


# Utilizing T-Lymphocyte Activation-Related Cytokines to Predict Non-Responsiveness to Treatment in Pediatric Kawasaki Disease

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**Objective:** To investigate the predictive value of T-lymphocyte activation-related cytokines in non-responsive Kawasaki disease.

**Methods:** Eighty-two children with Kawasaki disease, hospitalized from June 2022 to December 2023, were divided into two groups based on treatment response: the sensitive Kawasaki disease group (n=71) and the non-responsive Kawasaki disease group (n=11). Serum levels of T-lymph activation-related cytokines, including interleukin-2, 6, 7, 12, 15, 17, and tumor necrosis factor alpha, were measured before and after IVIG treatment in both groups. The differences in cytokine levels between the two groups were compared pre- and post-treatment. The ability of these cytokines to discriminate non-responsive Kawasaki disease was evaluated using ROC curves to determine the cut-off value.

**Results:** Before initial treatment, IL-2, IL-6, IL-7, IL-12, IL-15, IL-17, and tumor necrosis factor- $\alpha$  values were significantly higher in the non-responsive Kawasaki disease group compared to the sensitive Kawasaki disease group. Comparisons before and after initial treatment showed significant decreases in IL-6 and 17 in the sensitive Kawasaki disease group and significant decreases in IL-6 and 7 in the non-responsive Kawasaki disease group. IL-6 and 17 significantly increased in the sensitive group compared to the non-responsive group after initial treatment. The ROC curves indicated that IL-6 predicted the area under the curve (AUC) for non-responsive Kawasaki disease to be 0.859 before treatment and 0.920 after treatment. Similarly, IL-17 had AUC values of 0.699 before treatment and 0.884 after treatment.

**Conclusion:** Reassessing IL-6 and IL-17 following the initial treatment for Kawasaki disease may improve early warning signals for unresponsive Kawasaki disease.

**Keywords:** Kawasaki disease, unresponsive Kawasaki disease, cytokines, T-lymphocyte activation, immunoglobulin

## Introduction

Kawasaki disease (KD) is an acute systemic vasculitis that presents in early childhood. Its most significant complication is coronary artery aneurysm (CAA), which can cause myocardial ischemia or acute coronary syndromes. KD has become the leading cause of acquired heart disease in most developed countries and regions.<sup>1,2</sup> The standard treatment for KD is a single injection of intravenous immunoglobulin (IVIG) 2 g/kg and aspirin. However, approximately 10%~20% of children do not respond to IVIG and require additional IVIG therapy and/or other treatments. These patients are categorized as having immunoglobulin-unresponsive KD. Immunoglobulin-unresponsive KD is a high-risk factor for CAA.<sup>3-6</sup> The lack of response to IVIG may indicate severe underlying inflammation.<sup>7</sup> Additionally, more severe complications of the hyperinflammatory state, such as KD shock syndrome (KDSS) or KD combined with macrophage activation syndrome (MAS), may occur,<sup>8-10</sup> endangering children's lives. Non-responsive KD (also known as refractory KD) is a challenging problem for clinicians. It requires secondary treatment after standard therapy, and early recognition is crucial for initiating IVIG and additional treatments. Predicting IVIG resistance is key to enhancing initial therapy and

preventing cardiac complications.<sup>11</sup> Existing national scoring systems for predicting IVIG resistance vary among different ethnicities.<sup>12</sup> Since 2006, approximately 17 predictive models have been published globally, including those by Kobayashi (2006), Tang, Y. (2016), and Piram-M (2020). Most models are from Asia (China, Japan, Taiwan, and Israel), and two are from the West (France and the United States).<sup>13</sup> All studies are single-center studies. For example, the earliest Kobayashi score (2006) has some value in predicting treatment failure in unresponsive KD in the Japanese population but may have limited applicability in the UK, USA, and other regions.<sup>14</sup> There is a lack of objective and reliable experimental markers to predict drug resistance. Several studies have shown an association between T-cell activation and anti-IVIG KD. T-cell activation requires multiple co-stimulatory signals and cytokines.<sup>15,16</sup> Measurement of cytokines is commonly used in clinical practice. Therefore, cytokines associated with T-cell activation (IL-2, IL-7, IL-12, IL-15, and IL-17) and cytokines currently studied internationally (IL-6, TNF- $\alpha$ ) were selected. In this study, we compared IL-2, IL-6, IL-7, IL-12, IL-15, IL-17, and tumor necrosis factor-alpha (TNF- $\alpha$ ) in sensitive versus non-responsive KD patients. We investigated whether these cytokines can provide valid clues for non-responsive KD and enhance existing scoring mechanisms.

