White Blood Cell and Neutrophil Counts and Response to Intravenous Immunoglobulin in Kawasaki Disease

Global Pediatric Health
Volume 6: 1–9

DOI: 10.1177/2333794X19884826
journals.sagepub.com/home/gph
SAGE

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Abstract

We explored parameters to predicting the efficacy of intravenous immunoglobulin (IVIG) therapy for patients with Kawasaki disease (KD). We retrospectively analyzed the laboratory data of 77 children with KD treated with IVIG. Data obtained before and within 24 hours after IVIG therapy were compared between responders and nonresponders. The white blood cell (WBC) and neutrophil counts were significantly lower in responders than nonresponders within 24 hours after IVIG. The areas under the receiver operating characteristics curves of the WBC and neutrophil counts were 0.846 and 0.754, respectively. The WBC and neutrophil counts differed significantly between responders and nonresponders (the latter developed recurrent pyrexia after transient fever resolution). In conclusion, WBC and neutrophil counts within 24 hours after IVIG usefully predict the efficacy of IVIG therapy for those with KD, and identify nonresponders to such therapy.

Keywords

Kawasaki disease, intravenous immunoglobulin, white blood cell counts, neutrophil counts, nonresponder

Received June 12, 2019. Received revised August 20, 2019. Accepted for publication September 13, 2019.

Introduction

In Kawasaki disease (KD), coronary artery lesion (CAL) development is an important sequela with an incidence of 15% to 20% when left untreated.[1] The goal of acute treatment is to ameliorate vascular inflammation as soon as possible and prevent CAL. Early intravenous immunoglobulin (IVIG) administration is the most effective treatment. In Japan, 2 g/kg of immunoglobulin has been widely applied, leading to a marked decrease in CAL (less than 5%).[2,3] Some children with KD may be unresponsive to IVIG, developing pyrexia lasting for 24 hours or longer, or recurrent fever, even after IVIG. In such children, the incidence of CAL is estimated to be 19% to 40%.[2,4] To prevent CAL, it is important to determine whether IVIG will be effective, and to identify nonresponders requiring additional treatment.

Several scoring systems have been proposed to predict unresponsiveness to IVIG.[5-7] Some researchers reported that early treatment with a combination of IVIG and steroid pulse therapy improved acute clinical symptoms rapidly and reduced the incidence of CAL in patients presumed to be at high risk of unresponsiveness

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of IVIG.[8,9] Existing score systems try to determine the risk of unresponsiveness to IVIG prior to such treatment, based on patient background and laboratory data including age, gender and date of illness, and laboratory values including white blood cell (WBC) count, neutrophil ratio, hematocrit, platelet count, C-reactive protein (CRP), aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin (T-Bil), serum sodium (Na), and albumin.[5-7] However, these scores do not evaluate IVIG efficacy after therapy commences. At present, unresponsiveness to IVIG is defined based on the presence or absence of pyrexia after IVIG. It would be helpful if objective parameters were available to evaluate reliably the effect of IVIG; nonresponders require immediate additional treatment.

We retrospectively analyzed laboratory data collected within 24 hours after IVIG commencement from children with KD and sought parameters for predicting IVIG efficacy. We evaluated the utility of several parameters, including the WBC and neutrophil counts, in terms of predicting the efficacy of IVIG in children with KD.

Methods

We retrospectively analyzed data from 90 children with KD who were admitted to the Department of Pediatrics of Aichi Medical University Hospital from January 2013 to December 2014. Eleven children who did not undergo IVIG and 2 children who were not followed-up were excluded. Eventually, 77 children with KD treated with IVIG were included. The study was approved by the ethics committee of Aichi Medical University Hospital.

The diagnosis of KD was made based on the Japanese diagnostic guidelines for KD.[10] Complete KD was diagnosed when a child had 5 or more of the major KD symptoms. A diagnosis of incomplete KD was made when a child had 4 or fewer major KD symptoms after the exclusion of other illnesses with similar clinical features, including various viral and bacterial infections, cervical lymphadenitis, and toxic shock syndrome.

