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Research article

A risk score for predicting in-stent restenosis in patients with premature acute myocardial infarction undergoing percutaneous coronary intervention with drug-eluting stent

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ABSTRACT

Background: This study aimed at developing and validating a risk score to predict in-stent restenosis (ISR) in patients with premature acute myocardial infarction (AMI) undergoing percutaneous coronary intervention (PCI) with drug-eluting stent (DES).

Methods: This was a two-center retrospective study. A total of 2185 patients firstly diagnosed with premature AMI (age ≥18 years and <55 years in men, <65 years in women) from Xinjiang cohort were retrospectively analyzed. After filtering by exclusion criteria, patients were randomly divided into training cohort (n = 434) and internal validation cohort (n = 186) at a 7:3 ratio. Several candidate variables associated with ISR in the training cohort were assessed by the least absolute shrinkage and selection operator and logistic regression analysis. The ISR risk nomogram score based on the superior predictors was finally developed, and then validated in the internal validation cohort and in an independent Chengdu external validation cohort (n = 192). The higher total nomogram score, the greater the ISR risk.

Results: The eight variables in the final risk nomogram score, cardiovascular-kidney-metabolic (CKM) score included age, diabetes mellitus (DM), body mass index (BMI), systolic blood pressure (SBP), low-density lipoprotein cholesterol (LDLC), estimated glomerular filtration rate (eGFR), stent in left anterior descending coronary artery, minimum stent diameter <3 mm. The areas under the curve (AUC) and C-statistics [training cohort: 0.834 (95%CI: 0.787 to 0.882); internal validation cohort: 0.852 (95%CI: 0.784 to 0.921); Chengdu external validation cohort: 0.787 (95%CI: 0.692 to 0.882), respectively)] demonstrated the good discrimination of the CKM score. The Hosmer-Lemeshow test ($\chi^2 = 7.86$, $P = 0.448$; $\chi^2 = 5.17$, $P = 0.740$; $\chi^2 = 6.35$, $P = 0.608$, respectively) and the calibration curve confirmed the good calibration of the CKM score. Decision curve analysis (DCA) testified the clinical net benefit of the CKM score in the training and validation cohort.

Conclusion: This study provided a well-developed and validated risk nomogram score, the CKM score to predict ISR in patients with premature AMI undergoing PCI with DES. Given that these

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variables are readily available and practical, the CKM score should be widely adopted for individualized assessment and management of premature AMI.

1. Introduction

Acute myocardial infarction (AMI) poses a grave threat to human health, with a consistent rise in young patient admissions over recent decades [1]. Despite advances in treating premature AMI with drug-eluting stents (DES) via percutaneous coronary intervention (PCI), in-stent restenosis (ISR) remains a key contributor to ongoing cardiovascular risks, including cardiac death, recurrent AMI, and ischemia driven revascularization [2,3]. Studies have reported ISR rates ranging from 2.8 % to 23.9 % in patients with coronary stent implantation, emphasizing its impact on long-term PCI effectiveness [4–6]. However, a standardized ISR treatment approach is lacking, underscoring the need for early identification of patients at risk for ISR to mitigate cardiac events [7].

Actually, various predictors, including age, diabetes mellitus (DM), chronic kidney disease (CKD), low-density lipoprotein cholesterol (LDLC), systolic blood pressure (SBP), and stent dimensions, have been implicated in ISR risk stratification [4,8,9]. Unfortunately, evidence linking these factors to ISR occurrence in young patients with premature AMI is limited. Typically, young patients with AMI exhibited notable differences compared to older patients in terms of demographic variables, metabolic characteristics, and clinical prognosis [10,11]. This suggested that the risk prediction probability and the types of predictors may differ in premature AMI compared to older patients. Additionally, given the higher modifiability of risk factors in patients with premature AMI compared to older patients, conducting essential in-depth studies to identify ISR related indicators is imperative [11,12]. Furthermore, there is a lack of relevant models for predicting ISR in patients with premature AMI undergoing PCI with DES. Therefore, this study aimed to establish a risk score model based on commonly used and easily obtained traditional indicators, which should include demographic variables and multi-system clinical characteristics for comprehensive management of premature AMI patients. This risk score should be applicable not only to specialists but also to family physicians to reduce residual risk in patients with premature AMI. This model was presented in the following article in accordance with the TRIPOD reporting checklist (Table S1) [13].

2. Materials and methods

2.1. Study population

Although a total of 2185 patients with premature AMI underwent primary percutaneous coronary intervention (PCI) with drug-eluting stent (DES), only 743 patients who completed another coronary angiography (CAG) within 10–70 months after primary PCI were ultimately included from January 01, 2013, to September 31, 2023 in the First Affiliated Hospital of Xinjiang Medical University. These patients were hospitalized because of recurrence of discomfort such as chest pain or dyspnea. The cardiovascular specialist considered it to be caused by myocardial ischemia. After filtering by exclusion criteria, 620 patients were randomly assigned at a 7:3 ratio to the Xinjiang training cohort (n = 434) and internal validation cohort (n = 186). In order to determine whether there was

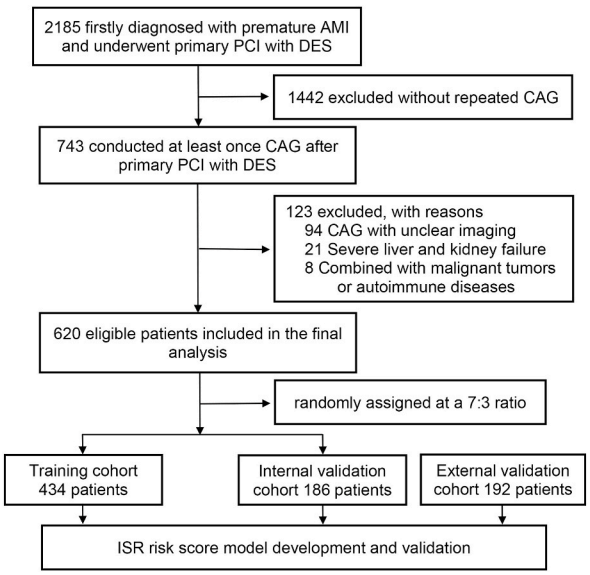

Fig. 1. Study flow diagram.
Note: AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; CAG, coronary angiography; DES, drug-eluting stent; ISR, in-stent restenosis.