## Materials and Methods

### Study Population

This study was conducted from June 2022 to December 2023 at a specialized children's hospital in Zhejiang Province, China. Children aged 1–14 years diagnosed with KD in the inpatient ward were included in the study. The study was approved by the Ethics Committee of the Institutional Review Board at Hangzhou Children's Hospital [Ethical Review Approval No.: (2020) Ethical Approval (Research) No. 10], Informed consent was obtained from the parents or guardians of the minor participants. Inclusion criteria: 1) compliance with the 2017 American Heart Association (AHA) guidelines for the diagnosis of KD;<sup>17</sup> 2) age range of 1–14 years, both sexes; 3) complete inpatient data. Exclusion criteria: 1) comorbidities with other immune or immunodeficiency disorders, such as systemic juvenile idiopathic arthritis and leukemia; 2) recent treatment with immunoglobulin; 3) incomplete inpatient data.

Grouping criteria: All patients received intravenous immunoglobulin (IVIG) at a dose of 2 g/kg and aspirin at a dose of 30–50 mg/kg within 10 days of diagnosis. Unresponsive KD<sup>18</sup> was defined as fever that did not subside ( $T > 38^{\circ}\text{C}$ ) after 36 hours of IVIG treatment or reappearance of fever 2–7 days after resolution, accompanied by at least one main clinical feature of KD. Criteria for coronary artery anomalies (CAL):<sup>19</sup> (1) Noninvasive: Z-value  $< 2$ ; (2) Abnormal: Z-value  $\geq 2$  or initial Z-value  $< 2$ , with a decrease in Z-value by  $\geq 1$  during follow-up.

Diagnostic criteria for KD comorbidity: (1) Hepatic insufficiency: Elevated ALT, serum ALT  $> 50$  U/L. (2) Myocardial damage: CK-MB  $> 50$  U/L or ultrasensitive troponin (hs-cTn)  $> 0.05$  ng/mL. (3) Hypoproteinemia: Total protein  $< 60$  g/L or albumin  $< 25$  g/L. (4) Cholestasis: Direct bilirubin  $> 17$   $\mu\text{mol/L}$ .

### T-Lymphocyte-Activated Cytokines Detection

The T lymphocyte activation-related cytokines test is performed using a yellow procoagulation blood collection tube to collect a 2mL blood sample from the child's peripheral vein. The sample is kept at room temperature for 15–30 minutes, then centrifuged at 2000g for 10 minutes at  $4^{\circ}\text{C}$ . After coagulation, the supernatant is collected and stored at  $-20^{\circ}\text{C}$  or lower for later use. Serum samples will be sent to Hangzhou Dacheng Biotechnology Co. for analysis. The levels of IL-2, IL-6, IL-7, IL-12, IL-15, IL-17, and TNF- $\alpha$  will be measured according to the instructions of the ELISA kit (ELK Biotechnology).

### Data Acquisition and Analysis

Clinical data collected included sex, age, clinical characteristics of the subjects, and clinical treatment received. Clinical characteristics primarily referred to complications meeting the diagnostic criteria for KD. Laboratory data were collected 24 hours before IVIG treatment and 3 days after the temperature returned to normal post-IVIG treatment.

## Statistical Analysis

SPSS 25.0 statistical software was used to analyze the data. The raw data were first tested for normality. If they conformed to a normal distribution, a two independent samples *t*-test was used; if they did not, a two-sample rank sum test was used. Numerical data were expressed as numbers and percentages (%) and compared using the chi-square test. One-way analysis of variance (ANOVA) was performed using GraphPad Prism 9, and graphs were plotted to test for equality of variance. If the variances are equal, ordinary ANOVA should be used; if they are not, Bonferroni and Welch ANOVA methods should be used. MedCalc statistical software was used to plot ROC curves. In all statistical analyses,  $P < 0.05$  was considered statistically significant.

