Complement 3 and Prognostic Nutritional Index Distinguish Kawasaki Disease from Fever Illness with Nomogram

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Abstract

Objective: This study aimed to establish a model to distinguish Kawasaki diseases(KD) from other fever illness using the prognostic nutritional index (PNI) and immunological factors.

Method: We enrolled a total of 692 patients (including 198 KD and 494 children with febrile diseases). Of those, 415 patients were selected to be the training group and 277 patients to be the validation group. Laboratory data, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), prognostic nutritional index (PNI), and immunological factors, were retrospectively collected for analysis after admission. We used univariate and multivariate logistic regression and nomogram for analysis.

Result: Patients with KD showed significantly higher C3 and lower PNI. After multivariate logistic regression, total leukocyte count, PNI, C3, and NLR showed significance ($p<0.05$) and then performed well with the nomogram model. The areas under the ROC in the training group and the validation group were 0.858 and 0.825, respectively. The calibration curves of the two groups for the probability of KD showed near agreement to the actual probability.

Conclusion: Compared to children with febrile diseases, patients with KD showed increased C3 and decreased nutritional index of PNI. The nomogram established with these factors can effectively identify KD from febrile illness in children.

Introduction

Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome (MCLS), is a form of acute febrile and systemic vasculitis that commonly occurs in children under 5 years old (1). The primary pathological changes of KD are systemic nonspecific vasculitis involving small and medium arteries, while the most serious complication is coronary artery lesions (CAL), including artery aneurysms, coronary artery stenosis, thrombosis, myocardial infarction, and sudden death (2). With an increasing number of patients in recent years, KD has become the main cause of acquired heart disease in children (3).

Both the etiology and pathogenesis of KD remain unknown but may be the result of combined effects from genetic heredity, infection (bacteria, mycoplasma, virus, COVID-19, fungus, etc.) and immune response (4). It is believed that certain pathogenic microbial infections and an immune response imbalance may lead to KD (5, 6). Therefore, speculation has indicated that inflammatory markers may have the potential to identify KD and disease prognosis (7). Recent studies have shown that the ratio of peripheral blood neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were associated with the severity of KD and CAL involvement (8).

The serum level of albumin is a negative acute-phase protein marker that decreases during inflammation or malnutrition. Inflammation reduces albumin concentration by lowering its rate of synthesis, causes leakage due to the increased permeability of blood vessels, and is associated with higher catabolic rates

(9). The serum levels of albumin play an important role in diagnosing incomplete KD according to the AHA supplementary criteria and predicting IVIG-resistant KD (10, 11). Onodera's prognostic nutritional index (Onodera's PNI) is composed of serum albumin value (ALB) and peripheral blood lymphocyte count (TLC), with the formula $PNI = ALB (g/L) + 5 \times TLC (10^9/L)$. This index was first proposed by Buzby and later established by Onodera (12). PNI is a scoring index used to assess the nutritional status of patients and predict the risk of surgery and prognosis of a variety of malignancy (13). PNI has been found to be a potentially important predictor of the disease activities and complications of autoimmune diseases (14). Tai et al. reported that PNI could be a candidate as an adjunctive predictor of CAL, as well as IVIG resistance. Together with low PNI, such factors as intravenous immunoglobulin (IVIG) resistance, male gender, and platelet count will contribute to high odds for predicting CAL within 6 months of illness (15).

A KD diagnosis primarily depends on clinical presentation and the exclusion of other clinically similar cases with known causes. Prompt administration of IVIG treatment can reduce the incidence of coronary artery aneurysms from 20–25% to 3–5% (10). The aim of this study is to explore the clinical value of PNI combined with immune factors in the identification of KD.

Materials And Methods

Study Participants

KD children hospitalized in Shenzhen Baoan Women's and Children's Hospital from August 2016 to July 2019 were enrolled in this study. Febrile children who were hospitalized on the same day were also enrolled as control group. Patients with autoimmune diseases, sepsis, or incomplete data were excluded, for a total of 51 KD patients and 105 fever controls). Clinical indicators were collected and compared between the two groups. The clinical diagnosis of KD was based on the revised diagnostic criteria of KD by the American Heart Association (AHA) in 2017. Clinical data of gender, age, weight, and clinical manifestations of enrolled children were collected for analysis. We also recorded laboratory results, including white blood cell (WBC), neutrophil, lymphocyte, platelet, albumin (ALB), immunoglobulin A (IgA), IgG, IgM, C3, C4, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and PNI for analysis.

