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ORIGINAL RESEARCH

A Nomogram for Predicting In-Stent Restenosis Risk in Patients Undergoing Percutaneous Coronary Intervention: A Population-Based Analysis

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Objective: In-stent restenosis (ISR) is a fatal complication of percutaneous coronary intervention (PCI). An early predictive model with the medical history of patients, angiographic characteristics, inflammatory indicators and blood biochemical index is urgently needed to predict ISR events. We aim to establish a risk prediction model for ISR in CAD patients undergoing PCI.

Methods: A total of 477 CAD patients who underwent PCI with DES (drug-eluting stents) between January 2017 and December 2020 were retrospectively enrolled. And the preoperative factors were compared between the non-ISR and ISR groups. The least absolute shrinkage and selection operator (LASSO) and multi-factor logistic regression were used for statistical analysis. The prediction model was evaluated using receiver operator characteristic (ROC) analysis, the Hosmer–Lemeshow 2 statistic, and the calibration curve.

Results: In this study, 94 patients developed ISR after PCI. Univariate analysis showed that post-PCI ISR was associated with the underlying disease (COPD), higher Gensini score (GS score), higher LDL-C, higher neutrophil/lymphocyte ratio, and higher remnant cholesterol (RC). The multi-factor logistic regression analysis suggested that remnant cholesterol (odds ratio [OR] = 2.09, 95% confidence interval [CI] [1.40–3.11], P < 0.001), GS score (OR = 1.01, 95% CI [1.00, 1.02], P = 0.002), medical history of COPD (OR = 4.56, 95% CI [1.98, 10.40], P < 0.001), and monocyte (OR = 1.30, 95% CI [1.04, 1.70], P < 0.001) were independent risk factors for ISR. A nomogram was generated and displayed favorable fitting (Hosmer-Lemeshow test P = 0.609), discrimination (area under ROC curve was 0.847), and clinical usefulness by decision curve analysis.

Conclusion: Patients with certain preoperative characteristics, such as a history of COPD, higher GS scores, higher levels of RC, and monocytes, who undergo PCI may have a higher risk of developing ISR. The predictive nomogram, based on the above predictors, can be used to help identify patients who are at a higher risk of ISR early on, with a view to provide post-PCI health management for patients.

Keywords: in-stent restenosis, ISR, percutaneous coronary intervention, PCI, coronary heart disease, CHD, nomogram map

Introduction

Coronary heart disease (CHD), with high morbidity and high mortality rate, is still a serious public health concern around the world. PCI is fast becoming a key instrument in revascularization for patients with CHD, as well as an important technology in the management of CHD patients.[1] Although the clinical application of coronary stents brought about a dramatic improvement in patients' clinical and procedural outcomes, the mid-and long-term outcome of stent implantation remains significantly hampered by the risk of developing ISR with a prevalence rate of 3–20% over time[1,2] Predictive models have the advantage of formally combining risk factors to allow more accurate risk estimation. And it is essential to establish a model to predict ISR in patients with CAD and drug-eluting stents (DESs) implantation.

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The risk factors for ISR after PCI were systematically summarized. The preoperative factors comprised the following: the morphological characteristics of the diseased vessel, the location of the lesion, the degree of stenosis, and part of blood biochemical indicators which are associated with inflammatory responses and lipid metabolism.[3–8] Among these, the levels of monocyte and LDL-C are considered to be critical factors related to inflammatory response and to lipid metabolism,[9–11] respectively.

Although a few previous studies have analyzed potential predictors related to the high incidence rate of ISR and established a relevant nomogram for ISR in patients undergoing PCI, there are still limitations to the predictive model. As a starting point, new factors for inflammatory response and lipid metabolism have emerged in recent years. Such as the neutrophil/lymphocyte ratio[12,13], which reflects the body's levels of oxidative stress and inflammation, as well as residual cholesterol, which is a more accurate indicator of the body's lipid metabolism than LDL cholesterol.[14,15] Secondly, the majority of prediction models lacked a quantitative predictor of coronary lesions before PCI, such as the GS score system, a technique based on the artery morphology, coronary anatomy, and severity of stenosis in lesions.

Currently, a new preoperative model based on preoperative blood biochemical parameters for PCI, a technique for assessment for the severity of CAD, and procedural characteristics are scarce to evaluate the probability of ISR. The aim of this study was to analyzed post-PCI ISR patients in preoperative blood biochemical parameters for PCI, GS scores,[16] and procedural characteristics. This work will generate fresh insight into developing a preoperative risk factor nomogram that may help clinicians discern high-risk ISR patients, optimize treatment strategies.

Materials and Methods

According to the Declaration of Helsinki, this study was approved by the Ethics Committee of the Central Hospital of Enshi Autonomous Prefecture. Due to the retrospective nature of this study, patient consent was waived for the evaluation of their medical information. This study was an analysis of an observational cohort study conducted from January 2017 to December 2020 at Enshi Central Hospital, China. A total of 1015 CAD patients undergoing PCI with DES were enrolled. All patients took statins and anti-platelet aggregation drugs regularly after surgery, and all received 6–24 months of follow-up coronary angiography. Patients were excluded if they (1) had a history of coronary artery bypass grafting, heart failure (cardiac function class more than 4), (2) active or acute inflammatory diseases, (3) had a liver failure or renal failure, (4) had evidence of active infection, such as fever, cough, or diarrhea, and (5) were missing clinical and angiographic data (Figure 1). The main outcome measure was ISR, which is defined as ≥50% luminal narrowing at follow-up angiography.

