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# Comparison of Gensini score and SYNTAX score for predicting in-stent restenosis in patients with coronary artery disease and drug-eluting stent implantation

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The present study was aimed to investigate whether Gensini score or SYNTAX score was a valuable tool to predict in-stent restenosis (ISR) in coronary artery disease (CAD) patients with drug-eluting stents (DES) implantation. A retrospective case-control study and a validating retrospective cohort study were designed. All subjects' information was collected from the First Affiliated Hospital of Xinjiang Medical University. A total of 916 patients were enrolled in the case-control study, and 961 subjects were included in the retrospective-cohort study. In the case-control study, significant differences were observed between the ISR and non-ISR groups regarding baseline characteristics and clinical examinations, including waist circumference, systolic blood pressure, blood glucose levels, ApoA1 levels, left ventricular ejection fraction, lesion vessels, Gensini score, and SYNTAX score (all  $P < 0.05$ ). All parameters showing significant differences were also associated with ISR (all  $P < 0.05$ ). However, after adjustment for confounders, both Gensini score [tertile 3 vs. tertile 1 with OR 95%CI: 15.61 (5.37–45.39)] and SYNTAX score [high risk  $\geq 33$  vs. low risk  $\leq 22$  with OR 95%CI 12.61 (5.14–30.94)] were still independently associated with ISR. Furthermore, Gensini score [AUC 95%CI: 0.81 (0.78–0.84)] and SYNTAX score [AUC 95%CI: 0.76 (0.72–0.79)] showed a moderate ability to predict ISR. The predictors were further verified in a cohort validation study, which confirmed that the Gensini score was a better predictor for ISR than SYNTAX score, with an AUC and 95%CI of 0.67 (0.60–0.73) and 0.53 (0.46–0.60), respectively. Gensini score showed a higher capability to predict ISR than SYNTAX score in CAD patients with DES implantation. SYNTAX score may also be a useful tool for assessing the risk of ISR in patients with multivessel lesions.

**Keywords** Gensini score, SYNTAX score, Coronary artery disease, In-stent restenosis, Drug-eluting stent

Coronary heart disease (CAD) is still one of the main causes of death worldwide. Its effective treatment including percutaneous coronary intervention (PCI), in which stents are implanted in coronary arteries to restore blood flow to myocardium, has been widely used in patients with CAD. However, the benefits of PCI have been partially offset by the occurrence of in-stent restenosis (ISR), which leads to myocardial infarction (MI) or repeat vessel revascularization. With millions of patients receiving stents each year, ISR has become a significant public health problem. Over the past decades, stents have evolved to address this problem. For example, drug-eluting stents (DES) and biodegradable stents have been developed and have significantly reduced the likelihood of ISR compared to bare-metal stents (BMS)<sup>1</sup>. Despite the widespread use of DES, ISR still occurs in approximately 5–10% of patients<sup>2,3</sup>, which remains an unavoidable obstacle to the application of stents and weakens the long-term benefits of PCI.

To date, many ISR-related risk factors have been developed, such as calcified lesions, bifurcation lesions, diabetes mellitus, stent diameter and length in terms of anatomy factors, clinical factors, and stent- and procedure-

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related factors<sup>4</sup>. Several novel predictive indicators including laboratory serological parameters or microRNAs, have also been proposed before coronary stenting<sup>5–8</sup>. Recently, prediction models and novel score systems have also been developed to assess the probability risk of ISR<sup>9</sup>, and our previous study showed that a prediction model based on platelet, blood pressure, blood cholesterol, and lesion vessel parameters was a feasible model to predict ISR in patients undergoing DES implantation<sup>10</sup>. However, to date, no widely accepted and efficient predictor has been practiced to assess the risk of ISR. Therefore, we wondered whether some score systems already frequently performed in clinics could also be considered as a score system to assess the likelihood of ISR. However, few score systems have been validated and accepted. One published study tried to use CHA2DS2-VASc score to predict ISR, but the result was not ideal<sup>11</sup>.

As we know, ISR exists some different mechanisms from the regular progression of coronary atherosclerosis in the pathophysiological process, such as the procedures of stent implantation, stent characters, the response of the platelet aggregation in the circulation and endothelial immunity in the vascular to the stents were part of the mechanisms contributing to adverse arterial remodeling and neointimal hyperplasia. However, most of the mechanisms of ISR were still the same as the mechanisms of atherosclerosis development, including the common risk factors of patient-related factors, anatomical factors, enhanced vascular inflammation, excessive proliferation of vascular smooth muscle cells, and structural remodeling of the vasculature<sup>4,12,13</sup>. One would naturally think that patients with more severe coronary artery stenosis would be more likely to experience ISR. However, whether the severity of coronary artery stenosis predicts the risk of ISR has not been well defined. Both the Gensini score and SYNTAX score have been widely applied to evaluate the complexity of CAD because they incorporate multiple elements, such as lesion severity, summed scores of each obstruction, and weighting of the roles of their location<sup>14,15</sup>. In addition, they have also been developed as predictors of adverse cardiovascular disease (CVD)<sup>16,17</sup>. However, whether Gensini score or SYNTAX score is a valuable tool for predicting ISR is still less evaluated. And investigation of this issue would help to find novel predictors and new functions of these score systems to perform risk stratification for ISR in patients with CAD and stent implantation.

