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Establishment and validation of a predictive model for coronary artery lesions in children with KDSS

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Abstract

Background Kawasaki Disease Shock Syndrome (KDSS) represents a severe manifestation of Kawasaki Disease (KD). In recent years, logistic regression prediction models have gained widespread application in forecasting the occurrence probabilities of various diseases. The objective of this study is to explore the clinical characteristics of pediatric patients with KDSS complicated by coronary artery lesions (CALs) and to develop and validate a logistic regression model for predicting the likelihood of CALs in children with KDSS.

Methods Our study enrolled 102 pediatric patients diagnosed with KDSS at the Cardiology Department of our hospital between January 2020 and March 2024, all of whom had comprehensive medical histories and physical examination results. Logistic regression analysis was employed to identify the most predictive variables. Utilizing a training set ($n=72$), we constructed a logistic regression model to predict CALs in children with KDSS. The model's predictive capabilities were further assessed using logistic regression. The Receiver Operating Characteristic (ROC) curve served as a tool to evaluate the performance of the logistic regression model. Additionally, a nomogram model was developed through the visualization of the calibration curve using a 1000-bootstrap resampling method. The efficacy of these results was validated in an independent validation set ($n=30$).

Results Univariate analysis revealed nine variables that exhibited significant differences between the CAL and normal coronary artery groups. Further logistic regression analysis identified fever duration, low hemoglobin levels, and low serum phosphorus as independent predictors of CALs in KDSS. The training set demonstrated an area under the ROC curve of 0.837, with a sensitivity of 83.3% and a specificity of 81.2%. The calibration curve indicated a strong agreement between the predicted values of the logistic regression model and the actual observed values in both the training and validation sets.

Conclusion We have successfully established a feasible and highly accurate logistic regression model for predicting CALs in patients with KDSS. This model holds potential for early prediction of CALs and possesses significant clinical implications.

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Keywords Children, Kawasaki disease, Kawasaki disease shock syndrome, Coronary artery lesions prediction model

Background

KDSS (Kawasaki Disease Shock Syndrome) represents a severe manifestation of Kawasaki Disease (KD). Clinically, it not only presents with shock and tissue hypoperfusion but also frequently involves multiple organ dysfunction, necessitating prompt and aggressive intervention. The clinical presentation of KDSS often lacks specificity and is frequently associated with incomplete forms of KD, leading to a high risk of misdiagnosis and missed diagnosis. This, in turn, contributes to an increased incidence of coronary artery lesions (CAL) [1]. Pathologically, Kawasaki Disease is characterized by vasculitis affecting medium-sized arteries and inflammation of various tissues and organs, with the coronary arteries being the most commonly involved [2]. CAL occur in 9 to 20% of patients with KD, while coronary artery aneurysms (CAA) are observed in 4% of cases [3, 4]. P Persistent CAL can progress to thrombosis, coronary stenosis, and, in severe instances, myocardial infarction [5]. The objective of this study is to devise a risk prediction model for CAL in pediatric patients with KDSS, aiming to facilitate informed clinical decision-making and improve disease management.

Methods

Study patients

Study cohort: A A cohort of 102 children, diagnosed with Kawasaki Disease Shock Syndrome (KDSS) at the Department of Cardiology, Beijing Children's Hospital, between January 2020 and March 2024, and possessing complete medical histories and physical examination results, were enrolled in this study. Based on their coronary artery status, the children were categorized into two groups: the coronary artery lesions group ($n = 37$) and the normal coronary artery group ($n = 65$).

Inclusion criteria: All participants met the diagnostic criteria for Kawasaki Disease outlined in the 2021 American College of Rheumatology/Vasculitis Foundation Guideline [6], as well as the diagnostic criteria for KDSS established by Kanegaye et al. [7]

Exclusion criteria: Children were excluded if they had: (1) incomplete data; (2) any serious underlying diseases; (3) immunodeficiency; or (4) a history of coronary artery disease.

During the course of the disease, the patient underwent a comprehensive echocardiographic examination, which was conducted by an experienced pediatric echocardiographer and subsequently reviewed and confirmed by two additional pediatric cardiology experts for accuracy. The criterion for coronary artery lesions was a Z score greater than 2, as published by the American Heart Association in 2017 [2]. (The Z-value is a comparative metric derived by assessing the internal diameter of an individual's coronary artery and contrasting it with the established reference value for individuals of the same age, gender, and body surface area within the normal population.) This encompassed coronary artery dilatation, coronary artery aneurysm, and coronary artery thrombosis.