In our hospital, oral administration of aspirin at 30 to 50 mg/kg and 2 g/kg of immunoglobulin were routinely used as the initial treatment for children with KD. IVIG was administered over 12 to 24 hours. When a child had liver dysfunction, aspirin was substituted with 3 to 5 mg/kg of oral flurbiprofen. As second-line therapy, methylprednisolone pulse therapy was prescribed for children judged to be unresponsive to IVIG within 8 days of such treatment, and additional IVIG was given to children who were unresponsive later than day 9 of illness. Third-line therapy was either infliximab, a urinastatin, or plasma exchange. IVIG was administered even before the diagnosis of complete KD when coronary echocardiography demonstrated high echodensity around coronary arteries. Laboratory examinations were performed on admission, before and within 24 hours after IVIG, and before discharge.

We focused on laboratory data obtained within 24 hours before IVIG and 12 to 24 hours after the completion of IVIG. We collected the following data: WBC, neutrophil, and monocyte counts; and hemoglobin (Hb), platelet count, T-Bil, AST, ALT, Na, and CRP levels. These items were selected because several previous studies supported their usefulness for predicting unresponsiveness to IVIG[5-7] and the data can be acquired in most hospitals at any time. We collected information from medical records including age, gender, dates of illness on admission, administration of IVIG, and first visit, duration of hospitalization, diagnosis, coronary artery change, and coronary lesions after discharge. IVIG was judged to be effective when a child did not have pyrexia $>37.5°C$ after IVIG. IVIG was judged to be ineffective when a child had persistent or recurrent pyrexia $>37.5°C$ for longer than 24 hours. In this study, CAL was defined as an internal coronary artery diameter ≥ 3 mm in children less than 5 years of age and ≥ 4 mm in children more than 5 years of age. Internal coronary artery diameter was measured echocardiographically.

We performed statistical analyses comparing laboratory data collected before and within 24 hours after IVIG between responders (resolution of pyrexia) and nonresponders (persisting or recurrent pyrexia necessitating second-line treatment). Nonresponders were divided into 2 groups: persisting pyrexia defined as persistent pyrexia for 24 hours or longer after IVIG, and recurrent pyrexia defined as transient resolution of pyrexia followed by recurrence of pyrexia longer than 24 hours after IVIG. We used the χ^2 and the Mann-Whitney U tests to compare categorical and numerical variables, respectively. The predictive value of laboratory data within 24 hours after IVIG was assessed by the area under the receiver operating characteristics (ROC) curve. The cutoff values for items with significant differences were determined by the Youden index in order to calculate the sensitivity and specificity of each item. We also compared laboratory data within 24 hours after IVIG among 3 groups: responders, nonresponders with persisting pyrexia, and nonresponders with recurrent pyrexia, using the Kruskal-Wallis test. The Steel-Dwass test was applied as a post hoc test when the Kruskal-Wallis test showed a significant difference. Chronological changes were analyzed using the Bonferroni test. A P value $<.05$ was considered to reflect statistical significance. All statistical analyses were performed with the aid of EZR version 1.33 (http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html).[11]

Table 1. Demographic Data.

	All (N = 77)	Responders (N = 57)	Nonresponders (N = 20)			P^a
			All (N = 20)	Recurrent Pyrexia (N = 13)	Persisting Pyrexia (N = 7)	
Age (months)[b]	21 (2-98)	24 (3-74)	17 (2-98)	17 (2-62)	21 (2-98)	.07
Gender (male–female)[b]	37:40	24:33	13:7	9:8	4:3	.08
Days of illness on admission[b]	4 (1-12)	5 (2-12)	4 (1-6)	4 (3-6)	3 (1-5)	.16
Days of illness at the initiation of IVIG[b]	5 (3-12)	5 (3-12)	5 (3-6)	6 (4-7)	5 (3-5)	.03
Incomplete KD	22 (29%)	20 (35%)	2 (10%)	2 (15%)	0 (0%)	.03
CAL during admission	4 (5%)	3 (5%)	1 (5%)	0	1 (14%)	.96
CAL after discharge	1 (1%)	1 (2%)	0	0	0	.55

Abbreviations: IVIG, intravenous immunoglobulin; KD, Kawasaki disease; CAL, coronary artery lesion.
[a]Responders vs non-responders
[b]Data are shown as median (range).

Ethics Approval and Informed Consent

This study was approved by the ethics committee of Aichi Medical University Hospital (Approval No. 2015-H830). The need for informed consent was waived because we retrospectively analyzed existing data; no patient was identifiable and opt-out choices were not revealed.