The aim of this study was to determine whether Gensini score or SYNTAX score from the primary angiographic examination is an effective tool for predicting the risk of ISR in CAD patients implanted with DES.

## Methods and materials

### Ethical approval

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (approval number: K202003-23) and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants or their legal guardians.

### Participants

This study firstly enrolled 916 patients in a case-control design, all of these subjects were recruited from the First Affiliated Hospital of Xinjiang Medical University from September 2014 to September 2018, and were diagnosed with CAD, implanted with DES, and had angiographic follow-up for more than 6 months. In addition, these recruited patients need to meet the inclusion and exclusion criteria. The inclusion criteria were that all subjects were over 18 years old, diagnosed with CAD, underwent the DES implantation, and accepted angiographic follow-up after stent implantation for more than 6 months. The exclusion criteria were that subjects had autoimmune diseases, coronary artery bypass surgery, malignant tumors, and heart failure. And the included patients were divided into ISR group and non-ISR group according to their angiographic diagnosis.

The distributions of the case and control groups were according to whether the participants had ISR. We then matched the case groups to the control group according to the age and sex of the control group.

Then we used our previously established retrospective cohort study of 961 CAD subjects<sup>10</sup> to verify the results of the case-control study. The inclusion and exclusion criteria were similar. Subjects in this cohort study were recruited between September 2010 and September 2013. (Fig. 1)

### Data collection

Demographic information, medical history, clinical data, biochemical results, and angiographic results of primary PCI were collected. Specifically, the information collected included sex, age, body mass index (BMI), history of hypertension, diabetes, smoking, echocardiographic data, angiographic results, procedural information of PCI, stent information, blood glucose, blood cholesterol, and angiographic follow-up results. Missing quantitative data were imputed by using the mean value of the variable close to the missing data in the statistics.

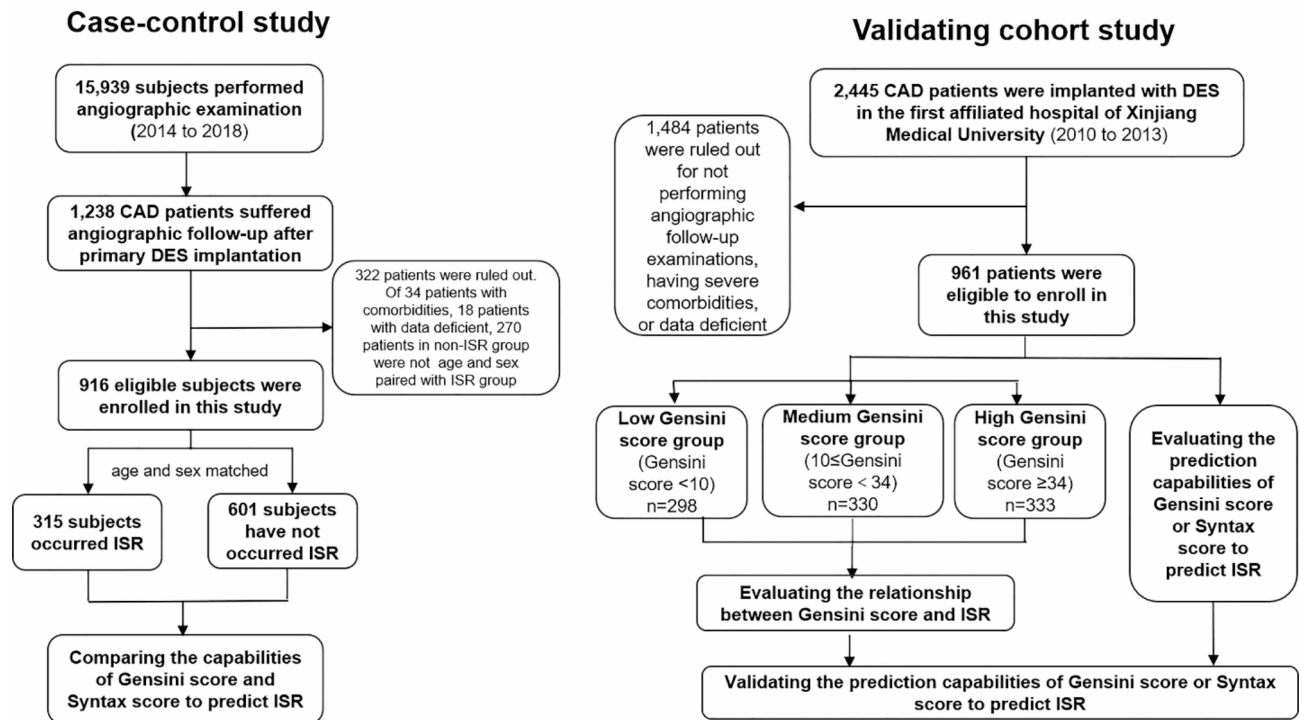
### Diagnostic criteria

The ISR is defined as the follow-up angiography results indicating that the degree of restenosis in the inner stents or 5 mm distance to the edge of the stent is more than 50%, if not were defined as non-ISR<sup>18</sup>.

The diagnosis of hypertension was made according to the guideline of hypertension, briefly was repeated measurement of systolic pressure  $\geq 140$  mmHg and/or diastolic pressure  $\geq 90$  mmHg in resting state, or taking antihypertensive medication<sup>19</sup>. The definition of diabetes mellitus (DM) was according to previously published guidelines<sup>20</sup>.

