.26, 203.65)	1.908	0.056
SII	620.12 (487.20, 844.37)	800.32 (604.16, 1024.40)	2.523	0.012
NHR	4.58 (3.55, 5.88)	4.63 (3.66, 6.35)	0.781	0.435

Note: TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; FBG: Fasting blood glucose; HbA1c: Glycated hemoglobin; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; NHR: Neutrophil to high-density lipoprotein cholesterol ratio.

Univariate logistic regression analysis was first performed to identify factors associated with ISR. Variables with $P < 0.05$ in the univariate analysis were entered into a multivariate logistic regression model to identify independent risk factors for ISR in ASO patients. A nomogram predictive model was constructed based on the selected independent risk factors. The predictive performance of the model was evaluated using receiver operating characteristic (ROC) curve analysis and calibration curves. External verification was performed using an independent cohort from the same center during a different time period. ROC and calibration curve analyses were repeated to verify the generalizability of the model. The associations of SII and HbA1c with ISR were analyzed using logistic regression models. Restricted cubic spline (RCS) analysis was further conducted to assess the dose-response relationships between SII, HbA1c, and ISR risk. A two-sided $P < 0.05$ was considered significant.

Results

Comparison of clinical data between non-ISR group and ISR group before and after PSM

Before PSM, patients in the ISR group exhibited significantly longer vascular lesion length and higher HbA1c and SII levels compared to

Table 2. Comparison of baseline clinical data between non-ISR group and ISR group after PSM

Item	non-ISR group (n=48)	ISR group (n=48)	$t/Z/\chi^2$	*P*
Age (years)	69.20±11.77	68.62±9.35	0.335	0.738
Gender [male/female, n (%)]	43/5	42/6	0.103	0.749
BMI (kg/m^2)	22.32±3.01	23.20±3.34	1.740	0.084
Coronary heart disease [n (%)]	7 (14.58)	7 (14.58)	0.000	> 0.999
Diabetes [n (%)]	16 (33.33)	18 (37.50)	0.182	0.670
Hypertension [n (%)]	33 (68.75)	36 (75.00)	0.464	0.496
Hyperlipidemia [n (%)]	9 (18.75)	10 (20.83)	0.066	0.798
History of chronic renal insufficiency [n (%)]	7 (14.58)	7 (14.58)	0.000	> 0.999
Smoking [n (%)]	29 (60.42)	25 (52.08)	0.677	0.411
Drinking [n (%)]	22	18	0.686	0.408
Number of diseased vessels (branches)	1 (1, 1)	1 (1, 1)	0.681	0.496
Lesion length (cm)	16.5 (9.50, 26.00)	21.00 (12.25, 25.00)	0.957	0.338
Total occlusion [n (%)]	41 (85.42)	42 (87.50)	1.861	0.173
White blood cell count (×10^9/L)	8.30±3.18	7.57±2.23	1.313	0.192
Neutrophil count (×10^9/L)	4.66±1.26	4.79±1.29	0.503	0.616
Platelet count (×10^9/L)	259.10±55.31	278.17±75.34	1.406	0.163
Lymphocyte count (×10^9/L)	1.98±0.77	1.75±0.49	1.800	0.075
TC (mmol/L)	4.35±1.33	4.18±1.08	0.673	0.503
TG (mmol/L)	1.66±1.02	1.59±1.05	0.333	0.740
HDL-C (mmol/L)	1.01±0.20	1.05±0.27	0.846	0.399
LDL-C (mmol/L)	3.03±1.05	2.87±0.87	0.793	0.430
Total bilirubin (μmol/L)	7.41±3.06	9.01±5.01	1.899	0.061
Albumin (g/L)	37.19±4.74	37.97±6.53	0.672	0.503
Serum creatinine (μmol/L)	88.00 (72.75, 111.25)	76.07 (64.25, 92.00)	1.258	0.212
Blood uric acid (μmol/L)	374.35±74.94	357.01±93.21	1.005	0.318
Glomerular filtration rate (mL/min)	49.17±21.81	57.23±26.37	1.633	0.106
FBG (mmol/L)	6.49±2.62	6.42±2.40	0.142	0.888
HbA1c (%)	5.82±1.10	6.40±1.09	2.635	0.010
NLR	2.30 (1.86, 3.42)	2.72 (2.08, 3.53)	1.682	0.093
PLR	121.73 (106.72, 187.50)	160.14 (132.48, 205.54)	1.926	0.057
SII	586.85 (490.03, 833.32)	781.96 (568.57, 1018.54)	2.894	0.004
NHR	4.55 (3.57, 6.69)	4.23 (3.49, 6.22)	0.092	0.927

