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ARTICLE

Predictive Value of Serum N-Terminal Pro-Brain Natriuretic Peptide, D-Dimer, Albumin Combined with T-Cell Subsets in Detecting Coronary Artery Damage in Children with Kawasaki Disease

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Abstract

Aims/Background Kawasaki disease (KD) is the common acute, self-limiting vasculitis in children, often affecting coronary arteries, which may lead to coronary artery dilation, stenosis, or in severe cases, myocardial infarction. This study aimed to identify new approaches for reducing or preventing coronary artery lesions (CAL) in KD patients by analyzing specific serological markers across various paediatric groups.

Methods Clinical data were collected from 100 children diagnosed with Kawasaki disease (KD) admitted at First Affiliated Hospital of Hebei North University between May 2023 and June 2024. These children were divided into two groups based on coronary artery injury status: Occurrence group (n = 31) and Non-occurrence group (n = 69). Additionally, data from 100 children with acute upper respiratory tract infections (URTI) and 100 healthy children who underwent routine physical examination during the same period (Healthy group) were included for comparison. Serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), D-dimer (D-D), albumin (ALB), and T-cell subsets were measured and compared across groups to evaluate their clinical utility in diagnosing coronary artery damage in KD.

Results NT-proBNP and D-D levels were highest in KD children with coronary artery injury and lowest in the healthy group, while ALB levels were lowest in KD children with coronary artery injury and highest in the healthy group, with statistically significant differences ($p < 0.001$). Analysis of T-cell subsets revealed that cluster of differentiation (CD)3^+, $CD4^+$, and $CD4^+/CD8^+$ levels were highest in the Healthy group, while $CD8^+$ levels were highest in the Occurrence group, with statistically significant differences ($p < 0.001$). The combined diagnostic model demonstrated an area under the curve (AUC) value of 0.885 (95% CI: 0.829–0.941), showing higher specificity and AUC value compared to each marker individually.

Conclusion The combination of serum NT-proBNP, D-D, ALB, and T-cell subsets offers valuable predictive insights for coronary artery damage in KD children and may serve as an auxiliary diagnostic tool.

Key words: pro-brain natriuretic peptide; fibrin fragment D; albumins; T-lymphocytes; mucocutaneous lymph node syndrome

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Introduction

Kawasaki disease (KD) primarily affects children aged 6 months to 5 years, with epidemiological showing a rising incidence globally (Burns, 2024; Peng and Yi, 2023). Although the exact etiology of KD is unknown, its epidemiological characteristics suggest a role in infection and genetic predisposition (Sakurai, 2019). KD is an acute, systemic vasculitis with an unclear origin that predominantly impacts infants and young children (Amir et al, 2023). Japan, in particular, reports a high prevalence, with 264.8 per 1,000,000 children under 5 diagnosed in 2012 (Seki and Minami, 2022).

The development of coronary artery lesions (CAL) in KD significantly increases the risk of cardiovascular complications, especially in children, representing one of the most severe acute and long-term sequelae; it can adversely impact long-term prognosis and elevate mortality rates (Huang et al, 2024; Philip et al, 2023). The diagnosis of KD with CAL is challenging as it relies primarily on clinical manifestations, such as polymorphic rashes, limb swelling, and mucosal congestion in the oropharynx, due to a lack of specific laboratory markers (Ae et al, 2021; Hu et al, 2022). Coronary artery damage often remains undetected until 2–3 weeks post-onset. While ultrasound is useful in KD diagnosis, it has limitations and may fail to detect early coronary changes. In contrast, biochemical markers can facilitate timely screening, allowing for early prediction of coronary artery damage and improving prognosis assessment in KD paediatric patients (Ohst et al, 2018). However, no single biomarker provides adequate predictive accuracy for CAL in children with KD. There is an urgent need for laboratory markers with higher specificity for CAL in KD and prompt, effective measures to mitigate CAL and improve long-term outcomes.

