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A visualized nomogram to predict intravenous immunoglobulin resistance in Kawasaki disease: a study based on the population in Southern China

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Abstract

Background A significant proportion of Kawasaki disease (KD) patients suffer from intravenous immunoglobulin (IVIG) resistance after initial IVIG treatment, which results in persistent coronary artery injury. This study aimed to analyze the risk factors including coagulation indicators and develop a visualized nomogram model to early predict KD patients who would be at high risk of IVIG-resistant.

Methods Consecutive KD patients receiving standard dose of IVIG in Xiamen Women and Children's Hospital between April 2014 and June 2024 were included in the study. Baseline variables were analyzed using univariate logistic regression and multivariable logistic regression to identify the predictors of IVIG-resistance and derive a nomogram model for the assessment of IVIG-resistance in KD patients. The performance of the nomogram was evaluated with the area under curve (AUC) of receiver operating characteristic, calibration curve, and decision curve analysis.

Results A total of 541 KD patients were finally enrolled in the present study, and 7.6% of KD patients suffered from IVIG-resistant. The predictive value of coagulation indicators for IVIG-resistance may be limited except for activated partial thromboplastin time (APTT). Other independent predictors include red blood cell count, globulin, Alanine aminotransferase, and weight. The training and testing sets of nomogram scored an AUC of 0.781 (95% CI, 0.688–0.874) and 0.749 (95% CI, 0.597–0.902). The nomogram was calibrated well, and the decision curve analysis showed that the nomogram would generate more net benefit when the threshold probabilities ranged from 10 to 70%.

Conclusion A visualized nomogram model was constructed to accurately predict the risk of IVIG-resistance for KD patients, and APTT may be a potential predictor of IVIG-resistant.

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Keywords Kawasaki disease, Intravenous immunoglobulin resistant, Activated partial thromboplastin time, Nomogram

Introduction

Kawasaki disease (KD) is an acute, self-limited febrile disease characterized by systemic vasculitis. The typical complication of KD is coronary artery lesions (CALs), which is the primary reason for acquired heart disease among children in some countries and regions. Intravenous immunoglobulin (IVIG) is the mainstay during the acute phase of KD according to American Heart Association [1]. Early standardized treatment mitigates arterial damage and inflammation and reduces the prevalence of CALs [2–4]. However, 7.5-26.8% of children with KD had persistent or recrudescent fever at least 36 h and <7 days after initial IVIG treatment, which is defined as "IVIG-resistance". The persistence of arterial damage and inflammation in IVIG-resistant children may result in a pathological process that is not relieved and interrupted in time. Children with IVIG resistance may suffer persistent arterial injury and consume resources and time, so early prediction of IVIG resistance is critical.

In recent years, several scoring models have been established to predict IVIG-resistant. The Kobayashi score [5], Egami score [6], and San Diego score [7] were established based on the characteristics of the Japanese population and the San Diego scoring system was constructed based on the USA population. However, a retrospective study shows that the Kobayashi score, the Egami score, and the San Diego score have limited utility in predicting IVIG-resistant among the Chinese population [8]. Furthermore, the predictive factors included in these scores were limited, and recent studies have indicated that coagulation factors may be related to the responsiveness to IVIG [9]. Therefore, developing a more reliable and simpler tool with overall applicability to predict IVIG-resistant in KD patients is essential.

A nomogram is a graphic calculating tool that allows quick prognosis prediction with selected clinical and laboratory parameters. Several studies have shown that Nomogram has been applied to predict the prognosis and help clinicians choose optimized therapy in the medical field, such as hepatocellular carcinoma [10], ocular myasthenia gravis [11], and pulmonary tuberculosis [12]. However, the nomogram to predict the probability of IVIG-resistant in KD patients is not found.

Here, the present study aims to evaluate the prognostic factors, including coagulation indicators, associated with IVIG-resistant and develop and validate a tool based on nomogram to early predict IVIG-resistant in KD patients, and more importantly, to provide individualized information and proper assessment to prevent the occurrence of severe CALs.

