

Interleukin 6 and high sensitive C reactive protein in predicting in-stent restenosis in patients undergoing percutaneous coronary intervention

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Article

Keywords: HsCRP, IL-6, Gensini score, in-stent restenosis

Posted Date: October 22nd, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11184350/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background and Aims: In-stent restenosis (ISR) remains a major limitation of percutaneous coronary intervention (PCI). Inflammatory biomarkers such as interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hsCRP) may contribute to ISR pathogenesis. This study aimed to evaluate the predictive value of IL-6, hsCRP, and the Gensini score (GS) for ISR in patients with coronary artery disease (CAD) undergoing drug-eluting stent implantation.

Methods and Results : A total of 262 CAD patients treated with PCI were enrolled. Patients were classified into ISR (n=107) and non-ISR (n=155) groups. ISR was assessed by protocol-driven coronary angiography performed between 6 and 12 months in all patients. Clinical, angiographic, and biochemical parameters were assessed. IL-6 and hsCRP levels were measured pre-procedurally, and CAD severity was evaluated by the Gensini score. Receiver operating characteristic (ROC) curve analysis was performed to determine predictive values. Serum IL-6, hsCRP levels, and GS values were significantly higher in the ISR group when compared with No ISR group ($p=0.012$, $p=0.017$, and $p=0.032$, respectively). ROC analysis showed moderate predictive value for IL-6 (AUC=0.717, $p=0.012$) and GS (AUC=0.674, $p=0.040$), whereas hsCRP did not reach statistical significance (AUC=0.602, $p=0.171$).

Conclusions: Elevated IL-6 and increased GS were significantly associated with ISR, highlighting the importance of both systemic inflammation and angiographic CAD severity in restenosis risk.

ClinicalTrials.gov Number: NCT03075566 (09/03/2017).

Introduction

Coronary artery disease (CAD), the major manifestation of ischemic cardiovascular disorder, is mainly caused by atherosclerosis and plaque formation in the coronary arteries, and has become the leading cause of cardiac events, in stent restenosis)ISR(and mortality [1]. A major complication to successful percutaneous coronary intervention)PCI) is ISR and the ability to predict the likelihood of restenosis stent implantation development is low. The attempt to define patients who benefit most from coronary artery stenting led to a search for biomarkers for restenosis processing [2]. ISR is happening into 2 steps, the first step is characterized by mechanical damage, vascular discontinuity, and continuous stimulus to the arterial wall caused by the stent material and its polymer coating. Various mechanisms have been postulated as the promotor of inflammatory response and platelet activation [3]. The second step initiates by different pathophysiological alterations as the proliferation and migration of vascular smooth muscle cells (VSMCs), and the production and deposition of extracellular matrix, which lead to neointimal hyperplasia and atherosclerosis [4]. Previous studies suggested that precipitating factors as inflammatory cytokines, smoking, lipid profile parameters, coronary angiographic characteristics, patient history have been widely used for evaluating disease severity and predicting ISR risk [5].

Preclinical and clinical studies have highlighted that the incidence of ISR can be reduced by down regulating the expression of inflammatory markers, which can decrease atherosclerosis development,

and optimized antiplatelet medications and reduce the in stent thrombotic restenosis [6]. The aim of this study was to evaluate the association between ISR and the severity of CAD, and to determine the role of inflammatory markers such as HsCRP and Interleukin – 6 as after successful coronary stent implantation in patients with CAD.

Material and Methods

Subjects

A total of 262 CAD patients who underwent PCI with drug-eluting stents implantation at Department of Cardiology, the University Hospital of Monastir, Tunisia was enrolled in this study. This study is a prospective observational cohort study conducted over a 12-month period, including patients undergoing coronary angiography. The population was divided into two groups: patients with in-stent restenosis and those without restenosis: ISR group (n = 107) and no-ISR group (n = 155) (figure B).