Ethical approval This study was granted approval by the Ethics Committee of Beijing Children's Hospital, affiliated with Capital Medical University. (Approval Number [2024]-E-178-R)

Clinical data collection

The Jiahe platform system of Beijing Children's Hospital was used to capture clinical data and establish KD database. No data screening or deletion was performed to ensure data integrity and objectivity. We collected data on gender, age, BMI, duration of fever, systolic blood pressure(SBP), diastolic blood pressure(DBP), and heart rate at admission, Laboratory tests included white blood cells (Wbc), hemoglobin < 110 g/L [n (%)](low Hgb), platelet (Plt), absolute neutrophil count (Anc), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), B-type natriuretic peptide (BNP), high-sensitivity troponin I (hs_cTnI), serum Na, serum K, serum Ca, serum P, serum Na, serum K, serum Ca, serum phosphorus < 1.1 mmol/L [n (%)](Low P), albumin (Alb), total protein (TP), creatinine (Cr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), glycocholic acid (CG), prothrombin time(PT), international standard normalized ratio(INR), activated partial thromboplastin time(APTT), thrombin time(TT), D-dimer, antithrombin III activity(AT-III). Cytokines included IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17, TNF, α-IFN and γ-IFN.

Statistical analysis

Descriptive analyses were conducted using SPSS 26.0, while subsequent statistical analyses were performed with R software, version 4.1.3. The dataset was randomly split into a training set and a validation set in a 7:3 ratio. The training set served for feature selection and model development, whereas the validation set was utilized to assess the performance of the trained model.

Univariate analysis

Quantitative data that followed a normal distribution were expressed as mean ± standard deviation and compared between groups using the t-test. For quantitative data that did not follow a normal distribution, medians

and interquartile ranges were reported, and groups were compared using the Mann-Whitney U test. Count data were presented as frequencies and percentages (%) and compared using the χ^2 test.

Variable selection and prediction model construction

A logistic regression model was employed to identify predictors of coronary dilation in children with KDSS. The stepwise method was utilized for variable selection ($P<0.1$). The top three variables were selected to construct the prediction model. Collinearity analysis was conducted to assess any associations between the selected variables, with the variance inflation factor (VIF) used to quantify the severity of collinearity. Variables without collinearity were then included in the binary logistic regression model.

Model performance evaluation

Receiver operating characteristic (ROC) curves were used to evaluate the model's accuracy in the training set. The area under the ROC curve (AUC) was calculated to determine the model's discriminatory ability. Calibration curves were applied to assess the agreement between predicted probabilities and observed outcomes. The model's calibration was evaluated by comparing predicted values to observations and visualized using a calibration graph with a 1000-bootstrap resampling procedure. Finally, the model was visualized using a column diagram.

Model validation

The validation set data were input into the model to predict the occurrence of coronary artery lesions in KDSS. Calibration curves were plotted to verify the model's accuracy and consistency, and the predictive value of the model was assessed.

Result

A total of 102 children diagnosed with KDSS at the Department of Cardiology of our hospital between January 2020 and March 2024 were enrolled in this study. Among them, 37 patients had coronary artery lesions, while 65 patients had normal coronary arteries. The training set comprised 24 children with coronary artery lesions and 48 children with normal coronary arteries. The validation set consisted of 13 children with coronary artery lesions and 17 children with normal coronary arteries. Missing data for certain variables were imputed using the mice package.

Establish a prediction model

Single factor analysis

Univariate analysis of clinical data was performed by T-test, Chi-square test and Mann-Uhlenbeck test, and the results showed that 9 indexes were statistically significant ($P<0.10$): fever time, WBC, low Hgb, Anc, Low P, IL-2, IL-4, IL-10, and IL-12p70.(Table 1).

Multifactor analysis

Based on the univariate analysis results,9 indexes were statistically significant ($P<0.10$): fever time, leukocyte, low hemoglobin, absolute value of neutrophil, low serum phosphorus, IL-2, IL-4, IL-10, and IL-12p70. These 9 indicators were further screened by stepwise regression, and finally 3 variables were selected by stepwise regression: fever time, low Hgb, and Low P.

Collinearity analysis

Three variables, including fever time, low Hgb, and Low P, were screened from the two regression models by the collinearity analysis. We use tolerances and VIF to quantify the collinearity severity. The tolerance of each variable was >0.2 and VIF was <5。 (Table 2).

Prediction model formula

A prediction model was established based on logistic regression coefficient and constant terms to predict the risk of coronary artery lesions in children with KDSS。The logistic regression equation is as follows:

Logit (P) = 0.454 × Fever days + 1.652 × Low Hgb− 1.804 × Low P− 4.663. (Table 3):

Logistic regression models evaluated in the training set

ROC curve analysis was used to evaluate the discriminant performance of the logistic regression model, with AUC = 0.837, sensitivity = 83.3%, specificity = 81.2%(Fig. 1; Table 4). The consistency was tested by calibration curve method. The calibration curve of logistic regression model drawn in the training set shows that the calibration curve fits the standard curve well and the model calibration effect is good (Fig. 2).

