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Article

Association Between the Neutrophil-to-Lymphocyte Ratio and Severity of Liver Injury in Children With Kawasaki Disease

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Abstract

Aims/Background: Kawasaki disease (KD) is an acute febrile illness characterized by rash in children. The disease can cause liver damage, and severe cases can affect the growth and development of children. This study aimed to explore the correlation between the neutrophil-to-lymphocyte ratio (NLR) and the severity of liver function injury in KD. **Methods:** A total of 123 children with KD admitted to the Affiliated Yangming Hospital of Ningbo University from September 2022 to September 2025 were selected and divided into a normal liver function group (normal group) and an abnormal liver function group (abnormal group) according to the presence of liver function injury. Routine blood and liver function indices were assessed in children with KD. According to alanine aminotransferase (ALT) levels, the children in the abnormal group were further divided into three groups: mild, moderate, and severe. Routine blood and liver function indices were compared among the three groups. Multivariate logistic regression analysis was performed to identify independent risk factors for liver function impairment in children with KD. The correlations between NLR and C-reactive protein (CRP) and liver function indices were analyzed using Spearman's correlation. A sensitivity analysis was also performed using ALT as the upper limit of normal pediatric sex-specific values. **Results:** The levels of neutrophils, NLR, and procalcitonin (PCT) in the abnormal group were significantly higher than those in the normal group ($p < 0.05$), while lymphocyte levels were significantly lower ($p < 0.05$). Among the 123 children with KD, 47 had liver function impairment, with higher aspartate aminotransferase (AST), ALT, and total bilirubin (TBIL) levels. The comparison of NLR among the three groups was statistically significant, and NLR increased with increasing severity and liver function injury ($p < 0.05$). After adjusting for potential confounding factors, including age, CRP, intravenous immunoglobulin (IVIG) response, and coronary artery lesions, NLR remained an independent risk factor for liver function impairment in children with KD ($p < 0.05$). NLR was positively correlated with AST, ALT, Gamma-Glutamyl Transferase (GGT) and TBIL ($p < 0.05$). Receiver operating characteristic (ROC) curve analysis showed that NLR achieved an area under the curve (AUC) of 0.664 (95% confidence interval (CI): 0.574–0.747) for identifying children with KD and liver function impairment, with an optimal cutoff value of 4.702 (sensitivity, 46.8%; specificity, 82.9%). **Conclusion:** NLR is significantly associated with the severity of liver function impairment in children with KD. As an indicator readily obtained from routine blood tests, NLR may help clinicians identify children at increased risk of liver function injury.

Keywords: kawasaki disease; neutrophil-to-lymphocyte ratio; liver function tests; correlation analysis

1. Introduction

Kawasaki disease (KD) is an acute, self-limiting systemic vasculitis that predominantly affects medium- and small-sized arteries. Its clinical manifestations include persistent fever accompanied by characteristic mucocutaneous lesions, lymphadenopathy, and skin changes [1]. The main complication of KD is coronary artery lesions (CAL), and the disease can also result in multisystem and multiorgan damage [2]. Notably, the incidence of KD-associated heart disease has exceeded that of rheumatic heart disease and has become an important cause of acquired heart disease in children [3].

In addition, factors such as genetic susceptibility, infection, and immune dysregulation are closely associated with the development of KD, although its exact etiology remains unclear. Liver damage is a common complication of KD and is more prevalent during the acute phase [4]. Compared with adults, whose liver accounts for only 2% to 3% of their body weight, the liver in children accounts for approximately 4% to 5% of body weight. In addition, hepatic blood flow and blood storage in children increase, thereby increasing the demand for oxygen. Due to immature liver development and relatively weak immune function, children are more susceptible to factors such as infection and ischemia, which can induce hepatocellular swelling and even necrosis in severe cases [5]. For example, a study by Mammadov et al. [6] found that a considerable proportion of patients with KD had liver dysfunction, including elevated alanine aminotransferase (ALT) levels. Although liver dysfunction is not a major contributor to morbidity or mortality in children with KD, abnormal liver function may reflect the severity of persistent inflammation to a certain extent and may be closely related to the therapeutic response in KD. The early manifestations of KD are highly similar to those of infectious fever, which may easily lead to misdiagnosis by clinicians. Therefore, it is necessary to clarify the clin-

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ical characteristics of children with KD and liver function injury to provide a basis for disease diagnosis and treatment.

The quantification of systemic inflammation relies on a range of biochemical and hematological indicators routinely measured in standard blood tests, as well as on ratios derived from these parameters [7]. The neutrophil-to-lymphocyte ratio (NLR), as a novel index of systemic inflammatory response, retains the advantages of routine blood indices, including rapid assessment, low cost, and easy availability, and can serve as a marker of systemic inflammation [8]. Neutrophils are considered markers of persistent inflammation, while lymphocytes are important indicators of the immune response. Therefore, a high NLR may indicate an imbalance between inflammation and the immune response. However, few studies have investigated the relationship between NLR and liver function injury in children with KD. Therefore, this study aimed to investigate the association between NLR and liver function impairment in children with KD, which may provide a simple and readily available biomarker for early identification and risk stratification of hepatic involvement in this population.