potential selection bias, a comparison of baseline characteristics of included and excluded patients were performed and reported in Table S2. The median follow-up time of premature AMI finally included in the Xinjiang training cohort was 33.4 months. In addition, 192 patients from another tertiary hospital in China–the First Affiliated Hospital of Chengdu Medical College were separately used as an independent Chengdu external validation cohort. In order to avoid overfitting of the regression model [14], we needed 40 to 100 ISR events in the training cohort to assess 8 to 10 potential predicting factors. Assuming that the prevalence of ISR was approximately 2.8–23.9 % in patients undergoing PCI with DES, a sufficient sample size was at least around 168. To ensure an adequate number of events, we identified data from 434 individuals to develop the predicting score (Fig. 1). The follow-up of the included patients in the two hospitals was shown in Fig. S1, and the incidence of ISR in the Xinjiang and Chengdu cohort was 13.2 % and 11.5 %, respectively.

Referring to the 2017 and 2020 ESC Guidelines for the Management of AMI, in the clinical setting, AMI was defined if there was evidence of myocardial injury with necrosis consistent with myocardial ischemia [15,16]. "Premature" was defined with reference to the general consensus of previous studies, referring to an age of onset of AMI of ≥18 years, <55 years in men, and <65 years in women [10,17,18]. The inclusion criteria were as follows: (1) age ≥18 years and <55 years in men, <65 years in women; (2) firstly diagnosed AMI and underwent primary PCI with DES; (3) conducted at least twice complete CAG including primary PCI; (4) the time interval between two CAGs ≥10 months. The exclusion criteria were as follows: (1) CAG with unclear imaging; (2) severe liver and kidney failure; (3) combined with malignant tumors or autoimmune diseases.

2.2. Data collection

Clinical baseline data, such as demographic variables, laboratory characteristics, imaging examinations and medical managements were collected from the first measurement at admission. Patients who self-reported smoking within the preceding 6 months were categorized as current smokers. Likewise, individuals who acknowledged alcohol consumption in the last half-year were classified as current drinkers. Conditions such as hypertension, diabetes mellitus, stroke, atrial fibrillation, and peripheral arterial disease were diagnosed in accordance with pertinent guidelines, with assessments relying on both medical history and comprehensive ancillary examinations. Severe kidney failure was defined as an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2. Severe liver failure was delineated by alanine transaminase (ALT) or aspartate aminotransferase (AST) levels exceeding five times the upper limit of normal, specifically AST >180 U/L and ALT >260 U/L. Medical interventions encompassed details regarding the type of antiplatelet agents, lipid-lowering therapy, and other prescribed medications.

2.3. ISR definition and assessment

ISR was confirmed by repeated coronary angiography (CAG). Coronary angiograms with the targeted vessel with DES implantation were recorded at baseline and follow-up periods, and were assessed by at least two physicians using quantitative coronary angiography (QCA) analysis software, Create Life Medical Imaging Workstation V3.1. All datasets blinded to the identity and clinical characteristics of the patients, were analyzed by at least one attending physician and quality controlled by one cardiologist. ISR was defined as ≥50 % luminal stenosis of the targeted vessels over the entire length of the implanted stent and/or the 5 mm proximal and distal to the stent margin [19]. Conversely, those did not meet the above criteria were defined as non-ISR. A representative ISR for the targeted vessel with DES implantation evaluating by CAG was shown in Figs. S2A and S2B.

2.4. Model development and validation

To develop a robust and valid predicting score, variables representing different disease states and filtered to be associated with ISR were progressively incorporated into the model to achieve maximum predictive discrimination. A nomogram represented the final ISR risk score developed in this Xinjiang training cohort. The cumulative score, referred to as the "total points", was computed as the summation of the individual scores associated with each of the variables incorporated in the nomogram model. The risk of ISR for the patients undergoing PCI with DES was estimated by the probability corresponding to the "total points". To evaluate the discrimination, calibration and clinical validity of the risk score, and compare the performance of this risk score with other representative models, a nomogram score for each individual was calculated in the Xinjiang internal validation cohort and Chengdu external validation cohort.

2.5. Statistical analysis

Continuous variables were reported as the mean ± SD using Student's t-test or median (interquartile range) using Mann-Whiney *U* test. Categorical variables were expressed as the frequencies (%) using chi-square tests or Fisher exact test. Univariate analyses were first used to determine possible predictors. The least absolute shrinkage and selection operator (LASSO) regression was used to screen the non-zero coefficient characteristic variables. Univariate and multivariate logistic regression with forward and stepwise selection procedures was then performed using significant factors from LASSO regression as inputs. The ISR risk score was ultimately constructed in the form of a nomogram model based on the results of multivariate logistic regression. The discriminative ability of the ISR risk score was assessed by calculating C-statistic and a receiver operating characteristic (ROC) curve and computed areas under the curve (AUC). The predictive accuracy of the risk score was evaluated using the Hosmer-Lemeshow test and calibration plot. The clinical application value of the risk score was assessed using decision curve analysis (DCA). A bootstrap procedure with 1000 bootstrap resamples was employed to correct the overestimation. All statistical analyses were performed using SPSS version 25.0 and R version 4.2.2. A two-tailed test P value < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

The patient baseline characteristics in the Xinjiang training cohort are provided in Table 1. Characteristics of echocardiogram, angiography and stents of included patients in the Xinjiang training cohort are provided in Table 2. Of the 434 included patients, 55 (12.7 %) patients experienced ISR in patients with premature AMI undergoing PCI with DES. Respectively, a total of 27 (14.5 %) and

Table 1
The baseline characteristics of included patients in the Xinjiang training cohort.

