

# A Nomogram Model for Predicting Recurrent Coronary Thrombosis in Kawasaki Disease Patients

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**Background:** Coronary thrombosis is a serious cardiovascular complication of Kawasaki disease (KD), and recurrence of coronary thrombosis increases the short-term risk of myocardial infarction and the long-term risk of coronary artery disease. However, there are currently no studies predicting the recurrence of coronary thrombosis, so the aim of this study was to develop and validate a nomogram to predict recurrent coronary thrombosis in KD patients.

**Methods:** This was a retrospective study of data from 149 KD patients who had a history of previous coronary disease at the Children's Hospital of Chongqing Medical University from 2013 to 2020. Independent risk factors were identified using univariate and multivariate logistic regression analyses, and a nomogram was constructed to predict recurrent coronary thrombosis.

**Results:** Multivariate analysis showed that large coronary artery aneurysm(CAA) (Odds Ratio [OR] 4.28; 95% Confidence Interval [CI] 1.39–13.12), saccular CAA (OR 5.03; 95% CI 1.55–16.29), first left anterior descending (LAD) thrombosis (OR 3.90; 95% CI 1.20–12.63), and persistent CAA (OR 43.27; 95% CI 12.23–153.12) were independent risk factors for recurrent coronary thrombosis. Based on these variables, a nomogram was constructed. The Area Under the Curve (AUC) of the nomogram was 0.943, and tenfold cross-validation (200 replicates) showed an average AUC of 0.929. Furthermore, the nomogram not only presented a favorable calibration curve but also demonstrated practical clinical utility.

**Conclusion:** Large CAA, saccular CAA, first LAD thrombosis and persistent CAA were independent risk factors for recurrent coronary thrombosis. The nomogram can visually show these independent risk factors and predict probabilities.

**Keywords:** Kawasaki disease, recurrent coronary thrombosis, nomogram, predictive value, logistic regression analysis

## Background

Kawasaki disease (KD) is an acute self-limited vasculitis that affects infants and young adults, results in coronary artery disease and has attracting increasing attention from clinicians.<sup>1,2</sup> It has replaced rheumatic heart disease as the main cause of acquired heart disease in children in developed countries.<sup>3</sup> If not treated in time, approximately 25% of KD patients will develop coronary artery aneurysm (CAA); even after prompt treatment with intravenous immunoglobulin (IVIG), 3% - 5% of KD patients still have CAA.<sup>4,5</sup> Architectural changes in the coronary artery wall caused by persistent CAA increase the risk of coronary thrombosis and stenosis, which may lead to cardiovascular events such as myocardial infarction and even death.<sup>6,7</sup> One study reported a significant increase in the risk of myocardial infarction due to coronary thrombosis within the first 2 years of onset.<sup>8</sup> Compared with that in coronary artery disease in atherosclerosis, the mass of the coronary thrombus is significantly greater in KD patients.<sup>9</sup> Continued progression or shedding of the thrombus may block the coronary artery, causing myocardial infarction. Therefore, long-term management of KD is mainly to prevent

coronary thrombosis and monitor coronary stenosis, thereby reducing the risk of cardiovascular events to maintain optimal cardiovascular health.<sup>10</sup>

Given the importance of the prevention of coronary thrombosis for the long-term management of KD patients, the American Heart Association (AHA) stratifies patients by risk of coronary thrombosis and recommends corresponding preventive regimens.<sup>9</sup> For patients at low risk of coronary thrombosis, such as those without architectural changes in the coronary arteries, treatment with antiplatelet drug has a significant effect on thromboprophylaxis.<sup>11</sup> However, for patients at high risk of coronary thrombosis, such as those with a recent history of coronary thrombosis, despite anticoagulation combined with both antiplatelet drug, coronary thrombosis still recurred frequently.<sup>12</sup> Recurrent coronary thrombosis remains a disaster for these patients, increasing the short-term risk of myocardial infarction and the long-term risk of myocardial ischemia.<sup>9</sup> There are no current reports on the prevention of recurrent coronary thrombosis in KD reported in existing guidelines, and an improved understanding of the risk factors for recurrent coronary thrombosis may contribute to clinical decision-making, including adjustment of thromboprophylaxis strategies and appropriate coronary revascularization.<sup>13</sup>

This study evaluated independent risk factors for recurrent coronary thrombosis in KD patients. Furthermore, we developed and verified a nomogram for predicting recurrent coronary thrombosis based on basic information, medical interventions, and echocardiography features.