Statistical Analysis

We used SPSS 13.0 software and R 3.5.1 software for statistical analysis, including single factor analysis and multi-factor analysis and expressed normal distribution measurement data as mean and standard deviation. Independent sample T test was used to compare the two groups. Median and interquartile range (IQR) were used to describe measurement data, and non-parametric the Mann-Whitney *U* rank sum test was used for comparison between groups without normal distribution. N and percentage were used to describe the counting data, and Pearson chi-square test (χ^2) was used to compare the counting data. We adopted R 3.5.1 software to make nomograms, calibration curves, and ROC. A value of $P < 0.05$ was considered statistically significant.

Results

Clinical Features

We included a total of 692 children in this study, including 422 male children (60.98%) and 270 female children (39.02%). The KD group consisted of 118 boys (59.6%) and 98 girls (40.4%), with a median age of 21 (13, 17) months. The febrile control group had 304 boys (61.54%) and 190 girls (38.46%), with a median age of 21 (11–41) months. Among them, 415 (60%) children were randomly selected as the training group and 295 (40%) as the verification group. The comparison of variables between groups is shown in Table 1. No significant difference was observed between the training group and the verification group ($p > 0.05$).

Table 1
Comparison of variables between the training group and the verification group

Variable	Total (N = 692)	Training group (N = 415)	Verification group (N = 277)	P
Age (month)	21 (11–40)	22 (12–40)	19 (11–40)	0.366
Male gender, N (%)	422 (60.98)	248 (59.76)	174 (62.82)	0.419
Body weight (Kg)	12.48 ± 4.73	12.66 ± 4.88	12.21 ± 4.5	0.215
WBC (*10 ⁹ /L)	10.4 (7.22–14.85)	10.2 (7.4–14.96)	11 (7.05–14.74)	0.955
IgA (g/L)	0.59 (0.4–1.01)	0.61 (0.41–1.03)	0.57 (0.37–0.96)	0.291
IgG (g/L)	7.27 ± 2.31	7.39 ± 2.33	7.1 ± 2.28	0.107
IgM (g/L)	1.04 (0.79–1.32)	1.04 (0.79–1.32)	1.03 (0.77–1.32)	0.766
C3 (g/L)	1.29 ± 0.27	1.28 ± 0.25	1.29 ± 0.28	0.532
C4 (g/L)	0.4 ± 0.13	0.4 ± 0.13	0.41 ± 0.14	0.401
NLR	1.3 (0.68–2.44)	1.31 (0.68–2.54)	1.27 (0.68–2.31)	0.371
PLR	83.85 (58.01–124.29)	83.07 (56.37–125.6)	84.98 (60.59–123)	0.576
PNI	60.92 ± 16.02	60.84 ± 15.28	61.05 ± 17.09	0.866
WBC: white blood cell; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M; C3: Complement 3; C4: Complement 4; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index				

Univariate Analysis

Single variable analysis of all variables in the training group revealed that gender, age, body weight, IgA, IgG, IgM, and C4 were not statistically significant between the KD group and the control group ($P > 0.05$).

WBC, PNI, NLR, PLR, and C3 demonstrated a significant difference between KD patients and febrile controls ($p < 0.05$) (Table 2).

Table 2
Comparison between Kawasaki disease patients and febrile controls (the training group)

	Febrile controls(N = 295)	KD(N = 120)	P-value
Age (month)	22 (11–41)	22 (15–37)	0.537
Male gender, N (%)	178 (60.34)	70 (58.33)	0.706
Body weight (Kg)	12.87 ± 5.39	12.16 ± 3.27	0.104
WBC (*10 ⁹ /L)	9.1 (6.8–12.7)	14.36 (10.52–17.94)	< 0.001*
IgA (g/L)	0.59 (0.4–1.03)	0.64 (0.44–1.05)	0.473
IgG (g/L)	7.43 ± 2.28	7.27 ± 2.46	0.530
IgM (g/L)	1.04 (0.79–1.31)	1.05 (0.79–1.32)	0.895
C3 (g/L)	1.21 ± 0.23	1.44 ± 0.25	< 0.001*
C4 (g/L)	0.4 ± 0.12	0.39 ± 0.13	0.343
NLR	1 (0.57–1.89)	2.7 (1.55–4.69)	< 0.001*
PLR	76.86 (52.18-115.23)	99.49 (70.25-162.26)	< 0.001*
PNI	62.41 ± 14.8	56.97 ± 15.81	< 0.001*
WBC: white blood cell; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M; C3: Complement 3; C4: Complement 4; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index			