2. Methods

2.1 Study Population and Data Collection

This was a retrospective study. A total of 123 children diagnosed with KD were admitted to the Affiliated Yangming Hospital of Ningbo University between September 2022 and September 2025. An a priori sample size calculation indicated that, assuming a moderate effect size (Cohen's $w = 0.30$), $\alpha = 0.05$, and a power of 0.80, the required sample size was 88 patients. The enrolled sample ($n = 123$) exceeded this threshold. Among the participants, 87 were male (70.73%), and 36 were female (29.27%), with a median age of 2 years (range: 1 month to 9 years). According to the presence of liver function injury, the participants were divided into the abnormal group and the normal group.

The inclusion criteria were as follows: (1) meeting the diagnostic criteria for KD [3]; (2) being in the acute phase of the disease upon admission; and (3) age ≤14 years. The exclusion criteria included: (1) incomplete clinical data; (2) coinfection with cytomegalovirus, Epstein-Barr virus, or bacterial pathogens; (3) recent drug-induced liver dysfunction; (4) a history of liver dysfunction; and (5) comorbid conditions such as hematologic malignancies, renal diseases, or inherited metabolic disorders.

Liver function injury was defined primarily by elevated alanine aminotransferase (ALT; ALT >40 IU/L) [9], with one or more abnormalities in gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), serum albumin (ALB), or total bilirubin (TBIL). According to ALT levels, liver function injury was further classified into three categories: mild liver function impairment (Mild group), defined as ALT >40 IU/L and ≤80 IU/L (1–2 times the upper limits of normal (ULN)); moderate liver injury (moderate group), defined as ALT >80 IU/L and ≤200 IU/L (2–5 times ULN); and severe liver injury (severe group), defined as ALT >200 IU/L (>5 times ULN) [10]. As a sensitivity analysis, liver function injury was reclassified using sex-specific pediatric upper limits of normal (ULN) for ALT, based on the National Health and Nutrition Examination Survey (NHANES) reference values (26 U/L for boys and 22 U/L for girls) [11]. Variables with $p < 0.05$ in univariate analysis, along with clinically recognized confounders (age, IVIG response, CAL, and CRP), were entered into the multivariate logistic regression model. Lymphocyte count and PCT were not included in the sensitivity analysis, which was restricted to a predefined set of core variables (age, IVIG response, CAL, NLR, and CRP). This core variable set was predefined based on variables that have been consistently reported as key risk factors for hepatic injury in KD in previous studies and on their clinical relevance, rather than on statistical significance in the present analysis.

2.2 Blood Sample Collection

All blood samples for complete blood count and liver function tests were obtained at admission, before the administration of intravenous immunoglobulin (IVIG) and aspirin, to minimize potential treatment-related effects on laboratory parameters.

2.3 Aspirin Regimen

Aspirin at anti-inflammatory doses (30–50 mg/kg/day) was administered to 112 of 123 participants (91.1%) during the febrile phase, and this dose was continued until the patient had been afebrile for 48 hours. Subsequently, aspirin was reduced to an antiplatelet dose (3–5 mg/kg/day) and continued for 6–8 weeks. The duration of high- and low-dose aspirin therapy was determined according to clinical judgment, based on fever resolution and follow-up protocols, respectively.

2.4 Observed Indices

All key data for the cases included in this study were extracted from complete electronic medical records. None of the core variables analyzed were missing; therefore, no data imputation or case exclusion due to missing data was required.

(1) Basic clinical data: Basic clinical data included sex, age, intravenous immunoglobulin (IVIG) response, IVIG dose, coronary artery lesions (CAL), Z value, and length of hospital stay. IVIG resistance was defined as persistent fever (temperature ≥38.0 ℃) or recrudescent fever occurring 36 hours after completion of the first IVIG infusion (2 g/kg), according to the 2017 American Heart Association (AHA) scientific statement [3]. CAL was defined according to the Japanese Ministry of Health and Welfare criteria as follows: (1) coronary artery internal diameter >3 mm in children <5 years of age or >4 mm in children ≥5 years of age; (2) a segmental diameter ≥1.5 times that of an

adjacent segment; or (3) a clearly irregular coronary lumen [12]. The coronary artery Z value was calculated using the Boston criteria as Z = (observed coronary artery diameter − predicted mean diameter for body surface area) / predicted SD for body surface area, where the predicted mean and SD were derived from the Boston normative dataset.

(2) Routine blood and inflammatory indicators: Routine blood and inflammatory indicators included white blood cell count (WBC), neutrophil count (Neu), lymphocyte count (Lym), neutrophil-to-lymphocyte ratio (NLR), hemoglobin (Hb), platelet (PLT) count, platelet-to-lymphocyte ratio (PLR), C-reactive protein (CRP), procalcitonin (PCT), and erythrocyte sedimentation rate (ESR).

(3) Liver function indicators: Liver function indicators included AST, ALT, and TBIL.