## Methods

### Patients and Study Design

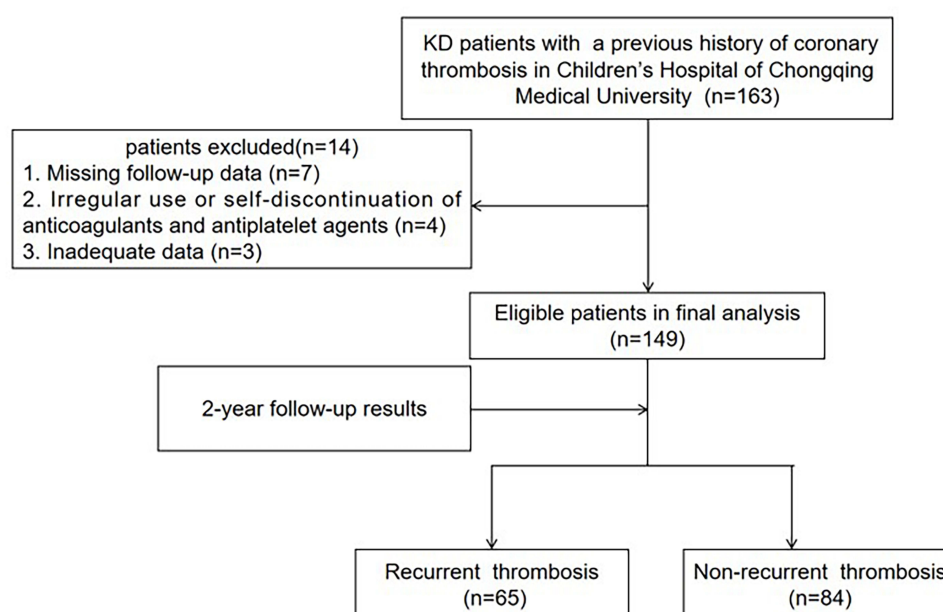
This clinical study was a single-center retrospective study that retrospectively identified all consecutive KD patients hospitalized at the Children's Hospital of Chongqing Medical University from January 2013 to December 2020. All KD patients were treated with standard treatment: IVIG combined with high-dose aspirin. According to the size of coronary artery, a combination of antiplatelet agents (aspirin and clopidogrel) with anticoagulant therapy (low molecular weight heparin (LMWH) or warfarin) was administered to achieve an international normalized ratio (INR) within the range of 2 to 3. All KD patients were rigorously diagnosed and followed up according to the AHA Guidelines.<sup>9,14</sup> The inclusion criteria were as follows: 1) age < 18 years; 2) met the diagnostic criteria for KD; and 3) previous history of coronary thrombosis. The exclusion criteria were as follows: 1) follow-up time less than 2 years; 2) irregular use or self-discontinuation of anticoagulants and antiplatelet agents; or 3) inadequate data. A total of 149 eligible patients participated in the study. The detailed flowchart is shown in Figure 1. The data of all eligible patients were analyzed retrospectively, and a nomogram was constructed to predict recurrent coronary thrombosis. Approval for this study was obtained from the Ethics Committee of the Chongqing Medical University Children's Hospital (2023444), and informed consent was obtained from the guardians of all eligible patients.

### Data Collection and Variables

Using an electronic medical record system, we collected all the medical records from the first diagnosis to the last follow-up, including demographics (age and sex) and medical interventions of KD patients at the time of initial diagnosis, echocardiography features at the time of the first coronary thrombosis, and status of CAA at follow-up. According to the pathological characteristics during natural onset of KD, the acute stage of KD was defined as occurring within 90 days after onset, while the chronic stage was more than 90 days after onset.<sup>15</sup>

Medical intervention included LMWH therapy (duration and first time of LMWH use) and IVIG therapy (IVIG time and IVIG resistance). IVIG time was divided into 2 categories: (1) 10 days and below and (2) over 10 days. IVIG resistance was defined as having an oral or rectal temperature  $\geq 38.0^{\circ}\text{C}$  at least 36 hours after the completion of the initial IVIG infusion.<sup>16</sup>

