Studies in Medical Sciences, Vol. 32(12), March 2022

Original Article

Evaluation of the Neutrophil to Lymphocyte Ratio in the Patients of Kawasaki Disease Resistant to Intravenous immunoglobulin (IVIg) Therapy

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Received 05 March 2022, **Accepted** for publication 23 July 2022

Abstract

Background & Aims: Kawasaki disease is a systemic vasculitis of unknown etiology that is common in the pediatric patients. The primary therapeutic strategy includes aspirin and Intravenous Immunoglobulin. The present study aimed to investigate the Neutrophil to Lymphocyte Ratio (NLR) in the patients with Kawasaki and its relationship with the resistance to IVIg therapy.

Materials and Methods: The present study included the patients presenting to the Motahari Hospital, Urmia, Iran, whom diagnosed with Kawasaki disease and received IVIg during 2008-2019. The authors collected the data from the patients' medical records and re-assessed the patients' data for meeting the diagnostic criteria for Kawasaki. Afterward, the data of eligible patients entered the analysis.

Results: The data from 460 patients were obtained and assessed for meeting the diagnostic criteria for Kawasaki. Of 460 patients, 241 met the eligibility criteria, and the data for other patients that meet exclusion criteria were excluded from the study. According to the results of our study, response to IVIg therapy had a significant relationship with the variables of blood and urinary leukocyte counts (p=0.013 and p=0.01, respectively). However, we didn't find any significant relationship between the response to IVIg therapy and the variables of age, gender, NLR, neutrophil count, lymphocyte count, C-Reactive Protein (CRP), serum albumin level, ALT, hemoglobin, platelet count, and the interval between onset of symptoms and treatment initiation.

Conclusion: High blood leukocyte count along with low urinary leukocyte count can predict the response to IVIg treatment and subsequent prognosis in the patients affected by the Kawasaki disease. However, the NLR did not show clinical relevance.

Keywords :Kawasaki Disease, Vasculitis, Neutrophil to Lymphocyte Ratio, IVIg therapy

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Introduction

Kawasaki disease (KD) is a common systemic vasculitis of unknown etiology in pediatric patients. The disease has a global distribution and has also been reported in Iran. This multisystemic vasculitis involves various body organs, including skin, mucous

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membranes, lymph nodes, meninges, intestines, liver, gallbladder, joints, genitalia, and heart. However, the primary damage is usually observed in the coronary arteries (1). Due to its increasing prevalence, Kawasaki has been the most common cause of pediatric cardiac disease in developed countries in the recent decade (2, 3). More than 85% of the disease cases are reported in the children aged 1-5, and an incidence out of the mentioned age range is rare and atypical (4).

This problem is usually a self-limiting disease, presenting with fever, cutaneous symptoms, mucositis, and other manifestations of systemic inflammation. The disease manifests itself with gastrointestinal and respiratory symptoms, followed by non-purulent conjunctivitis, erythematous, lip and oral mucosa, upper gastrointestinal tract epithelium alterations, polymorphic cutaneous rashes, fingertip changes, and cervical lymphadenopathy. The diagnosis is usually clinical and is based on the mentioned manifestations. The symptoms typically resolve within a maximum duration of 12 days. However, related complications caused by the systemic inflammation of medium-sized arteries including coronary artery aneurysms, decreased myocardial contractility, heart failure, myocardial infarction, arrhythmias, and peripheral artery occlusion, may lead to remarkable morbidity and mortality. At first, the related cardiac complications are mainly subclinical. However, they may lead to myocardial infarction or sudden death years after recovery (5-7).

The treatment strategy currently includes aspirin and high doses of IVIg during the first ten days after the onset of symptoms, which can significantly decrease the chance of developing coronary aneurysms. However, 10%-20% of pediatric patients do not respond to this treatment (8). Several scoring scales have been designed to predict the response to IVIg therapy in Japan, but these scales do not seem to be of much value in other countries. Alternatively, screening for inflammatory cytokines and T cell surface markers may be of predictive value in resistance to IVIg therapy. Still, this approach is not routinely available because it is not cost-effective (9). Since chronic and uncontrolled inflammation is the cause of observed coronary artery disease and resistance to IVIg treatment, inflammatory markers may be beneficial in predicting the resistance to IVIg.