Studies have demonstrated the high sensitivity and specificity of serological tests in the diagnosis of various diseases (Ho et al, 2020; Saschenbrecker et al, 2019). Serological diagnostics are versatile and have shown utility across conditions such as gastric cancer, type 1 diabetes, fatty liver, and brucellosis (Kriķe et al, 2024; Li et al, 2022). These methods are also popular among healthcare providers due to their simplicity, speed, and potential for automation. For example, the chemiluminescence assay is known for its user-friendliness, accuracy, and suitability for automation, making it a preferred method in antigen preparation (Saito et al, 2023). Despite the success of combined serum and immunologic markers in the diagnosis of KD and coronary artery damage, few studies have confirmed the effectiveness of this approach in the diagnosis of KD-associated CAL.

The present study aimed to enhance diagnostic accuracy for KD with coronary artery damage through the analysis of serum N-terminal pro-brain natriuretic peptide (NT-proBNP), D-dimer (D-D), albumin (ALB), and T-cell subsets as potential biomarkers. The findings from this study provide a scientific basis for timely clinical intervention and ultimately reduce the incidence of complications associated with KD.

Methods

General Information

Clinical data were collected and analyzed from 100 children with Kawasaki disease (KD), divided into the Occurrence group (n = 31) and the Non-occurrence group (n = 69) based on the presence of coronary artery injury. Additionally, data from 100 children with acute upper respiratory tract infections (URTI) and 100 healthy children who underwent routine physical examinations in outpatient clinics during the same period (Healthy group) were included. All children were admitted to First Affiliated Hospital of Hebei North University between May 2023 and June 2024. This study was approved by the Ethics Committee of the First Affiliated Hospital of Hebei North University (Approval No.: K2024236). All procedures followed the ethical principles outlined in the Declaration of Helsinki (World Medical Association, 2013), and informed consent was obtained from the parents or legal guardians of all the participants.

Inclusion and Exclusion Criteria

Inclusion Criteria

(a) KD group: ① Patients meeting diagnostic criteria for KD; ② Patients newly diagnosed with KD; ③ Informed consent obtained from legal guardians; ④ Blood tests conducted during the acute phase of KD, with coronary artery ultrasonography performed before and after intravenous immunoglobulin treatment; ⑤ Complete medical records available.

(b) Acute URTI group: ① Patients clinically diagnosed with acute URTI due to viral pathogens (Hirsch et al, 2013); ② Patients with fever prior to admission and initial consultation; ③ Haematological tests conducted before treatment; ④ Informed consent obtained from legal guardians; ⑤ Complete medical records available.

(c) Healthy group: ① Patients with no history of related infections or other symptoms, previously in good health; ② Normal results in laboratory tests and cardiac ultrasound examinations.

Exclusion Criteria

① Patients with history of vitamin D supplementation or related medication prior to admission.

② Patients undergoing diagnosis and treatment with immunoglobulin in other hospitals.

③ Patients failing to meet the inclusion criteria.

④ Patients with infections by pathogens other than those specified for the URTI group.

Diagnostic Criteria for KD and Coronary Artery Damage

KD was diagnosed by a specialist following the 6th revision of the Kawasaki Disease Diagnostic Guidelines (Kobayashi et al, 2020). Specific diagnostic criteria include fever, bilateral conjunctival congestion without purulent discharge, lip cracking and strawberry tongue, rashes including redness and swelling at scar sites, alterations in extremities such as erythema and oedema in palms and soles during

the acute phase, periungual desquamation resembling 'sock-like' peeling during the recovery phase, and nonpurulent cervical lymphadenopathy.

A complete KD diagnosis was made when five or more of these signs were present or when coronary artery damage was confirmed by echocardiography along with four of these signs. An incomplete KD diagnosis was made with the presence of three signs and confirmed coronary artery damage by echocardiography or with one to two signs after ruling out other diagnoses.

Coronary artery damage was diagnosed based on a coronary artery diameter Z-value $\geq$2.5, or a diameter $\geq$3 mm in children under 5 years and $\geq$4 mm in those over 5 years.

