This article can be cited as: Azadmanesh B, Seyyed Mohammadzad M, Shahabi Rabori V, et al. In-stent restenosis in patients with acute coronary syndrome: a case-control analysis of risk factors following drug-eluting stent implantation. Cardiovasc Biomed J. 2025; 5(2): 33-42.

Original Article

In-stent restenosis in patients with acute coronary syndrome: a case-control analysis of risk factors following drug-eluting stent implantation

Bahareh Azadmanesh [1], ***MirHossein Seyyed Mohammadzad*** [1], ***Venus Shahabi Rabori*** [2], ***Negar Jafari*** [1*]

[1] Department of Cardiology, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran
[2] Department of Cardiology, Derriford Hospital, Plymouth NHS Trust, UK

*** Corresponding Author:**
Address: Urmia, West Azerbaijan, Urmia, Shahid Asghari Street, 2nd Sixteen-Meter Street, Elaheh Building, Urmia, Iran. **Postal code:** 5718748983; **Tel:** +98 09144235519; **Email:** jnegar94@gmail.com

Article Information:
Received: 04 Nov 2025; Revised: 29 Nov 2025; Accepted: 25 Dec 2025 DOI: 10.18502/cbj.v5i2.21134

Abstract

Objectives: In-stent restenosis (ISR) remains a significant complication following percutaneous coronary intervention (PCI) with drug-eluting stents (DES), contributing to recurrent cardiovascular events and increased healthcare burden. To assess the occurrence of ISR and identify related risk factors in patients receiving PCI at a tertiary cardiac facility in northwestern Iran.

Methods: The present study is a case-control study involving 593 patients who underwent repeat coronary angiography after prior DES placement between 2020 and 2024 at Seyed ol-Shohadai Hospital in Urmia. The samples consisted of patients in two categories: ISR-positive (n = 209, 35.2%) and ISR-negative (n = 384, 64.8%). The researchers analyzed demographic information, cardiovascular risk factors, laboratory results, and procedural variables between the groups using independent t-tests and chi-square tests.

Results: ISR-positive patients were significantly older (67.61±8.71 vs. 60.13±8.01 years, P=0.03) with a higher prevalence of hypertension (55% vs. 41.4%, P=0.002). Positive C-reactive protein (CRP) was more frequent in ISR patients (63.2% vs. 14.1%, P<0.001). Mean triglyceride (118.48±81.86 vs. 100.95±60.73 mg/dL, P=0.003), LDL-cholesterol (LDL-C) (66.77±30.17 vs. 57.01±19.25 mg/dL, P<0.001), and reduced left ventricular ejection fraction (LVEF) <30% (7.7% vs. 1%, P=0.005) were significantly associated with ISR. Longer intervals between initial and repeat angiography (59.93±38.01 vs. 50.51±32.62 months, P=0.002) and stent length ≥20mm (32.5% vs. 14.3%, P<0.001) increased ISR risk. Everolimus stents showed higher ISR rates compared to sirolimus stents.

Conclusions: Advanced age, hypertension, systemic inflammation, dyslipidemia, impaired ventricular function, longer follow-up intervals, and specific stent characteristics were significantly associated with ISR development in univariate analysis. These findings suggest potential risk factors warranting further investigation through multivariate analysis. Enhanced surveillance and aggressive modification of risk factors in high-risk patients may decrease the incidence of ISR.

Keywords: In-stent restenosis, percutaneous coronary intervention, Drug-eluting stent, cardiovascular risk factors, Coronary artery disease

Introduction

Cardiovascular diseases represent the leading cause of mortality and disability worldwide, accounting for 16% of deaths and ranking as the second contributor to disability-adjusted life years in 2019[1]. In Iran, non-communicable diseases account for 82% of deaths, with cardiovascular conditions making up 43% of this total burden [2]. Ischemic heart disease specifically results in 112.5 deaths per 100,000 population each year, leading to 2,422.66 disability-adjusted life years per 100,000 individuals, with both statistics demonstrating alarming upward trends over the last decade [3]. Percutaneous coronary intervention (PCI) has become the leading revascularization method for coronary artery disease, leading to less invasive options than surgical bypass grafting [4].The introduction of drug-eluting stents (DES) in 2002 significantly lowered restenosis rates compared to bare-metal stents. It led to improving outcomes for patients with acute coronary syndromes (ACS) and stable ischemic heart disease [5, 6]. Nevertheless, despite these advancements, in-stent restenosis (ISR) continues to pose a significant clinical challenge, affecting 3-20% of patients who receive modern drug-eluting stents within 3-12 months after implantation [7, 8]. ISR is angiographically characterized by a diameter stenosis of more than 50% at the site of the stent or within 5-10mm of adjacent vessel segments, resulting from neointimal hyperplasia after stent insertion [9, 10]. The clinical consequences include recurrent angina, repeat revascularization procedures, myocardial infarction, and increased mortality, with associated healthcare costs amounting to 1-4 billion dollars annually in the United States alone[11, 12]. Various studies have identified several predictors of ISR, including patient-specific factors such as diabetes mellitus and renal insufficiency, as well as lesion characteristics (like length and complexity) and procedural variables (such as stent dimensions, deployment pressure, and the number of stents used) [13, 14] Nevertheless, reported findings show considerable heterogeneity across populations and stent generations, necessitating contemporary regional data to optimize risk stratification and preventive measures [15]. Despite Iran's significant burden of cardiovascular disease and the increasing use of coronary interventions, limited published data characterize patterns and determinants of ISR in this population. Previous studies predominantly examined bare-metal stents or first-generation DES, with few studies addressing modern stent technologies in Iranian cohorts [16]. However, regional variations in cardiovascular risk factor prevalence, genetic backgrounds, and healthcare delivery patterns may influence ISR development in ways not captured by international registries. This study addresses these knowledge gaps by analyzing the incidence of ISR and its associated risk factors within a large cohort of patients with ACS undergoing contemporary DES implantation at a tertiary cardiac center in northwestern Iran. Specifically, this investigation aimed to: (1) assess the incidence of ISR following modern DES placement in patients presenting with ACS, and (2) recognize demographic, clinical, laboratory, and procedural factors linked to the development of ISR through univariate comparative analysis to guide targeted preventive interventions that may reduce ISR burden and improve long-term outcomes after PCI.

