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Predictive Scoring Model for In-Stent Restenosis Risk in Coronary Artery Disease Patients

Authors' Contribution:

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF Pan Wang
ABCDE Juan Xu

Department of Internal Medicine, Peking University Shougang Hospital,
Beijing, PR China

Corresponding Author: Pan Wang, e-mail: WangPan1063@outlook.com

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Background: In-stent restenosis (ISR) after coronary stent implantation is a significant clinical challenge in patients with coronary artery disease (CAD). In this study we identified independent risk factors for ISR and developed a predictive scoring model based on these factors.

Material/Methods: We conducted a retrospective study of 256 CAD patients who underwent percutaneous coronary intervention (PCI) from January 2017 to December 2018. Based on follow-up angiography, patients were classified into ISR and non-ISR groups. Logistic regression analysis was used to identify independent predictors, and an ISR scoring model was developed. Receiver operating characteristic (ROC) curve analysis assessed predictive performance.

Results: Compared to the non-ISR group, the ISR group had significantly higher levels of LDL-C, D-dimer, HbA1c, and uric acid (all $P < 0.01$), along with higher rates of post-procedural smoking, poor blood pressure control, and family history of CAD. Logistic regression analysis identified elevated LDL-C (OR: 5.074), D-dimer (OR: 3.381), HbA1c (OR: 5.322), post-procedural smoking (OR: 4.364), and poor blood pressure control (OR: 5.168) as independent risk factors (all $P < 0.05$). LDL-C showed the highest predictive value (AUC: 0.9289). The ISR scoring model achieved an AUC of 0.8643, with 85.8% sensitivity and 73.9% specificity at a cut-off of 3.0 points.

Conclusions: Elevated LDL-C, D-dimer, HbA1c, post-procedural smoking, poor blood pressure control, and a family history of CAD were independent risk factors for ISR. The ISR scoring model provides a practical tool for predicting ISR risk and guiding clinical management to improve outcomes in patients undergoing PCI.

Keywords: **Coronary Artery Disease • Logistic Models • Percutaneous Coronary Intervention • Predictive Value of Tests • Risk Factors**

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Introduction

Coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality worldwide. It is characterized by the narrowing or blockage of the coronary arteries, which supply oxygen-rich blood to the heart muscle. This condition is primarily caused by the buildup of atherosclerotic plaques within the arterial walls, leading to reduced blood flow and, subsequently, to ischemia of the heart tissue [1,2]. CAD manifests in various forms, ranging from stable angina to acute coronary syndromes, including myocardial infarction. Given the high prevalence of CAD and its significant impact on public health, it is imperative to understand the underlying mechanisms and effective treatment strategies to manage this disease. One of the most widely used treatments for CAD is percutaneous coronary intervention (PCI), commonly involving placement of a stent. Stents are small, tube-like devices made of metal or polymer, which are inserted into the narrowed coronary artery to keep it open, thus restoring adequate blood flow [3,4]. The use of stents has revolutionized the management of CAD by reducing the need for more invasive procedures like coronary artery bypass grafting (CABG). The 2 main types of stents used are bare-metal stents (BMS) and drug-eluting stents (DES), with the latter being more effective in reducing the rate of restenosis due to the slow release of antiproliferative drugs [5,6].

Despite advances in stent technology, many patients undergoing stent implantation experience in-stent restenosis (ISR). ISR is defined as re-narrowing of the stented segment of the coronary artery, typically occurring within 3 to 12 months after implantation. This re-narrowing is primarily due to neointimal hyperplasia, a process involving the proliferation and migration of vascular smooth muscle cells, along with deposition of extracellular matrix within the stent [7,8]. ISR not only compromises the initial therapeutic success of stent implantation but also poses a risk for recurrent symptoms of angina, the need for repeat revascularization, and, in severe cases, myocardial infarction. Understanding the risk factors associated with ISR is crucial for development of targeted strategies to prevent its occurrence and to improve patient outcomes. Clinical, procedural, and biological factors have been identified as contributors to ISR [9,10]. Clinical factors include patient-related characteristics such as diabetes mellitus, hypertension, dyslipidemia, and smoking, which are known to promote atherosclerosis and adversely affect vascular healing [11-13]. Procedural factors relate to the characteristics of the stent and the technique of implantation, including stent length, diameter, and deployment pressure. Biological factors involve genetic predisposition, inflammatory responses, and endothelial dysfunction, all of which can influence the neointimal proliferation process.