Variables	ISR (n = 55)	Non-ISR (n = 379)	$t/\chi 2/Z$ value	*P* value
Demographics				
Age (years)	52.33 ± 7.44	49.01 ± 6.02	−3.71	<0.01
Male	39 (70.9 %)	318 (83.9 %)	5.56	0.018
Ethnicity				
Han	30 (54.5 %)	205 (54.1 %)	0.74	0.693
Uygur	20 (36.4 %)	125 (33.0 %)		
Others	5 (9.1 %)	49 (12.9 %)		
Clinical Information				
Family history of CAD	31 (56.4 %)	158 (41.7 %)	4.21	0.040
Smoking	27 (49.1 %)	177 (46.7 %)	0.11	0.740
Drinking	19 (34.5 %)	146 (38.5 %)	0.32	0.570
BMI(kg/m^2)	28.12 ± 3.25	26.85 ± 3.69	−2.42	0.016
SBP (mmHg)	130.40 ± 17.94	119.58 ± 17.46	−4.28	<0.01
DBP (mmHg)	82.56 ± 13.00	75.97 ± 12.26	−3.70	<0.01
HR (beats/min)	84.55 ± 12.82	78.85 ± 12.16	−3.22	0.001
Medical history				
Hypertension	27 (49.1 %)	174 (45.9 %)	0.19	0.658
Diabetes mellitus	26 (47.3 %)	79 (20.8 %)	18.29	<0.01
Stroke	3 (5.5 %)	22 (5.8 %)	0.01	0.917
Atrial fibrillation	12 (21.8 %)	39 (10.3 %)	6.16	0.013
Peripheral arterial disease	9 (16.4 %)	65 (17.2 %)	0.02	0.885
Laboratory characteristics				
WBC (× 10^9/L)	9.14 ± 3.13	8.48 ± 3.09	−1.47	0.143
Monocyte (× 10^9/L)	0.66 ± 0.25	0.58 ± 0.26	−2.11	0.035
Hb (g/L)	141.64 ± 21.91	145.32 ± 15.89	1.52	0.129
Platelet count (× 10^9/L)	256.58 ± 62.62	251.39 ± 78.88	−0.46	0.641
PDW (%)	14.06 ± 2.45	12.80 ± 2.77	−3.18	0.002
Creatinine (μmol/L)	81.54 ± 18.15	73.13 ± 25.93	−2.30	0.022
Urea (mmol/L)	5.56 ± 1.32	5.44 ± 1.85	−0.44	0.660
eGFR ($mL/min/m^2$)	87.58 ± 20.56	101.98 ± 24.29	4.18	<0.01
Uric Acid (μmol/L)	355.67 ± 83.59	350.61 ± 99.43	−0.35	0.727
ALT (U/L)	30.89 (21.15, 59.24)	34.04 (24.53, 52.20)	−0.48	0.631
AST (U/L)	28.94 (21.63, 63.37)	28.49 (21.40, 41.10)	−1.05	0.295
Serum albumin (g/L)	41.49 ± 4.63	41.80 ± 4.05	0.48	0.631
Serum sodium (mmol/L)	139.31 ± 3.40	139.80 ± 3.79	0.89	0.376
Serum potassium (mmol/L)	3.73 ± 0.47	3.72 ± 0.39	−0.13	0.900
Serum calcium (mmol/L)	2.27 ± 0.12	2.25 ± 0.12	−1.05	0.294
FBG (mmol/L)	8.84 ± 2.76	7.43 ± 3.75	−2.57	0.010
TC (mmol/L)	4.54 ± 1.34	3.99 ± 1.42	−2.50	0.013
TG (mmol/L)	2.66 ± 1.82	2.20 ± 1.76	−1.63	0.105
LDLC (mmol/L)	2.96 ± 1.15	2.40 ± 1.03	−3.73	<0.01
HDLC (mmol/L)	0.87 ± 0.21	0.88 ± 0.25	0.19	0.845
ApoAI (mmol/L)	1.06 ± 0.23	1.05 ± 0.23	−0.20	0.843
ApoB (mmol/L)	0.86 ± 0.28	0.81 ± 0.29	−0.84	0.400
LP(a) (mg/dL)	284.55 (114.59, 584.76)	157.99 (68.14, 349.98)	−2.43	0.015
CRP (mg/dL)	23.60 (10.35, 41.80)	13.35 (7.98, 21.43)	−3.12	0.002
NT-proBNP/100 (ng/mL)	2.96 (1.73, 11.70)	3.01 (0.94, 9.25)	−1.06	0.289
Medications				
DAPT	52 (94.5 %)	366 (96.6 %)	0.55	0.456
Statin	51 (92.7 %)	353 (93.1 %)	0.01	0.910
β-blockers	35 (63.6 %)	258 (68.1 %)	0.43	0.511
ACEI/ARB	26 (47.3 %)	193 (50.9 %)	0.26	0.613

Abbreviations: ISR, in-stent restenosis; CAD, coronary artery disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; WBC, white blood cell count; Hb, hemoglobin; PDW, platelet distribution width; eGFR, estimated glomerular filtration rate; ALT, alanine transaminase; AST, aspartate aminotransferase; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; ApoAI, apolipoprotein AI; ApoB, apolipoprotein B; LP(a), Lipoprotein(a); CRP, C-reactive protein; NT-proBNP, N-terminal pro b-type natriuretic peptide; DAPT, dual anti-platelet therapy in the first year after percutaneous coronary intervention; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers.

22 (11.5 %) patients were diagnosed with ISR in the Xinjiang internal validation cohort and Chengdu external validation cohort in Table S3. In the Xinjiang training cohort, compared with the non-ISR, patients with ISR had older age ($P < 0.01$), lower proportion of male ($P = 0.018$), higher proportion of family history of CAD ($P = 0.040$), diabetes mellitus (DM) ($P < 0.01$), atrial fibrillation ($P = 0.013$), stent in left anterior descending coronary artery (LAD) ($P < 0.01$), minimum stent diameter <3 mm ($P < 0.01$); higher levels of BMI ($P = 0.016$), SBP ($P < 0.01$), DBP ($P < 0.01$), heart rate (HR) ($P = 0.001$), monocyte counts ($P = 0.035$), platelet distribution width (PDW) ($P = 0.002$), creatinine ($P = 0.022$), fasting blood glucose (FBG) ($P = 0.010$), total cholesterol (TC) ($P = 0.013$), low-density lipoprotein cholesterol (LDLC) ($P < 0.01$), Lipoprotein(a) [LP(a)] ($P = 0.015$), C-reactive protein (CRP) ($P = 0.002$); lower levels of eGFR ($P < 0.01$). The baseline characteristics of included and excluded patients in the Xinjiang training cohort were shown in Table S2. The baseline characteristics between included and excluded patients did not exhibit significant differences ($P > 0.05$), suggesting a low probability of population selection bias in this study.

