BMC Pediatrics

RESEARCH Open Access

Changes in serum levels of Chitinase protein-40 in children with Kawasaki disease and its clinical significance

Yalin Liu[1,2], Shan Sun[2], Baolong Yu[1], Qianyun Wang[1], Hui Liu[1], Xianli Shao[1] and Huafeng Zhao[1*]

Abstract

Objectives Kawasaki disease (KD) is an acute immune-mediated vasculitis primarily affecting coronary arteries, with limited specific diagnostic biomarkers available. Chitinase protein-40 (YKL-40), a glycoprotein secreted by neutrophils and macrophages, has been associated with vascular inflammation in cardiovascular diseases. This study aimed to investigate the role of YKL-40 in KD by analyzing its serum levels, correlations with inflammatory markers, and potential as a diagnostic and prognostic biomarker.

Methods Serum YKL-40 and interleukin-6 (IL-6) levels were measured using enzyme-linked immunosorbent assay (ELISA) in 46 children with KD (16 with coronary artery lesions [CAL], 30 without CAL) and 30 healthy controls. Correlations between YKL-40, IL-6, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, and platelet (PLT) levels were analyzed.

Results YKL-40, IL-6, CRP, ESR, WBC, and PLT levels were significantly elevated in KD patients compared to controls. YKL-40 levels correlated positively with IL-6, CRP, and ESR. A serum YKL-40 threshold of ≥ 71.930 ng/mL predicted CAL with sensitivity and specificity of 0.875 and 0.800, respectively. Combining YKL-40 with IL-6 improved sensitivity and specificity to 0.938 and 0.833.

Conclusions YKL-40 is significantly elevated in KD and correlates with inflammatory markers, suggesting its involvement in disease pathogenesis. It is a promising inflammatory biomarker and independent risk factor for predicting CAL in KD, offering potential for improved diagnosis and prognosis.

Clinical trial number Not applicable.

Keywords Kawasaki disease, Coronary artery lesion, Chitinase protein-40, Interleukin-6, Diagnostic biomarkers

*Correspondence:
Huafeng Zhao
zhf123456edu@163.com
[1]Pediatric Internal Medicine Department, WeiFang People's Hospital, Shandong Second Medical University, Weifang 261000, China
[2]Emergency Department, WeiFang People's Hospital, Shandong Second Medical University, Weifang 261000, China

Introduction

Kawasaki disease (KD) is an acute systemic immune vasculitis predominantly affecting children and infants, characterized by inflammation in small- and medium-sized arteries [1]. Clinical manifestations include persistent fever, cervical lymphadenopathy, mucosal and conjunctival inflammation, polymorphic rash, and extremity edema with desquamation [2]. Cardiovascular complications, such as myocarditis, arrhythmias, coronary artery lesions (CAL), are the most severe outcomes, making KD a leading cause of acquired heart disease in children [3]. Genetic susceptibility is a well-established risk factor for KD, with genome-wide association studies (GWAS) identifying polymorphisms in immune-related genes such as ITPKC (inositol 1,4,5-trisphosphate 3-kinase C), CASP3 (caspase-3), and FCGR2A (Fc gamma receptor IIa) that influence disease susceptibility and CAL risk [4, 5, 6]. For example, the ITPKC rs28493229 polymorphism disrupts T-cell activation regulation, predisposing individuals to hyperinflammation and coronary aneurysms [7]. Similarly, FCGR2A variants alter IgG immune complex clearance, exacerbating endothelial injury [6]. These findings underscore the interplay between genetic predisposition and dysregulated immune responses in KD pathogenesis.

The etiology and pathogenesis of KD are not fully understood but likely involve interactions between infectious, environmental, immunological, and genetic factors [8]. Current evidence suggests that pathogen invasion in genetically predisposed individuals triggers immune activation and an inflammatory cascade, leading to widespread vascular endothelial damage and dysfunction [9]. Key cytokines, including Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), and Interferon-gamma (IFN-γ), play critical roles in vascular inflammation [10]. Early disease stages feature activation of monocytes, macrophages, and T lymphocytes, producing cytokines and chemokines that recruit inflammatory cells to the vascular wall. Subsequent platelet adhesion to endothelial cells exacerbates vascular injury by increasing permeability and extracellular matrix destruction, ultimately causing vascular dilation, fragility, and smooth muscle loss [11]. Elevated IL-6, in particular, has been associated with CAL in KD patients, highlighting its significance in vascular endothelial injury [12, 13].

Chitinase protein-40 (YKL-40), also known as chitinase-3-like protein 1, is a glycoprotein secreted primarily by neutrophils and macrophages in inflammatory tissues [14, 15]. While its exact biological function remains unclear, YKL-40 is implicated in inflammation-related pathways, extracellular matrix remodeling, and endothelial dysfunction [16]. Elevated serum YKL-40 levels are observed in diseases involving persistent inflammation and fibrosis, such as rheumatoid arthritis (RA), bronchial asthma, hepatic fibrosis, and cardiovascular conditions [16, 17]. In vasculitis, YKL-40 levels correlate with disease activity and endothelial dysfunction, suggesting its potential as a biomarker for vascular inflammatory diseases [18, 19, 20]. Furthermore, elevated YKL-40 levels have been linked to the progression of coronary artery disease and the severity of coronary lesions [21].

Given its role in inflammation and endothelial injury, YKL-40 may play a critical role in KD-related vascular damage. Thus, our study hypothesizes that serum YKL-40 levels are elevated in KD patients during the acute stage and correlate with inflammatory cytokines and clinical parameters of inflammation. Using Enzyme-Linked Immunosorbent Assay (ELISA), this research aims to quantify serum YKL-40 levels in acute-stage KD children and explore their associations with cytokines such as IL-6 and inflammatory markers (C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), White Blood Cell (WBC) count, and Platelet (PLT) count) to evaluate its clinical significance as a potential biomarker.