Methods

Study population

Consecutive KD patients receiving IVIG in Xiamen Women and Children's Hospital between April 2014 and June 2024 were included in the study. The inclusion criteria: (1) Patient with a discharge diagnosis of KD according to the diagnostic guidelines of the American Heart Association [1]; (2) Patients received a standard dose of IVIG (2 g/Kg) at the initial stage during the acute phase of KD. The exclusion criteria: (1) Patients who received non-standard IVIG treatment; (2) Patients who use corticosteroids or other immunosuppressive drugs before or in combination with the IVIG treatment; (3) Patients with presence of other serious complications such as macrophage activation syndrome, shock, severe infection, septic lesions, multi-organ dysfunction, hemophagocytic syndrome, etc.; (4) Patients with more than 10% missing variables.

After the initial diagnosis of KD was confirmed, all patients received a dose of 2 g/Kg IVIG and 30–50 mg/Kg/day aspirin. IVIG resistance is defined as persistent or recrudescent fever at least 36 h and <7 days after completion of the first IVIG infusion. According to the recommendations of the American Heart Association guidelines, a second dose of 2 g/kg IVIG was administered to IVIG-resistant patients after the end of the first IVIG infusion. In addition, Administration of high-dose pulse steroids may be considered as an alternative to a second infusion of IVIG or in combination with high-dose IVIG, usually methylprednisolone 20–30 mg/kg intravenously for 3 days. A dose of 5 mg/kg Infliximab can also serve as an alternative for retreatment.

The study population was randomly stratified into the training set and the testing set (7: 3), which meant that the proportion of IVIG-sensitive patients to IVIG-resistant patients were well-balanced. Patients with more than 10% missing values were excluded and multiple imputation were used to fill those missing values.

This study complied with the principles of the Declaration of Helsinki and postoperative ethical requirements. Ethical approval for the study was obtained from the Ethics Committee of Xiamen Women and Children's Hospital (document number: KY-2025-010-K01). Due to the retrospective nature of the study, the requirement for written informed consent was waived. This study was not concerned with confidential patient information.

Evaluated variables

Related clinical information of the patients was collected from the electronic case system. Demographic

variables included age, sex, and weight. CAL is assessed using echocardiographic z-score. A coronary artery with z-score more than 2 was considered as CAL [1]. The ultrasound reports were reviewed by experienced paediatric echocardiographers. Laboratory data included: (1) Blood biochemical indicators: albumin, globulin, alanine aminotransferase (ALT), aspartate aminotransferase, glucose, and γ-glutamyl transpeptidase. (2) Blood routine: Monocyte ratio, red blood cell (RBC) counts, eosinophil, hemoglobin (HGB), platelet, white blood cell count, and neutrophil%. (3) Inflammatory indicators: C-reactive protein and erythrocyte sedimentation rate. (4) Coagulation indicator: D-Dimer, international normalized ratio, thromboplastin time, activated partial thromboplastin time (APTT), prothrombin time, and fibrinogen.

Statistical analysis

Patient characteristics were compared between IVIG-sensitive KD and IVIG-resistant KD. Normally distributed continuous variables and nonnormally distributed continuous variables were described as mean ± SD and median (IQR), respectively. The percentages of events were used to describe categorical data. For continuous data, comparisons were made using the Mann-Whitney U-test and the independent Student's t-test, whereas categorical characteristics were contrasted by Pearson's Chi-square test. Then the variables with $p < 0.1$ were entered into multivariable logistic regression (maximum likelihood method) by backward stepwise method. Those variables that finally entered into the regression were used to calculate the probability of IVIG-sensitive in KD patients. The associations of risk factors with IVIG-sensitive were reported as odds ratios (ORs) with 95% CIs. The collinearity of variables that entered into the multivariable logistic regression was assessed using the Variance Inflation Factor (VIF), and VIF>2 indicates a certain degree of collinearity.