Our study fills a gap in the specific identification and integration of risk factors such as LDL-C, D-dimer, and HbA1c, extending the findings of studies like Song et al that focused on broader cardiovascular events [14]. While inflammation is a well-established mechanism in ISR, the genetic basis, particularly related to eNOS and other markers, remains under-explored, presenting a gap in current research that our study points to for further investigation [15]. The hypothesis of this study was that specific clinical, biochemical, and procedural risk factors, such as elevated LDL-C, D-dimer, and HbA1c, contribute significantly to the development of ISR in patients with coronary artery disease, and that a predictive scoring model based on these factors could improve risk stratification and guide clinical management. We sought to identify novel risk factors and to validate existing risk factors contributing to ISR following coronary stent implantation in patients with coronary artery disease. By elucidating these risk factors, we seek to inform clinical practice, guiding the development of preventive and therapeutic measures that can minimize the incidence of ISR, ultimately improving the long-term outcomes of patients with CAD undergoing stent implantation.

Material and Methods

Study Design

A comprehensive retrospective study was conducted at our hospital to assess the risk factors associated with ISR after coronary stent implantation in patients with CAD. The study included patients treated between January 2017 and December 2018. We included 256 patients who had undergone at least 1 coronary stent implantation at our institution and were subsequently readmitted for coronary angiography within 5 years after the intervention. During the follow-up angiography, patients were categorized into 2 groups based on the degree of luminal loss: those with luminal loss $\geq 50\%$ within the stented segment or within 5 mm of either stent edge were classified into the ISR group, while the remaining patients were assigned to the non-ISR group. The study's design, objectives, and protocols were aligned with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [16]. Informed consent was obtained from all subjects and/or their legal guardian(s), and verbal confirmation for the use of their clinical data was obtained via telephone. The study protocols, including methodology and objectives, were rigorously reviewed and approved by our hospital's ethics committee (2024-KY-SB-219), adhering strictly to relevant guidelines and the Declaration of Helsinki. All methods were conducted with the utmost confidentiality, ensuring participant privacy by anonymizing data before analysis.

Inclusion and Exclusion Criteria

Inclusion Criteria

1. Diagnosed with CAD who underwent at least 1 successful PCI with stent implantation at our hospital.
2. Readmitted for follow-up coronary angiography within 5 years after the initial stent implantation.
3. Complete clinical, angiographic, and procedural data available for analysis.
4. Adhered to regular antiplatelet therapy after PCI, as per standard medical guidelines.

Exclusion Criteria

1. Incomplete or missing clinical or angiographic data that could impact the analysis.
2. History of coronary artery bypass graft (CABG) surgery prior to or during the study period.
3. Severe comorbidities, such as advanced malignancies, chronic renal failure requiring dialysis, or severe hepatic dysfunction, which could influence the outcomes of stent implantation or follow-up assessments.
4. Lost to follow-up or did not undergo repeat coronary angiography within the specified 5-year period [17,18].

Data Collection and Variable Definitions

The data collection process encompassed a wide range of demographic, clinical, biochemical, and procedural variables, each playing a critical role in evaluating risk factors for ISR and long-term outcomes after coronary stent implantation.

Demographic variables included essential patient identifiers such as name, age, sex, and body weight. These basic demographic characteristics were collected to ensure a comprehensive understanding of the patient population and to account for potential baseline differences between groups.

Clinical variables provided insight into patient history and comorbid conditions that can contribute to ISR. These included the presence or absence of hypertension, as well as the degree of blood pressure control, with optimal control defined as maintaining values below 140/90 mmHg. Additionally, a history of diabetes mellitus, family history of coronary artery disease, and smoking status were documented. Smoking data were particularly detailed, recording both pre-procedure smoking habits and whether the patient continued to smoke in the 5 years after stent implantation.