Materials and methods

Subjects

A total of 46 children diagnosed with KD at the Department of Pediatrics, Weifang People's Hospital, were enrolled in the study (between January 1, 2020, and December 31, 2023). Additionally, 30 healthy children who underwent routine physical examinations at the same hospital served as the control group. Demographic information, including age and gender, was collected for all subjects. The study was approved by the Ethics Committee of Weifang People's Hospital, and informed consent was obtained from the parents of all participating children.

Inclusion criteria

KD was diagnosed according to the criteria established by the American Heart Association, which requires a fever lasting at least five days, with day 1 being the onset of fever, and at least four of the following five primary clinical signs:

(1) Changes in the limbs, such as acute erythema and edema of the palms and soles, hard edema of the hands and feet, and membranous desquamation of the fingertips and toes during the recovery period;
(2) Erythema multiforme;
(3) Bilateral non-exudative conjunctivitis;
(4) Lip congestion, cracking, diffuse congestion of the oral mucosa, and a "strawberry tongue" (a tongue resembling a waxberry tongue);
(5) Enlarged cervical lymph nodes with a diameter of ≥ 1.5 cm.

In cases where at least four clinical signs, especially redness and swelling of the hands and feet, were present, KD could be diagnosed after just four days of fever. In rare cases, experienced clinicians may confirm the diagnosis after only three days of fever.

Exclusion criteria

Children with any of the following conditions were excluded from the study:

(1) Immunodeficiency or moderate-to-severe malnutrition;
(2) Recurrent respiratory tract infections;
(3) Significant organ diseases such as heart failure or liver failure.

Diagnostic criteria for CAL

Cardiac ultrasound was performed within 7–14 days of the onset of symptoms to diagnose CAL. CAL was defined by the following criteria [2]:

(1) A coronary artery diameter of ≥ 3 mm in children under 5 years of age, or ≥ 4 mm in those older than 5 years;
(2) Significant irregularities in the coronary artery, with the diameter of the affected segment exceeding 1.5 times the diameter of adjacent normal segments.

The Z-Score was used to classify the severity of coronary artery abnormalities:

(1) No involvement: Z-Score < 2;
(2) Dilation only: Z-Score between 2 and < 2.5, or if initially < 2, a decrease in Z-Score ≥ 1 during follow-up;
(3) Small aneurysm: Z-Score ≥ 2.5 to < 5;
(4) Medium aneurysm: Z-Score ≥ 5 to < 10, with an absolute dimension < 8 mm;
(5) Large or giant aneurysm: Z-Score ≥ 10, or an absolute dimension ≥ 8 mm.

Instrumentation and reagents

Instrumentation

Automatic Enzyme-Linked Immunosorbent Assay (ELISA) System: Shenzhen Bred Bio; Micro-Adjustable Pipette: Thermo Fisher Scientific, USA; Electronic Luminescence Detector: Siemens, Germany; Low-Temperature Centrifuge: Anxin Baiyang; Vortex Mixer (Model XW-80): Shanghai Chitang; RO-DI Ultra-Pure Water System: Youchun; Automated Hematology Analyzer: Sysmex, Japan (Model XE-2100); Modular Fully Automatic Biochemical Analyzer: Jinan Feilan; Cobas e601 Fully Automated Immune Analyzer: Roche, Switzerland; Westergren's Blood Sedimentation Rack: Roche, Switzerland; Jiangsu Kangjie.

Reagents

YKL-40 Kit: Shanghai Shuangying Biotechnology; IL-6 Kit: Wuhan Boster Bioengineering; CRP Kit: Shanghai DiaSys Diagnostic Systems.

Methods

Inflammatory markers detection

Fasting venous blood samples were collected from children diagnosed with Kawasaki Disease (KD) the morning after admission (prior to intravenous immunoglobulin treatment) and from control subjects on the morning of their routine physical examination. Routine blood tests were performed using a Sysmex XE-2100 automated hematology analyzer with the corresponding reagent kits. ESR was measured using the Westergren method, and CRP was measured using the Roche Modular biochemical analyzer with the DiaSys Diagnostic System CRP assay kit (immunoturbidimetry), according to the manufacturer's instructions.

Determination of serum YKL-40 and IL-6 levels

Fasting venous blood samples (5 mL) were collected from children diagnosed with Kawasaki Disease (KD) the morning after their admission, prior to receiving intravenous immunoglobulin treatment. For the control group, samples were collected on the morning of their scheduled physical examination. The blood samples were kept at room temperature for 30 min, then centrifuged at 4000 rpm for 15 min. 1 mL of the separated serum was transferred to a clean, sterile centrifuge tube and stored at -80 °C for further testing. Prior to analysis, the serum samples and reagents were equilibrated to room temperature for approximately 1 h.

Serum YKL-40 and IL-6 levels were determined using ELISA kits according to the manufacturer's instructions. The steps for IL-6 detection were identical to those for YKL-40. Briefly, 100 μL of serum samples and standard solutions were added to the designated wells of a 96-well ELISA plate. After incubation and washing, biotin-labeled antibodies and avidin-peroxidase complex working solutions were added sequentially, followed by incubation at 37 °C. The reaction was developed using TMB substrate, stopped with a stop solution, and the optical density (OD) was measured at 450 nm using an ELISA reader.

Statistical analysis

Data were analyzed using SPSS 25.0. For normally distributed data, independent sample t-tests and one-way analysis of variance (ANOVA) were applied. Non-normally distributed data were analyzed using the

Mann-Whitney U test and Kruskal-Wallis test. Correlations were assessed using Pearson and Spearman correlation analyses. Logistic regression models were employed to identify risk factors for CAL in children with KD. A multivariate logistic regression model was used to evaluate the independent risk factors. Receiver operating characteristic (ROC) curves were constructed to assess the diagnostic value of serum YKL-40 and IL-6 levels, both individually and in combination, for KD with CAL. $P < 0.05$ was considered statistically significant.