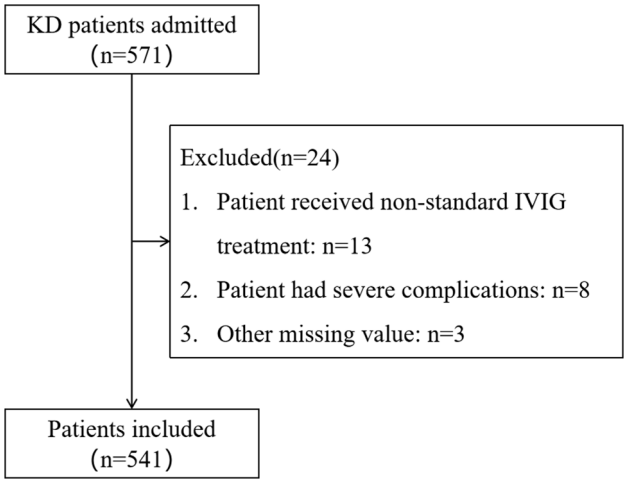

Fig. 1 Flowchart of patient inclusion and exclusion criteria. IVIG, intravenous immunoglobulin; KD, Kawasaki disease

Each variable in the nomogram was given a weighted score, which was then summed to create a total score and finally converted to individual risk of futile recanalization by the function between the total score and the probability of the outcome, and the nomogram model was built by the R software.

The performance of the nomogram was evaluated in the training and testing sets, including discrimination, calibration, and clinical application. The model's discrimination was evaluated by the area under the receiver operating characteristic (AUC) curves and to determine the thresholds that separate the IVIG-sensitive and IVIG-resistant groups. The nomogram is calibrated utilizing the Hosmer-Lemeshow goodness-of-fit test and calibration plot to measure how closely the predicted probabilities agree on the frequency of the observed IVIG-resistant. The clinical utility was evaluated through decision curve analysis (DCA) to explore the net benefit (NB) of the nomogram model.

The above Statistical analyses were implemented with SPSS version 25 (IBM Corporation, USA) and R version 4.4 (http://www.R-project.org/).

Results

Study population

As shown in Figs. 1 and 541 patients met the inclusion criteria and were eligible and included. 42 KD patients suffered from IVIG-resistant, accounting for 7.6% of KD patients. The median age of included KD patients was 16.5 (IQR: 8.00–31.00) months and 337 (61.6%) patients were men. The baseline statistics of both IVIG-sensitive and IVIG-resistant groups are shown in Table 1. Supplementary Table S1 shows that the analogous proportions of KD patients were established between training and testing sets (7.8 vs. 7.2%, $p > 0.05$) and all characteristics were well-balanced between the training set ($n = 382$, 69.8%) and testing set ($n = 165$, 30.2%).

Univariate and multivariate analyses

In the univariate logistic analysis, the albumin ($p = 0.039$), globulin ($p = 0.012$), RBC counts ($p = 0.002$), HGB ($p = 0.019$), and the APTT ($p = 0.026$) were found to be significantly associated with IVIG-resistant (Table 1).

The multivariate logistic regression analysis identified globulin (OR, 1.121; 95% CI, 1.049–1.198), RBC counts (OR, 0.123; 95% CI, 0.044–0.342), weight (OR, 0.959; 95% CI, 0.864–1.064), ALT (OR, 1.004; 95% CI, 1.000-1.007) and APTT (OR, 0.889; 95% CI, 0.812–0.973) as prognostic factors of IVIG-resistant (Table 2). The logistic regression model resulted: Log [p(x)/1-p(x)] = 6.315 + (0.114 × globulin) + (-2.096×RBC counts) + (-0.042×weight) + (0.004×ALT) + (-0.118×APTT); where p(x) was the