Research Methods

Fasting blood samples were collected from all study subjects, stored in dry tubes, and centrifuged at 3000 rpm for 10 minutes using a benchtop medical centrifuge (KD200D0.5, Batch No.: 2208, Kuaide Medical Technology Co., Ltd., Guangzhou, China). The samples were then stored at –70 °C until analysis. Serum NT-proBNP levels were determined via a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) using kits obtained from Zhengzhou Antu Bioengineering Co., Ltd. (Batch No.: 20232400682, Zhengzhou, China). Serum D-D concentrations were measured by immunoturbidimetry, while serum ALB concentrations were measured with a fully automated blood analyzer (Model HF-3800, Batch No.: 20210058, Wuhan Kangnai Medical Instrument Co., Ltd., Wuhan, China). T-lymphocyte subsets (cluster of differentiation (CD)3^+, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$) in the peripheral blood were quantified using a flow cytometer (Model Aurora, Batch No.: 202001264, Qingdao Jiading Analytical Instrument Co., Ltd., Qingdao, China). All procedures were performed by certified laboratory personnel following the manufacturer's instructions.

Statistical Methods

Data were analyzed using SPSS software (IBM Corp., Version: 26.0, Armonk, NY, USA). The Kolmogorov-Smirnov (K-S) test was used to determine the normality of continuous variables. Normally distributed data were expressed as mean $\pm$ standard deviation (Mean $\pm$ SD), and comparisons across multiple groups were made using one-way Analysis of Variance (ANOVA), with post hoc analysis conducted using the Least Significant Difference-Tukey Test (LSD-*t* test). Non-normally distributed data were expressed as median (P_{25}, P_{75}) and compared across groups using the Kruskal-Wallis (K-W) H nonparametric test, with pair-wise comparisons performed as needed.

Categorical variables were expressed as counts and percentages [n (%)] and analyzed using the chi-square test or Fisher's exact test, as appropriate. The diagnostic performance of each biomarker for coronary artery injury was assessed through receiver operating characteristic (ROC) curves. Logistic regression was employed to construct a comprehensive diagnostic model and calculate the predictive probability of combined indicators. A p-value < 0.05 was considered statistically significant.

Results

Baseline Data Comparison

No significant differences were observed between the four groups in terms of gender, age, height, weight, head circumference, or residence ($p > 0.05$). However, significant differences were detected in haemoglobin count, white blood cell count, platelet count, and urine protein levels ($p < 0.001$). Detailed baseline data are presented in Table 1.

Comparison of Serum Markers across Study Groups

Serum marker analysis showed that NT-proBNP and D-D levels were highest among KD children with coronary artery damage and lowest in the healthy control group. Conversely, serum ALB levels were highest in the healthy group and lowest in KD children with coronary artery damage, with statistically significant differences ($p < 0.001$) (Table 2).

Comparison of T-Cell Subset Levels

The analysis of T-cell subset levels across the four study groups indicated that healthy children exhibited the highest levels of $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ ratios. Meanwhile, $CD8^+$ levels were the highest in the KD Occurrence group, with statistically significant differences observed ($p < 0.001$) (Table 3).

Clinical Diagnostic Efficiency of Various Indicators

ROC curves were generated for the laboratory indicators to evaluate their diagnostic accuracy for KD with coronary artery damage. The combined diagnostic model demonstrated a higher area under the curve (AUC) than individual diagnostic indicators, along with improved sensitivity and specificity. Fig. 1 and Table 4 present these findings in detail.

Discussion

KD is a paediatric condition marked by systemic vasculitis and a rising incidence, now recognized as a leading cause of acquired heart disease in children in developed countries and parts of China (Huang et al, 2021; Pinna et al, 2008). Cardiovascular complications, especially CAL, pose a serious long-term health risk to KD patients, often leading to myocardial ischemia or infarction, which can be life-threatening (Brogan et al, 2020; Robinson et al, 2023). The medical community recognises coronary artery stenosis as the most critical complication inherent to KD.

The diagnosis of KD currently relies on the exclusion of other possible diseases, as no specific laboratory marker is available. Clinical manifestations of KD often mimic febrile illnesses, making differential diagnosis challenging and potentially leading to delays in the detection of coronary artery damage (Lee et al, 2022). This study aimed to support the early detection of KD with CAL through serological and immunological markers to improve diagnostic accuracy and promote timely intervention.

