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ORIGINAL RESEARCH

Nomogram for Predicting Regression of Persistent Coronary Artery Aneurysms in Kawasaki Disease: A Three-year Follow-up Cohort Study in Southwest China

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Video Abstract

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Objective: Coronary artery aneurysm (CAA) is a potentially life-threatening cardiovascular complications in Kawasaki disease (KD). This study aimed to construct and then validate a prognostic model to assess the likelihood of persistent CAA regression in KD.

Methods: Using Cox regression analysis, we constructed a prognostic nomogram model to estimate the probability of CAA regression at one-year, two-year, and three-year intervals in KD patients with CAA, followed by temporal external validation. The model's discriminative ability, calibration, and potential clinical benefit were evaluated by the area under the receiver operating characteristic curve (AUC), calibration plots, and decision curve analysis.

Results: A total of 658 KD with CAA were finally included. From January 2012 to July 2021, 557 participants were enrolled and subsequently allocated into a training set (n = 390) and a testing set (n = 167) using a 7:3 random split. The temporal external validation cohort consisted of 101 cases diagnosed as KD with CAA between August, 2021 and July, 2022. Four variables were retained in the final prognostic model: age at diagnosis (HR = 0.994, 95% CI 0.990–0.998); CAA enlargement category (reference: SCAA; MCAA: HR = 0.398, 95% CI 0.299–0.530; GCAA: HR = 0.058, 95% CI 0.027–0.125); platelet count (HR = 0.999, 95% CI 0.998–1.000); and fibrinogen level (HR = 1.143, 95% CI 1.042–1.255). The model demonstrated robust discriminative performance, with AUCs of 0.854, 0.919, and 0.910 at one, two, and three years in the training set; 0.844, 0.910, and 0.913 in the testing set; and 0.763, 0.886, and 0.986 in the external validation cohort.

Conclusion: We established a prognostic model capable of estimating the long-term outcomes in KD, and confirmed its favorable performance in terms of discrimination, calibration, and potential value for clinical application.

Keywords: kawasaki disease, coronary artery aneurysm, prognostic model, nomogram

Introduction

Kawasaki disease (KD), a self-limiting, acute vasculitis of unknown origin,[1] primarily involves small and medium sized vessels, and most frequently occurs in children younger than five years.[2] KD is more common in males and in Asian populations. Even with prompt intravenous immunoglobulin (IVIG) therapy, coronary artery aneurysm (CAA) remains the leading cardiovascular complication, occurring in roughly 4–5% of cases during the acute phase.[3] While about half of these aneurysms regress spontaneously within one to two years after onset,[4–6] a considerable number of KD patients with CAA, especially those of medium or large size persist and carry a heightened risk of thrombosis, progressive stenosis,[7] and severe outcomes, like myocardial infarction[8] or sudden cardiac death.[9] KD with persistent CAA is seen as high-risk,

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according to the American Heart Association (AHA) guidance on cardiovascular risk management in high-risk children.[10] Consequently, these patients constitute a subgroup warranting lifelong follow-up.

However, existing risk scores, many developed in Japanese cohorts (such as Kobayashi,[11] Egami,[12] and Sano[13] risk scores, et al), perform variably in non-Japanese populations,[14] and most prediction tools focus on acute IVIG response or early CAA occurrence rather than on long-term persistence and prognosis. At the same time, nomogram-based models and other multivariable prognostic tools have shown superior individualized predictive performance across a range of diseases and have recently been applied to KD to predict early coronary involvement[15–17] and IVIG response.[18–20] These developments suggest that an externally validated nomogram integrating clinical, laboratory, and imaging variables could meaningfully improve early identification of KD at risk for persistent CAA and guide individualized surveillance and therapeutic strategies.

In the present work, our objective was to determine the independent baseline factors influencing the regression of persistent CAA in KD, and to construct and validate a practical prognostic nomogram for regression in persistent CAA during one-year, two-year and three-year follow-up.

Materials and Methods

Study Population

This study enrolled pediatrics patients diagnosed with KD and CAA in the First Affiliated Hospital of Guangxi Medical University between January 2012 and July 2022 as the research subjects. During the global pandemic of SARS-CoV2 infection, all hospitalized children underwent screening for COVID-19, and only those who tested negative were included in this study to ensure that all enrolled patients were confirmed to have KD. Inclusion criteria included: (1) a confirmed diagnosis of KD preceding the onset of CAA; (2) a minimum follow-up duration of three years. Exclusion criteria included: (1) age over 18 years; (2) patients with repeated visits; (3) significant data deficiency. This study protocol received approval from the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (Approval No. 2019[KY-E240]) and adhered to the principles outlined in the Declaration of Helsinki.

Research Groupings

In this retrospective cohort, children diagnosed with KD complicated by CAA were followed from diagnosis to assess recovery of coronary artery diameter. The derivation cohort comprised patients enrolled between January 2012 and July 2021, which were split into the training set and the testing set at a ratio of 7:3 through random allocation. Another independent cohort, consisting of patients diagnosed from August 2021 to July 2022, was used for temporal external validation (Figure 1). The prognostic model was constructed using the training dataset, while its predictive performance for coronary artery diameter regression at one-year, two-year, and three-year follow-up was assessed using both the internal testing cohort and the external validation cohort.

Clinical Data Collection

Clinical information was retrospectively retrieved, covering demographic, clinical, and laboratory domains. Demographic characteristics included sex, age at diagnosis, and body mass index (BMI). Clinical information consisted of KD classification (KD or incomplete KD), fever duration (>10 or ≤10 days), IVIG responsiveness (responsive or resistant), classification of CAA, and time to CAA regression. Laboratory investigations during the acute stage of KD encompassed complete blood count [white blood cell count (WBC), haemoglobin (Hb), and platelet count (PLT)], and biochemical measures of liver function [serum albumin (ALB), globulin (GLB), alanine aminotransferase (ALT) and aspartate aminotransferase (AST)], together with inflammatory and coagulation parameters, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum sodium (Na^+), and fibrinogen (Fib). Transthoracic echocardiography was conducted on a regular basis in the acute stage. Following that, it was performed at 1, 3, 6, 12, 24, and 36 months after fever onset, or till the coronary artery diameter normalized. Coronary artery absolute dimension was recorded for all

