scientific reports

Check for updates

OPEN

The clinical value of dynamic monitoring of complete blood count in predicting immunoglobulin resistance in Chinese children with Kawasaki disease

Xiaoqian Fang

To examine changes in peripheral blood complete blood count (CBC) parameters during acute Kawasaki disease(KD), compare immunoglobulin(IVIG)-sensitive and IVIG-resistant groups, and develop an IVIG resistance model. A retrospective review of clinical and lab data from 282 KD patients (2014–2024) was conducted. CBC parameters were collected at initial, pre-IVIG, and post-IVIG stages. The rank-sum test assessed parameter differences over time. Patients were categorized into IVIG-resistant (n = 29) and IVIG-sensitive (n = 253) groups. Univariate and multivariate logistic regression analyses identified IVIG resistance risk factors, resulting in four predictive models (A, B, C, and D) based on blood changes and clinical experience. The models' effectiveness was evaluated using receiver operating characteristic (ROC) curves, the Hosmer–Lemeshow test, and decision curve analysis, with the bootstrap(BS) method confirming performance. Significant differences were found in post-IVIG blood parameters, including white blood cell count (WBC), neutrophils, lymphocytes, eosinophils, hemoglobin, platelets, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and mean platelet volume to lymphocyte ratio (MPVLR), compared to pre-IVIG and initial CBC ($P < 0.05$). In IVIG-resistant patients, NLR, PLR, MPVLR, neutrophil percentage were higher, while lymphocyte percentage was lower than in IVIG-sensitive patients ($P < 0.05$). The resistant group also showed smaller changes in neutrophil percentages (△N) and lymphocyte percentages (△L). Area under the curve (AUC) values for BS-ROC curves were as follows: model A: 0.758 (95% CI: 0.636–0.878), model B: 0.917 (95% CI: 0.852–0.982), model C: 0.949 (95% CI: 0.909–0.978), and model D (NLR post-IVIG administration combined with △L): 0.910 (95% CI: 0.857–0.963). Hosmer–Lemeshow test P values for all four models were > 0.05. DCA indicated clinical value for all models, especially model C. Blood routine parameters in children with KD vary over time, and IVIG administration alters these parameters. We developed and validated four prediction models for IVIG resistance in KD patients using blood routine data. This indicates that ongoing monitoring of these parameters can predict IVIG resistance and enhance patient outcomes.

Keywords Routine blood tests, Kawasaki disease, Immunoglobulin resistance

Kawasaki disease (KD) is an acute vasculitis of unknown origin, frequently seen in children and typically resolving on its own, with varying incidence rates reported across different regions. Coronary artery lesions (CAL) are the main complication of KD and the leading cause of acquired heart disease in children[1–3]. The main treatment for KD is intravenous immunoglobulin (IVIG) therapy and aspirin, a nonsteroidal anti-inflammatory drug[3]. It has been reported that timely IVIG administration can reduce the incidence of coronary artery dilation (CAA) during the acute phase from 25% to approximately 4%[3]. However,10%–20% of patients still have ongoing or recurring fever even after the initial IVIG treatment, indicating IVIG resistance, which significantly increases the risk of developing CAL[4,5]. Therefore, it is crucial to promptly identify IVIG sensitivity in KD patients.

Department of pediatrics department, Dongyang People's Hospital, Dongyang 322100, Zhejiang, China. email: Anita198706@163.com

Although various scoring systems have been developed globally to assess IVIG resistance in Kawasaki disease (KD) patients, their effectiveness in predicting IVIG resistance remains limited[6–8]. Among Asian cohorts, the Formosa score, one of the four scoring systems, showed the best sensitivity (0.76) for predicting IVIG resistance in KD, although its specificity was relatively low (0.46)[6]. Another meta-analysis externally validated five prediction models, all of which failed to accurately differentiate IVIG resistance in Kawasaki disease patients[9]. These findings suggest that the predictive accuracy of current scoring systems is still limited. Several risk factors for IVIG resistance in KD have been identified in previous studies, including the administration of IVIG within 4.0 days of symptom onset, elevated erythrocyte sedimentation rate (ESR), low hemoglobin and platelet counts, changes in the oral mucosa, cervical lymphadenopathy, limb swelling, polymorphic rash, increased neutrophil count, and higher neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR)[6,10]. Among these factors, hemoglobin, platelet count, NLR, and PLR are all derived from the complete blood count (CBC), a simple and widely available test. Studies have shown significant changes in CBC parameters during different stages of KD. For instance, the neutrophil percentage and NLR peak on the third day of illness, WBC and CRP levels peak on the fourth day, hemoglobin levels peak on the seventh day, and platelet count peaks around the same time[11]. Therefore, developing a prediction model for IVIG resistance in KD patients based on CBC parameters is feasible.

This study retrospectively collected clinical and laboratory data from KD patients, with the aim of establishing a CBC-based prediction model to assess IVIG resistance in KD.

Materials and methods

Participants

We conducted a retrospective review of collected clinical data from Kawasaki disease (KD) patients under 14 years of age who were hospitalized in our institution from June 2014 to June 2024. Diagnosis of KD followed the 2017 guidelines set by the American Heart Association (AHA)[3]. The diagnostic criteria include a sustained fever reaching 39℃ or above for a duration exceeding 5 days, along with at least four of the following five major clinical signs: (1) bilateral conjunctival injection, (2) polymorphic rash, (3) changes in oral mucosa, (4) erythema or other changes of the palms and soles, and (5) non-purulent cervical lymphadenopathy. Exclusion criteria were: (1) prior IVIG or corticosteroid treatment in other hospitals, (2) readmission due to KD recurrence, (3) history of congenital heart disease (e.g., coronary artery aneurysms), (4) presence of severe cardiovascular, hepatic, renal, metabolic, or hematologic diseases, (5) Incomplete medical history, laboratory data, or relevant auxiliary examination records (e.g., missing blood routine data within 36 h before and after IVIG administration), and (6) IVIG was not used, or allergic reactions interrupt its used, as shown in Fig. 1. This study was retrospective, utilizing existing data, and no sample size was calculated.

The retrospective study received the green light from the Ethics Committee at Dongyang People's Hospital (Approval No: 2024-YX-282). Since the study utilized general patient information, including medical history and data collected from existing records and databases, it was determined that written informed consent from participants was not required.