Table 1. Baseline data comparison among study groups.

Item	Occurrence group (n = 31)	Non-occurrence group (n = 69)	URTI group (n = 100)	Healthy group (n = 100)	χ^2/H	*p*-value
Gender					0.109	0.991
Male	17 (54.84%)	38 (55.07%)	55 (55.00%)	57 (57.00%)		
Female	14 (45.16%)	31 (44.93%)	45 (45.00%)	43 (43.00%)		
Ages (years)	5.00 (3.00, 8.00)	4.00 (1.50, 5.00)	4.00 (2.00, 6.00)	4.00 (3.00, 6.00)	7.610	0.055
Height (cm)	88.40 (76.50, 106.20)	97.40 (83.70, 109.20)	98.00 (82.05, 112.83)	91.20 (80.73, 108.63)	4.561	0.207
Weight (kg)	18.00 (13.00, 21.00)	17.00 (13.00, 20.00)	17.00 (14.00, 22.00)	18.00 (13.25, 21.00)	5.417	0.144
Haemoglobin count (g/L)	103.00 (98.00, 111.00)	103.00 (97.00, 108.50)	143.00 (138.00, 148.00)	129.50 (125.25, 133.00)	254.077	<0.001
WBC count (10^9/L)	29.27 (23.86, 35.02)	19.82 (17.18, 23.10)	16.89 (15.23, 18.51)	8.56 (6.97, 10.09)	242.460	<0.001
Platelet count (10^9/L)	398.00 (384.00, 423.00)	371.00 (349.00, 387.50)	314.00 (297.25, 331.75)	200.50 (146.50, 243.25)	260.637	<0.001
Urinary protein (mg/L)	121.00 (116.00, 124.70)	110.10 (103.00, 121.25)	100.50 (92.05, 109.15)	63.90 (50.85, 77.98)	233.652	<0.001
Head circumference (cm)	48.30 (47.00, 51.20)	50.50 (46.85, 53.10)	49.60 (47.63, 52.68)	50.40 (47.10, 53.00)	2.097	0.552
Place of residence					2.561	0.464
City	18 (58.06%)	29 (42.03%)	48 (48.00%)	44 (44.00%)		
Rural	13 (41.94%)	40 (57.97%)	52 (52.00%)	56 (56.00%)		

URTI, upper respiratory tract infections; WBC, White Blood Cell.

Table 2. Comparison of serum markers across study groups [P_{25}, P_{75}].

Group	NT-proBNP (pmol/L)	D-D (mg/L)	ALB (g/L)
Occurrence group (n = 31)	501.98 (413.20, 570.33)	0.92 (0.74, 1.51)	21.60 (17.20, 25.80)
Non-occurrence group (n = 69)	402.08 (387.09, 420.09)	0.75 (0.63, 0.85)	29.00 (24.30, 32.85)
URTI group (n = 100)	320.11 (298.55, 334.39)	0.61 (0.50, 0.70)	33.15 (30.25, 35.90)
Healthy group (n = 100)	241.22 (211.27, 264.68)	0.31 (0.21, 0.41)	46.80 (41.28, 50.55)
Z_1	–4.274	–3.925	–4.912
P_1	<0.001	<0.001	<0.001
Z_2	–8.383	–7.103	–6.905
P_2	<0.001	<0.001	<0.001
Z_3	–8.394	–8.397	–8.389
P_3	<0.001	<0.001	<0.001
Z_4	–11.006	–6.123	–5.276
P_4	<0.001	<0.001	<0.001
Z_5	–11.035	–11.037	–11.035
P_5	<0.001	<0.001	<0.001
Z_6	–11.645	–11.486	–12.107
P_6	<0.001	<0.001	<0.001

NT-proBNP, N-terminal pro-brain natriuretic peptide; D-D, D-dimer; ALB, albumin. Z_1 and P_1 represent comparison between the Occurrence and Non-occurrence groups; Z_2 and P_2 represent comparison between the Occurrence and URTI groups; Z_3 and P_3 represent comparison between the Occurrence and Healthy groups; Z_4 and P_4 represent the comparison between the Non-occurrence and URTI groups; Z_5 and P_5 represent the comparison between the Non-occurrence and Healthy groups; Z_6 and P_6 represent the comparison between the URTI and Healthy groups.