2.5 Statistical Analysis

SPSS version 27.0 statistical software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Continuous variables were first assessed for normality using the Shapiro-Wilk test. Normally distributed variables were expressed as mean ± standard deviation ($\bar{x} \pm s$), and between-group comparisons were performed using the independent-samples *t*-test. Non-normally distributed variables were expressed as median (interquartile range), and between-group comparisons were performed using the Mann-Whitney *U* test for two groups or the Kruskal-Wallis *H* test for three or more groups. For pairwise comparisons among multiple groups, *p*-values were adjusted using the Bonferroni correction to control for multiple testing errors. Categorical variables were expressed as cases (%), and between-group comparisons were performed using the chi-square (χ^2) test. Multicollinearity among independent variables was assessed using the variance inflation factor (VIF) and tolerance. All VIF values were <5 (tolerance >0.2), indicating no significant multicollinearity. Multivariate logistic regression analysis was performed to identify independent risk factors for liver function impairment in children with KD. Spearman's correlation analysis was used to assess correlations among NLR, CRP, and liver function indices. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminative performance of NLR for identifying liver function impairment in children with KD. The area under the curve (AUC) and corresponding 95% confidence interval (CI) were calculated. The optimal cutoff value was determined using the Youden index (maximum value of sensitivity + specificity - 1), and the corresponding sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were reported. A *p*-value < 0.05 was considered statistically significant.

3. Results

3.1 Comparison of General Characteristics Between the Two Groups of Children

A total of 123 patients with KD were included in this study, of whom 47 (38.21%) presented with liver function impairment and 76 (61.79%) did not. As shown in Table 1, there were no significant differences between the two groups in terms of sex, age, IVIG response, IVIG dose, CAL, *Z* value, length of hospital stay, or the proportions of patients receiving aspirin or methylprednisolone (all $p > 0.05$).

3.2 Comparison of Routine Blood, Inflammatory, and Liver Function Indices Between the Two Groups of Children With KD

As shown in Table 2, the neutrophil count was significantly higher in the abnormal group than in the normal group ($p < 0.05$), whereas the lymphocyte count was significantly lower ($p < 0.05$). Similarly, the NLR and PCT levels were significantly higher in the abnormal group than in the normal group ($p < 0.05$). No significant differences were observed in WBC, Hb, PLT, PLR, CRP, or ESR between the two groups (all $p > 0.05$). As expected, ALB, AST, ALT, GGT and TBIL differed significantly between the two groups, consistent with their role in defining hepatic injury.

3.3 Analysis of Factors Influencing Liver Function Impairment in Children With Kawasaki Disease

To control for potential confounding factors and independently evaluate the predictive value of NLR for liver injury in children with KD, multivariate logistic regression analysis was performed. To avoid over-adjustment and multicollinearity, variables that were inherent components of the outcome definition (e.g., ALB, AST, ALT, and TBIL) were not included in the final model, as they represent the phenotypic expression of liver injury rather than independent risk factors. Lymphocyte count and neutrophil count were also included based on its significant association in univariate analysis. Specifically, age, IVIG non-response, and coronary artery lesions are known clinical factors affecting KD outcomes, whereas CRP and PCT, as traditional inflammatory markers, were included to compare their predictive value with that of NLR.

As shown in Table 3, NLR was an independent risk factor for liver injury (adjusted odds ratio [aOR] = 1.283, 95% CI: 1.017–1.619, $p = 0.036$), indicating that each one-unit increase in NLR was associated with a 28.3% increase in the risk of liver function impairment in pediatric patients. Other variables included in the analysis, including the traditional inflammatory marker Neu, Lym, CRP, IVIG non-response, coronary artery lesions, and age, did not show statistically independent predictive value in this model (all $p > 0.05$).

Table 1. Comparison of baseline characteristics between the two groups of children.

Variable	Abnormal Group (n = 47)	Normal Group (n = 76)	Z/χ^2	*p*-value
Sex (n, %)			2.996	0.083
Male	29 (61.70)	58 (76.32)		
Female	18 (38.30)	18 (23.68)		
Age, n (%)			0.217	0.975
≤1 year	22 (46.81)	34 (44.74)		
2–3 years	12 (25.53)	22 (28.95)		
4–5 years	6 (12.77)	10 (13.16)		
≥6 years	7 (14.89)	10 (13.16)		
IVIG response, n (%)			2.398	0.121
Responsive	39 (82.98)	70 (92.11)		
Non-response	8 (17.02)	6 (7.89)		
IVIG dose, n (%)			Fisher's exact test	0.100
1 g/kg	2 (4.26)	1 (1.32)		
2 g/kg	38 (80.85)	71 (93.42)		
4 g/kg	7 (14.89)	4 (5.26)		
CAL, n (%)			0.783	0.376
No	41 (87.23)	70 (92.11)		
Yes	6 (12.77)	6 (7.89)		
Z value, M (P_{25}, P_{75})	0.76 (0.21, 1.36)	0.75 (0.20, 1.32)	0.479	0.632
Length of hospital stay, days, M (P_{25}, P_{75})	6 (5, 8)	6 (5, 7)	1.400	0.162
Aspirin use, n (%)	43 (91.49)	69 (90.79)	0.017	0.895
Methylprednisolone use, n (%)	2 (4.26)	2 (2.63)	Fisher's exact test	0.632

Abbreviations: IVIG, intravenous immunoglobulin; CAL, coronary artery lesions.

Table 2. Comparison of routine blood, inflammatory, and liver function indices between the two groups of children with KD.