Establishment of nomogram model

Utilizing the outcomes of the binary logistic regression analysis, we employed R software to develop and visually represent a nomogram model (Fig. 3). This model aims to forecast the occurrence of coronary artery lesions in children with KDSS. For each KDSS child, a perpendicular line is drawn from the axis corresponding to their fever duration, low hemoglobin level, and serum phosphorus level (if below the normal range) on the respective bar charts. The points assigned to each of these factors are then summed. Subsequently, a line is drawn perpendicular from this total point sum to the risk axis, indicating the predicted probability of coronary artery damage in the child with KDSS.

Table 1 Comparison of characteristics between CAL and non-CAL in training set

Factors	CAD	non-CAD	*P*-value
Demographic parameters			
Number [n (%)]	24 (33.3)	48 (66.7)	–
Sex (Man/Feman)	18/6	31/17	0.431
Age (years)	5 (3–7)	4.5 (3–6)	0.444
BMI (kg/m^2)	15.9 (14.2–19.5)	15.4 (13.6–17.6)	0.187
Clinical symptom parameters			
SBP (mmHg)	76.5 (67.5–81.8)	80 (75–83)	0.165
DBP (mmHg)	40.0 (35.3–47.3)	40 (36–46)	0.891
Heart rate	133 (115–140)	124 (110–140)	0.150
Fever days (days)	10.0 (7.3–14.0)	7 (7–10)	**0.001**
Rash [n (%)]	19 (79.2)	40 (83.3)	0.749
Blood count parameters			
Wbc (10^{12}/L)	14.8 (11.2–19.0)	11.7 (8.0-16.8)	**0.089**
Low Hgb [n (%)]	15 (62.5)	18 (37.5)	**0.045**
Plt (10^9/L)	241 (138–325)	185.5 (128.8-281.3)	0.345
Anc (10^9/L)	12.1 (9.1–18.6)	9.4 (5.6–13.6)	**0.042**
CRP (mg/L)	147.5 (78.5–180.0)	106.9 (65.8 -144.5)	0.145
ESR (mm/h)	88.5 (36.0-94.8)	62.5 (38.3–90.5)	0.336
BNP (pg/ml)	446.6 (121.5-1879.9)	277.2 (90.1-747.5)	0.126
HS-cTnI (ng/ml)	0.012 (0.006–0.061)	0.011 (0.004–0.037)	0.760
Blood isochemical parameters			
K (mmol/L)	3.67 (3.36–4.05)	3.75 (3.50–3.98)	0.702
Na (mmol/L)	132.2 (129.4-135.5)	130.4 (127.3-133.4)	0.147
Ca (mmol/L)	1.99 (1.86–2.15)	2.05 (1.93–2.14)	0.492
Low P[n (%)]	10 (41.7)	33 (68.9)	**0.027**
TP (g/L)	58.6 (54.5–62.3)	56.8 (52.9–61.3)	0.488
ALB (g/L)	31.9 (25.1–34.7)	31.9 (28.9–35.4)	0.430
Cr (umol/L)	36.7 (26.9–48.8)	29.9 (22.1–45.6)	0.221
AST (U/L)	31.2 (22.9–46.4)	38.9 (25.9–80.8)	0.321
ALT (U/L)	54.7 (21.7-124.2)	34.8 (18.4-116.7)	0.485
TBA (umol/L)	17.8 (7.4-111.9)	20.5 (9.5–40.2)	0.914
CG (mg/L)	4.6 (3.4–45.8)	7.0 (2.4–14.5)	0.858
Coagulation parameters			
PT (s)	13.3 (12.5–15.6)	13.1 (12.1–14.3)	0.251
INR	1.16 (1.10–1.37)	1.15 (1.07–1.25)	0.266
FIB (g/L)	4.97 (3.87–7.12)	4.58 (3.96–6.18)	0.201
D-Dimer (mg/L)	1.01 (0.63–2.82)	0.99 (0.50–2.08)	0.298
APTT (s)	34.9 (30.6–37.5)	34.3 (31.6–36.9)	0.519
TT (s)	14.6 (13.3–15.9)	14.5 (13.4–15.8)	0.783
AT-III (%)	82.5 (66.0–97.0)	87.5 (74.0–97.0)	0.607
Inflammatory parameters			
IL-1β	4.7 (2.4–19.1)	5.6 (2.5–21.8)	0.601
IL-2	2.4 (2.4–2.8)	2.4 (2.4–4.5)	**0.072**
IL-4	2.4 (2.4–2.9)	2.5 (2.4–4.1)	**0.059**
IL-5	2.5 (2.4–3.8)	2.5 (2.4–5.9)	0.775
IL-6	23.2 (7.1-142.5)	17.5 (6.0-79.9)	0.379
IL-8	4.1 (2.4–9.2)	8.5 (2.4–35.1)	0.148
IL-10	2.9 (2.4–29.9)	7.3 (2.5–35.9)	**0.064**
IL-12p70	2.4 (2.4–2.4)	2.4 (2.4–2.7)	**0.084**
IL-17	4.6 (2.4–15.7)	2.7 (2.4–15.7)	0.613
TNF	3.3 (2.4–9.9)	2.4 (2.4–7.7)	0.243