Table 1 Demographic and clinical data of the patients

Variable(s)	Total (*n* = 547)	IVIG-sensitive KD (*n* = 505, 92.3%)	IVIG-resistant KD (*n* = 42, 7.6%)	*p*-value
Patient characteristics				
Age, months, median (IQR)	16.5(8.00–31.00)	16.00(8.25-31.00)	18.50(7.00–28.00)	0.649
Male sex, n (%)	337(61.6)	308(60.9)	29(69.0)	0.327
weight, kg, median (IQR)	10.30(8.70-13.43)	10.30(8.73–13.50)	10.40(8.40-13.32)	0.686
CAL, n (%)	105(19.2)	94(18.6)	11(26.1)	0.231
Blood biochemical indicators				
ALB, g/L, mean(SD)	33.57(5.33)	33.73(5.24)	31.64(6.00)	0.039
GLB, g/L, mean(SD)	29.86(6.14)	29.63(5.77)	32.56(9.17)	0.012
Creatinine, umol/L, median (IQR)	35.60(29.55–42.72)	35.55(29.00-43.18)	37.65(30.85–40.22)	0.788
ALT, U/L, median (IQR)	30.00(17.00-88.08)	29.00(17.00-89.50)	37.00(18.50–78.33)	0.481
AST, U/L, median (IQR)	32.00(25.00–51.00	32.00(25.00–51.00)	32.50(23.00-44.50)	0.804
ALT: AST, median (IQR)	1.18(0.66–1.72)	1.19(0.67–1.73)	0.97(0.54–1.58)	0.252
Glucose, mmol/L, median (IQR)	5.87(5.31–6.54)	5.88(5.30–6.56)	5.83(5.26–6.38)	0.749
γ-GT, U/L, median (IQR)	35.00(15.00–95.00)	35.00(15.00–93.00)	65.00(19.00-110.75)	0.166
Blood routine				
Monocyte ratio, %, median (IQR)	6.98(4.90–9.20)	6.90(4.90–9.10)	8.30(5.90–9.88)	0.124
RBC, 10^12/L, median (IQR)	4.01(3.80–4.30)	4.03(3.82–4.31)	3.80(3.23–4.06)	0.002
Eosinophil, 10^9/L, median (IQR)	2.20(1.10–4.02)	2.20(1.10–3.99)	2.70(0.90–5.05)	0.942
HGB, g/L, median (IQR)	106.00(99.83–112.00)	107.00(100.00-112.00)	103.00(88.50-109.25)	0.019
PLT, 10^9/L, median (IQR)	387.00(310.50-466.33)	389.00(313.75–466.10)	365.00(243.25-457.25)	0.178
WBC, 10^9/L, median (IQR)	14.00(10.98–17.48)	14.00(10.96–17.49)	13.93(11.48–17.38)	0.939
NE%, median (IQR)	60.95(50.00-73.90)	60.80(49.33–73.98)	63.40(54.35–71.70)	0.079
Inflammatory indicators				
CRP, mg/L, median (IQR)	73.16(40.69-105.12)	74.07(43.28-105.17)	62.82(32.95–101.90)	0.258
ESR, mm/h, median (IQR)	59.50(43.75-80.00)	60.00(44.00-80.750	56.00(40.00–70.00)	0.339
Coagulation indicator				
D-Dimer, ng/mL, median (IQR)	464.50(316.50-615.50)	463.50(317.50-616.50)	489.00(257.25–597.50)	0.551
INR, median (IQR)	1.19(1.11–1.29)	1.19(1.11–1.29)	1.16(1.05–1.28)	0.141
TT, sec, median (IQR)	13.50(12.80–14.30)	13.50(12.90–14.30)	13.15(12.57–14.42)	0.357
APTT, sec, median (IQR)	34.65(31.30-37.53)	34.79(31.52–37.70)	32.85(29.68–35.92)	0.026
PT, sec, median (IQR)	13.50(12.60–14.50)	13.50(12.60–14.50)	13.20(12.38–14.92)	0.357
FIB, g/L, median (IQR)	4.94(4.36–5.44)	4.94(3.55–5.40)	4.90(4.29–5.56)	0.988

IQR, interquartile range; SD, standard deviation; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; CAL, coronary artery lesions; ALB, albumin; GLB, globulin; TBL, total bilirubin; DBL, direct bilirubin; IBL, indirect bilirubin; CK, creatine kinase; CKMB, creatine kinase, MB Form; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, γ-glutamyl transpeptidase; RBC, red blood cell count; HGB, hemoglobin; PLT, platelet; WBC, white blood cell count; NE%, neutrophil%; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; INR, international normalized ratio; TT, thromboplastin time; APTT, activated partial thromboplastin time; PT, prothrombin time; FIB, fibrinogen