Note: TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; FBG: Fasting blood glucose; HbA1c: Glycated hemoglobin; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; NHR: Neutrophil to high-density lipoprotein cholesterol ratio.

Table 3. Assignment table

Factor	Variables	Assignment
HbA1c (%)	X1	Original value entry
SII	X2	Original value entry

Note: PSM: propensity score matching; ASO: Arteriosclerosis obliterans; ISR: in-stent restenosis; HbA1c, glycosylated hemoglobin; SII: systemic immune-inflammation index.

the non-ISR group (P < 0.05; **Table 1**). After 1:1 PSM, the ISR group still exhibited significantly higher HbA1 c and SII levels compared to the non-ISR group (P < 0.05; **Table 2**).

Logistic regression analysis of influencing factors for ISR in ASO patients after PSM

Variables with P < 0.05 in the univariate analysis (after PSM) were included in the multivariate logistic regression analysis, with ISR occurrence in ASO patients as the dependent variable. The assignment for each variable is shown in **Table 3**. Multivariate logistic regression analysis showed that elevated HbA1c and SII levels were independently associated with an increased risk of ISR in ASO patients (P < 0.05; **Table 4**).

Table 4. Logistic regression analysis of intendent risk factors for ISR in ASO patients after PSM

Index	β	SE	Wald χ^2	*P*	OR	95% CI
HbA1c (%)	0.475	0.213	4.988	0.026	1.608	1.060-2.440
SII	0.002	0.001	6.670	0.010	1.002	1.001-1.004
Constant	-4.634	1.480	9.800	0.002	-	-

Note: PSM: propensity score matching; ASO: Arteriosclerosis obliterans; ISR: in-stent restenosis; HbA1c, glycosylated hemoglobin; SII: systemic immune-inflammation index.

