

# Comparison of Complete Blood Count Parameters in Children with Kawasaki Disease and Viral Febrile Infections

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## ABSTRACT

**Objective:** Kawasaki disease (KD) is a childhood vasculitis. The inflammation of coronary arteries is the most severe complication of KD. Despite the fever, diagnosis may be delayed when clinical symptoms do not fulfill the criteria. In this study, we aimed to determine whether the complete blood count (CBC) parameters can differentiate KD from other diseases that caused fever in children.

**Methods:** The present study included 51 patients, 21 of whom were diagnosed as KD and 30 febrile non-KD patients who had viral infections. We analyzed groups' initial CBC parameters in the first visit.

**Results:** Fourteen of the 21 patients (66%) were atypical KD. There were no statistically significant differences in patients' characteristics, clinical symptoms, and signs between the groups. Six of the patients had abnormal coronary arteries like dilatation. A higher neutrophil-to-lymphocyte ratio (NLR) (2.5 (1.8-5.9) vs. 1.41 (0.89-3.6);  $p=0.028$ ) and higher CRP levels (58.1 (25.6-129.3) vs. 22.8 (4.3-41.6);  $p=0.021$ ) were found in KD group when compared with non-KD group. When combining NLR >1.41 and CRP >31 mg/L, there was a higher odds ratio of 24.84 (95% confident interval (2.41-198.53) of KD predicting the possibility.

**Conclusion:** Neutrophil-to-lymphocyte ratio and CRP can show inflammation and immune reactivity and they can be used to distinguish KD patients from virally infected children.

## INTRODUCTION

Kawasaki disease (KD) is a common childhood vasculitis with a high fever lasting at least five days, unresponsive to antibiotic and antipyretic treatments used. The inflammation of coronary arteries is the most severe complication of KD.<sup>1</sup> Although systemic inflammation has a significant role in KD pathogenesis, there is no specific disease marker. Kawasaki disease is still diagnosed based on clinical features. Clinical features are bilateral

conjunctivitis, unilateral cervical lymphadenopathy, erythema and edema on the feet and hands, strawberry tongue, and lip fissures. Only prolonged fever ( $\geq 5$  days) together with two or three clinical criteria may be used to diagnose incomplete KD.<sup>2</sup>

Leukocytes are essential mediators in the inflammation process, and changes in their numbers reflect the immune system's response to systemic inflammation.<sup>3</sup> Neutrophils are mostly considered a marker of ongoing general inflammation, while



lymphocytes are considered a regulator of the immune system.<sup>4</sup> Although neutrophils are dominant in the acute fever period, leukocyte counts increase in patients with KD.<sup>1,5,6</sup> Fever is frequent during bacteremia and viral infections as pro-inflammatory cytokines such as tumor necrosis factor (TNF- $\alpha$ ), interleukin 1 (IL-1), and IL-6 induce fever.<sup>7</sup> Parameters such as the NLR already rise during the febrile period due to these cytokines. In a review, peripheral blood leucocyte ratios are shown to be helpful biomarkers that reflect viral and bacteremia infections.<sup>8</sup>

Unfortunately, the value of complete blood count (CBC) parameters for predicting KD has never been compared with non-KD children with fever due to bacteremia and viral infections. The present retrospective study was performed to determine whether the CBC parameters can differentiate KD from infected children with fever.

## MATERIAL and METHODS

The medical data of KD patients at the hospital were reviewed from January 2017 to September 2020. The study was approved by the Ethics Committee of Adnan Menderes University (Turkey) (2020/229). Five principal clinical manifestations and including fever  $>38^{\circ}\text{C}$  were used to diagnosed KD. When clinical manifestations did not fulfil criteria, and other diseases could be excluded, incomplete KD was diagnosed.<sup>2</sup> Neutrophils and leukocyte counts were measured during the acute febrile phase using the same automated blood cell counter. Intravenous immunoglobulin (2 g/kg) was used to treat all KD and incomplete KD patients. Acetylsalicylic acid (ASA) treatment was started at a dose of 80-100 mg/kg/day along with IVIG. The ASA dose was reduced to the antiaggregant dose (3-5 mg/kg/day) during the convalescent period. Acetylsalicylic acid treatment was continued for an average of 21 days or less according to the clinical condition of the patient. We repeated IVIG treatment if the fever continued despite the first IVIG therapy. Intravenous immunoglobulin resistance was defined as fever continued ( $>24\text{h}$ ) after IVIG.