### Calculation and classification of Gensini score and SYNTAX score

We calculated the Gensini score according to its formula<sup>14</sup> and the SYNTAX I score by software (<https://syntaxscore.org/>). The calculation of Gensini score is depends on the location of the stenosis in the coronary arteries and the degree of stenosis. Specifically, stenosis degrees of 25%, 50%, 75%, 90%, 99%, and total occlusion were given scores of 1, 2, 4, 8, 16, and 32, respectively, and then multiplied by the scores in the location of proximal, middle, and distal parts of each artery, and finally summed the scores in each artery for each subject<sup>21</sup>. SYNTAX scores



**Fig. 1.** The study flow diagram. CAD coronary artery disease, ISR in-stent restenosis, DES drug-eluting stents.

were obtained by clicking on the appropriate choices in the SYNTAX I score software for each patient to obtain their calculated score. The Gensini score was classified according to the statistical methods of tertile in order to facilitate a more profound comprehension of the characteristics and trends exhibited by the data. The SYNTAX score was categorized as low risk ( $\leq 22$ ), moderate risk (23–32), and high risk ( $\geq 33$ )<sup>22,23</sup>.

### Statistical analyses

All results were analyzed according to their value categories. The continuous variables had normal distributions, tested by the Kolmogorov–Smirnov test, expressed as means  $\pm$  SD and tested by the independent T-test or one-way ANOVA test. Categorical variables were presented as frequencies and percentages, and compared using the  $\chi^2$  test. Continuous variables that were not normally distributed were expressed as medians (first quartile, third quartile), and analyzed by the Wilcoxon signed-rank test. Univariate and forward stepwise multivariable logistic regression analyses were performed to identify independent risk factors. Receiver operating characteristic (ROC) curves were used to determine the capability to predict ISR. In addition, the Youden Index was applied to figure out the optimal cut-off values for potential variables. Statistical tests of *P* value were two-sided. When a *P* < 0.05 was considered as statistically significant. All statistical procedures were conducted by SPSS 23.0 (SPSS Inc., Chicago, IL, USA).

## Results

### Characteristics of subjects in the ISR and non-ISR group

There were 916 patients recruited, of 315 patients in the ISR group and 601 patients in the non-ISR group. The mean age ( $60.09 \pm 9.85$  years vs.  $60.30 \pm 10.88$  years, *P* > 0.05) and male proportion (80.32% vs. 79.13%, *P* > 0.05) were comparable between the ISR and non-ISR groups. The comparisons between the ISR and non-ISR groups in aspects of baseline characteristics, medical history, and clinical results are displayed (Table 1). And angiographic results and stent information were presented in Table 2. The frequencies of smoking, drinking, history of hypertension, diabetes, arrhythmia, atrial fibrillation, the levels of BMI, lipoprotein (a), total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), creatinine, and uric acid were showed no differences between groups (all *P* > 0.05, Table 1). However, the parameters of waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), blood glucose, frequencies of myocardial infarction (MI), ApoA1, and left ventricular ejection fraction (LVEF) were significantly different between groups (all *P* < 0.05, Table 1).

### Comparisons of characteristics of angiography and stents

The characteristics of angiographic results in Table 2 indicated that the distributions of stenosis in left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX), right coronary artery (RCA), and the average number of lesion vessels were significantly higher in the ISR group than the non-ISR groups (all *P* < 0.05). But the average numbers of implanted stent and total stent length were similar between the two

Parameters	Non-ISR group (n = 601)	ISR group (n = 315)	P values
Demographic information			
Age (years)	60.3 ± 10.9	60.1 ± 9.9	0.778
Male, n (%)	474 (79.1)	253 (80.3)	0.559
Current smoking, n (%)	351 (80.3)	175 (78.8)	0.682
Alcohol intake, n (%)	73 (17.1)	42 (19.4)	0.455
Waist circumference (cm)	91.9 ± 13.0	95.2 ± 13.2	0.002
BMI (kg/m <sup>2</sup> )	26.4 ± 3.4	26.6 ± 3.4	0.348
SBP (mmHg)	144.0 ± 32.9	150.5 ± 31.2	0.019
DBP (mmHg)	88.6 ± 22.2	93.7 ± 21.6	0.007
Medical history			
Hypertension, n(%)	343 (57.2)	191 (60.6)	0.324
Diabetes, n(%)	137 (22.8)	80 (25.4)	0.414
MI, n(%)	56 (9.3)	46 (14.6)	0.019
Arrhythmia (%)	38 (6.3)	17 (5.4)	0.661
Atrial fibrillation, n(%)	8 (1.3)	6 (1.9)	0.573
Laboratory data			
TC (mmol/L)	4.0 ± 2.1	4.2 ± 2.3	0.212
TG (mmol/L)	2.9 ± 5.2	2.8 ± 4.7	0.728
HDL (mmol/L)	3.6 ± 15.5	3.5 ± 14.7	0.922
LDL (mmol/L)	3.9 ± 16.5	2.9 ± 7.8	0.356
Blood glucose (mmol/L)	6.1 ± 3.0	6.8 ± 3.9	0.007
Glycated serum protein (mmol/L)	4.6 ± 11.9	4.2 ± 10.9	0.628
Creatine (μmol/L)	79.6 ± 37.8	79.3 ± 31.1	0.915
ApoA1 (g/L)	1.2 ± 0.3	1.1 ± 0.2	0.006
Uric acid (μmol/L)	310.6 ± 112.5	320.2 ± 110.5	0.227
LVEF (%)	61.1 ± 8.9	59.4 ± 8.3	0.024
Gensini score	18.3 ± 24.4	50.7 ± 38.4	< 0.001

**Table 1.** Characteristics of study subjects. Data are expressed as means ± SD, median with IQR, and numbers with percentages depending on their data categories and distributions. *ISR* in-stent restenosis, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MI* myocardial infarction, *PDW* platelet distribution width, *LDL-C* low-density lipoprotein cholesterol, *HDL* high density lipoprotein, *TC* total cholesterol, *TG* triglyceride, *LVEF* left ventricular ejection fraction.