Demographic information, biochemical parameters, clinical, and angiographic characteristics were collected. Demographic information and clinical characteristics included age, gender, chronic obstructive pulmonary disease, diabetes, stroke, smoking, and patient medication history (ACEI, diuretic). Biochemical parameters included platelet parameters of platelet distribution width (PDW), leukocytes, monocytes, mean platelet volume (MPV), glucose (GLU), neutrophils (N), lymphocyte, monocyte, hemoglobin (Hb), platelet, procalcitonin (PCT), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), the width of red blood cell volume distribution (RDW), alanine transaminase (ALT), creatinine (Cr) and left ventricular systolic function (EF%). The specific data concerning the angiography information included stent numbers, GS score, lesion location (left main coronary artery, left circumflex artery, left anterior descending branch, right coronary artery and others. RC = TC- LDL-C- HDL-C. The neutrophil/lymphocyte ratio = the neutrophil count /the lymphocyte count. The GS score was calculated using the scoring schema defined by Gensini et al.[16]

R software version 3.6.3 was used for statistical analysis, and two-tailed analysis with P. The Student's *t*-test was used to detect differences between continuous variables with a normal distribution. The chi-square test or Fisher's exact test was used to compare categorical variables. In the cases of skewed distribution, data were expressed as IQR and compared using the Mann–Whitney *U*-test. LASSO-penalized regression analysis, which is capable of estimating parameters in high-dimensional regression, was used to select ISR predictors with the R package Glmnet. The Hosmer–Lemeshow 2 statistic, calibration curve, and 1000-fold bootstrap were used to test the prediction model.

We assessed the nomogram model performance in terms of discrimination, calibration plots, and the Hosmer–Lemeshow 2 statistic. The discrimination of the model has been validated through Area under the ROC, which implies