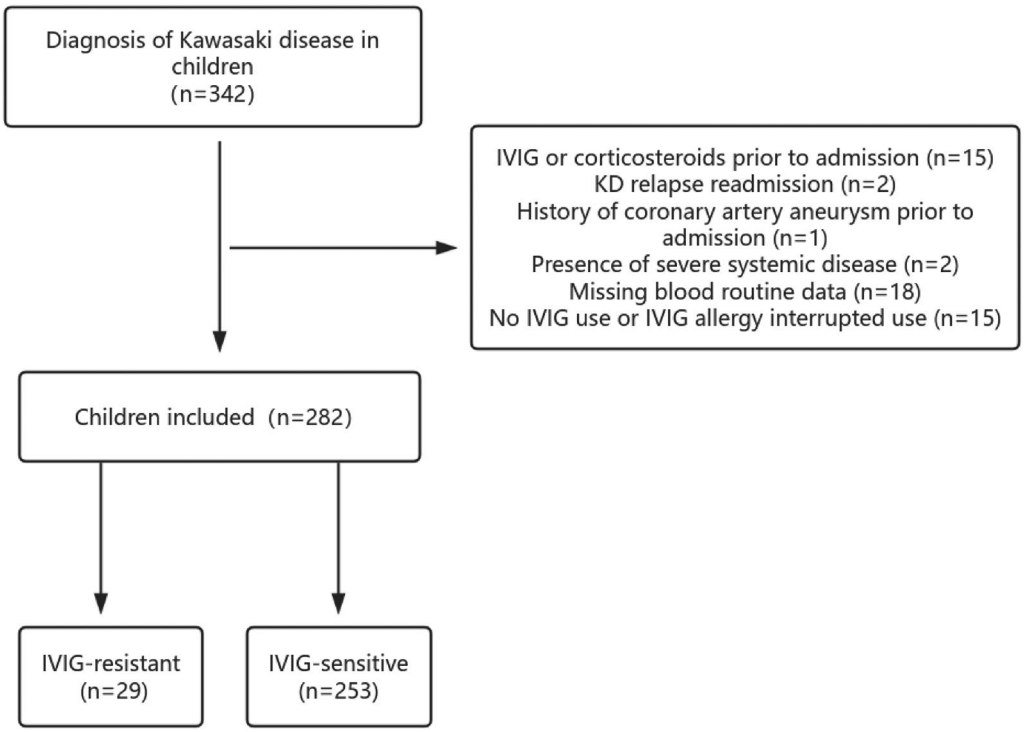

Fig. 1. Flow chart.

Definition of IVIG non-responsiveness

Following the diagnosis of Kawasaki disease (KD), all patients received standardized treatment[3], which included intravenous administration of 2 g/kg IVIG and oral aspirin at 30–50 mg/kg/day. After the fever subsided for 48–72 h, the aspirin dose was reduced to 3–5 mg/kg/day and maintained for 6–8 weeks. IVIG resistance was characterized by a continuous or returning fever exceeding 38.0°C that persisted for over 36 h following the first IVIG infusion[3]. Patients who met this criterion administered an additional 2 g/kg of IVIG or were treated with corticosteroids.

Complete blood count (CBC)

Peripheral blood samples were obtained from all patients at three different time points: during the first CBC upon admission to our hospital, within 36 h prior to IVIG administration, and within 36 h following IVIG administration. A 2 mL sample was collected in an EDTA tube and analyzed using a Sysmex XN-900 hematology analyzer (including XN-20, XN-10, SP-10, DI-60 systems). The main parameters evaluated included white blood cell count (WBC), neutrophil (NEU) percentage, lymphocyte (LYM) percentage, platelet (PLT) count, and hemoglobin (Hb) concentration.

Data collection

Upon admission, clinical data and demographic were collected, such as gender, age, body mass index (BMI), as well as the first CBC upon admission and CBC data before and after IVIG treatment. The collected CBC parameters included white blood cell count (WBC), neutrophil (NEU) percentage, lymphocyte (LYM) percentage, platelet (PLT) count, hemoglobin (Hb) concentration, C-reactive protein (CRP) concentration, mean platelet volume (MPV), and platelet distribution width (PDW). The neutrophil to lymphocyte ratio (NLR) was defined as the ratio of NEU to LYM, the platelet to lymphocyte ratio (PLR) as the ratio of PLT to LYM, and the mean platelet volume to lymphocyte ratio (MPVLR) as the ratio of MPV to LYM. The difference before and after treatment was denoted by $\triangle$, such as $\triangle$WBC for the difference in white blood cell count, $\triangle$CRP for the difference in CRP concentration, $\triangle$Hb for the difference in hemoglobin, $\triangle$N for the difference in neutrophil percentage, $\triangle$L for the difference in lymphocyte percentage, $\triangle$PLT for the difference in platelet count, and $\triangle$RBC for the difference in red blood cell count. Have other doctors in the department randomly review the data. Patients with missing blood routine data within 36 h before and after IVIG administration were excluded. For other questionable data, use the median replacement method if manual corrections aren't possible, ensuring replacements don't exceed 10%.

Statistical analysis

Statistical analysis was carried out with R version 4.3.1 software. The distribution of data was examined for normality using the Shapiro–Wilk test, and variance homogeneity was evaluated accordingly. Continuous variables were presented as median with interquartile range (IQR) or mean ± standard deviation (mean ± SD). For normally distributed data, group comparisons were performed using the independent two-sample t-test, while the Mann–Whitney U test was used for non-normally distributed data. Categorical data were expressed as percentages (%), and group comparisons were made using Fisher's exact test or the Chi-square test. Significantly differing variables in univariate analysis were used in logistic regression to determine independent risk factors for IVIG resistance and to create models. To evaluate the models' effectiveness, receiver operating characteristic (ROC) curves, the Hosmer–Lemeshow test, and decision curve analysis were employed, and the bootstrap method was used to confirm their performance. A p-value of less than 0.05 was regarded as statistically significant.

Results

Clinical characteristics of KD patients

This study included 282 children diagnosed with Kawasaki disease (KD) comprising 184 males (65.25%) and 98 females (34.75%), with a median age of 26 months. Among the 282 KD patients, 29 (10.28%) exhibited IVIG resistance. The changes in CBC parameters during the entire treatment process for KD patients are presented in Table 1. Demographic information, clinical characteristics, and laboratory parameters for the grouped KD patients are shown in Table 2.

The results revealed that, compared with pre-IVIG treatment, the percentage of lymphocytes, eosinophils, and platelet count (PLT) significantly increased after IVIG treatment, while the percentage of neutrophils, red blood cell (RBC) count, hemoglobin (Hb), platelet distribution width (PDW), C-reactive protein (CRP), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and mean platelet volume to lymphocyte ratio (MPVLR) significantly decreased, with statistical significance ($P < 0.05$).

In the IVIG-resistant group, NLR, PLR, MPVLR, neutrophil percentage before and after treatment, RBC count, post-treatment CRP and white blood cell count (WBC), and pre-treatment MPV were all higher than in the sensitive group ($P < 0.05$). The percentage of lymphocytes, monocytes, pre-treatment PLT, post-treatment Hb, and eosinophil percentage were all lower in the resistant group ($P < 0.001$). Additionally, the changes in CRP ($\triangle$CRP), neutrophil percentage ($\triangle$N), and lymphocyte percentage ($\triangle$L) were smaller, while the change in Hb ($\triangle$Hb) was larger in the resistant group ($P < 0.05$). The resistant group was slightly older than the sensitive group ($P = 0.049$), but no significant differences were observed between the two groups with respect of gender, BMI, pre-treatment WBC, Hb, or CRP ($P > 0.05$).