Table 1 (continued)

Factors	CAD	non-CAD	*P*-value
α-IFN	2.4 (2.4–3.6)	2.4 (2.4–4.1)	0.442
γ-IFN	12.7 (2.4–38.2)	11.7 (4.4-163.8)	0.419

Abbreviations: Alb, albumin; ALT, alanine aminotransferase; ANC, absolute neutrophil count; APTT, partial thromboplastin time; AST, aspartate aminotransferase; AT-III, antithrombinIII; BNP, brain natriuretic peptide; Ca, serum calcium; CAL, coronary artery lesions; CG, glycocholic acid; Cr, creatinine; CRP, C-reactive protein; DBP, Diastolic blood pressure; ESR, erythrocyte sedimentation rate; Fib, fibrinogen; Hs-cTnI, high-sensitivity cardiac troponin I; INR, international normalized ratio; Low Hgb (hemoglobin < 110 g/L [n (%)]); Low P(low serum phosphorus (*P* < 1.1 mmol/L [n (%)])); IL, interleukin; IFN, interferon; K, serum potassium; Na, serum sodium; Plt, platelet; PT, prothrombin time; SBP, Systolic blood pressure; TBA, total bile acid; TP, total protein; TT, thrombin time; TNF, tumor necrosis factor; WBC, white blood cell

Table 2 The collinearity diagnostic analysis of factors for predicting CAD in training set

Variables	Fever days	Low *P*	Low Hgb
Tolerance	0.958	0.952	0.982
VIF	1.044	1.051	1.018

Abbreviations: Low Hgb (hemoglobin < 110 g/L [n (%)]); Low P(low serum phosphorus (*P* < 1.1 mmol/L [n (%)]))

Validation of logistic regression models in test sets

As shown in the figure, the predicted value of the logistic regression model was in good agreement with the actual value (Fig. 4).

Discussion

Kawasaki Disease Shock Syndrome (KDSS), a grave manifestation of Kawasaki Disease (KD), is distinguished by persistent hypotension and impaired peripheral circulation, yet its underlying pathophysiology remains incompletely understood. Nevertheless, research has established a strong correlation between KDSS and coronary artery damage. During the acute phase of KD, an intense inflammatory response and immune system hyperactivity result in endothelial dysfunction and vascular wall remodeling, ultimately leading to complications like coronary artery dilation, aneurysms, and thrombosis [8, 9]. The hallmark of coronary artery involvement during the acute inflammatory phase is necrotizing arteritis, which disrupts the artery's structure and can lead to the formation of coronary aneurysms and, albeit rarely, coronary artery rupture [10, 11].

Certain studies indicate that mild coronary dilation may resolve over time, whereas larger aneurysms tend to persist [12]. Furthermore, numerous investigations utilizing various parameters have suggested an increased risk of atherosclerosis in individuals with a history of KD [13]. The onset of KDSS may exacerbate these coronary artery injuries, resulting in more severe clinical outcomes.

Interleukins (ILs) are a class of signaling molecules produced by immune cells that play crucial roles in regulating immune responses and mediating inflammatory processes. IL-10, in particular, is a potent anti-inflammatory cytokine that may ameliorate the outcomes of CAWS-induced vasculitis by inhibiting the release of pro-inflammatory mediators, such as TNF and IL-1β, from innate immune cells infiltrating the tissues [14]. According to the research conducted by Mingming Zhang et al., IL-10 has been identified as a risk factor for the development of Kawasaki Disease Shock Syndrome (KDSS) [15]. In this study, IL-2, IL-4, IL-10, and IL-12p70 showed statistically significant differences, but they were not included in the logistic regression model. Further research with a larger sample size is needed to investigate these findings.

In this study, we developed a predictive model for coronary artery lesions in KDSS to assess the risk of such lesions early in the disease course and further delve into the pathophysiology of KDSS. This model was constructed using multivariate logistic regression analysis. By retrospectively analyzing clinical data from children with KDSS, we identified independent risk factors for coronary artery damage in this condition, including fever duration and low hemoglobin levels. These risk factors serve as crucial components in the construction of our coronary artery lesion prediction model.