## Results

### General Information

Eighty-two children with KD were included in this study. Among them, 48 were males and 34 were females, with a male-to-female ratio of 1.44:1. There were 19 cases in the 1–12 months age group, 24 cases in the 13–24 months age group, 21 cases in the 25–60 months age group, and 18 cases in the >60 months age group. According to whether the fever did not subside ( $T > 38^{\circ}\text{C}$ ) after 36 hours of initial IVIG (2g/kg/day) treatment or reappeared 2–7 days after subsiding, along with at least one main clinical feature of KD, the cases were divided into 71 in the sensitive KD group and 11 in the non-responsive KD group. The 11 cases of non-responsive KD were treated with a second full dose of IVIG (2g/kg/day, total dose 4g/kg) in combination with corticosteroids (1–2mg/kg each time, twice a day for 3–5 days, tapered off within 15 days after temperature stabilization and C-reactive protein reduction). In one case, after the second round of IVIG combined with hormone therapy, fever reappeared when the hormone dose was reduced. Infliximab (IFX) (5 mg/kg) was administered once, and the fever did not recur.

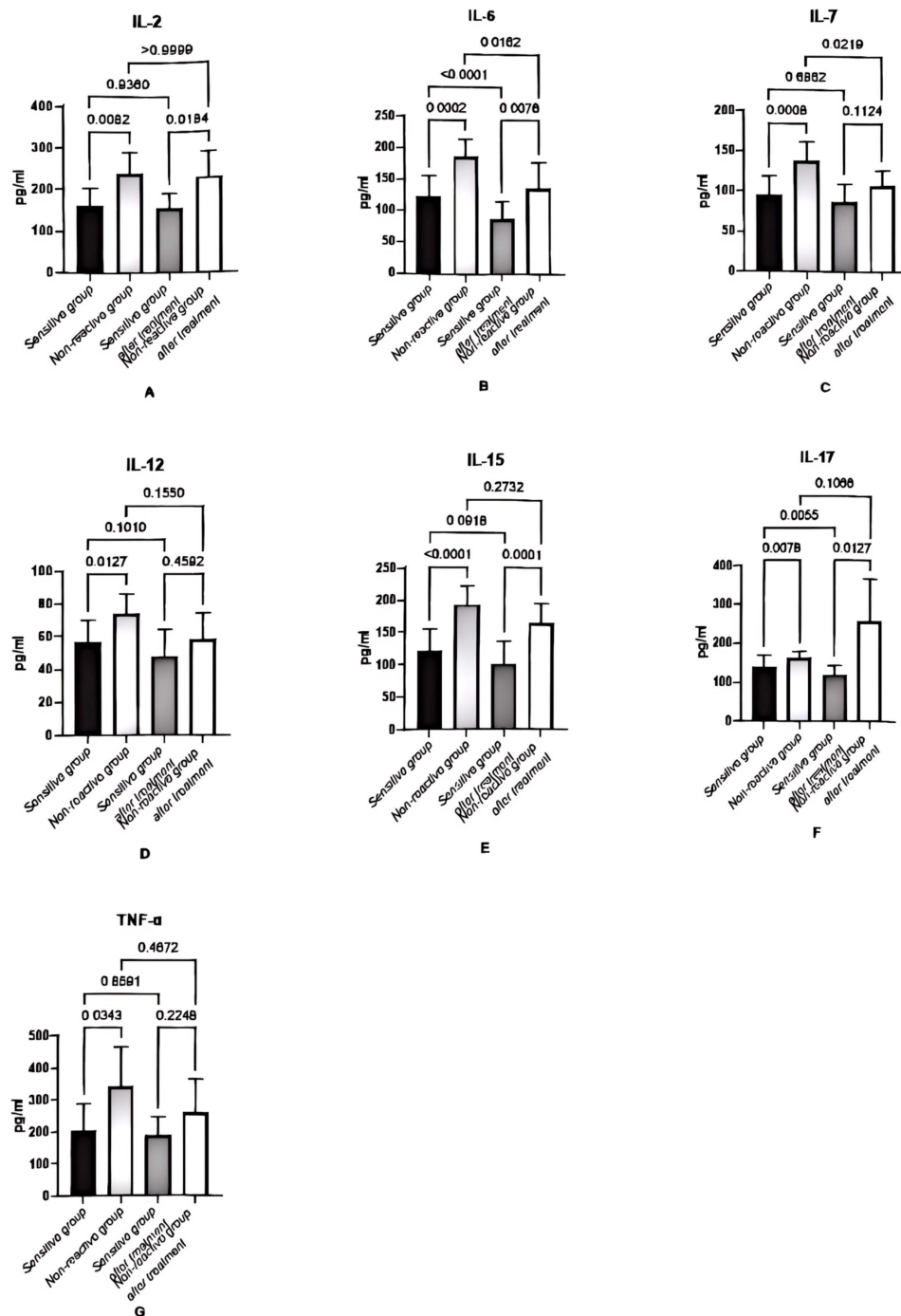
There was a significant increase in the proportion of unresponsive KD cases combined with hepatic insufficiency ( $p=0.004$ ). There was no statistically significant difference when comparing other comorbidities (Table 1).

