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ORIGINAL RESEARCH

Efficacy Analysis of a 12-Cytokine Panel for the Diagnosis of Kawasaki Disease and Prediction of Intravenous Immunoglobulin Resistance

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Purpose: To evaluate the diagnostic and predictive value of a 12-cytokine panel for Kawasaki disease (KD) and intravenous immunoglobulin (IVIG) resistance.

Patients and Methods: A retrospective case-control study was conducted using clinical data from children diagnosed with KD at Children's Hospital, Zhejiang University School of Medicine, between December 1, 2023, and March 30, 2025. Demographic characteristics, laboratory findings, and echocardiographic results were collected. KD patients were compared with febrile controls without KD. Differences in sex, age, 12-cytokine profile, complete blood count, C-reactive protein level, and erythrocyte sedimentation rate were analyzed. Additionally, cytokine levels were compared between IVIG-resistant and IVIG-responsive KD patients to assess their predictive value for IVIG resistance.

Results: A total of 686 KD patients and 101 febrile non-KD controls were enrolled. Compared with controls, KD patients were significantly younger and presented higher levels of IFN-α, IL-10, IL-1β, IL-2, IL-4, IL-5, IL-6, and IL-8, as well as elevated neutrophil counts and white blood cell counts. Logistic regression analysis identified age (in months), IL-10, IL-5, and the absolute neutrophil count as independent predictors of KD diagnosis. Among the KD patients, 80 were IVIG resistant. Compared with IVIG-responsive patients, IVIG-resistant patients presented significantly higher levels of IFN-γ, IL-10, IL-17, IL-2, IL-5, IL-6, and IL-8 but lower levels of IFN-α. Logistic regression revealed that IL-10 and IL-8 were independent predictors of IVIG resistance. When the concentration of IL-10 exceeded 14.70 pg/mL, the sensitivity and specificity for predicting IVIG resistance were 0.675 and 0.748, respectively. Similarly, when the concentration of IL-8 exceeded 23.55 pg/mL, the sensitivity and specificity were 0.725 and 0.658, respectively.

Conclusion: The 12-cytokine panel has potential as a diagnostic and predictive tool for KD. Elevated IL-10 and IL-5 levels are independent predictors of KD diagnosis, whereas elevated IL-10 and IL-8 levels are independent predictors of IVIG resistance. These findings support the clinical utility of cytokine profiling in KD management.

Keywords: Kawasaki disease, 12-cytokine panel, intravenous immunoglobulin resistance, child

Introduction

Kawasaki disease (KD) is an acute systemic vasculitis predominantly affecting children and represents one of the leading causes of acquired heart disease in pediatric populations.[1] Although standard treatment with intravenous immunoglobulin (IVIG) combined with aspirin has significantly reduced the incidence of coronary artery lesions (CALs), approximately 10–20% of patients remain unresponsive to IVIG therapy. These non-responders are at markedly increased risk of

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developing CALs.[2,3] Early prediction could facilitate timely adjustments to the treatment strategy-such as the early combination of glucocorticoids-which may play a crucial role in improving patient outcomes and shortening the disease course.[4] Therefore, early identification of KD and prediction of IVIG resistance are critical for optimizing clinical management and improving outcomes.

Immune dysregulation plays a central role in the pathogenesis of KD. Previous studies have demonstrated that dynamic changes in the Th1/Th2 cytokine profile are closely associated with disease progression.[5] Our prior research[5] revealed that a low pretreatment level of tumor necrosis factor-alpha (TNF-α < 2 pg/mL) was predictive of IVIG resistance, with a specificity of 74.2% and a sensitivity of 66.7%. Additionally, an elevated pretreatment interleukin-10 (IL-10 > 8 pg/mL) level was associated with CALs (sensitivity 75.0%, specificity 64.4%), while post-treatment IL-6 > 10 pg/mL showed even greater predictive value (specificity 81.7%). Furthermore, non-responders exhibited delayed clearance of IL-6 and IL-10, along with a paradoxical increase in TNF-α levels following IVIG administration.

However, the immunological network underlying KD extends beyond the traditional Th1/Th2 paradigm. Recent evidence suggests that Th17-mediated inflammatory responses and monocyte-derived cytokines (eg, IL-1β and IL-8) play pivotal roles in endothelial injury and vascular inflammation.[6–9] Moreover, most previous studies have focused on a limited panel of 6–8 cytokines, and a comprehensive analysis of the broader immune landscape is lacking.

In this study, we aimed to evaluate a panel of 12 key cytokines to establish a multifactor predictive model for KD diagnosis and IVIG responsiveness. By integrating multidimensional immunological indicators, we sought to explore the potential of cytokines as biomarkers for therapeutic response and to provide a novel basis for risk stratification and individualized treatment in KD patients.