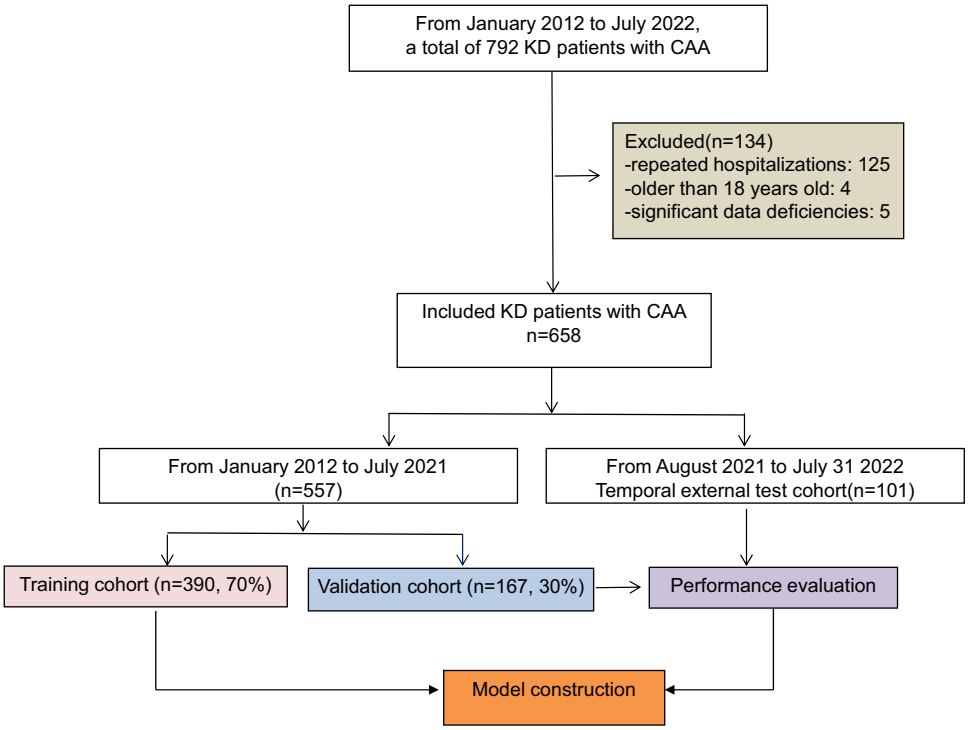

Figure 1 Flowchart for selecting the study population.
Abbreviations: KD, Kawasaki disease; CAA, coronary artery aneurysm.

included patients. The absolute dimension of coronary artery was then converted into Z-scores derived by the Lambda-Mu-Sigma approach.[21]

Data Preprocessing

A series of preprocessing procedures were undertaken. Each variable was systematically screened for incompleteness, outliers, and biologically implausible observations before initiating model development. For the variables (ESR, Na^+, ALT, AST, ALB, GLB, Fib) enrolled with a missing value less than 20%, imputation was carried out using either the mean or the median values. After assessment of normality, ALB was the only variable that demonstrated a normal distribution, whereas the remaining variables with missing values were skewed. Accordingly, missing values for ALB were imputed using the mean, while missing values for skewed variables were imputed using the median.

Diagnostic Criteria

The diagnosis of KD and CAA stratification in this study followed the recommendations outlined in the 2017 AHA guidelines.[2] Patient identification was undertaken via the hospital information system using the search terms "Kawasaki disease" or "mucocutaneous lymph node syndrome". Medical records were subsequently reviewed in detail, and only cases fulfilling the 2017 AHA diagnostic criteria were included. CAA was determined when the body surface area-adjusted Z-score was over 2.5. Then, CAAs were further stratified into small [SCAA, Z-score: [2.5, 5)], medium [MCAA, Z-score: [5, 10)], and giant (GCAA, Z-score≥ 10). Z-scores regressed to between 2 and 2.5 was classified as coronary dilatation, and was not considered to have returned to the normal range. Regression of CAA was considered when the Z-score dropped below two on follow-up echocardiography.

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Study Outcome

The study outcome was regression of the luminal diameter of CAAs to the normal range (Z-score < 2) in patients with KD. This was evaluated at one-year, two-year, and three-year intervals, as well as during prolonged follow-up (with the maximum duration of 161 months).

Statistical Analysis

Statistical processing was conducted with SPSS version 27.0 and R version 4.5.1. Conforming to a normal distribution, continuous variables were summarized as mean ± standard deviation, and differences between subgroups were assessed by independent-sample t tests. For skewed data, values were described as medians with interquartile ranges, and group comparisons were performed by the Mann–Whitney *U*-test. Categorical variables were reported as frequencies and percentages, and the intergroup differences were examined by the Pearson Chi-squared test.

To identify prognostic factors, univariate Cox proportional hazards models were first applied, after that variables with $P < 0.05$ were entered into multivariable Cox regression. Based on the independent predictors, a nomogram was constructed. Model discrimination across the training, internal testing, and external validation cohorts was quantified by receiver operating characteristic (ROC) curves, while calibration curves were used to verify the match between the predicted results and real-world findings. The Brier scores and calibration slopes were then supplemented to objectify the calibration plots. The nomogram prognostic model's clinical applicability was further explored through decision curve analysis (DCA).[22] P value < 0.05 was deemed to be statistically significant.

Results

Annual Incidence of KD at Our Center from January 2012 Through July 2022

From January 2012 to July 2022, the annual number of KD cases at our center showed an overall upward trend. The total number of CAAs remained relatively stable from 2012 to 2020, but increased markedly during the COVID-19 pandemic (2020–2022). Over this 10.5-year period, the proportion of CAAs among KD cases fluctuated between 63.9% and 90.3% (Figure 2A).

At our institution, the annual incidence of KD and KD-associated CAAs per 100,000 population demonstrated a progressive increase. The incidence of KD and KD-associated CAAs was 60.0–125.8 and 42.7–101.6 per 100,000 children, respectively, between 2012 and 2022 (Figure 2B).

Baseline Characteristics

Among the 792 KD cases with CAA identified during the study period, 125 were excluded due to repeat hospitalizations, five due to significant data deficiencies, and four because they were older than 18 years. Finally, 658 patients met the inclusion criteria, with an average age of 32.1 months. The cohort consisted of 476 boys and 182 girls (male-to-female ratio: 2.6:1). Among these, 460 patients (69.9%) had SCAA, 133 (20.2%) had MCAA, and 65 (9.9%) had GCAA. The CAA regression rates at one, two, and three years for the overall cohort were 68.2% (449/658), 78.1% (514/658), and 84.8% (558/658), respectively. Stratified by aneurysm size, regression rates for SCAA were 71.2% (327/459), 81.9% (376/459), and 87.4% (401/459); for MCAA, 63.2% (84/133), 71.4% (95/133), and 82.0% (109/133); and for GCAA, 56.9% (37/65), 64.6% (42/65), and 72.3% (47/65), respectively.

Among them, 557 cases admitted between January 2012 and July 2021 were randomly allocated in a 7:3 proportion to the training cohort (n = 390) and the internal testing cohort (n = 167). An independent temporal external validation cohort comprised 101 patients diagnosed with KD and CAA between August 2021 and July 2022. In the training set, the one-year, two-year and three-year regression rates were 67.2% (262/390), 76.2% (297/390), and 83.1% (324/390), respectively. As for the internal testing set, the corresponding rates were 71.9% (120/167), 81.4% (136/167), and 86.2% (144/167). In the external validation cohort (Supplementary Table 1), rates were 66.3% (67/101), 80.2% (81/101), and 89.1% (90/101). Comparison of baseline demographic and clinical features showed no statistical difference between the training and the internal testing cohorts ($P > 0.05$) (Table 1).