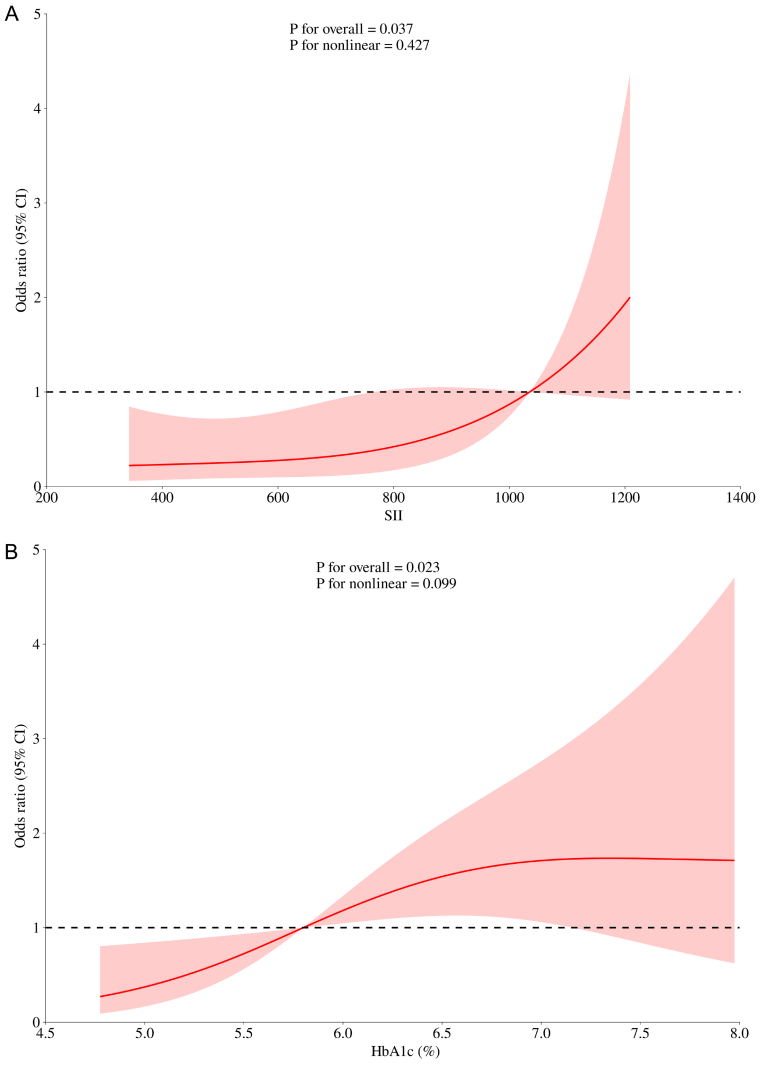

Figure 2. Dose-response relationship between SII, HbA1c, and ISR in ASO patients. A. Dose-response relationship between SII and ISR; B. Dose-response relationship between HbA1c and ISR. Notes: ASO: Arteriosclerosis Obliterans; ISR: in-stent restenosis; SII: systemic immune-inflammation index.

Dose-response relationship between SII, HbA1c, and ISR

As shown in **Figure 2**, RCS analysis, adjusted for relevant confounding factors, showed a linear dose-response relationship between SII and ISR risk ($P_{total\ trend}$=0.037, $P_{nonlinear}$=0.427). Similarly, a linear dose-response relationship was also observed between HbA1c and ISR risk ($P_{total\ trend}$=0.023, $P_{nonlinear}$=0.099).

Nomogram construction

A nomogram prediction model for ISR in ASO patients was constructed based on the independent risk factors identified in multivariate logistic regression analysis (HbA1c and SII) (**Figure 3**). The contribution of each factor to ISR risk was visualized. In this model, higher values of HbA1c and SII corresponded to increased nomogram scores, reflecting higher ISR risk.

Validation of the nomogram prediction model

The predictive performance of the model was validated using post-PSM data. The ROC curve analysis showed that SII alone predicted ISR with an AUC of 0.671 (95% CI: 0.563-0.780), a sensitivity of 68.80%, and a specificity of 58.33%. HbA1c alone predicted ISR with an AUC of 0.684 (95% CI: 0.577-0.790), a sensitivity of 56.30%, and a specificity of 75.00%. Combining SII and HbA1c improved the model's predictive performance, with an AUC of 0.705 (95% CI: 0.599-0.811), a sensitivity of 77.10%, and a specificity of 58.30% (**Figure 4**). Calibration curves indicated good agreement between predicted and observed ISR probabilities (**Figure 5**).

External verification

An external validation cohort (n=72; January-December 2024) was used to verify the generalizability of the predictive model, comprising

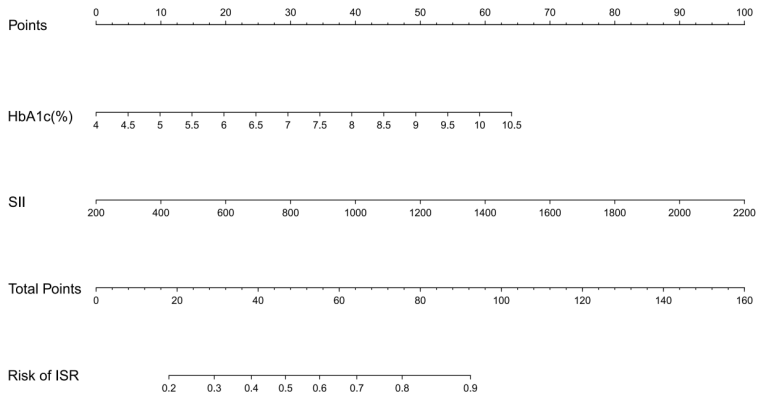

Figure 3. Nomogram for predicting the risk of in-stent restenosis in patients with arteriosclerosis obliterans. Notes: ASO: Arteriosclerosis Obliterans; ISR: in-stent restenosis; SII: systemic immune-inflammation index; HbA1c: Glycated Hemoglobin A1c.