Variable	Abnormal Group (n = 47)	Normal Group (n = 76)	*Z* value	*p*-value
WBC (4.0–10.0 × 10^9/L)	13.40 (9.45, 16.20)	12.85 (10.20, 15.45)	0.677	0.499
Neu (2.0–7.0 × 10^9/L)	9.00 (6.70, 12.00)	7.70 (5.28, 9.95)	2.134	0.033
Lym (0.8–4.0 × 10^9/L)	2.20 (1.30, 3.70)	3.50 (2.48, 4.03)	2.699	0.007
NLR	3.53 (1.92, 8.33)	2.27 (1.27, 3.75)	3.068	0.002
Hb (120–160 g/L)	114.00 (111.00, 118.00)	113.50 (106.00, 117.25)	1.230	0.219
PLT (100–320 × 10^9/L)	308.00 (258.00, 369.50)	336.50 (272.75, 408.00)	1.689	0.091
PLR	136.67 (81.73, 251.54)	103.43 (76.61, 144.33)	1.797	0.072
CRP (<10 mg/L)	67.20 (47.25, 102.95)	52.95 (34.73, 87.33)	1.809	0.070
PCT (<0.1 ng/mL)	0.55 (0.31, 2.20)	0.28 (0.16, 0.79)	3.220	0.001
ESR (0–10 mm/h)	48.00 (39.00, 71.50)	52.50 (35.50, 69.25)	0.036	0.971
ALB (40–55 g/L)	37.90 (36.25, 40.05)	40.35 (38.35, 42.33)	3.584	<0.001
AST (15–35 U/L)	63.00 (47.00, 157.00)	26.00 (22.75, 31.00)	7.312	<0.001
ALT (7–40 U/L)	118.00 (66.00, 212.00)	14.50 (10.75, 20.50)	9.297	<0.001
TBIL (0–23 µmol/L)	8.90 (4.75, 15.25)	5.50 (3.70, 7.13)	3.399	<0.001
GGT (5–40 U/L)	95.00 (54.50, 146.00)	13.00 (11.00, 26.25)	8.336	<0.001

Note: Data are presented as median (P_{25}, P_{75}).

Abbreviations: WBC, white blood cell count; Neu, neutrophil count; Lym, lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; Hb, hemoglobin; PLT, platelet; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein; PCT, procalcitonin; ESR, erythrocyte sedimentation rate; ALB, serum albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin.

When liver function injury was reclassified using sex-specific pediatric upper limits of normal (ULN) for ALT (26 U/L for boys, 22 U/L for girls, derived from NHANES), multivariate logistic regression adjusting for age, IVIG response, CAL, and CRP demonstrated that NLR remained an independent risk factor for hepatic injury (adjusted OR = 1.145, 95% CI: 1.016–1.290, $p = 0.026$). None of the other covariates, including age ($p = 0.092$), IVIG response ($p = 0.800$), CAL ($p = 0.848$), or CRP ($p = 0.147$), reached statistical significance (Table 4). These findings are consis-

Table 3. Multivariate logistic regression analysis of factors associated with liver function impairment in children with Kawasaki disease.

Variable	β	SE	Wald	OR	95% CI	*p*-value	VIF
Age	–0.138	0.113	1.478	0.871	(0.698, 1.088)	0.224	1.744
IVIG response	0.110	0.691	0.025	1.116	(0.288, 4.326)	0.873	1.252
CAL	0.562	0.673	0.697	1.754	(0.469, 6.565)	0.404	1.147
Lym	–0.074	0.080	0.842	0.929	(0.794, 1.087)	0.359	1.820
Neu	0.074	0.080	0.856	1.077	(0.921, 1.260)	0.355	2.245
NLR	0.249	0.119	4.405	1.283	(1.017, 1.619)	0.036	3.501
CRP	0.004	0.006	0.415	1.004	(0.993, 1.015)	0.519	1.344
PCT	0.044	0.086	0.257	1.045	(0.882, 1.237)	0.612	1.235

Abbreviations: β, Beta coefficient; SE, Standard Error; OR, Odds Ratio; CI, confidence interval; VIF, variance inflation factor. Reference groups: IVIG response, IVIG-responsive patients; CAL, patients without CAL.

tent with the primary analysis and confirm the robustness of the association between NLR and hepatic injury in children with KD.

Table 4. Multivariate logistic regression analysis of hepatic injury in children with Kawasaki disease using sex-specific pediatric upper limits of normal (boys: 26 U/L; girls: 22 U/L).

Variable	β	SE	Wald	OR	95% CI	*p*-value
Age	−0.167	0.099	2.845	0.846	0.697–1.027	0.092
IVIG response	0.180	0.709	0.064	1.197	0.298–4.803	0.800
CAL	0.126	0.659	0.037	1.134	0.312–4.124	0.848
NLR	0.135	0.061	4.924	1.145	1.016–1.290	0.026
CRP	0.007	0.005	2.099	1.007	0.998–1.016	0.147

ROC curve analysis was performed to evaluate the discriminative performance of NLR for identifying liver function impairment in children with KD. The AUC for NLR was 0.664 (95% CI: 0.574–0.747, $p = 0.001$; Fig. 1), indicating moderate discriminative performance. Using the Youden index, the optimal cutoff value for NLR was 4.702, yielding a sensitivity of 46.8%, specificity of 82.9%, PPV of 62.9%, and NPV of 71.6%.

3.4 Comparison of Basic Clinical Characteristics of Patients With Different Severities of KD Complicated by Liver Injury

According to the degree of liver injury, children with KD were stratified into a mild group (n = 18), moderate group (n = 16), and severe group (n = 13). Table 5 shows the clinical characteristics of the three groups. The results showed no significant differences in age, sex, IVIG response, IVIG dosage, coronary artery lesions, *Z* value, or length of hospital stay among the three groups ($p > 0.05$).