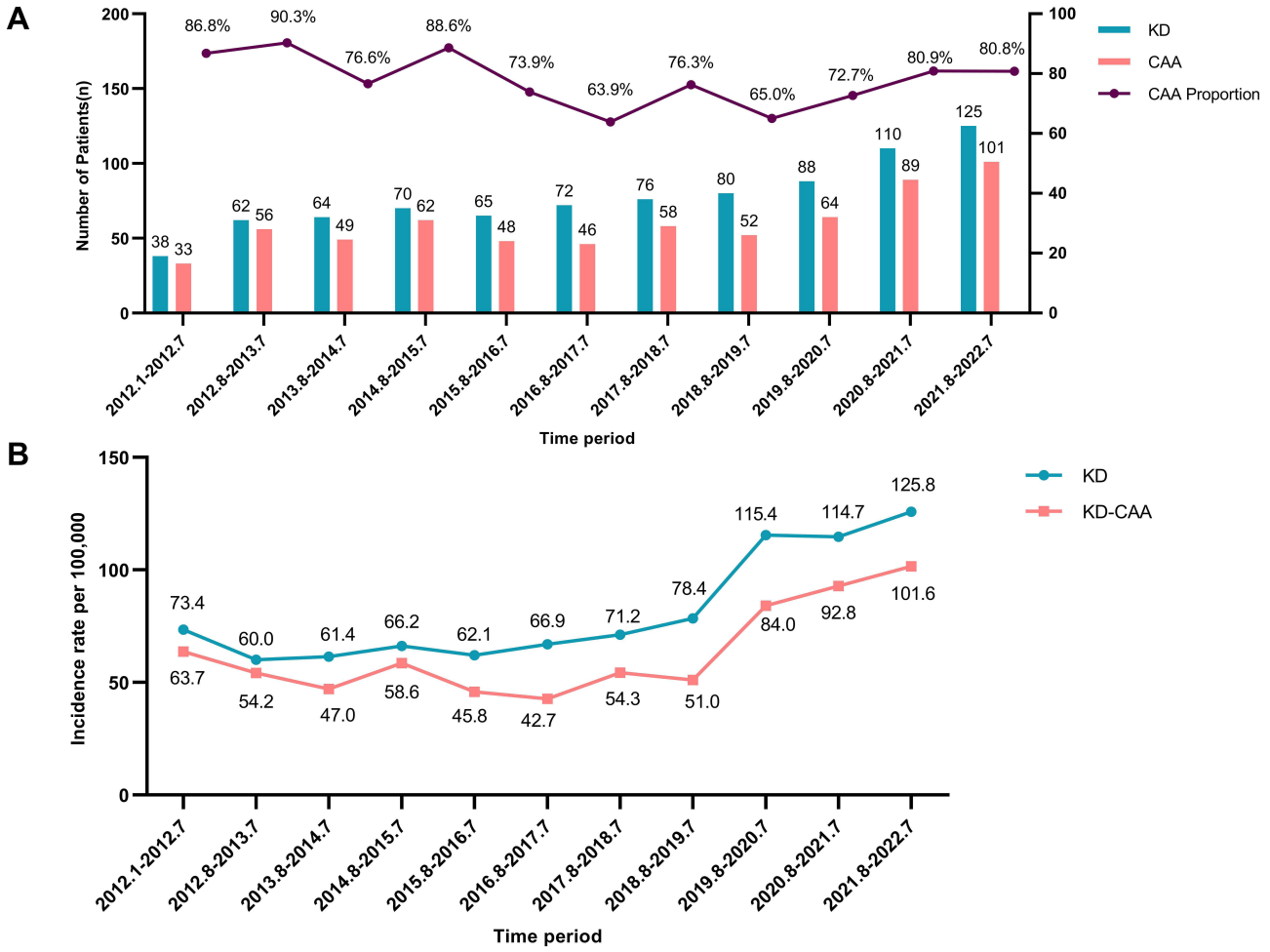

Figure 2 Annual total number of KD cases, CAA cases, CAA Proportion and incidence of KD and CAA between January 2012 and July 2022. (**A**) Annual total number of KD cases, CAA cases and CAA Proportion between January 2012 and July 2022. (**B**) Annual incidence rates per 100,000 children of KD and CAA between January 2012 and July 2022.
Abbreviations: KD, Kawasaki disease; CAA, coronary artery aneurysm.

Treatments

All patients were administered IVIG at 2 g/kg together with oral aspirin at 30–50 mg/kg/day.

Once the body temperature returned to normal, the aspirin dosage was tapered to 3–5 mg/kg/day. The median time from fever onset to IVIG administration was eight days. Among the entire cohort, 29.0% (191/658) showed resistance to IVIG, adjunctive corticosteroid therapy, prednisolone or methylprednisolone was administered. Given that all participants had CAAs, antiplatelet and/or anticoagulant therapy was considered essential. For 69.9% (460/658) of patients with

Table 1 The Comparison in the Training Cohort and the Testing Cohort in Terms of the Clinical Characteristics

Variables	Training Cohort (n=390)	Testing Cohort (n=167)	t/Z/χ2	*P* value
Male gender	289(74.1%)	118(70.7%)	0.705	0.401
Age at diagnosis (months)	20(11,39)	21(11,36)	−0.407	0.684
BMI (kg/m^2)	15.6(14.3,16.6)	15.6(14.6,16.8)	−1.112	0.266
Proportion of incomplete KD	271(69.5%)	119(71.3%)	0.175	0.676
Fever duration lasting over 10 days	244(62.6%)	99(59.3%)	0.533	0.466
Proportion of IVIG-refractory cases	117(30%)	44(26.3%)	0.759	0.384

(*Continued*)

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Table 1 (Continued).

Variables	Training Cohort (n=390)	Testing Cohort (n=167)	t/Z/χ2	*P* value
Classification of CAA			1.900	0.387
SCAA	259(66.4%)	119(71.3%)		
MCAA	87(22.3%)	35(21.0%)		
GCAA	44(11.3%)	13(7.8%)		
CAA regression at one year	262(67.2%)	120(71.9%)	1.187	0.276
CAA regression at two years	297(76.2%)	136(81.4%)	1.886	0.170
CAA regression at three years	324(83.1%)	144(86.2%)	0.865	0.352
WBC ($\times 10^9$/L)	11.8(8.3,17.3)	11.3(8.5,15.8)	−0.747	0.455
Hb (g/L)	105.6±14.5	105.4±14.8	0.142	0.887
PLT ($\times 10^{12}$/L)	378.0(273.8,498.6)	388.6(266.1,519.5)	−0.273	0.785
CRP (mg/L)	34.0(10.0,90.5)	26.4(10.0,85.6)	−0.909	0.363
ESR (mm/h)	48.5(20.8,77.3)	48.5(23.0,79.0)	−0.276	0.782
Na^+ (mmol/L)	136.8(135.2,138.7)	137.0(135.2,138.6)	−0.782	0.434
ALT (U/L)	25.0(16.0,43.3)	25.0(17.0,44.0)	−0.626	0.532
AST (U/L)	32.0(25.0,46.0)	34.0(24.0,45.0)	−0.220	0.826
ALB (g/L)	37.4±5.5	37.3±6.0	0.190	0.849
GLB (g/L)	26.7(22.2,32.5)	26.1(22.0,32.2)	−0.186	0.853
Fib (g/L)	4.4(3.0,5.1)	4.4(3.4,5.0)	−0.689	0.491

Notes: Data are presented as mean and standard deviation (mean ± SD), median (interquartile range) [P50 (P25, P75)], or number (percentage) n (%).