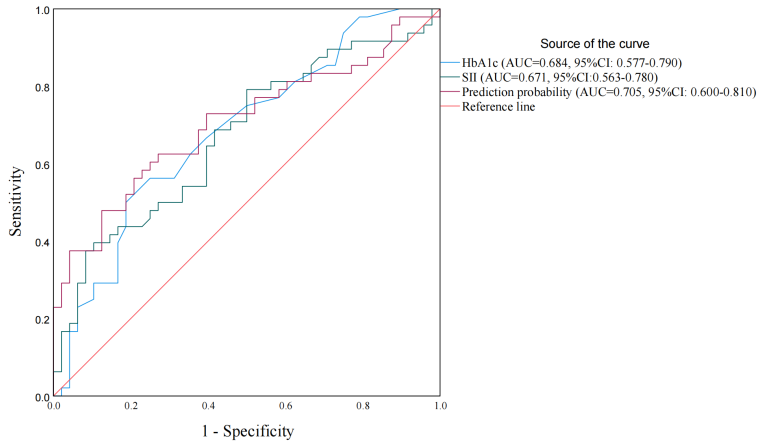

Figure 4. ROC curve analysis for the predictive model. Notes: ROC: receiver operating characteristic.

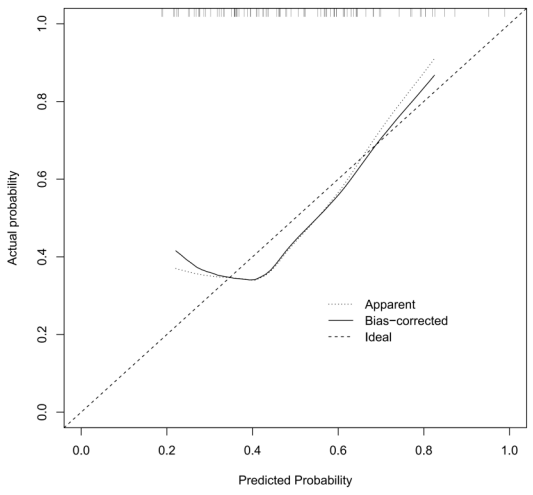

Figure 5. Calibration curves for the prediction model.

35 in the ISR group and 37 in the non-ISR group. Baseline characteristics were balanced between the two groups except for higher SII and HbA1c levels in the ISR group ($P < 0.05$; **Table 5**).

When applied to the external cohort, the predictive model yielded an AUC of 0.718 (95% CI, 0.594-0.841), a sensitivity of 54.3%, and a specificity of 89.2% (**Figure 6A**). Calibration analysis also demonstrated good agreement between predicted and observed ISR probabilities, indicating stable predictive performance (**Figure 6B**).

Discussion

ASO is a common arterial vascular disease and represents a major public health challenge, particularly in aging populations [13]. Endovascular stent implantation has become the primary surgical approach for ASO, offering advantages such as minimal invasiveness, rapid postoperative recovery, and favorable therapeutic efficacy.

Despite these advantages, postoperative in-stent restenosis (ISR) remains a major challenge of endovascular therapy, adversely affecting long-term clinical outcomes [14, 15]. As the use of stent implantation has expanded, a substantial proportion of patients have been noted to develop ISR during follow-up, resulting in recurrent ischemic symptoms, repeated interventions, and increased healthcare cost. In our study, ISR occurred in 71 out of 157 patients, corresponding to an incidence of 45.22%, which is consistent with previously reported rates [16, 17]. These observations indicate that ASO patients face a high risk of developing restenosis following stent placement. Therefore, accurately assessing the risk of ISR after stent implantation in ASO patients has become an urgent issue in clinical practice.