The duration of fever emerged as a significant factor in our model, indicating that a prolonged fever is associated with an increased risk of coronary artery damage in KDSS. This may be attributed to the sustained damage inflicted on blood vessel walls by a prolonged inflammatory response. In young infants, fever may be the sole manifestation of Kawasaki disease. Relevant studies have implicated circulating immune complexes in the formation of coronary artery damage in Kawasaki disease [16]. Maria et al. showed that delayed treatment and

Table 3 Coefficients of binary logistic regression for predicting CAL in training set

Variables	β	S.E.	Wald	*P* value	OR	95% CI for OR
Fever days	0.454	0.134	11.484	0.001	1.574	1.211–2.047
Low P	-1.804	0.699	6.660	0.010	0.165	0.042–0.648
Low Hgb	1.652	0.683	5.850	0.016	5.216	1.368–19.891
Constant	-4.663	1.278	13.317	< 0.001	–	–

Abbreviations: S.E., standard error; OR, odds ratio; CI, confidence interval; Abbreviations: Hgb, hemoglobin; P, serum phosphorus

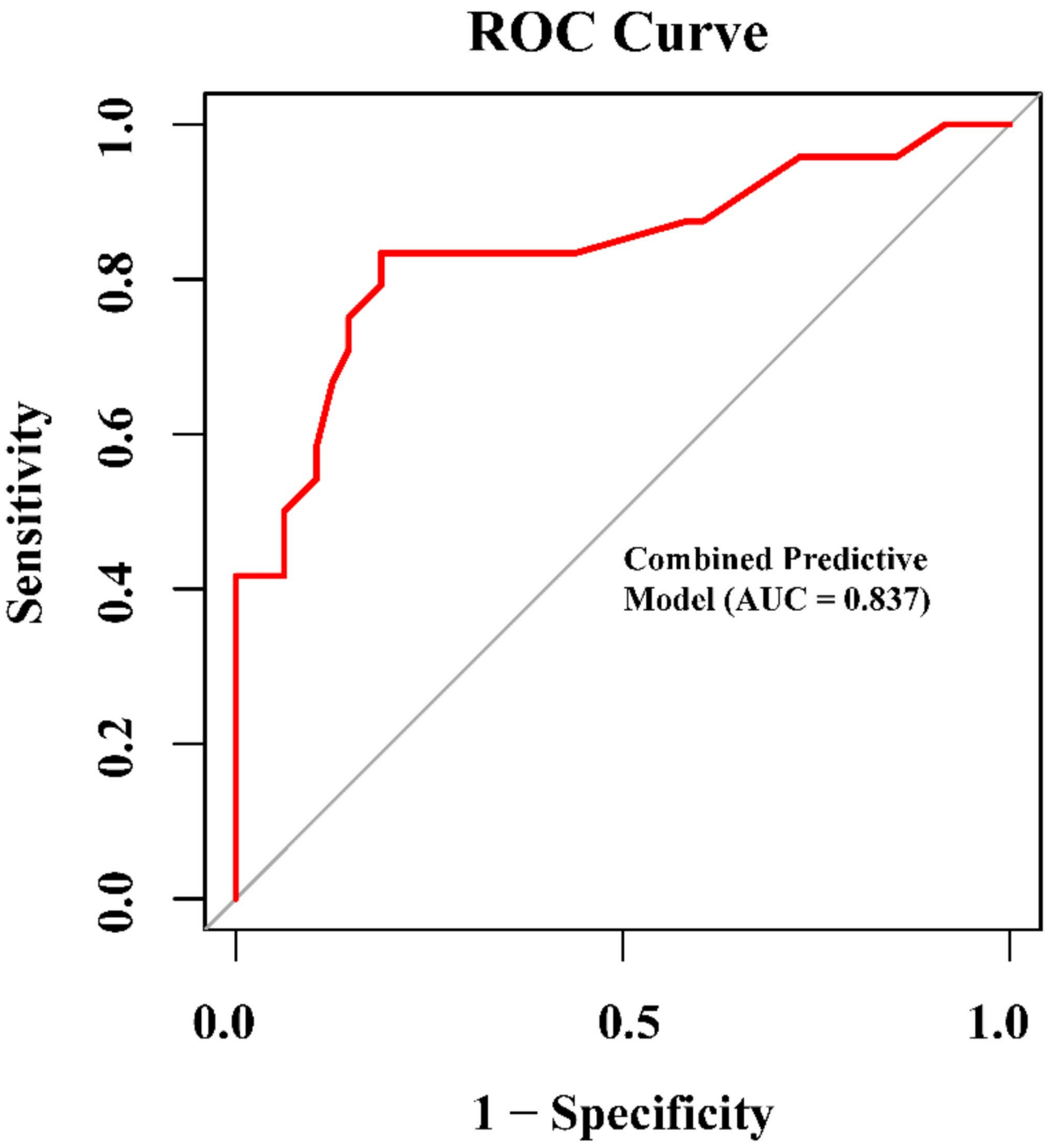

Fig. 1 The ROC curve of the combined predictive model for predicting CAL in training set

Table 4 The ROC analysis of the model in the training set

Variables	AUC	95%CI	*P* value	Cut-off value	Sensitivity (%)	Specificity (%)
predictive model	0.837	0.792–0.946	< 0.001	*P* ≥ 0.294	83.3	81.2

prolonged fever were closely related to the occurrence of coronary tumors in children with Kawasaki disease [17]. Similarly, Ryusuke et al. found that delayed admission and treatment of Kawasaki disease were not only associated with coronary artery dilation but also with subsequent coronary artery dilation [18]. Delay in IVIG treatment can increase the duration of coronary lesions [19]. These studies are consistent with the present study.