Abbreviations: BMI, body mass index; KD, Kawasaki disease; IVIG, intravenous immunoglobulin; CAA, coronary artery aneurysm; SCAA, small - sized CAA; MCAA, medium - sized CAA; GCAA, giant - sized CAA; WBC, white blood cell count; Hb, haemoglobin concentration; PLT, platelet count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Na^+, sodium concentrations; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, serum albumin; GLB, globulin; Fib, Fibrinogen.

SCAAs, monotherapy with aspirin was generally continued until aneurysm regression to normal dimensions. In 20.2% (133/658) of patients with MCAAs, clopidogrel was added to aspirin. For patients with GCAAs (9.9%, 65/658), dual antiplatelet therapy was combined with warfarin for anticoagulation, and metoprolol was administered temporarily to reduce myocardial oxygen demand.

Risk Factors Affecting the Regression of CAA

Cox proportional hazards regression was applied to develop the prognostic model (Table 2). In the training set, univariate analyses identified nine variables significantly linked to CAA regression, including age at diagnosis (months), duration of fever, IVIG responsiveness, classification of CAA, WBC, PLT, CRP, ESR, and fib (all $P < 0.05$). To assess collinearity among these predictors, tolerance and variance inflation factor (VIF) values were examined, and all variables satisfied the predefined thresholds (tolerance > 0.2; VIF < 5), suggesting the absence of multicollinearity (Supplementary Table 2). These candidate predictors were then incorporated into the multivariate Cox model. The analysis revealed that younger age at onset [hazard ratio (HR) = 0.994, 95% confidence interval (CI): 0.990–0.998], smaller aneurysm size (reference: SCAA; MCAA: HR = 0.398, 95% CI: 0.299–0.530; GCAA: HR = 0.058, 95% CI: 0.027–0.125), lower PLT (HR = 0.999, 95% CI: 0.998–1.000), and higher fib level (HR = 1.143, 95% CI: 1.042–1.255) were independent predictors favoring CAA regression in KD (Table 3). The percentage of variables with missing data included in the initial dataset are provided in Supplementary Table 3.

Construction and Validation of the CAA Regression Nomogram Prognostic Model

A parsimonious nomogram was constructed by integrating the four independent protective factors associated with CAA regression in KD. The model estimates the probability of CAA regression at one-year, two-year, and three-year post-diagnosis (Figure 3). For each patient, the sum of variable-specific scores yields a total score, which corresponds to the predicted probability of regression.

Table 2 Univariate Cox Regression Analysis of Factors Associated with CAA Regression in the Training Cohort

Variables	B	S.E.	Wald	HR (95% CI)	*P* value
Gender					
Female	Reference				
Male	−0.151	0.126	1.431	0.860 (0.671–1.101)	0.232
Age at diagnosis (months)	−0.007	0.002	11.354	0.993 (0.989–0.997)	0.001
BMI (kg/m^2)	−0.059	0.031	3.775	0.942 (0.887–1.001)	0.052
Type of KD					
Typical KD	Reference				
Incomplete KD	0.193	0.123	2.457	1.212 (0.953–1.543)	0.117
Fever duration					
Less than 10 days	Reference				
More than 10 days	−0.387	0.114	11.575	0.679 (0.543–0.849)	0.001
Response to IVIG					
IVIG responsiveness	Reference				
IVIG resistance	−0.571	0.129	19.661	0.565 (0.439–0.727)	<0.001
Classification of CAA			97.16		<0.001
SCAA	Reference				
MCAA	−0.957	0.143	44.621	0.384 (0.290–0.508)	<0.001
GCAA	−3.093	0.388	63.392	0.045 (0.021–0.097)	<0.001
WBC (×10^9/L)	−0.024	0.009	7.666	0.977 (0.960–0.993)	0.006
Hb (g/L)	0.000	0.004	0.005	1.000(0.993–1.007)	0.944
PLT (×10^{12}/L)	−0.001	0.000	17.324	0.999 (0.998–0.999)	<0.001
CRP (mg/L)	−0.003	0.001	6.145	0.997 (0.995–0.999)	0.013
ESR (mm/h)	−0.004	0.002	4.297	0.996 (0.993–1.000)	0.038
Na^+ (mmol/L)	0.004	0.02	0.038	1.004 (0.966–1.043)	0.845
ALT (U/L)	0.000	0.001	0.285	1.000 (0.999–1.002)	0.593
AST (U/L)	0.000	0	0.112	1.000 (0.999–1.001)	0.738
ALB (g/L)	0.007	0.009	0.605	1.007 (0.989–1.026)	0.437
GLB (g/L)	−0.007	0.006	1.355	0.993 (0.980–1.005)	0.244
Fib (g/L)	0.104	0.037	8.005	1.109 (1.032–1.192)	0.005

Abbreviations: BMI, body mass index; KD, Kawasaki disease; IVIG, intravenous immunoglobulin; CAA, coronary artery aneurysm; SCAA, small - sized CAA; MCAA, medium - sized CAA; GCAA, giant - sized CAA; WBC, white blood cell count; Hb, haemoglobin concentration; PLT, platelet count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Na^+, sodium concentrations; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, serum albumin; GLB, globulin; Fib, Fibrinogen.

Table 3 Multivariate Cox Regression Analysis of Factors Associated with CAA Regression in the Training Cohort

Variables	B	S.E.	Wald	HR (95% CI)	*P* value
Age at diagnosis (months)	−0.006	0.002	7.221	0.994 (0.990–0.998)	0.007
Fever duration					
Less than 10 days	Reference				
More than 10 days	0.126	0.127	0.973	1.134 (0.883–1.455)	0.324
Response to IVIG					

(*Continued*)

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Table 3 (Continued).

Variables	B	S.E.	Wald	HR (95% CI)	*P* value
IVIG responsiveness	Reference				
IVIG resistance	−0.263	0.135	3.78	0.769 (0.590–1.002)	0.052
Classification of CAA			81.726		<0.001
SCAA	Reference				
MCAA	−0.921	0.146	39.559	0.398 (0.299–0.530)	<0.001
GCAA	−2.848	0.394	52.329	0.058 (0.027–0.125)	<0.001
WBC (×10^9/L)	−0.015	0.011	1.764	0.986 (0.965–1.007)	0.184
PLT (×10^{12}/L)	−0.001	0	8.487	0.999 (0.998–1.000)	0.004
CRP (mg/L)	−0.002	0.001	2.429	0.998 (0.996–1.001)	0.119
ESR (mm/h)	0.001	0.002	0.222	1.001 (0.997–1.005)	0.637
Fib (g/L)	0.134	0.048	7.947	1.143 (1.042–1.255)	0.005

Abbreviations: IVIG, intravenous immunoglobulin; CAA, coronary artery aneurysm; SCAA, small - sized CAA; MCAA, medium - sized CAA; GCAA, giant - sized CAA; WBC, white blood cell count; PLT, platelet count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Fib, Fibrinogen.