3.2. Predictors selection

In order to select superior predictors, all variables that showed statistically significant differences in the above baseline characteristics were included into the LASSO regression analysis. As presented in Fig. 2A and B, although 20 significant possible variables entered the LASSO regression analysis, only 10 predictors remained with non-zero coefficient characteristics corresponding to the maximum λ within one standard deviation of the mean error. Next, all 10 predictors, including age, DM, BMI, SBP, PDW, LDLC, eGFR, CRP, stent in LAD, and minimum stent diameter <3 mm were determined by univariate logistic regression analyses, and further assessed by multivariable regression logistic analysis. As shown in Table 3, age (OR: 1.060, 95 % CI: 1.008 to 1.115, $P = 0.023$), DM (OR: 2.049, 95 % CI: 1.045 to 4.017, $P = 0.037$), BMI (OR: 1.112, 95 % CI: 1.023 to 1.209, $P = 0.013$), SBP (OR: 1.030, 95 % CI: 1.011 to 1.049, $P < 0.01$), LDLC (OR: 1.413, 95 % CI: 1.072 to 1.864, $P = 0.014$), eGFR (OR: 0.983, 95 % CI: 0.969 to 0.997, $P = 0.019$), stent in LAD (OR: 2.147, 95 % CI: 1.102 to 4.182, $P = 0.025$), and minimum stent diameter <3 mm (OR: 1.976, 95 % CI: 1.037 to 3.766, $P = 0.038$) were independent predictors for ISR.

3.3. Model development and display

In order to simplify and optimize the risk score model, the eight independent predictors were divided into age, cardiovascular parameters (stent in LAD, minimum stent diameter <3 mm), kidney variables (eGFR), and metabolic characteristics (DM, BMI, SBP, LDLC) according to their clinical information. Afterwards, four models were established in Fig. 3, including Cardiovascular score based on age and cardiovascular parameters [AUC, 0.719 (95%CI: 0.646 to 0.793)]; Kidney score based on age and kidney variables [AUC, 0.699 (95%CI: 0.626 to 0.773)]; Metabolic score based on age and metabolic characteristics [AUC, 0.789 (95%CI: 0.732 to 0.845)]; and CKM score based on age and all above characteristics [AUC, 0.834 (95%CI: 0.787 to 0.882)]. Given that the increase in predictors was associated with enhancing the discrimination of the prediction model,and had extensive clinical significance for individualized management, the CKM score was finally chosen to the fitted multivariate model. As shown in Fig. 4, eight independent predictors were used to build a nomogram model for predicting ISR in patients with premature AMI undergoing PCI with DES. The cumulative scores for each predictor within the nomogram model were aggregated, yielding a total score. The resultant probability value associated with

Table 2
Characteristics of echocardiogram, angiography and stents of included patients in the Xinjiang training cohort.

Variables	ISR (n = 55)	Non-ISR (n = 379)	$t/\chi 2/Z$ value	P value
Echocardiogram				
LVEF (%)	55.62 ± 8.02	57.40 ± 8.00	1.36	0.176
LAD* (mm)	33.36 ± 4.48	32.45 ± 5.33	1.21	0.229
LVDs (mm)	30.48 ± 3.69	30.16 ± 3.78	0.59	0.556
LVDd (mm)	48.50 ± 4.89	47.62 ± 4.63	1.31	0.192
Angiography				
Lesion vessels	2.56 ± 1.32	2.24 ± 1.18	1.85	0.065
Bifurcation lesion	4 (7.3 %)	18 (4.7 %)	0.64	0.425
Thrombus present	10 (18.2 %)	38 (10.0 %)	3.36	0.067
TIMI flow grade before PCI				
≤1	18 (32.7 %)	113 (29.8 %)	0.19	0.660
>1	37 (67.3 %)	266 (70.2 %)		
TIMI flow grade after PCI				
≤2	2 (3.6 %)	8 (2.1 %)	0.50	0.481
>2	53 (96.4 %)	371 (97.9 %)		
Stent characteristics				
Stent in LAD†	35 (63.6 %)	144 (38.0 %)	13.03	<0.01
Numbers of stent	2.08 ± 0.66	2.02 ± 0.51	0.78	0.434
Total stent length (mm)	33.21 ± 18.20	31.31 ± 14.12	0.89	0.371
Minimum stent diameter <3 mm	31 (56.4 %)	113 (29.8 %)	15.26	<0.01

Abbreviations: LVEF, left ventricular ejection fraction; LAD*, left atrial diameter; LVDs, left ventricular systolic diameter; LVDd, left ventricular diastolic diameter; TIMI, Thrombolysis In Myocardial Infarction; PCI, percutaneous coronary intervention; LAD†, left anterior descending coronary artery.

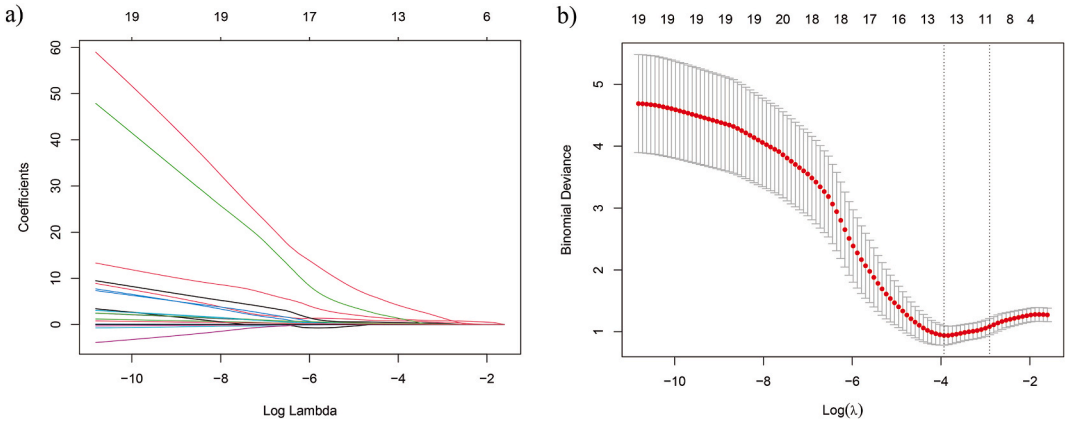

Fig. 2. The non-zero coefficient characteristic variables selected by the LASSO regression. (A) Plot of each variable's coefficient profile against log (lambda); (B) Ten-fold cross-validation used to validate the optimal lambda in the LASSO regression model.
Note: Fig. 2A: 20 variables entered the LASSO regression analysis; Fig. 2B: 10 predictors remained with non-zero coefficient characteristics. LASSO, the least absolute shrinkage and selection operator.