Echocardiography features included the size of the CAA, configuration of the CAA, number of CAAs, first coronary thrombosis time and first coronary thrombosis site. The coronary arteries, including the left main coronary artery (LMCA), left anterior descending artery (LAD), left circumflex coronary artery (LCX), and right coronary artery (RCA), and CAAs were primarily evaluated by converting coronary artery internal diameter to a Z score based on the



**Figure 1** Flowchart of participant selection.

lambda-mu-sigma method.<sup>17</sup> Large CAA was defined when the  $Z$  score was over 10 or the absolute dimension was  $\geq 8$  mm, and medium CAA was defined when the  $Z$  score was 5 to 10 and the absolute coronary dimension was  $< 8$  mm. The size of the CAA was defined using the maximum  $Z$  score. The number of CAAs was defined as the number of coronary arteries corresponding to the maximum  $Z$  score. According to the longitudinal dimension and transverse dimension proportion of the coronary artery on the echocardiography, the configuration of the CAA was divided into saccular type and fusiform type. The transverse dimension of the saccular type was greater than half of the longitudinal dimension, and the transverse dimension of the fusiform type was half of the longitudinal dimension or less.<sup>18</sup>

## Follow-Up

All eligible patients were followed up regularly in the outpatient department for more than 2 years. Follow-up assessments were weekly for the first 1 month, monthly for the last 11 months, and every 3–6 months thereafter, and anticoagulant doses were adjusted based on coronary arteries and coagulation outcomes. The coronary arteries were evaluated primarily by echocardiography by 2 senior physicians with 10 years of experience. Coronary thrombosis should be considered when echocardiography detects an abnormal echogenicity in the coronary artery. In addition, we determined the recurrence of coronary thrombosis based on changes in the location and size of the echocardiography echo during each follow-up period. We collected data on all echocardiography features from the first day to the last follow-up. Recurrent coronary thrombosis was the endpoint of this study.

## Statistical Analysis

Categorical variables are represented by numbers (percentages). For continuous variables, those with normal distributions are presented as the mean $\pm$ SD, and those with nonnormal distributions are represented as the median (interquartile). Univariate logistic regression analysis was used to screen for potential factors contributing to recurrent coronary thrombosis, followed by stepwise regression on potential factors using multivariate logistic regression analysis to identify independent risk factors. Based on the results of multivariate logistic regression analysis, a nomogram was developed to predict recurrent coronary thrombosis. Finally, internal validation was performed with 10-fold cross-validation to assess model stability. The predictive ability of the model was evaluated using the receiver operating characteristic (ROC) curve, the consistency of the prediction probability with the observed results was evaluated with a calibration curve drawn using the bootstrap method with 1000 resamplings, and the clinical utility of the model was assessed using

decision curve analysis (DCA).  $P < 0.05$  was considered statistically significant. All statistical analyses were performed using SPSS 26.0 software (SPSS, Inc., Chicago, USA) and R software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Patient Characteristics

A total of 149 consecutive KD patients with a previous history of coronary thrombosis from Children's Hospital of Chongqing Medical University were included in this study. Table 1 showed the detailed characteristics of all eligible patients. There were 111 (74%) males and 38 (26%) females, with a median age of 18 months (IQR, 7.5–39.5 months). For the medical interventions, all patients were treated with IVIG, 118 (79%) patients had decreased temperature and inflammatory index after treatment, and 31 (21%) patients had IVIG resistance. IVIG treatment was administered mainly within 10 days (60%). Over a follow-up period of more than two years, 65 patients (44%) experienced recurrent coronary thrombosis.

### Variable Analysis and Selection

Table 2 showed univariate and multivariate ORs for recurrent coronary thrombosis in KD patients. In the univariate logistic regression analysis, 14 potential variables were associated with recurrent coronary thrombosis, among which age (odds ratio [OR] 1.014; 95% confidence interval [CI] 1.001–1.026), large CAA (OR 15.11; 95% CI 6.73–33.92), saccular CAA (OR 5.24; 95% CI 2.59–10.58), first coronary thrombosis in the chronic phase (OR 3.17; 95% CI 1.40–7.19), first