Model validation was carried out using ROC curves, calibration plots, and DCA. The area under the ROC curve (AUC) values and 95% CI in the training set for predicting one-year, two-year, and three-year CAA regression were 0.854 (0.806–0.895), 0.919 (0.879–0.957), and 0.910 (0.859–0.953), respectively. As for the testing set, the corresponding AUCs and 95% CI were 0.844 (0.760–0.913), 0.910 (0.834–0.968), and 0.913 (0.835–0.971) (Figures 4A and B), indicating robust discriminatory capacity. Calibration plots (Figure 5) revealed good concordance between estimated

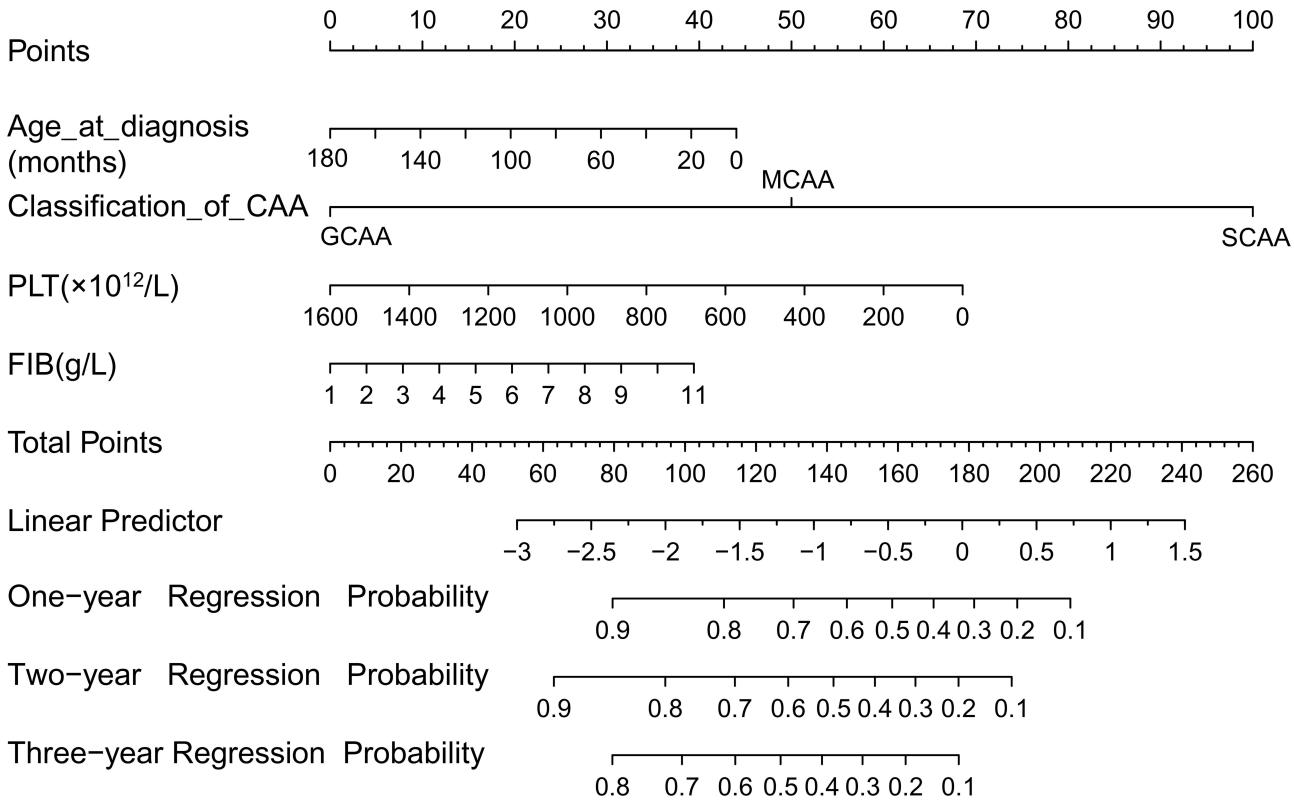

Figure 3 Nomogram to predict CAA regression in KD.
Abbreviations: KD, Kawasaki disease; CAA, coronary artery aneurysm; SCAA, small-sized CAA; MCAA, medium-sized CAA; GCAA, giant-sized CAA; PLT, platelet count; Fib, Fibrinogen.

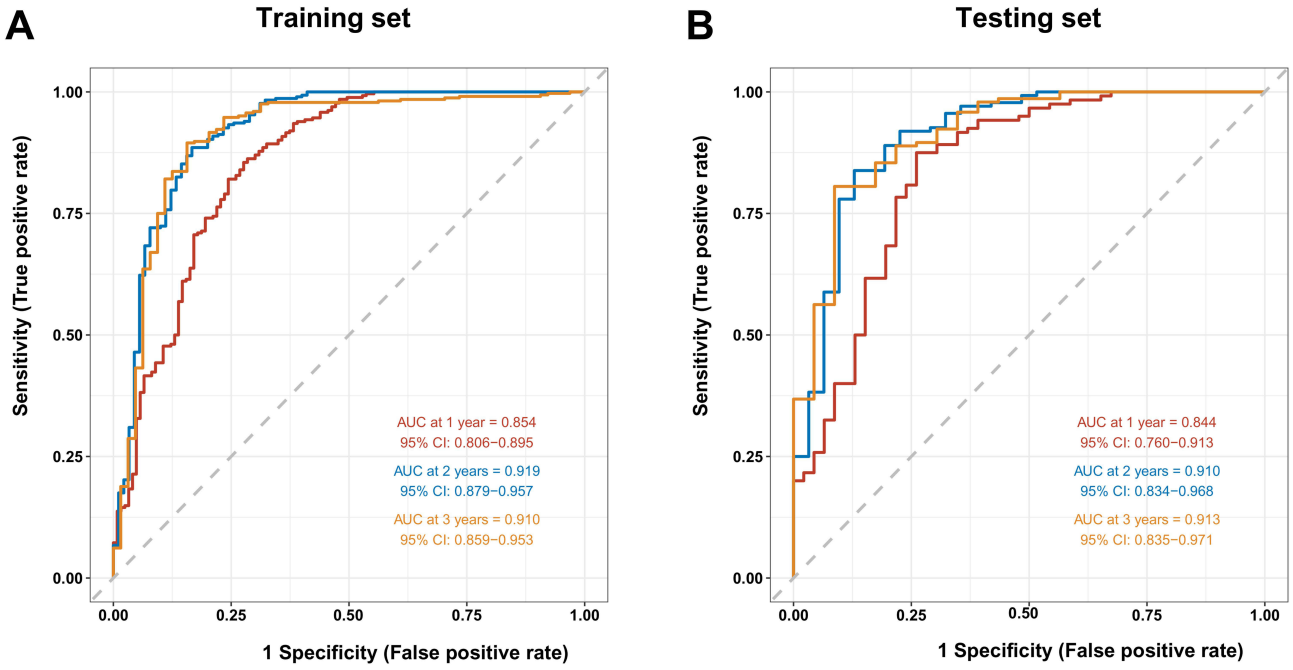

Figure 4 Receiver operating characteristic curves of the nomogram model to predict CAA regression in patients with KD. (**A**) Training set; (**B**) Testing set.
Abbreviations: AUC, area under the curve; CI, confidence interval; KD, Kawasaki disease; CAA, coronary artery aneurysm.