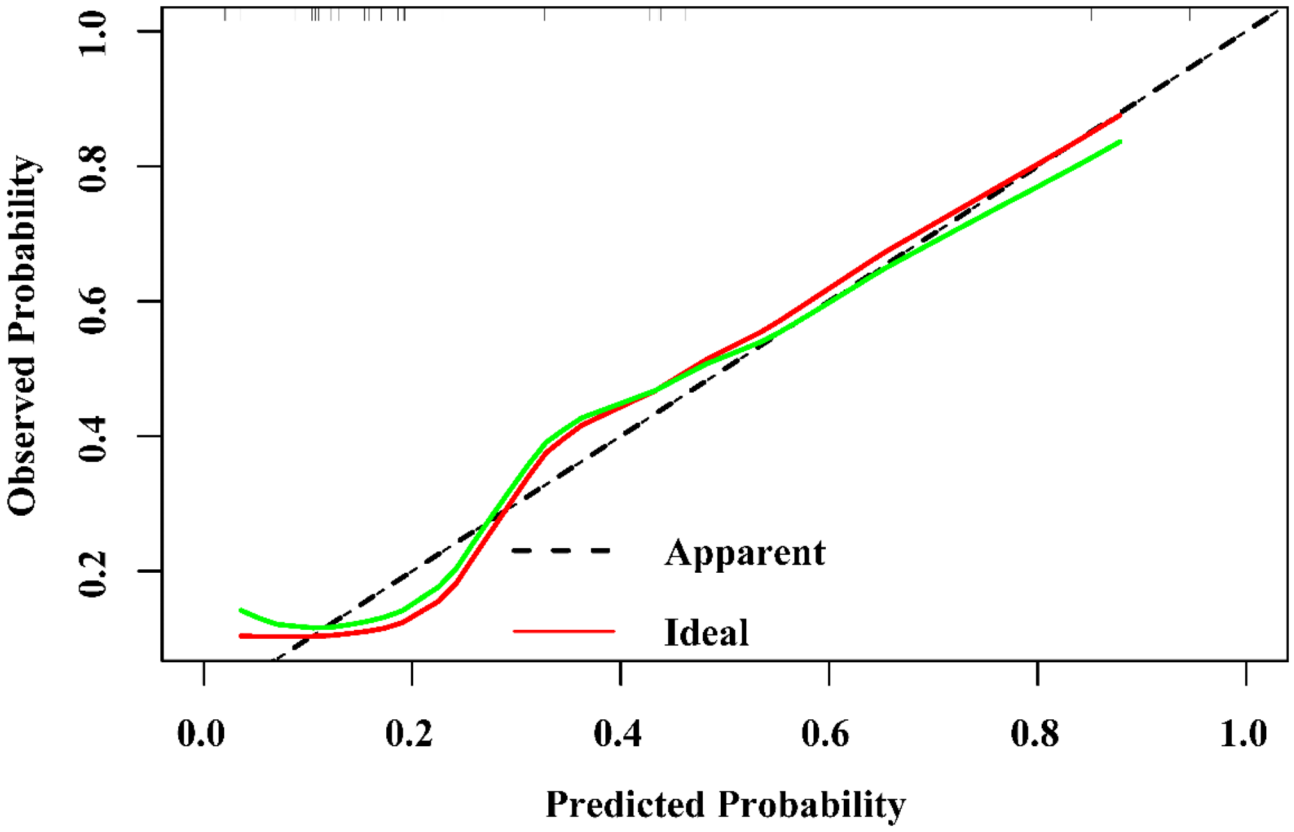

Fig. 2 Calibration of the nomogram for predicting CAL in the training set

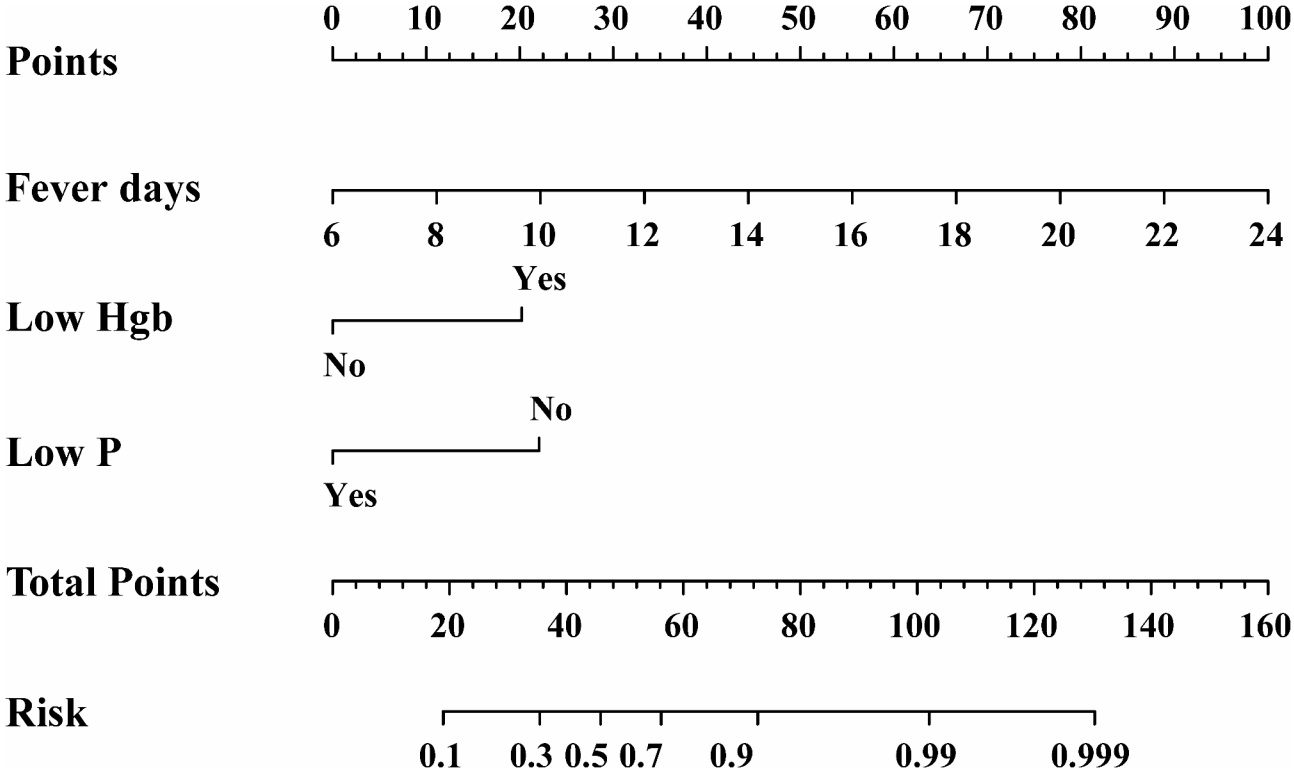

Fig. 3 Nomogram for predicting the CAL in the training set

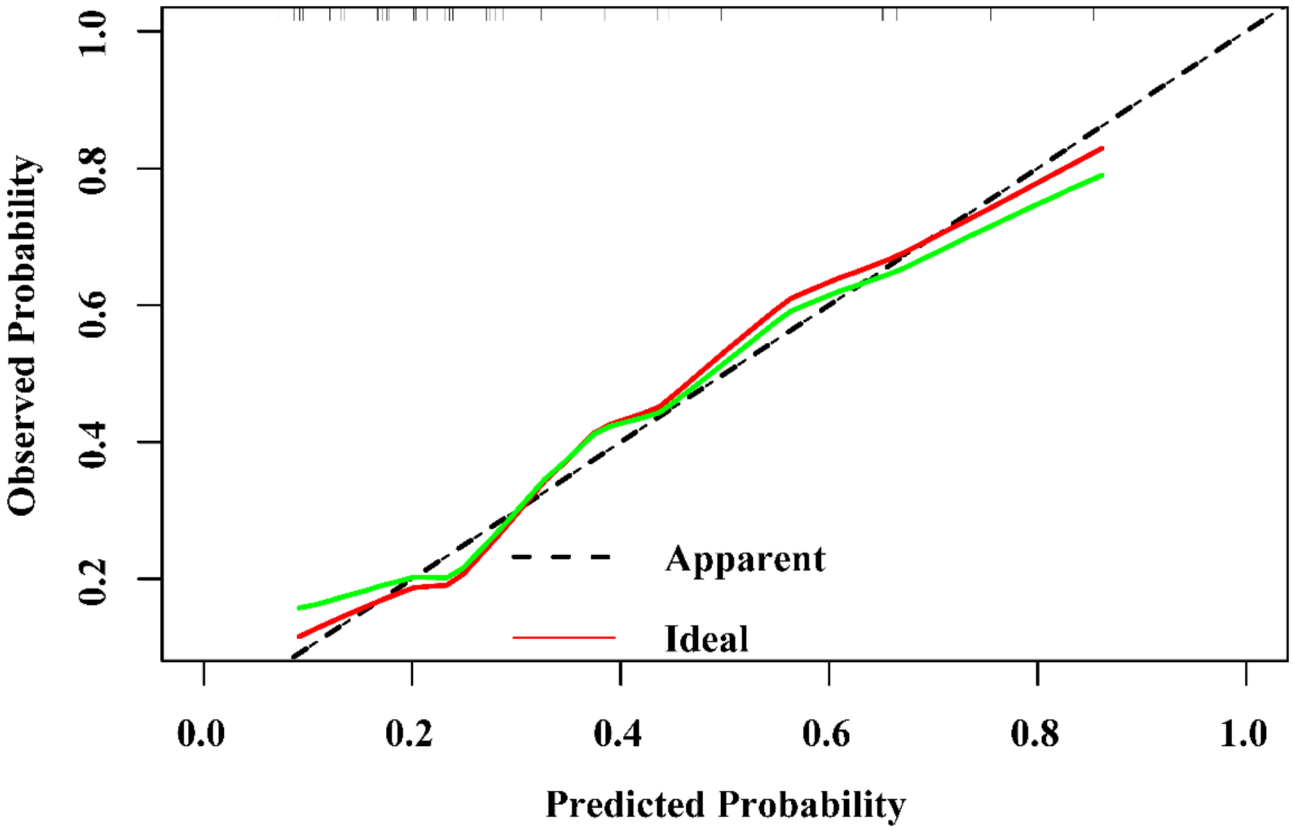

Fig. 4 Calibration of the nomogram for predicting CAL in the testing set

Relevant studies have shown that once a giant coronary tumor is formed, the long-term prognosis is poor, the coronary tumor is difficult to subside, and the probability of long-term adverse cardiovascular events is higher [5, 12, 20–22]. Coronary artery damage is frequently underdiagnosed and under-treated, leading to the progressive development of coronary thrombosis, coronary artery obstruction, or calcification, significantly increasing the risk of death in children [23].

Related studies have shown that decreased hemoglobin is associated with the occurrence and development of coronary artery damage [24]. This may be due to the reduced oxygen-carrying capacity of red blood cells in an anemic environment, resulting in an increase in circulating blood volume to meet the body's oxygen demands and subsequently increasing cardiac oxygen consumption. This increased myocardial oxygen consumption may stress the heart and exert additional pressure on the coronary arteries. Furthermore, decreased hemoglobin levels lead to tissue hypoxia, triggering sympathetic nerve excitation, excessive activation of the