Am J Transl Res 2026;18(11):9828-9838
www.ajtr.org /ISSN:1943-8141/AJTR0175199

Original Article

Coagulation activation and thrombotic burden are associated with in-stent restenosis after lower-extremity vascular stenting

Lin Shi[1*], Yulin Zhang[2*], Qin Wei[1], Tianping Xiong[1], Yingming Xu[1]

[1]Department of Vascular Surgery, Xingyi People's Hospital, Xingyi 562400, Guizhou, China; [2]Department of Radiology, Shengjing Hospital of China Medical University, Shenyang 110000, Liaoning, China. [*]Equal contributors.

Received July 6, 2026; Accepted August 29, 2026; Epub November 15, 2026; Published November 30, 2026

Abstract: Objectives: To evaluate time-to-event associations of coagulation markers and peri-procedural thrombus burden with in-stent restenosis (ISR) after lower-extremity arterial or iliac venous stenting. Methods: This single-center retrospective cohort study included 180 adults treated between January 2019 and August 2024. Month-level follow-up intervals were analyzed using Cox proportional hazards regression and Kaplan-Meier methods. The proportional hazards assumption was assessed using Schoenfeld residuals. Marker-model discrimination was evaluated using Harrell's C-index with 500-resample bootstrap optimism correction; 18-month calibration and Brier scores were also assessed. Results: ISR occurred in 45 patients (25.0%). Reverse Kaplan-Meier analysis estimated a median potential follow-up of 20.1 months (interquartile range, 15.7-24.2). In the final adjusted Cox model, D-dimer (per 0.5 mg/L: HR=1.604, 95% CI: 1.323-1.943) and high thrombus burden (HR=3.944, 95% CI: 1.962-7.930) were independently associated with earlier ISR. These associations remained in a sensitivity model additionally adjusting for residual stenosis and anticoagulation plus antiplatelet therapy. Adding thrombus burden to D-dimer increased the optimism-corrected C-index from 0.780 to 0.793. Conclusions: Higher D-dimer and high thrombus burden were independently associated with earlier ISR. Thrombus burden provided limited incremental discrimination, and external validation remains necessary.

Keywords: In-stent restenosis, D-dimer, thrombus burden, coagulation activation, lower-extremity vascular stent

Introduction

Lower-extremity arterial occlusive disease, iliac vein compression syndrome, and post-thrombotic syndrome impair limb perfusion or venous outflow. Endovascular stenting can restore flow and relieve symptoms, but in-stent restenosis (ISR) or occlusion remains an important cause of recurrent symptoms and repeat intervention in both arterial and venous territories [1-7].

ISR reflects an abnormal vascular healing response involving endothelial injury, inflammation, platelet activation, coagulation, smooth muscle cell proliferation, and neointimal formation [8, 9]. Traditional predictors such as diabetes, smoking, lesion complexity, and procedural factors do not fully capture the interaction between systemic thrombo-inflammation and local thrombus burden.

Routine blood counts and biochemical tests permit calculation of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and C-reactive protein-to-albumin ratio (CRP/ALB), while D-dimer and fibrinogen reflect coagulation-fibrinolytic activity. Prior studies have linked these indices, particularly SII, to peripheral arterial disease and post-intervention restenosis [10-15]. We therefore examined whether preoperative inflammatory indices, coagulation markers, and imaging/intraoperative thrombus burden were associated with time to ISR after lower-extremity arterial or iliac venous stenting and explored the incremental

https://doi.org/10.62347/FMKZ2737

discrimination of a combined marker framework.

Materials and methods

Study subjects

A single-center retrospective cohort was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [16]. Medical records were reviewed for adults who underwent lower-extremity arterial or iliac venous stent implantation in the Vascular Surgery/Interventional Radiology Department between January 2019 and August 2024. Of 236 screened patients, 56 were excluded and 180 were included: 110 underwent lower-extremity arterial stenting and 70 underwent iliac venous stenting.

The study was approved by the Ethics Committee of Xingyi People's Hospital (YXLL-20240929(Yan)-012). The requirement for informed consent was waived because of the retrospective design and use of de-identified data.

Inclusion and exclusion criteria

Inclusion criteria were: (1) age ≥18 years; (2) successful lower-extremity arterial or iliac venous stent implantation; (3) available preoperative blood, coagulation, biochemical, and imaging data; (4) at least one evaluable postoperative imaging assessment; and (5) determinable stent status. Exclusion criteria were: (1) malignancy, hematologic or autoimmune disease, or documented active infection before the index procedure; (2) recent preoperative high-dose corticosteroid or immunosuppressive treatment; (3) missing essential laboratory or imaging data; (4) failed stent implantation or perioperative death; and (5) no evaluable postoperative imaging follow-up. Postoperative infection did not alter baseline eligibility or retrospective group assignment but was considered a potential follow-up confounder.

Data collection

Collected variables included age, sex, body mass index, smoking and alcohol use, hypertension, diabetes, coronary artery disease, cerebral infarction, chronic kidney disease, previous thrombosis, and previous vascular intervention. Laboratory variables included blood cell counts, hemoglobin, C-reactive protein, albumin, D-dimer, fibrinogen, coagulation tests, lipid profile, fasting glucose, creatinine, and estimated glomerular filtration rate. These circulating laboratory markers are commonly evaluated in lower-extremity arterial disease [17]. NLR, PLR, SII, SIRI, and CRP/ALB were calculated from the preoperative measurements. Lesion and procedural variables included vessel category, lesion length and occlusion, ankle-brachial index (ABI) or venous clinical symptom score, number and cumulative length of stents, stent diameter, balloon dilation, mechanical thrombectomy or catheter-directed thrombolysis (CDT), drug-coated balloon use, residual stenosis, and postoperative antithrombotic therapy.