Risk factors for IVIG resistance in KD and development of a predictive model using CBC

Univariate logistic regression analysis revealed that elevated NLR, PLR, and MPVLR were significant risk factors for IVIG resistance in KD patients ($P < 0.05$). Using multivariate logistic regression, we developed three predictive models based on CBC parameters: Model A (before IVIG), Model B (after IVIG), and Model C

	The first time	Before using IVIG	After using IVIG	p Value
WBC ($\times 10^9$/L)	14.40 [11.10, 18.03]	14.26 [10.80, 17.35]	9.00 [6.87, 12.47] [bc]	< 0.001
Neutrophil (%)	0.68 [0.61, 0.77]	0.68 [0.59, 0.75]	0.35 [0.25, 0.44] [bc]	< 0.001
Lymphocyte (%)	0.22 [0.15, 0.30]	0.23 [0.17, 0.31]	0.53 [0.43, 0.62] [bc]	< 0.001
Monocyte (%)	0.06 [0.05, 0.08]	0.06 [0.05, 0.08]	0.06 [0.05, 0.08]	0.906
Eosinophilic Granulocyte (%)	0.01 [0.00, 0.02]	0.02 [0.01, 0.03] [a]	0.03 [0.02, 0.06] [bc]	< 0.001
RBC($\times 10^{12}$/L)	4.27 [4.10, 4.58]	4.16 [3.97, 4.38] [a]	4.07 [3.82, 4.31] [bc]	< 0.001
Hemoglobin (g/L)	114.00 [108.00, 120.00]	110.00 [104.00, 116.00] [a]	107.00 [101.00, 113.00] [bc]	< 0.001
Platelet ($\times 10^9$/L)	341.50 [273.25, 407.75]	364.00 [293.25, 438.75] [a]	496.00 [411.00, 598.00] [bc]	< 0.001
Platelet Distribution Width (fl)	10.50 [9.20, 15.20]	10.40 [9.20, 11.95]	9.80 [8.90, 10.88] [bc]	< 0.001
Mean platelet volume (fl)	9.30 [8.80, 9.88]	9.30 [8.60, 9.90]	9.20 [8.70, 9.70]	0.213
CRP (mg/L)	49.84 [29.33, 84.26]	60.03 [33.03, 89.62]	15.50 [6.29, 37.93] [bc]	< 0.001
NLR	3.04 [2.01, 5.16]	2.92 [1.91, 4.33]	0.65 [0.41, 1.02] [bc]	< 0.001
PLR	116.07 [85.35, 161.50]	119.04 [88.90, 169.18]	107.41 [77.97, 152.84] [c]	0.036
MPVLR	3.20 [2.29, 4.75]	3.05 [2.15, 4.59]	2.01 [1.45, 2.74] [bc]	< 0.001

Table1. Blood routine changes of KD patients. Data are presented as median interquartile range [IQR]. IVIG: immunoglobulin; WBC: white blood cell; RBC: red blood cell; CRP:C-reactive protein; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; MPVLR: mean platelet volume to lymphocyte ratio. a: Statistical difference between before medication and the first time blood routine. b: statistical difference between after medication and the first time blood routine. c: Statistical difference after medication and before medication.

(before and after IVIG). Model A revealed that elevated PLR and MPV were independent risk factors for IVIG resistance. Meanwhile, Models B and C, identified elevated NLR and PLR as independent risk factors for IVIG resistance, and in Model C, the smaller △L in the resistant group was also noted, as shown in Table 3. Based on clinical experience and data analysis, we found that NLR post-IVIG and △L changed significantly, and we constructed a prediction model (Model D) for the combination of both.

Predictive ability of CBC for IVIG resistance in KD

ROC curves and AUC were utilized to evaluate the predictive ability of various CBC parameters and models at different time points for IVIG resistance in KD. As shown in Fig. 2 and Table 3, the post-treatment NLR demonstrated higher predictive ability for IVIG resistance, with an AUC of 0.855 (95% CI 0.767–0.941). The pre-treatment NLR had an AUC of 0.660 (95% CI 0.524–0.776), while the post-treatment PLR had an AUC of 0.639 (95% CI 0.535–0.742). The AUC for the pre- and post-treatment △L was 0.852 (95% CI 0.794–0.907), and the combined post-treatment NLR and △L had an AUC of 0.878 (95% CI 0.811–0.943). The AUC for the pre-treatment CBC model (Model A) was 0.751 (95% CI 0.648–0.854), and the post-treatment CBC model (Model B) had an AUC of 0.859 (95% CI 0.767–0.949). The model that incorporated both before and after treatment data (Model C) showed significantly higher predictive power than Models A and B, with an AUC of 0.906 (95% CI 0.854–0.958), as shown in Figs. 2 and 3.

Verification of predictive models

We calculated the BS AUC values for four models using 500 bootstrap resamplings: model A: 0.758 (95% CI: 0.636–0.878), model B: 0.917 (95% CI: 0.852–0.982), model C: 0.949 (95% CI: 0.909–0.978), and model D: 0.910 (95% CI: 0.857–0.963), as shown in Fig. 4. Models B, C, and D demonstrate strong predictive ability. The Hosmer–Lemeshow test P values for all models were above 0.05 (P = 0.159, 0.556, 0.151, and 0.531), confirming consistency. Decision plots indicate net benefits for all models, with model B effective at threshold probabilities 0.03–0.83 and model C at 0.03–0.99. Models B and C were promising predictive tools for IVIG resistance in children with KD, as shown in Fig. 5.

Discussion

The etiology and pathogenesis of Kawasaki disease (KD) remain incompletely understood. However, it is primarily characterized by an inflammatory response that predominantly affects medium- and small-sized blood vessels. Coronary artery damage is the most serious and characteristic complication of Kawasaki disease (KD) and serves as a major cause of acquired heart disease in children[1,12]. Early diagnosis and timely administration of intravenous immunoglobulin (IVIG) and aspirin can greatly lower the chances of coronary artery dilation[3]. However, 10%-20% of patients experience recurrent fever, indicating IVIG resistance or lack of response, which increases the risk of coronary damage. Consequently, identifying markers related to IVIG resistance in KD