Materials and Methods

Study Population and Diagnostic Criteria

We conducted a retrospective case-control study involving pediatric patients admitted to Children's Hospital, Zhejiang University School of Medicine, between December 1, 2023, and March 30, 2025. Patients diagnosed with KD and febrile controls were enrolled for comparative analysis on the basis of clinical records, laboratory findings, and echocardiographic data. This study was approved by the Medical Ethics Committee of the Children's Hospital of Zhejiang University School of Medicine (2025-IRB-0318-P-01).

A KD diagnosis was established according to the following criteria: complete KD: presence of fever lasting ≥5 days and at least four of the following five principal clinical features: (1) bilateral bulbar conjunctival injection; (2) oral and lip changes, including erythema, cracking, strawberry tongue, or diffuse oral mucosal injection; (3) polymorphous rash, including isolated BCG scar erythema; (4) peripheral extremity changes, such as erythema or edema of the hands and feet in the acute phase, or periungual desquamation in the convalescent phase; and (5) cervical lymphadenopathy (≥1.5 cm in diameter), typically unilateral and nonsuppurative. Incomplete KD: Fever persisting ≥5 days with fewer than four principal clinical features, diagnosed according to the 2017 American Heart Association scientific statement guidelines.[2]

The febrile controls were defined as children with (1) a body temperature >38.5°C and (2) available results for the 12-cytokine panel.

Treatment Protocol

Upon confirmation of KD diagnosis, patients received IVIG at a single dose of 2 g/kg, along with moderate-dose aspirin (30–50 mg/kg/day). In cases where aspirin was contraindicated, clopidogrel (0.2–1 mg/kg/day) was used as an alternative.

Definitions of IVIG Resistance and CALs

IVIG resistance was defined as persistent or recurrent fever ≥38°C at least 36 hours after completion of the initial IVIG infusion or recurrence of fever within two weeks (typically between days 2–7) accompanied by at least one principal clinical feature of KD after excluding other potential causes of fever.[2] CALs were assessed by echocardiography and defined as a coronary artery *z* score ≥2.5 on the basis of the internal diameter adjusted for body surface area.[2]

Exclusion Criteria

Patients with incomplete clinical data, those who received IVIG or corticosteroids prior to admission, or those with delayed treatment (IVIG administration >10 days after onset) were excluded from the study.

Methodology

Cytokine Analysis: Venous blood samples were collected from patients with KD during the acute phase before IVIG treatment. For febrile controls, blood samples were obtained at the time of admission. A total of 1 mL of venous blood was transferred into a serum separation tube without anticoagulant and allowed to clot at room temperature for 30 minutes. Approximately 0.5 mL of serum was then separated and sent for analysis. All the samples were processed and analyzed within 4 hours of collection. If immediate analysis was not feasible, the serum samples were stored at 2–8°C for no more than 24 hours. Repeated freeze-thaw cycles were strictly avoided.

Serum levels of 12 cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17, IFN-α, IFN-γ, and TNF-α) were quantified using a multiplex immunofluorescence assay (cytometric bead array-based flow fluorescence technology) with a commercial kit (Jiangxi Saiji Biotechnology Co., Ltd). The assay is based on a sandwich immunoassay principle in which polystyrene microspheres, each with a distinct fluorescence intensity, are coated with monoclonal antibodies specific to individual cytokines. After incubation with serum samples, cytokines were captured by the corresponding microspheres, followed by the addition of phycoerythrin (PE)-labeled detection antibodies to form sandwich complexes. The fluorescence intensity was measured using a flow cytometer (BD FACS Calibur), and the cytokine concentrations were calculated based on standard curves.

Prior to analysis, all the samples were thawed at room temperature and processed strictly according to the manufacturer's instructions. The linear detection range was 2.5–2500 pg/mL for most cytokines (10–2500 pg/mL for IL-17), with a lower limit of detection of 2.5 pg/mL (10 pg/mL for IL-17). Each batch included negative controls and serially diluted standards to ensure accuracy and reproducibility.

Clinical characteristics, including sex, age in months, inflammatory markers, echocardiographic findings, treatment regimens, and outcomes, were retrospectively collected from electronic medical records.

Statistical Analysis

The normality of continuous variables was assessed using the one-sample Kolmogorov–Smirnov test. Normally distributed data were expressed as the means ± standard deviations and were compared via independent-sample *t* tests. Nonnormally distributed data were presented as medians (interquartile ranges, P25–P75) and were analyzed via the Mann–Whitney *U*-test. Categorical variables were expressed as counts and percentages (%) and were compared via the chi-square test. This study employed a binary logistic regression model to identify independent risk factors influencing (1) the diagnosis of KD (yes/no) and (2) IVIG resistance (yes/no).