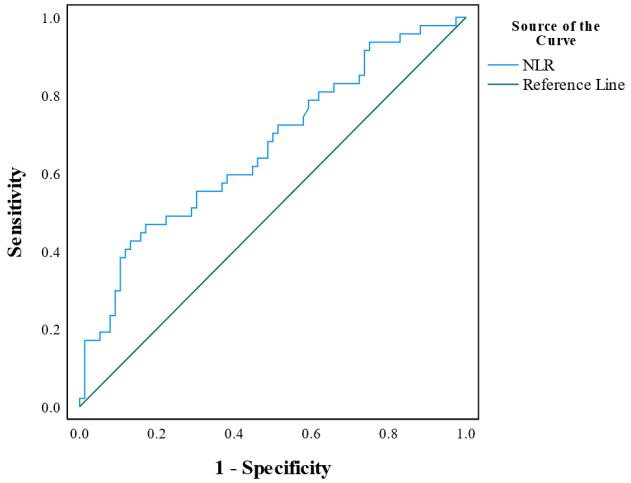


Fig. 1. Receiver operating characteristic (ROC) curve analysis of the neutrophil-to-lymphocyte ratio (NLR) for identifying liver function impairment in children with Kawasaki disease (KD).

3.5 Comparison of Routine Blood, Inflammatory, and Liver Function Indices in Children With KD With Different Degrees of Liver Injury

Table 6 summarizes the routine blood, inflammatory, and liver function indices in children with KD with different degrees of liver injury. Although no statistically significant differences were observed in absolute neutrophil or lymphocyte counts among subgroups with varying degrees of liver injury, a clear and consistent trend emerged. As liver injury worsened, neutrophil counts increased, whereas lymphocyte counts decreased. The Kruskal-Wallis *H* test showed a statistically significant difference in NLR among the three groups ($p < 0.05$). Post hoc pairwise comparisons showed a significant difference only between the mild and severe groups ($p < 0.05$). However, no significant differences were observed between the mild and moderate groups or between the moderate and severe groups. CRP levels also differed significantly among the three groups ($p <$

Table 5. Comparison of baseline clinical characteristics among children with different severities of KD complicated by liver injury.

Variable	Mild Group (n = 18)	Moderate Group (n = 16)	Severe Group (n = 13)	*H*/Fisher's Exact Test	*p*-value
Sex, n (%)					0.868
Male	11 (61.11)	9 (56.25)	9 (69.23)		
Female	7 (38.89)	7 (43.75)	4 (30.77)		
Age, n (%)					0.903
≤1 year	10 (55.56)	8 (50.00)	4 (30.77)		
2–3 years	4 (22.22)	4 (25.00)	4 (30.77)		
4–5 years	2 (11.11)	2 (12.50)	2 (15.38)		
≥6 years	2 (11.11)	2 (12.50)	3 (23.08)		
IVIG response, n (%)					0.177
Responsive	17 (94.44)	13 (81.25)	9 (69.23)		
Non-response	1 (5.56)	3 (18.75)	4 (30.77)		
IVIG dose, n (%)					0.094
1 g/kg	0 (0.00)	0 (0.00)	2 (15.38)		
2 g/kg	17 (94.44)	13 (81.25)	8 (61.54)		
4 g/kg	1 (5.56)	3 (18.75)	3 (23.08)		
CAL, n (%)					0.867
No	15 (83.33)	14 (87.50)	12 (92.31)		
Yes	3 (16.67)	2 (12.50)	1 (7.69)		
Z value, M (P_{25}, P_{75})	0.79 (0.49, 1.32)	1.12 (0.26, 1.38)	0.61 (0.42, 1.01)	2.140	0.343
Length of hospital stay, days, M (P_{25}, P_{75})	6.00 (5.00, 6.75)	6.00 (5.75, 7.50)	7.00 (5.00, 8.00)	1.380	0.502

0.05). However, after adjustment for multiple comparisons, only the moderate group showed significantly higher CRP levels compared with the mild group ($p < 0.05$), while no statistically significant differences were observed between the moderate group and the severe group ($p > 0.05$).

In contrast, no significant differences were observed among the three groups in WBC, Neu, Lym, Hb, PLT, PLR, PCT, ESR, or ALB (all $p > 0.05$). As anticipated based on the severity stratification criteria, AST, ALT, GGT and TBIL levels increased progressively with greater liver injury severity (all $p < 0.05$). These differences in hepatic biochemical indices reflect the defining characteristics of the severity classification and provide descriptive confirmation of the predetermined group definitions.

3.6 Correlation Analysis of NLR and CRP With Liver Function Indices

To further explore the relationship between inflammatory markers (NLR and CRP) and the degree of liver function impairment in children with KD, correlation analyses were performed to assess the associations of NLR and CRP with liver function indices (ALT, AST, and TBIL). Fig. 2 shows the correlations of NLR and CRP with liver function indices. As shown in Fig. 2, NLR demonstrated statistically significant correlations with ALB, AST, ALT, GGT and TBIL, while CRP demonstrated significant positive correlations with TBIL and GGT. In contrast, no significant correlations were observed between CRP and ALT, AST, ALB.