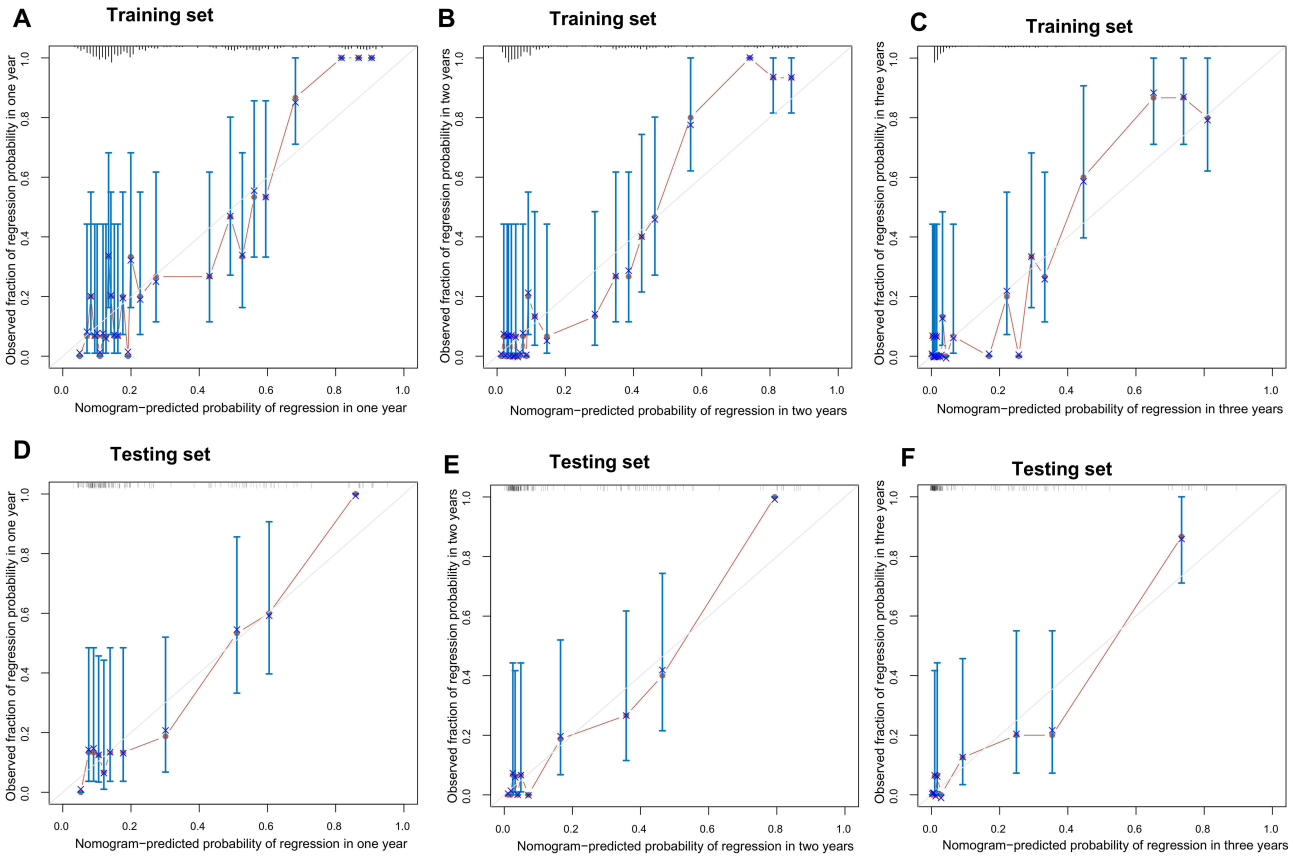

Figure 5 Calibration curve of the nomogram model to predict CAA regression in patients with KD. (**A**) Predicting one-year CAA regression in patients with KD in training set; (**B**) Predicting two-year CAA regression in patients with KD in training set; (**C**) Predicting three-year CAA regression in patients with KD in training set; (**D**) Predicting one-year CAA regression in patients with KD in testing set; (**E**) Predicting two-year CAA regression in patients with KD in testing set; (**F**) Predicting three-year CAA regression in patients with KD in testing set.
Abbreviations: KD, Kawasaki disease; CAA, coronary artery aneurysm.

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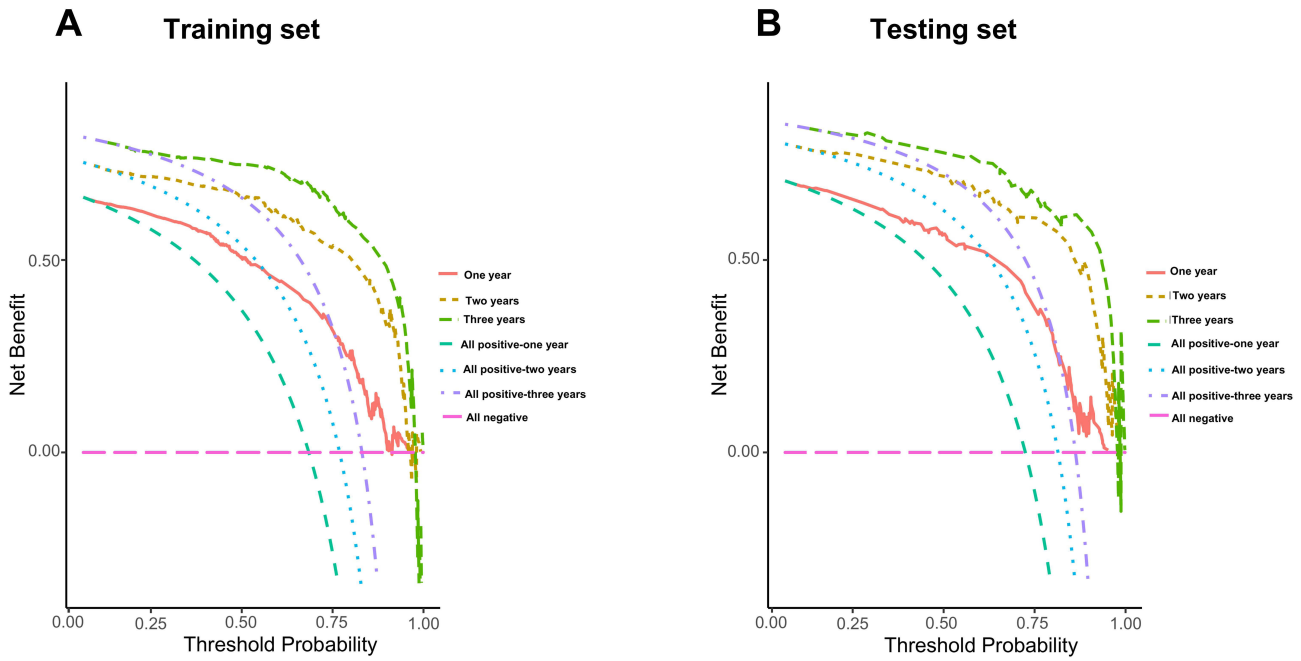

Figure 6 Decision curve analysis plots of the nomogram model to predict one-year, two-year and three-year CAA regression in patients with KD. (**A**) Training set; (**B**) Testing set.

probabilities and actual outcomes across both datasets. The Brier scores and calibration slope of in the training set for predicting CAA regression were 0.092 and 1.076 (one-year follow-up), 0.126 and 1.086 (two-year follow-up), 0.085 and 1.001 (three-year follow-up), as well as 0.084 and 1.177 (one-year follow-up), 0.120 and 1.167 (two-year follow-up), 0.075 and 1.076 (three-year follow-up) in the testing set, respectively.