The WBC Count and related indices are routinely used as classic determinants of the inflammation. In general, neutrophil counts reflect acute and nonspecific inflammation, while lymphocyte count is the primary marker of immune regulation. Therefore, the NLR may indicate the balance status between acute inflammation and immune regulation (10). According to previous studies, NLR is an essential inflammatory marker and can help in prognosis predicting in cardiovascular diseases and cancers. Moreover, there are reports that NLR might somehow correlate with surgical stress, systemic inflammation, sepsis, and even the severity of coronary artery disease. Some studies have suggested that the patients' NLR following the initiation of IVIg therapy may predict the resistance to treatment and subsequent coronary artery involvement in the Kawasaki patients (11). However, the substantial evidence favoring this effect is limited, and the related studies are controversial. Therefore, the present study aimed to investigate the NLR and its relationship with IVIg resistance in the Kawasaki patients presenting to the Motahari Hospital, Urmia, Iran.

Materials & Methods

The present study included the patients presenting to the Motahari Hospital, Urmia, Iran, who was diagnosed with Kawasaki disease and received IVIg during 2008-2018. The authors collected the data from the medical records of the patients and re-assessed the patients' data

for meeting the diagnostic criteria for Kawasaki, which was as follows:

Bilateral non-purulent conjunctivitis:

At least one of the following mucosal membrane changes of the upper respiratory tract: pharyngeal congestion, dry and cracked lips, congested lips, or strawberry tongue.

At least one of the following changes in extremities: extremity erythema, extremity edema, periungual desquamation, and disseminated scaling

Polymorphic rash (mainly on the trunk):

Cervical lymphadenopathy with a diameter of >1.5 cm

A patient is diagnosed with Kawasaki if having 4 of the above five criteria and fever for more than five days.

Inclusion criteria of the present study were as follows:

-The patients meeting the diagnostic criteria for Kawasaki based on the above explanations

-The patients meeting 2 or 3 criteria of the Kawasaki diagnostic criteria

-A fever of longer than five days and at least 3 of the complementary criteria, including anemia, thrombocytosis, increased neutrophil count, increased hepatic enzymes, and urinary leukocytosis

Exclusion criteria included the patients with incomplete medical records and without necessary data for study in their records or those with a fever due to another disease rather than the KD.

The patients' neutrophil count, lymphocyte count, NLR, and serum CRP levels were extracted from their medical records and analyzed. Afterward, the patients were divided into two groups of responsive and unresponsive, based on their response to IVIg therapy. The responsiveness was defined as a fever subsiding within 24 hours after treatment with no recurrence, while unresponsiveness was described as a fever persisting more than 24 hours after treatment or a recurrence of fever due to KD after a period of being non-febrile.

Data Analysis:

The results were described using the mean and SD for quantitative variables and frequency and percentage for qualitative variables. The related tables and graphs were plotted and prepared. Moreover, the comparisons between the mean values of the variables were performed using the t-test, and data were analyzed using SPSS software version 16. Logistic regression was used to control the confounding factors and to better explain the results. The significance level was considered at 0.05. In this analysis, the existence of response to treatment as a dependent variable and the variables of age, sex, duration of disease, CRP, WBC, and neutrophil to lymphocyte ratio as an independent variable were entered into the model then backward logistic regression was performed.

Results

At first, the data from 460 patients presenting to the Motahari Hospital in Urmia with a diagnosis of KD during 2008-2018 were obtained and assessed for meeting the diagnostic criteria for Kawasaki. Of 460 patients, 241 met the eligibility criteria, and data for other patients that meet exclusion criteria were excluded from the study (Tables 1 and 2).

Table 1. Comparison of means of quantitative variables in Kawasaki patients, according to the type of patient response to IVIg treatment. *Neutrophil to Lymphocyte ratio.

Variable	Responsive to the Treatment	Resistant to the Treatment	P-value
Age (week)	32.62±24.67	38.75±26.35	0.196

Time interval (day)	6.86±3.79	6.14±2.81	0.110
Neutrophil count (×102/mm3)	60.99±17.36	66.11±16.18	0.275
Lymphocyte count (×102/mm3)	35.46±33.8	26.14±14.83	0.142
N/L ratio*	3.06±2.89	4.00±3.51	0.058
CRP (mg/L)	40.79±26.33	43.84±29.88	0.163
Blood WBC (/mm3)	14266.3±6291	13450.3±4443.4	0.013

Table 2. Comparison of qualitative variables in Kawasaki patients, according to the type of patient response to IVIg treatment.