Parameters	Non-ISR group (n = 601)	ISR group (n = 315)	t/χ <sup>2</sup>	P values
Stenosis of coronary artery				
LM, n (%)	19 (3.2)	18 (5.7)	3.46	0.077
LAD, n (%)	201 (33.5)	253 (80.3)	181.11	< 0.001
LCX, n (%)	171 (28.5)	169 (53.6)	55.95	< 0.001
RCA, n (%)	173 (28.8)	179 (56.8)	68.37	< 0.001
Lesion vessels	1.3 ± 1.2	2.5 ± 1.2	- 14.39	< 0.001
Number of stents	1.1 ± 0.3	1.1 ± 0.3	0.03	0.980
Total of stents length (mm)	38.7 ± 23.9	35.0 ± 18.7	- 1.09	0.276
Gensini Score, M (Q1, Q3)	8.0 (2.0,25.0)	44.0 (18.5,72.0)	- 15.17	< 0.001
SYNTAX score, M (Q1, Q3)	6.0 (0.0,13.0)	16.5 (9.0,25.0)	- 12.30	< 0.001

**Table 2.** Comparisons of characteristics of angiography and stents. Data are expressed as means ± SD, median with IQR, and numbers with percentages depending on their data categories and distributions. *LM* left main coronary artery, *LCX* left circumflex coronary artery, *RCA* right coronary artery, *LAD* left anterior descending coronary artery.

groups ( $P > 0.05$ ). Furthermore, the results demonstrated that both the Gensini score and SYNTAX score were significantly higher in the ISR group than the non-ISR group ( $p < 0.05$ ). (Table 2)

### Logistic regression analysis was conducted to explore whether Gensini score and SYNTAX score were independently associated with ISR

The parameters existed differences in baseline characteristics and clinical results were proceed the further analysis of univariate and multivariate logistic regression analysis. Variables such as waist circumference, SBP, blood glucose, ApoA1, LVEF, number of lesion vessels, Gensini Score, and SYNTAX score were found to be associated with ISR (all  $P < 0.05$ ). When regarding the first tertile of Gensini score and low risk ( $\leq 22$ ) of SYNTAX score as references, respectively, and after adjusting confounding factors of waist circumference, SBP, blood glucose, ApoA1, LVEF, number of lesion vessels, the second and third tertiles of Gensini score and moderate (23–32) and high risk ( $\geq 33$ ) of SYNTAX score were still independently associated with ISR. Furthermore, their odds ratios (OR) of the second tertile and the third tertile of Gensini score and the moderate and high risk of SYNTAX score were gradually increased. (Table 3)

### ROC analysis to ascertain the predictability of the Gensini score and SYNTAX score for ISR in subjects with varying numbers of lesion vessels