	Sensitive group (n = 253)	Resistance group (n = 29)	*p* Value
Gender, n (%)			0.159
Female	84 (33.20%)	14 (48.28%)	
Male	169 (66.80%)	15 (51.72%)	
BMI	16.36 [15.22;17.42]	15.86 [14.73;17.75]	0.929
Age (month)	25.00 [14.00;44.00]	37.00 [18.00;59.00]	**0.049**
CAL, n(%)			0.164
0	232 (91.70%)	24 (82.76%)	
1	21 (8.30%)	5 (17.24%)	
WBC.1($\times 10^9$/L)	14.39 [11.12;18.00]	14.41 [9.90;19.02]	0.756
WBC. before	14.29 [10.80;18.00]	13.81 [11.56;16.20]	0.434
WBC. after	8.70 [6.79;11.73]	12.00 [8.55;16.00]	**0.004**
Neutrophil.1 (%)	0.68 [0.60;0.76]	0.76 [0.61;0.82]	0.070
Neutrophil. before	0.67 [0.59;0.74]	0.74 [0.62;0.82]	**0.013**
Neutrophil. after	0.33 [0.24;0.41]	0.61 [0.46;0.70]	**< 0.001**
Lymphocyte.1 (%)	0.22 [0.15;0.30]	0.15 [0.12;0.26]	**0.033**
Lymphocyte. before	0.23 [0.18;0.31]	0.16 [0.09;0.27]	**0.007**
Lymphocyte. after	0.55 [0.46;0.63]	0.27 [0.22;0.40]	**< 0.001**
Monocyte.1 (%)	0.06 [0.05;0.08]	0.06 [0.04;0.07]	**0.035**
Monocyte. before	0.06 [0.05;0.08]	0.05 [0.04;0.06]	**0.010**
Monocyte. after	0.06 [0.05;0.08]	0.05 [0.04;0.07]	**0.042**
Eosinophilic granulocyte.1 (%)	0.01 [< 0.01;0.03]	0.01 [< 0.01;0.02]	0.216
Eosinophilic granulocyte. before	0.02 [0.01;0.03]	0.02 [< 0.01;0.03]	0.452
Eosinophilic granulocyte. after	0.03 [0.02;0.06]	0.02 [0.01;0.05]	**0.039**
RBC.1 ($\times 10^{12}$/L)	4.28 [4.11;4.59]	4.23 [4.03;4.53]	0.414
RBC. before	4.18 [4.01;4.40]	4.03 [3.86;4.15]	**0.005**
RBC. after	4.07 [3.86;4.32]	3.68 [3.58;4.19]	**0.002**
Hemoglobin.1 (g/L)	114.00 [108.00;120.00]	116.00 [106.00;122.00]	0.891
Hemoglobin. before	110.00 [104.00;116.00]	107.00 [102.00;113.00]	0.178
Hemoglobin. after	107.00 [102.00;113.00]	102.00 [95.00;107.00]	**0.006**
PLT.1 ($\times 10^9$/L)	343.00 [277.00;407.00]	339.00 [260.00;416.00]	0.414
PLT. before	366.00 [300.00;450.00]	338.00 [264.00;395.00]	**0.047**
PLT. after	496.00 [414.00;604.00]	430.00 [341.00;577.00]	0.051
MPV.1 (fl)	9.30 [8.80;9.80]	9.50 [9.10;9.90]	0.187
MPV. before	9.20 [8.60;9.90]	9.60 [9.20;10.20]	**0.016**
MPV. after	9.20 [8.70;9.70]	9.10 [8.80;9.70]	0.687
PDW.1 (fl)	10.50 [9.20;15.20]	10.80 [9.00;12.50]	0.981
PDW. before	10.40 [9.10;12.00]	10.40 [9.40;11.80]	0.684
PDW. after	9.80 [8.80;10.80]	9.80 [9.30;11.80]	0.116
CRP.1 (mg/L)	49.26 [29.21;86.70]	53.05 [32.00;72.78]	0.986
CRP. before	59.26 [33.00;88.00]	64.02 [35.31;101.45]	0.851
CRP. after	15.00 [5.61;30.60]	53.05 [22.07;66.00]	**< 0.001**
NLR.1	2.99 [2.00;4.88]	4.91 [2.38;6.87]	**0.040**
NLR. before	2.89 [1.88;4.18]	4.65 [2.39;9.47]	**0.008**
NLR. after	0.62 [0.39;0.91]	2.04 [1.15;3.27]	**< 0.001**
PLR.1	112.95 [85.06;157.17]	150.89 [101.53;232.73]	**0.032**
PLR. before	115.80 [86.67;166.61]	188.10 [96.13;282.73]	**0.008**
PLR. after	104.85 [77.16;151.84]	128.75 [106.56;176.33]	**0.015**
MPVLR.1	3.10 [2.22;4.50]	4.53 [3.38;5.78]	**0.002**
MPVLR. before	2.93 [2.08;4.20]	5.40 [3.04;7.52]	**< 0.001**
MPVLR. after	1.95 [1.42;2.68]	2.53 [2.08;3.95]	**0.001**
△WBC($\times$109/L)	− 4.16 [− 7.81;-0.43]	− 1.84 [− 4.30;1.91]	**0.003**
△N (%)	− 0.33 [− 0.41;-0.25]	− 0.16 [− 0.23;-0.09]	**< 0.001**
Continued			

	Sensitive group (n = 253)	Resistance group (n = 29)	*p* Value
△L (%)	0.30 [0.22;0.38]	0.12 [0.07;0.18]	**< 0.001**
△Hb(g/L),	− 3.00 [-8.00;2.00]	− 5.00 [− 9.00;-2.00]	**0.031**
△CRP (mg/L)	− 37.42 [− 63.00;-14.30]	− 8.72 [− 28.63;19.30]	**< 0.001**
△PLT(× 109/L)	123.00 [59.00;204.00]	85.00 [47.00;174.00]	0.430
△RBC (× 1012/L)	− 0.11 [− 0.29;0.07]	− 0.19 [− 0.38;0.00]	0.257

Table 2. Differential analysis of IVIG sensitive and drug resistant groups. Data are presented as median [IQR], n (%). MPV: Mean platelet volume; PDW: Platelet Distribution Width. .1: the first complete blood count upon admission; .before: the complete blood count data before IVIG treatment; .after: the complete blood count data after IVIG treatment. △: the difference before and after IVIG treatment.

	Univariate logistic analysis		Multivariate logistic analysis					
			Model A[1]		Model B[2]		Model C[3]	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	1.02 (1.01 ~ 1.03)	**0.007**						
MPV-before	1.62 (1.10 ~ 2.37)	**0.013**	1.59 (1.06 ~ 2.38)	**0.026**				
RBC-before	0.28 (0.10 ~ 0.80)	**0.017**	0.32 (0.11 ~ 0.97)	**0.044**			0.20 (0.06 ~ 0.72)	**0.014**
NLR-before	1.12 (1.05 ~ 1.20)	**< 0.001**						
PLR-before	1.01 (1.01 ~ 1.01)	**< 0.001**	1.01 (1.01 ~ 1.01)	**< 0.001**			1.01 (1.01 ~ 1.01)	**0.049**
MPVLR-before	1.22 (1.11 ~ 1.35)	**< 0.001**						
NLR-after	3.88 (2.52 ~ 5.98)	**< 0.001**			5.84 (3.21 ~ 10.63)	**< 0.001**	2.71 (1.28 ~ 5.74)	**0.009**
PLR-after	1.01 (1.01 ~ 1.01)	**0.008**			0.99 (0.98 ~ 0.99)	**0.032**	0.99 (0.98 ~ 0.99)	**0.016**
RBC-after	0.22 (0.08 ~ 0.60)	**0.003**			0.22 (0.07 ~ 0.72)	**0.012**		
△WBC	1.12 (1.04 ~ 1.21)	**0.002**						
△N	534.57 (43.33 ~ 6595.28)	**< 0.001**						
△L	0.00 (0.00 ~ 0.01)	**< 0.001**					0.00 (0.00 ~ 0.45)	**0.024**
△Hb	0.95 (0.91 ~ 0.99)	**0.034**					0.92 (0.86 ~ 0.99)	**0.028**
MPVLR-after	1.54 (1.22 ~ 1.94)	**< 0.001**						

Table 3. Construction of the predictive model. Model A1 was Before IVIG; Model B2 was After IVIG; Model C3 was incorporated both before and after IVIG treatment data. Significant values are in bold.