**Table 1** Demographics, Medical Interventions and Echocardiography Characteristics

Characteristic	Total (n = 149)
Age (months), median (IQR)	18 (7.5–39.5)
Male gender (%)	111 (74%)
First time of LMWH use(days)	14 (10–17.5)
Duration time of LMWH use (days)	9 (7–14)
IVIG time ≤10 days (%)	89 (60%)
IVIG resistance (%)	31 (21%)
Size of CAA	
Large	72 (48%)
Medium	77 (52%)
Number of CAA	
Single	51 (34%)
Multiple	98 (66%)
Configuration of CAA	
Fusiform type	81 (54%)
Saccular type	68 (46%)
Coronary thrombosis time	
Acute phase	133 (89%)
Chronic phase	16 (11%)
First RCA thrombosis	64 (43%)
First LMCA thrombosis	25 (17%)
First LAD thrombosis	80 (54%)
Follow-up status of CAA	
Regressed CAA	88 (59%)
Persistent CAA	61 (41%)

**Abbreviations:** LMWH, low-molecular-weight heparin; IVIG, intravenous immunoglobulin; CAA, coronary artery aneurysm; RCA, right coronary artery; LMCA, left main coronary artery; LAD, left anterior descending artery.

**Table 2** Univariate and Multivariate Logistic Regression Analysis of Recurrent Coronary Thrombosis in KD Patients

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (months)	1.014 (1.001–1.026)	0.037*	–	0.128
Gender				
Female	Reference			
Male	1.807 (0.516–2.289)	0.827		
First time of LMWH use(days)	0.963 (0.906–1.023)	0.222		
Duration time of LMWH use (days)	1.027 (0.973–1.084)	0.334		
IVIG time				
≤10 days	Reference			
>10 days	1.230 (0.636–2.387)	0.539		
IVIG resistance				
No	Reference			
Yes	0.917 (0.412–2.041)	0.831		
Size of CAA				
Medium	Reference		Reference	
Large	15.11 (6.73–33.92)	<0.001*	4.28 (1.39–13.12)	0.011
Number of CAA				
Single	Reference			
Multiple	1.164 (0.587–2.309)	0.664		
Configuration of CAA				
Fusiform type	Reference		Reference	
Saccular type	5.24 (2.59–10.58)	<0.001*	5.03 (1.55–16.29)	0.007*
Coronary thrombosis time				
Acute phase	Reference			
Chronic phase	3.17 (1.40–7.19)	0.006*	–	0.587
First RCA thrombosis				
No	Reference			
Yes	1.128 (0.587–2.168)	0.718		
First LMCA thrombosis				
No	Reference			
Yes	0.589 (0.245–1.415)	0.237		
First LAD thrombosis				
No	Reference		Reference	
Yes	2.435 (1.249–4.745)	0.009*	3.90 (1.20–12.63)	0.023*
Follow-up status of CAA				
Regressed CAA	Reference		Reference	
Persistent CAA	54 (19.68–148.18)	<0.001*	43.27 (12.23–153.12)	<0.001*

**Note:** \*P value<0.05.

**Abbreviations:** LMWH, low-molecular-weight heparin; IVIG, intravenous immunoglobulin; CAA, coronary artery aneurysm; RCA, right coronary artery; LMCA, left main coronary artery; LAD, left anterior descending artery.