Biochemical variables were gathered through fasting blood samples collected before the second coronary angiography. These laboratory values included low-density lipoprotein cholesterol

(LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), D-dimer levels, uric acid, total bilirubin, and glycated hemoglobin (HbA1c), which collectively provided a comprehensive picture of the patient's metabolic and cardiovascular health. Additionally, renal function was assessed through the estimated glomerular filtration rate (eGFR), which is a key indicator of kidney health and a potential factor influencing ISR outcomes.

Procedural variables focused on the characteristics of the coronary stents themselves. Data were collected on the duration of stent placement, whether the stents were placed in tandem, the use of bifurcation techniques, the total number of stents implanted, the cumulative stent length, and the minimum stent diameter. These procedural details are crucial, as stent configuration and placement technique can significantly impact the likelihood of restenosis.

Statistical Analysis

Statistical analysis was performed using SPSS version 27.0. Continuous variables with normal distribution are expressed as mean±standard deviation (±SD), and comparisons between groups were made using the independent-samples *t* test. For continuous variables that did not follow a normal distribution, data are presented as median and interquartile range (M [P25, P75]), and the Wilcoxon rank-sum test was used for between-group comparisons. Categorical variables are presented as frequencies and percentages (n [%]), and group comparisons were conducted using the chi-square (χ^2) test. Logistic regression analysis was used to assess the independent risk factors for ISR. Additionally, receiver operating characteristic (ROC) curves were generated to calculate the area under the curve (AUC) for evaluating the predictive ability of risk factors for ISR and revascularization. To validate the ISR scoring model, a 10-fold cross-validation model was performed, partitioning the dataset into 10 subsets. Nine subsets were used for training, with the remaining subset used for validation, repeated 10 times, and the average AUC, sensitivity, and specificity were calculated. All *P* values were two-sided, and a significance level of $P \leq 0.05$ was considered statistically significant.

Results

Comparative Analysis of Risk Factors for In-Stent Restenosis in Coronary Artery Disease Patients

The comparative analysis of risk factors between the non-ISR and ISR groups revealed several significant differences. Among the biochemical variables, patients in the ISR group had higher levels of LDL-C (2.7 ± 0.8 mmol/L vs 2.3 ± 0.6 mmol/L, $P < 0.001$), D-dimer (0.88 [$0.68, 1.15$] $\mu\text{g/L}$ vs 0.58 [$0.25, 0.93$] $\mu\text{g/L}$,

Table 1. Comparative analysis of risk factors for in-stent restenosis in coronary artery disease patients.

Variable	Non-ISR group (n=136)	ISR group (n=120)	Statistics (t/ χ^2 /W)	P value
Minimum stent diameter (mm)	2.8±0.3	2.8±0.3	0.00	1
Tandem stenting n (%)	53 (39%)	47 (39%)	0.01	0.97
Number of stents n	2 (1, 3)	2 (1, 4)	0.28	0.56
eGFR (ml/min/1.73 m ²)	87±21	85±28	0.65	0.52
Body weight (kg)	72±13	71±11	0.69	0.49
Bifurcation stenting n (%)	9 (7%)	12 (10%)	0.97	0.33
HDL-C (mmol/L)	1.14±0.21	1.10±0.25	1.39	0.17
Hypertension n (%)	113 (83%)	106 (88%)	1.42	0.23
Creatinine (μmol/L)	90±26	95±30	1.43	0.15
Total stent length (mm)	52±27	58±33	1.6	0.11
Male n (%)	91 (67%)	89 (74%)	1.61	0.2
Age (years)	72±10	70±9	1.67	0.1
TG (mmol/L)	1.5±0.9	1.7±1.0	1.68	0.09
Total bilirubin (μmol/L)	12±4	13±5	1.78	0.08
Pre-procedural smoking n (%)	78 (57%)	80 (67%)	2.34	0.13
Uric acid (μmol/L)	314 (269, 378)	346 (284, 429)	3.98	<0.01
HbA1c (%)	6.9±1.1	7.5±1.3	4.00	<0.01
LDL-C (mmol/L)	2.3±0.6	2.7±0.8	4.56	<0.001
D-dimer (μg/L)	0.58 (0.25, 0.93)	0.88 (0.68, 1.15)	5.89	<0.001
Post-procedural smoking n (%)	25 (18%)	43 (37%)	9.95	<0.01
Family history of CAD n (%)	33 (24%)	54 (45%)	13.05	<0.001
Diabetes n (%)	60 (44%)	80 (67%)	13.08	<0.001
BP controlled n (%)	131 (96%)	94 (78%)	19.39	<0.001