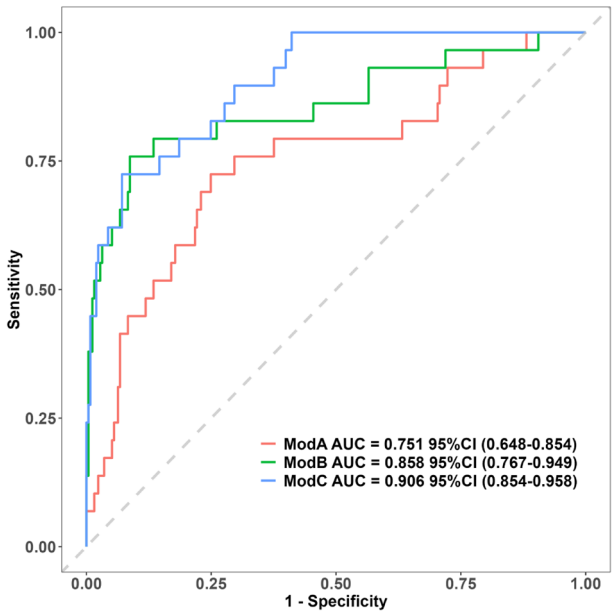

Fig. 2. The ROC plot of the prediction models.

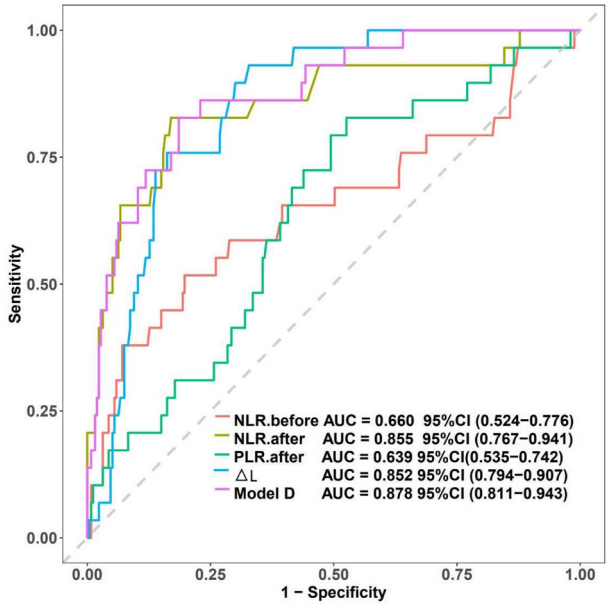

Fig. 3. Predictive ability of various conventional blood parameters for immunoglobulin resistance in KD.

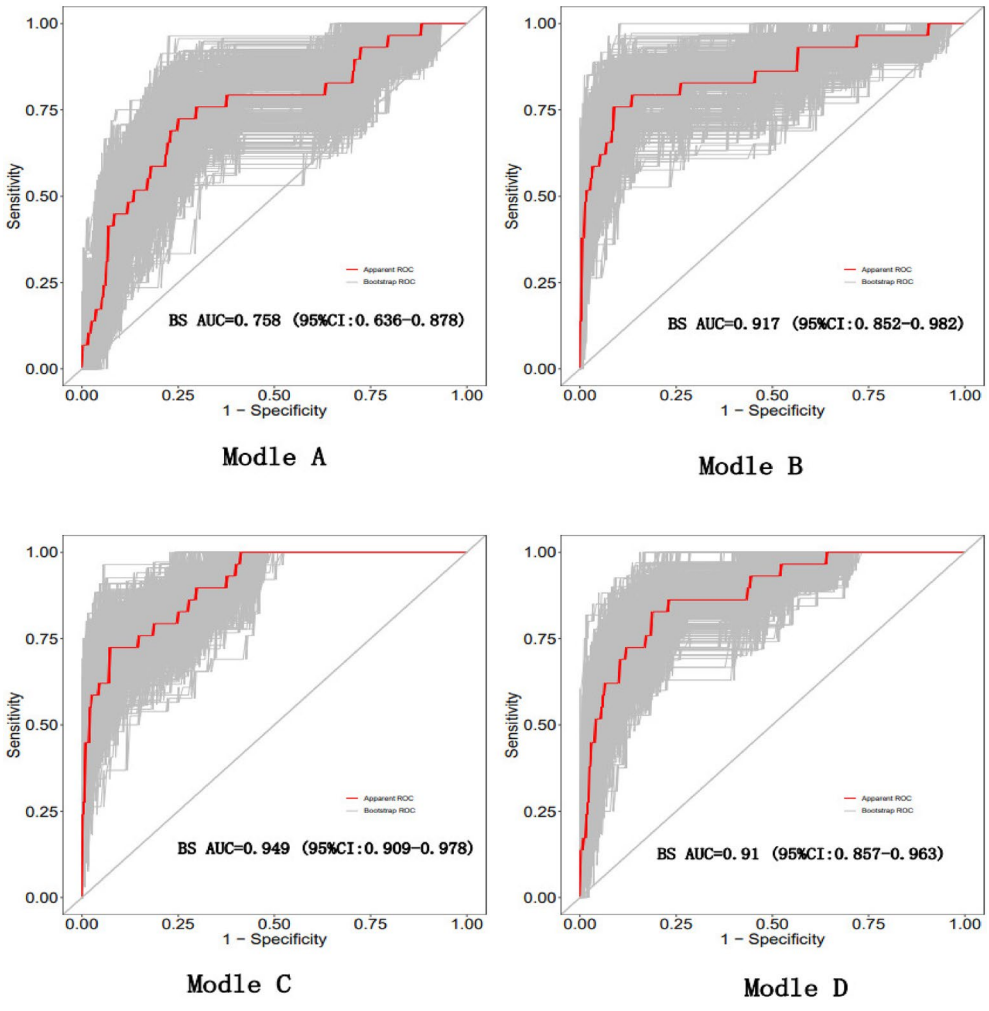

Fig. 4. The BS-ROC plot of four prediction models.