Table 5. Comparison of clinical data between ISR and non-ISR groups in the external validation cohort

Item	non-ISR group (n=37)	ISR group (n=35)	$t/Z/\chi^2$	*P*
Age (years)	67.74±8.92	66.74±8.23	1.027	0.308
Gender [male/female, n (%)]	33/4	31/4	0.007	0.934
BMI (kg/m^2)	22.69±2.98	23.43±3.55	0.954	0.343
Coronary heart disease [n (%)]	5 (13.51)	4 (11.43)	0.071	0.789
Diabetes [n (%)]	11 (29.73)	15 (42.86)	1.343	0.246
Hypertension [n (%)]	26 (70.27)	28 (80.00)	0.908	0.341
Hyperlipidemia [n (%)]	7 (18.92)	8 (22.86)	0.169	0.681
History of chronic renal insufficiency [n (%)]	5 (1.51)	5 (14.29)	0.009	0.925
Smoking [n (%)]	22 (59.46)	17 (48.57)	0.859	0.354
Drinking [n (%)]	16 (43.24)	12 (34.29)	0.607	0.436
Number of diseased vessels (branches)	1 (1, 1)	1 (1, 1)	0.681	0.496
Lesion length (cm)	21.00 (12.50, 25.00)	21.00 (12.00, 26.00)	0.079	0.937
Total occlusion [n (%)]	41 (85.42)	42 (87.50)	1.861	0.173
White blood cell count (×10^9/L)	8.24±3.53	7.63±2.35	0.863	0.391
Neutrophil count (×10^9/L)	4.64±1.34	4.69±1.23	0.180	0.858
Platelet count (×10^9/L)	262.43±52.50	280.46±84.45	1.094	0.278
Lymphocyte count (×10^9/L)	2.05±0.83	1.73±0.51	1.978	0.052
TC (mmol/L)	4.40±1.47	4.31±1.20	0.283	0.778
TG (mmol/L)	1.56±0.84	1.66±1.09	0.414	0.680
HDL-C (mmol/L)	1.03±0.17	1.06±0.29	0.529	0.598
LDL-C (mmol/L)	3.03±1.05	2.90±0.96	0.535	0.595
Total bilirubin (μmol/L)	7.39±2.89	8.67±4.23	1.497	0.139
Albumin (g/L)	37.12±5.03	38.86±7.13	1.204	0.233
Serum creatinine (μmol/L)	89.18 (75.50, 110.50)	76.44 (66.00, 92.00)	1.865	0.062
Blood uric acid (μmol/L)	382.59±73.72	371.24±97.15	0.560	0.577
Glomerular filtration rate (mL/min)	52.64 (35.51, 65.90)	51.83 (38.42, 67.02)	0.603	0.547
FBG (mmol/L)	6.42±2.71	6.75±2.60	0.527	0.600
HbA1c (%)	5.75±1.01	6.49±1.14	2.921	0.005
NLR	2.27 (1.86, 3.03)	2.08 (2.62, 3.51)	1.808	0.071
PLR	121.35 (103.71, 195.91)	162.11 (132.61, 215.91)	1.865	0.062
SII	553.07 (481.15, 841.04)	782.16 (553.17, 1024.40)	2.236	0.025
NHR	4.42 (3.53, 5.65)	4.11 (3.37, 6.14)	0.152	0.879

Note: TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; FBG: Fasting blood glucose; HbA1c: Glycated hemoglobin; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; NHR: Neutrophil to high-density lipoprotein cholesterol ratio.

As a retrospective study, random allocation was not feasible, which may have resulted in selection bias and baseline imbalances between groups. To minimize the influence of confounding factors, PSM was performed. By matching individuals with similar propensity scores, the distribution of confounders can be effectively balanced between groups, thereby approximating the conditions of a randomized study and improving the reliability of the findings. After matching, both HbA1c and SII levels remained significantly higher in the ISR group than the non-ISR group. Furthermore, logistic regression analysis identified elevated HbA1c and SII levels as independent risk factors for ISR in ASO patients. These findings suggest that disturbances in glucose metabolism and systemic inflammatory activation may play important roles in the development of ISR.