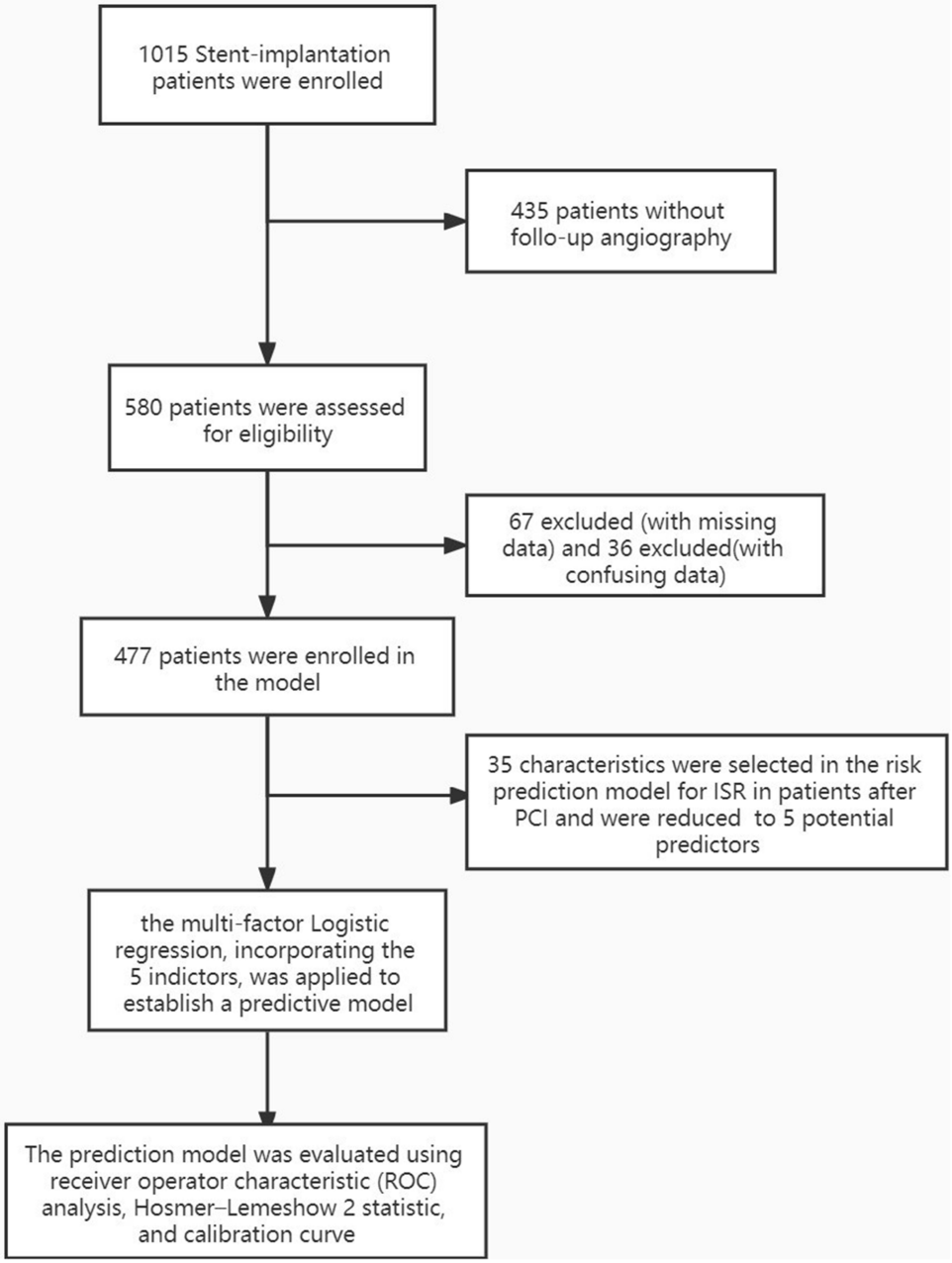

Figure 1 The study design and the selection procession of CAD patients.
Abbreviation: receiver operator characteristic.

the better accuracy of the nomogram. The diagnostic value of models whose AUC is between 0.7 and 0.8 and Hosmer–Lemeshow 2 > 0.05 is acceptable A very perfect agreement was observed in the calibration plot of our nomogram. Concerning its clinical usefulness, we performed decision curve analysis (DCA) to assess if clinical decisions taken based on this model would improve patient outcomes.

Results

According to the inclusion and exclusion criteria, 1015 patients were screened, and 477 patients with complete follow-up data were selected. A total of 477 patients was enrolled and divided into the ISR group (94) and the non-ISR group (383), according to the main outcome indicator (ISR). The baseline characteristics of the patients are shown in Table 1.

Table 1 The Baseline Characteristics of the Patients

Characteristics	ISR=No (n=383)	ISR=Yes (n=94)	P-value
Gender, N (%)			0.977
Female	82 (21.4)	20(21.3)	
Male	301 (78.6)	74(78.7)	
Hypertension, N (%)			0.961
No	194 (50.8)	48(51.1)	
Yes	188 (49.2)	46(48.9)	
COPD, N (%)			< 0.001
No	368 (96.1)	80 (85.1)	
Yes	15 (3.9)	14 (14.9)	
Diabete, N (%)			0.342
No	325 (84.9)	76(80.9)	
Yes	58 (15.1)	18(19.1)	
Stroke, N (%)			0.389
No	377 (98.4)	91 (96.8)	
Yes	6 (1.6)	3 (3.2)	
Smoking, N (%)			0.226
No	169 (44.1)	35 (37.2)	
Yes	214 (55.9)	59 (62.8)	
Multi_vessel, N (%)			0.84
No	102 (26.6)	26 (27.7)	
Yes	281 (73.4)	68(72.3)	
Left main coronary artery, N (%)			0.259
No	344 (89.8)	88 (93.6)	
Yes	39 (10.2)	6 (6.4)	
Left circumflex artery, N (%)			0.264
No	163 (42.6)	46 (48.9)	
Yes	220 (57.4)	48 (51.1)	
Left anterior descending branch, N (%)			0.631
No	46 (12)	13 (13.8)	
Yes	337 (88)	81 (86.2)	
Right coronary artery and others, N (%)			0.401
No	137 (35.8)	38 (40.4)	
Yes	246 (64.2)	56 (59.6)	
ACEI, N (%)			0.113
No	70 (18.3)	24 (25.5)	
Yes	313 (81.7)	70 (74.5)	
Diuretic, N (%)			0.352
No	321 (83.8)	75 (79.8)	
Yes	62 (16.2)	19 (20.2)	
Age, median(IQR)	61 (54,68)	63 (55,68)	0.48
The_number_of_stents, median(IQR)	1 (1,2)	1 (1,2)	0.772
GS_grade, median(IQR)	40 (22.5,68)	48 (38,80.8)	< 0.001
Leukocyte(10^9/L), median(IQR)	7.2 (5.8,8.9)	6.8 (5.6,8.3)	0.172
N(10^9/L), median(IQR)	4.6 (3.5,6.4)	4.6 (3.6,6.3)	0.623
Lymphocyte(10^9/L), median(IQR)	1.6 (1.2,2)	1.6 (1,2.1)	0.902
Monocyte(10^9/L), median(IQR)	0.4 (0.3,0.5)	0.4 (0.4,0.6)	0.112
Hb(g/L), median(IQR)	136 (124,147)	138.5 (129.2148.8)	0.474
PDW	16.4 (16.1,16.6)	16.4 (16.2,16.6)	0.415
Platelet(10^9/L), median(IQR)	188 (157,227.5)	183.5 (162.2213)	0.473
MPV(fl), median(IQR)	10.8 (9.9,11.7)	10.4 (9.6,11.7)	0.256
PCT, median(IQR)	0.2 (0.2,0.2)	0.2 (0.2,0.2)	0.716

(*Continued*)

Table 1 (Continued).