DCA (Figure 6) demonstrated that application of the nomogram yielded superior clinical net benefit over a broad spectrum of threshold probabilities.

External Validation

Between August 2021 and July 2022, 101 children with KD and CAA were included in the external validation cohort to independently evaluate the model's predictive performance. In this cohort, the AUCs and 95% CI for predicting one-year, two-year, and three-year regression were 0.763 (0.651–0.865), 0.886 (0.783–0.969), and 0.986 (0.958–1.000), respectively (Figure 7A). Calibration plots indicated good concordance between predicted probabilities and observed outcomes (Figures 7B–D), and DCA demonstrated that the model provided added clinical value and net benefit (Figure 7E). In the external validation cohort, the Brier scores were 0.104 at one year, 0.154 at two years, and 0.074 at three years, with corresponding calibration slopes of 1.197, 1.191, and 1.259. A comparison of baseline characteristics and the independent predictors between the testing and external validation sets is provided in Supplementary Table 1.

Discussion

KD is a systemic vasculitic disorder affecting multiple organs. CAA linked to KD has been recognized as the primary cause of acquired heart disease in both Chinese nations and developed countries.[23] Clinically, regression of persistent CAAs is a critical determinant of the prolonged prognosis in KD. To aid in early identification of KD at risk, quite a few scoring systems have been proposed to estimate the likelihood of CAA development during the subacute phase, including those by Son,[24] Hu[15] and Yang,[16] et al. More recently, Gong et al[25] and Peng et al[26] proposed models in 2023 and 2024, respectively, to predict persistent CAAs at one-year follow-up. In contrast, we identified younger age, smaller aneurysm size, lower PLT, and higher Fib levels as independent protective factors for regression of persistent CAAs, and conducted a longer-term prognostic assessment with a larger sample size of KD-associated CAAs.

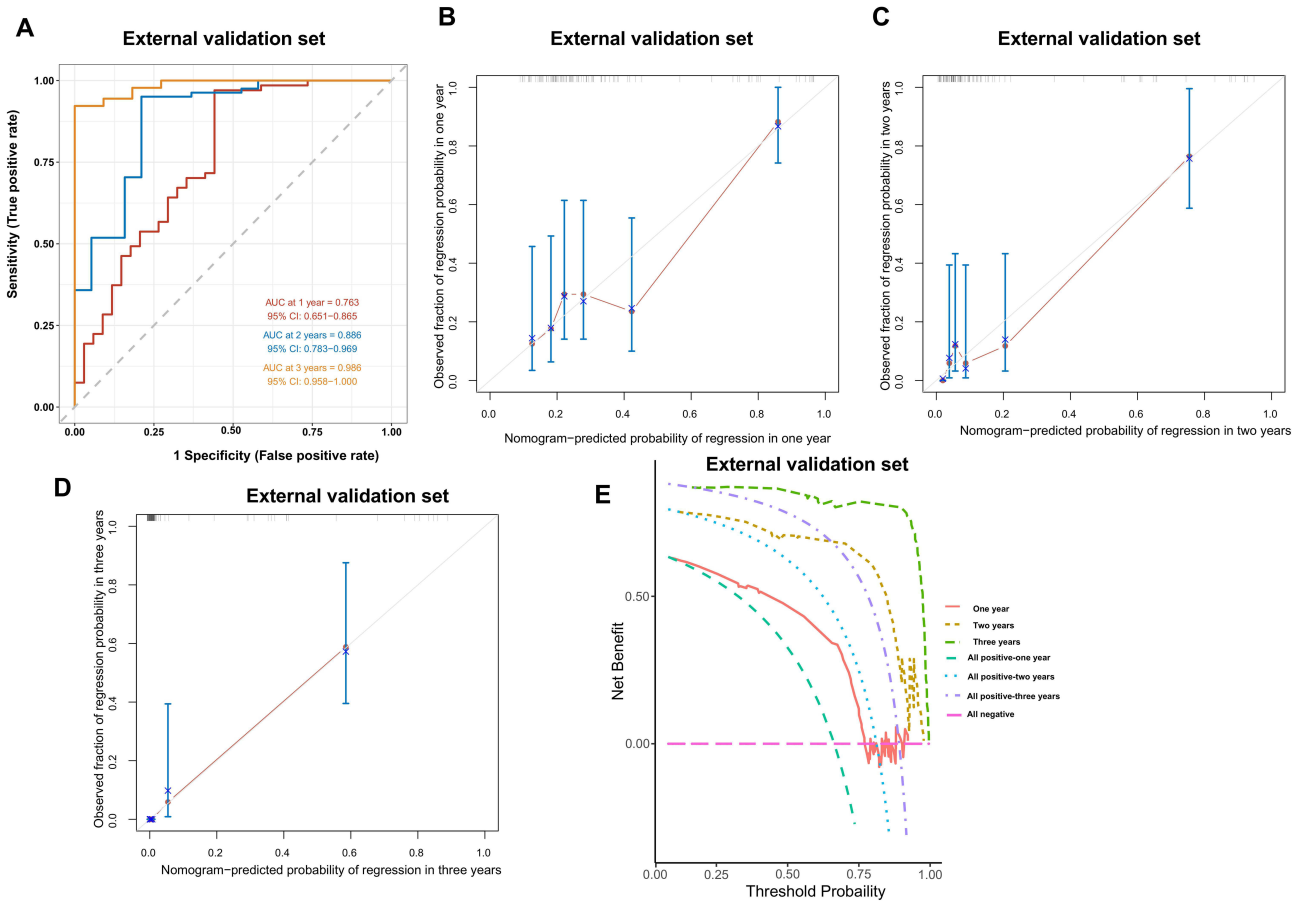

Figure 7 The results of external validation set. (**A**) Receiver operating characteristic curves of the nomogram model to predict CAA regression in the external validation. (**B**) Calibration curve of the nomogram model to predict one-year CAA regression in the external validation. (**C**) Calibration curve of the nomogram model to predict two-year CAA regression in the external validation. (**D**) Calibration curve of the nomogram model to predict three-year CAA regression in the external validation. (**E**) Decision curve analysis plots of the nomogram model to predict one-year, two-year and three-year CAA regression in the external validation set.
Abbreviations: CAA, coronary artery aneurysm; AUC, area under the curve; CI, confidence interval.