Materials and Methods

This case-control study included patients who underwent repeat coronary angiography after previous drug-eluting stent implantation at Seyyed ol-Shohadai Hospital, Urmia, Iran, between March 2020 and March 2024. The study obtained ethical approval from the Urmia University of Medical Sciences Research Ethics Committee (approval code: IR: UMSU.REC.1403.146). The study population consisted of patients who presented with acute coronary syndromes and had previously received percutaneous coronary intervention with drug-eluting stent placement. During the four-year study period, a total of 743 patients underwent repeat angiography before stent implantation. After excluding 150 patients due to incomplete procedural records or unavailable prior angiographic data, 593 patients formed the final analytical cohort. Patients were categorized into two groups based on the presence or absence of in-stent restenosis (ISR), as defined by the Academic Research Consortium. [17]:

- **ISR$^+$ (In-Stent Restenosis Positive):** Patients with more than 50% stenosis detected within the stent or within 1–3 mm of the stent margins on coronary angiography.
- **ISR$^-$ (In-Stent Restenosis Negative):** Patients who, following percutaneous coronary intervention (PCI) and stenting, exhibited less than 50% restenosis in or around the stented segment.

We included adult patients aged 18 years or older who had previously undergone drug-eluting stent

implantation for coronary artery disease, presenting with acute coronary syndrome during the study period. All patients underwent repeat coronary angiography. We excluded patients with active severe infectious diseases, confirmed malignancies, or autoimmune disorders. Additionally, we excluded patients with significant hepatic dysfunction, which was defined as alanine aminotransferase or aspartate aminotransferase levels exceeding three times the upper limit of normal. Patients with significant renal dysfunction, an estimated glomerular filtration rate below 30 mL/min/1.73m², were also excluded. Additionally, we ruled out patients for whom baseline angiographic data or procedural records were unavailable, as well as those with documented non-compliance with prescribed dual antiplatelet therapy.

Data Collection

Comprehensive clinical data were extracted from medical records and catheterization laboratory databases. The study aimed to compare patient characteristics, lesion-specific features, stent-related data, and the Interval between index PCI and repeat angiography. The study collected demographic data, including age, sex, and body mass index (BMI), calculated as weight in kg divided by height in m². The identified cardiovascular risk factors included: Hypertension (systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or antihypertensive medication), diabetes mellitus (fasting plasma glucose ≥ 126 mg/dL, HbA1c ≥ 6.5%, or antidiabetic medication), and hyperlipidemia (LDL cholesterol > 100 mg/dL, HDL cholesterol < 40 mg/dL for males and < 50 mg/dL for females, triglycerides > 150 mg/dL, total cholesterol > 200 mg/dL, or lipid-lowering therapy). Additionally, smoking history and alcohol consumption were recorded, along with chronic kidney disease (eGFR < 60 mL/min/1.73m² for ≥ 3 months). Clinical presentation types included unstable angina and myocardial infarction. Left ventricular function was assessed using echocardiography, with ejection fraction categorized as normal (> 50%), mild (40%-50%), moderate (30%-40%), or severe (< 30% Laboratory parameters measured included fasting blood glucose, cholesterol levels, and C-reactive protein (categorized as positive if > 3 mg/L). Troponin was not analyzed, as the ISR diagnosis was just based on angiographic criteria rather than biomarkers. Cardiovascular medications reviewed included aspirin, clopidogrel, and statins, but medication adherence data were inconsistent. The researchers recorded the procedural variables, including intervals between interventions, stent specifications, and target vessel locations. Angiographic analysis was conducted by blinded interventional cardiologists who assessed stenosis severity applying definitions for in-stent restenosis in line with the Academic Research Consortium-2 criteria.

