Post-Print Analysis of Risk Factors for Coronary Artery Lesions in Kawasaki Disease Based on Peripheral Blood Cytokine and Lymphocyte Expression Profiles

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Abstract

Abstract Objective: To investigate the expression characteristics of peripheral blood cytokines and lymphocytes in children with Kawasaki disease (KD) and analyze the influencing factors associated with coronary artery lesions.

Methods: Fifty children with KD admitted to the Department of Cardiology, Hebei Children's Hospital from August 2021 to October 2022 were enrolled. Forty-six children with simple fever (excluding KD) during the same period were selected as the fever control (FC) group, and 54 children undergoing routine physical examination served as the normal control (NC) group. The expression levels of peripheral blood cytokines and lymphocytes were measured in all three groups. Binary logistic regression was performed to analyze differential indicators between the KD and FC groups, as well as between the coronary artery lesions (CAL) and no coronary artery lesions (NCAL) groups. Receiver operating characteristic (ROC) curves were constructed.

Results: 1. The KD group exhibited higher levels of IL-4, IL-6, IL-10, IL-5, and IL-8 compared with the FC group, and higher levels of IL-4, IL-6, IL-10, TNF-α, IFN-γ, IL-1β, IL-5, IL-12p70, IFN-α, and IL-8 compared with the NC group. The CAL group showed higher IL-4 and IL-1β levels but lower IL-6 level compared with the NCAL group, with all differences being statistically significant ($P<0.05$). 2. The KD group had higher CD4+ T cells and total B cells but lower proportions of total T cells and CD8+ T cells compared with the FC group. Compared with the NC group, the KD group showed higher total B cells but lower proportions of CD8+ T cells and NK cells. The CAL group had higher NK cells but lower proportion of CD8+ T cells compared with the NCAL group, with all differences being statistically significant ($P<0.05$). 3. Binary logistic regression revealed: (1) Elevated IL-6 was an independent risk

factor for KD, with an odds ratio (OR) and 95% confidence interval (95%CI) of 1.071 (1.019, 1.126). (2) CD8+ T cells and NK cells were independent risk factors for CAL, with ORs and 95%CIs of 0.750 (0.611, 0.921) and 1.652 (1.192, 2.289), respectively. The combination of these two parameters for predicting CAL yielded a sensitivity of 81.25%, specificity of 94.12%, Youden's index of 0.75, area under the curve (AUC) of 0.901, and 95%CI of (0.783, 0.967).

Conclusion: Elevated IL-6 is a significant risk factor for KD development, while decreased CD8+ T cells combined with increased NK cells demonstrate predictive value for CAL occurrence in children with KD.

Full Text

Analysis of Factors Influencing Coronary Artery Lesions in Kawasaki Disease Based on Peripheral Blood Cytokine and Lymphocyte Expression Profiles

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Abstract

Objective: To investigate the expression characteristics of peripheral blood cytokines and lymphocytes in children with Kawasaki disease (KD) and identify factors associated with coronary artery lesions (CAL).

Methods: Fifty children with KD admitted to the Department of Cardiology at Children's Hospital of Hebei Province between August 2021 and October 2022 were enrolled. Forty-six children with simple febrile illness (excluding KD) served as febrile controls (FC group), and 54 healthy children undergoing routine physical examination served as normal controls (NC group). Peripheral blood cytokine and lymphocyte expression levels were measured across the three groups. Binary logistic regression was used to analyze differential indicators between the KD and FC groups, as well as between the CAL and non-CAL (NCAL) groups. Receiver operating characteristic (ROC) curves were constructed for evaluation.

Results: (1) The KD group exhibited significantly higher levels of IL-4, IL-6, IL-10, IL-5, and IL-8 compared to the FC group ($P<0.05$), and higher levels of IL-4, IL-6, IL-10, TNF-α, IFN-γ, IL-1β, IL-5, IL-12p70, IFN-α, and IL-8 compared