Clinical exclusion criteria were acute and chronic infections, autoimmune diseases, renal or liver failure, malignancies, allergic diseases, ST-elevation myocardial infarction (STEMI) diagnosis. This study was approved by the National Committee for Medical and Research Ethics of Farhat Hached University Hospital (Sousse, Tunisia) and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

ISR diagnosis

Follow-up was based on protocol-driven coronary angiography performed between 6 and 12 months after stent implantation. All patients included in the study underwent scheduled angiographic evaluation, regardless of the presence or absence of symptoms. The unit of analysis in this study was the patient. ISR was defined at the patient level as the presence of $\geq 50\%$ diameter stenosis in any stented segment or within 5 mm of the stent at follow-up angiography. Total occlusion was defined angiographically as complete interruption of coronary flow (TIMI 0 flow) in the affected vessel, irrespective of occlusion duration. In patients with multiple stents, the occurrence of restenosis in at least one treated lesion led to classification in the ISR group, whereas patients without restenosis in all treated segments were classified in the non-ISR group. Each patient was counted once in the analysis regardless of the number of implanted stents [7]. Significant lesion was considered as a diameter stenosis of $\geq 50\%$ occurring in the most severe narrowing vessel. All patients underwent coronary angiography 6 months after stent implantation. Coronary angiographic data such as minimal stent diameter, average stent length and stenosis percent, were collected from patient catheterization laboratory records and reviewed independently by interventional cardiologists.

Calculation of Gensini score

The severity of CAD was evaluated by the Gensini scoring system, which was defined according to stenosis severity as 1-point for < 25% stenosis, 2-point for 26%– 50% stenosis, 4-point for 51%–75% stenosis, 8-point for 76%–90% stenosis and 32-point for total occlusion. The score was then multiplied by a factor that represents the importance of the lesion's position in the coronary arterial system. For example, 5 for the LM, 2.5 for the proximal LAD or proximal LCX, 1.5 for the mid-region and 1 for the distal LAD [8].

Laboratory analysis

Venous blood samples were obtained just prior to coronary angiography for testing biochemical parameters levels using standard laboratory methods. Blood samples for lipid profiles were collected from patients taking statin for more than 2 weeks. The total cholesterol (TC), TG and high density lipoprotein-cholesterol (HDL-c) levels were determined using an analyser (Cobas Integra 600, Roche Diagnostic, Germany). Low density lipoprotein-cholesterol (LDL-c) was estimated by the Friedewald equation [9]. The determination of high-sensitive C-reactive protein (hs-CRP) levels was by means of immunoturbidimetry were measured using an analyser (Cobas Integra 400, Roche Diagnostic, Germany). Serum samples were collected from study participants, and stored in aliquots at -80°C until use.

Extreme values of hsCRP and IL-6 were identified and excluded before the final analysis.

Serum interleukin-6 measurements

Serum interleukin-6 (IL-6) levels were measured by electrochemiluminescence immunoassay (ECLIA) using a Cobas E601 analyzer (Roche Diagnostics, Germany).

Statistical analysis

Data were processed using Statistical Package for the Social Sciences (SPSS, version 23.0). Categorical data were expressed as frequencies or percentages. Continuous variables data were presented as mean $\pm$ standard deviation (normally distributed data) or median (minimum - maximum) (non-normally distributed data). Comparison between two groups was determined by chi-square test, t test or Mann–Whitney U test, as appropriate. P value < 0.05 was considered significant. Receiver operating characteristic (ROC) curve analysis was used to determine the optimum cut-off level of pre-procedural hsCRP, IL6 and GS values to predict ISR.

Results

Characteristics of CAD patients

Among the 262 CAD patients, 107 were ISR patients and 155 were no-ISR patients. For the comparison between patient groups, the percentages of patients with multiple stenting, DM, and Previous MI ($p >$

0.05) were higher in ISR patients compared with no-ISR patients but not significant (Table 1).

Table 1: Baseline characteristics of the study population

Characteristics	No ISR	ISR	p
Age, years	62.2 ± 11.9	59.5 ± 10.4	0.355
UA, n (%)	32.1	37.2	0.951
NSTE-ACS, n (%)	68.9	62.8	
BMI, kg/m²	29.3 ± 4.7	27.2 ± 4.3	0.130
Gender, n (%)			0.992
Male	88(82.1)	108(70.3)	
Female	19(17.9)	75(20.7)	
Smoker, n (%)	46(42.9)	59(38.5)	0.718
Yes	61(57.1)	96(61.5)	
No			
Hypertension, n (%)	65(60.7)	65(42.1)	0.135
Yes	41(39.3)	90(57.9)	
No			
Diabetes, n (%)	67 (71.7)	90(57.9)	0.818
Yes	40(37.8)	65(42.1)	
No			
Multiple stenting, n (%)			0.371
One stent	74(68.8)	85(55.6)	
Multiple stent	33(31.3)	70(44.4)	

BMI: body mass index, ISR: in-stent restenosis, No ISR: No in-stent restenosis, NSTE-ACS: non ST elevation acute coronary syndrome. UA: unstable angina. Values are expressed as the mean ± SD or n (%).