**Table 1** Presents the Essential Clinical Data [Cases (%) and Represented by X2, M (P25, P75)]

Indicators	Sensitive Group (n=71)	Non-Responsive group (n=11)	Z/x2 value	P
General				
Male	39(54.9)	5(45.4)	0.344	0.558
Age (months)	23(12,60)	24(18,47)	0.085	0.932
Past history				
History of Kawasaki disease	1(1.4)	0	0.157	0.692
Congenital heart disease	1(1.4)	0	0.157	0.692
Comorbidities				
Shock	1(1.4)	0	0.157	0.692
Coronary artery dilatation (Z-score > 2)	3(4.2)	1(9.1)	0.199	0.656
Liver insufficiency	20(28.1)	8(72.7)	8.409	0.004
Myocardial damage	3(4.2)	0	0.482	0.487
Granulocytopenia	4(5.2)	0	0.651	0.420
Gastrointestinal disorders	5(7.0)	2(18.1)	1.514	0.219
Hypoproteinemia	1(1.4)	1(9.1)	2.362	0.124
Cholestasis	1(1.4)	0	0.157	0.692
Pericardial effusion	1(1.4)	0	0.157	0.692
Arthritis	1(1.4)	0	0.157	0.692
Primary Treatment				
2 injections of human immunoglobulin	0	11(100)	82.000	<0.001
Methylprednisolone	11(15.4)	11(100)	34.648	<0.001
Infliximab	0	1(9.1)	6.534	0.011

## T-Lymphocyte Activation-Related Cytokine Levels

Differences in changes in T-lymphocyte-activating cytokines IL-2, IL-6, IL-7, IL-12, IL-15, IL-17, and TNF- $\alpha$  before and after treatment were compared between the sensitive and non-responder groups (see Figure 1). Before initial treatment, IL-2,



**Figure 1** The study assessed the variations in cytokine levels associated with T lymphocyte activation (IL-2, 6, 7, 12, 15, 17, and TNF- $\alpha$ ) across different groups. **(A)** Significant differences in IL-2 levels were noted between the sensitive and non-responsive groups, both before and after treatment ( $P < 0.05$ ). **(B)** Statistically significant differences in IL-6 levels were observed in the sensitive group compared to the non-reactive group before and after treatment, as well as within each group over the treatment period ( $P < 0.05$ ). **(C)** Statistically significant differences were observed pre-treatment between the sensitive and non-responsive group before and after treatment ( $P < 0.05$ ). **(D)** There was a significant difference in IL-12 levels between the sensitive and non-responsive groups before treatment ( $P < 0.05$ ). **(E)** Statistically significant differences were noted between the IL-15-sensitive and non-responsive groups before and after treatment ( $P < 0.05$ ). **(F)** Significant variations in IL-17 levels were noted between the sensitive and non-responsive groups before and after treatment, including changes within the sensitive group itself ( $P < 0.05$ ). **(G)** A significant difference in TNF- $\alpha$  levels was found between the sensitive and non-responsive groups before treatment ( $P < 0.05$ ).