Receiver operating characteristic (ROC) curves were constructed using clinical features and cytokine levels from all KD patients and febrile controls. The sensitivity and specificity for predicting KD and IVIG resistance were calculated on the basis of optimal cutoff values derived from ROC analysis. All the statistical analyses were performed via SPSS version 23.0. A two-tailed P value <0.05 was considered statistically significant.

Results

Comparison Between Kawasaki Disease Patients and Febrile Controls

Between December 2023 and March 2025, a total of 864 children diagnosed with KD were hospitalized at our institution. After cases with incomplete data, prior use of IVIG or corticosteroids, or delayed treatment (IVIG administration >10 days after onset) were excluded, 686 KD patients were ultimately enrolled, including 409 males and 277 females, with a mean age of 70.0 (38.0, 109.0) months. Additionally, 101 febrile children without KD admitted during the same period were included as controls (Figure 1). All children have been followed up for more than six months.

Comparative analysis revealed that KD patients were significantly younger than control patients were, while no significant difference in sex distribution was detected. Compared with those in the controls, the serum levels of IFN-α,

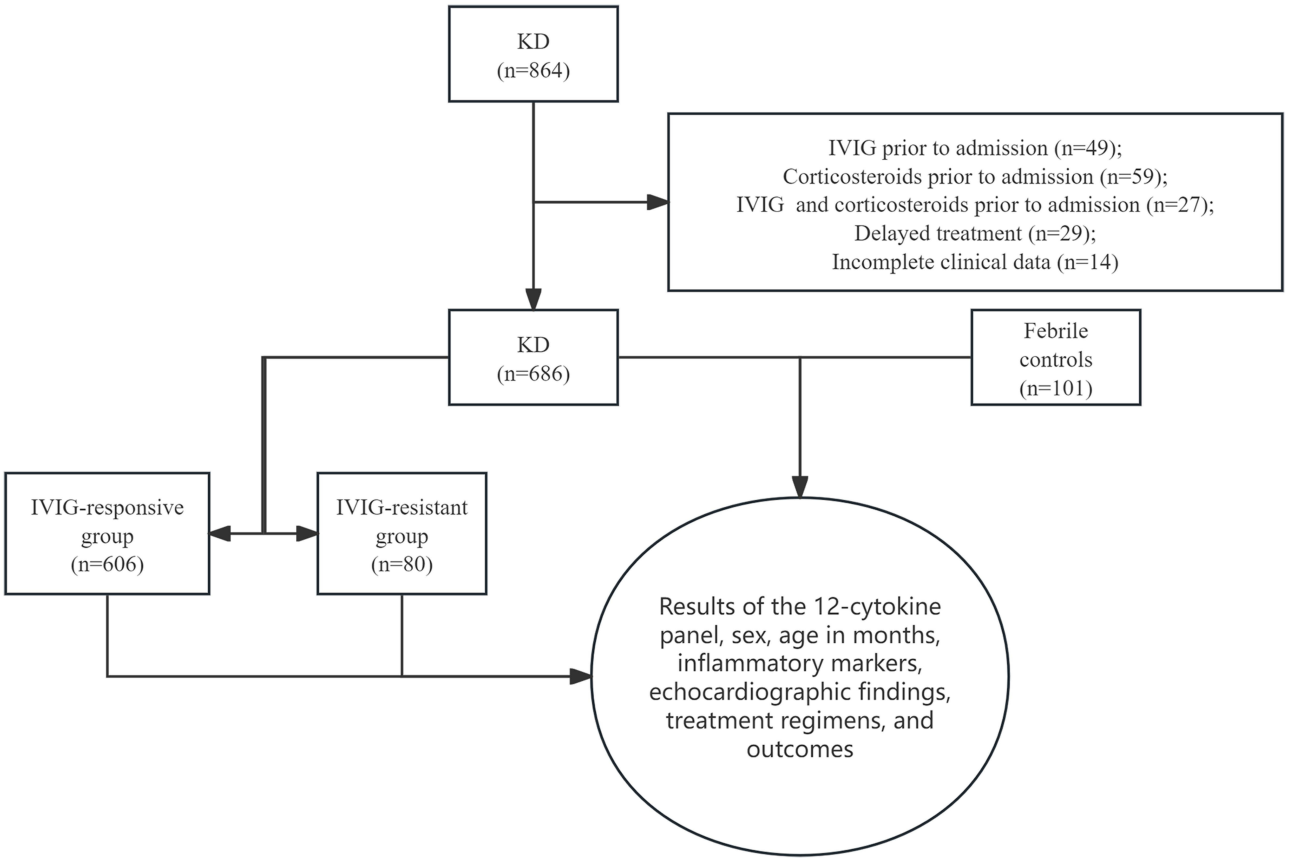

Figure 1 Flow of participants through the study.