Characteristics	ISR=No (n=383)	ISR=Yes (n=94)	P-value
RDW, median(IQR)	12.9 (12.5,13.3)	12.8 (12.4,13.3)	0.295
ALT, median(IQR)	27 (18,43)	27 (21,39)	0.963
TC, median(IQR)	4.7 (4.1,5.4)		0.062
TG, median(IQR)	1.6 (1.1,2.2)	1.5 (1.1,2)	0.506
HDL_C[(mmol/L), IQR]	1 (0.9,1.2)	1.1 (0.8,1.2)	0.917
LDL_C[(mmol/L), IQR]	3 (2.5,3.5)	2.6 (2,3.1)	< 0.001
Glu(IQR)	5.3 (4.7,6.3)	5.4 (4.7,6.4)	0.571
Cr[(umol/L), IQR]	73.2 (62.7,85.8)	71.2 (60.5,83)	0.459
EF%, median(IQR)	60 (54,66)	60 (54.2,63.8)	0.345
RC(mmol/L), median(IQR)	0.6 (0.4,0.8)	0.7 (0.4,1.2)	< 0.001
Ratio, median(IQR)	2.7 (2,4)	3.3 (1.9,5.4)	0.124

Abbreviations: COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitors; N, neutrophils; GS scores, Gensini score; Hb, hemoglobin; PCT, platelet, procalcitonin; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RC, remnant cholesterol; RDW, the width of red blood cell volume distribution; ALT, alanine transaminase; Cr, creatinine; Ef%, left ventricular systolic function.

Of CAD patients included in our study, 94 subjects (19.3%) had ISR. Most of the baseline characteristics between the two groups were similar, such as gender, underlying disease (hypertension, diabetes, stroke), medication history (diuretic, ACEI), smoking, lesion location, ALT, Hb, PDW, RDW, MPV, PLT, TG, TC, TG, HDL-C, monocyte, neutrophil/lymphocyte ratio and Cr. However, as Tables 1 shown, underlying disease (COPD), GS score, LDL-C, and RC showed significant differences between the groups (all $P < 0.05$).

The feature selection of the risk prediction model for ISR in patients after PCI is based on the 477 patients in the cohort (parameter selection is shown in Figure 2). 35 features were reduced to 5 potential predictors, and non-zero coefficients were used in the LASSO regression model. Those factors include: history of COPD, GS score of vascular assessments before PCI, monocyte, RC, and neutrophil/lymphocyte ratio. The Norman diagram based on the regression coefficient is shown in Figure 3.

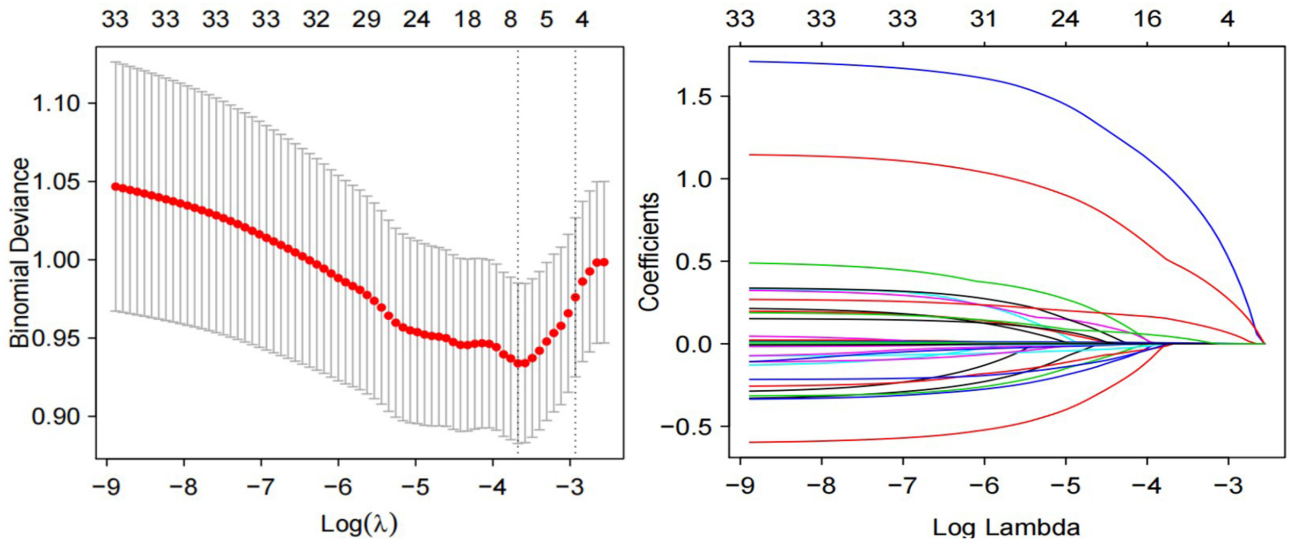

Figure 2 Risk factors selecting using LASSO model.
Notes: (Left panel) Optimal parameter (lambda) selection for the LASSO model was cross validated five the minimum criterion. Partial likelihood deviation (binomial deviation) curves versus log(lambda). Dotted vertical lines are drawn at the best values of 1SE (1-SE criterion) using the minimum criterion and the maximum criterion. (Right) LASSO coefficient profiles for 35 characteristics. The coefficient profiles were produced from log (lambda) sequences.The vertical lines are drawn on the value selected using five fold cross validation, where the best lambda resulted in non-zero coefficients for five features.