Variable		Response to the treatment (n)		P-value
		Responsive	Resistant	
Sex	Male	85	52	0.80
	Female	67	36	
Serum Albumin	<3 gr/dL	6	7	0.18
	≥3 gr/dL	147	81	
Anemia	Positive	111	71	0.15
	Negative	42	17	
ALT	Elevated	25	21	0.15
	Normal	128	67	
Platelets	≥450,000/mm3	60	31	0.53
	<450,000/mm3	93	57	
Blood WBC	≥15,000/mm3	50	26	0.25
	<15,000/mm3	103	62	
Urine leukocytes	≥10	46	27	0.01
	<10/HPF	61	107	

Age:

The participants' mean age was 34.86±25.6 months with an age range of 2-132 months. Moreover, the mean age of the patients responsive and unresponsive to IVIg therapy was 32.62±24.97 months and 38.75±26.35 months, respectively. Therefore, age did not significantly correlate with response to IVIg therapy (p-value = 0.192).

Gender:

The present study included 137 (56.8%) male and 104 (43.2%) female patients. From them, 85 male and 52 female patients were responsive to IVIg therapy, while 67 males and 36 females did not respond to the treatment. Therefore, there was no significant relationship between gender and response to treatment (p-value = 0.8).

Conjunctivitis:

According to our results, from a total of 241 patients, 130 (53.9%) had conjunctivitis, while 110 (46.1%) did not develop this symptom.

Mucosal Membrane Changes:

The mucosal changes investigated in the present study included pharyngeal hyperemia or erythema, dry and cracked lips, erythematous lips, and strawberry

tongue. According to our findings, 195 (80.9%) patients developed at least one of these symptoms, while 46 (19.1%) had no mucosal changes.

Extremity Changes:

The extremity changes investigated in the present study included extremity erythema or edema, periungual desquamation, and disseminated scaling. According to our findings, 58 (24.1%) patients developed at least one of these symptoms, while 183 (75.9%) had no extremity changes.

Polymorphic Rash and Hand or Foot Erythema:

In the present study, 117 (48.5%) patients developed polymorphic rashes mainly on the trunk, while 124 (51.5%) patients did not show this symptom. Regarding the hand or foot erythema, we showed that 48 (19.9%) patients developed this symptom, whilst 193 (80.1%) did not show that.

Lymphadenopathy:

The present study investigated cervical lymphadenopathy with more than 1.5 cm diameter in the Kawasaki patients, showing that 66 (27.4%) patients were affected by this manifestation. In contrast, 175 (72.6%) patients did not show this manifestation.

Neutrophil-to-Lymphocyte Ratio:

According to our findings, the mean NLR was 3.06±2.89 and 4±3.51 in the responsive and unresponsive patients to IVIg therapy, respectively. Therefore, responsive patients had a significantly lower NLR compared to unresponsive patients (p-value = 0.058).

Blood Neutrophil and Lymphocyte Counts:

The mean value of neutrophil and lymphocyte counts in all the patients with Kawasaki was 6286±1708 and 3150±2983 per mm^3, respectively. Moreover, none of these variables had a significant relationship with the response to IVIg therapy (p-value for neutrophil count = 0.27, p-value for lymphocyte count = 0.14).

C - Reactive Protein:

The present study investigated the quantitative levels of the acute phase reactant CRP. The mean CRP of the total patients was 27.65±41.90 mg/L. Moreover, the patients responsive and unresponsive to IVIg therapy had mean CRP levels of 40.79±26.33 mg/L and 43.84±29.88 mg/L, respectively. Therefore, there was no significant relationship between CRP levels and response to IVIg therapy (p-value = 0.16).

Blood Leukocyte Count:

The mean WBC count was 14266±6291 per mm^3 and 13450±4443 per mm^3 in the patients responsive and resistant to IVIg therapy, respectively, showing a significantly higher WBC count in the responsive patients compared to the resistant patients (p-value=0.013).

Albumin:

The present study defined the albumin levels lower than 3 g/dL as hypoalbuminemia. According to our results, 13 patients (5.4%) had hypoalbuminemia, whilst 228 patients (94.6%) had albumin levels of 3 g/dL or higher. Moreover, we found no significant relationship between the albumin levels and response to IVIg therapy (p-value=0.18).

Alanine Transaminase:

At first, the ALT levels were adjusted based on the participants' age. According to our findings, 46 patients (19.1%) had elevated ALT levels, whilst 195 (80.9%) had normal ALT levels. Also, we found no significant relationship between the ALT levels and response to IVIg therapy (p-value=0.15).