IL-10, IL-1β, IL-2, IL-4, IL-5, IL-6, and IL-8 were significantly elevated in the KD group. In addition, the absolute neutrophil count and white blood cell count were significantly greater in KD patients. However, no significant differences in C-reactive protein (CRP) or the erythrocyte sedimentation rate (ESR) were detected between the two groups (Table 1).

Table 1 Comparison of Clinical Characteristics Between Kawasaki Disease Patients and Febrile Controls

Item	Controls	KD	Z	*P*
Case number	101	686		
Age (month)*	70.0 (38.0, 109.0)	31.0 (17.0, 55.0)	−7.592	<0.001
Number of boys (%)	57 (56.4%)	409 (59.6%)	0.370	0.543
IFN-γ	4.10 (2.75, 10.20)	3.90 (2.80, 5.80)	−1.439	0.150
IFN-α*	1.90 (1.40, 2.40)	2.10 (1.68, 2.70)	−2.505	0.012
IL-10*	3.40 (2.15, 6.30)	7.55 (4.10, 18.30)	−7.813	<0.001
IL-12p70	3.20 (2.65, 4.10)	3.30 (2.60, 4.10)	−0.288	0.773
IL-17	5.50 (3.55, 9.25)	5.70 (3.58, 9.60)	−0.348	0.728
IL-1β*	5.80 (4.30, 7.75)	6.60 (5.10, 8.70)	−2.812	0.005
IL-2*	3.40 (2.60, 4.25)	4.00 (3.20, 4.90)	−5.245	<0.001
IL-4*	3.20 (2.60, 4.05)	3.40 (2.80, 4.10)	−2.077	0.038
IL-5*	1.60 (1.20, 1.90)	2.50 (1.80, 4.40)	−8.899	<0.001
IL-6*	26.60 (13.05, 59.30)	53.50 (26.60, 112.93)	−5.304	<0.001
IL-8*	9.60 (5.80, 16.65)	18.30 (10.30, 34.43)	−6.535	<0.001

(*Continued*)

Table 1 (Continued).

Item	Controls	KD	Z	*P*
TNF-α	2.20 (1.50, 3.25)	2.30 (1.60, 3.13)	−0.292	0.770
Neutrophil (%)	63.10 (44.25, 73.65)	62.80 (46.58, 74.75)	−0.747	0.455
Neutrophil*	5.22 (3.24, 8.21)	6.88 (4.11, 10.02)	−2.887	0.004
White blood cell*	9.03 (6.48, 12.15)	11.18 (8.25, 14.54)	−3.673	<0.001
Platelet	346.0 (252.5, 460.0)	355.5 (287.0, 445.3)	−1.275	0.202
Hemoglobin	112.0 (104.0, 119.0)	109.0 (103.0, 116.0)	−1.364	0.173
CRP	40.62 (15.61, 68.66)	39.20 (16.16, 74.47)	−0.343	0.731
ESR	54.60 (42.43, 68.83)	51.63 (33.58, 73.56)	−1.021	0.307

Note: *$P<0.05$.
Abbreviations: IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Table 2 Logistic Regression Model of Variables Independently Associated with Kawasaki Disease Compared with Febrile Controls

Effect	Sig.	Exp(B)	95% C.I. for EXP(B)	
			LL	UL
Age in months*	<0.001	0.974	0.966	0.982
IFN-α	0.719	1.002	0.990	1.014
IL-10*	0.005	1.068	1.020	1.117
IL-1β	0.519	1.017	0.966	1.070
IL-2	0.537	1.075	0.855	1.352
IL-4	0.896	0.982	0.750	1.286
IL-5*	<0.001	1.935	1.385	2.703
IL-6	0.849	1.000	0.997	1.003
IL-8	0.989	1.000	0.984	1.017
Neutrophil*	0.021	1.170	1.024	1.337
White blood cell*	0.037	0.878	0.777	0.992
Intercept	0.063	3.756		

Note: *$P<0.05$. Note. Omnibus tests of model coefficients (model) $\chi2 = 164.743$, $P<0.001$; Hosmer and Lemeshow test $\chi2 = 13.077$, $P=0.109$.
Abbreviations: CI, confidence interval; LL, lower limit; UL, upper limit; IFN, interferon; IL, interleukin.

A logistic regression model was subsequently constructed to identify independent predictors of KD compared with febrile controls. The analysis revealed that age in months (OR=0.974, CI [0.966, 0.982], $P<0.001$), IL-10 level (OR=1.068, CI [1.020, 1.117], $P=0.005$), IL-5 level (OR=1.935, CI [1.385, 2.703], $P<0.001$), absolute neutrophil count (OR=1.170, CI [1.024, 1.337], $P=0.021$), and white blood cell count (OR=0.878, CI [0.777, 0.992], $P=0.037$) were independent predictive factors associated with KD (Table 2).

