

Predictive Value of Fever Duration and C-Reactive Protein for Kawasaki Disease: An Interaction Analysis

Yi Yu

Fuqing Affiliated Hospital of Fujian Medical University

Chengkai Yang

Fujian Cancer Hospital, Clinical Oncology School of Fujian Medical University

Yingzhi Wang

Fudan University

Guo Tingyao

371006724@qq.com

Fuqing Affiliated Hospital of Fujian Medical University

Research Article

Keywords: Kawasaki disease, fever duration, C-reactive protein, interaction effect, prediction model, systemic inflammatory response index

Posted Date: August 6th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10262398/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Predictive Value of Fever Duration and C-Reactive Protein for Kawasaki Disease: An Interaction Analysis

YiYu^{1†} Chengkai Yang^{2†} Yingzhi Wang^{3†} Tingyao Guo¹

1 Department of Pediatrics, Fuging City Hospital Affiliated to Fujian Medical University, Fuqing, Fujian 350300, China

2 Department of Hepatopancreatobiliary Oncologic Surgery, Fujian Cancer Hospital, Clinical Oncology School of Fujian Medical University, Fuzhou, Fujian 350014, China.

3 Zhongshan Hospital, Fudan University, Shanghai 200032, China.

† These authors have contributed equally to the work.

Correspondence to:

Guo Tingyao

Department of Pediatrics, Fuging City Hospital Affiliated to Fujian Medical University, Fuqing, Fujian 350300, China.

Email: 371006724@qq.com.

Abstract

Background

Early diagnosis of Kawasaki disease (KD) remains challenging because its initial manifestations are often nonspecific, particularly in children with incomplete KD. Although fever duration and C-reactive protein (CRP) are established inflammatory markers, the potential interaction between them has not been adequately investigated. This study evaluated the interaction between fever duration and CRP and its value in the early prediction of KD.

Methods

This retrospective study included 430 febrile children admitted between January 2020 and December 2025, including 193 patients with KD and 237 febrile controls. Candidate variables were selected using least absolute shrinkage and selection operator (LASSO) regression and entered into multivariable logistic regression to identify independent predictors of KD. A base prediction model and an interaction model incorporating the fever duration $\times$ CRP interaction term were established. Model performance was assessed using receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA).

Results

Multivariable analysis identified fever duration, CRP, alanine aminotransferase, and systemic inflammatory response index (SIRI) as independent risk factors for KD, whereas age, albumin, and alkaline phosphatase were independently associated with a lower risk of KD. A significant interaction between fever duration and CRP was observed (adjusted OR = 0.551, 95% CI: 0.370–0.849, $P = 0.005$). Simple slope

analysis demonstrated that the predictive effect of fever duration was strongest at moderate CRP levels, weaker at low CRP levels, and no longer significant at high CRP levels. Compared with the base model, the interaction model showed a slightly higher discriminative ability (AUC: 0.894 vs. 0.885) and demonstrated better calibration and greater clinical net benefit.

Conclusions

Fever duration and CRP were independently associated with KD, and their interaction provided additional predictive information. Incorporating this interaction improved model performance and may facilitate earlier identification and risk stratification of KD in febrile children.

Keywords: Kawasaki disease; fever duration; C-reactive protein; interaction effect; prediction model; systemic inflammatory response index

1 Introduction

Kawasaki disease (KD) is an acute, self-limited systemic vasculitis primarily involving medium-sized arteries and predominantly affecting children younger than 5 years of age. It is one of the leading causes of acquired heart disease in children[1, 2]. Although the etiology of KD has not been fully elucidated, current evidence suggests that genetic susceptibility, infectious triggers, and dysregulated immune-inflammatory responses collectively contribute to its pathogenesis[2]. In recent decades, with increasing awareness of the disease and continuous improvements in surveillance systems, the incidence of KD has shown a sustained upward trend, particularly in East Asian countries and regions such as Japan, China, and South Korea[3, 4]. Coronary artery lesions (CALs) are the most serious complication of KD. Without treatment, approximately 15%–25% of affected children develop coronary artery dilatation or coronary artery aneurysms, whereas timely administration of intravenous immunoglobulin (IVIG) reduces this proportion to below 5%[5]. Therefore, early recognition and timely intervention are essential for reducing coronary artery complications and improving the long-term prognosis of children with KD.

The diagnosis of KD still relies primarily on persistent fever and characteristic clinical manifestations[1]. However, during the early stage of the disease, particularly in children with incomplete KD, clinical manifestations are often nonspecific and may be limited to persistent fever accompanied by elevated inflammatory markers, making KD difficult to distinguish from common febrile infectious diseases and consequently delaying diagnosis and treatment[6]. With the development of precision medicine, identifying objective laboratory biomarkers for the early diagnosis of KD and establishing robust and reliable prediction models have become major focuses of recent clinical research[7, 8].

C-reactive protein (CRP) is the most widely used acute-phase reactant in clinical practice. Its level reflects the intensity of systemic inflammation and is closely associated with disease activity, intravenous immunoglobulin resistance, and the risk of coronary artery lesions in patients with KD[9, 10]. Persistent fever is the hallmark

clinical manifestation of KD and one of its earliest presenting symptoms. Previous studies have demonstrated that fever duration is closely associated with disease severity and prognosis and may provide early warning information for KD[11, 12]. However, previous studies investigating fever duration and CRP in KD risk prediction have mainly focused on their independent effects, whereas whether an interaction exists between these two variables and how such an interaction influences KD risk prediction remain largely unexplored[13, 14].

Therefore, in this retrospective case-control study, we included clinical data from 430 febrile children. Candidate variables were identified using least absolute shrinkage and selection operator (LASSO) regression, followed by multivariable logistic regression analysis to construct a prediction model. Furthermore, an interaction term between fever duration and CRP was incorporated into the model to investigate its association with the risk of KD and to evaluate its clinical value for the early identification of KD, with the aim of providing new evidence for KD risk stratification and early diagnosis.

2 Materials and Methods

2.1 Study design and participants

This was a single-center retrospective case-control study. Clinical data were retrospectively collected from consecutive febrile children admitted to Fuqing Hospital Affiliated to Fujian Medical University between January 2020 and December 2025. The KD group consisted of 193 children diagnosed with KD according to the 2017 American Heart Association (AHA) diagnostic criteria[1]. During the same period, 237 febrile children who were ultimately diagnosed with diseases other than KD were enrolled as the control group. All study participants were identified through the hospital electronic medical record system.