eGFR – estimated glomerular filtration rate; HDL-C – high-density lipoprotein cholesterol; TG – triglycerides; LDL-C – low-density lipoprotein cholesterol; HbA1c – glycated hemoglobin; CAD – coronary artery disease; BP – blood pressure.

$P<0.001$), and uric acid (346 [284, 429] μmol/L vs 314 [269, 378] μmol/L, $P<0.01$). Additionally, HbA1c was significantly higher in the ISR group (7.5±1.3% vs 6.9±1.1%, $P<0.01$), indicating poorer glycemic control as a potential risk factor for restenosis. Lifestyle factors also showed significant associations with ISR. Post-procedural smoking was substantially more common in the ISR group (37% vs 18%, $P<0.01$), further suggesting the negative impact of continued smoking on vascular outcomes. A family history of CAD was present in a higher proportion of ISR patients (45% vs 24%, $P<0.001$), as was a higher incidence of diabetes (67% vs 44%, $P<0.001$), further underscoring the role of genetic and metabolic factors in restenosis development (Table 1).

Regarding procedural and clinical factors, BP control was significantly less frequent in the ISR group (78% vs 96%, $P<0.001$), emphasizing the importance of hypertension management in preventing ISR. However, other procedural variables, such as stent characteristics – including minimum stent diameter, tandem stenting, total stent length, and the number of stents – did not show statistically significant differences between the 2 groups. Interestingly, several demographic factors, such as age, sex, and body weight, were not significantly associated with ISR risk, and no notable differences in creatinine levels or eGFR were observed between groups, indicating similar renal function (Table 1). In summary, ISR was more likely in patients with elevated LDL-C, D-dimer, uric acid, and HbA1c

Table 2. Logistic regression analysis for risk factors of in-stent restenosis.

Variable	β	Wald χ^2	OR	95% CI	P value
D-dimer	1.119	6.371	3.381	1.255-9.392	<0.05
Family history of CAD	1.091	3.901	2.639	1.007-8.890	<0.05
HbA1c	1.792	10.536	5.322	1.945-14.066	<0.05
LDL-C	1.531	8.828	5.074	1.793-15.741	<0.05
Post-procedural smoking	1.331	5.574	4.364	1.374-13.600	<0.05
Poor blood pressure control	1.518	8.121	5.168	1.386-11.588	<0.05

CAD – coronary artery disease; HbA1c – glycated hemoglobin; LDL-C – low-density lipoprotein cholesterol; BP – blood pressure.

levels, as well as in those with a family history of CAD, diabetes, and poor post-procedural BP control. Smoking, particularly post-procedural, was also a critical risk factor, highlighting the need for stringent lifestyle and metabolic management in patients undergoing coronary stenting.

Logistic Regression Analysis of Risk Factors for In-Stent Restenosis

The logistic regression analysis identified several significant independent risk factors associated with the development of ISR in patients with coronary artery disease (CAD). Elevated levels of D-dimer were strongly associated with ISR, with an odds ratio (OR) of 3.381 (95% CI: 1.255-9.392, $P<0.05$), indicating that increased thrombotic activity may contribute to restenosis. Similarly, patients with a family history of CAD had a significantly higher likelihood of developing ISR, with an OR of 2.639 (95% CI: 1.007-8.890, $P<0.05$). This suggests that genetic predisposition plays a notable role in the pathophysiology of restenosis. Metabolic factors also emerged as critical contributors. Elevated HbA1c levels, a marker of poor glycemic control, were strongly predictive of ISR, with an OR of 5.322 (95% CI: 1.945-14.066, $P<0.05$). Likewise, increased LDL-C levels were associated with a markedly higher risk of ISR (OR: 5.074, 95% CI: 1.793-15.741, $P<0.05$), reinforcing the importance of lipid management in this patient population (Table 2).