Table 2 shows that ISR patients had the highest percentages of total occlusion (p = 0.021). The ISR group had significantly smaller stent diameter compared to the no-ISR group 2.2 ± 0.3 vs 2.8 ± 0.4 mm, p < 0.001). There was no significant difference between the two groups on angiographic examination. II-6 levels (p = 0.012), hsCRP levels (p = 0.017) and GS values (p = 0.032) were significantly elevated in ISR patients compared to no-ISR patients.

Clinical characteristics (all $p > 0.05$), homocysteine levels ($p = 0.260$) and lipid profile parameters didn't show significant difference between ISR patients and non-ISR patients (Tables 2 and 3).

Table 2: Clinical and angiographic characteristics of patients

Characteristics	No ISR	ISR	p
SBP, mmHg	132 ± 22	136 ± 24	0.623
DBP, mmHg	73 ± 11	76 ± 12	0.738
Heart rate, b/min	74.0 ± 14.1	74.2 ± 13.2	0.951
Ejection Fraction	46.8 ± 18.4	50.7 ± 14.0	0.659
Target Vessels, n (%)			
LM	0(0)	9(6.1)	0.300
LCx	31 (29.4)	65(42.4)	0.369
IVA	82(76.5)	80(51.5)	0.088
RCA	25(23.5)	66(42.4)	0.187
Previous MI, n (%)	88(82.1)	126(81.6)	0.050
Stenosis, 70%, n (%)	36(71.4)	99(64.3)	0.743
Total occlusion, n (%)	17(15.8)	74(48.3)	0.021
Multivessel Lesion, n (%)	61(57.1)	97(62.9)	0.672
Multiple stent, n (%)	33(31.3)	69(44.4)	0.371
Stent diameter (mm)	2.8 ± 0.4	2.2 ± 0.3	<0.001
Stent length (mm)	16.3 ± 2.8	15.9 ± 3.4	0.591
Stenting months	10.9 ± 3.5	7.8 ± 5.4	0.125
Statin, n (%)	107(100)	125(80.8)	0.118
β blockers, n (%)	53(50.0)	99.2(64.0)	0.445
CEI, n (%)	71(66.7)	111(72.0)	0.740
Clopidogrel, n (%)	39(36.4)	89(57.7)	0.235
Aspirin, n (%)	89(83.3)	120(77.8)	0.527

CEI: conversion enzyme inhibitor, DBP: diastolic blood pressure, ISR: in-stent restenosis, LAD: left anterior descending, LCx: left circumflex, LDL-c: low density lipoprotein cholesterol, LMCA: Left main

coronary artery, LVEF: left ventricular ejection fraction, No ISR: No in-stent restenosis, RCA: right coronary artery, SBP: systolic blood pressure. Values are expressed as the mean $\pm$ SD or n (%).

Table 3
Biochemical characteristics of patients

Characteristics	No ISR	ISR	P
Glucose, mmol/L	11.6 $\pm$ 8.6	10.1 $\pm$ 5.3	0.437
HbA1c, %	9.2 $\pm$ 2.7	8.4 $\pm$ 2.1	0.462
Urae, mmol/L	6.1 $\pm$ 1.7	6.9 $\pm$ 5.5	0.457
Creatinin, μ mol/L	100.7 $\pm$ 26.6	88.8 $\pm$ 30.1	0.125
TC, mmol/L	3.8 $\pm$ 1.3	4.3 $\pm$ 1.5	0.290
TG, mmol/L	1.4 $\pm$ 0.8	1.8 $\pm$ 1.0	0.103
HDL-c, mmol/L	0.9 $\pm$ 0.3	1.0 $\pm$ 0.3	0.311
LDL-c, mmol/L	2.4 $\pm$ 1.3	2.5 $\pm$ 1.2	0.845
Hcy, μ mol/L	15.0 $\pm$ 8.2	20.8 $\pm$ 12.1	0.260
IL-6, pg/mL	4.3 (1.5-139.6)	9.4 (3.7–1957.0)	0.012
hsCRP, mg/L	5.0 (0.2–25.0)	10.7 (0.8–500.0)	0.017
SAA	6.5 (1.0-176.0)	8.5 (1.5–455.0)	0.447
GS	32.3 $\pm$ 25.0	52.8 $\pm$ 35.7	0.032

GS: gensini score, HbA1c: glyated hemoglobin, Hcy: homocysteine, HDL-c: high density lipoprotein cholesterol, Hs-CRP: high sensitivity C-reactive protein, IL-6: interleukin 6, LDL- c: low density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides. Values are expressed as the mean $\pm$ SD.