Table 2 The multivariate logistic regression analysis

Variable(s)	VIP	B	SE	*p*-value	OR(95%CI)
GLB	1.233	0.114	0.034	0.001	1.121(1.049–1.198)
RBC	1.128	-2.096	0.521	0.000	0.123(0.044–0.342)
weight	1.323	-0.042	0.053	0.428	0.959(0.864–1.064)
ALT	1.056	0.004	0.002	0.026	1.004(1.000-1.007)
APTT	1.005	-0.118	0.046	0.010	0.889(0.812–0.973)

GLB, globulin; RBC, red blood cell count; ALT, Alanine aminotransferase; APTT, activated partial thromboplastin time

probability of IVIG-resistant. Then the model was converted into a graphic nomogram (Fig. 2).

Performance of nomogram

According to Fig. 3A and B, the training and testing sets of nomogram scored an AUC of 0.781 (95% CI, 0.688–0.874) and 0.749 (95% CI, 0.597–0.902), showing a good discriminative ability of this model. The calibration curve was plotted in the training set (Fig. 4A) and testing set (Fig. 4B), the mean squared error of the training and testing sets was 0.006 and 0.018, which also showed a strong level of calibration performance of the nomogram in the present study. The Hosmer–Lemeshow goodness-of-fit test demonstrated the nomogram had good calibration in the training ($\chi2 = 5.2085$, $p = 0.735$) and testing ($\chi2 = 11.234$, $p = 0.189$) sets, which indicated that the nomogram predicted probabilities of IVIG-resistant was in good agreement with the actual probabilities. When the threshold probabilities ranged from 10 to 70%, the DCA showed that the nomogram would generate more

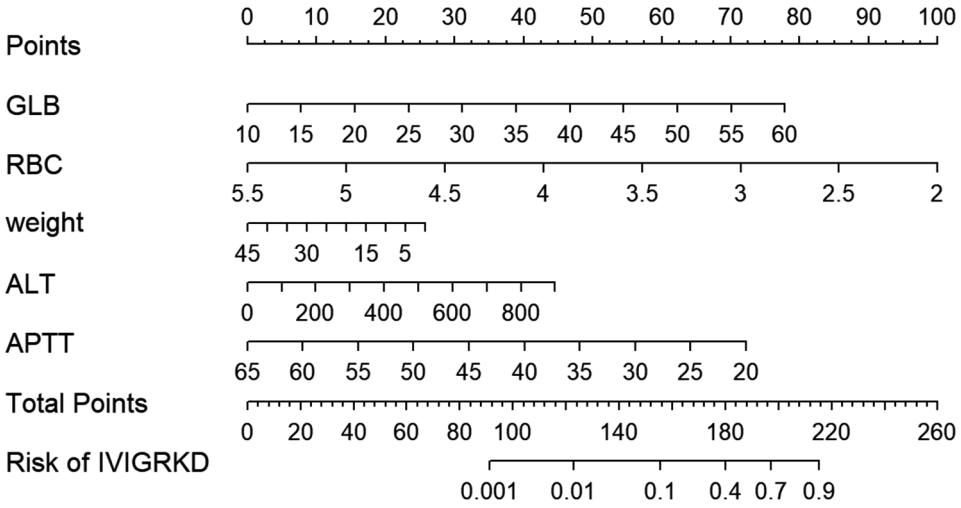

Fig. 2 The nomogram developed for predicting IVIG resistance in KD patients. IVIG, intravenous immunoglobulin; KD, Kawasaki disease; ALT, alanine aminotransferase; activated partial thromboplastin time (APTT)