Post-procedural smoking was another significant factor, with an OR of 4.364 (95% CI: 1.374-13.600, $P<0.05$), highlighting the detrimental effect of continued smoking on stent patency and vascular healing. Furthermore, inadequate BP control was found to be a strong predictor of ISR, with an OR of 5.168 (95% CI: 1.386-11.588, $P<0.05$). This emphasizes the necessity of maintaining optimal blood pressure to reduce the risk of restenosis following stent implantation (Table 2). In conclusion, our logistic regression analysis results show the multifactorial nature of ISR, with thrombotic, genetic, metabolic, and lifestyle factors all contributing significantly to its occurrence. Effective management of these risk factors, particularly

through strict control of blood glucose, lipid levels, and blood pressure, as well as smoking cessation, is crucial in minimizing the risk of ISR in patients with CAD.

Predictive Value of Risk Factors for ISR Using ROC Curve Analysis

The predictive value of various factors for ISR following PCI was assessed using ROC curve analysis. The results demonstrated that several clinical and biochemical factors exhibited significant predictive capabilities. LDL-C had the highest predictive value for ISR, with an AUC of 0.9289 ($P<0.01$). The optimal cut-off value for LDL-C was 2.36 mmol/L, with a sensitivity of 86.9% and a specificity of 95.6%, highlighting its strong diagnostic accuracy in predicting ISR. D-dimer, a marker of thrombotic activity, also showed a significant association with ISR risk, with an AUC of 0.7364 ($P<0.01$). The optimal threshold for D-dimer was 0.50 $\mu\text{g/L}$, yielding a sensitivity of 62.8% and a specificity of 86.2%. Although the sensitivity was moderate, the specificity indicates that D-dimer remains a valuable marker for excluding ISR in certain cases. Glycemic control, as measured by HbA1c, was also predictive of ISR, with an AUC of 0.7439 ($P<0.01$). The best cut-off value for HbA1c was 7.43%, with a sensitivity of 56.8% and a specificity of 97.6%, emphasizing that poor glycemic control is an important predictor of restenosis, despite its relatively lower sensitivity (Figure 1).

Post-procedural smoking was another significant factor, with an AUC of 0.7279 ($P<0.01$), a sensitivity of 67.3%, and a specificity of 81.1%. This reinforces the role of smoking in promoting ISR and suggests that smoking cessation should be a key component of post-PCI management to reduce the risk of restenosis. Although family history of CAD was evaluated, its predictive value was not statistically significant (AUC=0.5821, $P=0.068$), indicating that while genetic predisposition can contribute to ISR, it is not a robust standalone predictor. Blood pressure control was found to be a reliable predictor of ISR, with an AUC of 0.7719 ($P<0.01$). The sensitivity and specificity were 77.6% and 86.5%, respectively, demonstrating that

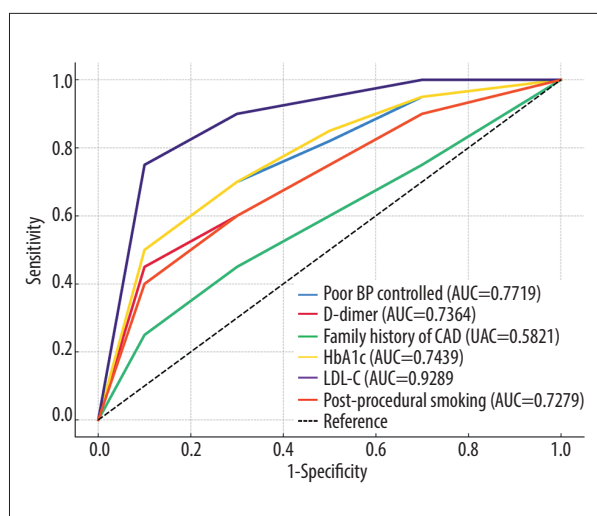


Figure 1. ROC curve analysis of the predictive value of risk factors for in-stent restenosis.

effective management of blood pressure is essential for minimizing ISR risk (**Figure 1**). In summary, LDL-C, D-dimer, HbA1c, post-procedural smoking, and blood pressure control emerged as significant predictive factors for ISR following PCI. These findings underscore the importance of addressing modifiable risk factors, such as lipid levels, glycemic control, and smoking status, in the post-PCI period to reduce the incidence of ISR.