to the NC group (P<0.05). The CAL group showed elevated IL-4 and IL-1β but reduced IL-6 levels relative to the NCAL group (P<0.05). (2) The KD group demonstrated higher CD4+ T cell and total B cell percentages but lower total T cell and CD8+ T cell percentages compared to the FC group; compared to the NC group, the KD group had higher total B cells but lower CD8+ T cells and NK cells (P<0.05). The CAL group exhibited higher NK cells but lower CD8+ T cells compared to the NCAL group (P<0.05). (3) Binary logistic regression revealed that elevated IL-6 was an independent risk factor for KD (OR=1.071, 95%CI: 1.019–1.126). CD8+ T cells and NK cells were independent risk factors for CAL (OR=0.750, 95%CI: 0.611–0.921; OR=1.652, 95%CI: 1.192–2.289, respectively). The combination of these two markers predicted CAL with 81.25% sensitivity, 94.12% specificity, a Youden index of 0.75, and an AUC of 0.901 (95%CI: 0.783–0.967).

Conclusion: Elevated IL-6 represents a significant risk factor for KD development, while decreased CD8+ T cells combined with increased NK cells demonstrate predictive value for CAL occurrence in children with KD.

Keywords: Kawasaki disease; cytokines; lymphocytes; coronary artery lesions

Introduction

Kawasaki disease (KD) is an acute febrile illness of unknown etiology predominantly affecting children under five years of age. The disease primarily involves small and medium-sized vessels throughout the body, with coronary artery lesions (CAL) representing its most severe complication, including coronary artery dilation and aneurysm formation. Consequently, KD has become the leading cause of acquired heart disease in children [1]. Currently, the absence of specific laboratory tests for early KD diagnosis makes differentiation from other febrile illnesses challenging, often resulting in delayed treatment and significantly increased risk of CAL.

CAL diagnosis relies heavily on echocardiography, which assesses coronary artery damage by measuring internal diameter and calculating Z-scores. However, Z-score calculation methods remain non-unified internationally due to variations in geography, ethnicity, and population characteristics [2]. Moreover, echocardiography cannot predict CAL development in its early stages, and reliable laboratory markers for early prediction are lacking. Identifying robust laboratory indicators could provide a theoretical foundation for early CAL prediction, enabling clinicians to intervene promptly and reduce CAL incidence. This study analyzed the expression patterns of inflammatory cytokines and lymphocyte subsets in KD and febrile children, aiming to provide evidence for early clinical diagnosis and CAL prediction in pediatric KD patients.

Methods

1.1 Study Population 1.1.1 Subjects

Fifty children with KD hospitalized in the Department of Cardiology at Children's Hospital of Hebei Province between August 2021 and October 2022 were enrolled (KD group). Diagnosis followed the American Heart Association (AHA) guidelines for Kawasaki disease and coronary artery lesions. Forty-six febrile children without KD served as febrile controls (FC group), and 54 healthy children undergoing routine physical examination served as normal controls (NC group). Coronary ultrasound was performed before intravenous immunoglobulin (IVIG) administration, and KD patients were stratified into CAL and NCAL groups based on Z-scores: Z$ $2but < 2.5indicateddilation; smallaneurysmwasdefinedasZ$ $2.5but < 5; mediumaneurysmasZ$ $5but < 10withabsolutediameter < 8mm; andlarge/giantaneurysmasZ$ $10 or absolute diameter $ $8 mm. This study was approved by the Ethics Committee of Children's Hospital of Hebei Province. Baseline characteristics are presented in .

TABLE:1 Baseline characteristics of study participants

Inclusion and Exclusion Criteria for KD Patients

Inclusion criteria: (1) Met AHA diagnostic criteria for KD and coronary artery lesions; (2) First episode of KD; (3) No prior treatment with immunoglobulin or steroids; (4) Parental informed consent obtained per the Declaration of Helsinki. *Exclusion criteria:* (1) Febrile illnesses not caused by KD; (2) Incomplete clinical data.

1.2 Laboratory Methods 1.2.1 Sample Collection

Fasting peripheral venous blood (2 ml) was collected in the morning and stored in EDTA anticoagulant tubes. Samples were centrifuged at 1780×g for 10 minutes. Plasma (0.5 ml) was separated and stored at -80°C for cytokine analysis; remaining blood samples were kept at 4°C for lymphocyte analysis.