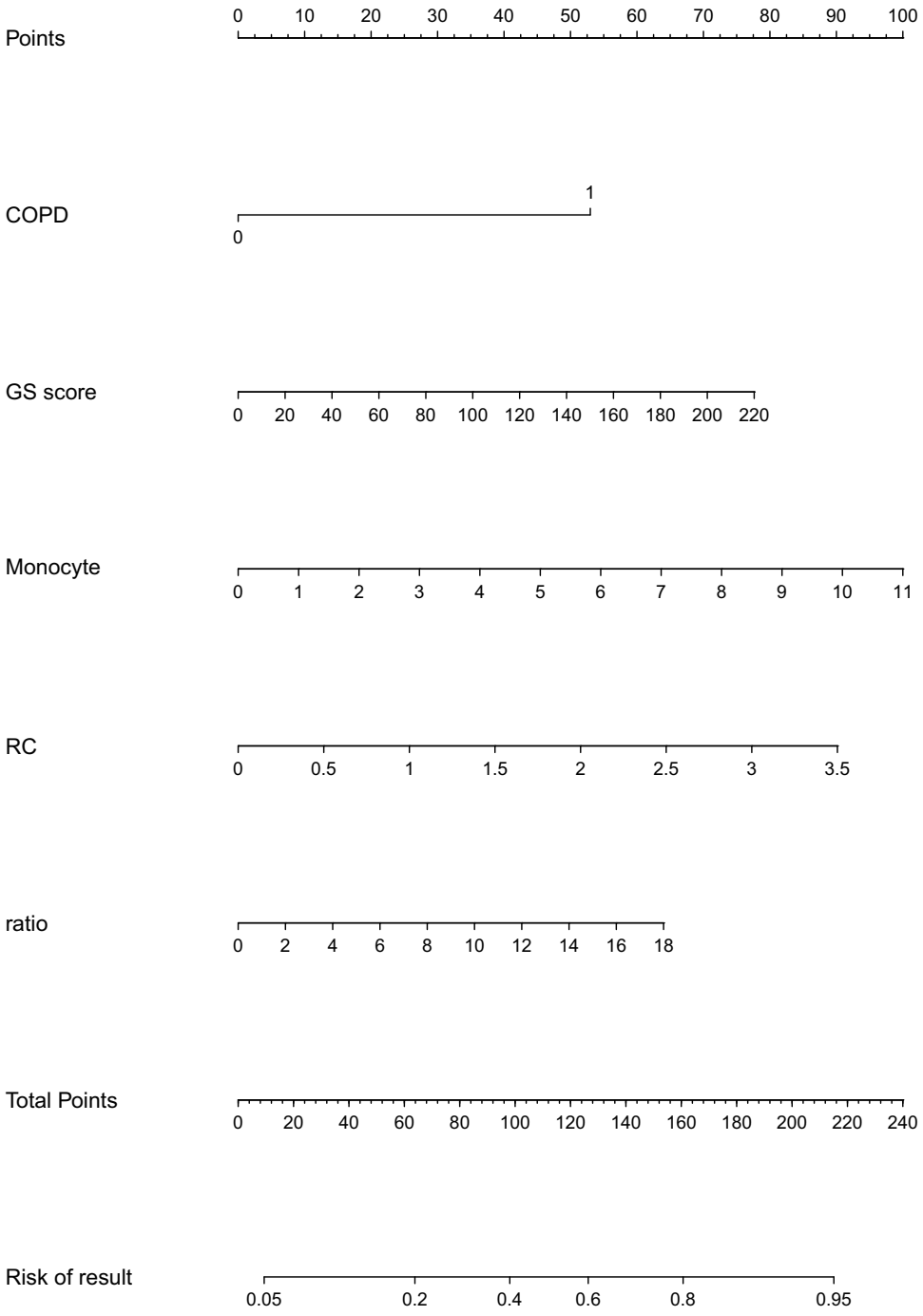

Figure 3 Nomogram to predict the probability of ISR in patients with stent implantation.
Notes: The nomogram included a medical history of COPD, GS score of vascular assessment before PCI, RC, monocyte, neutrophil/lymphocyte ratio.
Abbreviations: COPD, chronic obstructive pulmonary disease; GS scores, Gensini score; RC, remnant cholesterol.

The binary multivariate logistic regression comprised features selected from the lasso-penalized regression analysis (Table 2). The 5 independent risk factors for ISR were COPD, GS score, monocyte, RC, and neutrophil/lymphocyte ratio. The collinearity diagnostic test indicated that there was no significant collinearity between the independent variables in the regression model, and the variance inflation factors (VIFs) were 1.012, 1.006, 1.024, 1.037, and 1.008, respectively (all VIFs<10).