Table 3. Comparison of T-cell subset levels across study groups [P_{25}, P_{75}].

Group	$CD3^+$ (cells/μL)	$CD4^+$ (cells/μL)	$CD8^+$ (cells/μL)	$CD4^+/CD8^+$
Occurrence group (n = 31)	760.00 (646.00, 902.00)	583.0 (499.00, 637.00)	1607.00 (1460.00, 1765.00)	0.37 ± 0.09
Non-occurrence group (n = 69)	935.00 (869.50, 998.00)	628.00 (586.00, 673.50)	1513.00 (1404.50, 1661.50)	0.41 ± 0.06
URTI group (n = 100)	1235.50 (864.00, 1618.00)	687.00 (537.50, 911.50)	1330.50 (1256.00, 1394.25)	0.53 (0.40, 0.71)
Healthy group (n = 100)	1904.00 (1431.00, 2333.25)	997.50 (769.50, 1226.75)	735.00 (504.25, 978.25)	1.33 (0.87, 1.82)
Z_1/t_1	–5.109	–2.724	–2.202	4.950
P_1	<0.001	0.006	0.028	0.028
Z_2	–6.071	–2.978	–7.189	–5.390
P_2	<0.001	0.003	<0.001	<0.001
Z_3	–8.315	–6.650	–8.394	–8.389
P_3	<0.001	<0.001	<0.001	<0.001
Z_4	–4.225	–7.189	–8.100	–4.912
P_4	<0.001	<0.001	<0.001	<0.001
Z_5	–10.248	–8.556	–11.035	–11.035
P_5	<0.001	<0.001	<0.001	<0.001
Z_6	–7.196	–6.491	–12.122	–11.100
P_6	<0.001	<0.001	<0.001	<0.001

Note: Z_1 and P_1 represent comparison between the Occurrence and Non-occurrence groups; Z_2 and P_2 represent comparison between the Occurrence and URTI groups; Z_3 and P_3 represent comparison between the Occurrence and Healthy groups; Z_4 and P_4 represent the comparison between the Non-occurrence and URTI groups; Z_5 and P_5 represent the comparison between the Non-occurrence and Healthy groups; Z_6 and P_6 represent the comparison between the URTI and Healthy groups. t_1, *t*-value; CD, cluster of differentiation.