Results

Demographic data are shown in Table 1. We enrolled 37 boys and 40 girls of median age 21 months. The median number of days of illness at the initiation of IVIG was 5 (range = 3-12 days). A diagnosis of incomplete KD was made in 22 patients. CAL was observed in 4 patients during admission and one of them had CAL after discharge. There were 57 responders and 20 nonresponders. All nonresponders received additional doses of immunoglobulin. In addition, 1 patient underwent combined plasma exchange/methylprednisolone pulse therapy, and another was prescribed urinastatin. There was a significant difference in the days of illness at the initiation of IVIG, whereas median values were similar between responders and nonresponders. Incomplete KD was more frequent in responders than in non-responders.

Laboratory data before IVIG are shown in Table 2. T-Bil and ALT were significantly higher, and Na was significantly lower in nonresponders than responders. Among the 3 existing prediction scores for IVIG unresponsiveness, only the Kurume score was significantly correlated with responsiveness to IVIG in our patients.

Laboratory data obtained within 24 hours after IVIG are shown in Table 3. A significant difference was observed in WBC, neutrophil, and monocyte counts, and Hb, T-Bil, AST, ALT, Na, and CRP levels between responders and nonresponders. Among them, WBC and neutrophil counts, and Na levels had $P < .001$. The areas under the curve (AUCs) of the ROC curve of WBC and neutrophil counts, and Na levels were 0.867 (95% confidence interval [CI] = 0.773-0.96), 0.835 (95% CI = 0.705-0.965), and 0.789 (95% CI = 0.646-0.932), respectively. However, the difference between median Na values in responders and nonresponders was quite small (138 mEq/L in responders and 136 mEq/L in non-responders). These results indicate that WBC and neutrophil counts are more clinically useful than Na level for the prediction of non-responders within 24 hours after IVIG.

Next, laboratory data were compared among 3 groups: responders, patients with persisting pyrexia, and those with recurrent pyrexia (Table 4). Clinically, second-line treatment should commence immediately in children with persisting pyrexia. However, in those with recurrent pyrexia, immediate second-line treatment is not always simple. To avoid delay in initiation of second-line treatment, early identification of patients with recurrent pyrexia is desirable. Therefore, we explored whether patients with recurrent pyrexia could be distinguished from responders based on laboratory data derived within 24 hours after IVIG. The WBC and neutrophil counts, and the Hb, T-Bil, AST, and Na levels, differed significantly between responders and patients with recurrent pyrexia. Of these parameters, the WBC and neutrophil counts and the Na level were associated with $P < .01$. However, the difference between the median Na values of responders and nonresponders was rather small (138 mEq/L in responders and 136 mEq/L in those with recurrent pyrexia). The areas under the ROC curves (AUCs) of the WBC and neutrophil counts were 0.846 (0.721-0.972) and 0.754 (0.569-0.937), respectively. At a WBC count cutoff of 7100, the sensitivity, specificity, and

Table 2. Laboratory Data Before Intravenous Immunoglobulin.

	Responders (N = 57)	Nonresponders (N = 20)	*P*
WBC (/μL)[a]	13 800 (7100-24 900)	13 000 (6800-23 900)	.18
Neutrophil count (/μL)[a]	9394 (3124-23 157)	9246 (3696-21 271)	.51
Monocyte count (/μL)[a]	712 (122-2576)	540 (138-1740)	.07
Hb (g/dL)[a]	11.2 (8.2-13.9)	11.3 (9.0-12.5)	.78
Platelet count ($\times 10^4$/μL)[a]	33.2 (18.5-51.5)	33.9 (19.6-51.0)	.78
T-Bil (mg/dL)[a]	0.60 (0.12-2.45)	1.37 (0.59-5.05)	<.001
Alb (g/mL)[a]	3.5 (2.7-4.5)	3.5 (2.5-4.1)	.62
AST (U/L)[a]	32 (18-599)	76 (20-1352)	.060
ALT (U/L)[a]	19 (12-109)	98 (9-203)	.004
Na (mEq/L)[a]	135 (131-144)	134 (129-139)	.021
CRP (mg/dL)[a]	6.0 (1.7-20.6)	7.3 (2.8-15.7)	.24
Gunma score ≥ 5[b]	11 (19%)	7 (35%)	.20
Kurume score ≥ 3[b]	12 (21%)	11 (55%)	.008
Osaka score ≥ 2[b]	8 (14%)	5 (25%)	.26