Further analysis revealed the diagnostic performance of individual and combined markers for KD patients compared with febrile controls. The area under the curve (AUC) of the ROC curve for single indicators was as follows: 0.734 for age in months, 0.741 for IL-10, 0.774 for IL-5, 0.613 for white blood cell count, and 0.589 for absolute neutrophil count. The AUC for the combined diagnostic model was 0.853, with a sensitivity of 0.758 and specificity of 0.812 (Figure 2).

When the IL-10 concentration was greater than 7.25 pg/mL, the sensitivity and specificity for diagnosing KD were 0.517 and 0.832, respectively. When the concentration of IL-5 exceeded 1.950 pg/mL, the sensitivity and specificity were 0.678 and 0.772, respectively. Similarly, at a cutoff of 2.050 pg/mL for IL-5, the sensitivity and specificity were 0.638 and 0.812, respectively.

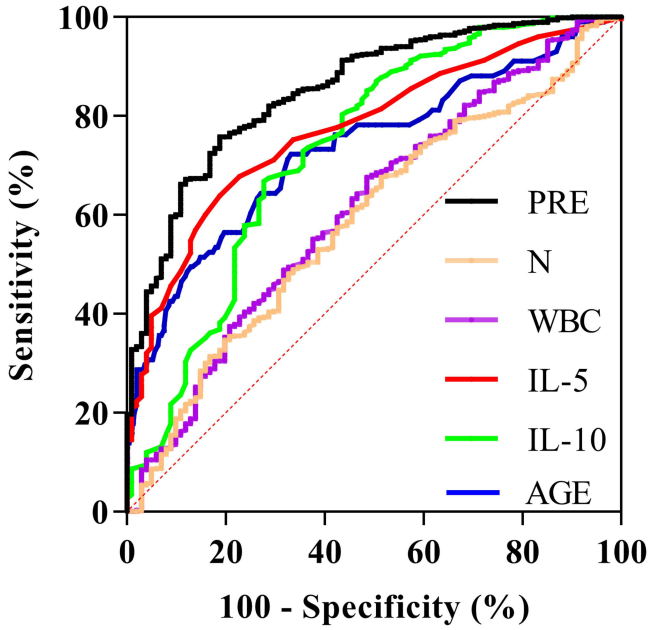

Figure 2 Receiver operating characteristic (ROC) curves for the diagnosis of Kawasaki disease.
Abbreviations: PRE, predicted probability; N, absolute neutrophil count; WBC, white blood cell count; IL, interleukin; AGE, age in months.

Efficacy of the 12-Cytokine Panel in Predicting IVIG Resistance

Among the 686 KD patients included in the analysis, there were no significant differences in age or sex between the IVIG-responsive and IVIG-resistant groups. A total of 606 patients were classified as IVIG-responsive, while 80 were identified as IVIG-resistant. Univariate analysis revealed that the levels of IFN-γ (5.20 (3.43, 7.75) vs 3.80 (2.80, 5.50), $P<0.001$), IL-10 (22.05 (8.90, 71.60) vs 6.85 (3.80, 14.83), $P<0.001$), IL-17 (6.55 (4.20, 12.45) vs 5.60 (3.50, 9.40), $P=0.043$), IL-2 (4.80 (3.70, 5.60) vs 4.00 (3.10, 4.80), $P<0.001$), IL-5 (3.15 (1.90, 6.30) vs 2.50 (1.70, 4.20), $P=0.013$), IL-6 (124.50 (57.95, 233.18) vs 48.50 (24.73, 94.83), $P<0.001$), and IL-8 (44.90 (21.05, 108.33) vs 16.95 (9.80, 30.50), $P<0.001$) were significantly higher in the IVIG-resistant group compared to the IVIG-responsive group. In contrast, IFN-α levels (1.80 (1.50, 2.40) vs 2.10 (1.70, 2.70), $P=0.001$) were significantly lower in the IVIG-resistant group (Figure 3).

A logistic regression model was subsequently constructed to identify independent predictors of IVIG resistance in KD patients. The analysis revealed that IL-10 (OR=1.006, CI [1.000, 1.013], $P=0.047$) and IL-8 (OR=1.016, CI [1.009, 1.024], $P<0.001$) were independent predictive factors associated with IVIG unresponsiveness (Table 3).

To evaluate the predictive value of individual and combined cytokines for IVIG resistance in KD patients, ROC curve analysis was performed. The AUC for individual markers was 0.752 for IL-10 and 0.738 for IL-8. The AUC for the combined diagnostic model was 0.749, with a sensitivity of 0.713 and a specificity of 0.670 (Figure 4).