Assessment of thrombus burden

Thrombus burden was graded semi-quantitatively using preoperative computed tomography angiography, digital subtraction angiography, computed tomography venography, and/or intraoperative angiography. Low burden indicated a focal filling defect with preserved flow; moderate burden indicated segmental thrombus with substantial but incomplete flow reduction; and high burden indicated long-segment or multisegment thrombus, complete occlusion, or thrombus requiring mechanical thrombectomy or CDT. Two vascular interventional specialists reviewed the images independently and resolved disagreements by consensus. The original records did not preserve the two readers' separate ratings; therefore, an interobserver agreement coefficient could not be retrospectively calculated.

Definition of outcomes

The primary outcome was time to imaging-confirmed ISR, defined as ≥50% luminal narrowing within the stent or within 5 mm of either stent edge; complete occlusion within the same segment was classified as ISR. Target-lesion revascularization was not included as a separate study endpoint in the present analysis. For the time-to-event analysis, the available month-level follow-up interval was operationalized as the interval from the index procedure to the first imaging assessment documenting ISR for patients with ISR and to the last evaluable postoperative imaging assessment for patients without ISR. Exact calendar dates and a uni-

form administrative censoring date were not retained in the analysis dataset. Arterial stents were evaluated by duplex ultrasonography, computed tomography angiography, or digital subtraction angiography; iliac venous stents were evaluated by computed tomography venography, venous ultrasonography, or venography. Other secondary outcomes included symptom recurrence, insufficient improvement in ABI or venous symptom score, bleeding, and recurrent thrombosis; recurrent thrombosis was recorded separately from ISR and did not determine group assignment. Patients without evaluable postoperative imaging follow-up were excluded before outcome analysis. Antithrombotic therapy was prescribed according to contemporary recommendations [18, 19].

Statistical methods

Statistical analyses were performed in R 4.3.2 and Python 3.11. Continuous-variable distributions were assessed using the Shapiro-Wilk test and histograms. Normally distributed variables are presented as mean ± standard deviation and were compared using the independent-samples t test; skewed variables are presented as median (interquartile range) and were compared using the Mann-Whitney U test. Categorical variables are presented as n (%) and were compared using the chi-square test or Fisher exact test. Potential follow-up duration was summarized by the reverse Kaplan-Meier method. Time to ISR was analyzed using Kaplan-Meier curves, the log-rank test, and Cox proportional hazards regression with the Efron method for ties. The proportional hazards assumption was evaluated using Schoenfeld residuals. The final adjustment set included age, sex, diabetes, vessel type, D-dimer, and high thrombus burden. SII and fibrinogen were reported in univariable analyses but were not retained in the final proportional-hazards model because residual diagnostics suggested time-varying effects. A sensitivity model additionally adjusted for residual stenosis and anticoagulation combined with antiplatelet therapy. Variance inflation factors were used to assess multicollinearity. For exploratory marker performance, Cox models containing D-dimer alone and D-dimer plus ordinal thrombus burden (low = 0, moderate = 1, high = 2) were compared using Harrell's C-index. Internal validation used 500 bootstrap resamples to estimate optimism-corrected C-indices and 18-month inverse-probability-of-censoring-weighted Brier scores. Calibration at 18 months was examined by comparing mean predicted risk with Kaplan-Meier observed risk across quintiles. Kaplan-Meier and exploratory subgroup analyses used the predefined comparison of high thrombus burden versus low or moderate burden. All tests were two-sided, and $P<0.05$ was considered statistically significant.

Results

Study population and baseline characteristics

Among 236 screened patients, 56 were excluded: 13 had malignancy, documented active preoperative infection, or immune disease; 18 had incomplete laboratory or imaging data; 5 had failed stent implantation or perioperative death; and 20 had no evaluable postoperative imaging follow-up. The final analysis included 180 patients, comprising 70 iliac venous stent recipients and 110 lower-extremity arterial stent recipients. The final analysis included 180 patients, comprising 70 iliac venous stent recipients and 110 lower-extremity arterial stent recipients (**Figure 1**). ISR occurred in 45 patients (25.0%), including 20 venous and 25 arterial stent recipients. Reverse Kaplan-Meier analysis estimated a median potential follow-up of 20.1 months (interquartile range, 15.7-24.2). Baseline characteristics are summarized in **Table 1**; no statistically significant between-group differences were observed for the variables listed in that table.

Comparison of markers for inflammation, coagulation and thrombus burden

Compared with the non-ISR group, the ISR group had higher neutrophil, monocyte, platelet, NLR, PLR, SII, SIRI, C-reactive protein, CRP/ALB, D-dimer, and fibrinogen values and lower lymphocyte and albumin values (all $P<0.05$). Median SII was 1168.6 (849.8, 1443.3) versus 660.7 (488.9, 952.2), median D-dimer was 1.32 (0.92, 1.58) mg/L versus 0.70 (0.51, 0.91) mg/L, and mean fibrinogen was 4.00±0.54 g/L versus 3.43±0.60 g/L. High thrombus burden was more frequent in the ISR group than that in the non-ISR group (75.6% vs 17.8%, $P<0.001$). Prothrombin time, activated

