Development and Validation of a Risk Prediction Nomogram for In-Stent Restenosis in Patients Undergoing Percutaneous Coronary Intervention

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Abstract

Background: This study aimed to develop and validate a nomogram to predict probability of in-stent restenosis (ISR) in patients undergoing percutaneous coronary intervention (PCI).

Methods: Patients undergoing PCI with drug-eluting stents between July 2009 and August 2011 were retrieved from a cohort study in a high-volume PCI center, and further randomly assigned to training and validation sets. The least absolute shrinkage and selection operator (LASSO) regression model was used to screen out significant features for construction of nomogram. Multivariable logistic regression analysis was applied to build a nomogram-based predicting model incorporating the variables selected in the LASSO regression model. The area under the curve (AUC) of the receiver operating characteristics (ROC), calibration plot and decision curve analysis (DCA) were performed to estimate the discrimination, calibration and utility of the nomogram model respectively.

Results: A total of 463 patients with DES implantation were enrolled and randomized in the development and validation sets. The predication nomogram was constructed with five risk factors including prior PCI, hyperglycemia, stents in left anterior descending artery (LAD), stent type, and absence of clopidogrel, which proved reliable for quantifying risks of ISR for patients with stent implantation. The AUC of development and validation set were 0.706 and 0.662, respectively, indicating that the prediction model displayed moderate discrimination capacity to predict restenosis. The high quality of calibration plots in both datasets demonstrated strong concordance performance of the nomogram model. Moreover, DCA showed that the nomogram was clinically useful when intervention was decided at the possibility threshold of 9%, indicating good utility for clinical decision-making.

Conclusions: The individualized prediction nomogram incorporating 5 commonly clinical and angiographic characteristics for patients undergoing PCI can be conveniently used to facilitate early identification and improved screening of patients at higher risk of ISR.

Background

Coronary heart disease severely threatens the health of individuals worldwide with a rising incidence and a leading cause of mortality. Revascularization with percutaneous coronary intervention (PCI) is a well-established and effective therapeutic strategy for advanced coronary heart disease, particularly following the introduction of drug-eluting stents (DES) [1]. While DES substantially reduce the incidence of in-stent restenosis (ISR) and target lesion revascularization in contrast to the bare-metal stents (BMS), they do not eliminate it. In clinical practice, some patients treated with DES still need to receive revascularization again even if they adhere to standard drug therapy after PCI. ISR after DES implantation with an incidence of 3%~20% remains a pervasive clinical problem which should not be neglected [2–4]. Given that, tools for the identification of individual patients at higher risk for ISR with stents implantation are additionally warranted.
Although several prior studies have analyzed potential predictive factors associated with a high incidence of ISR based on patient and procedure related factors, there are still some limitations that restrict clinical application. Prediction model for ISR is yet to be fully developed and validated. Quite a few of studies in DES populations have been thoroughly validated in an independent dataset, raising questions as to whether the development model had wide adaptability in the other independent cohort as well [5–7]. Of note, most studies have only focused on comprehensively identifying the predictors of ISR or developing prediction models without an individual risk prediction tool, while the simplicity and ease of use for the clinicians and patients were not well considered [7–9]. Thus, we believe that accurate prognostication of future events requires a more solid, well-validated and easy-to-use clinical model for all patients with stent implantation, in particular for clinical decision in primary prevention.

The nomogram-based predicting model has been widely implemented in clinical studies. Featured by the advantage of visualization, a well-developed nomogram based on statistical regression models is a forceful tool to make clinical decisions for clinicians and to assess straightforward the probability of disease for individual patients without complex formula, thus could benefit both doctors and patients.

Based on these premises, the aim of this study was to identify factors correlated to the risk of ISR for individual patients undergoing PCI, using data from an observational single-center registry study. These factors were used to develop and validate a nomogram-based clinical prediction model. This model could help clinicians discern high-risk ISR patients, optimize treatment strategy, and improve prognosis of these patients.