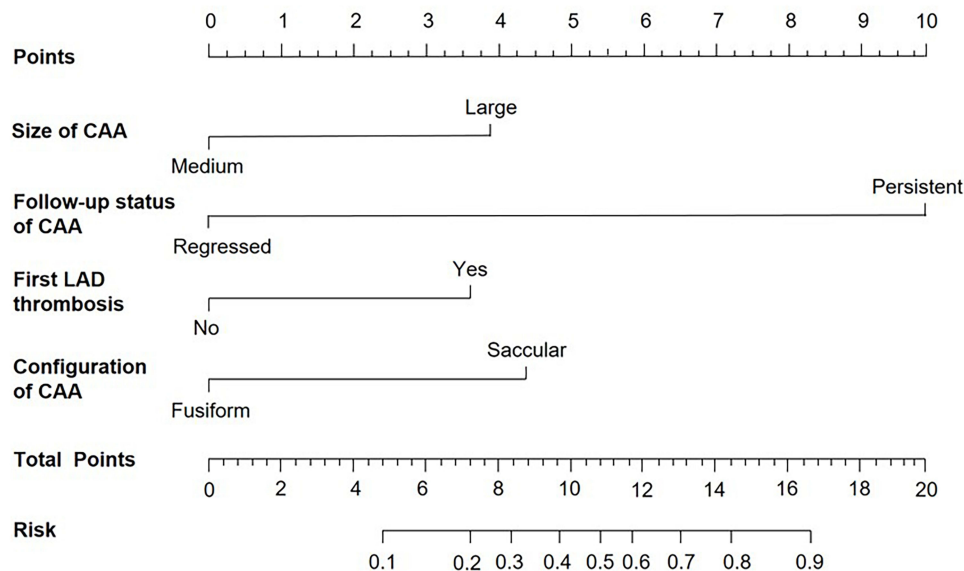
LAD thrombosis (OR 2.435; 95% CI 1.249–4.745), and persistent CAA (OR 54.00; 95% CI 19.68–148.18) were potential independent predictors. Based on the potential independent predictors of univariate logistic regression analysis, we performed multivariate logistic regression analysis, and multivariate logistic regression analysis showed that large CAA (OR 4.28; 95% CI 1.39–13.12), saccular CAA (OR 5.03; 95% CI 1.55–16.29), first LAD thrombosis (OR 3.90; 95% CI 1.20–12.63), and persistent CAA (OR 43.27; 95% CI 12.23–153.12) were independent risk factors for recurrent coronary thrombosis.

# Nomogram Construction and Validation

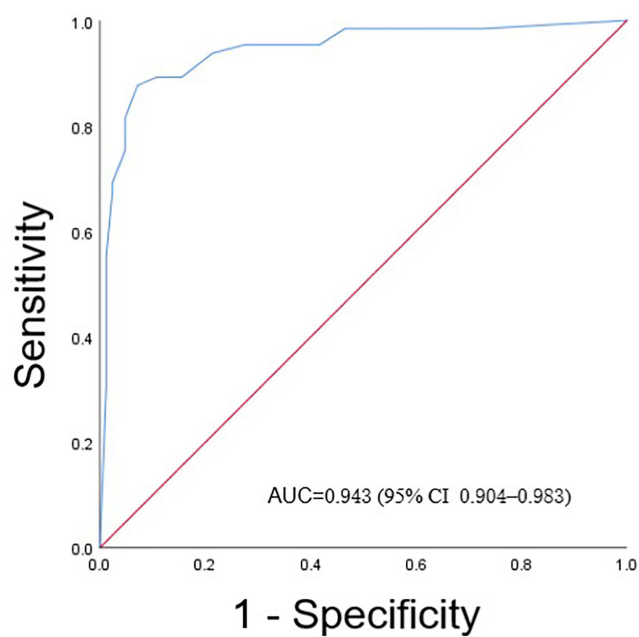
Based on the results of the multivariate logistic regression analysis, a nomogram model containing 4 independent variables was constructed to predict recurrent coronary thrombosis. The model emphasized the predictive power of each independent variable and assigned corresponding scores. The total score was obtained by summing the scores of all independent variables, and the prediction probability was obtained according to the position of the total score on the base reference value (Figure 2). The nomogram demonstrated a high level of predictive accuracy, as evidenced by an AUC of 0.943 (95% confidence interval: 0.904–0.983) (Figure 3). Additionally, the nomogram exhibited a sensitivity of 0.877 and a specificity of 0.929, underscoring its robust ability to predict outcomes effectively. Tenfold cross-validation was used for internal validation of the nomogram, and the AUC of 10-fold cross-validation was 0.929 for 200 repetitions, indicating the excellent stability of the nomogram. The calibration curve showed that the predicted value of the model and the predicted value of the model obtained by bootstrapping were highly consistent with the actual results, indicating good predictive accuracy between the predicted probability and actual probability (Figure 4). In addition, the nomogram showed a significant positive net benefit from the risk of recurrence, indicating good clinical value in predicting recurrent coronary thrombosis (Figure 5).