Predicting values of potential factors for ISR risk.

To further explore the predicting values of IL-6, HsCRP and GS for ISR risk, ROC curves analysis showed that the AUCs were 0.717 (95% CI: 0. 560-0. 874), $p = 0. 012$), (0.602 (95% CI: 0.459 - 0.745), $p = 0.171$), 0.674 (95% CI: 0.523 - 0.824), $p = 0.04$) for IL-6, HsCRP and GS respectively (figure A).

Discussion

In this study, we examined the association between angiographic complexity assessed by GS and some serum inflammatory factors and risk of developing coronary ISR in patients previously treated with PCI. The serum concentrations of hs-CRP and IL-6, and GS values were significantly higher in patients with ISR compared to patients without ISR indicating an association between the angiographic severity of CAD and the pathogenesis of ISR ($p < 0.05$). However, although hsCRP levels were significantly elevated in ISR patients, its low AUC suggests limited clinical utility as a standalone predictive biomarker.

It is well established that coronary stent implantation is currently the main effective procedure in the treatment of patients with CHD. However, ISR is a common complication of coronary intervention and a cause of morbidity [10, 11]. ISR is the formation of neointimal hyperplasia mediated by biological, mechanical, technical and complex factors related to the patient, stent and procedure which will lead to increase heart disease events occurrence [12]. The pathological mechanism underlying neoatherosclerosis is based on the formation of de-novo lipid-laden macrophages within the neointimal region. Endothelial dysfunction with poorly formed cell junctions would cause decreased antithrombotic molecule expression and reduced nitric oxide production. The resulting penetration of high levels of LDL into the subendothelial space leads to a local vascular reaction in the vessel wall inducing a systemic inflammatory cascade, which initializes the development of atherosclerosis [13].

Numerous previous studies have suggested the association of systemic inflammation with ISR that was related to various inflammatory biomarkers. Various biomarkers related to inflammatory reactions have been demonstrated to be effective in predicting ISR occurrence [14]. Studies have noted that local inflammation following stent implantation leads to inflammatory interleukins liberation such as IL-1, IL-6 and tumor necrosis factor- α (TNF- α) which mediates an inflammatory systemic response. These interleukins cause CRP production increase in the blood secretion [15]. IL-6 is one of the most important factors and has multiple effects on human vascular pathophysiology. In a previous study, the data showed an enhanced production of IL-6 by monocytes in response to CRP in patients with unstable angina [16]. Hence, IL-6 was a powerful stimulus for CRP production.

In previous study [17], the data showed an enhanced production of IL-6 by monocytes in response to CRP in patients with unstable angina. Moreover, IL-6 is a powerful stimulus for CRP production. Elevated hsCRP concentrations were associated with endothelial dysfunction, differentiation of macrophages, smooth muscle cell proliferation and plaque vulnerability.

These inflammatory factors are involved in acute coronary syndrome development by atheroma formation stimulation, destabilization of damaged atherosclerotic plaques, formation of occlusive thrombi and eventually thrombotic complications [18].

Intriguingly, despite its potentially atherosclerosis involvement, CRP level fails to predict the risk of drug eluting stents restenosis [19]. The eluted drug can halt the local inflammation response leading to ISR in patients with high CRP level. Previous studies has indicated that CRP is elevated at risk for future cardiovascular events [20]. Pre- and postprocedural CRP and IL-6 levels are associated with the bare metal stents restenosis (BMS) restenosis and are significant predictors for BMS restenosis [21, 22]. It was shown that, 24 h after PCI, the increase of inflammatory markers (CRP and interleukins such as IL-1Ra and IL-6) is associated with ISR independently of treatment procedure and implanted stent number [23].

A previous study has already shown that serum levels of CRP and interleukin-10 could predict late coronary in-stent restenosis 6 months after elective stenting. The results reported a very important role of inflammatory mechanisms not only shortly after stent implantation but also in longer follow-up. As a

result, CRP and IL-10 could strongly predict the ISR risk by evaluating their circulating levels six months after stent implantation [21]. In support of this, Li JJ. et al. have also noted significant levels increases in coronary circulating IL-6 immediately after percutaneous transluminal coronary angioplasty. This increase could be explained by its secretion from activated macrophages, vascular endothelium, and stenosis, during de novo synthesis [22].