When the IL-10 concentration was greater than 14.70 pg/mL, the sensitivity and specificity for predicting IVIG resistance were 0.675 and 0.748, respectively. Similarly, when the concentration of IL-8 was greater than 23.55 pg/mL, the sensitivity and specificity were 0.725 and 0.658, respectively.

Discussion

Cytokines, secreted by immune and selected non-immune cells, are pivotal mediators and modulators of immune responses and inflammatory processes.[10] The pathogenesis of KD is considered multifactorial, integrating genetic susceptibility with infectious, environmental, or other antigenic triggers that precipitate an exaggerated inflammatory cascade in predisposed individuals, in which cytokines play a central role.[11] In the present study, we evaluated the diagnostic and predictive utility of a 12-cytokine panel in KD. Elevated IL-10 and IL-5 have emerged as independent predictors of KD diagnosis, whereas elevated IL-10 and IL-8 independently predict IVIG resistance.

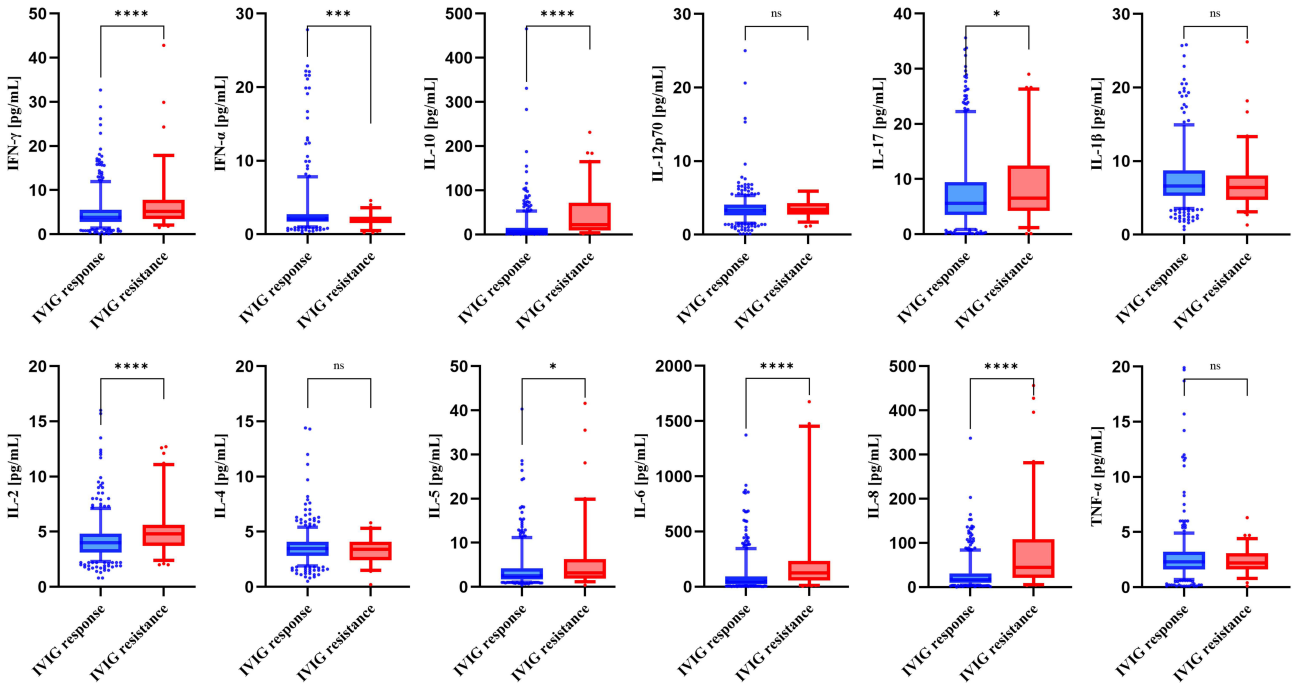

Figure 3 Comparison of 12-cytokine profiles between the IVIG-responsive and IVIG-resistant groups. *P < 0.05, ***P < 0.001, ****P < 0.0001.
Abbreviations: IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

Cytokines are centrally implicated in the pathogenesis of KD. During the acute phase, multiple pro-inflammatory cytokines—such as TNF-α, IL-6, IL-10, and IFN-γ—along with chemokines (eg, CCL2) and growth factors (eg, VEGF) are markedly elevated, orchestrating endothelial injury and systemic inflammation.[5,12–14] These mediators activate immune cells (monocytes and neutrophils) and the vascular endothelium, amplifying the release of inflammatory molecules and upregulating the expression of endothelial adhesion molecules, thereby precipitating vasculitis.[15] In the present study, we evaluated the diagnostic utility of a 12-cytokine panel in KD and identified younger age, high IL-10, high IL-5, elevated white blood cell count, and increased absolute neutrophil count as independent predictors. The combined model yielded an AUC of 0.853, with a sensitivity of 0.758 and a specificity of 0.812.