**Methods**

**Study Population**

This study was a secondary analysis of an observational cohort study conducted between July 2009 and August 2011, in a high-volume PCI center, in Henan Province, China [10]. A total of 2,533 patients undergoing PCI with drug-eluting stents were enrolled and the median follow-up time was 29.8 months. The protocol was approved by the ethical committee in accordance with local regulations. The original work was in accordance with the Creative Commons Attribution Non-Commercial (CC BY-NC 3.0) license. The datasets analyzed during the current study are available in the Dryad data repository, https://doi.org/10.5061/dryad.13d31 [11]. Dyrad belonging to public databases is a non-profit membership organization that is committed to making data available for research and educational reuse. Informed consent was waived because this is a post-hoc study using available data.

The goal of this study was to identify factors associated with ISR in the patients with DES implantation, considering individual patient characteristics and their independent connection with ISR events. Generally, binary angiographic restenosis is defined as $\geq 50\%$ luminal narrowing at follow-up angiography. Thus, we excluded 1,930 patients who were lost to angiographic follow-up and 116 patients with missing data.
In addition, 24 patients with > 1 type of stent but whose location of stents remained uncertain were also screened out. After these exclusions, 463 patients were randomized and analyzed (Fig. 1).

**Risk Factors**

A total of 36 candidate variables potentially associated with ISR events based on clinical plausibility and previous studies were identified for further processing. The variables considered in this study were clinical characteristics (age, gender, presentation, old myocardial infarction, prior PCI, heart failure, atrial fibrillation, hypertension, diabetes mellitus, smoking), laboratory tests (systolic BP, diastolic BP, glycemia, uric acid, LDL-C), lesion and procedure characteristics (acute occlusion lesions, chronic total occlusions, restenotic lesions, location of stents, number of treated vessels, stent type, stent number, total stent length, stent diameter), and use of medications (aspirin, clopidogrel, statins, β-receptor blockers, ACEIs/ARBs, calcium channel blockers).

**Statistical analysis**

To facilitate ease of use, all independent variables were transformed into categorical variables and expressed as count (%) based on confirmation that the gradient of effect was maintained. Statistical analysis was performed using the R software version 3.6.3, and two-tailed analysis with $P < 0.05$ was considered statistically significant.

We randomly designated 70% of the study population as the development set, while the rest were divided into the validation set. Patients in the development and validation set were compared using Chi-square test. The LASSO-penalized regression analysis, which is competent to estimate the parameters in high-dimensional regression, was applied to select predictors of ISR using the R package Glmnet [12, 13]. After the ISR predictors were confirmed, multivariable logistic regression analysis was used in the development set to evaluate the predictors and construct a nomogram predicting model along with their associated odds ratios (OR), 95% confidence intervals (CI), β-coefficients, and $P$-value.

The nomogram model performance was evaluated in terms of discrimination and calibration. The discrimination of the model was assessed by calculating the area under the curve (AUC) of the receiver operating characteristics (ROC), which indicated the predictive accuracy of the nomogram. Generally, the diagnostic accuracy with an AUC equal or above 0.6 is considered acceptable [14, 15]. Calibration plots were used for the comparison between the predicted and observed probabilities in both sets, and a significant difference implies the poor calibration of the prediction model. Furthermore, decision curve analysis (DCA) plotted net benefit (NB) at a range of clinically reasonable risk thresholds, helping assess the clinical usefulness of the model for decision making [16].

**Results**

**Patient characteristics**
A total of 463 patients undergoing PCI with drug-eluting stents were enrolled and randomized in this study, including 325 in the development set and 138 in the validation set. Table 1 lists 36 variables including the following aspects: clinical characteristics, laboratory findings, lesion and procedure characteristics, and use of medications for all randomized patients. Of these, 111 patients (77 in the development set and 34 in the validation set) developed in-stent restenosis. Comparisons between the development and validation sets showed no significant differences in all ISR risk-related variables (all P > 0.05).
Table 1
Baseline characteristics of the development set and validation set.