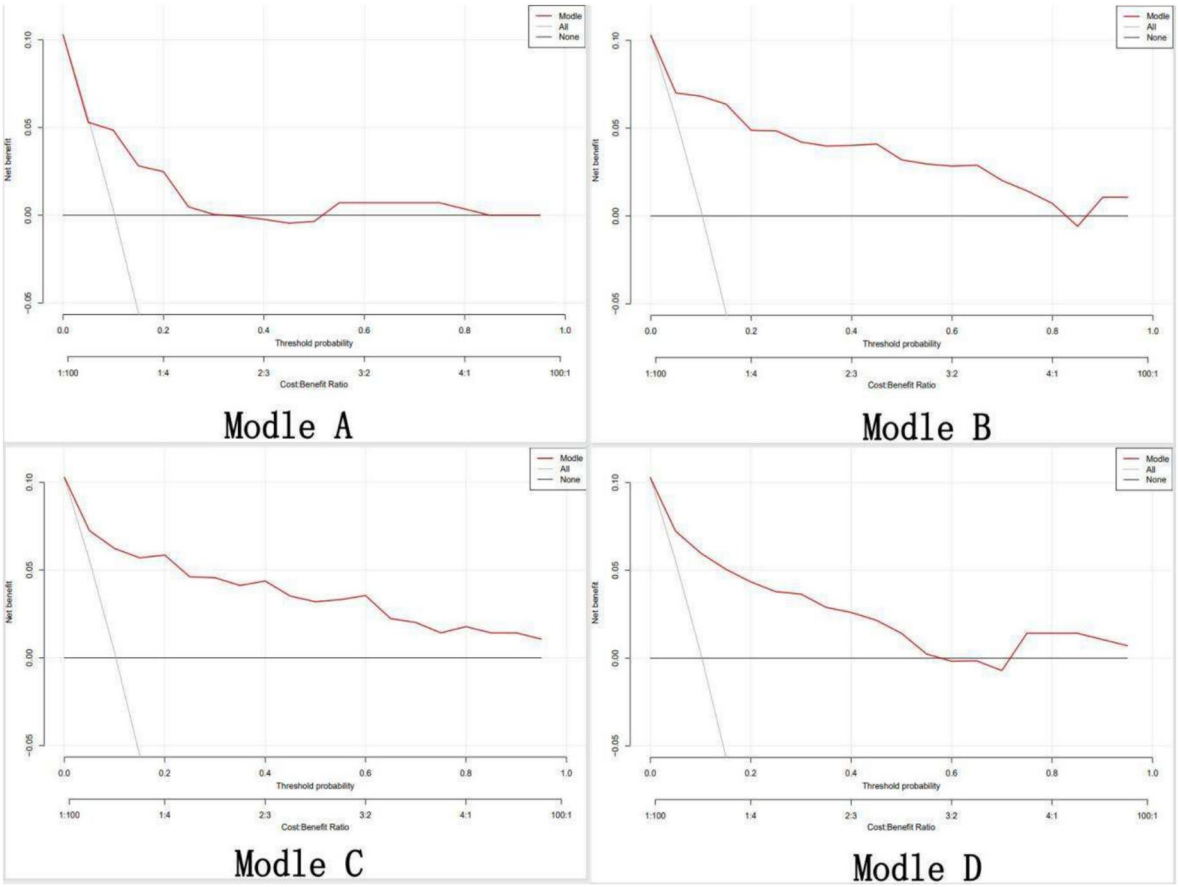

Fig. 5. DCA of four prediction models.

quickly, accurately, and conveniently remains a clinical research focus. An increasing body of research has demonstrated that many parameters in the complete blood count (CBC), such as white blood cells (WBC), platelets (PLT), neutrophils (NEU), lymphocytes (LYM), NLR, and PLR, change during different stages of KD, and several studies have demonstrated that these CBC parameters, including WBC, neutrophils, platelets, NLR, and PLR, hold good predictive value for IVIG resistance and the development of coronary artery dilation in KD[13–17]. Therefore, this study focused on examining the changes in CBC parameters before and after IVIG administration in KD patients, with the aim of developing a predictive model for IVIG resistance based on CBC data.

We analyzed data from 282 children to investigate the dynamic changes in CBC parameters during the course of KD and to identify factors associated with IVIG resistance. Several models were developed based on these findings. Our results indicated statistically significant differences in various CBC parameters before and after IVIG administration, including WBC count, lymphocyte ratio, eosinophil percentage, platelet count, hemoglobin (Hb), RBC, NLR, PLR, and MPVLR. Additionally, there were significant differences in neutrophil and lymphocyte percentages, △WBC, △N, △L, and △Hb between the IVIG-resistant group and the sensitive group. These results could be linked to the vascular inflammation seen in KD.

Kawasaki disease is a vascular inflammatory condition, and peripheral blood leukocyte counts and their subtypes are typical markers of inflammation. According to the pathophysiology of KD, early-stage neutrophil infiltration in the coronary arteries produces inflammatory cytokines, leading to endothelial damage, while lymphocytes, which possess anti-inflammatory properties, become dominant in the later stages and contribute to the immune response[18]. The NLR represents a combination of neutrophils and lymphocytes and is regarded as an indicator of the inflammatory and immune balance. Therefore, NLR is elevated during the acute phase of KD and gradually decreases in the later stages. In our study of 282 children, the lymphocyte percentage significantly increased after IVIG treatment compared to before or at the first measurement, while the neutrophil percentage markedly decreased. The NLR also gradually declined, consistent with the pathophysiology of KD. Additionally, numerous studies have shown that high NLR and PLR are positively correlated with inflammatory responses and are closely related to IVIG resistance and coronary artery dilation[14,19,20]. In our study, the IVIG-resistant group exhibited a higher neutrophil percentage, while the sensitive group had a higher lymphocyte percentage. After IVIG administration, the sensitive group was predominantly lymphocytes, whereas the resistant group remained neutrophil-dominant. Furthermore, the change in lymphocyte percentage in the sensitive group was more pronounced than in the resistant group. This aligns with the inflammatory role of neutrophils and the anti-inflammatory properties of lymphocytes. In the sensitive group, IVIG effectively suppressed the inflammatory

response, whereas the resistant group showed limited effects. This phenomenon may be attributed to the ability of IVIG to induce neutrophil apoptosis in a dose-dependent manner and to inhibit the formation of neutrophil extracellular traps. Additionally, it may be linked to alterations in lymphocyte subsets, including T and B lymphocytes, as a result of the immunoregulatory functions of IVIG. For example, IVIG has been shown to inhibit T cell proliferation and modulate T cell differentiation. Furthermore, it interferes with the interaction between natural killer (NK) cells and other cell types, leading to enhanced activity of NK cells and an increase in circulating CD16 + cells[21]. Both NLR and PLR, whether before or after treatment, the levels in the resistant group surpassed those in the sensitive group. These findings indicate that the inflammatory response is more intense in the resistant group, aligning with previous studies[14,20] and aligns with the overall pathophysiological process and the mechanism of IVIG action.