Development of the ISR Scoring Model

A scoring model for predicting ISR was constructed based on the independent risk factors identified through logistic regression analysis. The model was developed by selecting the smallest regression coefficient (1.091) as the reference point. The regression coefficients of the other factors were divided by this value and rounded to assign a score for each factor. The scoring method assigned points as follows: patients with HbA1c levels $\geq 7.43\%$ were assigned 2 points; LDL-C > 2.36 mmol/L was also assigned 2 points; D-dimer levels > 0.50 $\mu\text{g/L}$ were assigned 1 point. Additionally, both a family history of CAD and post-procedural smoking were each assigned 1 point, while inadequate blood pressure control was also assigned 1 point. This generated an ISR score ranging from 0 to 7 points. To evaluate the predictive value of the ISR scoring model, ROC curve analysis was performed. The results indicated that the AUC for the ISR score was 0.8643 ($P < 0.01$), demonstrating a high predictive value for the occurrence of ISR. The optimal cut-off value was 3.0 points, with a corresponding Youden index of 0.568, sensitivity of 85.8%, and specificity of 73.9% (**Figure 2**). These findings suggest that the ISR scoring model, incorporating factors such as elevated HbA1c, LDL-C, D-dimer, family history of CAD, and post-procedural smoking, provides an effective and clinically useful tool for predicting ISR risk in patients undergoing PCI.

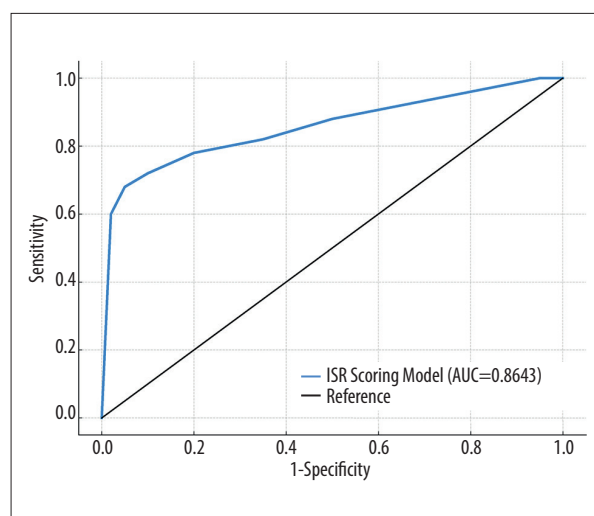


Figure 2. ROC curve analysis of the predictive value of the ISR scoring model.

Cross-Validation Analysis

A 10-fold cross-validation was conducted to further validate the predictive performance of the ISR model. The analysis yielded an average AUC of 0.86, demonstrating robust ability to discriminate between ISR and non-ISR patients. The model achieved an average sensitivity of 85.8% and a specificity of 73.9%, indicating its reliable performance in identifying true ISR cases and excluding non-ISR cases, respectively. These cross-validation results are consistent with the initial ROC analyses reported (eg, LDL-C AUC=0.9289; ISR scoring model AUC=0.8643), thereby confirming the stability and robustness of the model across different data splits. In summary, the 10-fold cross-validation substantiates that the ISR predictive model had high accuracy and reliability for predicting in-stent restenosis in the current patient cohort.

Post Hoc Power Analysis

Using a weighted post hoc power analysis, the overall power to detect significant differences in ISR risk factors was estimated to be 98%. For the multivariable logistic regression model – incorporating key predictors such as LDL-C, HbA1c, D-dimer, post-procedural smoking, and blood pressure control – the combined weighted power was estimated at approximately 95%. These values exceed the conventional threshold of 80%, thereby confirming that the study is adequately powered to support the observed associations.