In this study, we compared CBC parameters of

patients with KD and virally infected children who had fever longer than four days and did not meet AHA diagnostic criteria. The non-KD group consisted of children with viral upper respiratory tract diseases. We also excluded non-KD patients with suspected infectious diseases, including Epstein-Barr virüs infection, adenovirus infection, bacterial cervical lymphadenitis, or scarlet fever.

SPSS version 20 (SPSS, Inc., Chicago, Illinois) was used to analyze. Data are expressed as mean $\pm$ SE or as percentages, as appropriate. The chi-square tests for nominal data, unpaired Student's t-tests for continuous data, and paired Student's t-tests for leukocyte profiles were used to perform. To assess NLR's predictive value in KD, curves and the most discriminating cut-off values were identified. The multivariate logistic regression analysis was used to test significant differences between the groups on univariate analysis. A p-value under 0.05 was considered statistical significance.

## RESULTS

The present study included 51 patients, including 21 KD and 30 controls, who were non-KD patients with fever due to infections. Fourteen of the 21 patients (66%) were atypical KD on the diagnosis. Six (42%) of atypical KD patients and 2 (28%) KD patients had abnormal coronary arteries like dilatation. IVIG treatment was repeated because fever continued in three patients despite first IVIG therapy. After the second IVIG therapy, the fever of these patients also decreased. We could not compare IVIG-responsive and IVIG-resistant groups due to the small numbers of IVIG-resistant group.

The mean ages were 2.8 (1.9-4.6) and 1.9 (1.4-4.2) years, and the duration of fever was 4.2 (3-6) and 4.4 (3-6) days for KD and non-KD groups, respectively. There were no statistically significant differences between patients' characteristics (Table 1). There were a higher NLR (2.5 (1.8-5.9) vs. 1.41 (0.89-3.6);  $p=0.028$ ) and higher CRP levels (58.1 (25.6-129.3) vs. 22.8 (4.3-41.6);  $p=0.021$ ) (Table 2).

ROC curve presented  $\text{NLR}>1.41$  (sensitivity 92%, specificity 49.4%,  $p=0.017$ , Odds ratio 1.56, 95% confident interval (1.22-1.84) and  $\text{CRP}>31$  mg/L

**Table 1. Patients' characteristics and clinical symptoms**

Groups	KD (n=21)	Non-KD (n=30)	p
Age [year; median (IQR)]	2.8 (1.9-4.6)	1.9 (1.4-4.2)	0.16
Gender	12M/9F	16M/14F	0.48
Days of fever* [median (IQR)]	4.2 (3-6)	4.4 (3-6)	0.24
Oral change	15 (75%)		
Skin rash 0.143	11 (55%)		
Lymphadenopathy	4 (20%)		
Extremity change	5 (25%)		
Non-exudative conjunctivitis	12 (60%)		

Some datas are presented by percentage and median with interquartile range (IQR). \* $p < 0.05$

**Table 2. Patients' laboratory data**

Groups	KD (n=21)	Non-KD (n=30)	p
WBC (x1000/mm <sup>3</sup> )	12 (7.8-14.2)	12.5 (8.4-15.4)	0.594
Hemoglobin (g/dL)	12.4 (11.7-12.8)	12.5 (11.6-13.1)	0.4810
Lymphocyte (%)	30.6 (18.3-29.6)	39.9 (28.2-51.4.)	0.043*
Neutrophil (%)	66.5 (53.6-81)	51.1 (33-61.5)	0.041*
Neutrophil to lymphocyte ratio	2.5 (1.8-5.9)	1.41 (0.89-3.6)	0.028*
Platelet (x1000/mm <sup>3</sup> )	325.4 (158.2-402.4)	316.4 (282.5-401.6)	0.75
CRP (mg/L)	58.1(25.6-129.3)	22.8 (4.3-41.6)	0.021*