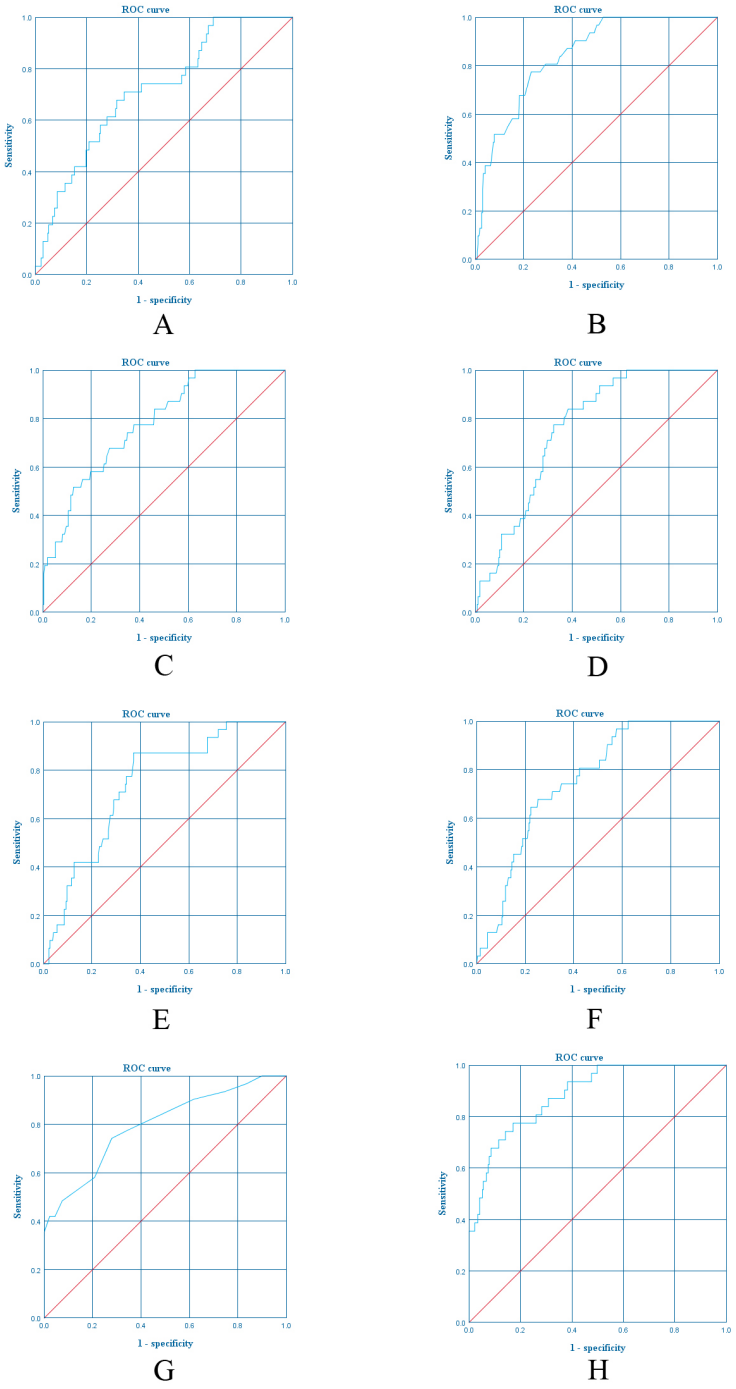

Fig. 1. Receiver operating characteristic (ROC) curves for various clinical indicators in the diagnosis of Kawasaki disease (KD) with coronary artery damage. (A) ROC curve for KD diagnosis with coronary artery damage using serum N-terminal pro-brain natriuretic peptide (NT-proBNP). (B) ROC curve for KD diagnosis with coronary artery damage based on serum D-dimer (D-D). (C) ROC curve for KD diagnosis with coronary artery damage using serum albumin (ALB). (D) ROC curve for KD diagnosis with coronary artery damage using the immune biomarker $CD3^+$. (E) ROC curve for KD diagnosis with coronary artery damage using immune biomarker $CD4^+$. (F) ROC curve for KD diagnosis with coronary artery damage using the immune biomarker $CD8^+$. (G) ROC curve for KD diagnosis with coronary artery damage based on the $CD4^+/CD8^+$ ratio. (H) ROC curve representing the combined diagnostic approach.

Table 4. Diagnostic efficiency of various indicators for Kawasaki disease (KD) with coronary artery damage.

Indicator	AUC value	Cutoff value	Youden index	Sensitivity	Specificity	Standard error	95% CI
NT-proBNP	0.717	340.330	0.364	0.710	0.654	0.045	0.629–0.805
D-D	0.842	0.710	0.544	0.774	0.770	0.031	0.780–0.903
ALB	0.778	31.350	0.402	0.677	0.725	0.040	0.700–0.856
$CD3^+$	0.757	1025.500	0.456	0.839	0.617	0.035	0.688–0.825
$CD4^+$	0.742	654.500	0.499	0.871	0.628	0.041	0.661–0.822
$CD8^+$	0.754	1418.500	0.424	0.677	0.747	0.037	0.681–0.827
$CD4^+/CD8^+$	0.795	1.250	0.463	0.742	0.721	0.047	0.704–0.886
Combined Diagnostic Approach	0.885	0.134	0.603	0.774	0.829	0.029	0.829–0.941

NT-proBNP, N-terminal pro-brain natriuretic peptide; D-D, D-dimer; ALB, albumin; AUC, area under the curve.

Baseline data analysis among the four groups revealed significant differences in haemoglobin, white blood cell count, platelet count, and urine protein levels ($p < 0.001$). These findings reflect physiological alterations in KD patients, which include altered hematologic parameters resulting from inflammation and systemic responses to the disease.