Inclusion criteria: (1) age ≤ 18 years; (2) documented fever during hospitalization; (3) fulfillment of the AHA diagnostic criteria for KD in the KD group; (4) complete clinical data available.

Exclusion criteria: (1) receipt of intravenous immunoglobulin (IVIG) before the initial laboratory examination; (2) congenital heart disease, immunodeficiency, autoimmune disease, or hematologic disorders; (3) severe hepatic or renal dysfunction, or malignant tumors; (4) missing essential clinical data.

This study was approved by the Medical Ethics Committee of Fuqing Hospital Affiliated to Fujian Medical University (Approval No. K (2026) 40). As this was a retrospective study using anonymized data, the requirement for informed consent was waived by the Ethics Committee.

2.2 Data collection

General demographic characteristics and the results of the initial laboratory examination were collected. Laboratory parameters included C-reactive protein (CRP), procalcitonin (PCT), white blood cell count (WBC), neutrophil count, lymphocyte count, monocyte count, hemoglobin, platelet count, total bilirubin (TBil), direct bilirubin (DBil), albumin, globulin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and γ -glutamyl transferase (GGT).

Inflammatory indices were calculated from peripheral blood cell counts, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic inflammatory response index (SIRI), and systemic immune-inflammation index (SII).

The corresponding formulas were as follows:

$$\text{NLR} = \text{Neutrophil count} / \text{Lymphocyte count}$$

$$\text{PLR} = \text{Platelet count} / \text{Lymphocyte count}$$

$$\text{SIRI} = \text{Neutrophil count} \times \text{Monocyte count} / \text{Lymphocyte count}$$

$$\text{SII} = \text{Platelet count} \times \text{Neutrophil count} / \text{Lymphocyte count}$$

2.3 Variable selection and model construction

Univariable logistic regression analysis was first performed to evaluate the association between each variable and the risk of KD. Variables with statistical significance were subsequently entered into the least absolute shrinkage and selection operator (LASSO) regression analysis. Ten-fold cross-validation was performed to determine the optimal penalty parameter (λ), and candidate variables for multivariable analysis were selected to reduce multicollinearity and prevent model overfitting. All continuous variables were standardized using Z-score transformation before model construction to ensure comparability across variables with different measurement scales.

A multivariable logistic regression model (Base model) was constructed using the variables selected by LASSO regression. Based on the Base model, an interaction term between fever duration and CRP (fever duration $\times$ CRP) was further incorporated to establish the Interaction model. Based on the variables selected by LASSO regression, a multivariable logistic regression model was established and referred to as the Base model. Subsequently, an interaction term between fever duration and CRP (fever duration $\times$ CRP) was incorporated to construct the Interaction model.

2.4 Interaction analysis

The interaction between fever duration and CRP was evaluated by incorporating a multiplicative interaction term into the multivariable logistic regression model. To further characterize the interaction, simple slope analysis was performed after stratifying participants into low-, moderate-, and high-CRP groups according to the tertiles of CRP distribution (cutoff values: the 33.3rd and 66.7th percentiles). The association between fever duration and the risk of KD was estimated within each subgroup, and corresponding simple slope plots were generated to illustrate the interaction effect.

2.5 Model evaluation

Model discrimination was assessed using the area under the receiver operating characteristic (ROC) curve (AUC). The AUCs of the Base model and the Interaction model were compared using the DeLong test. Model calibration was evaluated using the Hosmer – Lemeshow goodness-of-fit test and calibration curves. The clinical utility of the models was evaluated using decision curve analysis (DCA).

2.6 Statistical analysis

All statistical analyses were performed using R software (version 4.3.0; R Foundation for Statistical Computing, Vienna, Austria). Normally distributed continuous variables were expressed as the mean $\pm$ standard deviation (SD) and compared using the independent-samples t test; Non-normally distributed continuous variables were presented as the median (interquartile range, IQR) and compared using the Mann – Whitney U test; Categorical variables were expressed as frequencies (percentages) and compared using the X^2 test or Fisher's exact test, as appropriate. The results of logistic regression analyses were reported as odds ratios (ORs) with 95% confidence intervals (CIs). All statistical tests were two-sided, and a P value <0.05 was considered statistically significant.

3 Results

3.1 Baseline characteristics

A total of 430 febrile children were included in this study, comprising 193 children with KD and 237 controls. Compared with the control group, children with KD were younger and had a longer fever duration. They also exhibited significantly higher levels of C-reactive protein (CRP), procalcitonin (PCT), white blood cell count (WBC), neutrophil count, lymphocyte count, monocyte count, platelet count, total bilirubin (TBil), direct bilirubin (DBil), γ -glutamyl transferase (GGT), globulin, alanine aminotransferase (ALT), systemic inflammatory response index (SIRI), and systemic immune-inflammation index (SII), whereas hemoglobin, alkaline phosphatase (ALP), albumin, and platelet-to-lymphocyte ratio (PLR) were significantly lower (all $P < 0.05$). No significant differences were observed between the two groups with respect to sex, aspartate aminotransferase (AST), or the neutrophil-to-lymphocyte ratio (NLR) (all $P > 0.05$). Detailed baseline characteristics are presented in Table 1.

Table 1. Baseline characteristics of the study participants.