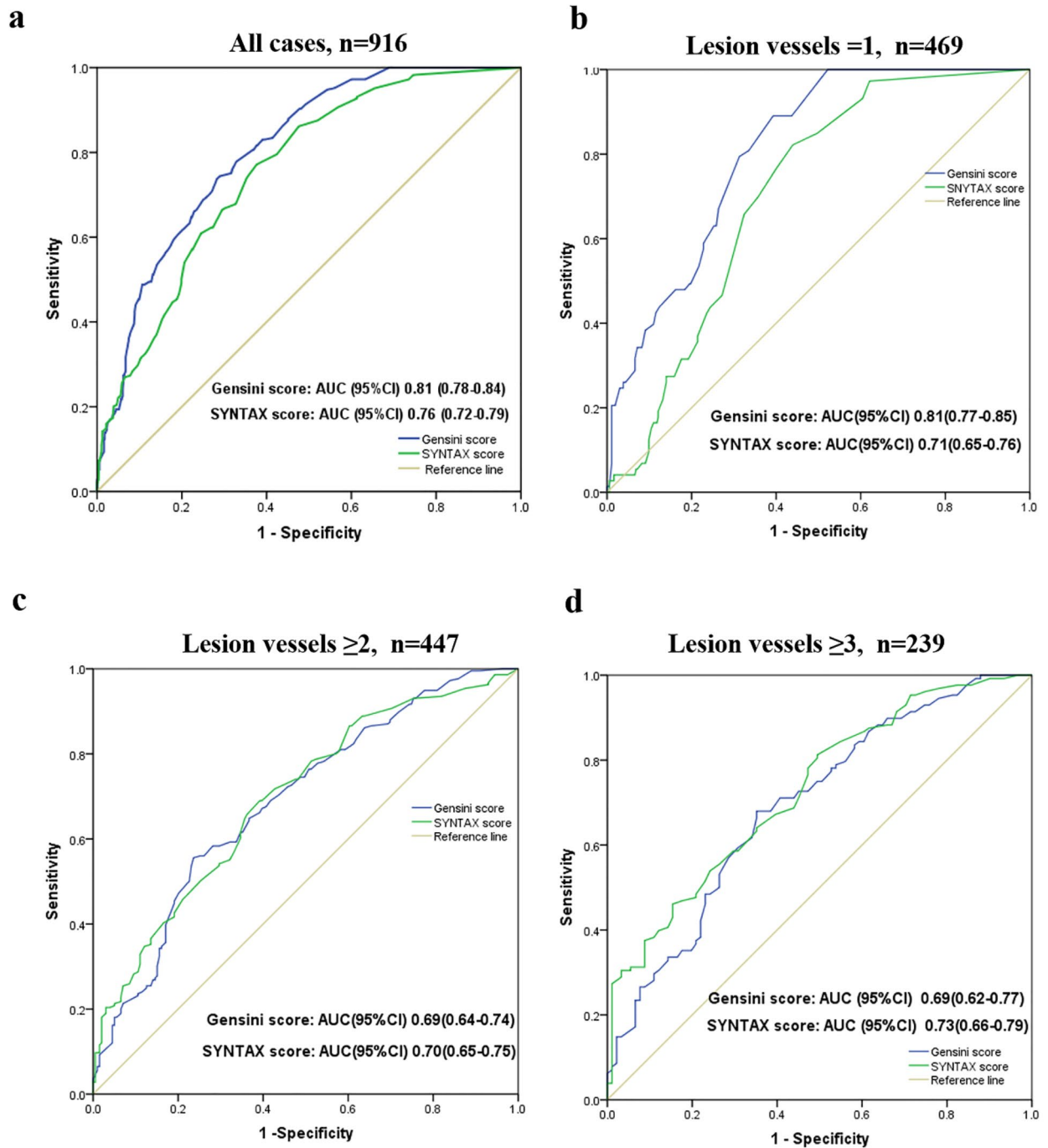
In the study, the subjects who exhibited one or more lesion vessels demonstrated superior predictability when assessed using the Gensini score in comparison to the SYNTAX score (Fig. 2a–b). The area under the curve (AUC) values were 0.81 (95% CI 0.78–0.84) for the Gensini score and 0.76 (95% CI 0.72–0.79) for the SYNTAX score, respectively (Fig. 2a). The optimal Gensini score cut-off value was determined to be 21.50, with a sensitivity of 73% and a specificity of 72%. Subjects with a SYNTAX score greater than 8.75 were found to be at a significantly elevated risk of ISR, with a sensitivity and specificity of 77% and 62%, respectively. A subsequent subgroup analysis was conducted on subjects with lesion vessels comprising more than two or three vessels. The SYNTAX score demonstrated superior predictability compared to the Gensini score. The AUC values were 0.69 (95% CI 0.64–0.74) for the Gensini score and 0.70 (95% CI 0.65–0.75) for the SYNTAX score in cases with more than two lesion vessels (Fig. 2c). The optimal SYNTAX score cut-off value was determined to be 14.75, with a sensitivity of 69% and a specificity of 61%. In cases involving three or more lesion vessels, the AUC was 0.69 (95% CI 0.62–0.77) for the Gensini score and 0.73 (95% CI 0.66–0.79) for the SYNTAX score (Fig. 2d).

### The baseline characteristics of the validating cohort study

As we observed that the Gensini score indicated a more efficient capability to predict ISR in the case-control designed study. To validate the findings observed in the case-control study, we analyzed the relationship between Gensini score and ISR in the validating cohort study. We firstly equally distributed subjects into three groups according to the first and third tertiles of Gensini score. The parameters of age, sex, smoking, BMI, waist circumference, TC, and LDL showed comparable results. However, the variables of DBP, blood glucose, ApoA1, LVEF, and lesion vessels showed significant differences among groups (all  $P < 0.05$ ). Meanwhile, the incidences of ISR were gradually raised from the first tertile to the third tertile of Gensini score ( $P < 0.05$ ). In addition, we observed that the SYNTAX scores were also gradually increased from the first-tertile group to the third tertile group of Gensini score ( $P < 0.05$ ). (Table 4)

Parameters	Univariate			Multivariate		
	OR	95% CI	P values	OR	95% CI	P values
SBP	1.01	(1.01–1.01)	0.008			
Waist circumference	1.02	(1.01–1.03)	0.002			
LVEF	1.66	(1.10–2.52)	0.017			
Blood glucose	1.06	(1.02–1.11)	0.006			
ApoA1	0.43	(0.23–0.79)	0.007			
Lesion vessels	1.50	(1.12–2.00)	< 0.001			
Gensini score						
T1, Gensini score < 8.00, n (%)	1 (Reference)			1 (Reference)		
T2, 8 ≤ Gensini score < 32, n (%)	3.13	(2.25–4.34)	< 0.001	2.44	(1.53–3.89)	< 0.001
T3, Gensini score ≥ 32.00, n (%)	23.80	(14.05–40.30)	< 0.001	15.61	(5.37–45.39)	< 0.001
SYNTAX score						
Low SYNTAX score (≤ 22)	1 (Reference)			1 (Reference)		
Intermediate SYNTAX score (22–33)	2.75	(1.82–4.17)	< 0.001	2.72	(1.69–4.36)	< 0.001
High SYNTAX score (≥ 33)	13.12	(5.74–29.97)	< 0.001	12.61	(5.14–30.94)	< 0.001

**Table 3.** Univariate and multivariate logistic regression analysis for Gensini score and SYNTAX score in subjects with ISR. Adjusted variables: SBP, Waist circumference, LVEF, blood glucose, APOA1, number of lesion vessels. ISR in-stent restenosis, OR odds ratio, SBP systolic blood pressure, LVEF left ventricular ejection fraction.