Hemoglobin:

At first, the hemoglobin levels were adjusted based on the participants' age. According to our findings, 182 patients (75.5%) had anemia, whilst 59 (24.5%) had normal hemoglobin levels. Also, there was no significant relationship between the hemoglobin levels and response to the treatment (p-value=0.15).

Platelet Count:

The present study defined the platelet count equal to 450,000 per mm^3 or higher as thrombocytosis. According to our findings, 150 patients (62.2%) had thrombocytosis, while 150 patients (62.2%) had platelet levels lower than 450,000 per mm^3. Moreover, we found no significant relationship between the platelet count and response to IVIg therapy (p-value=0.53).

Pyuria:

The present study defined the presence of more than 10 leukocytes per High Power Field (HPF) of urine analysis by microscope as pyuria. According to our findings, 73 patients (30.3%) had pyuria, whilst 168 patients (69.7%) did not have pyuria. Moreover, we found that the prevalence of pyuria was significantly higher in the patients responsive to IVIg therapy compared to the resistant patients (p-value=0.01).

Echocardiographic Criteria:

The echocardiographic criteria for KD investigated in the present study included the transparency of the LAD artery and the RCA with a Z-score of 2-2.5, no reduction in the vascular diameter, decreased left ventricular function, mitral valve insufficiency, and pericardial effusion. Only 6 patients (1.2%) had been reduced left ventricular function or vascular transparency (n=3 for each finding), while 98.8% did not have these two criteria. Moreover, 16 patients (2.9%) had no reduction in the vascular diameter, while 93.3% of the patients were normal in this regard. Also, 6 patients (2.5%) had mitral valve insufficiency of any severity, while only one patient (0.4%) had pericardial effusion.

Kawasaki Diagnostic Criteria:

According to our results, 128 patients (53.11%) met the diagnostic criteria for Kawasaki. In contrast, 109 (45.22%) had a fever of longer than 5 days, 2 or 3 of the main criteria, and at least 3 of the complementary criteria. Moreover, 4 patients (1.67%) met the echocardiographic criteria for the disease.

Responsiveness or Resistance to IVIg Therapy:

In the present study, the responsiveness to treatment was defined as a fever subsiding within 24 hours after IVIg therapy initiation with no recurrence, while resistance was defined as a fever persisting more than 24 hours after IVIg therapy initiation or a recurrence of fever due to KD after a period of being non-febrile. According to our findings, 153 patients (63.5%) responded to the treatment, whilst 88 patients (36.5%) were resistant to IVIg therapy.

The Interval between Onset of Symptoms and Treatment Initiation:

The mean duration between the onset of symptoms and treatment initiation was 6.36±3.79 days. Moreover, there was no significant relationship between this variable and the response to treatment (p-value=0.11).

Multivariant Analysis:

In this analysis, the existence of response to treatment as a dependent variable and the variables of age, sex, duration of disease, CRP, WBC, and neutrophil to lymphocyte ratio as an independent variable were entered into the model then backward logistic regression was performed. The results showed that only the variable of neutrophil to lymphocyte ratio was significantly associated with response to treatment (p-value=0.032).

Discussion

Kawasaki Disease (KD) is a common systemic vasculitis of unknown etiology that occurs in early childhood. This multisystemic vasculitis involves various body organs, including skin, mucous membranes, lymph nodes, meninges, intestines, liver, gallbladder, joints, genitalia, and heart. However, the main damage is usually observed in the coronary

arteries. Moreover, according to epidemiologic studies, boys are more susceptible to KD than girls.

The treatment strategy includes high doses of IVIg, which can significantly decrease the chance of developing coronary aneurysms. However, 10%-20% of the pediatric patients do not respond to this treatment. According to previous studies, the NLR of the patients after the IVIg therapy can predict the resistance to treatment and subsequent coronary artery disease (1, 8, 11, 12).

According to our findings, age did not significantly correlate with the response to IVIg therapy. However, Egami et al. (13) showed that babies younger than 6 months were significantly more likely to show resistance to IVIg therapy. Moreover, Kawamura et al. (9) also found a significant relationship between age and resistance to treatment. However, they reported that older children were more likely to be resistant to the treatment.

Up to now, 3 specific criteria have been developed for predicting the risk of IVIg therapy resistance by Japanese researchers, of which the Kobayashi score is the most widely used, with high sensitivity and specificity. Unfortunately, these criteria cannot be used in non-Japanese populations because they cannot detect all the children at risk for IVIg resistance and CAA (12).