Abbreviations: WBC, white blood cell count; Hb, hemoglobin; T-Bil, total bilirubin; Alb, albumin; AST, aspartate transaminase; ALT, alanine transaminase; Na, sodium; CRP, C-reactive protein.
[a]Data are shown as median (range).
[b]Gunma score, Kurume score, Osaka score are a score system predicting unresponsiveness to intravenous immunoglobulin. The following factors are included in each score. Gunma score: age, treatment start date, neutrophil ratio, platelet count, AST, serum Na, and CRP. Kurume score: age, treatment start date, platelet count, ALT, and CRP. Osaka score: AST, total bilirubin, and CRP.

positive and negative predictive values were 0.85, 0.81, 0.50, and 0.94, respectively. At a neutrophil count cutoff of 2500, the sensitivity, specificity, and positive and negative predictive values were 0.89, 0.64, 0.29, and 0.98, respectively. These results suggest that early identification of patients with recurrent pyrexia after IVIG may be possible on the basis of the WBC and neutrophil counts.

Of the responders, 3 exhibited mild coronary artery dilatation. Their neutrophil counts within 24 hours after IVIG were 1584 to 4161/μL. At discharge, the coronary artery remained dilated in 1 patient. Of the nonresponders, 1 child exhibited mild coronary artery dilatation. The neutrophil count within 24 hours after IVIG was 6867/μL. However, no CAL was apparent at discharge. Even in children with CAL, responsiveness (or not) to IVIG was distinguished by the neutrophil count using a cutoff of 4316/μL.

Discussion

We analyzed the laboratory data from 77 patients with KD to clarify their relationship to IVIG unresponsiveness and identify markers of unresponsiveness. In the laboratory data obtained before IVIG, T-Bil and ALT levels were higher and Na levels were lower in nonresponders than responders. In the laboratory data obtained within 24 hours after IVIG, several variables, including the WBC neutrophil counts, and T-Bil and Na levels, were significantly different between responders and nonresponders. Analysis of ROC curves suggested that the WBC and neutrophil counts obtained within 24 hours after IVIG predicted IVIG unresponsiveness, although our study was a retrospective single-center work with a relatively small number of patients.

We focused on laboratory data obtained within 24 hours after IVIG in children with KD. IVIG nonresponsiveness is obvious in patients with persisting pyrexia, but may not be apparent in patients with recurrent pyrexia, although such patients also require prompt second-line treatment. Thus, early discrimination between responders and nonresponders, especially in those with recurrent pyrexia, is important. We found that, in responders, the WBC and neutrophil counts rapidly decreased in response to IVIG. The WBC and neutrophil counts within 24 hours after IVIG were higher in nonresponders than responders and in those with recurrent pyrexia than in responders. The WBC count within 24 hours after IVIG can be used for early prediction of nonresponders and those with recurrent pyrexia (as distinct from responders) at the time of IVIG completion. Similarly, the neutrophil count within 24 hours after IVIG can be used to identify nonresponders and those with recurrent pyrexia, although the predictive value was slightly lower than that of the WBC count. Several parameters including the WBC and neutrophil counts potentially predict the severity of systemic inflammation in KD patients and IVIG unresponsiveness.[12,13] Hwang et al[14] found that the WBC and neutrophil counts after initial IVIG treatment were lower in responders than nonresponders. Our study also highlights the

Table 3. Laboratory Data Within 24 Hours After Intravenous Immunoglobulin.