Results

Demographic information

The mean ages of the KD with CAL group, KD without CAL group, and control group were 2.87 ± 1.61, 2.21 ± 1.45, and 3.01 ± 1.19 years, respectively, with no statistically significant differences ($P > 0.05$). The KD with CAL group included 10 boys and 6 girls, the KD without CAL group included 18 boys and 12 girls, and the control group comprised 15 boys and 15 girls, with no significant gender differences ($P > 0.05$) (Table 1).

Serum levels of YKL-40 and IL-6 in different groups

The serum YKL-40 level in the KD group (70.88 ± 17.24 ng/mL) was significantly higher than that in the control group (21.48 ± 15.15 ng/mL) (t = 12.796, $P < 0.01$). Similarly, the serum IL-6 level was significantly higher in the KD group (91.00 ± 16.49 ng/mL) compared to the control group (3.54 ± 1.65 ng/mL) (t = 35.696, $P < 0.01$). Additionally, serum YKL-40 levels in the KD with CAL group (85.12 ± 10.83 ng/mL) were significantly higher than in the KD without CAL group (63.28 ± 15.12 ng/mL), with statistical significance (t = -5.107, $P < 0.01$). IL-6 levels in the KD with CAL group (103.69 ± 16.38 ng/mL) were also significantly higher than in the KD without CAL group (84.23 ± 12.12 ng/mL) (t = -4.582, $P < 0.01$) (Table 1).

Inflammatory markers in different groups

Blood levels of WBC, PLT, CRP, and ESR in children with KD were significantly higher than in the control group ($P < 0.01$ for all comparisons). Specifically, the levels of WBC (16.29 ± 5.86), PLT (431.04 ± 151.92), CRP (53.48 ± 18.07), and ESR (56.32 ± 47.22) in the KD group were significantly elevated compared to the control group (6.90 ± 0.50, 241.00 ± 70.05, 16.50 ± 13.38, and 0.80 ± 0.60, respectively; $P < 0.01$). No significant differences in the blood levels of WBC, PLT, CRP, and ESR were observed between the KD with CAL and KD without CAL groups ($P > 0.05$ for all comparisons, Table 1).

Correlation between serum YKL-40 level and inflammatory markers in KD

As shown in Fig. 1A-C, the serum YKL-40 level in children with KD showed positive correlations with IL-6 ($r = 0.508$, $P < 0.01$), CRP ($r = 0.466$, $P < 0.01$), and ESR ($r = 0.369$, $P < 0.05$). However, no significant correlation was found between YKL-40 and the blood levels of PLT (r = -0.197, $P > 0.05$) or WBC ($r = 0.082$, $P > 0.05$) (Fig. 1D-E).

Logistic regression analysis of YKL-40 and IL-6 levels as risk factors for KD with CAL

Logistic regression analysis was conducted with KD without CAL and KD with CAL groups as the dependent variable, and serum YKL-40 and IL-6 levels as independent variables. The results indicated that serum YKL-40 ($N > 71.930$ ng/mL, OR = 1.093, 95% CI: [1.015–1.175], $P = 0.018$) and IL-6 ($N > 89.760$ pg/mL, OR = 1.097, 95% CI: [1.008–1.194], $P = 0.032$) were independent risk factors for KD with CAL.

Predictive value of serum YKL-40 and IL-6 for KD with CAL

ROC curves for YKL-40, IL-6, and their combination were constructed (Fig. 2). YKL-40 exhibited an AUC of 0.884 (95% CI: 78.81–98.07%), indicating high diagnostic accuracy for KD with CAL. IL-6 also showed high diagnostic performance with an AUC of 0.850 (95% CI: 73.45–96.55%). Notably, the combination of YKL-40 and IL-6 had a relatively high AUC of 0.917 (95% CI: 83.64–99.69%) (Table 2).

Table 2 summarizes the diagnostic performance of each marker: (1) The AUC for YKL-40 was 0.884, with an optimal threshold of 0.675 (sensitivity = 0.875, specificity = 0.800). (2) The AUC for IL-6 was 0.850, with an optimal threshold of 0.579 (sensitivity = 0.813,

Table 1 Demographic, inflammatory, and biomarker comparisons across groups

Parameter	KD with CAL ($n = 16$)	KD without CAL ($n = 30$)	Control ($n = 30$)	KD vs. Control	KD with CAL vs. KD without CAL
Age (years)	2.87 ± 1.61	2.21 ± 1.45	3.01 ± 1.19	F = 0.818, $P = 0.396$	-
Gender (Male)	10 (62.50%)	18 (60.00%)	15 (50.00%)	$\chi^2 = 3.114$, $P = 0.067$	-
YKL-40 (ng/mL)	85.12 ± 10.83	63.28 ± 15.12	21.48 ± 15.15	t = 12.796, $P = 0.000$**	t = -5.107, $P = 0.000$**
IL-6 (ng/mL)	103.69 ± 16.38	84.23 ± 12.12	3.54 ± 1.65	t = 35.696, $P = 0.000$**	t = -4.582, $P = 0.000$**
PLT ($\times 10^9$/L)	419.06 ± 140.47	437.43 ± 159.65	241.00 ± 70.05	t = 7.368, $P = 0.000$**	t = 0.387, $P = 0.701$
WBC ($\times 10^9$/L)	16.74 ± 5.01	16.06 ± 6.34	6.90 ± 0.50	t = 10.444, $P = 0.000$**	t = -0.371, $P = 0.712$
ESR (mm/h)	60.19 ± 16.13	49.90 ± 18.27	16.50 ± 13.38	t = 3.983, $P = 0.000$**	t = -1.891, $P = 0.065$
CRP (mg/L)	57.34 ± 34.48	55.77 ± 53.33	0.80 ± 0.60	t = 7.967, $P = 0.000$**	t = -0.107, $P = 0.916$