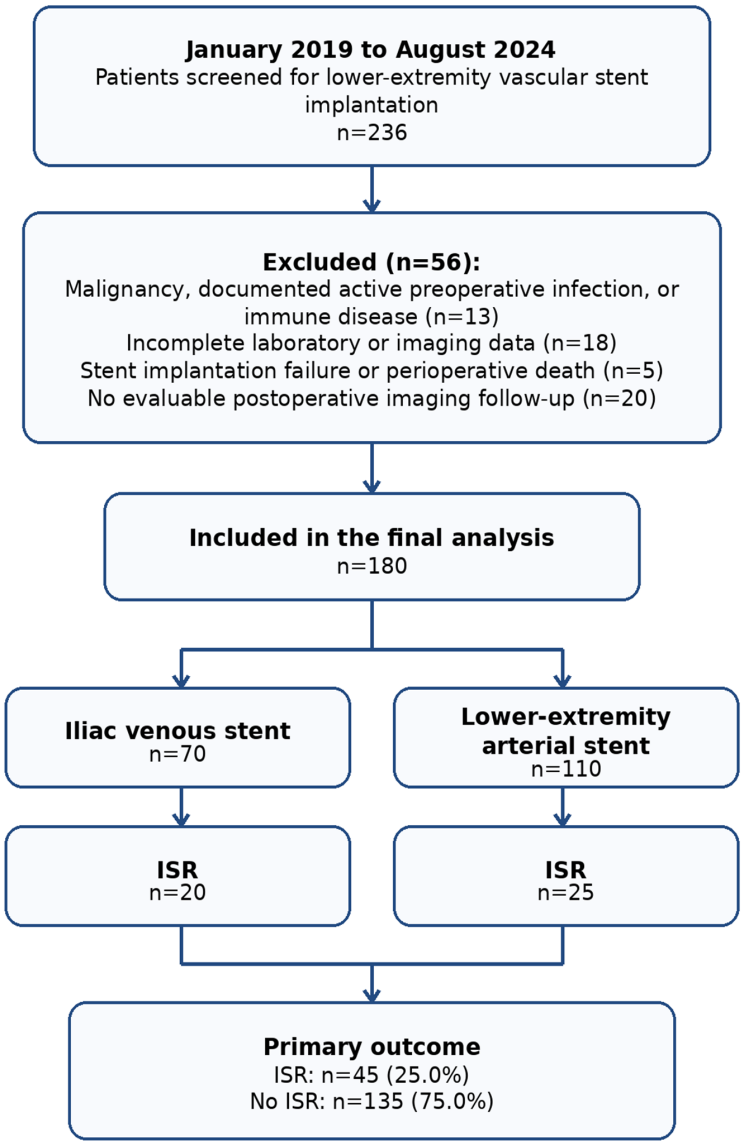


Figure 1. Flowchart of study participant selection.

partial thromboplastin time, and international normalized ratio did not differ significantly (**Table 2**).

Comparison of lesion and procedural characteristics

The ISR group had longer lesions, more stents, greater residual stenosis, more occlusive lesions, and more frequent mechanical thrombectomy or CDT than the non-ISR group (all P<0.05). Total stent length, stent diameter, drug-coated balloon use, balloon pre-dilation or post-dilation, and postoperative antithrombotic regimen did not differ significantly. Symptom recurrence, insufficient improvement, and recurrent thrombosis were more frequent in the ISR group, whereas bleeding rates were similar. Recurrent thrombosis occurred in 12 patients (8 ISR and 4 non-ISR) and was recorded independently of the imaging-based ISR classification (**Table 3**).

Time-to-event association of systemic inflammation and thrombotic burden with ISR

In univariable Cox analyses, SII, D-dimer, fibrinogen, high thrombus burden, residual stenosis, and anticoagulation combined with antiplatelet therapy were associated with time to ISR. In the preliminary eight-variable model, Schoenfeld residual tests indicated non-proportional effects for SII (P=0.041) and fibrinogen (P=0.002); these variables were therefore not retained in the final constant-hazard model. In the final adjusted model, D-dimer (per 0.5 mg/L increase: HR=1.604, 95% CI: 1.323-1.943, P<0.001) and high thrombus burden (HR=3.944, 95% CI: 1.962-7.930, P<0.001) were independently associated with earlier ISR after adjustment for age, sex, diabetes, and vessel type. The proportional-hazards assumption was not violated in the final model: variable-specific Schoenfeld test *P* values were 0.525 for age, 0.884 for sex, 0.212 for diabetes, 0.117 for vessel type, 0.551 for D-dimer, and 0.181 for high thrombus burden, and the global test *P* value was 0.242. In a sensitivity model additionally adjusting for residual stenosis and anticoagulation combined with antiplatelet therapy, D-dimer (HR=1.625, 95% CI: 1.330-1.986, P<0.001) and high thrombus burden (HR=2.830, 95% CI: 1.263-6.343, P=0.012) remained associated with earlier ISR. All variance inflation factors were <2 (**Table 4**).

Table 1. Comparison of baseline characteristics between the ISR and non-ISR groups

Variable	Total (n=180)	Restenosis group (n=45)	Non-restenosis group (n=135)	Statistic	*P*-value
Age (years)	64.4±9.1	64.0±9.5	64.5±9.0	t=-0.307	0.759
Body mass index (kg/m^2)	24.9±3.2	24.9±3.4	24.9±3.1	t=-0.003	0.998
Male	106 (58.9)	25 (55.6)	81 (60.0)	χ^2=0.275	0.600
History of smoking	75 (41.7)	22 (48.9)	53 (39.3)	χ^2=1.288	0.256
History of alcohol consumption	54 (30.0)	17 (37.8)	37 (27.4)	χ^2=1.728	0.189
Hypertension	99 (55.0)	25 (55.6)	74 (54.8)	χ^2=0.007	0.931
Diabetes mellitus	63 (35.0)	13 (28.9)	50 (37.0)	χ^2=0.985	0.321
Coronary heart disease	42 (23.3)	8 (17.8)	34 (25.2)	χ^2=1.035	0.309
History of cerebral infarction	35 (19.4)	7 (15.6)	28 (20.7)	χ^2=0.579	0.447
Chronic kidney disease	11 (6.1)	1 (2.2)	10 (7.4)	Fisher	0.296
History of thrombosis	65 (36.1)	21 (46.7)	44 (32.6)	χ^2=2.898	0.089
History of vascular intervention	25 (13.9)	6 (13.3)	19 (14.1)	χ^2=0.015	0.901
Lower extremity arterial stent	110 (61.1)	25 (55.6)	85 (63.0)	χ^2=0.779	0.377

Categorical variables are presented as n (%), normally distributed variables as mean ± standard deviation, and skewed variables as median (interquartile range).