IL-6, IL-7, IL-12, IL-15, IL-17, and tumor necrosis factor- $\alpha$  values were significantly higher in the non-responsive KD group compared to the sensitive KD group. Comparisons before and after initial treatment showed significant decreases in IL-6 and 17 in the sensitive KD group and significant decreases in IL-6 and 7 in the non-responsive KD group. IL-6 and 17 significantly increased in the sensitive group compared to the non-responsive group after initial treatment.

## Predictive Efficacy of IL-6 and IL-17 for Non-Responsive KD

ROC curve analysis revealed that the AUCs for predicting non-responsive KD were 0.859 and 0.920 before and after IL-6 treatment, and 0.699 and 0.884 before and after IL-17 treatment, respectively (Table 2 and Figure 2).

## Discussion

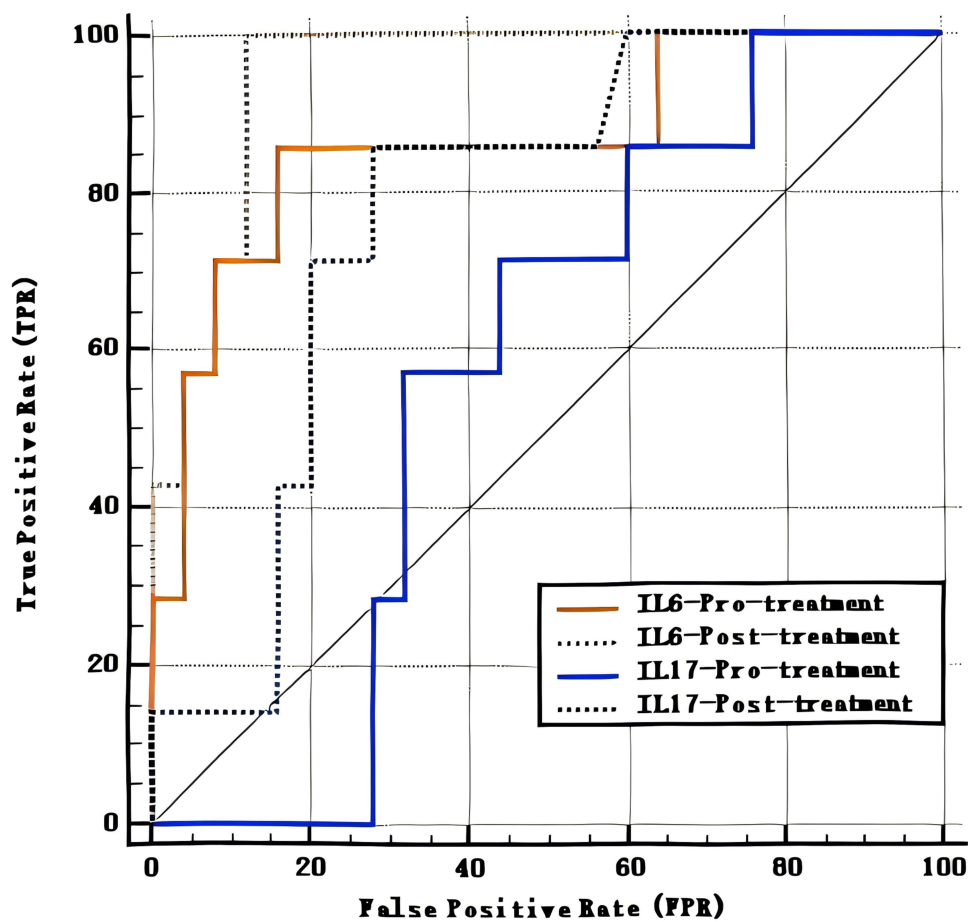
Vascular complications and IVIG response in KD are closely linked to inflammation. The exact pathogenesis of KD remains unknown<sup>20</sup> and is likely multifactorial,<sup>21</sup> potentially involving immune activation triggered by infections in genetically susceptible children, leading to an inflammatory cascade.<sup>22</sup> IVIG-unresponsive KD is less understood and may involve factors like insufficient IVIG dosage, hypermetabolism, neutrophil overactivation, elevated cytokine levels, and immature Fc receptor expression.<sup>23</sup> A large multi-ethnic cohort study identified a polymorphism in the FCGR2A gene, with upregulated Fc $\gamma$ R1IA mRNA levels associated with IVIG resistance. Fc $\gamma$ R1IA interacts with IgG antibodies to activate antigen-presenting cells, prompting T-cell activation.<sup>24</sup>