*$P < 0.05$, **$P < 0.01$

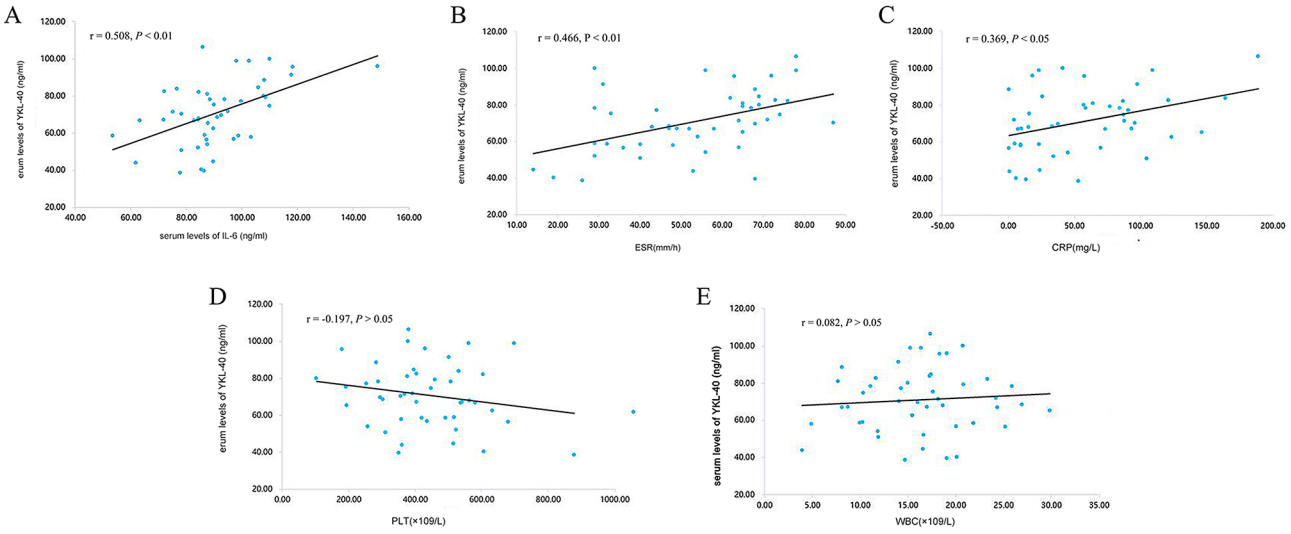

Fig. 1 Correlation between serum levels of YKL-40 and IL-6, ESR, CRP, PLT and WBC

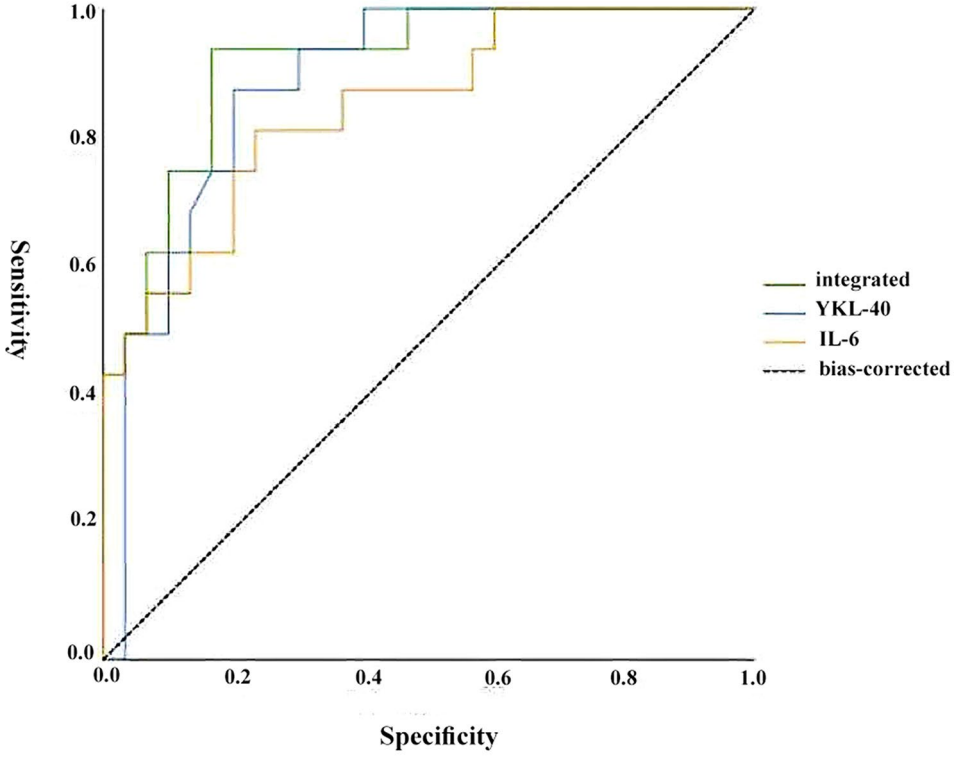

Fig. 2 ROC curves depicting the serum levels of YKL-40 and IL-6 for individual and combined diagnosis of KD combined with CAL

Table 2 Diagnostic performance of YKL-40 and IL-6

Biomarker	AUC (95% CI)	Optimal threshold	Sensitivity	Specificity	Cut-off	Statistical Significance (*P*)
YKL-40	0.884(0.788–0.981)	0.675	0.875	0.800	71.930	0.000**
IL-6	0.850 (0.734–0.966)	0.579	0.813	0.767	89.760	0.000**
YKL-40 + IL-6	0.917 (0.836–0.997)	0.771	0.938	0.833	-	0.000**

*$P < 0.05$, **$P < 0.01$

specificity = 0.767). (3) The combined AUC for YKL-40 and IL-6 was 0.917, with an optimal threshold of 0.771 (sensitivity = 0.938, specificity = 0.833).

This analysis suggests that the combination of YKL-40 and IL-6 offers superior diagnostic performance in identifying KD with CAL compared to each marker individually.