Table 2. Comparison of inflammatory, coagulation, and thrombus-burden indicators

Variable	Total (n=180)	Restenosis group (n=45)	Non-restenosis group (n=135)	Statistic	*P*-value
White blood cells (×10^9/L)	7.1±1.4	7.5±1.3	6.9±1.5	t=2.111	0.036
Neutrophils (×10^9/L)	4.7±1.1	5.5±0.9	4.5±1.1	t=5.708	<0.001
Lymphocytes (×10^9/L)	1.57±0.43	1.37±0.37	1.64±0.43	t=-3.886	<0.001
Monocytes (×10^9/L)	0.47±0.13	0.52±0.12	0.45±0.13	t=3.272	0.001
Platelets (×10^9/L)	251±45	268±49	245±43	t=3.045	0.003
Hemoglobin (g/L)	131±14	130±14	131±15	t=-0.566	0.572
Neutrophil-to-lymphocyte ratio	3.23 (2.12, 4.14)	4.22 (3.42, 5.15)	2.83 (2.02, 3.60)	Z=5.492	<0.001
Platelet-to-lymphocyte ratio	165.3 (120.0, 204.8)	197.4 (148.4, 263.8)	148.3 (115.2, 198.2)	Z=4.048	<0.001
Systemic immune-inflammation index	751.5 (532.1, 1112.5)	1168.6 (849.8, 1443.3)	660.7 (488.9, 952.2)	Z=5.631	<0.001
Systemic inflammation response index	1.44 (0.95, 2.06)	2.37 (1.52, 2.82)	1.22 (0.81, 1.79)	Z=5.780	<0.001
C-reactive protein (mg/L)	8.39 (5.50, 11.91)	9.54 (6.37, 13.84)	8.03 (5.15, 11.23)	Z=2.235	0.026
Albumin (g/L)	38.4±4.0	37.1±3.5	38.8±4.1	t=-2.447	0.015
C-reactive protein-to-albumin ratio	0.220 (0.151, 0.306)	0.271 (0.181, 0.376)	0.209 (0.133, 0.290)	Z=2.562	0.010
D-dimer (mg/L)	0.78 (0.57, 1.17)	1.32 (0.92, 1.58)	0.70 (0.51, 0.91)	Z=6.558	<0.001
Fibrinogen (g/L)	3.57±0.64	4.00±0.54	3.43±0.60	t=5.572	<0.001
Prothrombin time (s)	12.2±1.0	12.1±1.0	12.2±1.0	t=-0.182	0.856
Activated partial thromboplastin time (s)	31.4±3.7	31.4±3.5	31.4±3.8	t=-0.074	0.941
International normalized ratio	1.01±0.08	1.00±0.09	1.01±0.08	t=-0.482	0.630
Thrombus burden - Low	50 (27.8)	1 (2.2)	49 (36.3)	χ^2=53.813	<0.001
Thrombus burden - Medium	72 (40.0)	10 (22.2)	62 (45.9)		
Thrombus burden - High	58 (32.2)	34 (75.6)	24 (17.8)		

Categorical variables are presented as n (%), normally distributed variables as mean ± standard deviation, and skewed variables as median (interquartile range).

Subgroup and sensitivity analyses

Kaplan-Meier analysis showed a higher cumulative incidence of ISR among patients with high thrombus burden than those with low or moderate burden (log-rank P<0.001; **Figure 2**). Exploratory univariable subgroup analyses showed directionally consistent associations for high thrombus burden in the overall cohort (HR=5.768, 95% CI: 2.909-11.436), lower-extremity arterial stent sub-group (HR=7.447, 95% CI: 3.073-18.045), iliac venous stent subgroup (HR=4.152, 95% CI: 1.379-12.503), diabe-tes subgroup (HR=7.698, 95% CI: 2.083-

Table 3. Comparison of lesion, procedural, and follow-up characteristics

Variable	Total (n=180)	Restenosis group (n=45)	Non-restenosis group (n=135)	Statistic	*P*-value
Lesion length (mm)	130.1±36.4	140.5±36.0	126.6±36.0	t=2.231	0.027
Number of stents	2 (1, 2)	2 (2, 3)	1 (1, 2)	Z=3.000	0.001
Total stent length (mm)	148.2±40.0	154.6±40.9	146.1±39.6	t=1.240	0.217
Stent diameter (mm)	9.6±4.2	10.3±4.3	9.4±4.2	t=1.330	0.185
Residual stenosis (%)	15.4±5.0	18.3±4.8	14.4±4.8	t=4.696	<0.001
Preoperative ankle-brachial index (arterial stenting)	0.53±0.12	0.51±0.12	0.54±0.12	t=-1.108	0.270
Venous clinical symptom score (iliac venous stent; ISR n=20, non-ISR n=50)	10.1±2.6	11.0±2.4	9.7±2.7	t=1.828	0.072
Occlusive lesion	102 (56.7)	33 (73.3)	69 (51.1)	χ^2=6.787	0.009
Mechanical thrombectomy or catheter-directed thrombolysis	75 (41.7)	26 (57.8)	49 (36.3)	χ^2=6.408	0.011
Drug-coated balloon use	45 (25.0)	12 (26.7)	33 (24.4)	χ^2=0.089	0.766
Balloon predilation	126 (70.0)	31 (68.9)	95 (70.4)	χ^2=0.035	0.851
Balloon post-dilation	160 (88.9)	41 (91.1)	119 (88.1)	χ^2=0.300	0.584
Symptom recurrence	39 (21.7)	23 (51.1)	16 (11.9)	χ^2=30.649	<0.001
Insufficient improvement	40 (22.2)	22 (48.9)	18 (13.3)	χ^2=24.686	<0.001
Bleeding event	16 (8.9)	4 (8.9)	12 (8.9)	Fisher	1.000
Recurrent thrombosis	12 (6.7)	8 (17.8)	4 (3.0)	Fisher	0.002
Postoperative antithrombotic regimen - Dual antiplatelet therapy	83 (46.1)	21 (46.7)	62 (45.9)	χ^2=3.858	0.277
Postoperative antithrombotic regimen - Anticoagulation plus antiplatelet therapy	26 (14.4)	10 (22.2)	16 (11.9)		
Postoperative antithrombotic regimen - Anticoagulation alone	46 (25.6)	10 (22.2)	36 (26.7)		
Postoperative antithrombotic regimen - Single antiplatelet therapy	25 (13.9)	4 (8.9)	21 (15.6)		