Statistical Analysis

We conducted statistical analyses with SPSS version 26.0 to evaluate the data. The normality of continuous variables was calculated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For normally distributed data, we reported means and standard deviations, comparing groups with independent t-tests. In contrast, non-normally distributed variables were expressed as medians with interquartile ranges and compared using Mann-Whitney U tests. Categorical data were represented as frequencies and percentages, analyzed through chi-square tests or Fisher's exact tests where necessary. For the analysis focusing on ISR-positive versus ISR-negative groups, we employed univariate comparative statistics, utilizing chi-square tests for categorical variable associations with ISR status and t-tests or Mann-Whitney U tests for continuous variables where appropriate. A two-sided P-value of less than 0.05 was deemed statistically significant. Notably, as this study was exploratory, no adjustments were made for multiple comparisons.

Results

Patient Characteristics

Among 593 patients who underwent repeat coronary angiography, 209 (35.2%) demonstrated in-stent restenosis. The cohort was predominantly male (67.1%) with a mean age of 60.67±8.28 years and a mean body mass index of 27.35±3.06 kg/m². Cardiovascular risk factors were prevalent, including hypertension in 274 patients (46.2%), diabetes mellitus in 189 (31.9%), hyperlipidemia in 132 (22.3%), and smoking history in 127 (21.4%). Chronic kidney disease affected 39 patients (6.6%). Regarding clinical presentation, unstable angina was the most common diagnosis (427 patients, 72%), followed by non-ST-elevation myocardial infarction (89 patients, 15%) and ST-elevation myocardial infarction (77 patients, 13%).

Table1. Baseline Characteristics, Clinical Variables, and Laboratory Findings by In-Stent Restenosis Status

Variable	ISR-Positive (n=209)	ISR-Negative (n=384)	P-value
Demographics			
Age (years), mean±SD	67.61±8.71	60.13±8.01	0.03
Male sex, n (%)	140 (67.0)	258 (67.2)	0.50
BMI (kg/m²), mean±SD	28.19±3.68	27.73±2.86	0.09
Cardiovascular Risk Factors			
Hypertension, n (%)	115 (55.0)	159 (41.4)	0.002
Diabetes mellitus, n (%)	62 (29.7)	127 (33.1)	0.40
Hyperlipidemia, n (%)	47 (22.5)	85 (22.1)	0.90
Current smoking, n (%)	50 (23.9)	77 (20.1)	0.30
Alcohol consumption, n (%)	11 (5.3)	15 (3.9)	0.50
Chronic kidney disease, n (%)	14 (6.7)	25 (6.5)	0.90
Clinical Presentation			
Unstable angina, n (%)	126 (60.3)	325 (84.6)	<0.001
NSTEMI, n (%)	32 (15.4)	34 (8.9)	0.02
STEMI, n (%)	52 (24.9)	25 (6.5)	<0.001
LVEF Category			
Normal (>50%), n (%)	89 (42.6)	167 (43.5)	0.80
Mild (40-50%), n (%)	61 (29.2)	150 (39.1)	0.02
Moderate (30-40%), n (%)	43 (20.6)	63 (16.4)	0.20
Severe (<30%), n (%)	16 (7.7)	4 (1.0)	<0.001
Laboratory Parameters			
FBS (mg/dL), mean±SD	109.39±36.38	111.27±41.50	0.50
Total cholesterol (mg/dL), mean±SD	142.20±38.60	137.96±34.66	0.10
Triglycerides (mg/dL), mean±SD	118.48±81.86	100.95±60.73	0.003
LDL-C (mg/dL), mean±SD	77.64±27.68	67.88±24.63	<0.001
HDL-C (mg/dL), mean±SD	50.37±12.24	51.06±10.77	0.40
Creatinine (mg/dL), mean±SD	1.01±0.21	0.99±0.19	0.10
CRP positive, n (%)	155 (74.2)	87 (22.7)	<0.001
Temporal Variable			
Time to repeat angiography (months), mean±SD	59.93±38.01	50.51±32.62	0.002

Abbreviations: ISR, in-stent restenosis; BMI, body mass index; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; LVEF, left ventricular ejection fraction; FBS, fasting blood sugar; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein.

Demographic and Clinical Comparisons

Patients with ISR were older compared to those without restenosis (mean 67.61±8.71 vs. 60.13±8.01 years, P=0.03). In contrast, sex distribution and body mass index were comparable between the two groups (Table 1). The prevalence of hypertension was higher in the ISR group (55.0% vs. 41.4%, P = 0.002). However, other traditional cardiovascular risk factors, including diabetes mellitus, hyperlipidemia, current smoking status, alcohol use, and chronic kidney disease, showed similar rates in both groups (all P>0.05, Table 1). Among 593 patients who underwent repeat coronary angiography, 209 (35.2%) demonstrated in-stent restenosis. The cohort was predominantly male (67.1%) with a mean age of 60.67±8.28 years and a mean body mass index of 27.35±3.06 kg/m². Cardiovascular risk factors were prevalent, including hypertension in 274 patients (46.2%), diabetes mellitus in 189 (31.9%), hyperlipidemia in 132 (22.3%), and smoking history in 127 (21.4%). Chronic kidney disease affected 39 patients (6.6%). Regarding clinical presentation, unstable angina was the most common diagnosis (427 patients, 72%), followed by non-ST-elevation myocardial infarction (89 patients, 15%) and ST-elevation myocardial infarction (77 patients, 13%).