Table 2 Multivariable Logistic Regression Analysis of Predictors of ISR

Characteristics	OR	95% CI	P value
COPD	4.56	1.98–10.40	<0.001
GS scores	1.01	1.00–1.02	0.002
RC	2.09	1.40–3.11	<0.001
Monocyte	1.3	1.04–1.70	0.035
Neutrophil/lymphocyte ratio	1.11	1.01–1.21	0.021

Abbreviations: CI, Confidence interval; COPD, chronic obstructive pulmonary disease; RC, remnant cholesterol.

Internal validation was performed with 1000 repeats, and the results were consistent. In addition, the AUC of the prediction model was 0.841 (Figure 4). A Hosmer–Lemeshow goodness-of-fit test was performed to evaluate this prediction model, yielding P = 0.609, and a calibration curve was also provided in Figure 5, confirming no divergence between anticipated and observed probability. Figure 6 shows the decision curve analysis for the ISR nomogram. The results showed that the nomogram might be used to forecast the likelihood of ISR in patients having PCI with high accuracy and a broader range of threshold probabilities, and it could have clinical implications.

Discussion

PCI is the mainstay of revascularization in patients with coronary artery disease, and in-stent restenosis remains a problem that greatly affects the long-term prognosis of post-PCI patients. The safety of stent implantation has significantly increased in recent years as a result of technological developments. ISR, on the other hand, remains one of the most significant issues. The ISR rate reached 19.7% (94/477) in our research, which was consistent with previous studies (3–20%).[3] Life-threatening consequences can arise should the ISR continue to deteriorate without prompt recognition and treatment. Therefore, early identification of risk factors for ISR is crucial in preventing major

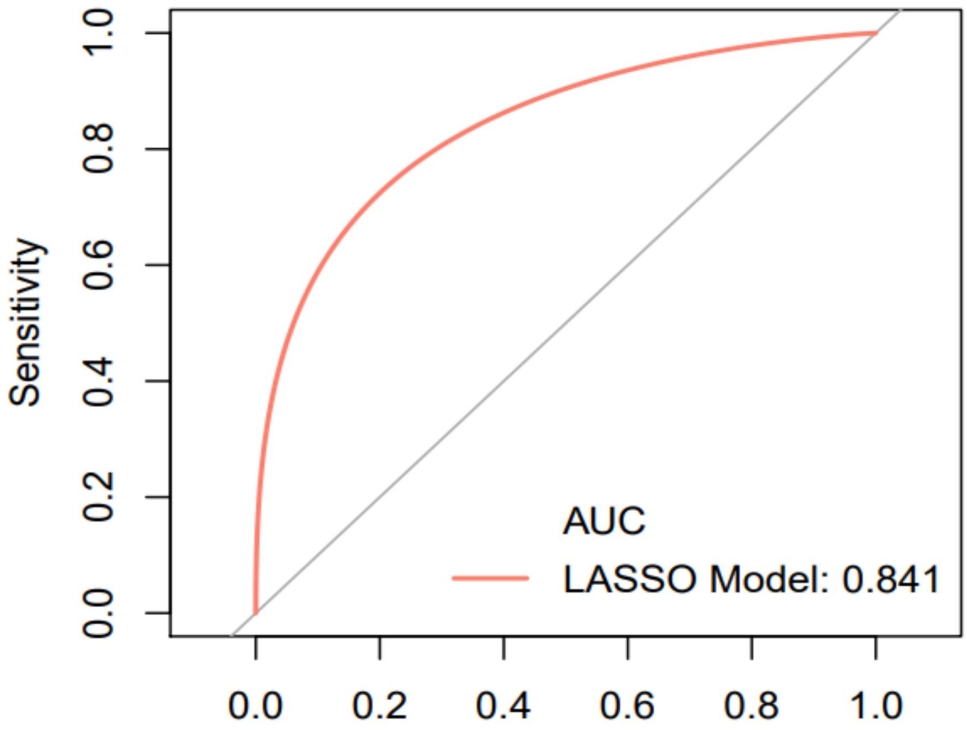

Figure 4 ROC curves for validating the discrimination power of nomogram.
Abbreviation: ROC, receiver operator characteristic.