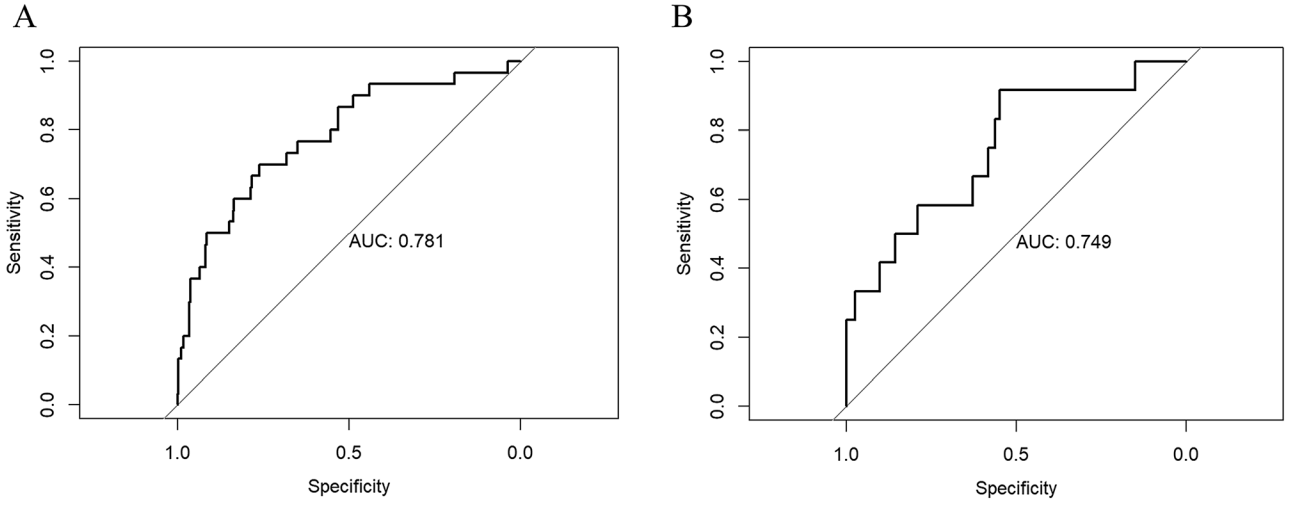

Fig. 3 The receiver operator characteristic (ROC) curves of the nomogram. (**A**) The ROC curve in the training set. (**B**) The ROC curves in the testing set

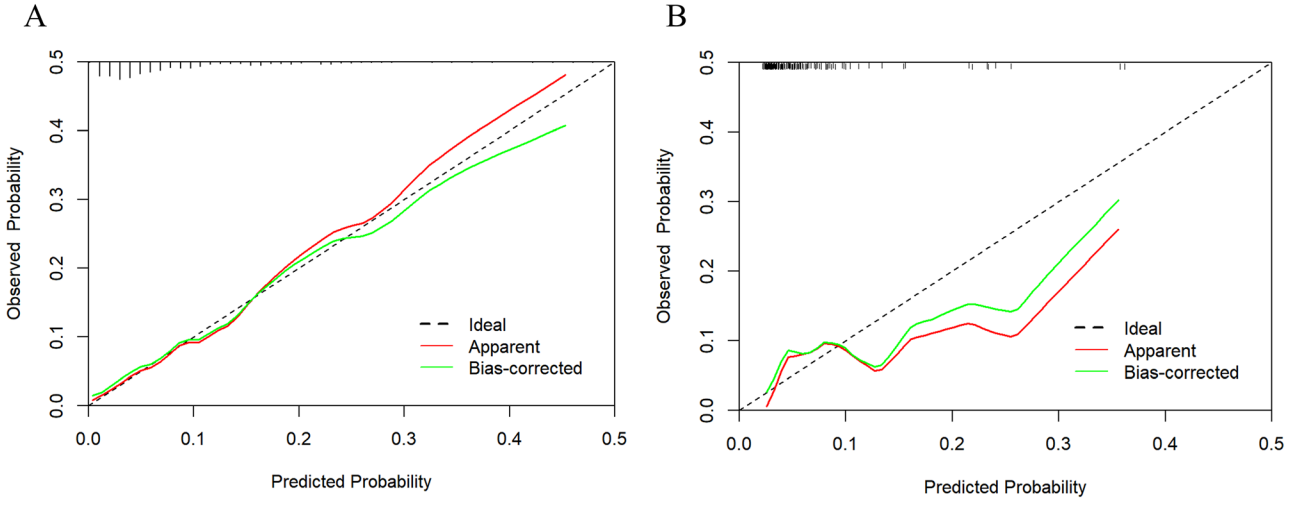

Fig. 4 The calibration plot of the nomogram. (**A**) The calibration plot in the training set. (**B**) The calibration plot in the testing set