1.2.2 Analysis of Peripheral Blood Cytokines and Lymphocytes

Serum cytokine concentrations (IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ, IL-17A, IL-1β, IL-5, IL-12p70, IFN-α, IL-8) were measured using cytometric bead array (CBA) technology. The cytokine detection kit was purchased from Jiangxi Saiji Biotechnology Company, and data were analyzed using the BD FACSCanto II system according to manufacturer protocols. Standard curves were generated for each cytokine, and concentrations were calculated from mean fluorescence intensity using the linear portion of the curve. Lymphocyte subset expression (CD3+, CD4+, CD8+, CD3+CD4-CD8-, CD21+, and CD16+CD56+) was assessed by flow cytometry using a Beckman Coulter flow cytometer.

1.2.3 Observation Indicators

Inflammatory cytokine and lymphocyte expression levels were compared among the KD, FC, and NC groups. Additionally, cytokine and lymphocyte levels were compared between CAL and NCAL subgroups within the KD cohort.

1.3 Statistical Analysis Data were analyzed using SPSS 25.0 software, with ROC curves generated using Medcalc 15.0. A two-tailed $P<0.05$ was considered statistically significant. Normally distributed continuous variables were expressed as mean±standard deviation (x±s) and compared between groups using independent samples t-tests. Non-normally distributed variables were expressed as median and interquartile range [M(Q1,Q3)] and compared using Mann-Whitney U tests. Variables showing significant differences were incorporated into binary logistic regression models to identify factors influencing lesion development. Model performance was evaluated using area under the ROC curve (AUC), sensitivity, specificity, and the Youden index.

Results

2.1 General Laboratory Findings General laboratory results are summarized in .

TABLE:2 General laboratory test results

2.2 Inflammatory Cytokine Levels Across Groups Serum cytokine levels are presented in and [Figure 1: see original paper]. Compared to the FC group, the KD group showed elevated IL-4, IL-6, IL-10, IL-5, and IL-8 levels. Compared to the NC group, the KD group exhibited significantly higher levels of IL-4, IL-6, IL-10, TNF-α, IFN-γ, IL-17A, IL-1β, IL-5, IL-12p70, IFN-α, and IL-8. Furthermore, the CAL group demonstrated significantly higher IL-4 and IL-1β but lower IL-6 levels compared to the NCAL group. These findings are detailed in and [Figure 2: see original paper].

TABLE:3 Serum inflammatory cytokine levels across three groups

FIGURE:1 Differential cytokine expression levels among the three groups

TABLE:4 Serum cytokine levels in CAL and NCAL groups

FIGURE:2 Differentially expressed factors between CAL and NCAL groups

2.3 Lymphocyte Subset Comparisons Compared to the FC group, the KD group exhibited elevated CD4+ T cells and total B cells but reduced total T cells and CD8+ T cells ($P<0.05$). Compared to the NC group, the KD group showed higher total B cells but lower CD8+ T cells and NK cells ($P<0.05$). Within the KD cohort, the CAL group had lower CD8+ T cells but higher NK cells compared to the NCAL group ($P<0.05$). These results are presented in , [Figure 3: see original paper], , and [Figure 4: see original paper].

TABLE:5 Comparison of lymphocyte subsets among three groups

FIGURE:3 Lymphocyte expression levels among three groups

TABLE:6 Lymphocyte comparison between CAL and NCAL groups

FIGURE:4 Lymphocyte expression levels between CAL and NCAL groups

2.4 Logistic Regression Analysis of Factors Associated with KD Development Binary logistic regression analysis of differential indicators between KD and FC groups revealed that IL-6 elevation was significantly associated with KD development, representing an independent risk factor (see).

TABLE:7 Logistic regression model for factors associated with KD development

2.5 Logistic Regression Analysis of Factors Influencing Coronary Lesions Variables showing significant differences between CAL and NCAL groups (IL-4, IL-6, IL-1β, CD8+ T cells, and NK cells) were entered into a binary logistic regression model. Analysis identified CD8+ T cells and NK cells as important influencing factors. Each unit increase in CD8+ T cells reduced lesion risk (OR=0.750, 95%CI: 0.611–0.921), while each unit increase in NK cells elevated lesion risk (OR=1.652, 95%CI: 1.192–2.289) (see).