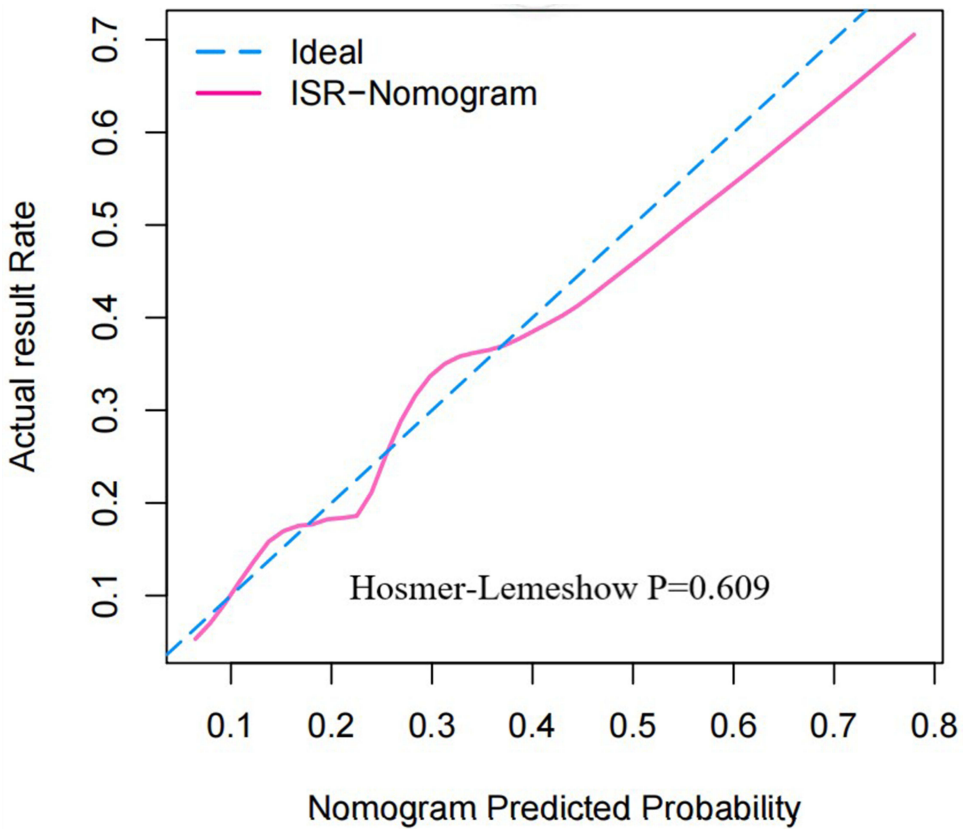

Figure 5 Calibration plots of the nomogram for the probability of PCI patients with ISR.
Notes: The x-axis represents prediction probability. The y-axis represents the actual probability. The diagonal dotted line represents a perfect prediction by an ideal model. The solid line represents the performance of the nomogram, of which a closer fit to the diagonal dotted line represents a better prediction.

postoperative complications. Herein, we firstly developed a nomogram utilizing the five preoperative predictors from the multivariate analysis: a medical history of COPD, monocytes, GS score, RC, and neutrophil/lymphocyte ratio.

Previous studies[5,6] summarized the predictors of ISR as follows: medication history (eg, clopidogrel), prior PCI, stent characteristics, and some indicators concerning inflammatory responses and lipid metabolism (eg, TC, LDL-C, CRP, monocyte).[11]

Similar to the previous studies,[11] we also found that monocytes can be one of the independent risk factors for ISR. Nan et al reported that activated monocytes release large amounts of pro-inflammatory cytokines, and then cause vasoconstriction and non-specific recruitment, proliferation, and activation of other cells, including vascular smooth muscle cells in the vascular wall, which may account for the results in our study.

Another systemic factor noted in our study to be closely related to ISR after PCI is preoperative neutrophil/lymphocyte ratio, the index associated with inflammatory response and neointimal proliferation,[4,5,17,18] which was consistent with the previous research that neutrophil/lymphocyte is a strong inflammatory marker[19–22] and closely associated with Cardiovascular disease. In contrast to previous reports, we also discovered that RC had a higher predictive value for ISR than LDL-C. According to relevant literature,[7,23,24] an increase in fasting RC level increases the degree of coronary atherosclerosis stenosis and RC may be a better indicator of lipid metabolism in the body than LDL cholesterol.

Interestingly, we also found that patients with chronic obstructive pulmonary disease may have a higher risk of developing ISR. According to relevant literature,[9,25–28] this could be due to the fact that COPD and CVD have similar risk factors. Low-grade systemic inflammation is one of the primary processes that may be responsible for the systemic impacts on distant illnesses and the increased rate of comorbidity, particularly cardiovascular comorbidity, in COPD