Variable	Overall	Control	KD	P value
Participants, n	430	237	193	
Male sex, n (%)	234 (54.4)	122 (51.5)	112 (58.0)	0.208
Age (months)	31.00 [15.00,	36.00 [15.00,	29.00 [16.00,	0.018

Variable	Overall	Control	KD	P value
	59.75]	74.00]	49.00]	
Fever duration (h)	48.00 [24.00, 96.00]	24.00 [16.00, 48.00]	72.00 [48.00, 120.00]	<0.001
C-reactive protein (mg/L)	37.53 [8.03, 86.37]	11.11 [3.93, 43.34]	74.60 [38.21, 113.68]	<0.001
Procalcitonin (ng/mL)	0.29 [0.13, 0.80]	0.25 [0.10, 0.59]	0.42 [0.18, 1.33]	<0.001
White blood cell count (×10 ⁹ /L)	12.62 [7.24, 16.94]	9.08 [6.00, 15.01]	14.75 [11.07, 18.95]	<0.001
Neutrophil count (×10 ⁹ /L)	8.44 [5.13, 12.17]	6.36 [3.85, 10.23]	10.22 [7.33, 13.44]	<0.001
Hemoglobin (g/L)	122.00 [114.00, 129.75]	127.00 [120.00, 133.00]	116.00 [109.00, 123.00]	<0.001
Lymphocyte count (×10 ⁹ /L)	1.92 [1.17, 3.51]	1.52 [0.90, 3.18]	2.44 [1.58, 3.96]	<0.001
Monocyte count (×10 ⁹ /L)	0.72 [0.52, 1.11]	0.65 [0.47, 0.98]	0.86 [0.61, 1.22]	<0.001
Platelet count (×10 ⁹ /L)	277.50 [228.25, 345.75]	251.00 [207.00, 296.00]	315.00 [272.00, 374.00]	<0.001
Total bilirubin (μmol/L)	7.80 [5.60, 11.88]	7.20 [5.20, 10.60]	9.30 [6.50, 14.70]	<0.001
Direct bilirubin (μmol/L)	2.10 [1.30, 3.30]	1.70 [1.20, 2.70]	2.70 [1.50, 5.30]	<0.001
Alkaline phosphatase (U/L)	191.00 [162.25, 235.50]	210.00 [176.00, 262.00]	177.00 [152.00, 206.00]	<0.001
Gamma-glutamyl transferase (U/L)	11.00 [8.00, 16.00]	9.80 [7.10, 12.00]	14.00 [9.10, 35.00]	<0.001
Albumin (g/L)	42.15 [38.90, 45.48]	44.40 [42.00, 46.10]	39.30 [35.00, 42.10]	<0.001

Variable	Overall	Control	KD	P value
Globulin (g/L)	26.30 [23.40, 29.20]	25.00 [22.90, 28.00]	28.00 [25.90, 30.30]	<0.001
Alanine aminotransferase (U/L)	17.30 [12.83, 27.40]	16.00 [12.40, 22.00]	20.00 [14.00, 48.00]	<0.001
Aspartate aminotransferase (U/L)	41.20 [30.00, 60.00]	44.60 [30.00, 59.00]	39.00 [30.20, 60.00]	0.702
Neutrophil-to-lymphocyte ratio	4.34 [2.20, 6.33]	4.22 [2.20, 6.06]	4.39 [2.23, 6.51]	0.407
Platelet-to-lymphocyte ratio	145.70 [87.01, 233.97]	158.52 [93.85, 260.87]	128.57 [82.09, 207.75]	0.031
Systemic inflammatory response index	3.00 [1.60, 5.82]	2.82 [1.48, 5.39]	3.53 [1.81, 6.38]	0.003
Systemic immune-inflammation index	1117.06 [630.67, 1996.04]	952.64 [572.47, 1701.43]	1339.53 [679.67, 2126.17]	0.001

Data are presented as median [interquartile range] or n (%).

3.2 Univariable logistic regression analysis

Univariable logistic regression analysis identified 21 variables significantly associated with KD (all $P < 0.05$), whereas SII showed borderline significance ($P = 0.052$). Sex and NLR were not associated with KD. The detailed results are presented in Table 2.

Table 2. Univariable logistic regression analysis for predictors of Kawasaki disease.

Univariate Logistic					
Variable	OR (95% CI)	P value	Variable	OR (95% CI)	P value
Albumin (g/L)	0.212 (0.150-0.292)	<0.001	Neutrophil count ($\times 10^9/L$)	1.810 (1.473-2.247)	<0.001
C-reactive protein (mg/L)	3.205 (2.453-4.287)	<0.001	Male sex	1.303 (0.889-1.914)	0.175
Fever duration (h)	2.725 (2.131-3.544)	<0.001	Gamma-glutamyl transferase	4.190 (2.400-8.281)	<0.001

Univariate Logistic					
Variable	OR (95% CI)	P value	Variable	OR (95% CI)	P value
			(U/L)		
Hemoglobin (g/L)	0.360 (0.275-0.464)	<0.001	Neutrophil-to-lymphocyte ratio	1.074 (0.886-1.312)	0.467
Platelet count ($\times 10^9/L$)	2.304 (1.828-2.954)	<0.001	Direct bilirubin ($\mu\text{mol/L}$)	3.154 (1.970-5.612)	<0.001
White blood cell count ($\times 10^9/L$)	1.963 (1.593-2.444)	<0.001	Total bilirubin ($\mu\text{mol/L}$)	1.608 (1.242-2.182)	<0.001
Globulin (g/L)	1.922 (1.540-2.428)	<0.001	Lymphocyte count ($\times 10^9/L$)	1.398 (1.150-1.712)	<0.001
Alkaline phosphatase (U/L)	0.576 (0.449-0.725)	<0.001	Aspartate aminotransferase (U/L)	1.631 (1.203-2.528)	0.009
Alanine aminotransferase (U/L)	6.248 (3.063-15.908)	<0.001	Procalcitonin (ng/mL)	1.407 (1.108-1.888)	0.012
Age (months)	0.653 (0.524-0.804)	<0.001	Monocyte count ($\times 10^9/L$)	1.277 (1.048-1.587)	0.019
Systemic inflammatory response index	1.330 (1.083-1.663)	0.009	Platelet-to-lymphocyte ratio	0.802 (0.637-0.985)	0.046
Systemic immune-inflammation index	1.239 (1.012-1.564)	0.052			

Abbreviations: OR, odds ratio; CI, confidence interval.

3.3 LASSO regression variable selection

Variables that were significantly associated with KD in the univariable logistic regression analysis were subsequently entered into the least absolute shrinkage and selection operator (LASSO) regression analysis. The optimal penalty parameter (λ) was determined using 10-fold cross-validation. At the optimal λ value, 11 variables with non-zero coefficients were retained, including age, fever duration, C-reactive protein (CRP), hemoglobin, albumin, platelet count, white blood cell count (WBC), globulin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), and the

systemic inflammatory response index (SIRI). The LASSO coefficient profiles and cross-validation results are presented in Figure 1A,B.