renin-angiotensin system, and damage to the coronary artery wall, thereby promoting the occurrence and development of coronary artery lesions (CALs). Consequently, reduced hemoglobin levels suggest a higher risk of coronary artery damage in children with Kawasaki disease [25–27]. Smorczewska-Kiljan et al. also identified low hemoglobin as an independent risk factor for coronary artery lesions [28].

There is a paucity of research examining the direct correlation between hypophosphatemia and coronary artery lesions. Currently, there lacks definitive evidence to substantiate the notion that hypophosphatemia serves as a protective factor against coronary artery damage in pediatric patients with Kawasaki shock syndrome. Nevertheless, this does not diminish the potential significance of hypophosphatemia in the context of Kawasaki disease shock syndrome in children. Future investigations may delve deeper into the association between hypophosphatemia and coronary artery lesions in this patient population, with the aim of uncovering novel insights and therapeutic strategies for clinical management.

While the KDSS coronary lesion model developed in this study demonstrates high predictive accuracy and practical utility, it is not without its limitations. Indeed, sample size is a crucial consideration in any predictive modeling study. We are actively seeking opportunities for multicenter collaborations to expand our sample size in future studies. Notably, the model's foundation rests on retrospective data, which may be influenced by factors such as the quality and quantity of the data available. Furthermore, the model's predictive capabilities require

further validation and refinement through larger, prospective studies.

Conclusion

In conclusion, the establishment of this model not only advances our understanding of the pathophysiological mechanisms underlying KDSS, but also equips pediatricians with a valuable tool for the early identification of potential coronary artery damage in KD. This, in turn, facilitates the prompt formulation of treatment plans to mitigate the risk of coronary artery damage in this patient population.

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Author contributions
ZZH contributed to conceptualization, data curation, methodology, investigation and writing. YY, GL, LQR, ZZ and LHX contributed to data curation, investigation and project administration. ZSY and XYY contributed to conceptualization, investigation and supervision. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Compliance with ethical
This study was approved by the Ethics Committee of Beijing Children's Hospital affiliated with Capital Medical University. (Approval Number [2024]-E-178-R).

Consent for publication
Not applicable.

Competing interests
The authors declare that we have no competing interest. Author details.

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