Categorical variables are presented as n (%), normally distributed variables as mean ± standard deviation, and skewed variables as median (interquartile range). Recurrent thrombosis was recorded as a separate follow-up event and was not used to define ISR status.

Table 4. Cox proportional hazards analysis of time to in-stent restenosis

Variable	Univariable HR (95% CI)	Univariable statistic	Univariable *P*-value	Multivariable HR (95% CI)	Multivariable statistic	Multivariable *P*-value
Age	1.002 (0.969-1.035)	Wald χ^2=0.014	0.908	1.013 (0.973-1.055)	Wald χ^2=0.392	0.533
Male	0.783 (0.432-1.419)	Wald χ^2=0.650	0.421	0.569 (0.294-1.102)	Wald χ^2=2.799	0.095
Diabetes	0.743 (0.389-1.420)	Wald χ^2=0.809	0.368	0.531 (0.243-1.165)	Wald χ^2=2.506	0.114
History of smoking	1.720 (0.945-3.132)	Wald χ^2=3.148	0.076			
Lower-extremity arterial stent	0.848 (0.466-1.542)	Wald χ^2=0.292	0.589	1.381 (0.640-2.983)	Wald χ^2=0.676	0.411
SII (per 100-unit increase)	1.100 (1.050-1.153)	Wald χ^2=15.941	<0.001			
D-dimer (per 0.5 mg/L increase)	1.573 (1.376-1.797)	Wald χ^2=44.251	<0.001	1.604 (1.323-1.943)	Wald χ^2=23.226	<0.001
Fibrinogen (per 1 g/L increase)	2.672 (1.726-4.136)	Wald χ^2=19.435	<0.001			
High thrombus burden	5.768 (2.909-11.436)	Wald χ^2=25.178	<0.001	3.944 (1.962-7.930)	Wald χ^2=14.832	<0.001
Lesion length (per 10 mm increase)	1.074 (0.992-1.162)	Wald χ^2=3.130	0.079			
Residual stenosis (per 5% increase)	1.758 (1.290-2.395)	Wald χ^2=12.776	<0.001			
Anticoagulation combined with antiplatelet therapy	2.101 (1.028-4.294)	Wald χ^2=4.144	0.042			

HR, hazard ratio; CI, confidence interval. The final multivariable model included age, sex, diabetes, vessel type, D-dimer, and high thrombus burden. SII and fibrinogen were not retained because Schoenfeld residual diagnostics suggested non-proportional effects. A sensitivity model was additionally adjusted for residual stenosis and anticoagulation combined with antiplatelet therapy. Follow-up time was recorded in months to first documented ISR or censored at the last evaluable imaging assessment.

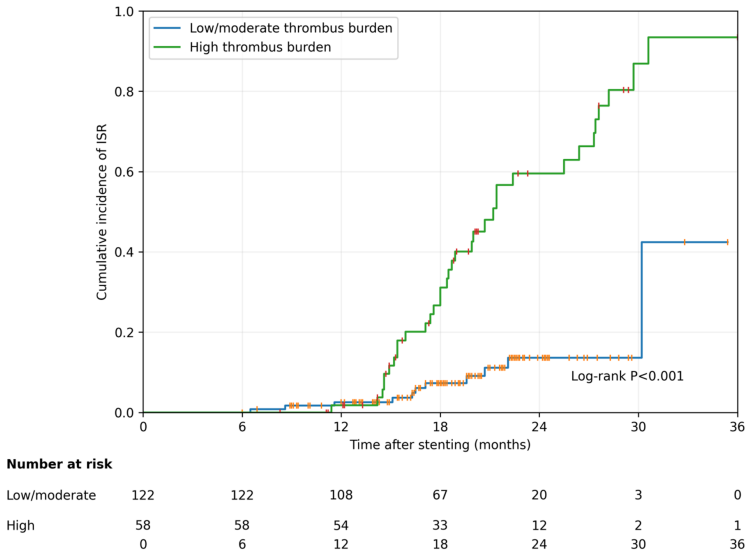


Figure 2. Kaplan-Meier cumulative incidence curves for ISR according to high versus low or moderate thrombus burden.