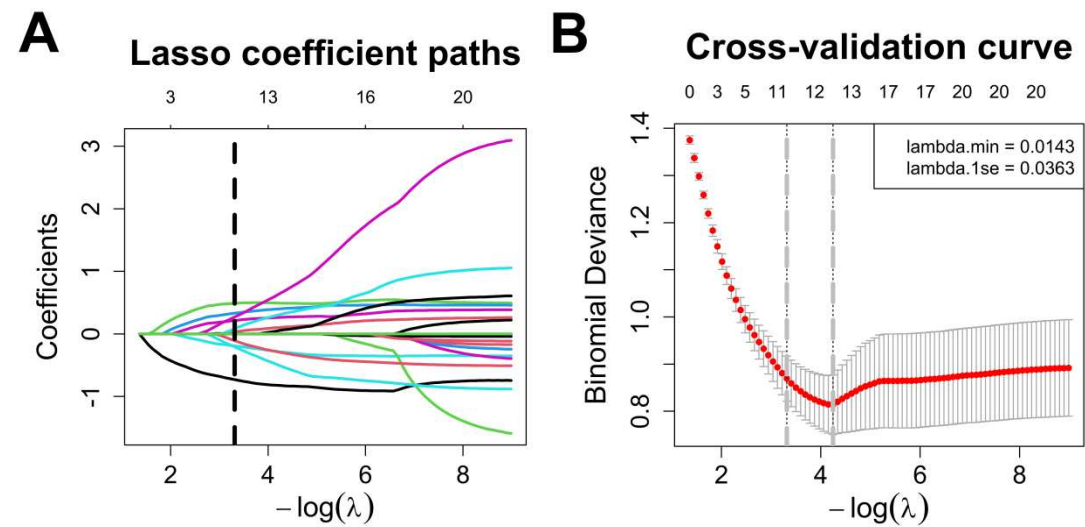


Figure 1. Feature selection using LASSO regression.

- (A) LASSO coefficient profiles of the candidate variables.
 (B) Ten-fold cross-validation for selection of the optimal penalty parameter (λ). The optimal λ was determined according to the minimum cross-validation error.

3.4 Multivariable logistic regression analysis

The 11 variables selected by LASSO regression were entered into a multivariable logistic regression model to construct the Base model. The results showed that age (OR = 0.587, 95% CI: 0.393–0.847, $P = 0.006$), albumin (OR = 0.403, 95% CI: 0.254–0.620, $P < 0.001$), and alkaline phosphatase (ALP) (OR = 0.380, 95% CI: 0.238–0.601, $P < 0.001$) were independently associated with a lower risk of KD, whereas C-reactive protein (CRP) (OR = 1.692, 95% CI: 1.174–2.482, $P = 0.006$), fever duration (OR = 1.617, 95% CI: 1.161–2.236, $P = 0.004$), alanine aminotransferase (ALT) (OR = 6.663, 95% CI: 2.357–27.344, $P = 0.002$), and the systemic inflammatory response index (SIRI) (OR = 1.825, 95% CI: 1.256–2.717, $P = 0.002$) were independently associated with an increased risk of KD (Table 3).

An Interaction model was subsequently established by incorporating the interaction term between fever duration and CRP into the Base model. In the Interaction model, the association between fever duration and KD was markedly attenuated (OR = 1.206, 95% CI: 0.833–1.765, $P = 0.326$), whereas CRP remained an independent predictor (OR = 1.712, 95% CI: 1.173–2.556, $P = 0.007$). In addition, the interaction term between fever duration and CRP was statistically significant (OR = 0.551, 95% CI: 0.370–0.849, $P = 0.005$), indicating that the predictive effect of fever duration on KD varied according to CRP levels (Table 3).

Table 3. Multivariable logistic regression analyses of the base model and interaction model for predicting Kawasaki disease.

Base model	Interaction model
------------	-------------------

Variable	OR (95% CI)	P-value	OR (95% CI)	P value
Albumin (g/L)	0.403 (0.254-0.620)	<0.001	0.367 (0.227-0.571)	<0.001
C-reactive protein (mg/L)	1.692 (1.174-2.482)	0.006	1.712 (1.173-2.556)	0.007
Fever duration (h)	1.617 (1.161-2.236)	0.004	1.206 (0.833-1.765)	0.326
Hemoglobin (g/L)	0.675 (0.449-1.005)	0.055	0.653 (0.431-0.982)	0.042
Platelet count (×10 ⁹ /L)	1.380 (0.983-1.936)	0.061	1.413 (1.008-1.985)	0.045
White blood cell count (×10 ⁹ /L)	0.986 (0.923-1.050)	0.657	0.964 (0.899-1.030)	0.288
Globulin (g/L)	1.169 (0.789-1.736)	0.435	1.219 (0.828-1.809)	0.318
Alkaline phosphatase (U/L)	0.380 (0.238-0.601)	<0.001	0.358 (0.219-0.584)	<0.001
Alanine aminotransferase (U/L)	6.663 (2.357-27.344)	0.002	7.273 (2.515-30.501)	0.002
Age(months)	0.587 (0.393-0.847)	0.006	0.533 (0.352-0.779)	0.002
Systemic inflammatory response index	1.825 (1.256-2.717)	0.002	1.908 (1.297-2.881)	0.001
Fever duration × C-reactive protein	–	–	0.551 (0.370-0.849)	0.005
AUC (95% CI)	0.885 (0.852–0.918)		0.894 (0.864–0.925)	
P for DeLong test			0.114	

Abbreviations: OR, odds ratio; CI, confidence interval; AUC, area under the receiver operating characteristic curve.

3.5 Simple slope analysis

To further characterize the interaction effect, simple slope analysis was performed to evaluate the association between fever duration and the risk of KD across the low-, moderate-, and high-CRP tertiles. The association between fever duration and KD was strongest in the moderate-CRP tertile, followed by the low-CRP tertile, whereas no statistically significant association was observed in the high-CRP tertile. The results are presented in Figure 2.