	Responders (N = 57)	Nonresponders (N = 20)	*P*	AUC of ROC Curve	Cutoff Value	Sensitivity	Specificity
WBC (/μL)	5600 (2800-47 000)[a]	9800 (4500-20 000)[a]	<.001	0.867 (0.773-0.96)[b]	7300	0.850	0.807
Neutrophil count (/μL)	1872 (236-5960)[a]	5700 (855-10 101)[a]	<.001	0.835 (0.705-0.965)[b]	4316	0.647	0.923
Monocyte count (/μL)	340 (88-1053)[a]	488.5 (96-1800)[a]	.02	0.666 (0.514-0.819)	438	0.650	0.763
Hb (g/dL)	10.7 (7.7-12.7)[a]	10.3 (8.7-12.1)[a]	.041	0.655 (0.519-0.791)[b]	10.3	0.600	0.667
Platelet count ($\times 10^4$/μL)	39.1 (10.0-71.2)[a]	35.9 (25.3-75.5)[a]	.86				
T-Bil (mg/dL)	0.31 (0.11-0.59)[a]	0.41 (0.14-0.82)[a]	.007	0.72 (0.569-0.87)[b]	0.38	0.611	0.761
Alb (g/mL)	3.1 (2.3-3.9)[a]	3.0 (2.0-3.9)-[a]	.32				
AST (U/L)	31 (9-95)[a]	38 (17-125)[a]	.017	0.68 (0.536-0.823)[b]	34	0.750	0.632
ALT (U/L)	17 (8-128)[a]	37 (11-179)[a]	.015	0.684 (0.548-0.819)[b]	19	0.800	0.544
Na (mEq/L)	138 (135-142)[a]	136 (133-141)[a]	<.001	0.789 (0.646-0.932)[b]	136	0.650	0.909
CRP (mg/dL)	2.6 (0.41-10.5)[a]	4.4 (0.36-12.7)[a]	.015	0.685 (0.538-0.831)[b]	4.9	0.500	0.860

Abbreviations: AUC, area under the curve; ROC, receiver operator characteristics; WBC, white blood cell count; Hb, hemoglobin; T-Bil, total bilirubin; Alb, albumin; AST, aspartate transaminase; ALT, alanine transaminase; Na, sodium; CRP, C-reactive protein.

[a]Data are shown as median (range).

[b]Data are shown as value (95% confidence interval).

Table 4. Comparison Among Responders, Patients With Persistent Pyrexia, and Those With Recurrent Pyrexia[a].

		Nonresponders		
	Responders (N = 57)	Recurrent Pyrexia (N = 13)	Persisting Pyrexia (N = 7)	*P*
WBC (/μL)	5600 (2800-47 000)	10 900 (7400-20 000)	8600 (4500-13 400)	<.001[b]
Neutrophil count (/μL)	1872 (236-5960)	6579 (4316-10 101)	3920 (855-7888)	<.001[c]
Monocyte count (/μL)	340 (88-1053)	438 (96-1508)	1162 (218-1800)	.005[d]
Hb (g/dL)	10.7 (7.7-12.7)	10.2 (8.8-12.1)	10.3 (8.7-11.6)	.10
T-Bil (mg/dL)	0.31 (0.11-0.59)	0.40 (0.22-0.76)	0.41 (0.14-0.82)	.025[e]
AST (U/L)	31 (9-95)	37 (25-59)	41 (17-125)	.040[f]
ALT (U/L)	17 (8-128)	31 (11-51)	61 (12-179)	.035[f]
Na (mEq/L)	138 (135-142)	135 (133-139)	136 (133-141)	<.001[g]
CRP (mg/dL)	2.6 (0.41-10.5)	7.1 (2.4-12.7)	3.4 (0.36-8.1)	.035[h]

Abbreviations: WBC, white blood cell count; Hb, hemoglobin; T-Bil, total bilirubin; AST, aspartate transaminase; ALT, alanine transaminase; Na, sodium; CRP, C-reactive protein.
[a]Data are shown as median (range).
[b]$P < .001$, responders versus persistent pyrexia; $P < .001$, responders versus recurrent pyrexia.
[c]$P < .05$, responders versus persistent pyrexia; $P < .001$, responders versus recurrent pyrexia.
[d]$P < .001$, responders versus persistent pyrexia.
[e]Post hoc test showed no significant differences.
[f]$P < .05$, responders versus persistent pyrexia.
[g]$P < .05$, responders versus persistent pyrexia; $P < .01$, responders versus recurrent pyrexia.
[h]$P < .05$, responders versus recurrent pyrexia.

importance of the WBC and neutrophil counts; these can be used to distinguish responders from those with recurrent pyrexia.