Japanese researchers have reported that in a study of 979 children across 230 hospitals, mild anemia commonly developed 1–2 days after IVIG administration, with levels returning to baseline around one week later[22]. Age-related anemia is also one of the diagnostic criteria for incomplete Kawasaki disease[3]. In line with these findings, our study shows a decrease in hemoglobin levels following IVIG administration in Kawasaki disease patients, which is consistent with the Japanese study. Additionally, our research indicates that the decrease in hemoglobin levels is more pronounced in the IVIG-resistant group, indirectly supporting the notion that a significant reduction in hemoglobin is a risk factor for coronary artery lesions (CAL) in KD patients[23,24]. This could be linked to the inflammatory response, which results in a decrease in hemoglobin levels. Previous research has indicated a relationship between hemoglobin levels and inflammatory markers like SII and CRP[25,26]. This phenomenon may also be associated with hemolysis subsequent to the administration of IVIG. A systematic review of multiple studies in the literature indicates that hemolysis occurs in 0–20% of patients following IVIG administration, with approximately 11% of patients experiencing hemolysis at a dosage of 2 g/kg[27]. Therefore, hemoglobin levels may significantly decrease during the acute phase of Kawasaki disease.

Besides white blood cell counts and its subtypes, as well as hemoglobin, our study also noted significant changes in platelet-related parameters before and after IVIG treatment. We found that platelet count significantly increased after IVIG administration, while PDW and MPVLR decreased. However, there was no significant change observed in MPV before and after treatment. Regarding the comparison between the IVIG-resistant and sensitive groups, there were differences in PLT and MPV before treatment, but no differences after treatment. Both groups showed statistically significant changes in MPVLR before and after treatment, whereas PDW did not show any significant changes.

According to literature, platelets are activated during the acute phase of KD, with platelet counts typically increasing 2–3 weeks after onset and then returning to normal levels. During this period, platelets activate and release myosin light chain 9(Myl9), which aggregates with neutrophils, lymphocytes, and macrophages at sites of thrombosis or inflammation, exacerbating inflammation and initiating thrombosis[15,28]. Plasma Myl9 levels in patients with KD exhibited a significant increase during the acute phase, followed by a decrease in response to successful IVIG treatment and subsequent recovery. Conversely, Myl9 levels did not decrease in pediatric patients who failed to respond to IVIG therapy. These findings indicate that IVIG may contribute to the attenuation of inflammation through the reduction of Myl9 level[28]. Additionally, PDW and MPV, which indicate changes in platelet size, activity, and aggregation ability, are reported to be lower in KD patients compared to healthy individuals[29]. However, some studies have reported no significant differences in platelet count, MPV, or PDW before and after IVIG administration between the two groups[29–31]. In our study, the IVIG administration time was generally between 5 to 10 days. As a result, platelet counts increased after treatment, while PDW decreased, and there was no difference in MPV. There was a difference in PLT and MPV before treatment, but no difference after treatment, which contrasts with the results reported in the literature. This observation may be influenced by the limited data available in the current literature or the concurrent administration of high-dose aspirin, which is known to inhibit the enhancement of platelet aggregation by CD40L through the suppression of myosin light chains[32]. Some studies suggest that MPVLR (mean platelet volume to lymphocyte ratio) is a good indicator for predicting short-term adverse cardiovascular outcomes in patients with ST-segment elevation myocardial infarction and may serve as a potential new biomarker for inflammation and thrombosis[33]. Our findings align with this, as MPVLR was significantly higher in the IVIG-resistant group compared to the sensitive group before and after treatment. This is consistent with our observation of statistical differences in MPVLR before and after IVIG treatment between the two groups in Kawasaki disease patients. However, since MPVLR is the ratio of MPV to lymphocyte count, and no significant difference in MPV was observed between groups before or after IVIG treatment, we should be cautious in interpreting these differences in MPVLR, as they might be influenced by lymphocyte count variations.

Various scoring systems have been developed globally to assess the risk of IVIG resistance in Kawasaki disease (KD) patients, tailored to different populations and regions[6,34]. However, these scoring systems are relatively complex and exhibit significant regional variations. IVIG serves as the primary therapeutic intervention for KD, effectively engaging with various immune cells, including platelets, neutrophils, and B cells, through binding to Fcγ receptors, thereby attenuating cytokine release[21]. Routine peripheral blood examinations, encompassing parameters such as platelet, neutrophil, and lymphocyte counts, are straightforward to conduct and broadly applicable. In this study, all four models exhibited strong predictive value, consistency, and net benefit; however, each model also presented specific limitations. Model A demonstrated relatively low predictive capability, whereas Model B yielded a singular result post-administration, susceptible to influences such as sampling time and blood concentration. Model C incorporated an extensive dataset, yet its clinical applicability was limited. Based on the pathophysiology of Kawasaki disease and the mechanism of action of IVIG, it was observed that the transformation of neutrophils or lymphocytes was particularly notable. The NLR and the change in lymphocyte count ($\triangle$L) of 282 patients exhibited significant alterations following IVIG treatment. Consequently, although Model D demonstrated commendable predictive value, it did not confer as substantial a net benefit as Model BC.

There are several limitations to this study. Firstly, being a single-center retrospective study, it is subject to inherent selection bias. Additionally, the sample size is relatively small, particularly for cases of IVIG resistance. Second, the study covers a long period, with IVIG treatment administered between 5 and 10 days after disease onset, which introduces potential timing bias in blood sample collection. Considering the natural course of Kawasaki disease, this could lead to bias. Third, during the data processing phase, patients were excluded if a complete blood count was not available within 36 h before or after the administration of IVIG. In certain instances, the blood test conducted prior to medication administration was the initial test, resulting in data duplication. For a limited number of cases with abnormal data, the median imputation method was employed when manual correction was unfeasible, which may have introduced bias. Fourth, the etiology and pathogenesis of KD remain incompletely understood; various factors, including genetic, immunological, infectious, and environmental influences, may interact. However, these interactions have not been explored in this study. Therefore, it is necessary to conduct larger, multicenter, prospective studies involving diverse populations to externally validate this model.

Conclusion

This study observed significant differences before and after IVIG treatment. Additionally, significant differences in blood routine parameters were also found between the sensitive and resistant groups, particularly lymphocyte-related parameters such as lymphocyte percentage, NLR, PLR, and MPVLR. Increased NLR, PLR, and MPVLR were identified as risk factors for IVIG resistance in KD patients. Post-treatment NLR and the change in lymphocyte percentage before and after treatment showed good predictive value for IVIG resistance. Continuous monitoring of peripheral blood routine tests can help assess IVIG resistance in a timely manner and improve the prognosis of KD patients.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Received: 2 January 2025; Accepted: 20 May 2025
Published online: 23 May 2025