Effect of Fever Duration Across CRP Levels

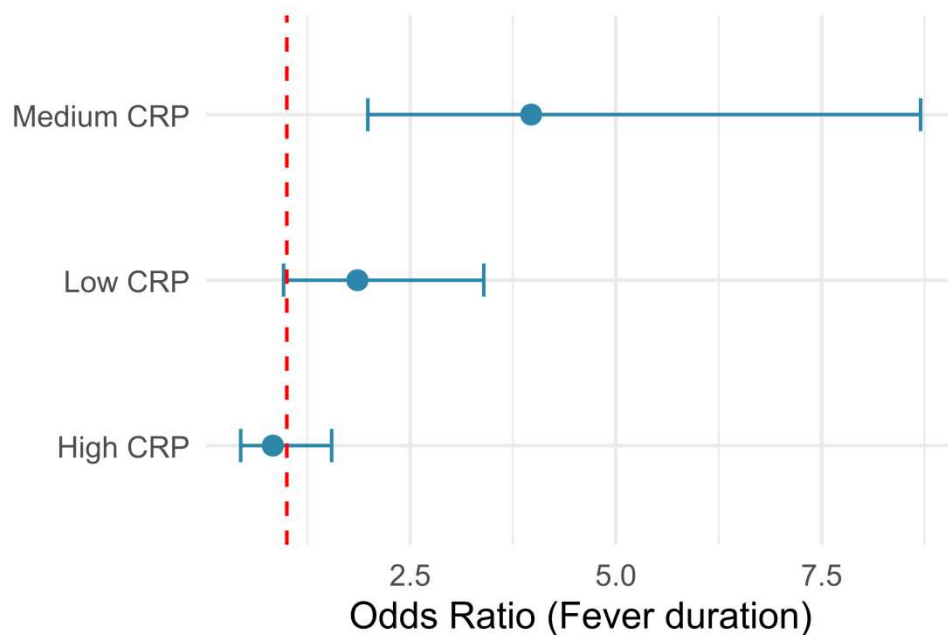


Figure 2. Simple slope analysis illustrating the association between fever duration and the predicted probability of Kawasaki disease across low-, moderate-, and high-CRP tertiles.

3.6 Model performance

Receiver operating characteristic (ROC) curve analysis demonstrated that the Base model achieved an area under the curve (AUC) of 0.885 (95% CI: 0.852–0.918), whereas the Interaction model achieved an AUC of 0.894 (95% CI: 0.864–0.925). DeLong's test showed no statistically significant difference between the two models ($P = 0.1138$). The ROC curves of the two models are presented in Figure 3.

According to the Youden index, the optimal cutoff values for predicting KD were 36 h for fever duration and 28.6 mg/L for C-reactive protein (CRP). The corresponding ROC curves are shown in Figure 4.

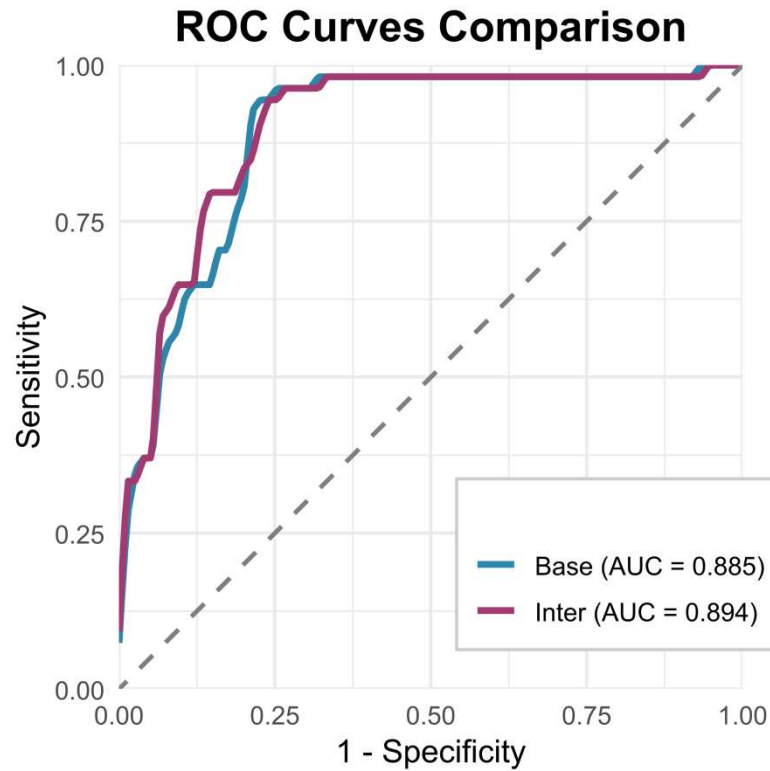


Figure 3. Receiver operating characteristic (ROC) curves of the Base model and Interaction model for predicting Kawasaki disease.

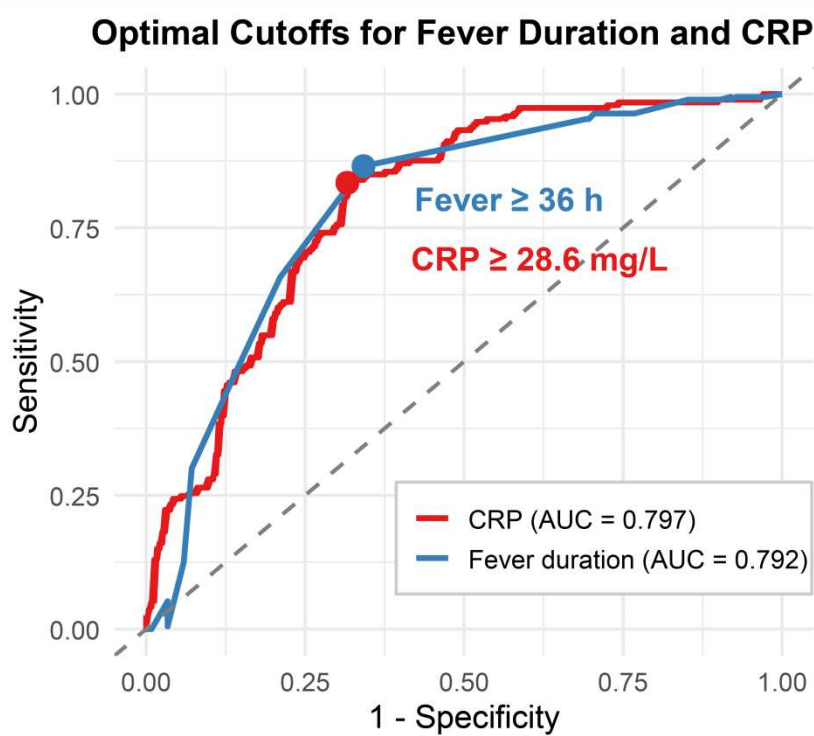


Figure 4. Receiver operating characteristic (ROC) curves of fever duration and C-reactive protein (CRP) for predicting Kawasaki disease. The optimal cutoff values

were determined using the Youden index.