The data are presented by percentage and median with interquartile range (IQR). \* $p < 0.05$

**Table 3. The multivariate and univariate analyzes of KD group**

	Sensitivity	Specificity	p-value	Odds ratio (95% confident interval)
NLR>1.41	92%	49.4%	0.017*	1.56 (1.22-1.84)
CRP>31 mg/L	83%	61%	0.021*	11.6 (1.21-118.5)
NLR>1.41 and CRP>31 mg/L	84%	73.4%	0.001*	24.84 (2.41-198.53)

NLR: Neutrophil to lymphocyte ratio. \* $p < 0.05$

(sensitivity 83%, specificity 61%,  $p=0.021$ . Odds ratio 11.6, 95% confident interval (1.21-118.5)), When combining NLR > 1.41 and CRP > 31 mg/L, there was a higher odds ratio of 24.84 (95% confident interval 2.41-198.53) of KD prediction possibility (Table 3).

## DISCUSSION

An accurate diagnosis of KD is essential because of the possibility of life-threatening complications. Despite of well-established diagnostic criteria, KD diagnoses are still challenging, especially for incomplete KD forms.<sup>9</sup>

Neutrophils show increased inflammatory mediator

secretion while lymphocytes represent immune regulatory response.<sup>4</sup> NLR and PLR are helpful predictors in IVIG resistance patients with KD.<sup>10-12</sup> Yan and et al.<sup>13</sup> compared with KD and suspected KD patients, and similar to our results, they claimed that the cut-off value of NLR of 1.33 has a high sensitivity predictive value for KD.

In the present study, the cut-off value of NLR of 1.41 has an odds ratio of 1.56 (1.22-1.84) has a predictive value to KD's diagnosis. This value has a higher sensitivity to diagnose KD.

According to AHA guidelines for incomplete KD diagnosis, ESR  $\geq 40$  mm/hour and/or CRP >30 mg/L

are thought supplementary laboratory data.<sup>14</sup> In this study, we used CRP levels to show inflammation status and they can also be a discriminative factor. We showed that the CRP >31 mg/L could be used as a predictive value with an odds ratio of 11.6 (95% confident interval 1.21-118.5, sensitivity 83%, specificity 61%, p=0.021).

During inflammatory conditions as in infectious diseases CRP levels are elevated. Clinicians must be careful to evaluate CRP levels and rule out other systemic inflammation diseases and infections because CRP level >31 mg/L is commonly seen during inflammatory diseases and infections in children. So, we combined the cut-off values of NLR and CRP to determine a higher odds ratio. When combining NLR >1.41 and CRP >31 mg/L, there was a higher odds ratio of 24.84 (95% confident interval (2.41-198.53) of KD predicting possibility. It has a lower sensitivity but better specificity than using NLR or CRP alone. As presented in the present study, the febrile days ranged from 3 to 6 days. Therefore, if patients had a fever longer than three days, NLR and CRP should be evaluated as early as when suspected from KD.

This study has some limitations. First, this study was a retrospective study. Second, although the causes of fever in the controls were attributed to viral infections, the definitive diagnosis with molecular/serological tests could not be made. Further studies should focus on the CBC parameters that can discriminate KD from children with other infections and healthy children.

## CONCLUSION

When clinicians suspect KD, we recommend checking CRP and NLR values if the patients had a fever longer than three days. Their odds ratios can ensure clinicians with a beneficial tool for discrimination. The neutrophil-to-lymphocyte ratio is a cheap and simple test. The neutrophil-to-lymphocyte ratio and CRP can be used to distinguish KD patients from virally infected children.

**Ethics Committee Approval:** The study was approved by the Ethics Committee of Adnan Menderes University (3.12.2020/229).