| Measure                        | Development set (n = 325) | Validation set (n = 138) | P Value |
|--------------------------------|---------------------------|--------------------------|---------|
|                                |                           |                          |         |
| Clinical characteristics       |                           |                          |         |
| Age, year, n (%)               |                           |                          | 0.579   |
| < 50                           | 78 (24.0)                 | 27 (19.6)                |         |
| 50 ~ 70                        | 195 (60.0)                | 88 (63.8)                |         |
| ≥ 70                           | 52 (16.0)                 | 23 (16.7)                |         |
| Gender, n (%)                  |                           |                          | 0.282   |
| Female                         | 104 (32.0)                | 52 (37.7)                |         |
| Male                           | 221 (68.0)                | 86 (62.3)                |         |
| Presentation, n (%)            |                           |                          | 0.415   |
| STEMI with Urgent PCI          | 12 (3.7)                  | 3 (2.2)                  |         |
| STEMI with Delayed PCI         | 59 (18.2)                 | 20 (14.5)                |         |
| NSTE-ACS                       | 198 (60.9)                | 95 (68.8)                |         |
| SA                             | 56 (17.2)                 | 20 (14.5)                |         |
| OMI, n (%)                     |                           |                          | 0.381   |
| No                             | 294 (90.5)                | 129 (93.5)               |         |
| Yes                            | 31 (9.5)                  | 9 (6.5)                  |         |
| Prior PCI, n (%)               |                           |                          | 0.616   |
| No                             | 294 (90.5)                | 122 (88.4)               |         |
| Yes                            | 31 (9.5)                  | 16 (11.6)                |         |
| Heart failure, n (%)           |                           |                          | 1       |
| No                             | 286 (88.0)                | 121 (87.7)               |         |
| Yes                            | 39 (12.0)                 | 17 (12.3)                |         |
| Atrial fibrillation, n (%)     |                           |                          | 0.288   |
| No                             | 320 (98.5)                | 133 (96.4)               |         |
| Yes                            | 5 (1.5)                   | 5 (3.6)                  |         |
| Hypertension, n (%)            |                           |                          | 0.664   |
| Measure                  | Development set (n = 325) | Validation set (n = 138) | P Value |
|-------------------------|---------------------------|--------------------------|---------|
|                        |                           |                          |         |
| No                      | 169 (52.0)                | 68 (49.3)                |         |
| Yes                     | 156 (48.0)                | 70 (50.7)                |         |
| Diabetes mellitus, n (%)|                           |                          | 0.815   |
| No                      | 259 (79.7)                | 112 (81.2)               |         |
| Yes                     | 66 (20.3)                 | 26 (18.8)                |         |
| Smoke, n (%)            |                           |                          | 0.496   |
| No                      | 209 (64.3)                | 94 (68.1)                |         |
| Yes                     | 116 (35.7)                | 44 (31.9)                |         |
| Laboratory tests        |                           |                          |         |
| Systolic BP, n (%)      |                           |                          | 0.749   |
| < 90 mmHg               | 92 (28.3)                 | 44 (31.9)                |         |
| 90 ~ 140 mmHg           | 181 (55.7)                | 68 (49.3)                |         |
| 140 ~ 160 mmHg          | 40 (12.3)                 | 20 (14.5)                |         |
| 160 ~ 180 mmHg          | 11 (3.4)                  | 5 (3.6)                  |         |
| ≥ 180 mmHg              | 1 (0.3)                   | 1 (0.7)                  |         |
| Diastolic BP, n (%)     |                           |                          | 0.76    |
| < 60 mmHg               | 18 (5.5)                  | 6 (4.3)                  |         |
| 60 ~ 80 mmHg            | 143 (44.0)                | 65 (47.1)                |         |
| 80 ~ 100 mmHg           | 150 (46.2)                | 59 (42.8)                |         |
| ≥ 100 mmHg              | 14 (4.3)                  | 8 (5.8)                  |         |
| Glycemia, n (%)         |                           |                          | 0.837   |
| < 6.1 mmol/L            | 237 (72.9)                | 104 (75.4)               |         |
| 6.1 ~ 11.1 mmol/L       | 79 (24.3)                 | 30 (21.7)                |         |
| ≥ 11.1 mmol/L           | 9 (2.8)                   | 4 (2.9)                  |         |
| Creatinine, n (%)       |                           |                          | 0.321   |
| < 110 mmol/L            | 313 (96.3)                | 136 (98.6)               |         |
| ≥ 110 mmol/L            | 12 (3.7)                  | 2 (1.4)                  |         |
| Measure                          | Development set (n = 325) | Validation set (n = 138) | P Value |
|---------------------------------|---------------------------|--------------------------|---------|
| **Uric Acid, n (%)**            |                           |                          |         |
| < 400 µmol/L                    | 283 (87.1)                | 120 (87.0)               | 1       |
| ≥ 400 µmol/L                    | 42 (12.9)                 | 18 (13.0)                |         |
| **LDL-C, n (%)**                |                           |                          | 0.06    |
| < 1.80 mmol/L                   | 66 (20.3)                 | 17 (12.3)                |         |
| 1.80 ~ 3.63 mmol/L              | 220 (67.7)                | 96 (69.6)                |         |
| 3.63 ~ 4.14 mmol/L              | 24 (7.4)                  | 12 (8.7)                 |         |
| ≥ 4.14 mmol/L                   | 15 (4.6)                  | 13 (9.4)                 |         |
| **Lesion & procedure characteristics** |                           |                          |         |
| Acute occlusion lesions, n (%)  |                           |                          | 0.645   |
| No                              | 283 (87.1)                | 123 (89.1)               |         |