Discussion

ISR remains a significant complication following coronary stent implantation in patients with CAD. Despite advancements in

stent technology, including the development of drug-eluting stents, ISR continues to occur, impacting patient outcomes and increasing the need for repeat revascularization procedures. The pathophysiology of ISR is complex, involving multiple factors such as neointimal hyperplasia, inflammation, and thrombosis, all of which contribute to the re-narrowing of the artery within the stented segment [19,20]. This study provides a comprehensive analysis of the risk factors associated with ISR in patients with CAD after PCI and stent implantation. The findings from our comparative analysis, logistic regression, and ROC curve analysis collectively highlight the multifactorial nature of ISR, with thrombotic, metabolic, genetic, and lifestyle factors contributing significantly to its development. For example, elevated LDL-C promotes foam cell formation and vascular smooth muscle proliferation, while high HbA1c enhances inflammation and endothelial dysfunction – both of which accelerate neointimal growth. Elevated D-dimer reflects prothrombotic activity that can lead to microthrombi and delayed healing. Smoking and poor blood pressure control further impair endothelial repair and promote oxidative stress, all of which are pathophysiologically linked to ISR. Furthermore, we developed an ISR scoring model that can be applied clinically to predict ISR risk, offering a practical tool for patient management. To translate risk identification into clinical practice, our findings support targeted interventions – such as intensive lipid and glycemic control, optimized antithrombotic therapy, smoking cessation, and strict blood pressure management – guided by individualized risk stratification through the ISR scoring model.

One of the most significant findings in our study was the strong predictive value of elevated LDL-C levels in the development of ISR. Our results demonstrated that patients with LDL-C levels >2.36 mmol/L had a markedly higher risk of ISR, with an odds ratio of 5.074 and an AUC of 0.9289. This supports the notion that lipid management plays a crucial role in maintaining long-term stent patency. The mechanistic basis for this association may lie in the role of LDL-C in promoting atherosclerosis and inflammatory processes, which can accelerate neointimal hyperplasia and restenosis within the stented segment. Elevated LDL-C increases the risk of plaque instability and endothelial dysfunction, both of which are key contributors to ISR [21,22]. The high specificity and sensitivity of LDL-C as a predictor of ISR underscore the importance of aggressive lipid-lowering therapy, particularly with statins, in reducing restenosis risk in post-PCI patients.

Thrombotic activity, as measured by D-dimer levels, also emerged as a significant independent risk factor for ISR. Patients with elevated D-dimer levels (>0.50 $\mu\text{g/L}$) exhibited a 3.381-fold increase in ISR risk, and the ROC analysis revealed an AUC of 0.7364. D-dimer is a marker of fibrin degradation and reflects ongoing thrombus formation and breakdown, suggesting that persistent thrombotic activity post-stenting can contribute

to ISR development. This finding aligns with the established role of thrombosis in stent failure, where thrombus formation can impede endothelialization and promote smooth muscle cell proliferation, leading to neointimal hyperplasia [23,24]. Antithrombotic therapy, including dual antiplatelet therapy, is critical in mitigating this risk, and our findings suggest that patients with elevated D-dimer levels may benefit from closer monitoring and prolonged antithrombotic regimens. Glycemic control, as measured by HbA1c, was another important factor associated with ISR. Elevated HbA1c levels ($\geq 7.43\%$) were predictive of ISR, with an odds ratio of 5.322 and an AUC of 0.7439. This association shows the role of diabetes and hyperglycemia in restenosis development [25,26]. Hyperglycemia promotes endothelial dysfunction, increases oxidative stress, and exacerbates inflammatory processes, all of which contribute to the pathophysiology of ISR. Moreover, high glucose levels are associated with abnormal vascular smooth muscle cell proliferation and impaired endothelial healing, which can lead to accelerated neointimal formation. These findings underscore the need for stringent glycemic control in diabetic patients undergoing PCI to reduce ISR risk. Glycemic targets should be achieved through lifestyle modifications, oral hypoglycemic agents, and insulin therapy, as appropriate [27].