3.7 Calibration and decision curve analysis

The calibration curve demonstrated good agreement between the predicted and observed probabilities of KD in the Interaction model. Decision curve analysis (DCA) showed that the Interaction model provided a greater net clinical benefit than the Base model across most threshold probabilities. The calibration and decision curves are shown in Figure 5A,B.

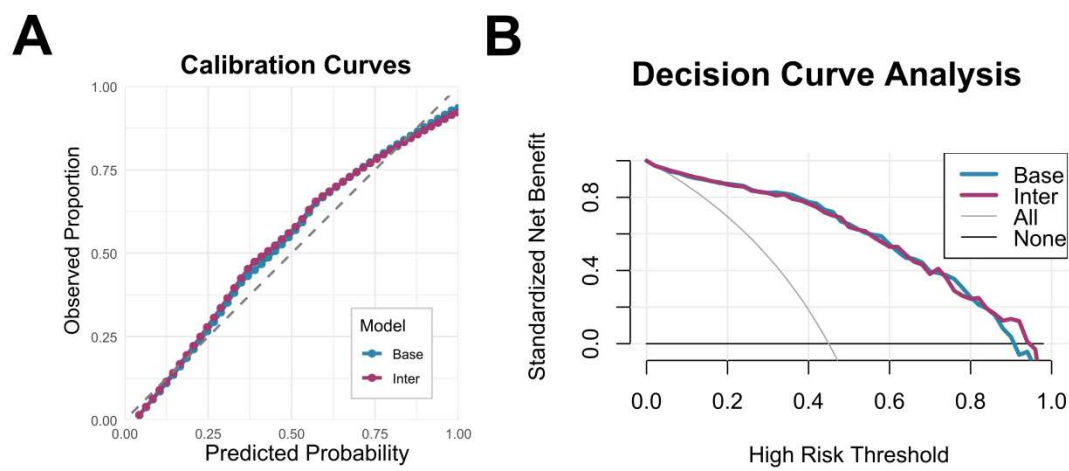


Figure 5. Calibration and decision curve analysis of the Base model and Interaction model.

(A) Calibration curves comparing the predicted and observed probabilities of Kawasaki disease for the Base model and Interaction model.

(B) Decision curve analysis (DCA) comparing the net clinical benefit of the Base model and Interaction model across different threshold probabilities.

4 Discussion

Kawasaki disease (KD) is a systemic vasculitis characterized by dysregulated immune and inflammatory responses. Because its early clinical manifestations are often nonspecific and can be easily confused with other febrile infectious diseases, identifying reliable early predictive markers remains a major focus of KD research[15, 16]. Based on a cohort of 430 febrile children, we developed a risk prediction model for KD. Fever duration, C-reactive protein (CRP), alanine aminotransferase (ALT), and the systemic inflammatory response index (SIRI) were independently associated with an increased risk of KD, whereas age, albumin, and alkaline phosphatase (ALP) were independently associated with a lower risk of KD. In addition, a significant interaction between fever duration and CRP was identified. Incorporating this interaction term provided additional predictive information for early KD risk assessment, suggesting that the combined evaluation of these two variables may

facilitate the early identification of KD. These findings suggest that KD risk assessment should consider not only individual predictors but also the interactions among relevant clinical variables[17].

In the present study, children with KD had significantly longer fever duration and higher levels of inflammatory markers, blood cell parameters, bilirubin indices, liver function biomarkers, and composite inflammatory indices than children with non-KD febrile illnesses, whereas age, hemoglobin, albumin, alkaline phosphatase (ALP), and the platelet-to-lymphocyte ratio (PLR) were significantly lower. These findings are consistent with previous reports[18-20]. Acute KD is characterized by dysregulated immune activation and systemic inflammation. Sustained release of pro-inflammatory cytokines, including interleukin-1 β , interleukin-6, and tumor necrosis factor- α , contributes to vascular endothelial injury and inflammatory cell infiltration while stimulating hepatic synthesis of acute-phase proteins. Consequently, elevated inflammatory markers, leukocytosis, reactive thrombocytosis, and abnormalities in liver function-related biomarkers are frequently observed during the acute phase of KD[21-23]. Collectively, these laboratory abnormalities further support the presence of persistent systemic inflammation in acute KD and provide objective evidence for its early identification.

Recently, several novel inflammation-based indices derived from peripheral blood cell counts have been increasingly investigated in patients with KD[18]. The systemic inflammatory response index (SIRI), which integrates neutrophil, monocyte, and lymphocyte counts, reflects both inflammatory activation and immune regulation.[24]. In the present study, SIRI remained an independent predictor of KD after multivariable adjustment, suggesting that it may more comprehensively reflect the systemic inflammatory response during the acute phase of KD than individual inflammatory markers. Notably, the lymphocyte count was higher in children with KD than in those with non-KD febrile illnesses, which is inconsistent with some previous studies[25]. This discrepancy may be attributable to differences in the spectrum of control diseases, timing of clinical presentation, or blood sampling. Nevertheless, the more pronounced increases in neutrophil and monocyte counts contributed to the overall elevation of SIRI, which may explain its superior predictive performance. Although the systemic immune-inflammation index (SII) has also been proposed as a potential biomarker for KD, it was not retained in the final prediction model in our study, suggesting that its predictive information may partially overlap with that provided by CRP or SIRI. Similar findings have been reported previously[26].