Discussion

KD was first identified by Tomisaku Kawasaki in Japan in the 1960s and has now been recognized for over 50 years [22]. KD predominantly affects preschool children, with the highest incidence seen in those under the age of five [2]. Clinically, KD presents as acute systemic vasculitis, primarily targeting small- and medium-sized arteries [1]. Common symptoms include oral mucosal lesions, persistent fever, bulbar conjunctiva hyperemia, and polymorphic rashes. The major complication of KD is CAL, which may lead to coronary artery dilation, aneurysm formation, and other cardiovascular issues [23, 24]. Due to the lack of specific diagnosis methods, the diagnosis of KD mainly relies on clinical features, highlighting the importance of exploring novel technologies for its diagnosis and treatment [25].

The pathogenesis of KD is complex and involves multiple factors, including infection, environmental influences, immune responses, and genetic predisposition [8]. Immunological studies show that the immune response in KD is highly active, with inflammatory cytokine cascades playing a crucial role in the development of vasculitis [3]. In particular, pro-inflammatory cytokines are central to the immune response in KD, potentially promoting endothelial damage and thereby contributing to the development of CAL [12, 13] Currently, specific serum biomarkers for diagnosing KD are limited, with commonly used markers such as ESR, CRP, and white blood cell count. IL-6, a multi-functional cytokine synthesized primarily by neutrophils, monocytes, and macrophages, plays a critical role in acute immune responses during infections and trauma [26]. It also contributes to various forms of vasculitis and has been implicated in the pathogenesis of systemic inflammatory diseases, including juvenile idiopathic arthritis, systemic lupus erythematosus, and KD [27, 28]. Consistent with previous studies, our results demonstrated a significant increase in serum IL-6 levels in children with KD, particularly in those with CAL. ROC analysis revealed that a serum IL-6 level of ≥ 89.760 ng/mL had a sensitivity of 0.813 and a specificity of 0.767 for detecting KD with coronary artery involvement.

YKL-40, an inflammation-related glycoprotein with a structure resembling bacterial chitinase's 18-glycosyl hydrolase [29], is primarily synthesized by macrophages, vascular smooth muscle cells, chondrocytes, and neutrophils [30, 31]. While the precise biological function of YKL-40 remains unclear, it is thought to modulate the expression of various inflammatory cytokines, participate in inflammation-related signaling pathways, and promote cellular processes such as proliferation, differentiation, migration, extracellular matrix remodeling, and angiogenesis [16]. This makes YKL-40 a potentially valuable marker for a wide range of inflammatory conditions, including KD, where its role in immune response and tissue remodeling could be crucial in understanding disease progression and complications. Elevated serum levels of YKL-40 are associated with numerous inflammatory and fibrotic diseases, including cardiovascular diseases [32], diabetes [33], rheumatoid arthritis [19], liver fibrosis [34], and cancers [35], which has garnered increased research interest. Kocyigit et al. [18] observed that elevated YKL-40 levels contributed to endothelial dysfunction and proteinuria in nephrotic syndrome patients, while Kazakova et al. [36] found that YKL-40 levels in both serum and synovial fluid were significantly increased in patients with rheumatoid arthritis and correlated with the degree of angiogenesis and synovial membrane thickening. YKL-40's role in promoting chemotaxis, adhesion, and migration of endothelial cells suggests its involvement in endothelial dysfunction and the progression of coronary heart disease [37]. Additionally, studies have shown that YKL-40 levels correlate positively with coronary artery disease severity, as indicated by the number of affected arteries and the Gensini score [38], positioning YKL-40 as a promising cardiovascular biomarker.

In our study, serum YKL-40 levels were significantly elevated in children diagnosed with KD, and these levels exhibited a positive correlation with other key inflammatory markers, including IL-6, CRP, and ESR. This observation aligns with its established role as a biomarker of inflammation and tissue remodeling in cardiovascular and immune-mediated diseases [32]. YKL-40 secreted by activated neutrophils, macrophages, and endothelial cells, is not merely a passive marker but an active contributor to vascular injury through multifaceted mechanisms [14]. Mechanistically, YKL-40 amplifies vascular inflammation by binding to receptors such as IL-13Rα2 and syndecan-1, activating MAPK/NF-κB pathway that drives pro-inflammatory cytokine production (IL-6, TNF-α) [39, 40], ultimately leading to endothelial dysfunction. Moreover, YKL-40 upregulates the expression of vascular endothelial growth factor (VEGF), stimulating the proliferation and migration of endothelial cells and promoting abnormal angiogenesis [41]. Additionally, it modulates the activity of matrix metalloproteinases—such as MMP-9—accelerating the degradation and remodeling of the extracellular matrix and compromising the structural integrity of the vascular wall [42]. Together,

these molecular mechanisms may contribute to the onset and progression of CAL in patients with KD.

Emerging mechanisms such as anti-endothelial cell autoantibodies (AECAs) and immunothrombosis further highlight the complexity of KD pathogenesis. AECAs, which target endothelial antigens, may exacerbate vascular injury by promoting complement activation, leukocyte recruitment, and endothelial apoptosis [43–44]. Recent studies propose that AECAs contribute to coronary artery damage in KD by amplifying immune-mediated endothelial dysfunction. Concurrently, immunothrombosis—a process linking inflammation and thrombosis—has been implicated in KD-related vascular complications. Activated neutrophils and platelets release prothrombotic factors and extracellular traps (NETs), which may drive microvascular occlusion and coronary aneurysm formation [45]. While our study focused on serum biomarkers, future investigations should explore interactions between YKL-40, IL-6, and these novel mechanisms to unravel their synergistic roles in CAL development.