| Yes                             | 42 (12.9)                 | 15 (10.9)                |         |
| Chronic total occlusions, n (%) |                           |                          | 0.157   |
| No                              | 294 (90.5)                | 131 (94.9)               |         |
| Yes                             | 31 (9.5)                  | 7 (5.1)                  |         |
| Ostial lesions, n (%)           |                           |                          | 0.646   |
| No                              | 288 (88.6)                | 125 (90.6)               |         |
| Yes                             | 37 (11.4)                 | 13 (9.4)                 |         |
| Bifurcation lesions, n (%)      |                           |                          | 0.676   |
| No                              | 257 (79.1)                | 106 (76.8)               |         |
| Yes                             | 68 (20.9)                 | 32 (23.2)                |         |
| Restenotic lesions, n (%)       |                           |                          | 0.603   |
| No                              | 316 (97.2)                | 136 (98.6)               |         |
| Yes                             | 9 (2.8)                   | 2 (1.4)                  |         |
| Location of stents, n (%)       |                           |                          |         |
| LM, n (%)                       |                           |                          | 1       |
| No                              | 312 (96.0)                | 132 (95.7)               |         |
| Measure                              | Development set | Validation set | P Value |
|-------------------------------------|-----------------|----------------|---------|
|                                     | (n = 325)       | (n = 138)      |         |
| Yes                                 | 13 (4.0)        | 6 (4.3)        |         |
| LAD, n (%)                          |                 |                | 0.56    |
| No                                  | 84 (25.8)       | 40 (29.0)      |         |
| Yes                                 | 241 (74.2)      | 98 (71.0)      |         |
| LCX, n (%)                          |                 |                | 0.413   |
| No                                  | 187 (57.5)      | 73 (52.9)      |         |
| Yes                                 | 138 (42.5)      | 65 (47.1)      |         |
| RCA, n (%)                          |                 |                | 1       |
| No                                  | 198 (60.9)      | 84 (60.9)      |         |
| Yes                                 | 127 (39.1)      | 54 (39.1)      |         |
| Number of treated vessels, n (%)    |                 |                | 0.946   |
| 1                                   | 177 (54.5)      | 73 (52.9)      |         |
| 2                                   | 106 (32.6)      | 46 (33.3)      |         |
| 3                                   | 42 (12.9)       | 19 (13.8)      |         |
| Stent type, n (%)                   |                 |                | 0.157   |
| Sirolimus-eluting                   | 213 (65.5)      | 87 (63.0)      |         |
| Paclitaxel-eluting                  | 53 (16.3)       | 32 (23.2)      |         |
| > 1 type                            | 59 (18.2)       | 19 (13.8)      |         |
| Stent number, n (%)                 |                 |                | 0.785   |
| 1                                   | 120 (36.9)      | 47 (34.1)      |         |
| 2 ~ 3                               | 143 (44.0)      | 67 (48.6)      |         |
| 4 ~ 5                               | 52 (16.0)       | 19 (13.8)      |         |
| ≥ 6                                 | 10 (3.1)        | 5 (3.6)        |         |
| Total stent length, n (%)           |                 |                | 0.407   |
| < 20 mm                             | 49 (15.1)       | 21 (15.2)      |         |
| 20 ~ 60 mm                          | 165 (50.8)      | 69 (50.0)      |         |
| 60 ~ 100 mm                         | 73 (22.5)       | 38 (27.5)      |         |
| Measure                                      | Development set (n = 325) | Validation set (n = 138) | P Value |
|----------------------------------------------|--------------------------|--------------------------|---------|
| ≥ 100 mm                                     | 38 (11.7)                | 10 (7.2)                 | 0.437   |
| Stent diameter, n (%)                        |                          |                          |         |
| < 3 mm                                       | 134 (41.2)               | 63 (45.7)                |         |
| ≥ 3 mm                                       | 191 (58.8)               | 75 (54.3)                |         |
| **Medications**                              |                          |                          |         |
| Aspirin, n (%)                               |                          |                          | 1       |
| No                                           | 1 (0.3)                  | 1 (0.7)                  |         |
| Yes                                          | 324 (99.7)               | 137 (99.3)               |         |
| Clopidogrel, n (%)                           |                          |                          | 0.235   |
| No                                           | 10 (3.1)                 | 1 (0.7)                  |         |
| Yes                                          | 315 (96.9)               | 137 (99.3)               |         |
| Statins, n (%)                               |                          |                          | 0.224   |
| No                                           | 20 (6.2)                 | 4 (2.9)                  |         |
| Yes                                          | 305 (93.8)               | 134 (97.1)               |         |
| β-receptor blockers, n (%)                   |                          |                          | 1       |
| No                                           | 89 (27.4)                | 38 (27.5)                |         |
| Yes                                          | 236 (72.6)               | 100 (72.5)               |         |
| ACEIs/ARBs, n (%)                            |                          |                          | 0.721   |
| No                                           | 162 (49.8)               | 72 (52.2)                |         |
| Yes                                          | 163 (50.2)               | 66 (47.8)                |         |
| Calcium channel blockers, n (%)             |                          |                          | 0.593   |
| No                                           | 254 (78.2)               | 104 (75.4)               |         |
| Yes                                          | 71 (21.8)                | 34 (24.6)                |         |