4. Discussion

KD is a systemic vasculitis that can affect multiple organ systems. The pediatric liver exhibits significantly greater blood flow and storage capacity compared with that of adults. Coupled with the relatively immature immune system in children, the liver becomes more vulnerable to inflammatory and infectious stimuli, which can lead to hepatic injury [5]. Furthermore, inflammation of the hepatic vasculature may cause local congestion and subsequent liver damage. Although liver injury is not a major cause of mortality in children with KD, it can adversely affect a child's development and overall health. Therefore, clarifying the clinical features of KD-associated liver injury is valuable for guiding therapeutic strategies and improving patient management.

Neutrophils are central to the immune-inflammatory response and constitute the first line of innate immune defense. Lymphocytes, as essential cellular components of adaptive immunity, function both to defend against external infections and to monitor internal cellular abnormalities [13]. Lymphocyte count can reflect the responsiveness of the immune system. A decrease in lymphocytes may indicate an impaired immune response to infection, which may, in turn, exacerbate the progression of inflammation. This also indirectly supports the proposal that, although the pathogenesis of KD with liver injury is multifactorial, inflammation remains a critical contributing factor. The results of this study showed that, compared with the KD with normal liver function group, patients in the

Table 6. Comparison of routine blood, inflammatory, and liver function indices among children with KD with different degrees of liver injury.

Variable	Mild Group (n = 18)	Moderate Group (n = 16)	Severe Group (n = 13)	*H*	*p*-value
WBC (4.0–10.0 × 10^9/L)	12.40 (9.40, 13.73)	13.80 (11.60, 17.68)	14.00 (9.40, 17.20)	2.103	0.350
Neu (2.0–7.0 × 10^9/L)	8.00 (5.90, 9.83)	10.35 (6.70, 13.35)	11.00 (7.40, 13.70)	4.150	0.126
Lym (0.8–4.0 × 10^9/L)	3.10 (1.83, 4.80)	2.30 (1.80, 3.35)	1.30 (1.10, 2.30)	5.503	0.064
NLR	2.10 (1.42, 5.64)	3.29 (2.51, 9.97)	6.82 (5.07, 14.50)*	6.732	0.035
Hb (120–160 g/L)	113.00 (110.25, 114.75)	112.00 (109.75, 117.25)	117.00 (114.00, 119.00)	3.855	0.146
PLT (100–320 × 10^9/L)	299.50 (264.25, 378.50)	313.50 (258.75, 368.25)	306.00 (257.00, 342.00)	0.383	0.826
PLR	91.28 (58.04, 234.69)	142.32 (88.61, 196.07)	235.38 (103.04, 340.00)	5.587	0.061
CRP (<10 mg/L)	50.00 (34.33, 71.98)	99.15 (58.28, 115.55)*	90.30 (46.60, 100.90)	8.141	0.017
PCT (<0.1 ng/mL)	0.36 (0.25, 0.90)	0.51 (0.35, 2.84)	1.21 (0.51, 3.21)	4.486	0.106
ESR (0–10 mm/h)	46.00 (36.50, 69.75)	50.00 (38.00, 62.00)	62.00 (46.00, 74.00)	1.390	0.499
ALB (40–55 g/L)	36.50 (35.43, 39.45)	37.90 (37.20, 41.08)	38.10 (37.30, 39.90)	3.930	0.140
AST (15–35 U/L)	42.00 (27.25, 56.50)	80.50 (59.50, 161.75)*	164.00 (104.00, 455.00)*,#	24.839	<0.001
ALT (7–40 U/L)	63.50 (54.50, 66.00)	143.50 (116.00, 171.25)*	244.00 (226.00, 409.00)*	40.670	<0.001
TBIL (0–23 μmol/L)	5.80 (3.83, 9.58)	10.70 (6.00, 16.58)	11.80 (5.50, 45.50)*	6.766	0.034
GGT (5–40 U/L)	54.50 (32.50, 76.50)	98.00 (78.25, 149.75)*	164.00 (125.00, 227.00)*	19.788	<0.001

Note: Data are presented as median (P_{25}, P_{75}). *p*-values for pairwise comparisons were adjusted using the Bonferroni correction. *$p < 0.0167$, compared with the mild group; #$p < 0.0167$, compared with the moderate group.

liver injury group exhibited significant alterations in neutrophil and lymphocyte counts and the NLR. As expected, hepatic biochemical indices (AST, ALT, GGT and TBIL) were markedly higher in the liver injury group, consistent with the diagnostic criteria used for group allocation. Notably, NLR, an indicator not used to define group membership, was significantly and progressively elevated across the severity subgroups, suggesting that systemic inflammatory imbalance is closely associated with the occurrence and severity of hepatic involvement in KD. ROC curve analysis showed that NLR achieved an AUC of 0.664 (95% CI: 0.574–0.747) for identifying children with KD and liver function impairment, with an optimal cutoff value of 4.702 (sensitivity, 46.8%; specificity, 82.9%). In addition, 40%–60% of children showed mild to moderate elevations in serum transaminases or gamma-glutamyl transpeptidase, and 10% presented with mild hyperbilirubinemia [14]. In this cohort, 47 children with KD had concurrent liver function injury, representing an incidence of 38.21%, consistent with the findings of Hu et al. [9]. The predominant increase in ALT observed in children with KD complicated by liver function injury is primarily attributable to its cytoplasmic localization within hepatocytes, which facilitates rapid release into the bloodstream following mild cellular damage, in contrast to the predominantly mitochondrial localization of AST. Therefore, ALT elevation tends to be more pronounced in these cases.