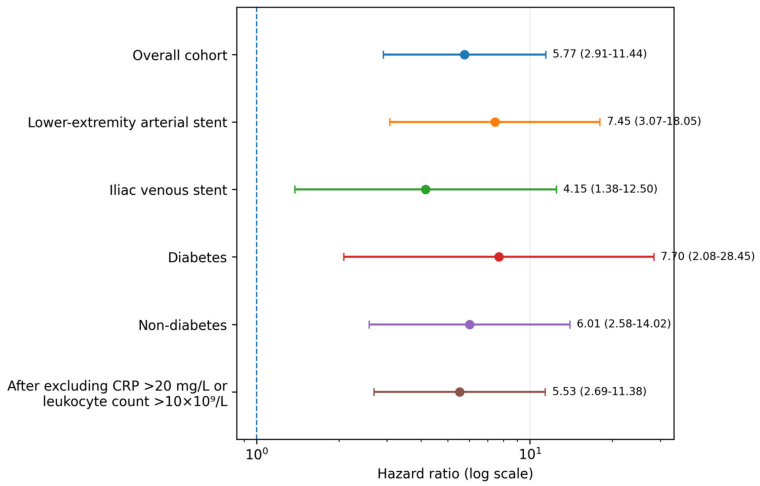


Figure 3. Exploratory Cox subgroup and sensitivity analyses for high thrombus burden versus low or moderate burden.

28.452), and non-diabetes subgroup (HR=6.013, 95% CI: 2.580-14.016). The association remained after excluding patients with C-reactive protein >20 mg/L or leukocyte count >10×10^9/L (HR=5.531, 95% CI: 2.687-11.382) (**Figure 3**).

Internal validation and calibration of combined marker models

The D-dimer-only Cox model had an apparent C-index of 0.780 (bootstrap 95% CI: 0.710-0.851) and an optimism-corrected C-index of 0.780. Adding ordinal thrombus burden increased the apparent C-index to 0.797 (bootstrap 95% CI: 0.729-0.862) and the optimism-corrected C-index to 0.793, corresponding to apparent and corrected increments of 0.017 and 0.013, respectively. The corrected 18-month Brier score decreased from 0.121 to 0.118. Quintile-based calibration of the D-dimer plus thrombus-burden model showed general agreement between predicted and Kaplan-Meier observed 18-month risk, although confidence intervals were wide because of the limited number of events (**Table 5** and **Figure 4**).

Subgroup and sensitivity analyses

Kaplan-Meier analysis showed a higher cumulative incidence of ISR among patients with high thrombus burden than those with low or moderate burden (log-rank P<0.001; **Figure 2**). Exploratory univariable subgroup analyses showed directionally consistent associations for high thrombus burden in the overall cohort (HR=5.768, 95% CI: 2.909-11.436), lower-extremity arterial stent subgroup (HR=7.447, 95% CI: 3.073-18.045), iliac venous stent subgroup (HR=4.152, 95% CI: 1.379-12.503), diabetes subgroup (HR=7.698, 95% CI: 2.083-28.452), and non-diabetes subgroup (HR=6.013, 95% CI: 2.580-14.016). The association remained after excluding patients with C-reactive protein >20 mg/L or leukocyte count >10×10^9/L (HR=5.531, 95% CI: 2.687-11.382) (**Figure 3**).

Discussion

In this cohort of 180 patients, ISR occurred in 25.0%. The final proportional-hazards model showed that higher D-dimer and high thrombus burden were independently associated with earlier ISR after adjustment for age, sex, diabetes, and vessel type. These associations

Table 5. Internal validation and 18-month calibration of cox marker models

Model or calibration group	n	Apparent C-index (95% CI)	Optimism-corrected C-index	Apparent 18-month Brier score	Corrected 18-month Brier score
D-dimer	180	0.780 (0.710-0.851)	0.780	0.117	0.121
D-dimer + thrombus burden	180	0.797 (0.729-0.862)	0.793	0.113	0.118
18-month calibration quintile	n	Mean predicted risk	KM-observed risk (95% CI)	ISR events	
Quintile 1	36	0.019	0.000 (0.000-0.000)	0	
Quintile 2	36	0.050	0.030 (0.004-0.196)	2	
Quintile 3	36	0.081	0.096 (0.025-0.332)	4	
Quintile 4	36	0.191	0.181 (0.079-0.384)	14	
Quintile 5	36	0.403	0.445 (0.291-0.636)	25	

CI, confidence interval; KM, Kaplan-Meier. Internal validation used 500 bootstrap resamples. Brier scores were calculated at 18 months using inverse probability of censoring weights; lower values indicate better overall prediction error. Thrombus burden was entered ordinally as low = 0, moderate = 1, and high = 2. Calibration groups are quintiles of predicted 18-month ISR risk from the D-dimer plus thrombus-burden Cox model.

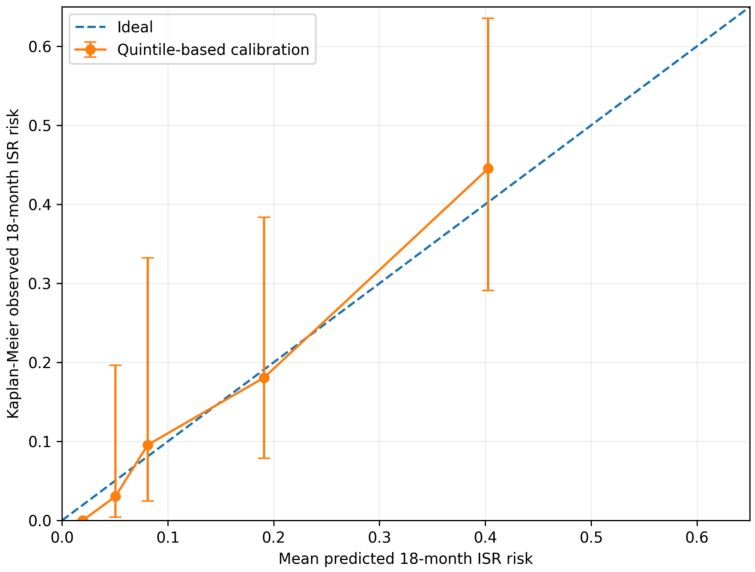


Figure 4. Quintile-based calibration of the D-dimer plus thrombus-burden Cox model for 18-month ISR risk.

remained after additional adjustment for residual stenosis and anticoagulation combined with antiplatelet therapy. Diabetes was included in the adjusted model but was not independently associated with ISR (adjusted HR=0.531, 95% CI: 0.243-1.165, P=0.114). SII and fibrinogen were associated with ISR in univariable analyses, but residual diagnostics suggested time-varying effects, so they were not interpreted as constant adjusted hazard ratios. These results support a thrombo-inflammatory mechanism but do not establish causality [3-7].