Furthermore, our results underscore the significance of YKL-40 in KD with CAL. We found that serum levels of YKL-40, along with IL-6, were significantly higher in KD patients with CAL compared to those without CAL. This finding is consistent with previous studies linking both IL-6 and YKL-40 to endothelial dysfunction and coronary artery disease [37–38]. IL-6 is known to be a critical mediator in the acute phase of KD, and its elevated levels have been associated with coronary artery involvement in this disease [13, 27]. Our study reinforces this connection by demonstrating that elevated serum levels of both YKL-40 and IL-6 serve as independent risk factors for the development of CAL in KD, providing further evidence of their role in the pathophysiology of this condition.

Importantly, our study introduces YKL-40 as a novel biomarker candidate in the context of KD, particularly highlighting its potential utility in predicting CAL. The novelty lies in identifying a marker potentially reflecting specific pathways of vascular inflammation and tissue remodeling central to KD, moving beyond traditional, less specific inflammatory markers like CRP and ESR. Our findings suggest a potential pathway for integrating YKL-40 assessment into current KD management protocols. Specifically, measuring serum YKL-40 levels at the time of diagnosis could serve as a valuable tool for risk stratification. When the serum level of YKL-40 was ≥71.930 ng/mL, the sensitivity for predicting KD with CAL was 0.800, highlighting the independent predictive potential of YKL-40, a relatively unexplored marker in this specific clinical setting. More notably, our research distinctively demonstrates that the combination of YKL-40 and IL-6 further enhanced diagnostic performance, achieving a sensitivity of 0.938 and specificity of 0.833 for predicting CAL. This combined strategy offers a potentially more robust and mechanistically informative approach compared to relying solely on traditional biomarkers, which often lack specificity and fail to fully capture the complex immune dysregulation driving CAL development. Therefore, incorporating YKL-40 into diagnostic or prognostic panels could aid clinicians in identifying high-risk patients early, potentially allowing for more vigilant monitoring or guiding decisions regarding adjunctive therapies in refractory cases, representing a significant and novel advancement in personalized risk assessment for KD. Further prospective studies are warranted to validate these findings and definitively establish the clinical role of YKL-40 in routine KD.

Conclusions

In children with KD, serum YKL-40 levels were significantly elevated and positively correlated with IL-6, CRP, and ESR levels. These findings suggest that YKL-40 may play a role in the pathogenesis of KD and could serve as an effective inflammatory marker for the disease. Additionally, elevated serum levels of both YKL-40 and IL-6 were identified as independent risk factors for the development of CAL in KD. Notably, serum YKL-40 levels may serve as a reliable predictor of KD with CAL, offering potential for improved diagnosis and early intervention.

Limitations and future perspectives

While this study provides novel insights into the role of YKL-40 as a biomarker in KD, several limitations should be acknowledged. First, the single-center design and modest sample size may limit the generalizability of our findings. Future multi-center studies with larger cohorts are essential to validate the diagnostic thresholds of YKL-40 and IL-6 across diverse populations. Second, while we focused on acute-phase biomarkers, longitudinal data tracking YKL-40 dynamics during disease progression are lacking. Incorporating serial measurements could clarify whether YKL-40 normalization correlates with clinical outcomes or residual vascular injury. Third, our analysis did not explore the direct biological role of YKL-40 in endothelial dysfunction or emerging mechanisms such as AECAs and immunothrombosis. Mechanistic studies using in vitro models or animal systems are needed to dissect how YKL-40 interacts with these processes to drive coronary artery lesions.

Acknowledgements

We thank all co-authors for commenting on the manuscript.

Author contributions

Yalin Liu: Methodology, Investigation, Data curation, Formal analysis, Writing - original draft. Shan Sun: Methodology, Investigation, Data Curation. Qianyun Wang: Formal analysis, Writing - review & editing. Baolong Yu: Formal analysis, Methodology. Software, Formal analysis. Hui Liu: Investigation. Writing - review & editing. Xianli Shao Conceptualization, Funding acquisition, Methodology.

Huafeng Zhao Conceptualization, Funding acquisition, Supervision, Project administration. All authors have read and approved the manuscript.

Funding
This work was supported by the Weifang Health Committee (Nos. WFWSJK-2023-380).

Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval
The study was approved by the Ethics Committee of Weifang People's Hospital, Shandong Second Medical University (KYLL20240318-4), and informed consent was obtained from the parents of all participating children. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Human ethics and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 28 November 2024 / Accepted: 29 April 2025
Published online: 17 May 2025