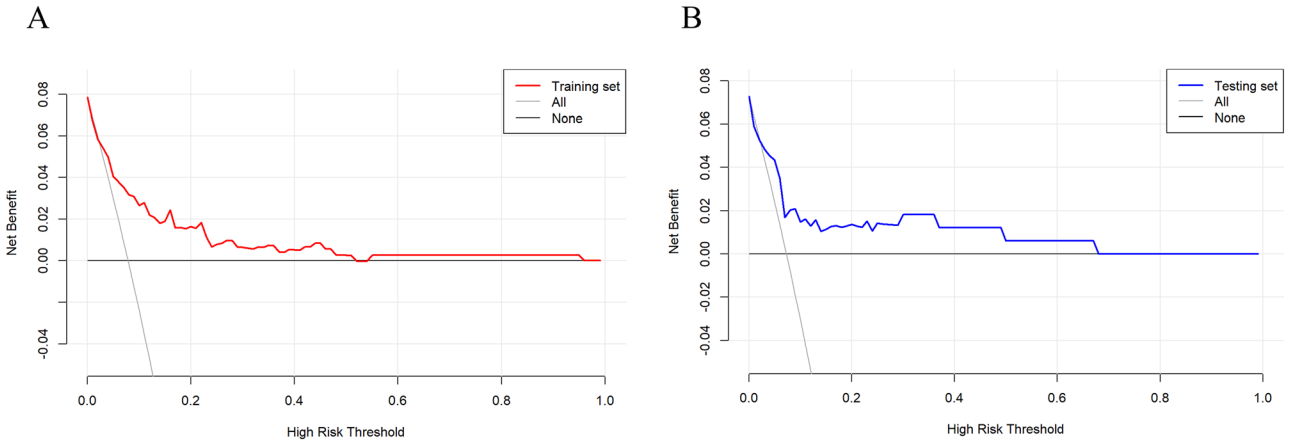

Fig. 5 The decision curve analysis of the nomogram. (**A**) The decision curve analysis in the training set. (**B**) The decision curve analysis in the testing set

NB than the "treat all" or "treat none" strategies both in the training and testing sets (Fig. 5A and D).

Discussion

In the present study, a visualized nomogram was developed for the evaluation of IVIG-resistant in patients with KD. Seven variables were identified as potential predictors of IVIG-resistant in KD children, including globulin, RBC counts, weight, ALT, and APTT. The nomogram based on these factors exhibits good predictive performance in the training set and testing set, with an AUC of 0.781 and 0.749. Ultimately, the explicit goal of this nomogram was to assist pediatrics in identifying KD patients with high risk of IVIG-resistant.

One of the advantages of this article is that it incorporates coagulation indicator-related into the analysis and develops a visualized nomogram including APTT. Significantly, our primary emphasis on coagulation indicator-related stems from the recognition that inflammation triggered by acute infection can result in the activation of the coagulation system by up-regulating the expression of cytokines [13]. In addition, previous studies have shown the relationship between the coagulation system and the immune system in immune-mediated diseases [14]. The present study showed that shorter APTT was significantly associated with a higher rate of IVIG-resistant, which indicated that APTT may be a potential predictor of IVIG-resistant. However, only a few studies have previously determined the roles of APTT in IVIG-resistant. Shuran Shao et al. [9] in 2020 found that APTT was significantly increased in IVIG-resistant patients. Wei-Xing Kong et al. [15] in 2019 failed to find significant differences in APTT in IVIG-resistant patients and IVIG-sensitive patients. These observations are partly controversial and with small sample size. Additionally, many studies have shown that KD patients with IVIG-resistant are at a high risk of developing coronary artery thrombosis and stenoses, resulting in severe coronary artery lesions [16–18]. A few other studies conducted previously showed that a shortened APTT was correlated with acute arterial thrombosis [19, 20]. The activation of the coagulation system may be one of the factors contributing to the increased susceptibility of KD patients with IVIG-resistance to developing CALs.