SII reflects neutrophil-mediated inflammation, platelet activity, and relative lymphocyte suppression. Prior lower-extremity studies have reported associations between SII and restenosis or adverse outcomes [13-15]. In the present dataset, SII was associated with ISR in univariable analysis, but Schoenfeld residual diagnostics suggested that its effect was not constant over follow-up. It was therefore not retained in the final proportional-hazards model. This finding does not make SII uninformative; rather, it indicates that larger studies with prespecified time-varying effects are needed before a constant adjusted HR can be interpreted [10-15].

D-dimer remained independently associated with earlier ISR, consistent with activation of coagulation and fibrinolysis in peripheral vascular disease [20, 21]. Fibrinogen showed a univariable association, but its effect was not adequately represented by a constant proportional hazard in this dataset. A high thrombus burden may disturb local flow, increase platelet-leukocyte adhesion, prolong endothelial exposure to fibrin-rich material, and delay endothelial recovery. These mechanisms provide a plausible link between systemic coagulation activation and the local substrate for neointimal growth, but they remain mechanistic interpretations rather than direct measurements in this study [21, 22].

The combined-marker analysis still requires cautious interpretation. Adding thrombus burden to D-dimer increased the apparent C-index from 0.780 to 0.797 and the optimism-corrected C-index from 0.780 to 0.793, a corrected increment of only 0.013. The corrected 18-month Brier score improved only modestly from 0.121 to 0.118. Calibration across quintiles was broadly concordant but imprecise, particularly in the lower-risk groups. SII was not included in this constant-hazard performance comparison because it did not satisfy the proportional-hazards assumption. Thus, thrombus burden contributed limited incremental performance rather than a large clinical gain. Bootstrap correction reduces but does not eliminate overfitting, and the model should not guide treatment or surveillance intensity without external validation [4, 23].

The direction of association for high thrombus burden was similar in arterial and venous subgroups, but confidence intervals were wide. Additional limitations include the single-center retrospective design, mixing arterial and venous stent populations, exclusion of 20 patients without evaluable postoperative imaging, lack of a baseline comparison between excluded and included patients, and possible residual confounding. The analysis dataset retained month-level follow-up intervals rather than exact calendar dates and did not retain a uniform administrative censoring date; time-to-event estimates may therefore be affected by interval measurement. Under the imaging-based definition, complete stent occlusion within the stented segment was classified as ISR rather than a separate endpoint, and target-lesion revascularization was not analyzed as an independent study outcome. Recurrent thrombosis was recorded as a separate follow-up event and did not determine ISR classification. Thrombus burden was graded semi-quantitatively without predefined quantitative length or luminal-filling thresholds. Although two specialists reviewed the images independently, their separate ratings were not preserved, preventing retrospective calculation of interobserver agreement. SII and fibrinogen showed evidence of non-proportional effects, and their time-varying associations could not be characterized reliably with only 45 events. The combined marker model was internally validated by bootstrap and assessed for 18-month calibration, but no external validation was available. Multicenter prospective studies should record exact imaging and event dates, use standardized quantitative thrombus measurements, retain separate reader ratings, and externally validate time-to-event models in arterial and venous cohorts separately.

Conclusion

Higher D-dimer and high thrombus burden were independently associated with earlier ISR after lower-extremity arterial or iliac venous stenting. The associations remained after additional adjustment for residual stenosis and antithrombotic regimen. SII and fibrinogen showed univariable associations but could not be represented by constant adjusted hazard ratios. Adding thrombus burden to D-dimer produced only a small optimism-corrected improvement in discrimination. External validation is required before clinical use.

Disclosure of conflict of interest

None.

Address correspondence to: Yingming Xu, Department of Vascular Surgery, Xingyi People's Hospital, No. 1, Yingxiong Road, Huangcao Street, Xingyi 562400, Guizhou, China. Tel: +86-0859-3225970; E-mail: xym1559@163.com

References

[1] Gornik HL, Aronow HD, Goodney PP, Arya S, Brewster LP, Byrd L, Chandra V, Drachman DE, Eaves JM, Ehrman JK, Evans JN, Getchius TSD, Gutiérrez JA, Hawkins BM, Hess CN, Ho KJ, Jones WS, Kim ESH, Kinlay S, Kirksey L, Kohlman-Trigoboff D, Long CA, Pollak AW, Sabri SS, Sadwin LB, Secemsky EA, Serhal M, Shishehbor MH, Treat-Jacobson D and Wilkins LR; Peer Review Committee Members. 2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS guideline for the management of lower extremity peripheral artery disease: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. Circulation 2024; 149: e1313-e1410.

[2] Bates KJ, Moore MM and Cibotti-Sun M. 2024 lower extremity peripheral artery disease guideline-at-a-glance. J Am Coll Cardiol 2024; 83: 2605-2609.

[3] El Khoury R, Asha A, Bystrom PV, Weiss R, Jacobs CE and Schwartz LB. In-stent restenosis. J Cardiovasc Surg (Torino) 2024; 65: 439-453.