Lifestyle factors, particularly post-procedural smoking, also played a significant role in ISR risk. The logistic regression analysis revealed that continued smoking after PCI increased the likelihood of ISR by 4.364 times, and the ROC analysis showed an AUC of 0.7279. Smoking exacerbates vascular inflammation, promotes endothelial dysfunction, and increases platelet aggregation, all of which contribute to stent failure and restenosis. Smoking cessation interventions should be a cornerstone of post-PCI care, as quitting smoking can significantly reduce ISR risk and improve overall cardiovascular outcomes. BP control was another critical factor in ISR prevention. Inadequate BP control was associated with a significantly higher risk of ISR, with an odds ratio of 5.168 and an AUC of 0.7719. Hypertension contributes to ISR by increasing arterial wall stress, promoting vascular remodeling, and exacerbating inflammation within the stented segment [28,29]. Maintaining optimal BP control after PCI is essential in preventing restenosis, and patients should be closely monitored for adherence to antihypertensive therapy and lifestyle modifications aimed at lowering BP. Our ISR scoring model, which incorporates key risk factors such as HbA1c, LDL-C, D-dimer, family history of CAD, and post-procedural smoking, proved to be an effective predictive tool, with an AUC of 0.8643. This model provides clinicians with a practical method for stratifying patients according to their ISR risk and tailoring preventive strategies accordingly. The high sensitivity and specificity of the model suggest that it can be reliably used to identify high-risk patients who may benefit from more aggressive risk factor management [30,31].

In this study, we first employed univariate statistical tests (eg, *t* tests, chi-square tests) to identify significant differences between the ISR and non-ISR groups. However, these tests do not account for potential confounding factors. In contrast, logistic regression allowed us to control for multiple confounders simultaneously, identifying independent risk factors for ISR. While some variables were significant in univariate analyses, logistic regression provides adjusted odds ratios (ORs) that reflect the unique contribution of each factor, accounting for interactions with other variables. The ISR scoring model integrates these independent risk factors into a single, clinically applicable predictive tool. By incorporating key variables such as HbA1c, LDL-C, D-dimer, post-procedural smoking, and blood pressure control, the model improves risk stratification. Importantly, it offers incremental predictive value over individual risk factors by providing a more precise, integrated approach to patient assessment. This consolidated score enhances ISR risk prediction compared to evaluating individual factors separately and supports more informed clinical decision-making and personalized patient management. Thus, the ISR scoring model is a meaningful advancement over traditional risk assessments, serving as a valuable addition to clinical practice for predicting and managing ISR risk.

This study has several limitations. First, the retrospective nature of the analysis can introduce selection bias and limit the ability to establish causal relationships between risk factors and ISR. Additionally, the study was conducted at a single center, potentially reducing the generalizability of the findings to broader populations with diverse demographics and clinical characteristics. Given its retrospective, single-center design, the findings should be interpreted with caution, as selection bias and limited external validity may affect the generalizability of the

ISR scoring model. Furthermore, certain risk factors such as genetic predisposition were not comprehensively explored, limiting our understanding of their role in ISR development. Future research should focus on conducting multicenter, prospective studies with larger, more diverse cohorts to validate the findings and to externally validate the ISR scoring model and confirm its clinical applicability. Investigating the impact of emerging biomarkers and genetic factors on ISR risk could provide deeper insights into its pathophysiology. Moreover, exploring novel therapeutic strategies, including more targeted pharmacological interventions and advancements in stent technology, may further improve treatment of patients at high risk of ISR.

Conclusions

This study identified elevated LDL-C, D-dimer, HbA1c, post-procedural smoking, poor blood pressure control, and a family history of CAD as significant risk factors for ISR after coronary stent implantation. These findings underscore the importance of comprehensive management strategies targeting metabolic, thrombotic, and lifestyle factors to help mitigate the risk of ISR and improve long-term outcomes in patients with coronary artery disease. The ISR scoring model developed in this study can assist clinicians in better stratifying patients, allowing for more personalized treatment approaches and tailored follow-up care.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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