Although the absolute neutrophil and lymphocyte counts did not reach statistical significance across subgroups with varying liver injury severity, likely due to limited sample size, a consistent trend was observed: as liver injury worsened, neutrophil counts tended to increase, while lymphocyte counts tended to decline. This reciprocal shift ultimately resulted in a significant, graded increase in NLR across subgroups. During the acute phase of KD, cytokines such as IL-1β, IL-6, and TNF-α drive excessive neutrophil activation and recruitment. Activated neutrophils infiltrate the liver via adhesion molecules such as ICAM-1 and release proteases and reactive oxygen species that damage hepatocytes and endothelial cells [15]. Moreover, neutrophil extracellular traps contribute to liver injury through direct cytotoxicity, promotion of thrombosis, and amplification of inflammation [16]. Concurrently, lymphocytopenia during the acute phase is a characteristic feature of KD and is associated with increased apoptosis, migration, or inhibition of lymphogenesis by inflammatory factors [17]. Immune dysregulation, including impaired anti-inflammatory Treg cell function and activation of pro-inflammatory Th17 cells [18], may further aggravate localized inflammation and contribute to liver injury, particularly within the portal areas.

As a novel inflammatory marker, NLR has garnered increasing attention in recent years because of its simplicity and accessibility through peripheral blood testing. A growing body of evidence has demonstrated a relationship between NLR and liver function impairment [19,20,21] and has also demonstrated its prognostic value in oncology and immune-related disorders [22,23,24]. Recent studies have also shown that NLR may help assess the progression and prognosis of various cardiovascular diseases [25]. In this study, children with KD and different severities of liver function injury were analyzed. Those with severe liver injury exhibited significantly higher NLR levels, with statistically significant differences among the groups. NLR showed significant positive correlations with liver function indices (AST, ALT, GGT and TBIL), suggesting that higher