Multiple other factors can contribute to ISR arise, and the underlying mechanisms remain elusive. High circulating levels of Homocysteine (Hcy) were not associated with high risk for the long-term cardiac mortality and morbidity after stent implantation [23]. Our findings showed elevated Hcy levels but without significant association with ISR in our population. Previous study noted that Hcy levels could be a valuable biomarker in prognosing ISR [24]. Various mechanisms have been postulated that high Hcy levels can activate lymphocytes and metalloproteinases, promotes the secretion of many inflammatory factors such as monocyte chemoattractant protein, tumor necrosis factor and interleukins leading to neutrophil migration and vascular endothelium lesion [23, 24].

Another study results showed that GS score can be an independent predictor of ISR. As angiographic characteristics were shown as independent factors of stenosis development, the culprit vessel, the degree of stenosis and the location of the lesion, can complicate PCI procedures and increase the risk of preoperative vessel injury, leading to ISR. Despite this score combine all these factors, which have been shown to be independent risk factors for ISR, previous studies didn't noted whether the GS, could be a powerful predictor of ISR in view of no quantitative assessments of diseased vessels have been considered studied [25, 26]. Moreover, the analysis revealed that each incremental point in the GS was associated with an approximately 3% increase in the probability of ISR occurrence [27]. The GS was identified as independent predictors of ISR in patients with CAD following DES implantation. Multivariate analysis indicated that high GS and other factors, participate in the developing of ISR [28].

In conclusion, our study demonstrated that elevated serum IL-6 levels, higher Gensini score are significantly associated with in-stent restenosis in patients with CAD undergoing PCI with drug-eluting stents. These findings highlights the interplay between systemic inflammation and angiographic severity of CAD in the development of ISR. Although hsCRP levels were higher in ISR patients, their predictive value was limited compared to IL-6 and GS.

Several limitations must be concerned in this study. Firstly, as the sample size was small, it can't be potential enough to detect the related risk factors, more studies with important sample size on the risk factors for the ISR are needed in the future. Secondly, we only made a follow-up for one year, and a longterm follow-up can show the predictors factors for ISR. Third, we didn't not include patients among CAD outcomes, and our findings thus refer only to all CAD patients. In addition, we only measure the levels of these cytokines that occurred immediately before PCA, clinical significance of cytokine production is not specific for late restenosis in dilated vessels. Finally, as no multivariable adjustment was performed, due to sample size limitations, important clinical and procedural factors such as ACS presentation, prior myocardial infarction, stent diameter, and lesion complexity, circulating IL-6 and

hsCRP levels can be influenced by acute ischemic conditions, potentially reflecting inflammatory response to myocardial injury may have confounded the observed associations. Further studies with larger sample sizes, appropriate multivariable and stratified analyses are warranted.

Abbreviations

BMS
metal stents restenosis
CAD
Coronary artery disease
CEI
Conversion enzyme inhibitor
DBP
Diastolic blood pressure
GS
Gensini score
HbA1c
glycated hemoglobin
Hcy
Homocysteine
HDL-c
High density lipoprotein-cholesterol
HsCRP
High sensitivity C reactive protein
IL
Interleukin
ISR
in stent restenosis
LAD
Left anterior descending
LCx
Left circumflex
LDL-c
Low density lipoprotein-cholesterol
LMCA
Left main coronary artery
MI
Myocardial infarction
PCI
percutaneous coronary intervention

RCA
Right coronary artery
SBP
Systolic blood pressure
STEMI
ST-segment elevation myocardial infarction
TC
Total cholesterol
TG
Triglycerides
TNF
Tumor Necrosis Factor
VSMC
vascular smooth muscle cells

Declarations

Acknowledgements

The authors are grateful to the patients and volunteers for their collaboration, the entire team for collecting blood samples from patients (Cardiology Department, Fattouma Bourguiba University Hospital, Monastir, Tunisia) for their technical support. Our study was funded by research organizations in Tunisia (Ministry of Public Health and Ministry of Higher Education and Scientific Research).