It is interesting that variables correlated with unresponsiveness to IVIG differed before and within 24 hours after IVIG. Before IVIG, T-Bil, ALT, and Na levels were correlated with IVIG unresponsiveness in our study. Among the 3 existing unresponsiveness prediction scores, Na is included in the Gunma score,[5] ALT in the Kurume score,[6] and T-Bil in the Osaka score.[7] Our study supports the usefulness of these variables for predicting IVIG unresponsiveness before IVIG. By contrast, many variables, including WBC and neutrophil counts, and T-Bil, ALT, and Na levels, were correlated with IVIG unresponsiveness within 24 hours after IVIG. This suggests that laboratory data obtained within 24 hours after IVIG are strongly correlated with the effects of IVIG, and differences between responders and nonresponders should be evident. Laboratory data obtained within 24 hours after IVIG can be used as complementary markers of IVIG unresponsiveness when used in combination with the existing prediction scores. Based on the univariate analysis and ROC curves, we found that WBC and neutrophil counts, and Na level were useful markers of IVIG unresponsiveness within 24 hours after IVIG. Hyponatremia is the most common electrolyte disorder and can be encountered in a variety of inflammatory diseases, including vasculitis. However, in this study the difference in Na level within 24 hours after IVIG between responders and nonresponders was 2 mEq/L, which is very small. Therefore, the Na level is unlikely to find clinical application.

Neutrophils and monocytes are the major types of immune cells infiltrating the coronary arteries of KD patients and are generally regarded as the cellular mediators of cardiac pathology.[15-17] Monocytes and macrophages predominate among the cells infiltrating the CAL of KD patients throughout the course of disease,[18] whereas neutrophils infiltrate the lesion early in vasculitis development, accompanied by collapse of the vascular architecture.[15] Host immune cells, including cells of the macrophage lineage, control the damage-associated molecular patterns of host cells injured by infectious insults.[19,20] This control system plays a major role in recovery from KD. Therefore, severely affected KD patients (those with giant aneurysms) may be unable to counter or repair damage caused by KD agents or products of injured coronary artery cells.[21] We found that the monocyte counts within 24 hours after IVIG of responders were lower than those of children with persistent pyrexia, but we found no significant difference between responders and children with recurrent pyrexia. Increased levels of granulocyte colony-stimulating factor (G-CSF), interleukin-1 (IL-1), and interleukin-6 (IL-6) may induce neutrophilia during the acute phase of KD.[22] G-CSF is a hematopoietic growth factor produced by macrophages, vascular endothelial cells, and vascular smooth muscle cells; production is enhanced by

inflammatory cytokines such as TNF-α and IL-6 and G-CSF induces neutrophils to migrate from bone marrow into peripheral blood.[23,24] In a mouse model of KD, granulocyte macrophage colony-stimulating factor (GM-CSF) served as a potential initiator of cell migration during cardiac inflammation.[25] GM-CSF is rapidly expressed in the heart during the initial stages of cardiac disease. The decreased WBC and neutrophil counts after IVIG may reflect lower-level expression of GM-CSF. In KD patients, the G-CSF level and the number of granulocytes expressing CD177, which rise after G-CSF is expressed in peripheral blood, were significantly higher in nonresponders than responders.[26] High levels of IgG act directly on vascular endothelial cells to suppress the production of G-CSF and IL-6.[27] Thus, the decreased WBC and neutrophil counts indicate a favorable therapeutic response in children with KD.

There were some limitations in our study. First, this study was conducted in a single hospital; therefore, the number of patients was not large enough to perform multivariate analysis. Multicenter studies and a larger number of patients are needed to confirm the results of this study. In addition, it is unclear if our patients are representative of general patients with KD, although the clinical characteristics of our patients were not largely different from those of contemporary national data reported by the Kawasaki Disease Nationwide Survey.[2] Second, this study was retrospective; as such, the timing of blood sampling was not always consistent. Well-designed prospective studies should be performed to obtain more precise results. Moreover, we could not investigate the usefulness of laboratory data for predicting CAL because the number of patients with CAL was quite low. At present, the rate of CAL during the remote period in Japanese children with KD is 2.8%.[2] To clarify the usefulness of laboratory data for the prediction of CAL, a nationwide study may be necessary. Because of these limitations, the results of our study should be verified in future works with larger number of patients.

In summary, this study revealed that there are differences in laboratory data obtained within 24 hours after IVIG between responders and nonresponders among children with KD. The WBC and neutrophil counts decreased rapidly in response to IVIG in responders. The WBC and neutrophil counts obtained within 24 hours after IVIG were higher in nonresponders than responders, and in those with recurrent pyrexia than responders. The WBC count within 24 hours after IVIG can be used for early prediction of nonresponders and those with recurrent pyrexia; these become distinct from responders soon after IVIG. This renders it possible to initiate second-line treatment rapidly.

Author Contributions

TM: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

YM: Contributed to conception; contributed to acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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AO: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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