Our primary results were compatible with the study done by Kobayashi et al. that reported no significant relationship between response to treatment and age (14). However, a study done by Hong et al. (15) on KD patients showed that those with the NLR <5 were significantly younger than those with elevated NLR (≥5), which was not compatible with our study which reported no significant relationship between NLR and response to IVIg treatment (p-value=0.058). In contrast, the studies done by Kawamura et al. and Ha et al. (9, 10) reported an enormously significant relationship between response to IVIg therapy and NLR (p-value <0.001), with significantly higher NLR in the patients resistant to the treatment compared to those responsive to treatment. Finally, we performed a backward logistic regression to assess the multivariant analysis and the results indicated only the NLR was significantly associated with response to treatment.

Moreover, only a study by Ha et al. (10) reported a significant correlation between male gender and resistance to treatment, while other mentioned studies (9, 13, 14, 16) reported no significant relationship between gender and response to treatment, which was compatible with our results, reporting no significant relationship between gender and resistance to treatment.

CRP is one of the essential inflammatory markers in children, especially in rheumatic diseases and vasculitis (17). However, we found no significant relationship between CRP levels and response to treatment. Moreover, some studies (3, 13, 14, 16) reported a significant relationship between these two, while the study by Ha et al. (10) reported an insignificant relationship.

According to our results, there was no significant relationship between neutrophil or lymphocyte counts and the response to treatment. However, some previous studies have reported a significant relationship between neutrophil or lymphocyte counts and the response to IVIg therapy (9, 10, 13-16).

In addition, we found a significant relationship between WBC count and response to treatment, with significantly higher WBS counts in the patients who responded to treatment compared to those resistant. These findings were compatible with the study by Lee et al. (16) and incompatible with some other studies (9, 10, 13-15).

Moreover, we reported no significant relationship between albumin levels and response to treatment, which was incompatible with the study by Kobayashi et al. (14) and compatible with the studies by Kawamura et al., Egami et al., and Lee et al. (9, 13, 16).

According to our results, there was no significant relationship between ALT levels and response to treatment, which was compatible with the study done by Ha et al. (10) and incompatible with the studies by Kawamura et al., Egami et al., and Lee et al. (9, 13, 14). However, it should be noted that previous studies did not adjust the ALT levels based on the patient's age, which was incompatible with our study.

Moreover, we found no significant relationship between hemoglobin levels and response to treatment, which was compatible with the study by Egami et al. (13). Also, our study and that of Egami et al. adjusted the hemoglobin levels based on the patients' age.

To the best of our knowledge, no study has ever investigated the relationship between pyuria and response to treatment, and our study was the first to evaluate this relationship in the Kawasaki patients. We found that the patients with pyuria, defined as the presence of 10 leukocytes per HPF or higher, were significantly more likely to be resistant to treatment. Moreover, even some of the present study participants had been initially admitted by the nephrology service with the presentations of fever, restlessness, pyuria, and a suspected diagnosis of urinary tract infections. Afterwards, the patients developed the Kawasaki symptoms were finally diagnosed with Kawasaki (12). Therefore, these findings highlight the presence of renal or urological involvement in Kawasaki and can be explained by the possibility of lower renal inflammation in the patients without pyuria and a subsequent higher chance of response to treatment. However, further studies are needed to illustrate the ambiguities in this regard.

Also, we found no significant relationship between platelet count and response to treatment. Our study divided the patients into two groups; the patients with thrombocytosis and those without it. However, most studies investigated the relationship between absolute platelet count and response to treatment, reporting controversial results. For example, the study by Egami et al. (13) reported a significant positive correlation between response to treatment and platelet count, while Kawamura et al. (9) reported a significant negative correlation between these two. Moreover, the studies by Kobayashi et al. (14) and Lee et al. (16) did not report a significant relationship between platelet count and response to treatment.

Given the relationship between the response to treatment and the interval between onset of symptoms and treatment initiation, the present study did not find a significant relationship between these two. However, some studies reported a significant relationship between the response to treatment and the interval between onset of symptoms and treatment initiation. For example, Kawamura et al. (9) reported a positive correlation between these two variables, while Kobayashi et al. (14) and Lee et al. (16) reported a negative correlation.