Table 3 Logistic Regression Model of Variables Independently Associated with IVIG Resistance Compared with IVIG Responsiveness

Effect	Sig.	Exp(B)	95% C.I. for EXP(B)	
			LL	UL
IFN-γ	0.087	0.967	0.930	1.005
IFN-α	0.553	0.975	0.898	1.059
IL-10*	0.047	1.006	1.000	1.013
IL-17	0.923	1.002	0.967	1.038
IL-2	0.836	0.987	0.873	1.116
IL-5	0.710	1.006	0.976	1.036
IL-6	0.095	1.001	1.000	1.002
IL-8*	<0.001	1.016	1.009	1.024
Intercept	<0.001	0.067		

Notes: *P<0.05. Omnibus tests of model coefficients (model) $\chi 2$=74.222, P<0.001; Hosmer and Lemeshow test $\chi 2$=3.937, P=0.863.
Abbreviations: CI, confidence interval; LL, lower limit; UL, upper limit; IFN, interferon; IL, interleukin.

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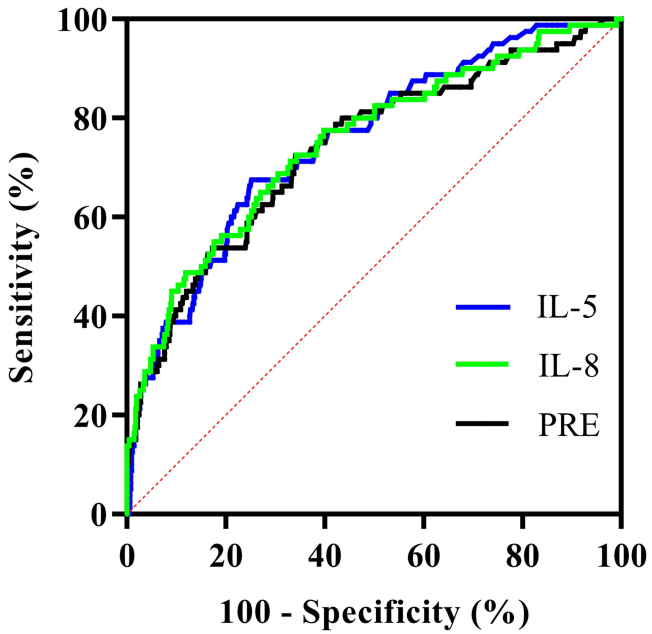

Figure 4 ROC curves of cytokines for predicting IVIG resistance in Kawasaki disease.
Abbreviations: IL, interleukin; PRE, predicted probability.

Approximately 10–20% of children with KD exhibit resistance to IVIG, and IVIG nonresponse constitutes an independent risk factor for coronary artery lesions.[2] Consequently, several studies have recommended that patients at high predicted risk of IVIG resistance receive initial combination therapy with IVIG plus corticosteroids such as methylprednisolone or even biologics such as infliximab.[4,16] Accumulating evidence indicates that elevated cytokine levels correlate with IVIG refractoriness, underscoring the pivotal role of these mediators in KD pathogenesis and treatment response.[17] In the present work, we evaluated a 12-cytokine panel for its ability to predict IVIG resistance and identified high IL-10 and high IL-8 levels as independent predictors of non-response. At a cut-off of 14.70 pg/mL for IL-10, the sensitivity and specificity for predicting IVIG resistance were 0.675 and 0.748, respectively, whereas an IL-8 threshold of 23.55 pg/mL yielded a sensitivity of 0.725 and a specificity of 0.658. Previously published models for predicting IVIG resistance, both domestically and internationally, have consistently included CRP.[18,19] Cytokines act as upstream signals, whereas CRP functions as a downstream effector; the two are closely correlated, especially for IL-6.[20] Therefore, CRP was not included in our IVIG-resistance prediction model.