HbA1c is a well-established indicator of glycemic control over the preceding 8-12 weeks and reflects long-term glucose metabolism status. Elevated HbA1c levels indicate persistent hyperglycemia and poor glycemic control. Chronic hyperglycemia may promote the generation of reactive oxygen species, thereby exacerbating oxidative stress responses. Su-

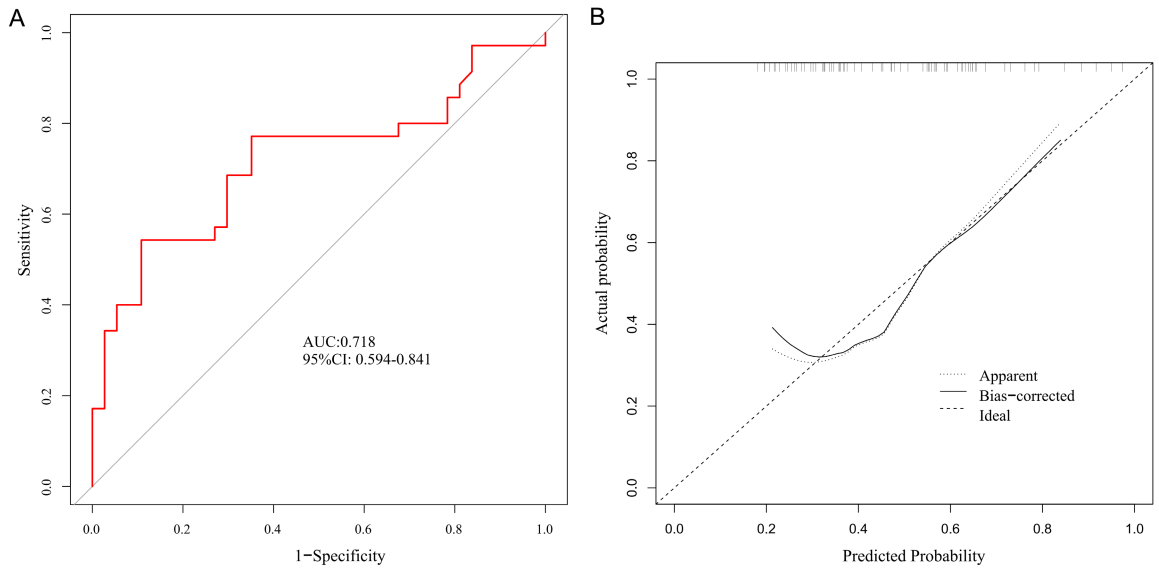

Figure 6. External validation of the predictive model for ISR in ASO patients. A. ROC curve of the predictive model integrating SII and HbA1c for ISR after stent implantation; B. Calibration curve of the predictive model in the external validation cohort. Notes: ASO: Arteriosclerosis Obliterans; ISR: in-stent restenosis; ROC: receiver operating characteristic.

stained vascular endothelium injury may increase vascular permeability and stimulate the production of vasoconstrictors such as angiotensin II, endothelin, and prostaglandins, all of which are factors associated with atherosclerotic plaque formation and subsequent vascular remodeling, ultimately increasing the risk of ISR following stent implantation [18, 19].

Elevated HbA1c levels can lead to an increased production of glycation end products (AGEs). AGEs can activate protein kinases p38 and p44/42, which subsequently activate downstream signaling pathways involving NF-κB. This cascade promotes the production of multiple pro-inflammatory cytokines and chemokines, including TNF-α, IL-1, and COX-2, thereby amplifying inflammatory responses and upregulating pro-coagulant gene expression. Persistent endothelial injury and dysfunction induced by these mechanisms contribute to neointimal hyperplasia, vascular remodeling, and progression of atherosclerosis, ultimately increasing the risk of ISR following stent implantation [20, 21].