References

1. Noval Rivas M, Arditi M. Kawasaki disease: pathophysiology and insights from mouse models. Nat Rev Rheumatol. 2020;16(7):391–405.
2. Lin Y, Li X, Shi L. Interpretation of the 2017 edition of diagnosis,treatment,and Long-term management of Kawasaki disease: A scientific statement for health professionals from the American heart association. Chin J Practical Pediatr. 2017;32(9):641–8.
3. Del Principe D, Pietraforte D, Gambardella L, Marchesi A, de Jacobis IT, Villani A, Malorni W, Straface E. Pathogenetic determinants in Kawasaki disease: the haematological point of view. J Cell Mol Med. 2017;21(4):632–9.
4. Kumrah R, Vignesh P, Rawat A, Singh S. Immunogenetics of Kawasaki disease. Clin Rev Allergy Immunol. 2020;59(1):122–39.
5. Onouchi Y, Ozaki K, Buns JC, Shimizu C, Hamada H, Honda T, Terai M, Honda A, Takeuchi T, Shibuta S, Suenaga T, Suzuki H, Higashi K, Yasukawa K, Suzuki Y, Sasago K, Kemmotsu Y, Takatsuki S, Saji T, Yoshikawa T, Nagai T, Hamamoto K, Kishi F, Ouchi K, Sato Y, Newburger JW, Baker AL, Shulman ST, Rowley AH, Yashiro M, Nakamura Y, Wakui K, Fukushima Y, Fujino A, Tsunoda T, Kawasaki T, Hata A, Nakamura Y, Tanaka T. Common variants in CASP3 confer susceptibility to Kawasaki disease. Hum Mol Genet. 2010;19(14):2898–906.
6. Khor CC, Davila S, Breunis WB, Lee YC, Shimizu C, Wright VJ, Yeung RSM, Tan DEK, Sim KS, Wang JJ, Wong TY, Pang JX, Mitchell P, Cimaz R, Dahdah N, Cheung YF, Huang GY, Yang WL, Park IS, Lee JK, Wu JY, Levin M, Burns JC, Burgner D, Kuijpers TW, Hibberd ML, Lau YL, Zhang J, Ma XJ, Liu F, Wu L, Yoo JJ, Hong SJ, Kim KJ, Kim JJ, Park YM, Hong YM, Sohn S, Jang GY, Ha KS, Nam HK, Byeon JH, Yun SW, Han MK, Lee KY, Hwang JY, Rhim JW, Song MS, Lee HD, Kim DS, Lee JM, Chang JS, Tsai FJ, Liang CD, Chen MR, Chi H, Chiu NC, Huang FY, Chang LY, Huang LM, Kuo HC, Huang KP, Lee ML, Hwang B, Huang YC, Lee PC, Odam M, Christiansen FT, Witt C, Goldwater P, Curtis N, Palasanthiran P, Ziegler J, Nissen M, Nourse C, Kuipers IM, Ottenkamp JJ, Geissler J, Biezeveld M, Tacke C, Filippini L, Brogan P, Klein N, Shah V, Dillon M, Booy R, Shingadia D, Bose A, Mukasa T, Tulloh R, Michie C, Newburger JW, Baker AL, Rowley AH, Shulman ST, Mason W, Takahashi M, Melish ME, Tremoulet AH, Viswanathan A, Rochtchina E, Attia J, Scott R, Holliday E, Harrap S. Hong Kong-Shanghai Kawasaki Dis, G.; Korean Kawasaki Dis Genetics, C.; Taiwan Kawasaki Dis Genetics, C.; Int Kawasaki Dis Genetics, C.; Consortiu, U. S. K. D. G.; Blue Mt Eye, S., Genome-wide association study identifies FCGR2A as a susceptibility locus for Kawasaki disease. *Nature Genetics* 2011, *43* (12), 1241–1246.
7. Parthasarathy P, Agarwal A, Chawla K, Tofighi T, Mondal TK. Upcoming biomarkers for the diagnosis of Kawasaki disease: A review. Clin Biochem. 2015;48(16–17):1188–94.
8. Lo MS. A framework for Understanding Kawasaki disease pathogenesis. Clin Immunol. 2020;214:108385.
9. Zhou Q, Wu J, Qiu H. Research progress on the etiology and pathogenesis of Kawasaki disease. Zhejiang Med J. 2019;41:1443–6.
10. Yao D, Dong M, Dai C, Wu S. Inflammation and inflammatory cytokine contribute to the initiation and development of ulcerative colitis and its associated Cancer. Inflamm Bowel Dis. 2019;25(10):1595–602.
11. Abe J. Cytokines in Kawasaki disease. Nihon Rinsho. 2014;72(9):1548–53.
12. Lin CY, Lin CC, Hwang BT, Chiang B. SERIAL CHANGES OF SERUM INTERLEUKIN-6, INTERLEUKIN-8, AND TUMOR-NECROSIS-FACTOR-ALPHA AMONG PATIENTS WITH KAWASAKI-DISEASE. J Pediatr. 1992;121(6):924–6.
13. Shen W, Jiang L, Li S, Liu W, Li X, Yang X. Significance of the alteration of Th17 cells in the acute phase of Kawasaki disease. Chin J Immunol. 2010;26(5):458–61.
14. Blazevic N, Rogic D, Pelajic S, Miler M, Glavcic G, Ratkajec V, Vrkljan N, Bakula D, Hrabar D, Pavic T. YKL-40 as a biomarker in various inflammatory diseases: A review. Biochemia Med 2024, *34* (1).
15. Kastrup J. Can YKL-40 be a new inflammatory biomarker in cardiovascular disease? Immunobiology. 2012;217(5):483–91.
16. He Y, Liao M, Qu L. The role of YKL-40 in inflammatory response and its related signaling pathways. J Med Res Combat Trauma Care. 2016;29:883–8.
17. Zhao T, Su Z, Li Y, Zhang X, You Q. Chitinase-3 like-protein-1 function and its role in diseases. Signal Transduct Target Ther. 2020;5(1):201.
18. Kocyigit I, Gungor O, Dogan E, Karadavut S, Karakukcu C, Eroglu E, Orscelik O, Unal A, Dogan A, Sipahioglu MH, Tokgoz B, Oymak O. The serum YKL-40 level is associated with vascular injury and predicts proteinuria in nephrotic syndrome patients. J Atheroscler Thromb. 2015;22(3):257–64.
19. Jafari-Nakhjavani MR, Ghorbanihaghjo A, Bagherzadeh-Nobari B, Malek-Mahdavi A, Rashtchizadeh N. Serum YKL-40 levels and disease characteristics in patients with rheumatoid arthritis. Caspian J Intern Med. 2019;10(1):92–7.
20. Sun Y, Kong X, Wu S, Ma L, Yan Y, Lv P, Jiang L. YKL-40 as a new biomarker of disease activity in Takayasu arteritis. Int J Cardiol. 2019;293:231–7.
21. Kucur M, Isman FK, Karadag B, Vural VA, Tavsanoglu S. Serum YKL-40 levels in patients with coronary artery disease. Coron Artery Dis. 2007;18(5):391–6.
22. Burns JC, Kushner HI, Bastian JF, Shike H, Shimizu C, Matsubara T, Turner CL. Kawasaki disease: A brief history. Pediatrics. 2000;106(2):E27.
23. Hu J, Ren W. Analysis of the risk factors in prognosis of Kawasaki disease with coronary artery lesions. Front Pediatr. 2021;9:798148.
24. Pan S, Liu F, Luo G. Interpretation of revision of diagnostic guidelines for Kawasaki Disease(6th revised edition). Chin J Practical Pediatr. 2020;35(11):846–9.
25. Kuo HC. Diagnosis, progress, and treatment update of Kawasaki disease. Int J Mol Sci. 2023;24:18.
26. Kang S, Kishimoto T. Interplay between interleukin-6 signaling and the vascular endothelium in cytokine storms. Exp Mol Med. 2021;53(7):1116–23.
27. Yasuda H, Ikeda T, Hamaguchi Y, Furukawa F. Clinically amyopathic dermatomyositis with rapidly progressive interstitial pneumonia: the relation between the disease activity and the serum interleukin-6 level. J Dermatol. 2017;44(10):1164–7.
28. Palizgir MT, Akhtari M, Mahmoudi M, Mostafaei S, Rezaiemanesh A, Shahram F. Curcumin reduces the expression of Interleukin 1β and the production of Interleukin 6 and tumor necrosis factor alpha by M1 macrophages from patients with Behcet's disease. Immunopharmacol Immunotoxicol. 2018;40(4):297–302.
29. Pouyafar A, Heydarabad MZ, Mahboob S, Mokhtarzadeh A, Rahbarghazi R. Angiogenic potential of YKL-40 in the dynamics of tumor niche. Biomed Pharmacother. 2018;100:478–85.
30. Abd El-Fattah AA, Sadik NAH, Shaker OG, Kamal AM. Single Nucleotide Polymorphism in SMAD7 and CHI3L1 and Colorectal Cancer Risk. *Mediators of Inflammation* 2018, *2018*.
31. Long X, He X, Ohshimo S, Griese M, Sarria R, Guzman J, Costabel U, Bonella F. Serum YKL-40 as predictor of outcome in hypersensitivity pneumonitis. Eur Respir J 2017, *49* (2).
32. Kjaergaard AD, Johansen JS, Bojesen SE, Nordestgaard BG. Role of inflammatory marker YKL-40 in the diagnosis, prognosis and cause of cardiovascular and liver diseases. Crit Rev Clin Lab Sci. 2016;53(6):396–408.
33. Dieset I, Mørch RH, Hope S, Hoseth EZ, Reponen EJ, Gran JM, Aas M, Michelsen AE, Reichborn-Kjennerud T, Nesvåg R, Agartz I, Melle I, Aukrust P, Djurovic S, Ueland T, Andreassen OA. An association between YKL-40