Consistent with previous studies, the results in the present study manifest that the lower the value of RBC counts, the more likely the incidence of IVIG-resistant [21]. KD inflammatory reaction would alter the RBC homeostasis and affect the balance between RBC production and RBC clearance. Previous studies have confirmed that cytokines such as plasma IL-6 and TNF-α participate in inflammation during the acute phase of KD and were significantly elevated in IVIG IVIG-resistant patients compared with IVIG-sensitive patients [22–24]. IL-6 can reduce RBC production through various mechanisms. IL-6 is a key mediator of RBC because it regulates the hormone hepcidin, an acute-phase protein mainly produced by hepatocytes, limiting the iron supply for RBC [25, 26]. IL-6 has also been proven to inhibit the expression of erythropoietic cytokine erythropoietin in the kidney [27]. The TNF production induces PU.1 expression in hematopoietic stem cells (HSC) through NF-κB signaling [28]. Overexpression of PU.1 and TNF stimulation reduces the potential of HSC selfrenewal [29], thereby affecting the number of RBCs.

Our analysis also shows that the globulin, ALT, and weight were independent predictors of IVIG-resistant. Generally, globulin and ALT were identified as predictors of IVIG-resistant [21, 30, 31]. As shown in Table 2, the higher globulin and higher ALT were significantly associated with a higher risk of IVIG-resistant in the current analysis. The conclusions for the two variables were similar to the previous findings [21, 30, 31]. Such results are easy to understand because ALT is an important indicator of liver function in the body. The association of the degrees of hepatobiliary dysfunction with IVIG-resistant

in KD patients has been reported [32]. Globulin is a significant indicator of inflammation. Therefore, we hypothesize that patients with IVIG-resistant suffer more severe inflammatory responses compared to patients sensitive to IVIG and activate their monocyte/macrophage and T, B lymphocyte system, leading to higher levels of globulin.

In the present study, we developed a nomogram model consisting of five common variables in routine clinical practice to assess the risk of IVIG-resistant among KD patients. After receiving initial standardized treatment, the persistence of high inflammatory response in IVIG-resistant patients fails to block the pathological process of vasculitis timely, which results in a noticeably increased occurrence of CALs. As a simple tool to evaluate the efficacy of IVIG, the nomogram model in the present study could identify high-risk patients of IVIG-resistant early. More importantly, to ensure timely administration of the IVIG plus glucocorticoid therapy and enhance the monitoring of these patients to reduce the incidence of CALs.

There are several limitations to our study. Firstly, the nomogram in the present study lacks external validation and this model still needs the evaluation of external generalizability. To address this issue, detailed information about the study cohort was provided in Table 1 to be used directly in other medical institutions. Secondly, the present study has several inherent disadvantages typical of retrospective studies, such as such as collection and entry bias. For example, although data preprocessing has been carried out, the bias of cases of missing data could not be completely avoided. Finally, it is necessary for the nomogram developed in the present study to be further validated with external data.

Conclusions

In summary, the nomogram developed in the present study demonstrated good performance in predicting KD patients with IVIG-resistant, and APTT may be a potential predictor of IVIG-resistant. Results in the present study can provide meaningful insights into individualized information for KD patients and reveal new prognostic factors for those patients receiving IVIG.

Abbreviations

KD	Kawasaki disease
IVIG	Intravenous immunoglobulin
AUC	Area under curve
APTT	Activated partial thromboplastin time
CALs	Coronary artery lesions
ALT	Alanine aminotransferase
RBC	Red blood cell
HGB	Hemoglobin
VIF	Variance Inflation Factor
NB	Net benefit
HSC	Hematopoietic stem cells

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13052-025-01964-2.

Supplementary Material 1

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Author contribution

XL and YL formed the conception and study design. SC and SL did the data collection. XL did the data analysis. XL and YL drafted the manuscript. WZ and XY made significant revisions and supplied valuable improvement suggestions. All authors approved the final version. All authors have read and agreed to the published version of the manuscript.

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Data availability

The datasets used and analyzed in the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Quanzhou Women's and Children's Hospital's Ethic Committee. All procedures in this study involving human participants were carried out in line with the principles of Helsinki Declaration. As this study is a retrospective study, formal consent is not required.

Consent for publication

The written informed consent was waived because of the retrospective and anonymous nature of the data.

Competing interests

The authors declare no competing interests.

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