SII is a novel marker of systemic inflammatory status and has been reported to serve not only as an independent risk factor for cardiovascular diseases but also as a tool for assessing lesion severity [8, 22, 23]. The potential mechanisms underlying the association between elevated SII and ISR are multifaceted. Elevated neutrophil counts promote the release of pro-inflammatory cytokines, reactive oxygen species, and other bioactive mediators, thereby exacerbating inflammatory responses. Neutrophils also secrete myeloperoxidase and matrix metalloproteinases, which facilitate the degradation and rupture of fibrous caps, increasing plaque vulnerability. In addition, neutrophil-derived granule proteins can activate macrophages and promote foam cell formation, further aggravating endothelial dysfunction and vascular inflammation [24, 25]. Endothelial injury subsequently enhances platelet activation and aggregation and stimulates the CD40/CD40L signaling pathway, leading to increased metalloproteinase expression and sustained vascular inflammatory responses. Platelets not only contribute to acute intravascular thrombosis but also participate in chronic inflammatory responses within vascular walls. Collectively, these processes contribute to neointimal proliferation, adverse vascular remodeling, and an increased risk of ISR after stent implantation [26, 27].

In this study, RCS analysis revealed that the risk of ISR increased progressively with higher levels of both SII and HbA1c in ASO patients

undergoing stent implantation. These findings suggest that preoperative measurement of serum SII and HbA1c may help assess the risk of ISR in ASO patients. Validation using post-PSM data showed that SII alone predicted ISR with an AUC of 0.671 (95% CI: 0.563-0.780), and HbA1c alone predicted ISR with an AUC of 0.684 (95% CI: 0.577-0.790). After integrating SII with HbA1c into a nomogram model, the predictive performance was improved, with an AUC of 0.705 (95% CI: 0.599-0.811). Calibration curves indicated good agreement between predicted and observed ISR probabilities, confirming the reliability of the model.

Our findings are consistent with previous studies demonstrating a positive association between SII and ISR risk. Li et al. [28] reported that elevated SII was significantly associated with increased ISR risk in patients with acute coronary syndrome, with RCS analysis showing a J-shaped nonlinear correlation (P for overall trend < 0.001, P for nonlinearity =0.0058) and a threshold effect at SII=620. Another study also identified SII as an independent predictor of in-stent neoatherosclerosis (ISNA) and thin-cap fibroatheroma (TCFA) [29]. Additionally, an optimal SII cutoff value of 545.29 for predicting ISR was reported, confirming SII as an independent predictor of ISR [30]. However, Yang et al. [31] observed a nonlinear association between the systemic inflammation response index (SIRI) and ISNA. In our study, however, RCS analysis revealed a linear relationship between SII and ISR. This discrepancy may be attributed to differences in study populations (coronary vs. peripheral arteries), sample sizes, or the use of PSM in our study to reduce confounding bias. To our knowledge, this is the first study to combine SII with HbA1c for ISR risk prediction in ASO patients and to validate the prediction model using an independent external cohort, thereby enhancing the robustness and generalizability of the findings.

This study has several limitations. First, it was a retrospective analysis with a relatively small and homogeneous sample, which may limit the generalizability of findings to the broader ASO population. Second, although PSM controlled for some measurable confounders, it also resulted in the exclusion of certain patients, potentially altering overall cohort characteristics and reducing sample representativeness. Third, SII and HbA1c were measured only once before stent implantation; dynamic changes in these markers over time were not captured, which may provide additional prognostic information. Fourth, the optimal cutoff values for SII and HbA1c were not determined in this study, which could further facilitate clinical risk stratification. Future studies with larger sample sizes, multi-center designs, and prospective randomized approaches are warranted to validate and extend these findings.

Conclusion

Both HbA1c and SII were associated with the risk of ISR in ASO patients. Elevated levels of SII, in particular, were linearly correlated with increased ISR risk following stent implantation, highlighting the potential utility of combining SII and HbA1c as biomarkers for early identification of high-risk patients.

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Disclosure of conflict of interest

None.

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