Left Ventricular Function

Severe left ventricular dysfunction (LVEF <30%) occurred more frequently in patients with ISR (7.7% vs. 1.0%, P<0.001). Conversely, mild dysfunction (LVEF 40-50%) was less common in this group (29.2% vs. 39.1%, P=0.02). The distribution of normal and moderate LVEF categories did not vary by restenosis status Table 1.

Laboratory Parameters

Lipid profiles differed between groups, with higher mean triglycerides (118.48±81.86 vs. 100.95±60.73 mg/dL, P = 0.003) and LDL-cholesterol (77.64±27.68 vs. 67.88±24.63 mg/dL, P<0.001) observed in the ISR group. Positive CRP was more frequent among patients with restenosis (74.2% vs. 22.7%, P<0.001). Other laboratory parameters, including fasting blood sugar (109.39±36.38 vs. 111.27±41.50 mg/dL), total cholesterol (142.20±38.60 vs. 137.96±34.66 mg/dL), HDL-cholesterol (50.37±12.24 vs. 51.06±10.77 mg/dL), and creatinine (1.01±0.21 vs. 0.99±0.19 mg/dL), were similar between groups all P>0.05, Table 1.

Clinical Presentation

The mode of clinical presentation at repeat angiography differed notably between groups. Myocardial infarction, both STEMI (24.9% vs. 6.5%, P<0.001) and NSTEMI (15.4% vs. 8.9%, P=0.02), was more frequent in patients with ISR, whereas unstable angina was the predominant presentation among controls (84.6% vs. 60.3%, P<0.001) Table 1.

Temporal Parameters

The mean interval from index PCI to repeat angiography was 53.73±34.60 months (range 1-224 months). The interval was longer in patients with ISR compared to controls (59.93 ± 38.01 vs. 50.51 ± 32.62 months, P = 0.002) Table 1.

Table 2. Procedural and Angiographic Characteristics by In-Stent Restenosis Status

Variable	ISR-Positive (n=209)	ISR-Negative (n=384)	P-value
Stent Characteristics			
Number of stents, mean±SD	1.21±0.41	1.19±0.39	0.40
Stent length ≥20mm, n (%)	68 (32.5)	55 (14.3)	<0.001
Stent diameter <3mm, n (%)	37 (17.7)	74 (19.3)	0.60
Stent Type			
Sirolimus-eluting, n (%)	55 (26.3)	203 (52.9)	<0.001
Everolimus-eluting, n (%)	127 (60.8)	100 (26.0)	<0.001
Paclitaxel-eluting, n (%)	20 (9.6)	1 (0.3)	<0.001
Rapamycin-eluting, n (%)	7 (3.3)	80 (20.8)	<0.001
Zotarolimus-eluting, n (%)	0 (0)	5 (1.3)	0.30
Vessel Complexity			
Single-vessel disease, n (%)	107 (51.2)	108 (28.1)	<0.001
Two-vessel disease, n (%)	82 (39.2)	204 (53.1)	0.001
Three-vessel disease, n (%)	20 (9.6)	73 (19.0)	0.003
Target Vessel Location			
LAD, n (%)	113 (54.1)	176 (45.8)	0.059
LCX, n (%)	45 (21.5)	80 (20.8)	0.80
RCA, n (%)	51 (24.4)	128 (33.3)	0.02

Abbreviations: LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery

Procedural Characteristics

The stent number and diameter did not differ by restenosis status (mean 1.21±0.41 vs. 1.19±0.39 stents per patient, P=0.40; diameter <3mm in 17.7% vs. 19.3%, P=0.60). However, longer stent length (≥20mm) was more common in the ISR group (32.5% vs. 14.3%, P<0.001) Table 2.

Stent Type Distribution

The distribution of drug-eluting stent types varied notably between groups. Everolimus-eluting stents were used more frequently in patients who developed ISR (60.8% vs. 26.0%, P<0.001), while sirolimus-eluting stents were less common (26.3% vs. 52.9%, P<0.001). Paclitaxel-eluting stents were also more prevalent in the ISR group (9.6% vs. 0.3%, P<0.001), whereas rapamycin-eluting stents showed the opposite pattern (3.3% vs. 20.8%, P<0.001). Zotarolimus-eluting stents were rarely used in either group Table 2.

Coronary Artery Disease Complexity

Single-vessel disease predominated in patients with ISR (51.2% vs. 28.1%, P<0.001). In contrast, both two-vessel (39.2% vs. 53.1%, P = 0.001) and three-vessel disease (9.6% vs. 19.0%, P = 0.003) were less

frequent in this group compared to controls Table 2.

Target Vessel Location

RCA lesions occurred less frequently in the ISR group (24.4% vs. 33.3%, P =.02). A trend toward higher LAD involvement was observed in patients with restenosis, though this did not reach statistical significance (54.1% vs. 45.8%, P =.059). LCX involvement was similar between groups (21.5% vs. 20.8%, P =.80) Table 2.