**Predictors of ISR**

36 variables were reduced to five potential predictors on the basis of 463 patients with the 1-SE of the minimum criteria and nonzero coefficients in the lasso-penalized regression model (Fig. 2A and B). These
predictors associated with the ISR of patients included the history of prior PCI, glycemia, stent in LAD, the type of stent, and absence of clopidogrel (Table 2).

| Intercept and variable | β   | Odds ratio (95% CI)          | P-value |
|------------------------|-----|----------------------------|---------|
| Intercept              | -2.656 | 0.070 (0.030 ~ 0.149)  | < 0.001 |
| Prior PCI              | 1.356 | 3.881 (1.656 ~ 9.131)   | 0.002   |
| Glycemia               | 1.533 | 4.634 (1.087 ~ 20.965)  | 0.037   |
| Stent in LAD           | 1.037 | 2.821 (1.377 ~ 6.260)   | 0.007   |
| Stent type             | 1.041 | 2.832 (1.466 ~ 5.452)   | 0.002   |
| Absence of Clopidogrel | 1.762 | 5.821 (1.463 ~ 25.669)  | 0.013   |

**Construction of nomogram**

Features screened from the lasso-penalized regression analysis were included in the binary multivariate logistic regression in the development set. The five factors of prior PCI, glycemia, stents in LAD, the type of stent, and absence of clopidogrel were independent risk factors of ISR (Table 2) (all \( P < 0.05 \)). Collinearity diagnostic test did not indicate significant collinearity between independent variables in the regression model, and the variance inflation factors (VIFs) were 1.032, 1.016, 1.063, 1.053 and 1.013, respectively (all VIFs < 10). We then established an individualized nomogram that incorporated the five significant predictive factors based on the logistic multivariate regression analysis (Fig. 3).