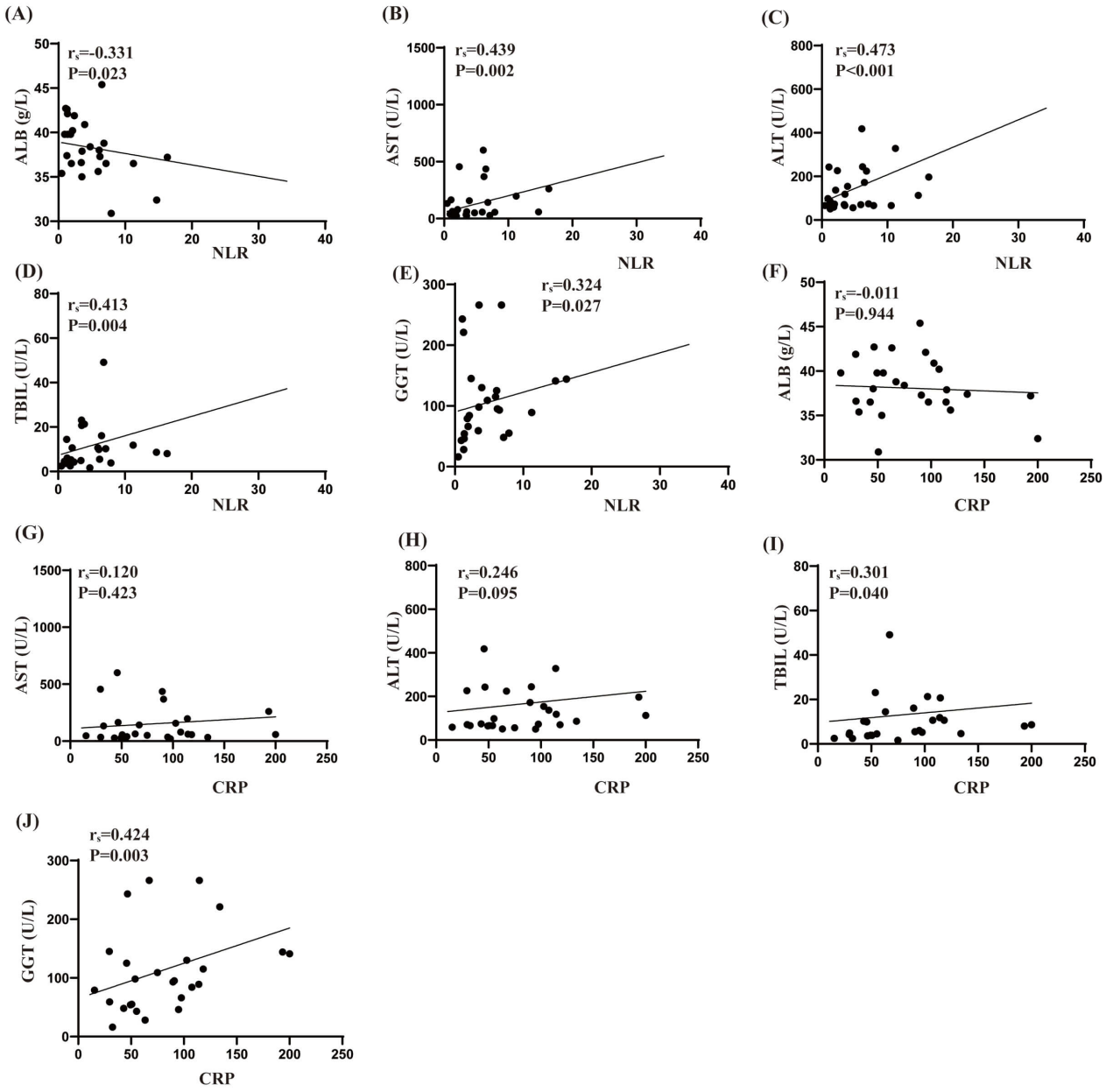


Fig. 2. Correlations of NLR and CRP with liver function indices in children with KD. (A) Correlation between NLR and serum ALB; (B) correlation between NLR and AST; (C) correlation between NLR and ALT; (D) correlation between NLR and TBIL; (E) correlation between NLR and GGT; (F) correlation between CRP and ALB; (G) correlation between CRP and AST; (H) correlation between CRP and ALT; and (I) correlation between CRP and TBIL; (J) correlation between CRP and GGT.

NLR values are associated with more severe hepatic involvement in KD.

Although previous studies have used other inflammatory indicators, including CRP, ESR, and PLR, to assess inflammation in KD, NLR may offer unique clinical advantages for evaluating KD-associated liver injury. Unlike classic acute-phase reactants such as CRP and ESR, which are elevated in nearly all children with KD and may therefore have limited specificity for identifying hepatic involvement [26], NLR can simultaneously reflect the imbalance between innate immune activation and relative adaptive immune suppression [27]. This imbalance may contribute to endothelial cell damage in multiple organs, including the liver. PLR incorporates platelet counts; however, platelet counts in KD undergo dynamic changes, ranging from normal or decreased levels in the early stage to reactive increases in the later stage of the disease, potentially limiting their reliability in early assessment. In contrast, this study demonstrated a significant positive correlation between NLR and the degree of liver enzyme elevation (ALT and AST), suggesting that NLR may more specifically reflect the intensity of systemic inflammation associ-

ated with hepatic injury. The advantage of NLR is that it is derived from routinely measured complete blood count parameters, which require no additional cost, thus making it a practical, real-time risk assessment tool suitable for outpatient, emergency, and resource-limited settings. Our findings suggest that NLR may have potential utility comparable to or superior to that of some of the aforementioned composite inflammatory markers in predicting moderate-to-severe liver injury in children with KD. However, this conclusion requires validation through direct comparisons in larger, prospective, multicenter studies.

A pertinent question is whether NLR provides information beyond routine admission ALT. Although NLR and ALT are derived from the same blood draw, they reflect distinct biological dimensions: ALT reflects hepatocellular injury, whereas NLR captures systemic inflammatory imbalance. Second, complete blood count results are typically available faster than liver function panels, potentially enabling earlier risk assessment. Third, our ROC analysis showed that NLR achieved an AUC of 0.664 for discriminating between children with KD who had and those who did not have liver injury, supporting its moderate discriminative performance. Nevertheless, we acknowledge that this cross-sectional study cannot establish whether NLR provides incremental predictive value beyond ALT. Future prospective studies incorporating serial measurements are needed to determine whether an elevated admission NLR predicts subsequent liver injury.

Both aspirin and IVIG, standard therapies for KD, may affect hepatic enzyme levels. High-dose salicylate is a recognized cause of hepatocellular injury in children [28]. However, because blood samples were obtained before the administration of IVIG and aspirin, the observed transaminase elevations are unlikely to be attributable solely to these medications. Nevertheless, their potential contribution in some participants cannot be entirely excluded, underscoring the complexity of attributing transaminase elevations to a single etiology in KD, where systemic inflammation and pharmacological interventions may both contribute.

5. Limitation

This study has several limitations. First, as a single-center retrospective study, it is subject to inherent selection bias. The sample size was relatively small, and the etiology and pathogenesis of KD remain incompletely understood. Second, the analysis did not include a comprehensive multivariate adjustment for all potential confounders that may influence liver function. Third, the numbers in each severity subgroup were relatively small (n = 18, 16, and 13), which reduced the statistical power of between-group comparisons and may have limited the ability to detect subtle but clinically relevant differences. Consequently, the observed trend of increasing NLR with worsening liver injury should be interpreted with caution and requires validation in larger prospective cohorts.

6. Conclusion

In summary, NLR is significantly associated with the severity of liver function impairment in children with KD and demonstrates moderate discriminative performance for identifying children with KD and concurrent liver injury. These findings support a cross-sectional association between NLR and liver injury severity. However, whether admission NLR can prospectively predict subsequent liver injury warrants further validation in longitudinal studies.

Key Points

• KD is an acute febrile rash disease in children that can cause liver damage, and severe cases can affect the growth and development of children.

• After adjusting for confounding factors such as age, CRP, PCT, IVIG response, and CAL, NLR remained an independent risk factor for liver function impairment in children with KD.

• NLR increased with increasing severity of liver injury, and a significant difference was observed among the three groups.

• NLR was positively correlated with AST, ALT, and TBIL, and negatively correlated with ALB.

Availability of Data and Materials

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

Author Contributions

ZFC and QY had the original conception of the work. ZFC and QY collected the clinical data. ZFC and QY performed the research. QY drafted the manuscript. Both authors contributed to the important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both 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 Review Committee of the Affiliated Yangming Hospital of Ningbo University (2025-11-002) and strictly adhered to the Declaration of Helsinki. The guardians of all patients included in the study provided written informed consent.

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Conflicts of Interest

The authors declare no conflicts of interest.

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