Discussion

This case-control study examined factors associated with in-stent restenosis following percutaneous coronary intervention in 593 patients. We observed an ISR incidence of 35.2%, markedly higher than the 3-10% rates reported in contemporary drug-eluting stent trials but consistent with real-world registry data [1, 2]. The findings are based on univariate comparative analysis. Relationships observed may be influenced by confounding variables not accounted for in this exploratory study. Patients with ISR were older than controls, with a mean difference of 7.5 years (67.6±8.7 vs. 60.1±8.0 years, P = .03). This aligns with observations from Wang et al. [18] and Li et al. [19], who demonstrated progressive endothelial dysfunction and impaired vascular healing capacity in elderly populations undergoing PCI. Importantly, this age difference may confound other observed associations since many cardiovascular risk factors and inflammatory markers increase with advancing age. Hypertension was more prevalent among those with restenosis (55% vs. 41.4%, P = .002), representing the only traditional cardiovascular risk factor to achieve statistical significance in our analysis [18, 23]. This association likely reflects chronic endothelial injury, increased oxidative stress, and sustained activation of the renin-angiotensin-aldosterone system. These mechanisms may promote neointimal hyperplasia even in the presence of contemporary antiproliferative stent coatings. However, the higher prevalence of hypertension in older patients suggests that age-related confounding may partially explain this relationship. The difference in C-reactive protein (CRP) positivity between the groups was significant (74.2% vs. 22.7%, p < 0.001), highlighting the potential role of systemic inflammation in the pathophysiology of restenosis. [10, 11, 18]. Elevated CRP serves as both a biomarker and a mediator of vascular injury. Previous studies suggest it may trigger smooth muscle cell proliferation and extracellular matrix deposition through multiple inflammatory cascades. This finding confirms the potential benefit from intensified anti-inflammatory strategies in high-risk patients. However, further investigation with multivariate analysis is needed to establish CRP as a predictor after accounting for confounders. Lipid profiles also differed by restenosis status. Mean triglycerides (118.5±81.9 vs. 101.0±60.7 mg/dL, p=.003) and LDL cholesterol (77.6±27.7 vs. 67.9±24.6 mg/dL, p<.001) were elevated in the ISR group, indicating atherogenic dyslipidemia's potential role in compromising stent healing and promoting neointimal proliferation [20, 21]. The triglyceride-glucose index, as reported by Zhu et al., is a strong predictor of metabolic dysfunction and the subsequent risk of restenosis in patients with insulin resistance. However, it remains unclear whether these lipid parameters are truly independent risk factors or if they are influenced by age, diabetes status, or medication. Further investigation using multivariate modeling is needed. Severe left ventricular dysfunction (ejection fraction <30%) occurred more frequently in patients with in-stent restenosis (ISR), with rates of 7.7% compared to 1.0% (p =.005). This relationship may be attributed to systemic neurohormonal activation, endothelial dysfunction, and impaired myocardial perfusion, which collectively compromise stent endothelialization. These patients should be considered for more intensive surveillance protocols and possibly modified antiplatelet regimens. Conversely, mild dysfunction (LVEF 40-50%) was less common in the restenosis group, with rates of 29.2% compared to 39.1% (p=.02). The distribution of normal and moderate LVEF categories did not vary by restenosis status. Stent length (≥20 mm) showed a significant association with ISR, occurring in 32.5% of cases versus 14.3% (p<.001). This is likely due to greater mechanical injury, an amplified inflammatory response, and an increased surface area susceptible to neointimal hyperplasia. This finding underscores the importance of precise lesion preparation and optimal stent sizing to minimize unnecessary stent length. In contrast, the number of stents per patient and stent diameter did not differ based on restenosis status, with a mean of 1.21 ± 0.41 stents versus 1.19 ± .39 stents (p =.40) and stent diameter <3 mm in 17.7% versus 19.3% (p =.60). This suggests that stent length may be more critical than the total number of devices used.The distribution of drug-eluting stent types varied notably between groups. Everolimus-eluting stents were used more frequently in patients who developed ISR (60.8% vs. 26.0%, p<0.001), while sirolimus-eluting stents were less common (26.3% vs. 52.9%, p<0.001). Paclitaxel-eluting stents were also more prevalent in the ISR group (9.6% vs. 0.3%, p<0.001), whereas