# Discussion

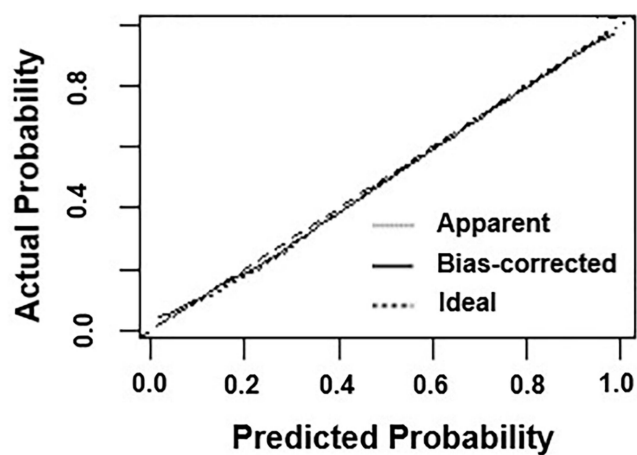
After the formation of CAA, coronary thrombosis is likely to occur when blood flow passes through this abnormal area due to platelet activation and coronary artery wall structural changes.<sup>19,20</sup> At present, there is no effective medical treatment for the structural changes of the coronary artery during the chronic phase of KD patients, and the prevention of coronary thrombosis is mainly antiplatelet and/or anticoagulant therapy. For KD patients with a previous history of coronary thrombosis, the efficacy of preventing recurrent coronary thrombosis is unclear. In this study, we aimed to identify independent risk factors for recurrent coronary thrombosis in KD patients, focusing on recurrent coronary thrombosis to maximize the avoidance of secondary coronary lesions. Therefore, we studied 149 eligible patients who were followed up for more than 2 years, of whom 65 (44%) had recurrent coronary thrombosis. In the logistic regression analysis, 4 significant factors were found to be associated with recurrent coronary thrombosis and were used to construct a nomogram to predict recurrent coronary thrombosis. Subsequently, we used the AUC value, calibration curve, and DCA to evaluate and verify the model.



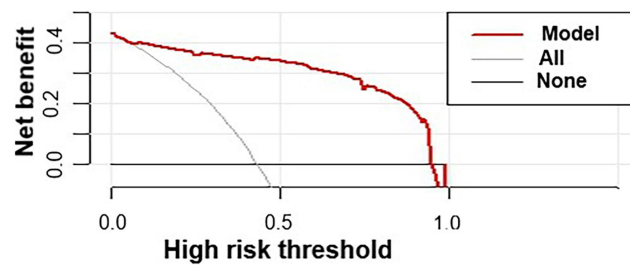
**Figure 2** Nomogram to predict recurrent coronary thrombosis in Kawasaki disease patients.  
**Abbreviations:** CAA, coronary artery aneurysm; LAD, left anterior descending artery.



**Figure 3** The receiver operating characteristic curves and area under the curve of the nomogram.



**Figure 4** Calibration curve of the nomogram.



**Figure 5** Decision curve analysis of the nomogram.



As mentioned above, coronary thrombosis was associated with multiple factors, and the results of our multivariate logistic regression analysis showed that large CAA, saccular CAA, first LAD thrombosis and persistent CAA were independent risk factors for recurrent coronary thrombosis.

Our previous research reports focused on a nomogram to predict coronary thrombosis in KD patients, which suggested a close association between CAA and coronary thrombosis.<sup>21</sup> CAA indicated the prognosis of KD, in the long-term follow-up, the prognosis of a small CAA was good, but that of some medium CAAs and most large CAAs were poor.<sup>15,22</sup> Previous studies have shown that a large CAA is an independent risk factor for coronary thrombosis,<sup>15</sup> and our study also found that a large CAA was strongly associated with recurrent coronary thrombosis. We hypothesized that the larger lumen diameter of large CAAs not only led to endothelial cell dysfunction and increased adhesion to the vascular intima surface, led to platelet aggregation, but also caused myofibroblast proliferation, resulting in a low shear stress environment and abnormal blood flow.<sup>23</sup> As there is currently no effective treatment for the chronic phase, CAAs only wait for natural contraction, and persistent CAAs still lead to recurrent coronary thrombosis. Interestingly, this study also found that persistent CAA was an independent risk factor for recurrent coronary thrombosis, further confirming the hypothesis.