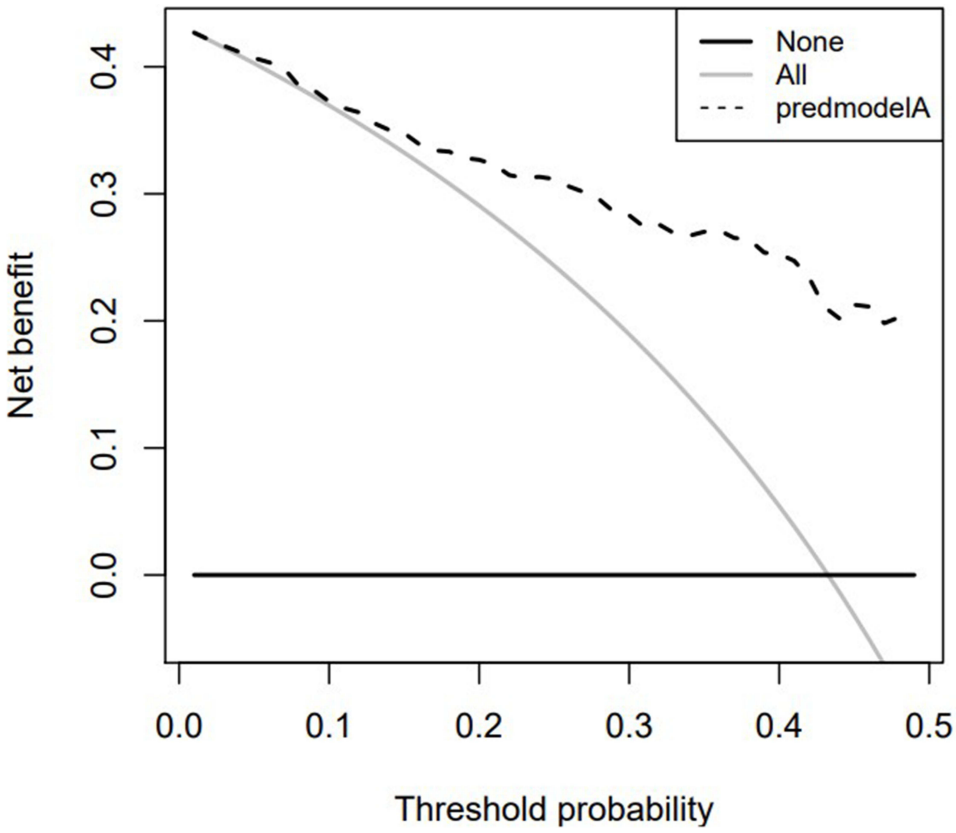

Figure 6 Decision curve analysis for the ISR prediction nomogram.
Notes: The ISR risk nomogram is represented by the dotted line. The thin solid line denotes the expectation that all patients are affected by ISR. The thick solid line denotes the assumption that there are no patients with ISR. When the threshold probability is >4.5, decision curve analysis demonstrates that adopting this ISR prediction nomogram has a net benefit.

patients.[28] Regretfully, no relevant mechanistic investigations have been conducted to explain why a history of COPD can predict the occurrence of ISR, which will be the subject of our next research.

The most interesting finding was that GS score is an independent predictor of ISR. It is known that the morphological characteristics of the diseased vessel, the location of the lesion, and the degree of stenosis can make PCI procedures more difficult and increase the risk of preoperative vascular injury, leading to ISR. These factors have been shown to be independent risk factors for ISR,[2] but no quantitative assessments of diseased vessels have been considered in any published models and no studies have examined whether the GS score, which combines these characteristics, is a strong predictor of ISR. And we improved that GS score is a strong predictor of ISR in CAD patients for the first time.

And in previous studies,[8,29,30] the level of the prognostic utility of the ISR prediction model was still not entirely satisfactory, with a C-statistic below 0.7. We, therefore, developed a predictive model based on the GS score, a proxy for coronary lesion factors,[31,32] and other predictors for patients undergoing PCI in the Enshi region.

Nevertheless, the research still has several limitations. First of all, its validity is limited by the small sample size and the low number of events although our sample size had met the required the minimum sample size of building the model 0.80 is 140. Furthermore, this was a single-Center study with no external validation. Despite an internal validation, the prediction model's generalization may be compromised. Lastly, the study had a retrospective design with an inadequate level of evidence.

Conclusion

Above all, in the Enshi population, we created a new prediction model based on the history of COPD, GS score of vascular assessment before PCI, monocyte, RC, and neutrophil/lymphocyte ratio, to help clinicians discern high-risk ISR patients, optimize treatment strategy, thus improve the prognosis of these patients. Furthermore, we visualized the

prognostic risk factors in LASSO regression by using nomogram, evaluated the accuracy and clinical practicability of the predictive model by using DCA and Calibration curve. And it is found that the model is satisfactory in terms of goodness of fit, clinical usefulness, and accuracy.

Abbreviations

ISR, in-stent restenosis; DES, drug-eluting stents; PCI, percutaneous coronary intervention; LASSO, least absolute shrinkage and selection operator; ROC, receiver operator characteristic; RC, residual cholesterol; GS score, Gensini score; TC, total cholesterol; DCA, decision curve analysis; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; PDW, platelet distribution width; MPV, mean platelet volume; GLU, glucose; N, neutrophils; LY, lymphocyte; MNC, monocyte; Hb, hemoglobin; PLT, platelet count; TC, total cholesterol; TG:triglycerides; HDL-C: high-density lipoprotein cholesterol,; LDL-C, low-density lipoprotein cholesterol; RDW, width of red blood cell volume distribution; ALT, alanine transaminase; AST, aspartate transaminase; LpA1, lipoprotein A1; LpB1, lipoprotein B1; Apo a, apolipoprotein a; Cr, creatinine; TSH, thyroid-stimulating hormone; EF%, left ventricular ejection fraction; SD, standard deviation; PCT, procalcitonin.

Data Sharing Statement

All relevant data supporting the conclusions of this article are included within the article.

Ethical Approval

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patient for publication of this study and any accompanying images. The study was approved by Ethical Committees of Central Hospital of Enshi Tujia and Miao Autonomous Prefecture. The data are anonymous, and the requirement for informed consent was therefore waived.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

Yinhua Luo and Ni Tan are co-first authors for this study. The authors report no conflicts of interest in this work.

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