**Validation of nomogram**

The ISR nomogram was assessed for internal validation by measuring discrimination, calibration, and clinical usefulness in the development and validation sets. The AUC associated with the ISR nomogram in the development set was 0.706 and was confirmed to be 0.662 in the validation set (Fig. 4A and B), indicating the nomogram prediction model has moderate discrimination. Meanwhile, high quality of calibration plots in both datasets showed that the nomogram model had strong concordance performance compared with an ideal model (\( P = 0.943 \), and \( P = 0.417 \), respectively) (Fig. 5A and B), which suggested no significant deviation between predicted and actual probability in the both sets.

The decision curve analysis for the ISR nomogram is presented in Fig. 6. The results indicated that using the nomogram to predict ISR could acquire much more benefit if the threshold probability is > 9%. Therefore, it could be used to predict the risk of ISR in patients undergoing PCI with high accuracy and a wider range of threshold probabilities, and it might have potentially great significance in clinical application.
Discussion

Stent implantation is an effective therapy for coronary artery disease. However, ISR has always been one of the most common complications, even in the era of DES. Thus, establishing a predication model of ISR for risk-tailored screening and preventive measure implementation may be pivotal to improve clinical outcomes of patients undergoing PCI. In the present study, five clinical and angiographic characteristics including the history of prior PCI, glycemia, stents in LAD, the type of stent, and absence of clopidogrel were found to independently predict ISR in DES recipients. Moreover, the nomogram prediction model based on these independent factors was constructed and validated, which could provide clinicians with a simple-to-use clinical tool for individualized assessments of patients with high-risk of ISR. Notably, visually and prospectively informing patients of the benefits of risk factor control may improve the patient's understanding of treatment and compliance of therapies, which has great significance for reducing the risk of ISR after stent implantation.

Although the exact mechanism of ISR in DES is unclear and probably multifactorial, it is currently accepted that factors including biological, mechanical, and technical issues can facilitate the adverse neointimal hyperplasia and contribute to ISR after stent implantation [2]. Several studies have attempted to identify the independent predictors of ISR. Stolker et al [17] developed a risk model for predicting restenosis of DES from the EVENT registry and identified age < 60, prior PCI, unprotected left main PCI, saphenous vein graft PCI, minimum stent diameter \( \leq 2.5 \text{ mm} \), and total stent length \( \geq 40 \text{ mm} \) as the predictors of ISR. In another study evaluating the incidence and predictors of target vessel revascularization among 27,107 patients undergoing implantation of BMS or DES, significant predictors of restenosis included prior PCI, emergency or salvage PCI, prior coronary artery bypass grafting (CABG), peripheral vascular disease, diabetes mellitus (DM), and angiographic characteristics [8]. Lately, Zheng et al [18] analyzed 944 stented lesions from 394 patients with 2nd-generation DES implantation. Factors including DM, previous PCI, postprocedural diameter stenosis and CRP levels were found to independently predict target lesion revascularization. A large patient data pooled analysis from 6 prospective and randomized trials, which included 10,072 patients undergoing DES implantation, suggested that vessel diameter, DM, prior CABG, and prior PCI were patient- and lesion-related predictors of target lesion failure [19].

Individual predictors likely vary between different studies on account of difference in the complexity of patients and candidate variables. However, the overlap in predictive factors, such as prior PCI, prior CABG, and DM, are strongly interlinked with accelerated ISR and repeated target lesion revascularization. Similar to those found in previous studies identifying predictors of ISR, our study also indicates that patient populations with prior PCI and history of DM are prone to ISR.