The coronary artery is the blood system that supplies blood to the heart muscle; because of its trend on the heart surface, it is mainly divided into four main branches: RCA, LMCA, LAD, and LCX. LAD is a predilection site for thrombotic occlusion in atherosclerosis.<sup>24</sup> Our findings suggest that LAD thrombosis is an independent risk factor for recurrent coronary thrombosis, potentially linked to turbulence caused by specific anatomical structures and reduced flow velocity due to cardiac malformations.<sup>25</sup> CAAs are categorized into saccular and fusiform types base on the enlargement of the coronary lumen. Previous study has suggested that saccular CAA has a worse prognosis than fusiform CAA.<sup>26</sup> Our study identified saccular CAA as an independent risk factor for recurrent coronary thrombosis, which may be related to its specific hemodynamics. A lower velocity of blood flow through saccular aneurysms is more prone to turbulence, leading to flow arrest.<sup>27</sup>

In this study, we established a prognostic statistical model to assess the risk of recurrent coronary thrombosis in KD patients, and the nomogram not only visually showed the independent risk factors in multivariate regression analysis but could also be predicted using simple graphics. Regression analysis is the core basis of this model.<sup>28</sup> We identified independent risk factors for recurrent coronary thrombosis by univariate and multivariate regression analysis, and developed a nomogram for predicting such events. The ROC curve, calibration curve and DCA demonstrated that the model has a strong predictive capability for recurrent coronary thrombosis and closely aligns with actual incidence data. This tool will enable doctors to accurately predict recurrent coronary thrombosis and provide a powerful tool for clinical management.

Future research may be focused on several key directions. Firstly, optimizing personalized treatment strategies is essential. By further validating the model's applicability across different populations, particularly regarding varying responses to antithrombotic therapy, more accurate treatment recommendations can be provided for patients. Multicenter clinical trials can assist physicians in adjusting treatment plans based on the unique risks of individual patients, thereby reducing the occurrence of recurrent thrombosis. Secondly, the role of inflammation and immune response in Kawasaki disease-related coronary artery lesions is significant and should not be overlooked. The formation of coronary aneurysms is closely associated with inflammation of the vascular wall. Future studies can explore the relationship between different inflammatory markers (such as CRP, IL-6, etc) and immune responses, and the impact on the risk of recurrent thrombosis. This could lead to insights into how immune modulation might reduce this risk and offer new therapeutic targets for patients. In addition, genetic factors associated with coronary artery lesions in Kawasaki disease merit attention. Future genomic studies could explore gene mutations or polymorphisms related to thrombosis formation, helping to understand how genetic predisposition affects the risk of recurrence and providing a foundation for personalized treatment approaches. Long-term evaluation of interventions is also crucial. Future research should focus on assessing the long-term effects of interventions such as medication, interventional therapy, and surgery, particularly in patients with persistent coronary artery lesions. By integrating nomogram predictions with long-term follow-up studies, evaluating the effectiveness of different interventions in preventing recurrent thrombosis will help optimize clinical decision-making. In summary, future research will enhance the model's predictive capabilities and clinical value through the optimization of personalized treatment strategies, in-



depth exploration of inflammatory and immune mechanisms, genetic research, etc. These efforts will further safeguard the long-term health of Kawasaki disease patients.

There are some limitations to this study. For instance, as this study was a retrospective study, selection bias were inevitable. Second, this was a single-center study with a relatively small number of cases. Although the internal validation model was stable, there was a lack of external data to validate the applicability of the model. Prospective multicenter studies are therefore needed to further improve the nomogram model.

## Conclusions

In brief, we first identified independent risk factors for recurrent coronary thrombosis based on univariate and multivariate logistic regression analysis, and of these four independent risk factors, all were irreversible. Therefore, the importance of forecasting and management is more prominent. Based on this independent risk factor, a nomogram model for predicting recurrent coronary thrombosis was developed, and this will help clinicians effectively identify recurrent coronary thrombosis in KD patients with a previous history of coronary thrombosis. For these patients, we should close follow up and evaluate myocardial ischemia using exercise electrocardiography, cardiac magnetic resonance imaging and myocardial perfusion imaging. If necessary, coronary interventions should be performed to avoid major adverse cardiac events.

## Data Sharing Statement

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

## Ethical Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval for this study was obtained from the Ethics Committee of the Chongqing Medical University Children's Hospital (2023444).

## Consent for Publication

Informed consent was obtained from the guardians of all patients.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas, and took part in drafting, revising or critically reviewing the article. Additionally all authors gave final approval of the version to be published, agreed on the journal to which the article has been submitted, and also agreed to take responsibility and be accountable for the contents of the article.

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## Disclosure

The authors declare no conflict of interest.

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