Multivariate Logistic Regression Analysis

Significant indicators of univariate analysis, including WBC, C3, NLR, PLR, and PNI, were included in multivariate analysis to screen out independent risk factors of KD, and a nomogram was established based on the results of the multivariate analysis. The statistics showed that WBC, C3, NLR, and PNI were independent risk factors of KD (Table 3).

Table 3
Multivariate logistic regression analysis

	P-value	OR	95% C.I. for OR	
			Lower	Upper
WBC(*10 ⁹ /L)	< 0.0001	1.201	1.121	1.288
C3 (g/L)	< 0.0001	22.631	6.867	74.585
NLR	0.025	1.218	1.025	1.446
PNI	0.002	0.958	0.932	0.984
Constant	< 0.0001	0.006		
WBC: white blood cell; C3: Complement 3; NLR: neutrophil-to-lymphocyte ratio; PNI: prognostic nutritional index; OR, Odds ratio; CI, confidence interval				

Scoring System for Predicting KD

The logistic regression results of the training group were used to make the nomogram (Fig. 1). In the model, the maximum scores corresponding to each predictor were WBC (100 points), C3 (51 points), NLR (60 points), and PNI (75 points), and the occurrence probability of KD corresponding to the scores is shown in Table 4.

Table 4
The incidence risk of
Kawasaki disease
corresponding to the total
score

Total Points	Risk of KD
61	0.01
69	0.02
79	0.05
87	0.1
96	0.2
102	0.3
107	0.4
111	0.5
115	0.6
120	0.7
126	0.8
135	0.9
143	0.95
161	0.99
186	0.999
194	0.9995

Performance of the Nomogram

The ROC curve was applied to verify the nomogram results in the training group and the validation group and showed good differentiation with an area under the curve of ROC of 0.815 (95% confidence interval: 0.815–0.901) in the training group and 0.825 (95% confidence interval: 0.769–0.881) in the validation group (Fig. 2). The nomogram was calibrated using the calibration curve (16). A calibration curve of the nomogram for the training group and the validation group is presented in Fig. 3, which shows that the prediction of KD by the nomogram agreed well with the actual probabilities in both groups. The calibration curves for KD outcome in the two groups demonstrated nearly no apparent departure from fit, with good correspondence between predicted outcome and actual outcome.

The black dashed line is the reference line for where an ideal nomogram would lie.

The red dotted line is the performance of the nomogram, while the blue solid line corrects for any bias in the nomogram. figure a is for training group, figure b is for validation group)

Discussion

The accurate diagnosis of KD remains a challenge for clinicians because its clinical manifestations are often similar to or overlap with other febrile infectious diseases in children, and no specific laboratory test is currently available to confirm the diagnosis. A recent study reported the existence of over diagnosis KD(17). The challenge for clinicians is to prevent the occurrence of coronary artery aneurysms (CAAs) based on the accurate diagnosis and precise treatment of KD. Therefore, establishing a prediction model to identify KD from other febrile infectious diseases is crucial. In this report, we reviewed the clinical data of 216 patients with KD and 394 patients with other febrile infectious diseases and established a new prediction model with high accuracy.

Peripheral blood total WBC is one of the predictors in this model, and it increases in the acute phase of KD. WBC can be used as a non-specific inflammatory indicator in combination with clinical manifestations to predict KD (18). WBC may also be able to predict the severity of systemic inflammation and IVIG non-reactivity in KD patients (19). Other studies have shown that a WBC count greater than $16 \times 10^9/L$ is positively correlated with heart damage (20). Therefore, although the specificity of WBC is not high for KD, it is widely used in clinical practice and has practical significance for the clinical diagnosis of KD (21).

In this model, NLR (the ratio of neutrophil count to lymphocyte count of peripheral blood) is an important predictor for identifying KD. The immune response to inflammation includes neutrophils moving to the site of inflammation, releasing inflammatory cytokines, and activating T cells, which play a key role in the development of vascular inflammation. Lymphocytes are produced by lymphoid organs and play an important role in the body's immune response; they can also be used as a marker of immune regulation. Therefore, NLR is a reflection between inflammatory response and immunity balance. Some studies have shown that the higher the NLR value, the heavier the inflammatory response (22, 23). Recent studies have indicated that a high level of NLR is an independent influencing factor of IVIG resistance in KD (24).

