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USEFULNESS OF THE NEUTROPHIL TO LYMPHOCYTE RATIO FOR RISK STRATIFICATION AFTER INITIAL INTRAVENOUS IMMUNOGLOBULIN THERAPY IN KAWASAKI DISEASE

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ABSTRACT: Objective: Initial single intravenous immunoglobulin (IVIG) therapy with delayed use of anti-inflammatory drugs (DUA) is a challenging for preventing large coronary artery lesions (CAL) caused by Kawasaki disease. However, the parameters to guide rescue therapies after initial IVIG therapy have not been established. In this study, I investigated the usefulness of the neutrophil to lymphocyte ratio (NLR) for risk stratification in Kawasaki disease. Methods: I recruited 163 patients who received initial IVIG therapy with DUA from January 2004 to August 2016. These patients were divided into 126 IVIG-responders (responder group) and 37 IVIG-resistant patients (resistant group). The 37 IVIG-resistant patients were divided into two groups, a rescue group with 13 patients who received rescue therapies for initial IVIG therapy resistance and a non-rescue group with 24 children who did not receive the rescue therapy for resistance. The NLRs after initial IVIG therapy were retrospectively investigated. Results: The median values of the NLRs between the resistant vs. responder groups and between the rescue vs. non-rescue groups were 2.35 (range, 0.33–12.65) vs. 0.74 (range, 0.01–4.42), $P < 0.001$ and 5.42 (range, 0.52–12.65) vs. 1.645 (range, 0.33–4.08), $P = 0.003$, respectively. The NLR values were also significantly different among the rescue, non-rescue, and responder groups ($P < 0.001$). Only one patient in the rescue group had CAL after day 30 of illness, and she had the highest NLR value. Conclusion: NLR after initial IVIG therapy with DUA may be useful for risk stratification in Kawasaki disease.

KEYWORDS: Kawasaki disease, neutrophil to lymphocyte ratio, intravenous immunoglobulin therapy, coronary artery lesions

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1. INTRODUCTION

Kawasaki disease is an acute systemic vasculitis of unknown cause that mainly affects infants and children [1]. Coronary artery lesions (CAL) are one of the most important complications of this disease, and intravenous immunoglobulin (IVIG) resistance is one of the most important factors for CAL development during the acute phase of Kawasaki disease. Recent studies have disclosed that aspirin and flurbiprofen have a negative impact on the suppressive effects of initial IVIG therapy for CAL development during the acute phase of Kawasaki disease and that initial single IVIG therapy with delayed use of anti-inflammatory drugs (DUA) might be effective for CAL suppression [2]. An initial single IVIG therapy with DUA is a challenging for preventing significant CAL caused by Kawasaki disease [3]. A recent study suggested that the decision to perform rescue therapy at 3 to 4 days after initial IVIG therapy with DUA was appropriate for preventing large CAL in initially IVIG-resistant patients [4]. However, the parameters to guide rescue therapies have not been established. The c-reactive protein (CRP) ratio, defined as the ratio of CRP values after/before initial IVIG therapy, appeared to be useful for guiding rescue therapy [4]. However, this parameter could not identify high risk patients associated with CAL after 30 days of illness [4]. Recent studies showed that the neutrophil to lymphocyte ratio (NLR) may be useful for risk stratification in patients with Kawasaki disease [5–7]. The objective of this study is to clarify the usefulness of NLR for risk stratification after initial IVIG therapy with DUA in Kawasaki disease.

2. MATERIAL AND METHODS

This retrospective study included 163 consecutive patients who received an initial 2 g/kg/dose of IVIG therapy with DUA for Kawasaki disease between January 2004 and August 2016 at the Department of Pediatrics, Aomori Prefectural Central Hospital. Anti-inflammatory drugs (aspirin or flurbiprofen) were initiated within 24 h after the end of initial IVIG infusion [2]. Diagnosis of Kawasaki disease was based on the *Japanese Criteria* (Fifth Edition) [8]. In this study, recurrence and relapse were defined differently. When Kawasaki disease recurred after an initial disappearance of major symptoms and improvement of the test results, it was defined as a recurrence. If there was an interval of at least two months from the onset of the first Kawasaki disease illness to the onset of a new episode, it was defined as a recurrence [9]. If a child became afebrile during the acute phase, an exacerbation or reappearance of major symptoms without other pyrogenic disease was defined as a relapse. Defervescence was defined as a body temperature < 37.5 °C for 24 h, and the time of the defervescence was defined as when the body temperature reached < 37.5 °C. IVIG-resistance was defined as fever persistence or reappearance at 24 h after first-line treatment [10]. I excluded 29 patients who received concomitant IVIG and anti-inflammatory therapy because the objective of this study was to clarify the NLR ability regarding risk stratification after initial IVIG therapy with DUA. I excluded five patients who had developed CAL before the start of therapy because another objective of this study was to clarify the ability to prevent large CAL by initial IVIG therapy with