Table 3
Logistic regression analysis of predictors of ISR.

Variables	β	Univariate analysis			β	Multivariable analysis		
		OR	95 % CI	*P* value		OR	95 % CI	*P* value
Age	0.089	1.093	1.042–1.147	<0.01	0.058	1.060	1.008–1.115	0.023
DM	1.225	3.405	1.898–6.108	<0.01	0.717	2.049	1.045–4.017	0.037
BMI	0.091	1.095	1.016–1.181	0.017	0.106	1.112	1.023–1.209	0.013
SBP	0.032	1.033	1.017–1.049	<0.01	0.029	1.030	1.011–1.049	<0.01
PDW	0.155	1.168	1.058–1.288	0.002	0.572	1.771	0.950–3.304	0.072
LDLC	0.440	1.553	1.217–1.982	<0.01	0.346	1.413	1.072–1.864	0.014
eGFR	−0.026	0.974	0.962–0.987	<0.01	−0.017	0.983	0.969–0.997	0.019
CRP	0.037	1.037	1.017–1.058	<0.01	0.095	1.099	0.983–1.229	0.096
Stent in LAD	1.049	2.856	1.587–5.138	<0.01	0.764	2.147	1.102–4.182	0.025
Minimum stent diameter <3 mm	1.112	3.041	1.708–5.412	<0.01	0.681	1.976	1.037–3.766	0.038

Abbreviations: ISR, in-stent restenosis; DM, Diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; PDW, platelet distribution width; LDLC, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; LAD, left anterior descending coronary artery.

the aggregate score denoted the likelihood of ISR.

3.4. Nomogram model evaluation and validation

The discrimination of the nomogram model was evaluated by AUC of the ROC and the C-statistic in the Xinjiang training cohort. The model was proved to be accurate in predicting ISR in patients with premature AMI undergoing PCI with C-statistic or AUC of 0.834 (95 % CI: 0.787 to 0.882). The Hosmer-Lemeshow test indicated that the nomogram model had good calibration ($\chi^2 = 7.86$, $P = 0.448$), and the calibration curve also demonstrated good calibration between the anticipated and observed probability of ISR shown in Fig. 5. The clinical net benefit of the nomogram model was evaluated by DCA presented in Fig. 6, suggesting that the employment of this model for clinical decisions made more benefit than the scenarios of "no intervention" or "all intervention" within the threshold probability range of 0.0–1.0 for ISR.

The C-statistic from a 1000 sample bootstrap resampling showed good internal validation with a value of 0.852. The AUC in the Xinjiang internal validation cohort was 0.852 (95%CI: 0.784 to 0.921), as shown in Fig. S3A. The Hosmer-Lemeshow test validated that the nomogram model has good calibration ($\chi^2 = 5.17$, $P = 0.740$), and the calibration curve of the nomogram also demonstrated a good agreement between the anticipated and observed outcomes (Fig. S3B). The results of DCA are presented in Fig. S3C, showing that the use of this model made clinical net benefit when the threshold probability of ISR was between 0.0 and 1 in the Xinjiang internal validation cohort.

The C-statistic also reached 0.787 in the Chengdu external validation cohort and the AUC was 0.787 (95%CI: 0.692 to 0.882), as shown in Fig. S4A. The Hosmer-Lemeshow test showed that the nomogram model had good calibration ($\chi^2 = 6.35$, $P = 0.608$), and the calibration curve of the nomogram model also suggested a good agreement between the anticipated and observed outcomes (Fig. S4B). The results of DCA also presented clinical net benefit of the nomogram model (Fig. S4C).

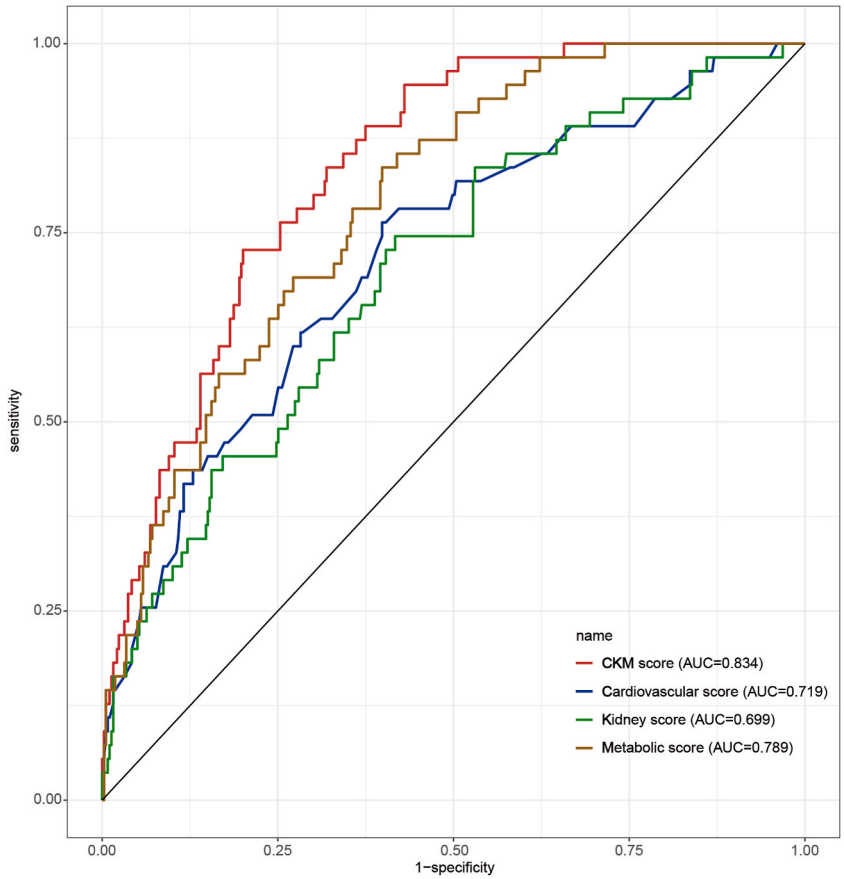

Fig. 3. ROCs curves of each score to predict ISR in the Xinjiang training cohort.
Note: The CKM score exhibited the best discrimination, compared to the other three risk scores. ISR, in-stent restenosis; ROCs, receiver operating characteristic curves; AUC, areas under the curve.