TABLE:8 Logistic regression model for factors influencing lesion development

2.6 ROC Curve Analysis ROC analysis demonstrated that CD8+ T cells predicted CAL with an AUC of 0.678 ($P<0.05$), while NK cells predicted CAL with an AUC of 0.724 ($P<0.05$). The combined use of both markers yielded an AUC of 0.901 (95%CI: 0.783–0.967), with 81.25% sensitivity, 94.12% specificity, and a Youden index of 0.75 (see [Figure 5: see original paper], [Figure 6: see original paper], and).

FIGURE:5 ROC curves for CD8+ T cells and NK cells in predicting coronary lesions

FIGURE:6 ROC curve for combined CD8+ T cells and NK cells in predicting coronary lesions

TABLE:9 Area under ROC curves

Discussion

Kawasaki disease is an acute febrile systemic vasculitis that leads to CAL in approximately 15–25% of untreated children. As the most severe complication of KD, CAL can result in coronary artery aneurysm (CAA), thrombosis, and even sudden death, making KD the most common cause of acquired heart disease in children [1]. Currently, KD diagnosis relies on clinical criteria and laboratory findings, with no specific biomarkers to distinguish KD from other febrile illnesses early, often causing diagnostic delays. Studies have shown that physician-related diagnostic delay is the sole significant independent risk factor for CAA development, with increased CAA risk associated with delayed

physician diagnosis rather than delayed parental seeking of care [3]. Therefore, identifying laboratory markers that facilitate early KD diagnosis is clinically crucial. Furthermore, combining multiple specific immunological markers to predict CAL may compensate for echocardiography's inability to provide early prediction. This represents the primary objective of our study.

3.1 Inflammatory Cytokines and Kawasaki Disease Kawasaki disease is considered a superantigen-mediated disorder that triggers non-specific T cell activation, leading to polyclonal T cell proliferation and widespread cytokine release [4]. During the acute phase, oxidative stress responses disrupt adaptive immunity while activating innate immune cells, generating numerous pro-inflammatory molecules including cytokines and chemokines. These responses recruit immune cells to arterial walls, causing vascular damage. Abnormal expression and production of immune-related cytokines, which indicate local or systemic immune dysfunction, play a critical role in KD pathogenesis [5].

Our study demonstrated close associations between inflammatory cytokines and both KD and CAL. IL-4, produced by T lymphocytes and myeloid cells, is the signature cytokine of type 2 immune responses [6]. Elevated IL-4 levels and Th2 cytokine predominance appear to be key features of acute KD [7], with serum IL-4 significantly higher in CAL patients compared to those without CAL [8]. IL-6 is a soluble inflammatory cytokine that enhances angiogenesis and vascular permeability by inducing excessive vascular endothelial growth factor production, representing a pathological hallmark of inflammatory diseases [9]. Wu et al. [10] reported markedly increased serum IL-6 during acute KD that normalized after IVIG treatment, though no significant difference was observed between children with and without CAA. IL-10 suppresses excessive inflammatory responses and limits unnecessary tissue destruction, playing indispensable roles in numerous infectious and inflammatory conditions [11]. Zhang et al. [12] found that IL-10 exhibited highly sensitive fluctuations across various KD states and correlated closely with CD19+ B cell percentages, though no significant difference was observed between KD groups with and without CALs [13]. Recent studies indicate that plasma IL-5 levels are altered in cardiovascular diseases including atherosclerosis and myocardial ischemia, potentially exerting regulatory effects [14]. Kuo et al. [15] demonstrated that pre-IVIG IL-5 levels were higher in KD patients, and post-IVIG elevation correlated with lower CAL incidence, suggesting an inverse relationship between IL-5 increase and CAL formation. IL-8 exerts diverse biological functions through binding to CXCR1 and CXCR2 receptors, including promoting inflammation (neutrophil recruitment) and angiogenesis [16]. Previous studies showed elevated IL-8 mRNA expression, protein levels, and neutrophil chemotactic activity during acute KD, suggesting IL-8 promotes neutrophil adhesion and migration. IVIG-induced IL-8 level modifications may inhibit leukocyte adhesion, protecting organs from neutrophil-mediated damage, improving KD symptoms, and reducing aneurysm risk [17]. Okada et al. [18] reported that the IL-33/ST2 axis contributes to vasculitis and CAL development in KD through increased IL-8 production in human coronary artery endothelial

cells. Finally, IL-1β is a potent pro-inflammatory cytokine produced by innate immune cells that is essential for host defense but exacerbates acute tissue injury [19]. Studies show that IL-1β inhibition ameliorates vasculitis in KD mouse models [20], and Si et al. [21] found significantly elevated serum IL-1β in KD children with CALs.