rapamycin-eluting stents showed the opposite pattern (3.3% vs. 20.8%, p<0.001). Zotarolimus-eluting stents were infrequently used in both groups (Table 2). These differences likely reflect changes in stent availability and clinical practice patterns over time rather than inherent differences in stent efficacy. The observational nature of this study and lack of randomization to stent type precludes definitive conclusions about comparative stent performance. Additionally, the time to repeat angiography differed between groups, which may have influenced the apparent differences in stent-type distribution. The mode of clinical presentation at repeat angiography differed notably. Myocardial infarction, both STEMI (24.9% vs. 6.5%, p<.001) and NSTEMI (15.4% vs. 8.9%, p =.02), was more frequent among patients with ISR [6, 18]. In contrast, unstable angina was the predominant presentation in controls (84.6% vs. 60.3%, p<0.001) (Table 1). This pattern suggests that the acute thrombotic milieu and heightened inflammatory state characteristic of MI may create a particularly adverse substrate for stent healing. However, the cross-sectional nature of this observation limits causal interpretation. Interestingly, single-vessel disease predominated in the ISR group (51.2% vs. 28.1%, p<0.001), while two-vessel (39.2% vs. 53.1%, p=0.001) and three-vessel disease (9.6% vs. 19.0%, p=0.003) were more common in controls (Table 2). This counterintuitive finding may reflect differences in patient management strategies. Patients with multi-vessel disease potentially received more aggressive medical therapy or more complete revascularization. Alternatively, this may represent referral bias, as patients with multi-vessel disease and good outcomes may have been less likely to undergo repeat angiography. In terms of target vessel location, RCA lesions were less common in the ISR group, occurring in 24.4% of patients compared to 33.3% in the non-ISR group (p = 0.02). There was a trend indicating a higher involvement of the LAD in patients with restenosis. However, this difference was not statistically significant (54.1% vs. 45.8%, p = 0.059). The involvement of LCX was similar between the two groups, with rates of 21.5% in the ISR group and 20.8% in the control group (p = 0.80). Additionally, the mean interval from the initial PCI to repeat angiography was longer in the restenosis group, at 59.9 ± 38.0 months, compared to 50.5 ± 32.6 months in the non-restenosis group (p = 0.002). These findings suggest that in-stent restenosis can occur even years after the initial stent placement, highlighting the need for long-term monitoring in high-risk patients (32.6 months, p =.002) (Table 1). This suggests that ISR can occur even years after initial stent placement, indicating the need for long-term surveillance in high-risk patients. However, this also introduces potential survival bias since patients developing very early complications may not have been included in this analysis. Other traditional cardiovascular risk factors, including diabetes mellitus (29.7% vs. 33.1%, p=0.40), hyperlipidemia (22.5% vs. 22.1%, p=0.90), current smoking (23.9% vs. 20.1%, p=0.30), alcohol consumption (5.3% vs. 3.9%, p=0.50), and chronic kidney disease (6.7% vs. 6.5%, p=0.90), showed similar rates in both groups (Table 1). Laboratory parameters, including fasting blood glucose (109.4±36.4 vs. 111.3±41.5 mg/dL), total cholesterol (142.2±38.6 vs. 138.0±34.7 mg/dL), HDL cholesterol (50.4±12.2 vs. 51.1±10.8 mg/dL), and creatinine (1.01±0.21 vs. 0.99±0.19 mg/dL), were comparable between groups (all p>0.05, Table 1). The 35.2% ISR incidence observed in our cohort substantially exceeds rates in recent randomized controlled trials, but aligns more closely with higher rates in real-world registries that employ broader inclusion criteria and longer follow-up periods [18, 19, 27, 29]. This discrepancy likely reflects the study's inclusion of complex patient populations, longer lesions, and small vessel disease. These factors are typically underrepresented in pivotal trials but prevalent in clinical practice [28]. Additionally, our clinically driven angiographic follow-up may have selectively identified symptomatic cases, potentially overestimating the true incidence of angiographic restenosis. These findings have several practical implications for clinical practice. Patients with multiple risk factors, particularly elderly hypertensive individuals with elevated inflammatory markers and dyslipidemia, may benefit from enhanced monitoring protocols and more intensive medical therapy. Procedural planning should consider ISR risk factors by minimizing stent length when feasible, employing optimal deployment techniques with adequate expansion and apposition, and ensuring systematic use of guideline-directed medical therapy [26, 28]. Pharmacological optimization should prioritize aggressive lipid management with high-intensity statins, stringent blood pressure control targeting <130/80 mmHg in appropriate patients, and consideration of anti-inflammatory strategies for high-risk individuals [30]. Risk stratification tools incorporating the factors identified in this analysis could potentially guide personalized surveillance and preventive strategies. These include age, hypertension, inflammatory markers, lipid parameters, ventricular function, and stent characteristics [26, 28]. However, development

and validation of such tools will require multivariate analysis in larger prospective cohorts to determine which factors remain predictive after accounting for potential confounders. This study has several important limitations that must be considered when interpreting the results. The retrospective design poses risks of selection and information bias. We excluded 20% of the original cohort (150 of 743 patients) due to incomplete records, which may have impacted results. Most critically, only univariate analyses were performed without multivariate regression. This prevents the establishment of independent predictive relationships and limits control for confounding variables. The associations described should therefore be considered preliminary and hypothesis-generating rather than definitive. Age, in particular, likely confounds multiple observed associations since hypertension, inflammation, and lipid abnormalities all increase with advancing age. Angiographic follow-up was clinically driven rather than systematic. This potentially led to overestimation of ISR incidence due to selective identification of symptomatic cases, while asymptomatic restenosis likely remained undetected.The study was conducted in a single center, which may limit its generalizability, since regional differences in patient characteristics, stent availability, and treatment protocols could affect applicability to other settings. Systematic quantitative coronary angiography measurements were not performed. We relied upon visual assessments by interventional cardiologists. The absence of routine intravascular imaging restricts detailed understanding of restenosis mechanisms and patterns. Follow-up duration varied widely among patients, ranging from 1 to 224 months, complicating the assessment of ISR temporal patterns. The patients underwent repeat angiography at different times, possibly capturing different stages of restenosis evolution. Finally, medication adherence data were inconsistently available, precluding analysis of dual antiplatelet therapy compliance, statin adherence, or other medication-related factors that may significantly influence ISR risk. These findings require validation through prospective studies employing multivariate statistical approaches. Such studies would identify predictors of ISR while controlling for confounding variables, particularly age and comorbidity interactions. Randomized controlled trials comparing intensive versus standard risk factor management in high-risk patients would help establish whether aggressive modification of identified factors can reduce restenosis rates [26, 27]. Biomarker-guided approaches using high-sensitivity C-reactive protein and other inflammatory markers warrant investigation to determine whether they can effectively tailor surveillance strategies and guide preventive interventions. Investigating genetic polymorphisms related to drug metabolism, inflammatory responses, and cellular proliferation could identify populations that may benefit from specific stent platforms or pharmacotherapies. Benefiting from advanced imaging techniques, including intravascular ultrasound and optical coherence tomography in prospective registries, would clarify mechanisms linking clinical risk factors to specific patterns of restenosis [28, 29], which could potentially enable more targeted interventional approaches. Long-term follow-up studies with systematic rather than clinically driven angiography would provide more accurate estimates of real-life ISR incidence. These studies would help distinguish symptomatic from asymptomatic restenosis, informing optimal surveillance strategies.