4. Discussion

This two-center retrospective cohort study for the first time established a risk nomogram score combined with eight predictors to identify those premature AMI patients undergoing PCI with DES prone to experience ISR. The main findings are as follows: (I) age, cardiovascular parameters (stent in LAD, minimum stent diameter <3 mm), kidney variables (eGFR), and metabolic characteristics (DM, BMI, SBP, LDLC) were independent predictors for ISR in patients with premature AMI undergoing PCI; (II) the CKM score finally established based on above characteristics for risk stratification of ISR showed excellent discrimination and robust prediction; and (III) the CKM score was well calibrated, showing good clinical net benefit in an external validation cohort of premature AMI patients with ISR.

Despite rigorous medical intervention, patients with AMI faced heightened risks of recurrent AMI, coronary events, and elevated all-cause mortality compared to the general patients with coronary artery disease (CAD) [20]. Young patients afflicted with AMI exhibited distinct clinical profiles compared to their older counterparts, characterized by differences in etiology, risk factors, clinical manifestations, therapeutic strategies, and prognostic outcomes. Unhealthy lifestyle habits, such as smoking, dyslipidemia, and obesity, which are predominantly modifiable, were commonly associated with AMI among the young [11,12,18]. Notably, atherosclerosis regression can occur in the initial disease phases. In young patients, the influence of LDLC and SBP on the progression of subclinical atherosclerosis was more significant, suggesting that early risk factor management may ameliorate atherosclerosis advancement, thereby reducing long-term clinical event risks [21]. Previous studies have shown that a notable incidence of ISR even following DES implantation [4–6]. However, specific predictors and prediction models tailored to premature AMI cases associated with ISR post-DES implantation remained lacking.

Importantly, the CKM score proposed in this study integrates established risk predictors, thus consolidating and extending prior research efforts, offering a robust predictive model for ISR management in premature AMI patients. Firstly, our study confirmed that despite adjustment for multiple factors, age remained an independent predictor of ISR in premature AMI patients undergoing PCI. A retrospective clinical study involving triple-vessel disease patients who underwent DES implantation revealed age escalation as a potential ISR risk factor during a median follow-up of 28.0 months [22]. Mechanistic insights into aging-related ISR were further

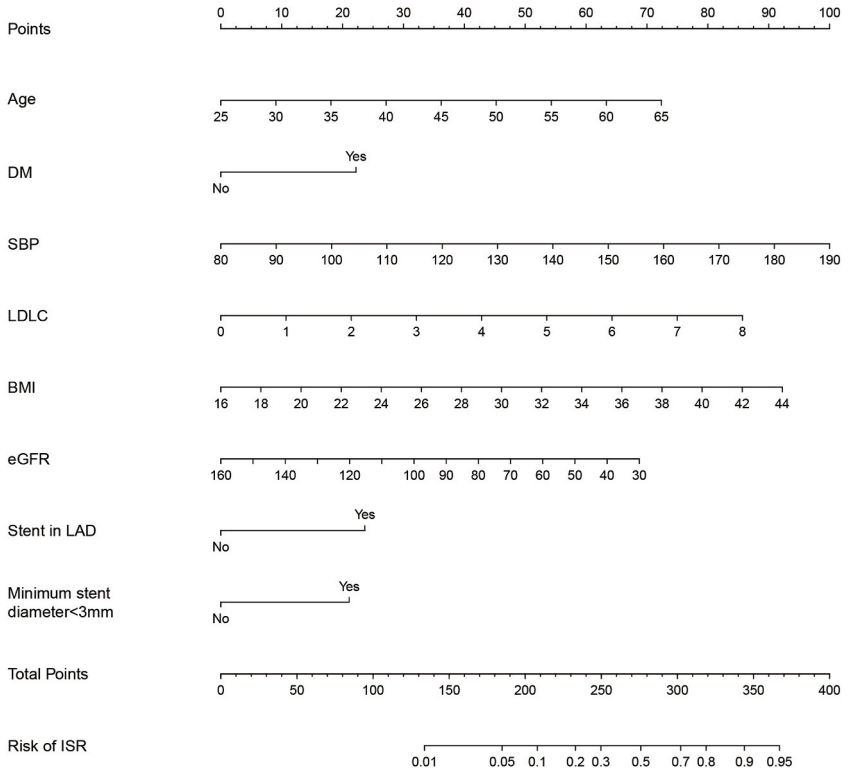

Fig. 4. The CKM score presented by nomogram model to predict the risk of ISR.
Note: The cumulative scores for each predictor within the nomogram model were aggregated, yielding a total nomogram score. The higher total nomogram score, the greater the ISR risk. ISR, in-stent restenosis; DM, diabetes mellitus; SBP, systolic blood pressure; LDLC, low-density lipoprotein cholesterol; BMI, body mass index; eGFR, estimated glomerular filtration rate; LAD, left anterior descending coronary artery.