Our findings revealed that compared to febrile controls, KD patients exhibited elevated IL-4, IL-6, IL-10, IL-5, and IL-8 levels, with IL-6 identified as an independent risk factor for KD ($P<0.05$). These markers may help differentiate KD from other febrile illnesses, potentially avoiding diagnostic delays and consequent delays in IVIG therapy that increase CAA risk. Additionally, the CAL group showed higher IL-4 and IL-1β but lower IL-6 levels compared to the NCAL group, partially consistent with previous reports. Although IL-4, IL-1β, and IL-6 differed between groups, none constituted independent CAL risk factors or showed predictive value, possibly attributable to our small sample size and single-center design.

3.2 Lymphocytes and Kawasaki Disease Lymphocytes are essential components of the immune system. Innate immune cells include neutrophils, monocytes/macrophages, and natural killer cells, while adaptive immunity comprises T and B lymphocytes. Based on T cell receptor expression, T cells are classified as CD4+ or CD8+. Conventional CD4+ T cells form the helper T (Th) lineage with T cell receptors restricted to MHC class II, whereas CD8+ coreceptor-expressing T cells (comprising CD8α and CD8β heterodimers) recognizing antigens in the context of MHC class I constitute the cytotoxic T cell lineage [22]. Superantigens from Staphylococcus and Streptococcus can activate large lymphocyte populations and may contribute to KD etiology. Kobayashi et al. [23] demonstrated histopathological features of KD vasculitis with characteristic T cell infiltration and abundant CD8+ T cells in vascular lesions. However, other studies report low peripheral blood T cell activation in KD. Research on peripheral B cell activation in KD has yielded inconsistent results, with some showing polyclonal B cell activation, increased absolute B cell counts, and elevated CD23 expression, while others report reduced circulating IgA+ B cells during acute KD and IgA plasma cell infiltration of coronary artery walls in fatal cases. NK cell studies in KD are limited, though reduced absolute CD16+ NK cell counts during acute KD have been observed, with unclear whether such changes are primary or secondary to the acute disease state [24].

Our study compared peripheral blood lymphocyte differences between KD patients and febrile controls, finding elevated total T cells, CD4+ T cells, and total B cells in KD patients, indicating immune dysregulation with imbalance between cellular and humoral immunity, and suggesting CD4+ T cell and B cell activation participate in KD pathogenesis. However, CD8+ T cell levels were lower than both FC and NC groups ($P<0.05$), consistent with previous reports [25]. We speculate this may result from the immunosuppressive factor activin A inhibiting peripheral CD8+ T cell activity in acute KD [26]. Our study also

found lower CD8+ T cells and higher NK cells in the CAL group compared to NCAL group, with the combined ROC curve showing excellent AUC and specificity. Furthermore, binary logistic regression identified CD8+ T cells and NK cells as risk factors for CAL, indicating that decreased CD8+ T cells and increased NK cells play important roles in coronary artery damage and may serve as auxiliary reference markers for CAL risk assessment in KD patients. Previous studies have reported CD8+ T cell infiltration in coronary artery walls of KD patients with CAL [27]. A plausible explanation for our observations is that activated CD8+ T cells redistributing from peripheral blood to inflammatory sites may partially account for peripheral CD8+ T cell reduction and their low-level activation in KD.

In summary, our study comprehensively characterized inflammatory cytokine and lymphocyte expression patterns in KD and febrile children, which may assist clinicians in rapid early identification and diagnosis of KD. We constructed a predictive model combining cytokines and lymphocyte subsets for KD patients with CAL, demonstrating that combined CD8+ T cells and NK cells can accurately predict CAL development early, compensating for echocardiography's limitations in early prediction and facilitating CAL risk assessment. However, our small sample size may have contributed to the lack of statistical significance for IL-4, IL-6, and IL-1β in predicting CAL, warranting further validation in larger cohorts.

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Note: Figure translations are in progress. See original paper for figures.