Further analysis revealed that serum NT-proBNP, D-D, and ALB were elevated in KD children with CAL compared to healthy controls. These findings may result from myocardial ischemia and infarction caused by coronary artery damage, which impairs cardiac function and leads to a decreased cardiac pumping ability (Qian et al, 2020). To maintain blood circulation, the heart necessitates compensatory mechanisms, including elevated NT-proBNP to regulate blood pressure and prevent fluid retention (Song et al, 2020). Additionally, the positive correlation between CAL severity and serum D-D levels suggests heightened thrombotic activity and vascular injury as CAL progresses (Medina-Leyte et al, 2021).

ALB synthesis occurs primarily in liver cells, and it maintains plasma colloid osmotic pressure to facilitate the transport and storage of various substances. KD impacts the cardiovascular system, which leads to the release of numerous inflammatory factors and cytokines. This inflammatory response impairs liver cell function and suppresses ALB synthesis, thus reducing serum ALB levels (Tsai et al, 2020). In addition, elevated capillary permeability caused by these inflammatory factors promotes ALB leakage into tissue fluid, resulting in decreased ALB concentrations (Zhang et al, 2024). Studies have indicated that serum ALB levels are significantly lower in children with CAL than in healthy children, which suggests that low ALB may reflect CAL severity in KD patients (Kelesoglu et al, 2021; Lu et al, 2021; Xu et al, 2024).

Children with KD and CAL exhibit notable immune dysfunction. KD impairs immune function through the promotion of persistent activation of the innate immune system, formation of immune complex, disruption of cellular immunity,

Th17/Treg imbalance, endothelial cell damage, and interactions between genetic susceptibility and environmental triggers (Xie et al, 2022). The role of the immune system in coronary artery disease (CAD) is complex and multifaceted. It responds to arterial wall injury through the initiation of an inflammatory response (Laera et al, 2023). These factors contribute to significant immune impairment following coronary artery damage.

The diagnostic performance of serum markers in KD with CAL was evaluated using ROC curves. The AUC values were highest for serum D-D and lowest for serum NT-proBNP. Currently, the diagnosis of KD complicated by CAL relies heavily on clinical criteria, domestically and internationally. However, the variability in clinical manifestations and the absence of specific markers make the diagnosis of CAL and assessment of KD severity challenging, and combined diagnostic approaches are emerging as a preferred trend (Huijuan et al, 2021). Analysis and plotting of combined diagnostic results revealed an AUC of 0.885, with sensitivity and specificity of 0.774 and 0.829, respectively. These findings demonstrate that the combination of these markers provides a reliable basis for early diagnosis of KD with coronary artery damage.

While this study provides valuable insights into the early diagnosis of KD with CAL, it has several limitations. Notable factors include a relatively small sample size and limitations in laboratory testing methods, which may impact the comprehensiveness and objectivity of the conclusions. These limitations underscore the importance of conducting future studies with increased rigor to enhance the accuracy and reliability of the findings and to minimize the impact of these potential limitations on experimental conclusions.

Conclusion

The combined analysis of serum NT-proBNP, D-D, ALB, and T-cell subsets enhances diagnostic accuracy for the detection of coronary artery damage in children with KD. This approach supports more informed selection and formulation of individualized treatment plans and demonstrates significant clinical application value.

Key Points

- KD with coronary artery damage is associated with alterations in specific serological markers in affected children.
- Coronary artery damage in KD also influences immune function to some extent.
- The integration of serological and immune markers improves the detection rate of coronary artery damage in KD patients and provides valuable guidance in the development of targeted treatment plans.

Availability of Data and Materials

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

Author Contributions

YW, JX, HG, HZ and ML designed the research study. HG, HZ and ML performed the research. YW, JX and ZL provided help and advice on the ELISA experiments. ZL analyzed the data. YW wrote the first draft. All authors contributed to revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Hebei North University (Ethics No.: K2024236). All procedures utilized in this study adhered to the ethical principles outlined in the Declaration of Helsinki, and informed consent was obtained from the parents or legal guardians of all the participants.

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Conflict of Interest

The authors declare no conflict of interest.

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