Onodera's PNI is an index reflecting nutritional status. PNI has been reported to be a strong indicator for predicting the prognosis of patients with malignant tumors and has been widely used in predicting the prognosis, postoperative complications, and quality of life of a variety of tumors (25, 26). PNI was found as a novel surrogate independent predictor for IVIG-resistant KD according to resent study(27). In KD patients, the ALB levels were significantly lower than those of the febrile control group and even lower in KD with CAL formation (28).

Recent studies have reported that reduced lymphocyte count can serve as an independent predictor for IVIG resistance in KD (29). Onodera's PNI score is calculated based on these two indicators of lymphocyte and albumin and can reflect nutritional status and immune function. In this study, Onodera's PNI was an important predictor for distinguishing KD from other febrile diseases.

The plasma level of C3 in the KD group was significantly higher than in febrile controls and is also one of the important indicators for distinguishing KD from controls. C3 is involved in the three complement pathways (classical, lectin, and alternative pathway) and plays an important role in the innate immune response. Yan et al. have found that compared with fever control group, the level of C3 was significantly higher in KD group, and it was higher in IVIG sensitive group compared with IVIG nonresponsive group(7). Dysregulation or over activation of the complement system is the pathogenesis of vascular inflammation and aortic aneurysm formation (30, 31). However, few studies have addressed the complement pathway of KD (32, 33). Katayama et al. reported that Ficolin 1 inhibitory antibody injection improved vasculitis of the KD mouse model, further suggesting that the lectin pathway may be involved in the pathogenesis of KD (34).

This study is a single-center retrospective study with a relatively small number of cases, and a randomized controlled study with a larger sample of multiple centers is needed to further verify the value of the prediction model.

Conclusion

Our study demonstrated that the nomogram has a good prediction ability with WBC, NLR, C3, PNI, and other predictors. This report is the first to use C3 and PNI as predictive factors to distinguish KD from febrile disease. This paper clarified the importance of C3 in KD and provided direction for further research on the pathogenesis of KD.

List Of Abbreviations

KD	Kawasaki disease
PNI	Prognostic nutritional index
NLR	Neutrophil-to-lymphocyte ratio
PLR	Platelet-to-lymphocyte ratio
C3	Complement 3
MCLS	Mucocutaneous lymphnode syndrome
CAL	Coronary artery lesions
ALB	Albumin
IVIG	Intravenous immunoglobulin
WBC	White blood cell
IgA	Immunoglobulin A

Declarations

Ethics Approval and Consent to Participate:

This study was conducted in accordance with the Declaration of Helsinki. It was approved by the ethics committee of Shenzhen Baoan Women's and Children's Hospital, Shenzhen, Guangdong, China. (with IRB No. LLSC2020-07-32-01-KS). Due to the retrospective nature of this study, informed consent did not have to be obtained from the parents/legally authorized representatives of the participants. The ethics committee waived the informed consent.

Consent for publication

Not applicable

Availability of supporting data

The dataset containing results from this article are available from the corresponding author upon request.

Conflicts of interest: We hereby declare that we have no conflicts of interest in relation to this work.

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Authors' contributions: YSH, XPL, and HCK conceptualized and designed the study, conceptualized the analyses for this article, drafted the manuscript, and revised each version of the manuscript. HBX conceptualized and designed the study, participated in the design of the questionnaire, and conceptualized the analyses for this article, supervised all data analyses. TZ reviewed and revised each version of the manuscript. LNC and JYZ participated in the design of the questionnaire, conducted the analyses, and created the tables. XLL, WDH, CYL, and XL all helped conceptualize this article, contributed to the interpretation of the study findings, and reviewed and revised the manuscript. All authors participated in team discussions of data analyses, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

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Figures

Figure 1

The nomogram for probability of Kawasaki diseases WBC: white blood cell; C3: Complement 3; NLR: neutrophil-to-lymphocyte ratio; PNI: prognostic nutritional index

Figure 2

Receiver operating characteristic (ROC) curve of the nomogram for the training group and the validation group.

Figure 3

The calibration curves for the nomogram of the training group and the validation group