explored. The study on implanted bioresorbable scaffolds investigated the role of exacerbated endothelial cell senescence and reduced wall shear stress in the aged vasculature in relation to intimal dysfunction and increased incidence of ISR [23]. Secondly, stent characteristics including diameter, length, and location have been associated with ISR occurrence in prior research [8,24]. Longer stents were associated with a higher likelihood of ISR, while stents with larger diameters had a lower risk [25]. The CKM score established in this study primarily tailored to premature AMI patients and reported the association between the minimum stent diameter, stent in LAD with the occurrence of ISR undergoing DES implantation. Previous studies have also confirmed an increased risk of ISR with stents placed in the LAD [4,26]. This observation can be attributed to the higher frequency of restenosis in LAD lesions compared to other native coronary arteries during coronary artery intervention [27,28]. Thirdly, in patients undergoing drug-coated balloon angioplasty for ISR, the presence of severe and end-stage CKD (eGFR <30 mL/min/1.73 m^2) was found to be associated with increased risks of target vessel failure, all-cause mortality, and repeated revascularization [29]. Individuals with CKD and lower eGFR (<60 mL/min/1.73 m^2) demonstrated enhanced neointimal growth during follow-up after DES implantation, resulting in higher ISR rates compared to those with preserved renal function [30]. Moreover, studies conducted in coronary bypass candidates, diabetic patients, and premature acute myocardial infarction (AMI) patients, including our study, consistently revealed that even with DES implantation, individuals with lower eGFR continued to experience a heightened risk of ISR compared to those with higher eGFR [31,32].

Lastly, our study in premature AMI patients identified metabolic variables, including DM, elevated LDLC, SBP, and BMI, as independent predictors of ISR, thus supporting and expanding upon existing research findings. While some studies indicated that metabolic syndrome did not heighten ISR risk, others have provided evidence that specific metabolic indicators independently forecasted ISR risk [24,33,34]. Restenosis progression commenced shortly after the intervention, with ISR arising from endothelial damage caused by PCI and subsequent neointimal and vascular smooth muscle cell (VSMC) proliferation. Metabolic disorders were known to accelerate this pathophysiological process [35]. Neointimal hyperplasia in patients with type 2 DM (T2DM) exhibited phenotypic distinctions compared to non-diabetic patients. VSMC specimens from individuals with T2DM displayed abnormal phenotypes and demonstrated more aggressive behavior (increased adhesion and migration) in cell culture settings [36,37]. Proinflammatory cytokines have the ability to induce VSMC transformation into a secretory state, while both glucose and insulin can promote VSMC mitogenesis [38]. Fasting blood glucose and hemoglobin A1c (HbA1c) have been extensively investigated as clinical biomarkers for predicting ISR risk [4,24]. Notably, patients with DM exhibited an accelerated rate of late loss in lumen diameter and an increased risk of ISR [26,39]. Hypertension was also recognized as one of the prominent factors influencing ISR. Hypertension

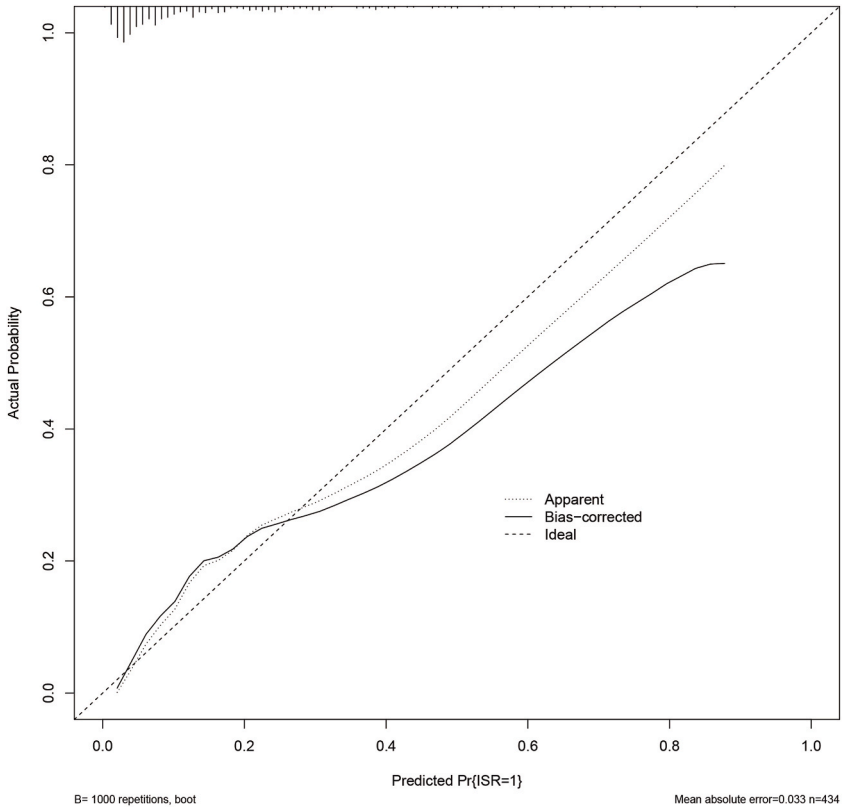

Fig. 5. The calibration curve of the CKM score in the Xinjiang training cohort.
Note: The calibration curve demonstrated good calibration between the anticipated and observed probability of ISR. ISR, in-stent restenosis.

enhanced the impact of blood flow on vessels, resulting in endothelial cell damage, atherosclerotic plaque formation, and ultimately elevating the risk of ISR [40]. Zhao et al. conducted a comprehensive analysis of 398 coronary artery disease (CAD) patients undergoing PCI with DES implantation, and independently identified hypertension as a predictor of increased ISR risk [41]. Xi et al. incorporated hypertension as a risk factor in their model for predicting ISR in CAD patients after DES implantation [24]. Chronic inflammation and LDLC uptake by macrophages mediated neo-atherosclerosis plaque progression. Elevated circulating LDLC levels played a crucial role in accelerating atherosclerosis progression [42]. Studies have reported LDLC elevation as an independent predictor, and its inclusion in ISR prediction models has shown promise [41,43]. Furthermore, obesity was associated with clinical restenosis which was previously defined as target lesion revascularization (TLR). Rana et al. examined 6186 patients with coronary stents and found that patients classified as obese (class II/III) had higher odds of undergoing TLR compared to normal-weight patients [44].