Conclusion

The current study identified several factors associated with in-stent restenosis in a cohort of Iranian patients following percutaneous coronary intervention. These include advanced age, systemic hypertension, elevated inflammatory markers, atherogenic dyslipidemia, severe left ventricular dysfunction, extended stent length, and longer time to follow-up angiography. The observed 35.2% incidence of ISR with extended follow-up exceeds rates in contemporary clinical trials. This emphasizes the ongoing challenge of restenosis despite advancements in stent technology. The associations identified through univariate comparative analysis need further validation through multivariate modeling to determine which factors remain predictive when accounting for confounders. Many of these factors, such as hypertension, lipid abnormalities, and systemic inflammation, are potentially modifiable, indicating opportunities for preventive interventions aimed at reducing the burden of in-stent restenosis (ISR) and improving long-term outcomes following percutaneous revascularization. However, the degree to which aggressive modification of these factors can lower ISR rates still needs to be clarified through prospective randomized trials. Procedural considerations for minimizing stent length, ensuring optimal deployment, and selecting appropriate drug-eluting stent platforms based on patient risk profiles are crucial in clinical practice. Enhanced surveillance for high-risk groups may enable early detection of in-stent restenosis and prompt intervention before acute coronary events

occur. Tools for risk stratification using available clinical variables can guide follow-up intensity and preventive strategies [26, 28]. The analysis highlights ISR as a multifactorial issue influenced by patient-specific biological factors, systemic diseases, and procedural elements. A comprehensive strategy addressing modifiable factors through integrated medical management, procedural optimization, and tailored surveillance is vital for reducing ISR and improving long-term outcomes after percutaneous coronary intervention [30].

Acknowledgments
The authors express gratitude to all medical staff and catheterization laboratory personnel at Seyyed ol-Shohadai Hospital, Urmia, for their support in data collection and retrieval. Thanks are also extended to Dr. Mir Hossein Seyyed Mohammadzad for his valuable consultation during the study design phase.

Author Contributions
BA conceived and designed the study, collected and analyzed data, and drafted the manuscript. NJ supervised the study design and critically revised the manuscript. VSR extracted the manuscript from the thesis in English and revised the manuscript. MHSM provided methodological guidance and statistical consultation. All authors approved the final manuscript.

Conflicts of Interest
The authors declare no conflicts of interest related to this investigation.

Funding
This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical Statements
This study received ethical approval from the Urmia University of Medical Sciences Research Ethics Committee (approval code: IR.UMSU.REC.1403.146). All procedures were conducted in accordance with the Declaration of Helsinki. Given the retrospective nature of the study utilizing de-identified data, informed consent requirements were waived by the Ethics committee.

Use of AI Tools
In preparing this manuscript, artificial intelligence language tools (Claude by Anthropic) were used in a limited capacity to:
1. Paraphrase selected text passages to improve clarity and readability mainly in the introduction and discussion sections.
2. Assist with formatting and standardizing reference citations.
All research conceptualization, study design, data collection, statistical analysis, interpretation of findings, and conclusions were performed independently by the author without AI assistance.