**Fig. 2.** ROC analysis results of Gensini score and SYNTAX score for ISR in the case-control study.

### Logistic regression and ROC analysis demonstrated that the Gensini score was a practical, independent predictor of ISR in the validating cohort study

Further analysis confirmed that the Gensini score was also independently associated with ISR in the validating study, after adjusting for the confounding risk factors of DBP, LVEF, APOA1, blood glucose, and lesion vessels (Table 5). However, the SYNTAX score did not indicate significant associations with ISR in univariate and multivariate analysis. Furthermore, the ROC analysis was conducted to assess the predictive capacity of the Gensini score and the SYNTAX score for ISR. Ultimately, our findings demonstrated that the Gensini score exhibited superior predictive efficacy for ISR compared to the SYNTAX score. The respective AUCs (95% CI) were 0.67 (0.60–0.73) and 0.53 (0.46–0.60) (Fig. 3). A Gensini score of 25.50 was identified as the optimal cut-off point for predicting ISR, with a sensitivity and specificity of 72% and 57%, respectively.

Parameters	Gensini score $\leq 10$ ( $n = 298$ )	Gensini score 10–34 ( $n = 330$ )	Gensini score $\geq 34$ ( $n = 333$ )	$t/\chi^2$	$P$ value
Age (year)	58.3 $\pm$ 10.7	58.9 $\pm$ 10.9	59.8 $\pm$ 10.9	1.53	0.218
Male, n (%)	236 (79.2)	256 (77.6)	261 (78.4)	0.24	0.886
Smoking, n (%)	150 (50.3)	175 (53.0)	169 (50.8)	0.54	0.762
BMI (kg/m <sup>2</sup> )	26.4 $\pm$ 3.6	26.0 $\pm$ 3.7	26.1 $\pm$ 3.5	0.68	0.504
Waist circumference (cm)	92.2 $\pm$ 13.4	91.4 $\pm$ 13.3	93.1 $\pm$ 13.9	0.87	0.418
SBP (mmHg)	135.1 $\pm$ 34.7	138.0 $\pm$ 30.8	140.3 $\pm$ 33.2	1.92	0.147
DBP (mmHg)	93.4 $\pm$ 23.7	98.9 $\pm$ 26.0	96.0 $\pm$ 24.7	3.82	0.022
Blood glucose (mmol/L)	6.3 $\pm$ 2.7	6.3 $\pm$ 2.7	6.8 $\pm$ 3.3	3.66	0.026
TC (mmol/L)	4.2 $\pm$ 1.5	4.1 $\pm$ 1.3	4.3 $\pm$ 1.9	2.2	0.111
LDL (mmol/L)	2.5 $\pm$ 0.9	2.5 $\pm$ 0.9	2.4 $\pm$ 0.9	1.02	0.359
ApoA1 (g/L)	1.2 (1.0,1.3)	1.2 (0.9,1.3)	1.1(0.9,1.3)	10.01	0.007
LVEF (%)	61.9 $\pm$ 7.2	62.0 $\pm$ 6.1	60.6 $\pm$ 7.8	3.19	0.042
Lesion vessels	0.8 $\pm$ 1.0	2.3 $\pm$ 1.1	3.1 $\pm$ 1.2	347.77	< 0.001
ISR, n (%)	7 (12.9)	17 (31.5)	30 (55.6)	13.36	< 0.001
SYNTAX score	9.0 (4.0,19.0)	12.0 (8.0,19.0)	22.0 (14.0,31.0)	180.45	< 0.001

**Table 4.** The baseline characteristics of validating cohort study. Data are expressed as means  $\pm$  SD, median with IQR, and numbers with percentages depending on their data categories and distributions. *ISR* in-stent restenosis, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *LDL-C* low-density lipoprotein cholesterol, *TC* total cholesterol, *LVEF* left ventricular ejection fraction.