[4] Chen J, Tang Y, Shen Z, Wang W, Hou J, Li J, Chen B, Mei Y, Liu S, Zhang L and Lu S. Predicting and analyzing restenosis risk after endovascular treatment in lower extremity arterial disease: development and assessment of a predictive nomogram. J Endovasc Ther 2024; 31: 1140-1149.
[5] Majeed GM, Lodhia K, Carter J, Kingdon J, Morris RI, Gwozdz A, Saratzis A and Saha P. A systematic review and meta-analysis of 12-month patency after intervention for iliofemoral obstruction using dedicated or non-dedicated venous stents. J Endovasc Ther 2022; 29: 478-492.
[6] Zhang L, Jiang C, Chen Z, Song W, Zhao Y and Li F. Three-year outcomes, risk factors for restenosis after stenting for DVT combined with iliac vein compression syndrome. Clin Appl Thromb Hemost 2024; 30: 107602962412-83821.
[7] Kim MS, Park HS, Hong HP, Hyun D, Cho SK, Park KB, Shin SW, Choo SW and Do YS. Risk factors for stent occlusion after catheter-directed thrombolysis and iliac vein stenting in the treatment of May-Thurner syndrome with iliofemoral deep vein thrombosis: a retrospective cohort study. Quant Imaging Med Surg 2022; 12: 5420-5432.
[8] Dinc R. A review of the current state in neointimal hyperplasia development following endovascular intervention and minor emphasis on new horizons in immunotherapy. Transl Clin Pharmacol 2023; 31: 191-201.
[9] Donisan T, Madanat L, Balanescu DV, Mertens A and Dixon S. Drug-eluting stent restenosis: modern approach to a classic challenge. Curr Cardiol Rev 2023; 19: e030123212355.
[10] Kurniawan RB, Siahaan PP, Saputra PB, Arnindita JN, Savitri CG, Faizah NN, Andira LH, D'Oria M, Eko Putranto JN and Alkaff FF. Neutrophil-to-lymphocyte ratio as a prognostic biomarker in patients with peripheral artery disease: a systematic review and meta-analysis. Vasc Med 2024; 29: 687-699.
[11] Onofrei V, Crișan A, Adam CA, Marcu DTM, Haba MȘC, Tribus LC, Ceasovschih A, Eșanu IM, Petroaie AD, Crișan-Dabija R, Leon-Constantin MM, Cumpăt C and Mitu F. The role played by novel inflammatory markers in assessment of peripheral artery disease. Medicina (Kaunas) 2023; 59: 1557.
[12] Song Y, Zhao Y, Shu Y, Zhang L, Cheng W, Wang L, Shu M, Xue B, Wang R, Feng Z, Yin Y, Yu F and Jin S. Integrating the neutrophil-to-high-density lipoprotein ratio with systemic inflammation response index enhances prediction of peripheral arterial disease in type 2 diabetes mellitus patients: a cross-sectional study. Front Endocrinol (Lausanne) 2023; 14: 1100453.
[13] Tian SY. Systemic immune-inflammation index predicts restenosis after interventions for lower extremity arteriosclerosis obliterans. Heart Surg Forum 2023; 26: E225-E233.
[14] Erdoğan O, Erdoğan T, Panç C, Taşbulak Ö, Yalçın AA and Ertürk M. The aggregate index of systemic inflammation: a novel inflammatory marker for predicting restenosis risk in superficial femoral artery lesions after endovascular treatment. Ann Vasc Surg 2025; 120: 260-269.
[15] Aktemur T, Demirci G, Tasbulak O, Kahraman S, Avci Y, Celik O, Yalcin AA and Erturk M. A simple predictor for long-term mortality after percutaneous iliac artery intervention: systemic immune inflammatory index. Ann Vasc Surg 2023; 96: 276-283.
[16] Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ and Egger M; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Ann Intern Med 2007; 147: W163-W194.
[17] Ziegler L, Hedin U and Gottsäter A. Circulating biomarkers in lower extremity artery disease. Eur Cardiol 2022; 17: e09.
[18] Canonico ME, Piccolo R, Avvedimento M, Leone A, Esposito S, Franzone A, Giugliano G, Gargiulo G, Hess CN, Berkowitz SD, Hsia J, Cirillo P, Esposito G and Bonaca MP. Antithrombotic therapy in peripheral artery disease: current evidence and future directions. J Cardiovasc Dev Dis 2023; 10: 164.
[19] Gupta R, Majumdar M, Imran R and Yi J. A comprehensive review on antithrombotic therapy for peripheral artery disease. Semin Vasc Surg 2022; 35: 124-131.
[20] Arfan S, Zamzam A, Syed MH, Jain S, Jahanpour N, Abdin R and Qadura M. The clinical utility of D-Dimer and prothrombin fragment (F1+2) for peripheral artery disease: a prospective study. Biomedicines 2022; 10: 878.
[21] Miceli G, Basso MG, Rizzo G, Pintus C and Tuttolomondo A. The role of the coagulation system in peripheral arterial disease: interactions with the arterial wall and its vascular microenvironment and implications for rational therapies. Int J Mol Sci 2022; 23: 14914.
[22] Condello F, Spaccarotella C, Sorrentino S, Indolfi C, Stefanini GG and Polimeni A. Stent thrombosis and restenosis with contemporary drug-eluting stents: predictors and current evidence. J Clin Med 2023; 12: 1238.
[23] Xiang S, Lu K, Yu Z, Jin T and Wang X. Inflammatory biomarker-based risk prediction model for endovascular reconstruction in acute lower limb ischemia: a multicenter development and validation study. Ann Vasc Surg 2025; 120: 331-344.