The proportion of incomplete KD in our cohort was relatively high (69.5% in the training cohort and 71.3% in the testing cohort). Several factors likely contributed to this finding. Some epidemiological studies have reported an increasing proportion of incomplete KD in recent years, with some over 40%.[27,28] This trend may be attributable to the influence of the 2017 AHA guideline,[2] which incorporated expanded laboratory parameters and more sensitive echocardiographic criteria, as well as a generally lower diagnostic threshold aimed at preventing coronary complications.[28] Moreover, our study period overlapped with the COVID-19 pandemic, during which heightened clinical vigilance for febrile inflammatory syndromes has been shown to increase the recognition and referral of incomplete KD.[29,30] Prior studies have also suggested an association between incomplete KD and CAA, potentially related to diagnostic delay.[31,32] As a single-center retrospective cohort within a tertiary referral hospital, our institution receives a disproportionate number of children with atypical clinical features, diagnostic uncertainty, or delayed presentation, as well as patients already identified with coronary involvement-clinical scenarios in which incomplete KD is more frequently observed. Together taken, these may contribute to the comparatively high proportion of incomplete KD within our CAA cohort.

In the external validation cohort, the AUCs for predicting CAA regression at one and two years were lower than those in the internal testing cohort, whereas the three-year AUC was higher. The reduced short-term performance in the external validation may reflect, first, improvements in diagnostic equipment and imaging techniques over time, and second, substantial age differences between cohorts: the median age at diagnosis was 21 months in the internal testing cohort compared with 41 months in the external validation cohort ($P < 0.001$). Internal testing primarily assessed

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model calibration, while external validation evaluated generalizability, reflecting real-world clinical applicability and enhancing credibility. Despite the variation, all AUCs of the external validation exceeded 0.75, indicating that the model consistently demonstrated strong predictive performance over time.

In our study, younger age at KD diagnosis emerged as a protective factor for CAA regression. This finding is consistent with early observations by Takahashi et al[33] in 1987 and, more recently, by Kato et al[34] in 2023. In contrast, a three-year follow-up study of 120 KD patients with CAA in East China[35] reported that younger age was a risk factor for persistent CAA. This discrepancy may be attributable to regional and ethnic differences, or more importantly, differences in sample size. Takahashi[33] proposed that intimal thickening, primarily caused by smooth muscle cell proliferation, underlies the regression of CAA, and that younger children may retain a greater capacity for vascular smooth muscle cell division. Age-related changes in smooth muscle cell properties may therefore contribute to higher regression rates in younger patients.[36,37] Nevertheless, regression at a young age does not preclude future adverse cardiovascular events, as arterial wall elasticity damage may be irreversible, underscoring the need for prolonged follow-up.

Coronary artery size is another established determinant of lesion progression.[25,38–40] While SCAA often regress, 70–95% of MCAA and GCAA persist, and up to 20% progress to stenosis. In our cohort, most CAAs regressed within three years, including 72.3% of GCAAs, substantially higher than the 28.8–36.3% regression rate reported in Japanese KD patients after 10 years of follow-up.[34] Improvements in acute-phase treatment over time may partly account for this difference. Other contributing factors include variations in patient populations and data quality. Our cohort predominantly comprised Han Chinese from southern China, whereas the Japanese cohort consisted mainly of native Japanese patients. Furthermore, our data were collected from a single tertiary general hospital in Southwest China between 2012 and 2022, while the Japanese dataset was drawn from 44 institutions across Japan between 1981 and 2012. Although the sample sizes were similar (658 vs 754 cases), differences in data recording, diagnostic criteria, and examination equipment may have influenced the results. Despite variability in GCAA regression rates, both our findings and the Japanese study support a size-dependent trend toward improved prognosis in smaller CAAs.

Hyperactive PLT activity and systemic inflammation are additional contributors to KD-associated coronary damage.[41] Elevated PLT counts were identified as a risk factor for persistent CAAs in our study, consistent with prior reports from Kuwabara et al[42] and the 24th Japanese nationwide KD survey.[43] Platelet-monocyte aggregates (MPAs) are elevated in KD patients,[44] and mechanistic studies indicate that MPA formation drives hyperinflammation.[45] Therapeutic strategies targeting MPA formation or reducing PLT-derived transforming growth factor-β1 may therefore mitigate vasculopathy and facilitate CAA regression, highlighting the importance of PLT monitoring during long-term follow-up.

Fib could enhance endothelial barrier integrity.[46] KD children show continuous endothelial cell dysfunction.[47] In our cohort, elevated fib emerged as a protective factor for the regression of persistent CAAs in KD. Manuela et al reported that patients with KD exhibited elevated fib levels and impaired fibrinolytic responses to venous occlusion, potentially indicating sustained endothelial injury following the acute phase.[48] Clinically, although elevated fib often reflects systemic inflammation,[49] its presence in the resolution phase may signal active reparative processes that facilitate vascular remodeling and aneurysm regression. First, fib stabilizes endothelial glycocalyx by binding to syndecan-1 and activating downstream PAK1 signaling, thereby preserving endothelial barrier function.[50] Then in vascular injury models, fib inhibits metalloproteinase-9-mediated syndecan-1 shedding, protecting lung endothelial function.[51] Taken together, these findings suggest a dual role for fib in KD-associated vasculopathy: detrimental in the acute inflammatory phase yet potentially beneficial during recovery through glycocalyx stabilization and endothelial repair. Longitudinal mechanistic studies are warranted to elucidate the temporal dynamics of fib's effect on vascular healing and CAA regression.

The present study exists certain limitations that call for cautious interpretation, mainly due to its being conducted at a single center, although we have tried our best to increase the sample size to reduce this bias. Firstly, some CAAs persisted throughout the study, highlighting the need for extended follow-up. Secondly, the timing of echocardiography examinations was not standardized. The actual regression time of CAAs might be earlier than the time when regression was confirmed by coronary angiography. Additionally, it remains unknown that whether our findings are applicable to other races or regions since present cohort comprised patients from Southwest China. Hence, more evidence from multi-center, cross-racial is needed to verify our findings.

Conclusions

Younger age, smaller aneurysm size, lower PLT, and higher fib levels emerged as independent predictors favoring the regression of persistent CAAs. With these factors, a prognostic nomogram model to estimate the probability of CAA regression at one-year, two-year, and three-year follow-up was constructed. This model demonstrated good discrimination, calibration, and clinical applicability.

Abbreviations

KD, Kawasaki disease; CAA, coronary artery aneurysm; IVIG, intravenous immunoglobulin; AHA, American Heart Association; BMI, body mass index; WBC, white blood cell count; Hb, haemoglobin concentration; PLT, platelet count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Na^+, sodium concentration; AST, aspartate aminotransferase level; ALT, alanine aminotransferase level; GLB, globulin; ALB, albumin; Fib, fibrinogen; MPA, platelet-monocyte aggregates; VIF, variance inflation factor; ROC, receiver operating characteristic; AUC, area under the ROC curve; HR, hazard ratio; CI, confidence interval.

Data Sharing Statement

Data will be shared on reasonable request from the corresponding authors.

Ethics Approval

The study protocol was approved by the Medical Ethic Committee of the First Affiliated Hospital of Guangxi Medical University [Code number: 2021(KY-E-240)]. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). An informed consent was obtained from the parents of each subject. The patient data in this research have been anonymized, and sensitive personal information and commercial interests are not involved in the data processing and analysis.

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Author Contributions

Kaizhi Liang: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review and editing. Yusheng Pang: Conceptualization, Funding acquisition, Resources, Supervision, Writing – original draft, Writing – review and editing. Danyan Su: Conceptualization, Project administration, Resources, Supervision, Writing – original draft, Writing – review and editing.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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