Research on immune cell profiles during KD, particularly IVIG-unresponsive cases, is limited.<sup>25</sup> Abnormal lymphocyte activation, such as heightened CD8+ T cell activity, may contribute to IVIG resistance.<sup>15,16,26</sup> T cell activation requires antigen stimulation, co-stimulation, and cytokines, enabling differentiation into effector cells that produce immune mediators. Effector Th cells are classified into Th1, Th2, and Th17 subpopulations, regulated by specific cytokines: Th1 (IL-12): Produces IFN- $\gamma$  for cellular immunity. Th2 (IL-25/33): Produces IL-4, IL-5, and IL-13 for parasitic and allergic immunity. Th17 (IL-6): Produces IL-17, IL-21, and IL-22 for tissue inflammatory responses.<sup>27</sup> The  $\gamma$ -chain cytokine family (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21) plays a critical role in T cell differentiation, proliferation, and homeostasis.<sup>28</sup> Based on this, we analyzed IL-2, IL-6, IL-7, IL-12, IL-15, IL-17, and TNF- $\alpha$  for comparison.

In this paper, abnormal liver function was identified as statistically significant. Numerous studies have also highlighted it as a potential risk factor for unresponsive Kawasaki disease. The study further demonstrated significantly elevated levels of IL-2, IL-6, IL-7, IL-12, IL-15, IL-17, and TNF- $\alpha$  in the non-responder group, with IL-6 and IL-17 showing particular significance both before and after treatment. In non-responsive KD, T cell imbalances are observed, with reduced regulatory T cells (Treg) and increased inflammatory Th17 cells. T cell activation involves a complex system,<sup>27,29</sup> with cytokine release playing a critical role: Antigen recognition: T-cell receptors (TCRs) recognize antigens presented by Antigen-Presenting Cells (APCs) via Major Histocompatibility Complex (MHC) molecules. Co-stimulatory signaling: APC-expressed CD80/CD86 interact with CD28 on T cells, delivering essential secondary signals. T cell activation: T cells proliferate and differentiate into effector cells, such as CD8+ cytotoxic T cells and CD4+ T cells (eg, Th1, Th2, Th17). Cytokine release: Activated T cells release cytokines like IL-6 and IL-17 to regulate immune responses.

**Table 2** Pre- and Post-Treatment Efficacy of IL-6 and IL-17 Alone

Indicators	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	P-value
IL-6 Pre-treatment	0.859	0.757–0.930	0.703	87.50	82.81	<0.0001
IL-6 Post-treatment	0.920	0.780–0.984	0.789	90.91	88.00	<0.0001
IL-17 Pre-treatment	0.699	0.583–0.799	0.414	72.73	68.75	0.0153
IL-17 Post-treatment	0.884	0.728–0.968	0.760	100	76.00	<0.0001



**Figure 2** The ROC curves illustrate the pre- and post-treatment area under the curve for IL-6 and IL-17 in predicting nonresponsive Kawasaki disease.

In IVIG-unresponsive KD, hypercytokinemia with elevated TNF- $\alpha$  and IL-6 is a hallmark.<sup>30,31</sup> Studies show significantly higher plasma TNF- $\alpha$  levels in IVIG-unresponsive patients compared to responsive ones, strongly correlating with IVIG resistance.<sup>32,33</sup> Cytokines like IL-2,<sup>34</sup> IL-7, IL-12, IL-15, and IL-17, closely tied to T-cell activation, are also implicated in unresponsive KD. Additionally, IL-6 and TNF- $\alpha$  can be produced by neutrophils, monocytes, and macrophages, confirming that while T-cell activation is central to unresponsive KD, it is not the sole factor in its pathogenesis.