Author Contribution

Conceptualization, Hassen Ben Abdennabi; Data curation, Nadia Bouzidi; Formal analysis, Nadia Bouzidi and Majed Hassine; Investigation, Majed Hassine; Supervision, Hassen Ben Abdennabi; Writing – original draft, Nadia Bouzidi; Writing – review & editing, Majed Hassine and Hassen Ben Abdennabi. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data Availability Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval and consent to participate

The study was approved by the local Ethics Committee and was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

References

1. Jiro, A. & Kengo, T. Mechanisms of drug-eluting stent restenosis. *Cardiovasc. Interv Ther.* **36**, 23–29. <https://doi.org/10.1007/s12928-020-00734-7> (2021).
2. Hojo, Y. et al. Interleukin 6 expression in coronary circulation after coronary angioplasty as a risk factor for restenosis. *Heart* **84**, 83–87 (2000).
3. Jukema, J. W. et al. Restenosis after PCI. Part 1: pathophysiology and risk factors. *Nat. Rev. Cardiol.* **9**, 53–62 (2011).
4. Sonoda, S. et al. Impact of final stent dimensions on long-term results following sirolimus-eluting stent implantation: serial intravascular ultrasound analysis from the sirius trial. *J. Am. Coll. Cardiol.* **43**, 1959–1963 (2004).
5. Yanqiang, W. & Xianghua Fu. Comprehensive analysis of predictive factors for rapid angiographic stenotic progression and restenosis risk in coronary artery disease patients underwent percutaneous coronary intervention with drug-eluting stents implantation. *J. Clin. Lab. Anal.* **33**, e22666. [10.1002/jcla.22666](https://doi.org/10.1002/jcla.22666) (2019).
6. Wang, J. L. et al. New predictors of in-stent restenosis in patients with diabetes mellitus undergoing percutaneous coronary intervention with drug-eluting stent. *J. Geriatr. Cardiol.* **15**, 137–145 (2018).
7. Alfonso, F. et al. Value of the American College of Cardiology, American Heart Association angiographic classification of coronary lesion morphology in patients with in-stent restenosis. Insights from the Restenosis Intra-stent Balloon angioplasty versus elective Stenting (RIBS) randomized trial. *Am. Heart J.* **51**, e681–e689 (2006).
8. Chen, J. et al. Role of lipoprotein(a) in predicting the severity of new on-set coronary artery disease in type 2 diabetics: A Gensini score evaluation. *Diab Vasc Dis. Res.* **12**, 258–264. [10.1177/1479164115579004](https://doi.org/10.1177/1479164115579004) (2015).
9. Bouzidi, N. et al. Relationship of activin A levels with clinical presentation, extent, and severity of coronary artery disease. *Anatol. J. Cardiol.* **18**, 402–409 (2017).
10. Wang, Z., Liu, C. & Fang, H. Blood Cell Parameters and Predicting Coronary. *In-Stent Restenosis Angiol.* [10.1177/0003319719830495](https://doi.org/10.1177/0003319719830495) (2019). 70;711-8.