Fever is the cardinal clinical manifestation of KD and remains an essential component of the current diagnostic criteria[1]. In the present study, fever duration was identified as an independent predictor of KD, with an optimal cutoff value of 36 h. Importantly, fever duration referred to the interval from fever onset to the initial laboratory evaluation rather than the total duration of fever before diagnosis, making

this indicator more applicable to early clinical decision-making. Previous studies have primarily emphasized the diagnostic value of persistent fever lasting ≥ 5 days. More recent evidence, however, suggests that children with a shorter duration of fever but marked inflammatory responses should be evaluated comprehensively rather than waiting for the conventional diagnostic threshold to be reached[13]. Our findings further support this concept and indicate that fever duration may serve as an early warning indicator for KD risk stratification.

C-reactive protein (CRP) is the most widely used acute-phase reactant in clinical practice and an important laboratory marker for the diagnosis of KD[27]. Previous studies have demonstrated that CRP is closely associated with disease activity, intravenous immunoglobulin (IVIG) resistance, and the development of coronary artery lesions, and it has been incorporated into several risk scoring systems for predicting IVIG resistance[28]. Consistent with these findings, CRP remained an independent predictor of KD in the present study, with an optimal cutoff value of 28.6 mg/L. Moreover, our results suggest that CRP retains good discriminatory ability for identifying KD among children presenting with febrile illnesses.

The most notable finding of this study was the significant interaction between fever duration and CRP. After adjustment for age, albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), and the systemic inflammatory response index (SIRI), the interaction term remained statistically significant, indicating that CRP modified the association between fever duration and the risk of KD. Most existing prediction models treat fever duration and CRP as independent predictors while rarely considering their potential effect modification[29]. Simple slope analysis further demonstrated that the predictive value of fever duration varied across different CRP levels. Specifically, fever duration showed the strongest association with KD in the moderate-CRP tertile, whereas its predictive value became nonsignificant in the high-CRP tertile. One possible explanation is that once CRP reaches a markedly elevated level, it already reflects the intensity of systemic inflammation, thereby limiting the additional predictive information provided by fever duration. These findings suggest that the inflammatory response in KD is dynamic and that complex interactions may exist among different inflammatory indicators. Although the underlying biological mechanisms remain to be elucidated, incorporating interaction effects into prediction models may provide a novel strategy for improving risk assessment in children with suspected KD.

The model evaluation results further support the potential clinical value of incorporating the interaction term. Although the Base model already demonstrated good discriminative performance, the Interaction model achieved a slightly higher AUC. While this improvement did not reach statistical significance according to DeLong's test, calibration and decision curve analyses indicated better agreement between predicted and observed outcomes and greater net clinical benefit after inclusion of the interaction term. In recent years, evaluation of clinical prediction

models has increasingly emphasized calibration and clinical utility in addition to discrimination[30]. Therefore, the interaction term may provide incremental value for clinical risk assessment despite its limited impact on AUC.

Several limitations of this study should be acknowledged. First, this was a single-center retrospective study and was therefore subject to potential selection bias. Second, no independent external validation cohort was available, and the generalizability of the proposed model requires further validation. Third, this study focused on predicting the occurrence of KD and did not investigate whether the interaction between fever duration and CRP was associated with important clinical outcomes, such as coronary artery lesions or IVIG resistance. Future multicenter prospective studies incorporating echocardiographic findings and additional inflammatory biomarkers are warranted to further optimize and validate the proposed prediction model.

Conclusion

In conclusion, fever duration and C-reactive protein (CRP) are important predictors of Kawasaki disease, and a significant interaction exists between these two variables. Incorporating their interaction into the prediction model may provide additional information for clinical risk assessment and facilitate the early identification and risk stratification of children with suspected KD.

Acknowledgements

We would like to thank the Department of Pediatrics and the Medical Records Department of Fujian Medical University Affiliated Fuqing Hospital for their support in data collection and management.

Ethical approval

This retrospective study was approved by the Ethics Committee of Fujian Medical University Affiliated Fuqing Hospital (Approval K (2026) 40). The study was conducted in accordance with the Declaration of Helsinki. Owing to the retrospective study design and the use of anonymized data, the requirement for informed consent was waived by the Ethics Committee.

Authors' contributions

Y.Y., C.K.Y., and Y.Z.W. contributed equally to this work. Y.Y. and C.K.Y. designed the study, collected and analyzed the data, and wrote the manuscript. Y.Z.W. contributed to data interpretation and critically revised the manuscript. T.Y.G. participated in data acquisition and provided technical support. All authors read and approved the final version.

Consent for publication

Not applicable.

Funding

Not applicable.

Availability of data and materials

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

Conflict of Interest

The authors declare that they have no competing interests related to this article.

Clinical trial number

Not applicable.

References

1. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, Jackson MA, Takahashi M, Shah PB *et al*: **Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association.** *Circulation* 2017, **135**(17):e927-e999.
2. Burns JC, Glodé MP: **Kawasaki syndrome.** *Lancet* 2004, **364**(9433):533-544.
3. Uehara R, Belay ED: **Epidemiology of Kawasaki disease in Asia, Europe, and the United States.** *J Epidemiol* 2012, **22**(2):79-85.