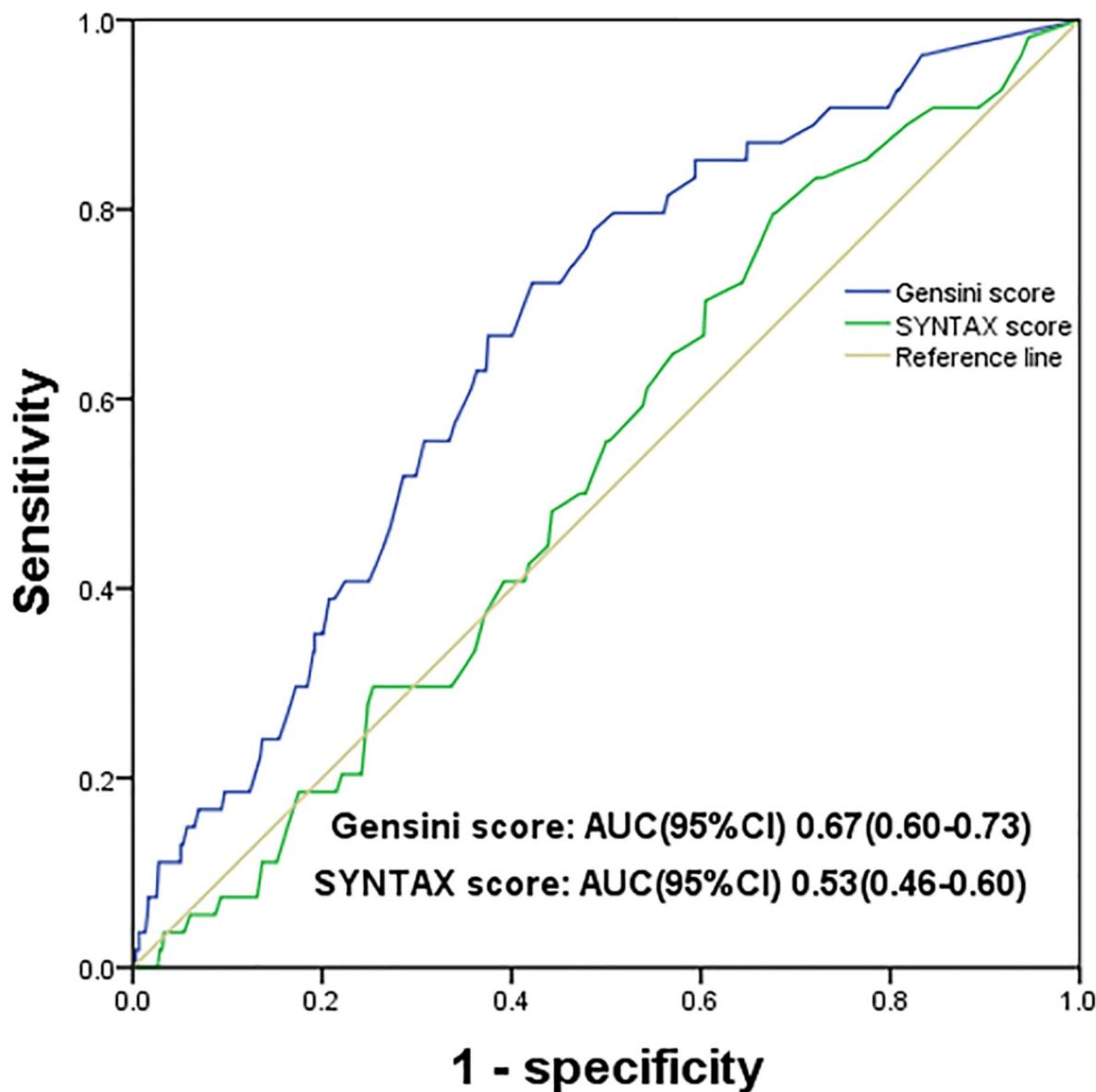
Parameters	Univariate			Multivariate		
	RR	95% CI	$P$ values	RR	95% CI	$P$ values
Gensini score						
T1, Gensini score < 8.00	1 (Reference)			1 (Reference)		
T2, 8 $\leq$ Gensini score < 32	2.26	(0.92–5.52)	0.074	1.55	(0.51–4.73)	0.443
T3, Gensini score $\geq$ 32.00	4.12	(1.78–9.52)	< 0.001	3.93	(1.43–10.75)	0.008
SYNTAX score						
Low SYNTAX score ( $\leq$ 22)	1 (Reference)			1 (Reference)		
Intermediate SYNTAX score (22–33)	1.23	(0.43–3.52)	0.705	0.97	(0.33–2.85)	0.951
High SYNTAX score ( $\geq$ 33)	1.67	(0.53–5.23)	0.378	1.48	(0.47–4.73)	0.505

**Table 5.** Logistic regression analysis for ISR in validation cohort study. Adjusted variables: *DBP*, *LVEF*, *APOA1*, blood glucose, number of lesion vessels. *ISR* in-stent restenosis, *DBP* systolic blood pressure, *LVEF* left ventricular ejection fraction.

## Discussion

In this study, we demonstrated that the Gensini score and SYNTAX score were independent predictors of ISR in patients with CAD who had undergone implantation of DES. Furthermore, our findings indicated that the Gensini score exhibited superior accuracy in predicting ISR compared to the SYNTAX score, as evidenced by the results of a case-control study and a validating cohort study. The optimal cut-off value for the Gensini score in predicting ISR was determined to be 21.50, exhibiting good sensitivity and specificity. The present study serves to verify and expand the application of the Gensini score as a reliable and practical tool for the prediction of ISR.

PCI represents one of the most efficacious methods for alleviating CAD disease and reducing mortality rates. A drug-eluting stent (DES) was identified as the optimal first-line treatment for PCI, given its superior efficacy<sup>24</sup>. Given that millions of people receive implanted DES every year, the 2–10% of incidence of ISR still means a large number of patients need to undergo coronary artery revascularization<sup>25,26</sup>. Except for some stent and implantation procedure factors that promote ISR, most mechanisms of ISR development, such as chronic inflammation and/or endothelial dysfunction-induced neo-atherosclerosis<sup>27</sup>, are similar to the generation of atherosclerosis. Studies have attempted to develop novel prediction models to provide prevention and stratification strategies for clinics<sup>5–8,26</sup>, but most of them have not been widely accepted by clinicians. Therefore, a widely accepted and convenient tool to predict ISR is necessary. Some people showed that the CHA2DS2-VASc score was a useful predictor for ISR in patients implanted with bare-metal stents<sup>28</sup>. It is established that the development of atherosclerosis and ISR share some of the same underlying mechanisms. It is well known that the Gensini score and SYNTAX score are commonly employed to assess the extent of stenosis and plaque burden in coronary arteries. However, there is a paucity of studies that have investigated their efficacy in evaluating the



**Fig. 3.** ROC analysis results of Gensini score and SYNTAX score for ISR in the validating cohort study.

risk of ISR, and there is currently a lack of evidence to determine which score system is more appropriate for predicting ISR.