11. Wang, P. et al. The characteristics and risk factors of in-stent restenosis in patients with percutaneous coronary intervention: what can we do. *BMC Cardiovasc. Disord.* 510. <https://doi.org/10.1186/s12872-020-01798-2> (2020).
12. Hong, L. et al. Percutaneous coronary intervention of patients with complex small coronary artery lesion unsuitable for coronary artery bypass graft. *Zhonghua Yi Xue Za Zhi.* **90**, 107–109 (2010).
13. Monraats, P. S. et al. Genetic inflammatory factors predict restenosis after percutaneous coronary interventions. *Circulation* **12**, 2417–2425 (2005).
14. Murat, S. N. et al. The Relationship between Lymphocyte- to-Monocyte Ratio and bare-metal stent in-stent Restenosis in patients with stable coronary artery disease. *Clin. Appl. Thromb. Hemost.* **23**, 235–240. [10.1177/1076029615627340](https://doi.org/10.1177/1076029615627340) (2017).
15. Murat, S. N. et al. Comparison of changes in early inflammatory markers between sirolimus- and paclitaxel-eluting stent implantation. *Cardiovasc. Drugs Ther.* **23**, 137–143. [10.1007/s10557-008-6149-0](https://doi.org/10.1007/s10557-008-6149-0) (2009).
16. Pesarinia, G. Cytokines release inhibition from activated monocytes, and reduction of in-stent neointimal growth in humans. *Atherosclerosis* ; 242–248. (2010).
17. Bouzidi, N. et al. Relationship between high sensitivity C-reactive protein and angiographic severity of coronary artery disease. *J. Geriatr. Cardiol.* **17**, 256–263. [10.11909/j.issn.1671-5411.2020.05.003](https://doi.org/10.11909/j.issn.1671-5411.2020.05.003) (2020).
18. Benslaiman, S. H. et al. Pathophysiology of Atherosclerosis. *Int. J. Mol. Sci.* <https://doi.org/10.3390/ijms23063346> (2022). 23;3346.
19. Murayama, H. et al. Deficiency of tumour necrosis factor-alpha and interferon-gamma in bone marrow cells synergistically inhibits neointimal formation following vascular injury. *Cardiovasc. Res.* **80**, 175–180 (2008).
20. Jakubiak, G. K. et al. Pathogenesis and Clinical Significance of In-Stent Restenosis in Patients with Diabetes. *Int. J. Environ. Res. Public. Health.* **15**, 11970. [10.3390/ijerph182211970](https://doi.org/10.3390/ijerph182211970) (2021).
21. Żurkowski, A. et al. Plasma levels of C-reactive protein and interleukin-10 predict late coronary in-stent restenosis 6 months after elective stenting. *Kardiol Pol.* **67**, 623–630 (2009).
22. Li, J. J. et al. Impact of C-Reactive Protein on In-Stent Restenosis. *Heart Inst. J.* **37**, 49–57 (2010).
23. Bouzidi, N. et al. Association of the methylenetetrahydrofolate reductase gene rs1801133 C677T variant with serum homocysteine levels, and the severity of coronary artery disease. *Sci. Rep.* 2210064. [10.1038/s41598-020-66937-3](https://doi.org/10.1038/s41598-020-66937-3) (2020).
24. Kugler, E. et al. C Reactive Protein and Long-Term Risk for Chronic Kidney Disease: A Historical Prospective Study. *J. Nephrol.* **28**, 321–327. [10.1007/s40620-014-0116-6](https://doi.org/10.1007/s40620-014-0116-6) (2015).
25. Luo, Y., Tan, N. & Zhao, J. el. A Nomogram for Predicting In-Stent Restenosis Risk in Patients Undergoing Percutaneous Coronary Intervention: A Population-Based Analysis. *Int. J. Gen. Med.* (3), 2451–2461. [10.2147/IJGM.S357250](https://doi.org/10.2147/IJGM.S357250) (2022).

26. Gai, M. T. et al. Comparison of Gensini score and SYNTAX score for predicting in-stent restenosis in patients with coronary artery disease and drug-eluting stent implantation. *Sci. Rep.* **7**, 1077. 10.1038/s41598-025-85191-z (2025).
27. Yıldırım, E. et al. Relationship between the extent of coronary artery disease and in-stent restenosis in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Turk. Kardiyol Dern Ars.* **45**, 702–708. 10.5543/tkda.2017.72921 (2017).
28. Wang, J. et al. Predictors of Stent Restenosis in Han and Uygur Patients with Coronary Heart Disease after PCI in the Xinjiang Region. *Cardiol. Res. Pract.* 2022 **312022**:7845108. 10.1155/2022/7845108