A history of PCI, which was a consistent and independent predictor of ISR, is closely related to the primary risk factors of atherosclerosis and represents the overall risk of severe coronary lesions requiring further intervention. It is also reported that repeated revascularization is more likely to occur for culprit lesions at a site of previous restenosis [9]. As for DM, patients have a higher risk of developing ISR due to the higher
inflammatory response, endothelial dysfunction, platelet hyperreactivity and more aggressive neointimal
hyperplasia accompanied by elevated plasma glucose levels [20, 21]. Generally, DM is associated with
complicated coronary artery disease characterized by multivessel lesions and diffuse lesions in small
vessels, which requires multiple stents with small diameter during PCI. Thus, it can explain at least partly
why variables like the total length and minimum diameter of stents were not included in the prediction
model in this study. In addition, a noteworthy finding of our study is that uncontrolled glycemia in
patients with DM has more predictive value for ISR rather than DM itself ignoring whether the glycemia
level is controlled or not.

Although several of the factors associated with ISR in our study are concordant with previous findings,
some key predictors including stents in LAD, type of stent, and absence of clopidogrel have not been
reported consistently in literature. Most studies suggested that coronary artery intervention restenosis
was more frequent for lesions in the LAD than other native coronary arteries, confirming that the LAD may
be another potential risk factor for ISR [22–24]. However, different views have also been proposed by
other researchers. To the contrary, lesions located in the LAD were also reported to have a decreased
restenosis rate [25, 26]. In fact, in the present study the results observed after stent implantation for LAD
lesions were very similar to those observed in most studies and we believe that stents located in the LAD
were associated with an elevated incidence of ISR. For lesions in LAD and other complicated lesions,
intravascular ultrasound (IVUS), optical coherence tomography (OCT) and other coronary imaging
techniques are recommended for optimizing the treatment strategy. In addition, our findings figured out
that sirolimus-eluting stent (SES) was associated with a lower risk of ISR than paclitaxel-eluting stent
(PES). Sirolimus and its analogs have a cytostatic effect on coronary artery endothelial cells, while
paclitaxel has a cytotoxic effect. Several studies have also indicated that use of SES has a less late
luminal loss [7, 27, 28] and a lower rate of late stent thrombosis [29], as compared with use of PES,
suggesting a better performance of SES in reducing restenosis. Finally, drugs and polymers of DES can
inhibit the excessive neointimal hyperplasia. However, it delays the repair of endothelial cells. Therefore,
antiplatelet drugs are still the cornerstone in the treatment of coronary heart disease, especially after PCI.
Gianluca et al investigated the clinical outcome of patients undergoing PCI for ISR with short (6 months)
or long (24 months) dual antiplatelet therapy (DAPT) [30]. The main findings of this study were that
patients receiving revascularization for ISR may benefit from long-term administration of aspirin plus
clopidogrel. Similarly, our study showed that the absence of clopidogrel increased the risk of ISR after
PCI, suggesting the benefit of appropriately prolonged DAPT duration for patients with high risk of ISR
after DES implantation.

Predictors identification and risk assessment are essential and important to an effective medical decision
making for preventing restenosis. However, the levels of prognostic utility of prediction models of ISR in
prior studies remained less than totally satisfying with c-statistic below 0.7 [8, 9, 17, 31]. In the present
study, the best c-statistic derived from the nomogram model in the development set was 0.706 and was
confirmed to be 0.662 in the validation set as well, suggesting that the distinct predictors improved the
overall discrimination of the models. Moreover, calibration plots and decision curve analysis for the
nomogram-based predication model were also performed well, making our findings more convincing and providing broad applicability in clinical practice.

**Limitations**

There are several limitations in this study. First, although we applied strict criteria for inclusion and exclusion to truly reflect the actual condition of disease occurrence in the population underwent PCI as much as possible, it was inevitable to suffer potential selection bias in the screening procedure. The patients for whom ISR actually occurs without clinical symptoms but angiographic follow-up is not routinely performed may have been missed. Second, the moderate c-statistic (0.706) of the ISR nomogram indicates that this prediction model remains suboptimal using included candidate variables. Some potential variables unmeasured were not thoroughly informed such as stent gap, stent under-expansion, lesion complexity and other procedure details. Finally, it may not be enough to examine the robustness of the nomogram with only internal validation. As a single-center study, the nomogram still needs to be improved. Larger sample sizes and evidence from other centers are required for further external validation and generalizability evaluation.