In this study, pairwise comparisons within each group identified IL-6 and IL-17 as significant factors. IL-6 showed statistically significant changes before and after treatment, both between and within the sensitive and non-responsive groups. The IL-17-sensitive group also demonstrated significant differences compared to the non-responsive group before and after treatment, as well as within the group itself. It was found that IL-6 and IL-17 were significantly elevated in the acute phase of non-responsive KD and remained high after initial IVIG treatment. Specifically, IL-6 showed statistical significance both between and within groups before and after treatment. Numerous studies confirm IL-6 predicts IVIG non-responsive KD.<sup>23,35,36</sup> IL-6 promotes lymphocyte proliferation, macrophage activation, and interaction between immune cells, further activating other immune and inflammatory cells. Thus, IL-6 plays a critical role in immune response, inflammation, and antibody production. As a pleiotropic proinflammatory factor, IL-6 activates various signaling mechanisms involved in CD4+ T cell regulation and vascular growth, contributing to complex disease pathophysiology. It is suggested that IL-6 is highly sensitive but not very specific for unresponsive KD.<sup>37</sup> IL-17, produced mainly by CD4+ T cells, activates Th17 cells and plays a crucial role in inflammation and tissue damage. Th17 cells produce IL-17 and are associated with autoimmunity and tissue damage. IL-17 induces additional pro-inflammatory cytokines, including IL-6, TNF- $\alpha$ , and IL-8,<sup>38</sup> and the IL-17 family, especially IL-17A, signals to non-hematopoietic cells to initiate immune defense mechanisms. High blood levels of IL-17A correlate with KD severity. IL-

17A levels are higher in IVIG-resistant KD patients<sup>39</sup> and in CAL-positive sensitized groups compared to CAL-negative ones.<sup>40</sup> IVIG inhibits Th17 differentiation and IL-17A/F production,<sup>41</sup> and IL-17 may serve as a diagnostic marker for KD and a risk factor for coronary artery aneurysms.<sup>42</sup> Overexpression of IL-17 is hypothesized to inhibit IVIG's anti-inflammatory effects. Both IL-6 and IL-17, mainly derived from CD4+ T cells, are involved in non-responsive KD.<sup>43</sup> ROC curve analysis showed IL-6 predicted non-responsive KD with an AUC of 0.859 before and 0.920 after treatment, while IL-17's AUC was 0.699 and 0.884, respectively, indicating higher predictive value after IVIG treatment. Thus, re-testing IL-6 and IL-17 within 36 hours post-IVIG treatment is recommended. If IL-6 shows minimal decrease and/or IL-17 continues to rise, non-responsive KD is strongly suggested. Combined with clinical manifestations, this approach could enhance the predictive value and supplement existing scoring systems.

This study has several limitations. First, the sample size is relatively small, and only a limited range of T-cell activation-related cytokines was analyzed. Moreover, as a single-center study, its findings may lack generalizability, necessitating future large-scale, multi-center studies for more robust and reliable results. Second, IL-17 was not further subtyped, with future studies expected to focus specifically on IL-17A. Third, the optimal method for assessing T-cell activation, such as T-cell flow cytometry, was not utilized in this study due to the constraints of experimental time and blood sample storage during specimen collection.

## Conclusion

The involvement of cytokines related to T-cell activation, particularly through retesting IL-6 and IL-17 after initial treatment, enhances the predictability of unresponsive KD. This indicates that T-cell-activated cytokines are implicated in the pathogenesis of refractory Kawasaki disease, highlighting the need for further investigation. Unresponsive KD remains a clinical diagnosis, and the findings of this study aim to aid clinicians in initiating early treatment to minimize the severe consequences of unresponsive KD.

## Ethical Approval

This study was in compliance with the Declaration of Helsinki, and approved by the Ethical Committees of Hangzhou children's Hospital.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; 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 declare that the research was conducted without any commercial or financial relationships that might be interpreted as potential conflicts of interest.

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