Figures

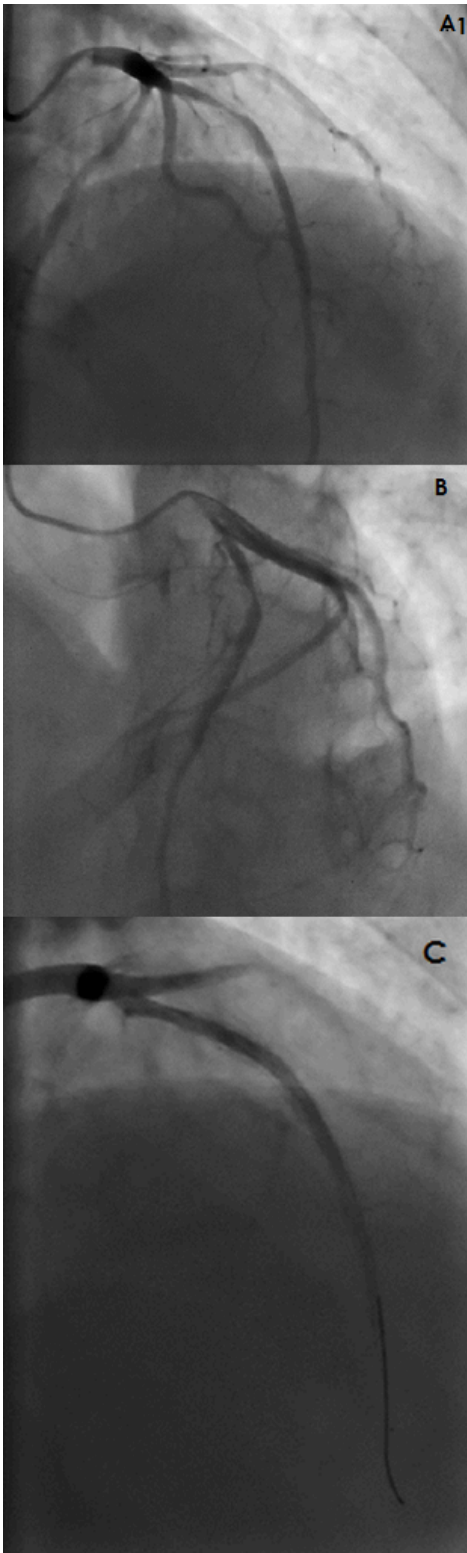


Figure 1

Receiver operating characteristic curve of IL-6, HsCRP, GS in predicting ISR in CAD patients who underwent drug-eluting stent implantation. ROC area analysis were A: 0.674 (95% CI: 0.523 - 0.824), $p = 0.04$); (B: 0.602 (95% CI: 0.459 - 0.745), $p = 0.171$); C: 0.717 (95% CI: 0.560-0.874), $p = 0.012$), for GS, HsCRP and IL-6 respectively.

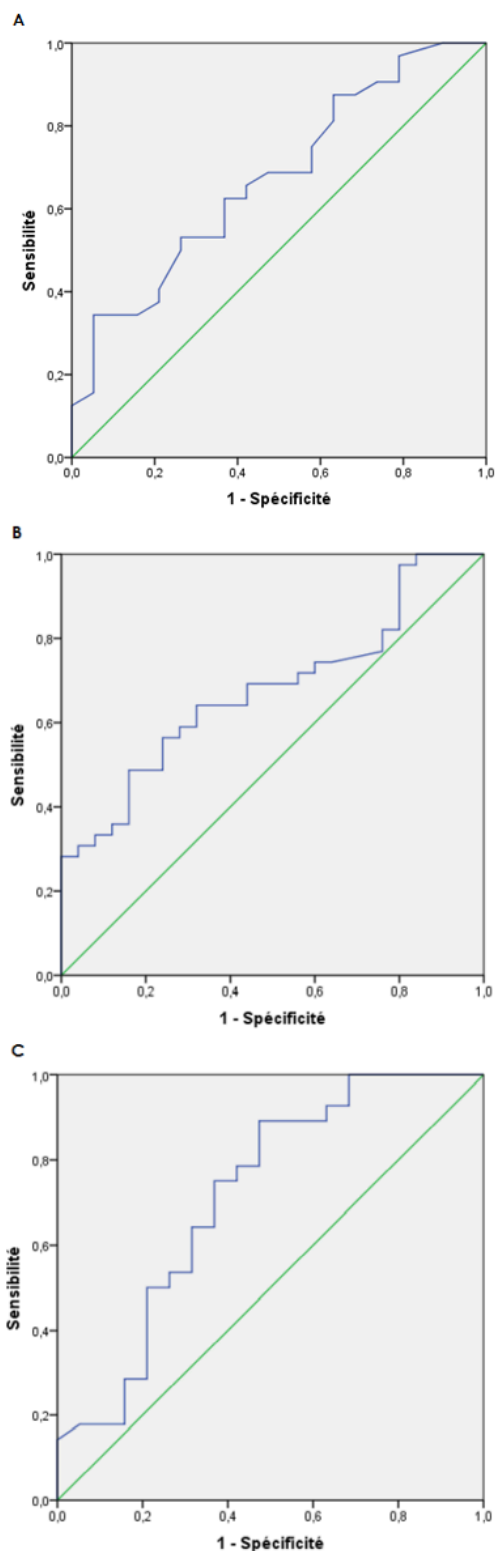


Figure 2

A coronary angiography performed revealing a focal in-stent restenosis with reduction $\geq 50\%$ of the luminal diameter (Figure 2A, 2B), which was successfully treated with drug coated balloons (Figure 2 C).