Conclusion

According to our findings, we concluded that the Kawasaki patients with leukocytosis were significantly more likely to respond to IVIg therapy, while pyuria could significantly increase the chance of being resistant to IVIg therapy. Therefore, these two factors can predict the response to treatment in the patients with KD.

Declarations

Ethical Considerations and Participation Consent:

The present study maintained the complete confidentiality of all the patients' data. Moreover, we followed the ethical principles of the Helsinki Agreement (18) in all the study steps. Also, the present study was approved by the Ethics Committee of the Urmia University of Medical Sciences with the ethics code of I.R.UMSU.REC.1398.257.

Consent for publication:

The patients' legal guardians gave signed consent for publication.

Availability of supporting data:

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

Conflict of Interest:

The authors declare that they have no conflict of interest.

Funding:

The Urmia University of Medical Sciences sponsored the present study. There was no other organizational or governmental funding. The funding body did not have any role in the design of the study and collection, analysis, and interpretation of data, and in writing the manuscript.

Authors' contributions:

RF and AS participated in data collection, analysis, and original draft writing. HH and MG participated in supervision, study design, and final draft review.

Acknowledgments:

We want to acknowledge all the healthcare providers of the Motahari Pediatric Center, particularly the personnel of the Immunology and Allergy ward.

References

1. Burns JC, Glode MP. Kawasaki syndrome. Lancet 2004;364(9433):533-44.
2. Narayanan SN, Ahamed MZ, Safia M. Cardiovascular involvement in Kawasaki disease. Indian Pediatr. 2005;42(9):918-22.
3. Ng YM, Sung RY, So LY, Fong NC, Ho MH, Cheng YW, et al. Kawasaki disease in Hong Kong, 1994 to 2000. Hong Kong Med J 2005;11(5):331-5.
4. Krohn C, Till H, Haraida S, Kurnik K, Boehm R, Grantzow R, et al. Multiple intestinal stenoses and peripheral gangrene: a combination of two rare surgical complications in a child with Kawasaki disease. J Pediatr Surg 2001;36(4):651-3.
5. Baker AL, Lu M, Minich LL, Atz AM, Klein GL, Korsin R, et al. Associated symptoms in the ten days before diagnosis of Kawasaki disease. J Pediatr 2009;154(4):592-5.
6. Burns JC, Mason WH, Glode MP, Shulman ST, Melish ME, Meissner C, et al. Clinical and epidemiologic characteristics of patients referred for evaluation of possible Kawasaki disease. United States Multicenter Kawasaki Disease Study Group. J Pediatr 1991;118(5):680-6.
7. Cai Z, Zuo R, Liu Y. Characteristics of Kawasaki disease in older children. Clin Pediatr 2011;50(10):952-6.
8. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, 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(17):e927-e99.
9. Kawamura Y, Takeshita S, Kanai T, Yoshida Y, Nonoyama S. The Combined Usefulness of the Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in Predicting Intravenous Immunoglobulin Resistance with Kawasaki Disease. J Pediatr 2016;178:281-4.
10. Ha KS, Lee J, Jang GY, Lee J, Lee KC, Son CS, et al. Value of neutrophil-lymphocyte ratio in predicting outcomes in Kawasaki disease. Am J Cardiol 2015;116(2):301-6.
11. Zahorec R. Ratio of neutrophil to lymphocyte counts--rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001;102(1):5-14.
12. Kliegman RM. Nelson textbook of pediatrics. 21st edition. ed. Philadelphia, MO: Elsevier;2019.
13. Egami K, Muta H, Ishii M, Suda K, Sugahara Y, Iemura M, et al. Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. J Pediatr 2006;149(2):237-40.
14. Kobayashi T, Inoue Y, Takeuchi K, Okada Y, Tamura K, Tomomasa T, et al. Prediction of intravenous

immunoglobulin unresponsiveness in patients with Kawasaki disease. Circulation 2006;113(22):2606-12.

15. Cho HJ, Bak SY, Kim SY, Yoo R, Baek HS, Yang S, et al. High neutrophil: lymphocyte ratio is associated with refractory Kawasaki disease. Pediatr Int 2017;59(6):669-74.

16. Lee SM, Lee JB, Go YB, Song HY, Lee BJ, Kwak JH. Prediction of resistance to standard intravenous immunoglobulin therapy in kawasaki disease. Korean Circ J 2014;44(6):415-22.

17. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003;111(12):1805-12.

SOURCE: STUD MED SCI 2022: 32(12): 953-962 ISSN: 2717-008X