In this study, we demonstrated that both the Gensini score and the SYNTAX score were independent predictors of ISR in the case-control study. Our findings indicated that the Gensini score was more predictive of ISR than the SYNTAX score in patients with one or more lesions who had undergone DES in both case-control study and also validating cohort study. It is a widely accepted clinical practice to use the Gensini score or the SYNTAX score as a means for comprehensively evaluating the degree of stenosis and plaque burden in coronary arteries. Several published studies mentioned that the Gensini score and the SYNTAX score are involved in the development of ISR. Jiao Wang et al. proposed that the Gensini score and ApoB level would serve as predictors for ISR in Chinese Uygur CAD patients<sup>29</sup>. Jian-Long Wang et al. proposed that a higher SYNTAX score in conjunction with elevated serum levels of very-low-density lipoprotein cholesterol (VLDL-C) and uric acid (UA) may serve as predictors for ISR in patients with diabetes mellitus (DM) and with DES implantation<sup>30</sup>. The aforementioned published studies provided partial support for our conclusion that the Gensini score and SYNTAX score are independent predictors of ISR. However, our study, which had a larger sample size and was



further validated in another study. In addition, we demonstrated that the Gensini score is more advanced than the SYNTAX score in predicting ISR in patients with DES implantation.

In the present study, the Gensini score indicated its advancement to predict ISR. The Gensini score is calculated based on the importance and corresponding area of blood supply of the coronary arteries where lesions occurred, as well as the percentage of stenosis in each coronary artery<sup>14</sup>. This assessment may be more adherent to the strategies of PCI and more specifically to the characteristic of culprit vessel. Nevertheless, the SYNTAX score incorporates a more intricate set of parameters. These characteristics are more indicative of the anatomic complexity of the coronary arteries than they are of the lesion burdens<sup>31,32</sup>. The anatomical characteristics of coronary artery dominance, bifurcation, and tortuosity were included in the SYNTAX score<sup>32</sup>, which may not closely related to the stent implantation or ISR, but potentially increase the confounding factors for ISR evaluation. Furthermore, in comparison to the intricate anatomical structures, the factors that facilitate the overall development of coronary artery lesions demonstrate a greater propensity for more severe inflammation or endothelial dysfunction in arteries that contribute to lesion formation, as opposed to limited complex artery anatomy. Similarly, Anil Avci and colleagues proposed that the Gensini score, rather than the SYNTAX score, was an independent predictor of carotid stenosis<sup>31</sup>. It is therefore proposed that the Gensini score is a more suitable predictor of ISR in clinical practice for patients with DES implantation. When subjects have a Gensini score above 21.50, they are more likely to experience ISR.

A subgroup analysis of the present study revealed that the SYNTAX score is an effective method for predicting ISR in patients with more than two or three lesion vessels. This implied that the SYNTAX score might be a valuable predictor for assessing multivessel coronary disease when patients with complex multivessel coronary arteries disease. Cavalcante et al. demonstrated that the SYNTAX score is an effective tool for assessing long-term outcomes and anatomic complexity in patients with multivessel disease who have undergone recanalization intervention<sup>33</sup>. In light of these findings, it seems reasonable to suggest that the SYNTAX score may also be a useful tool for assessing the risk of ISR in patients with multivessel lesions, particularly when the SYNTAX score is higher than 14.75. However, further validation in more complex circumstances and a prospective study with larger sample size is required to determine whether the Gensini score or the SYNTAX score is more suitable for evaluating the risk of ISR.

It should be noted that the present study is subject to a number of limitations. Firstly, the study was retrospective and single-center designed, which may have resulted in the inclusion of confounding factors. Secondly, the optimal examination methods were not employed to assess the characteristics of ISR in greater detail. Thirdly, although the subjects were implanted with an equivalent number of stents in different groups, the locations of the stents were not distinguished, which may potentially influence the accuracy of the results.

## Conclusion

The Gensini score and SYNTAX score were found to be independent predictors of ISR in patients with CAD who had undergone DES implantation. The Gensini score exhibited a greater predictive capacity for ISR than the SYNTAX score. In clinical practice, patients with a Gensini score exceeding 21.50 are likely to be at a high risk of ISR. While, SYNTAX score may also be a useful tool for assessing the risk of ISR in patients with multivessel lesions, with an optimal cut-off of 14.75.

## Data availability

Data is available from the corresponding author upon reasonable request.

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## Author contributions

The study was designed and conceived by XM.G and MT.G. MT.G and SQ.Y drafted the manuscript, A.R, L.Z, Q.L.L, B.H.Z, A.X.D, and S.H performed data collection; MY.W and SQ.Y conducted Gensini score and SYNTAX score calculation; XM.G revised the manuscript. All authors reviewed the manuscript.

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## Declarations

### Competing interests

The authors declare no competing interests.

### Additional information

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