References
1. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J Am Coll Cardiol*. 2020; 76(25):2982-3021.
2. Herrington W, Lacey B, Sherliker P, et al. Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease. *Circ Res*. 2016; 118(4):535-46.
3. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019; 40(2):87-165.
4. Condello F, Spaccarotella C, Sorrentino S, et al. Stent thrombosis and restenosis with contemporary drug-eluting stents: predictors and current evidence. *J Clin Med*. 2023; 2(3):1238.
5. Bajeu IT, Niculescu AG, Scafa-Udriște A, et al. Intrastent Restenosis: A Comprehensive Review. *Int J Mol Sci*. 2024; 25(3):1715.
6. Giustino G, Colombo A, Camaj A, et al. Coronary in-stent restenosis: JACC state-of-the-art review. *J Am Coll Cardiol*. 2022; 80(4):348-372.
7. Guidener U, Kessler T, Von Scheidt M, et al. Machine learning identifies new predictors on restenosis risk after coronary artery stenting in 10,004 patients with surveillance angiography. *J Clin Med*.2023; 12(8):2941.
8. Klein LW, Nathan S, Maehara A, et al. SCAI expert consensus statement on management of in-stent restenosis and stent thrombosis. *J Soc Cardiovasc Angiogr Interv*. 2023; 2(4):100971.
9. Clare J, Ganly J, Bursill CA, et al. The mechanisms of restenosis and relevance to next generation stent design. *Biomolecules*. 2022; 12(3):430.
10. Selvakumar PP, Rafuse MS, Johnson R, et al. Applying principles of regenerative medicine to vascular stent development. *Front Bioeng Biotechnol*. 2022; 10:826807.
11. Tamez H, Secemsky EA, Valsdottir LR, et al. Long-term outcomes of percutaneous coronary intervention for in-stent restenosis among Medicare beneficiaries. *EuroIntervention*. 2021; 17(5):e380-387.
12. Giustino G, Colombo A, Camaj A, et al. Coronary in-stent restenosis: JACC state-of-the-art review. *J Am Coll*

Cardiol. 2022; 80(4):348-372.
13. Buccheri D, Piraino D, Andolina G, et al. Understanding and managing in-stent restenosis: a review of clinical data, from pathogenesis to treatment. *J Thorac Dis*. 2016; 8(10):E1150-E1162.
14. Buccheri D, Piraino D, Andolina G, et al. Understanding and managing in-stent restenosis: a review of clinical data, from pathogenesis to treatment. *J Thorac Dis*. 2016; 8(10):E1150-E1162.
15. Spadafora L, Quarta R, Martino G, et al. From mechanisms to management: tackling in-stent restenosis in the drug-eluting stent era. *Curr Cardiol Rep*. 2025; 27(1):53.
16. Sajadian M, Alizadeh L, Ganjifard M, et al. Factors affecting in-stent restenosis in patients undergoing percutaneous coronary angioplasty. *Galen Med J*. 2018; 7:e961.
17. Garcia-Garcia HM, McFadden EP, Farb A, et al. Standardized end point definitions for coronary intervention trials: the Academic Research Consortium-2 consensus document. *Circulation*. 2018; 137(24):2635-50.
18. Wang P, Qiao H, Wang R, et al. The characteristics and risk factors of in-stent restenosis in patients with percutaneous coronary intervention: what can we do? *BMC Cardiovasc Disord*. 2020; 20(1): 510.
19. Li M, Hou J, Gu X, et al. Incidence and risk factors of in-stent restenosis after percutaneous coronary intervention in patients from southern China. *Eur J Med Res*. 2022; 27(1):12.
20. Zhu Y, Liu K, Chen M, et al. Triglyceride-glucose index is associated with in-stent restenosis in patients with acute coronary syndrome after percutaneous coronary intervention with drug-eluting stents. *Cardiovasc Diabetol*. 2021; 20(1):137.
21. Hu H, Wang S, Tang G, et al. Impact of anemia on in-stent restenosis after percutaneous coronary intervention. *BMC Cardiovasc Disord*. 2021; 21(1):548.
22. Paramasivam G, Devasia T, Ubaid S, et al. In-stent restenosis of drug-eluting stents in diabetic versus nondiabetic patients: clinical presentation and outcomes in a 'real-world' scenario. *Egypt Heart J*. 2019; 71(1):28.
23. Alexandrescu DM, Mitu O, Costache II, et al. Risk factors associated with intra-stent restenosis after percutaneous coronary intervention. *Exp Ther Med*. 2021; 22(4):1141.
24. Cheng G, Chang FJ, Wang Y, et al. Factors influencing stent restenosis after percutaneous coronary intervention in patients with coronary heart disease: a clinical trial based on 1-year follow-up. *Med Sci Monit*. 2019; 25:240-247.
25. Zhang J, Zhang Q, Zhao K, et al. Risk factors for in-stent restenosis after coronary stent implantation in patients with coronary artery disease: a retrospective observational study. *Medicine (Baltimore)*.2022; 101(47):e31707.
26. Yi M, Tang WH, Xu S, et al. Investigation into the risk factors related to in-stent restenosis in elderly patients with coronary heart disease and type 2 diabetes within 2 years after the first drug-eluting stent implantation. *Front Cardiovasc Med*. 2022; 9:837330.
27. Kufner S, Joner M, Thannheimer A, et al. Ten-year clinical outcomes from a trial of three limus-eluting stents with different polymer coatings in patients with coronary artery disease. *Circulation*. 2019; 139(3):325-333.
28. Theodoropoulos K, Mennuni MG, Dangas GD, et al. Resistant in-stent restenosis in the drug eluting stent era. *Catheter Cardiovasc Interv*. 2016; 88(5):777-785.
29. Waldo SW, O'Donnell CI, Prouse A, et al. Incidence, procedural management, and clinical outcomes of coronary in-stent restenosis: insights from the National VA CART Program. *Catheter Cardiovasc Interv*. 2018; 91(3):425-433.
30. Vrints C, Andreotti F, Koskinas KC, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. *Eur Heart J*. 2024; 45(36):3415-3537.