We observed a dual predictive role for IL-10 in both the diagnosis of KD and the identification of IVIG resistance, echoing our 2013 finding that pretreatment with IL-10 > 8 pg/mL is associated with CALs. Functionally, IL-10 suppresses the production of key inflammatory mediators—including TNF-α, IL-6, and IL-1—thereby attenuating excessive inflammation.[21] Consistent with a compensatory counter-regulatory response, the serum IL-10 concentration increases markedly during the acute phase of KD and decreases after therapy.[22,23] This temporal pattern has been corroborated in patients with KD shock syndrome (KDSS), in whom IL-10 concentrations are significantly higher than those in uncomplicated KD patients and correlate with disease severity, supporting its potential as a biomarker for KDSS.[24] At the genetic level, polymorphisms within the IL-10 promoter (eg, −627 A/C and −592 A>C) have been linked to an increased risk of coronary aneurysms, implying that heritable variation in IL-10 expression modulates individual susceptibility and clinical progression.[25,26] Collectively, the pleiotropic effects of IL-10 in KD include both anti-inflammatory modulation and, under certain conditions, the promotion of vascular pathology, underscoring the value of serial IL-10 measurements for disease monitoring and prognostic assessment.

IL-5, a cytokine secreted by Th2 lymphocytes, mast cells, and eosinophils, exerts its biological effects via the IL-5 receptor.[27] It drives B-cell differentiation and antibody production, governs eosinophil development and function, and participates in immune regulation.[28–30] Consequently, IL-5 is implicated in allergic disorders (eg, asthma and allergic

rhinitis), parasitic infections, autoimmune diseases, and selected malignancies.[29,30] In the present study, serum IL-5 levels were significantly elevated in KD patients relative to febrile controls and were further increased in those exhibiting IVIG resistance. These findings suggest that IL-5 may contribute to KD pathogenesis and modulate therapeutic responsiveness and suggest that IL-5–targeted therapy could constitute a novel treatment paradigm for KD.

IL-8 (CXCL8), a prototypical CXC chemokine, serves as a central mediator of inflammation, orchestrating chemotaxis and cellular activation, endothelial regulation, pro-inflammatory cascades, tissue injury, and angiogenesis in chronic inflammation.[31] During the acute phase of KD, plasma IL-8 concentrations are markedly elevated and form a synergistic pro-inflammatory network with IL-6, IL-10, and TNF-α. This axis may drive neutrophil-mediated vascular injury, activate the NF-κB signaling pathway, and modulate endothelial dysfunction, thereby contributing to the vasculitic process in KD.[32–34] In the present cohort, IL-8 levels were significantly higher in IVIG-resistant patients; at a cutoff of 23.55 pg/mL, IL-8 predicted IVIG unresponsiveness with a sensitivity of 0.725 and a specificity of 0.658.

Compared with prior investigations, the present study extends the breadth and integrates the depth of existing knowledge. By incorporating IL-5, IL-8, and IL-17 into the panel, we revealed the independent predictive value of Th2-related IL-5 and the chemokine IL-8 and constructed a multidimensional model integrating "cytokine–immune cell–clinical parameter" information (eg, the IL-5 + IL-10 + younger age diagnostic score).

Nevertheless, several limitations must be acknowledged. First, as a retrospective single-center study with a modest sample size, potential geographic and ethnic biases may limit generalizability to other populations. Second, post-treatment 12-cytokine measurements were not performed, precluding longitudinal kinetic analyses. Third, the use of contemporaneous febrile patients as controls may introduce selection bias. Prospective validation with larger cohorts and, if warranted, multicenter randomized controlled trials are needed to confirm these findings.

Conclusion

The 12-cytokine panel effectively supports both the diagnosis of KD and the prediction of IVIG resistance. Elevated IL-10 and IL-5 are independent predictors of KD diagnosis, whereas elevated IL-10 and IL-8 independently predict IVIG unresponsiveness.

Abbreviations

KD, Kawasaki disease; IVIG, intravenous immunoglobulin; CALs, coronary artery lesions; AUC, area under the curve.

Data Sharing Statement

Anonymized research data are available from the corresponding author upon reasonable request.

Ethics Declarations

This retrospective study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The medical ethics committee of the Children's Hospital of Zhejiang University School of Medicine approved this study (NO.: 2025-IRB-0318-P-01). Since the information was anonymized and the submission did not include images that may identify the person, The medical ethics committee of the Children's Hospital of Zhejiang University School of Medicine waived the need of obtaining individual informed consent forms.

This study was conducted and reported in accordance with the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines.

Author Contributions

Weixing Kong: Conceptualization, Data curation, Investigation, Methodology and Writing – original draft; Lichao Gao: Conceptualization, Data curation, Formal analysis, Methodology and Writing – original draft; Jian Hu: Investigation, Supervision and Writing – review and editing; Zhufei Xu: Investigation, Supervision and Writing – review and editing; Qing Zhang: Investigation, Supervision and Writing – review and editing; Yujia Wang: Investigation, Supervision and Writing – review and editing; Songling Fu: Investigation, Supervision and Writing – review and editing; Chunhong Xie:

Investigation, Supervision and Writing – review and editing; Fangqi Gong: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision and Writing – review and editing. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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