References

1. Miura, M. et al. Association of Severity ofrtery Aneurysms in Patients With Kawasaki Disease and Risk of Later Coronary Events. *JAMA Pediatr.* **172**, e180030 (2018).
2. Day-Lewis, M., Beth, F. M. & Lo, M. Kawasaki disease: Contemporary perspectives. *Lancet Child Adolesc. Health.* **8**, 781–792 (2024).
3. Brian, W. M., Anne, H. R., Jane, W. N., Jane, C. B. & Anne, F. B. Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. *Circulation* **135**, e927–e999 (2017).
4. Chen, J. et al. Nomogram for predicting coronary artery lesions in patients with Kawasaki disease. *Clin. Cardiol.* **46**, 1434 (2023).
5. Fukazawa, R. et al. On behalf of the Japanese Circulation Society Joint Working Group. *Circ. J.* **84**, 1348–1407 (2020).
6. Chiang, W., Huang, P., Kuo, H., Huang, Y. & Chang, L. Evaluation of Formosa score and diagnostic sensitivity and specificity of four Asian risk scores for predicting intravenous immunoglobulin resistance in Kawasaki disease: A bivariate meta-analysis. *Front. Cardiovasc. Med.* **10**, 1164530 (2023).
7. Ummusen, K. et al. Comparison of IVIG resistance predictive models in Kawasaki disease. *Pediatr Res.* **91**, 621–626 (2022).
8. Lim, Y. T., Kwon, J. E. & Kim, Y. H. Evaluating the performance of egami, kobayashi and sano scores in predicting IVIG resistance in infant kawasaki disease. *BMC Pediatr.* **24**, 606 (2024).
9. Kuniyoshi, Y. et al. Prediction Models for Intravenous Immunoglobulin Resistance in Kawasaki Disease: A Meta-analysis. *Pediatrics* **151**, e2022059175 (2023).
10. Li, X. et al. Predictors of intravenous immunoglobulin-resistant Kawasaki disease in children: A meta-analysis of 4442 cases. *Eur. J. Pediatr.* **177**, 1279–1292 (2018).
11. Ge, H. et al. Blood routine risk factors for coronary artery aneurysm in infants younger than 8 months with Kawasaki disease. *BMC Pediatr.* **22**, 29 (2022).
12. Miura, M. Follow up of Kawasaki disease based on the nationwide survey data in Japan. *Pediart int.* **64**, e15316 (2022).
13. Muto, T. et al. White Blood Cell and Neutrophil Counts and Response to Intravenous Immunoglobulin in Kawasaki Disease. *Glob. Pediatric Health*. https://doi.org/10.1177/2333794X19884826 (2019).
14. Lu, Y. et al. Predicting immunoglobulin resistance in Kawasaki disease: An assessment of neutrophil to lymphocyte platelet ratio. *Ital J. Pediatr.* **48**, 208 (2022).
15. Arora, K. et al. Platelets in Kawasaki disease: Is this only a numbers game or something beyond?. *Genes Dis.* **7**, 62–66 (2019).
16. Noval, R. et al. Platelets in Kawasaki disease: Mediators of vascular inflammation. *Nat Rev Rheumatol.* **20**, 459–472 (2024).
17. Chen, Y. et al. Neutrophil-to-Lymphocyte Ratio Predicts Intravenous Immunoglobulin-Resistance in Infants Under 12-Months Old With Kawasaki Diseas. *Front Pediatr.* **19**(7), 81 (2019).
18. Papayannopoulos, V. Neutrophil extracellular traps in immunity and disease. *Nat. Rev. Immunol.* **18**, 134–147 (2018).
19. Yuan, Y., Sun, J., Li, P., Wei, C. & Yu, Y. Values of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in predicting sensitivity to intravenous immunoglobulin in Kawasaki disease. *Chinese J. Contemporary Pediatr.* **19**, 410–413 (2017).
20. Kanai, T. et al. The combination of the neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as a novel predictor of intravenous immunoglobulin resistance in patients with Kawasaki disease: a multicenter study. *Heart Vessels.* **35**(10), 1463–1472 (2020).
21. Nadig, P. L. et al. Intravenous Immunoglobulin in Kawasaki Disease-Evolution and Pathogenic Mechanisms. *Diagnostics (Basel).* **13**(14), 2338 (2023).
22. Takeuchi, M., Ito, S., Nakamura, M. & Kawakami, K. Changes in Hemoglobin Concentrations Post-immunoglobulin Therapy in Patients with Kawasaki Disease: A Population-Based Study Using a Claims Database in Japan. *Pediatr. Drugs.* **20**, 585–591 (2018).
23. Cai, W. & Ding, S. Retrospective analysis of clinical characteristics and related influencing factors of Kawasaki disease. *Medicine* **101**, e32430 (2022).
24. Chen, C., Chen, Q., Zhang, T. & Ling, Y. Coronary artery lesions in children with Kawasaki disease: Status quo and nursing care. *Front. Cardiovasc. Med.* **11**, 1272475 (2024).

25. Cheng, C., Hsu, T., Yang, Y. & Huang, Y. Hemoglobin and Its Z Score Reference Intervals in Febrile Children: A Cohort Study of 98,572 Febrile Children. *Children* **10**, 1402 (2023).
26. Chen, S. et al. Association of the systemic immune-inflammation index with anemia: A population-based study. *Front Immunol.* **15**, 1391573 (2024).
27. Cuesta, H. et al. Incidence and risk factors for intravenous immunoglobulin-related hemolysis: A systematic review of clinical trial and real-world populations. *Transfusion* **62**(9), 1894–1907 (2022).
28. Kobayashi, H. et al. Increased Myosin light chain 9 expression during Kawasaki disease vasculitis. *Front. Immunol.* **6**(13), 1036672 (2023).
29. Zheng, X., Wu, W., Zhang, Y. & Wu, G. Changes in and significance of platelet function and parameters in Kawasaki disease. *Sci. Rep.* **9**, 17641 (2019).
30. Lu, Y. et al. Prediction of repeated intravenous immunoglobulin resistance in children with Kawasaki disease. *BMC Pediatr.* **21**, 406 (2021).
31. Zhang, R. et al. Predictive value of albumin for intravenous immunoglobulin resistance in a large cohort of Kawasaki disease patients. *Ital. J. Pediatr.* **49**, 78 (2023).
32. Kojok, K. et al. Aspirin Reduces the Potentiating Effect of CD40L on Platelet Aggregation via Inhibition of Myosin Light Chain. *J. Am. Heart Assoc.* **9**(3), e013396 (2020).
33. Chen, X. et al. Prognostic value of the combination of GRACE risk score and mean platelet volume to lymphocyte count ratio in patients with ST-segment elevation myocardial infarction after percutaneous coronary intervention. *Exp. Ther. Med.* **19**, 3664 (2020).
34. Zhang, C. et al. Prediction of intravenous immunoglobulin retreatment in children with Kawasaki disease using models combining lymphocyte subset and cytokine profile in an East Asian cohort. *Clin. Transl. Immunol.* **13**, e1498 (2024).

Acknowledgements
The authors greatly thank home-for-researchers and other pediatricians for their support.

Author contributions
All the contents of the article have been completed by Xiaoqian Fang.

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
All experiments were performed in accordance with the Declaration of Helsinki. Ethical approval was granted by the Ethics Committee of Dongyang People's Hospital (Approval No: 2024-YX-282). Due to the retrospective nature of the study, the Institutional Review Board of Dongyang People's Hospital waived the need for obtaining informed consent.

Additional information
Correspondence and requests for materials should be addressed to X.F.