According to the Global Cardiovascular Risk Report, aging and cardiometabolic factors remain the primary drivers behind the increasing number of cardiovascular disease-related deaths [45]. The American Heart Association recently released a scientific statement highlighting the strong association between cardiovascular-kidney-metabolic (CKM) syndrome and adverse cardiovascular and kidney outcomes. However, there are significant knowledge gaps in terms of the scientific understanding, screening, and clinical management of CKM syndrome [46]. In this study, a novel CKM score incorporating traditional cardiovascular-kidney-metabolic characteristics was developed and validated to predict the occurrence of ISR in patients with premature AMI. The model demonstrated excellent discrimination, calibration, and clinical net benefit. As shown in the results section of this study, individual inclusion of these features yielded less discriminative results, with the area under the receiver operating characteristic curve (AUC-ROC) being 0.719 for the Cardiovascular score, 0.699 for the Kidney score, and 0.789 for the Metabolic score. However, when combined, the CKM score achieved an AUC-ROC of 0.834, outperforming other established ISR risk prediction models [4,6,9]. Furthermore, the predictive power of the CKM score was externally validated in an independent cohort, which is a rarity in most models [5,24,34]. In light of these findings, the newly proposed CKM score holds three practical implications for the assessment and management of patients with premature AMI. Firstly, it is the first ISR risk score specifically tailored to the premature AMI population. Secondly, it allows for the identification of individuals at risk of ISR without the need for invasive or costly testing. Lastly, the CKM score facilitates the individualized tailoring of medical treatment intensity for secondary prevention based on the integrated predictors within the framework.

Inevitably, several limitations should be acknowledged in this study. Firstly, its retrospective design introduces the possibility of selection and recall biases. The indications for repeated coronary angiography (CAG) were based on specific criteria such as new-onset chest discomfort, prior high-risk PCI, and ischemic findings in non-invasive testing, which may contribute to a higher prevalence of

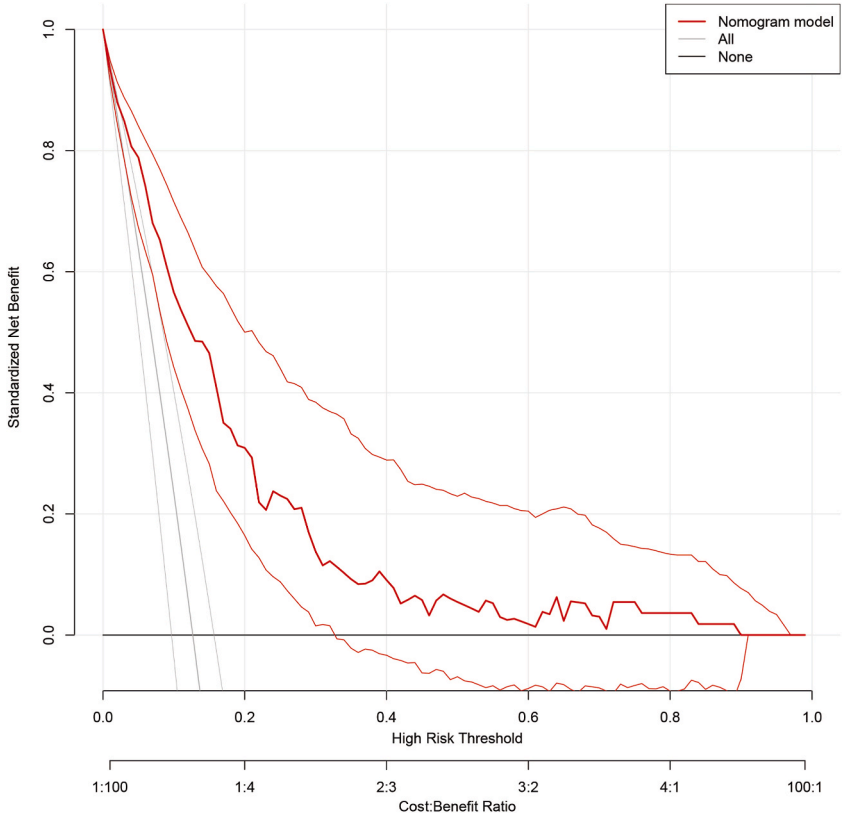

Fig. 6. The decision curve analysis of the CKM score in the Xinjiang training cohort.
Note: Decision curve analysis testified the clinical net benefit of the CKM score.

ISR. While internal and external validation using cohorts from two centers were conducted for the CKM score, prospective, multi-center, large sample studies are needed to enhance the accuracy and generalizability of the model. Secondly, CAG reassessment was performed at least 10 months after initial stent implantation. This may have excluded some ISR patients who underwent CAG reassessment earlier than 10 months, while some non-ISR patients who had CAG reassessment at 10 months may have been diagnosed with ISR if CAG reassessment occurred later (e.g. up to 20 months or more). This bias could potentially underestimate the accuracy of the predictive models. Thirdly, the CKM score does not include patient-related or biological factors, procedural factors, anatomic factors, and stent-related factors that have been reported as risk factors for ISR [47]. Our team is currently working on further feature selection to develop a more comprehensive model with improved predictive performance.

5. Conclusion

This study provided a well-developed and validated risk nomogram score, the CKM score to predict ISR in patients with premature AMI undergoing PCI with DES based on cardiovascular parameters, kidney variables and metabolic characteristics. Given that these variables are readily available and practical, the CKM score should be widely adopted for individualized assessment and management of premature AMI.

Statement of ethics

This study was approved by the Research Ethics Committee of First Affiliated Hospital of Xinjiang Medical University (approval No. K202306-22), and informed consent from patients was not needed. This was a retrospective cohort study, and was conducted in adherence to the Declaration of Helsinki.

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Data availability statement

Data will be made available on reasonable request to the corresponding author, [Zhenyan Fu].

CRediT authorship contribution statement

Sen Liu: Writing – review & editing, Writing – original draft, Software, Funding acquisition, Data curation, Conceptualization. **Hong Yang:** Writing – original draft, Software, Methodology, Data curation, Conceptualization. **Cheng Liu:** Writing – review & editing, Funding acquisition. **Ziyang Liu:** Writing – review & editing. **Jixin Hou:** Methodology, Investigation, Data curation. **Mengwei Wei:** Software, Investigation. **Sifu Luo:** Software. **Yaqi Zhou:** Data curation. **Peijian Wang:** Writing – review & editing, Funding acquisition, Formal analysis, Conceptualization. **Zhenyan Fu:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34077.

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