and type 2 diabetes in psychotic disorders. Acta Psychiatrica Scandinavica. 2019;139(1):37–45.
34. Del Turco S, De Simone P, Ghinolfi D, Gaggini M, Basta G. Comparison between galectin-3 and YKL-40 levels for the assessment of liver fibrosis in cirrhotic patients. Arab J Gastroenterology: Official Publication Pan-Arab Association Gastroenterol. 2021;22(3):187–92.
35. Wang Z, Wang S, Jia Z, Hu Y, Cao D, Yang M, Liu L, Gao L, Qiu S, Yan W, Li Y, Luo J, Geng Y, Zhang J, Li Z, Wang X, Li M, Shao R, Liu Y. YKL-40 derived from infiltrating macrophages cooperates with GDF15 to Establish an immune suppressive microenvironment in gallbladder cancer. Cancer Lett. 2023;563:216184.
36. Kazakova MH, Batalov AZ, Mateva NG, Kolarov ZG, Sarafian VS. YKL-40 and cytokines - a new diagnostic constellation in rheumatoid arthritis?? Folia Medica. 2017;59(1):37–42.
37. Ma CY, Xu ZY, Wang SP, Peng HY, Liu F, Liu JH, Ren FX. Change of inflammatory factors in patients with acute coronary syndrome. Chin Med J (Engl). 2018;131(12):1444–9.
38. Zheng JL, Lu L, Hu J, Zhang RY, Zhang Q, Chen QJ, Shen WF. Increased serum YKL-40 and C-reactive protein levels are associated with angiographic lesion progression in patients with coronary artery disease. Atherosclerosis. 2010;210(2):590–5.
39. Johansen JS, Jensen BV, Roslind A, Nielsen D, Price PA. Serum YKL-40, a new prognostic biomarker in cancer patients? Cancer Epidemiol Biomarkers Prev. 2006;15(2):194–202.
40. Li XZ, Zhao SC, Cai XL, Wang YF, Chen J, Ma XF, Zhang H, DIFFERENCES IN EXPRESSION OF YKL-40 AND TLR4 IN NASAL SINUS MUCOSA OF CHRONIC SINUSITIS PATIENTS WITH AND WITHOUT NASAL POLYPS. J Biol Regul Homeost Agents. 2018;32(3):537–43.
41. Francescone RA, Scully S, Faibish M, Taylor SL, Oh D, Moral L, Yan W, Bentley B, Shao R. Role of YKL-40 in the angiogenesis, radioresistance, and progression of glioblastoma. J Biol Chem. 2011;286(17):15332–43.
42. Libreros S, Garcia-Areas R, Shibata Y, Carrio R, Torroella-Kouri M, Iragavarapu-Charyulu V. Induction of Proinflammatory mediators by CHI3L1 is reduced by Chitin treatment: decreased tumor metastasis in a breast cancer model. Int J Cancer. 2012;131(2):377–86.
43. Jackson AM, Sigdel TK, Delville M, Hsieh SC, Dai H, Bagnasco S, Montgomery RA, Sarwal MM. Endothelial cell antibodies associated with novel targets and increased rejection. J Am Soc Nephrology: JASN. 2015;26(5):1161–71.
44. Cacciola R, Gentilini Cacciola E, Vecchio V, Cacciola E. Impact of Anti-Endothelial cell antibodies (AECAs) in patients with polycythemia Vera and thrombosis. Diagnostics (Basel Switzerland) 2022, *12* (5).
45. Sakurai Y. Autoimmune aspects of Kawasaki disease. J Investigat Allergol Clin Immunol. 2019;29(4):251–61.

Publisher's note