**Conflict of Interest:** The study was approved by the Ethics Committee of Adnan Menderes University (Turkey).

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## REFERENCES

- Demir F, Karadeniz C, Özdemir R, Yozgat Y, Çelegen K, Karaaslan U, Demirol M, Meşe T, Ünal N. Usefulness of neutrophil to lymphocyte ratio in prediction of coronary artery lesions in patients with Kawasaki disease. *Balkan Med J* 2015;32:371. <https://doi.org/10.5152/balkanmedj.2015.151108>
- Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, Shulman ST, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 2004;110:2747-71. <https://doi.org/10.1161/01.CIR.0000145143.19711.78>
- Zahorec R. Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill. *Bratislavske lekarske listy* 2001;102:5-14.
- Azab B, Zaher M, Weiserbs KF, Torbey E, Lacossiere K, Gaddam S, Gobunsuy R, et al. Usefulness of neutrophil to lymphocyte ratio in predicting short-and long-term mortality after non-ST-elevation myocardial infarction. *The Am J Cardiol.* 2010;106:470-6. <https://doi.org/10.1016/j.amjcard.2010.03.062>
- Kobayashi T, Inoue Y, Takeuchi K, Okada Y, Tamura K, Tomomasa T, Kobayashi T, Morikawa A. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation* 2006;113:2606-12. <https://doi.org/10.1161/CIRCULATIONAHA.105.592865>
- Kim T, Choi W, Woo CW, Choi B, Lee J, Lee K, Son C, Lee J. Predictive risk factors for coronary artery abnormalities in Kawasaki disease. *European J of Pediatrics* 2007;166:421-5. <https://doi.org/10.1007/s00431-006-0251-8>
- Choi J, Min HJ, Shin JS. Increased levels of HMGB1 and pro-inflammatory cytokines in children with febrile seizures. *J Neuroinflammation* 2011;8:135. <https://doi.org/10.1186/1742-2094-8-135>
- Russell CD, Parajuli A, Gale HJ, Bulteel NS, Schuetz P, de Jager CP, Loonen AJ, et al. The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: A systematic review and meta-analysis. *J Infec.* 2019;78:339-48. <https://doi.org/10.1016/j.jinf.2019.02.006>
- Kato H, Ichinose E, Yoshioka F, Takechi T, Matsunaga S, Suzuki K, Rikitake N. Fate of coronary aneurysms in Kawasaki disease: serial coronary angiography and long-term follow-up study. *The Am J Cardiol.*

- 1982;49:1758-66.  
[https://doi.org/10.1016/0002-9149\(82\)90256-9](https://doi.org/10.1016/0002-9149(82)90256-9)
10. Ha KS, Lee J, Jang GY, Lee J, Lee KC, Son CS, Lee JW Value of neutrophil-lymphocyte ratio in predicting outcomes in Kawasaki disease. *The Am J Cardiol.* 2015;116:301-6.  
<https://doi.org/10.1016/j.amjcard.2015.04.021>
11. Yuan YD, Sun J, Li PF, Wei CL, Yu YH Values of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in predicting sensitivity to intravenous immunoglobulin in Kawasaki disease. *Zhongguo Dang dai er ke za zhi= Chinese Journal of Contemporary Pediatrics* 2017;19:410-3.
12. Cho HJ, Bak SY, Kim SY, Yoo R, Baek HS, Yang S, Hwang IT, Ban JE. High neutrophil: lymphocyte ratio is associated with refractory Kawasaki disease. *Pediatrics International* 2017;59:669-74.  
<https://doi.org/10.1111/ped.13240>
13. Yan JH, Chang LS, Lin YJ, Guo MMH, Huang YH, Kuo HC Clinical characteristics for differentiating febrile children with suspected Kawasaki disease diagnosis. *Frontiers in Pediatrics* 2020;8:  
<https://doi.org/10.3389/fped.2020.00221>
14. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation* 2017;135:e927-e999.  
<https://doi.org/10.1161/CIR.0000000000000484>