**Conclusions**

Our study has developed and validated a robust and individualized nomogram for predicting the risk of ISR among PCI patients. This nomogram consists of five common clinical and angiographic characteristics that are easy to obtain and offers clinicians a simple-to-use clinical tool with relatively good accuracy for the early identification and screening of high-risk patients for ISR. With an estimate of individual risk, clinicians and patients can pay more attention to early and reasonable interventions for risk factors.

**Abbreviations**

ISR: In-stent restenosis; PCI: Percutaneous coronary intervention; LASSO: Least absolute shrinkage and selection operator; AUC: Area under the curve; ROC: Receiver operating characteristics; DCA: Decision curve analysis; LAD: Left anterior descending artery; LM: Left main stem; LCX: Left circumflex coronary artery; RCA: Right coronary artery; DES: Drug-eluting stent; BMS: Bare-metal stent; BP: Blood pressure; LDL-C: Low-density lipoprotein; NSTE-ACS: Non-ST elevation acute coronary syndromes; OMI: Old myocardial infarction; STEMI: ST-elevation myocardial infarction; SA: Stable angina; ACEIs: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; OR: Odds ratio; CI: Confidence interval; NB: Net benefit; SE: Standard error; VIFs: Variance inflation factors; CABG: Coronary artery bypass grafting; DM: Diabetes mellitus; CRP: C-reactive protein; IVUS: Intravascular ultrasound; OCT: Optical coherence tomography; SES: Sirolimus-eluting stent; PES: Paclitaxel-eluting stent; DAPT: Dual antiplatelet therapy.
Declarations

Ethics approval and consent to participate

This study was a secondary analysis of an observational cohort study. The original work in accordance with the Creative Commons Attribution Non-Commercial (CC BY-NC 3.0) license was approved by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University. Informed consent was waived because this is a post-hoc study using available data.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are available in the Dryad data repository, https://doi.org/10.5061/dryad.13d31.

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Authors' contributions

WBH and CWX drafted the manuscript and revised it for intellectual content, contributed equally to this work. XYW, JYL, QFQ and YYH performed data analysis and/or interpreted the data for the work. DL contributed to the conception and design of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

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Figures
Figure 1

Study flow diagram for developing and validating the ISR risk model.
**Figure 2**

Risk factor selection using the LASSO regression model. Notes: (A) Optimal parameter (lambda) selection in the lasso model with the 1 SE of the minimum criteria (the 1-SE criteria). Dotted vertical lines were drawn at the optimal values by using the minimum criteria and the 1-SE criteria. (B) LASSO coefficient profiles of the 36 features. A coefficient profile plot was produced against the log (lambda) sequence.
Vertical line was drawn at the value selected, where optimal lambda resulted in five features with nonzero coefficients.

Figure 3

Nomogram to predict the probability of ISR in the patient with stent implantation. Note: The risk prediction nomogram was developed in the development set, with prior PCI, glycemia, stent in LAD, stent type and use of clopidogrel.
**Figure 4**

ROC curves for validating the discrimination power of the nomogram. (A) Development set. (B) Validation set. (AUC = 0.706 vs. 0.662).

**Figure 5**

Calibration plots of the nomogram for the probability of PCI patients with in-stent restenosis in the development set and validation set. (A) Development set. (B) Validation set. (All P>0.05).
Figure 6

Decision curve analysis for the ISR prediction nomogram in the development set. Notes: The y-axis measures the net benefit. The red line represents the ISR risk nomogram. The thin solid line represents the assumption that all patients suffer from ISR. The thick solid line represents the assumption that no patients suffers from ISR. The decision curve analysis indicated that using this ISR prediction nomogram could gain net benefit when the threshold probabilities >5%.