4. Makino N, Nakamura Y, Yashiro M, Ae R, Tsuboi S, Aoyama Y, Kojo T, Uehara R, Kotani K, Yanagawa H: **Descriptive epidemiology of Kawasaki disease in Japan, 2011-2012: from the results of the 22nd nationwide survey.** *J Epidemiol* 2015, **25**(3):239-245.
5. James KE, Kalot MA, Husainat NM, Dua AB, Byram K, Springer JM, Lin YC, Turgunbaev M, Villa-Forte A, Gorelik M *et al*: **Kawasaki Disease: A Systematic Review and Meta-Analysis of Benefits and Harms of Common Treatments.** *ACR Open Rheumatol* 2021, **3**(10):671-683.
6. Sundel RP: **Kawasaki disease.** *Rheum Dis Clin North Am* 2015, **41**(1):63-73, viii.
7. Rowley AH: **Is Kawasaki disease an infectious disorder?** *Int J Rheum Dis* 2018, **21**(1):20-25.
8. Takahashi K, Oharaseki T, Yokouchi Y: **Update on etio and immunopathogenesis of Kawasaki disease.** *Curr Opin Rheumatol* 2014, **26**(1):31-36.
9. Liu L, Chen R, Wang H, Yu H, Ai Z, Zhang X: **Nutrition-Associated Biomarkers in Predicting Intravenous Immunoglobulin Resistance and Coronary Artery Lesions in Kawasaki Disease: A Systematic Review and Meta-Analysis.** *Food Sci Nutr* 2025, **13**(1):e4647.
10. Zhang R, Shuai S, Zhang H, Cai J, Cui N, Tang M, Xing S, Gao Y, Liu X, Yang X: **Predictive value of albumin for intravenous immunoglobulin resistance in a large cohort of Kawasaki disease patients.** *Ital J Pediatr* 2023, **49**(1):78.
11. Xue M, Wang J: **Utility of color Doppler echocardiography combined with clinical markers in diagnosis and prediction of prognosis of coronary artery lesions in Kawasaki disease.** *Exp Ther Med* 2020, **19**(4):2597-2603.
12. Liu X, Wang F, Zhou K, Hua Y, Wu M, Liu L, Shao S, Wang C: **Clinical characteristics of Kawasaki disease in adolescents.** *J Int Med Res* 2021, **49**(11):3000605211056839.
13. Seo YM, Kang HM, Lee SC, Yu JW, Kil HR, Rhim JW, Han JW, Lee KY: **Clinical implications in laboratory parameter values in acute Kawasaki disease for early diagnosis and proper treatment.** *Korean J Pediatr* 2018, **61**(5):160-166.
14. Lee KY, Rhim JW, Kang JH: **Kawasaki disease: laboratory findings and an immunopathogenesis on the premise of a "protein homeostasis system".** *Yonsei Med J* 2012, **53**(2):262-275.
15. Wang S, Qian G, Liu Y, Li X, Huang H, Sun L, Lv H: **Kawasaki disease: insights into the roles of T cells.** *Front Immunol* 2025, **16**:1582638.
16. Wang C, Yu W, Wu X, Wang S, Chen L, Liu G: **Proteomic insights into molecular alterations associated with Kawasaki disease in children.** *Ital J Pediatr* 2025, **51**(1):56.
17. Niu M, Pan J, Wang K, Zhang L, Lin Z, Zhang F: **Circulating Inflammatory Factors and Bidirectional Mendelian Randomization Analysis in Patients with Kawasaki Disease.** *Vasc Health Risk Manag* 2025, **21**:99-108.
18. Yi C, Zhou YN, Guo J, Chen J, She X: **Novel predictors of intravenous immunoglobulin resistance in patients with Kawasaki disease: a retrospective study.** *Front Immunol* 2024, **15**:1399150.
19. Zou J, He X, Li W, Duan Y, Liu B, Jiang J, Luo D, Zhao J, Li G: **The association of serum CHI3L1 levels with the presence of Kawasaki disease.** *Sci Rep* 2025, **15**(1):7693.
20. Lee KY, Han JW, Hong JH, Lee HS, Lee JS, Whang KT: **Inflammatory processes in Kawasaki disease reach their peak at the sixth day of fever onset: laboratory profiles according to duration of fever.** *J Korean Med Sci* 2004, **19**(4):501-504.
21. Yang W, Guo W, Wang Z, Jiang L, Luo X, Chen K, Liu X, An C, Pi L, Xu Y *et al*: **Variant rs13045 reduces EIF2AK3 expression and inhibits pro-inflammatory cytokine secretion via the**

- MAPK-ERK1/2 pathway in Kawasaki disease.** *Biochim Biophys Acta Mol Basis Dis* 2026, **1872**(1):168032.
22. Yu L, Luo Q, Rao X, Xiao X, Wang P: **Unveiling the anti-inflammatory mechanism of exogenous hydrogen sulfide in Kawasaki disease based on network pharmacology and experimental validation.** *Sci Rep* 2025, **15**(1):7410.
 23. Chen Z, Zeng A, Yang P, Zhang J, Liu D, Li M, Jing F, Yi Q: **Role of leukocyte-associated Ig-like receptor-1 in the pathogenesis of Kawasaki disease and coronary artery aneurysms.** *Immunol Lett* 2025, **271**:106948.
 24. Ulu K, Çağlayan Ş, Coşkuner T, Vazgeçer EO, Öner T, Sözeri B: **Differentiating Kawasaki Disease and Multisystem Inflammatory Syndrome in Children Using Blood Composite Scores: Insights into Clinical Outcomes and Predictive Indices.** *Pediatr Cardiol* 2025, **46**(5):1390-1399.
 25. Chen Y, Yang M, Zhang M, Wang H, Zheng Y, Sun R, Li X: **Single-Cell Transcriptome Reveals Potential Mechanisms for Coronary Artery Lesions in Kawasaki Disease.** *Arterioscler Thromb Vasc Biol* 2024, **44**(4):866-882.
 26. Liu X, Shao S, Wang L, Zhang N, Wu M, Liu L, Zhao L, Hua Y, Zhou K, Luo C *et al*: **Predictive Value of the Systemic Immune-Inflammation Index for Intravenous Immunoglobulin Resistance and Cardiovascular Complications in Kawasaki Disease.** *Front Cardiovasc Med* 2021, **8**:711007.
 27. Yang TH, Huang YH, Lee YH, Lai JN, Chen KD, Guo MM, Pan Y, Chen CY, Wu WS, Kuo HC: **Identifying the risk of Kawasaki disease based solely on routine blood test features through novel construction of machine learning models.** *Comput Struct Biotechnol J* 2025, **27**:2832-2842.
 28. Li L, Xu X, Guo Y, Yan Y, Li M, Zhao H, Wang M, Kong Q, Zhao C: **C-reactive protein to high density lipoprotein cholesterol ratio for predicting coronary artery lesions, and intravenous immunoglobulin resistance in Kawasaki disease.** *Pediatr Rheumatol Online J* 2025, **23**(1):108.
 29. Wu Y, Wang S, Zhou Y, Yang Y, Li S, Yin W, Ding Y: **Clinical indicators combined with S100A12/TLR2 signaling molecules to establish a new scoring model for coronary artery lesions in Kawasaki disease.** *PLoS One* 2023, **18**(10):e0292653.
 30. Duan Y, Chen A, Cheng X: **A retrospective cohort study using machine learning to predict coronary artery lesions in children with Kawasaki disease.** *BMC Pediatr* 2025, **25**(1):583.