DUA. I excluded one patient who developed left ventricular dysfunction with a different protocol, including plasma exchange in the early stage. I included six patients with disease recurrence, and the first episodes of disease in these patients were included for analysis. The entire study population was divided into 126 initial IVIG-responders (responder group) and 37 IVIG-resistant patients (resistant group). The resistant group was divided into the two sub-groups, a rescue group with 13 patients who received rescue therapies for the initial IVIG therapy resistance and a non-rescue group with 24 children who did not receive rescue therapy for the initial IVIG resistance. NLR was defined as the ratio of the neutrophil count/lymphocyte count. The Egami score, which is the risk score for predicting IVIG-resistance using clinical findings, such as age, illness days, platelet count, alanine aminotransferase, and CRP, was evaluated before initial IVIG therapy [11].

2.1. Anti-inflammatory Drugs Therapy and Initial IVIG Therapy

The choice between aspirin and flurbiprofen was made by each doctor after considering the patient's liver function and risk of Reye syndrome during the influenza pandemic. Flurbiprofen was used in cases of severe aspirin hepatotoxicity in Japan, and Reye syndrome is not mentioned as an adverse effect or in flurbiprofen precautions [12]. Flurbiprofen was more commonly used before 2009 because of its advantage for hepatic dysfunction and Reye syndrome. Aspirin was more commonly used after 2009 because aspirin use became a global standard for Kawasaki disease. The recent study using logistic regression analysis showed that the type of anti-inflammatory drug (aspirin or flurbiprofen) was not a significant factor for CAL suppression [2]. Aspirin was initiated at a dose of 30 mg/kg/day and decreased to 5−10 mg/kg/day when the patients became afebrile. Flurbiprofen was initiated at a dose of 3–5 mg/kg/day and decreased to 3 mg/kg/day when the patients became afebrile. During the study period, an initial IVIG regimen of 2 g/kg/dose, starting on day 5 of the illness, was used as first-line therapy, when possible. A regimen of the initial IVIG therapy with DUA was used after 2004. Some patients received this therapy with DUA between 2004 and 2008. The choice between DUA and concomitant use of anti-inflammatory drugs was made by each doctor during this period. After 2009, the initial IVIG therapy with DUA was used for all patients [2].

2.2. Rescue Therapy

The decision for using rescue therapies in resistant patients was made between 48 and 72 h after the end of the initial IVIG therapy. The decision was comprehensively made according to clinical parameters, including the body temperature, major symptoms of Kawasaki disease, general condition, and laboratory data. There were no definite cut-off values of laboratory tests during this study.The blood samples were taken 2–4 days after initial IVIG therapy, and the samples before the decision was made were used in studies of IVIG-resistant patients. The blood samples were taken 2–5 days after initial IVIG therapy among IVIG-responders, and the first data after initial IVIG therapy were used in this study. Second-line therapy was rescue IVIG therapy, and third-line

therapy was ulinastatin infusion. Plasma exchange was adopted after 2014 as another third-line therapy option. This regimen was approved for use in Aomori Prefectural Central Hospital [13, 14]. Written informed consent was obtained from the parents or guardians of all children before initial therapy [2].

2.3. Diagnosis of CAL

CAL was diagnosed by echocardiography as follows [15]. CAL was diagnosed when any of these examinations had an internal lumen diameter ≧ 3 mm in a patient < 5 years of age or a diameter ≧ 4 mm in a patient ≧ 5 years of age. If the internal diameter of a segment was at least 1.5 times as large as that of an adjacent segment or if the lumen appeared irregular, transient CAL was defined as a disappearance of CAL within 30 days of illness. Myocardial ischemia due to CAL is one of the most important complications caused by Kawasaki disease. Long-term follow-up studies have shown that a maximum CAL size >5 mm was a significant predictive risk factor for myocardial ischemia as well as that CAL ≦ 5 mm in size regressed to a normal size [16]. Another study reported that the threshold diameter for acute phase CAL that developed into subsequent stenosis was 6.0 mm [17]. Therefore, prevention of CAL of >5 mm may be an important goal in acute treatment of Kawasaki disease to prevent coronary artery stenosis in later stages of the disease [3]. In this study, CAL were evaluated in mm for the entire population because of the goal of preventing coronary artery stenosis in later stages.

2.4. Statistical Analysis

Statistical analyses were performed with StatFlex Version 6 for Windows (Artech Co., Ltd., Osaka, Japan). The Chi-square, Fisher's exact, Mann–Whitney U, and Kruskal-Wallis tests were used as appropriate. A P value < 0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

The clinical findings, treatment, and laboratory values of each group are shown in Tables 1 and 2. All 13 patients in the rescue group received rescue IVIG therapies on day 8 (based on median; range, 7–11) of illness for initial IVIG therapy resistance, and the duration between the first and second IVIG therapies was a median of 3 (range, 3–4) days. Two of 13 patients received third-line therapy; one patient received an ulinastatin infusion, and another patient received plasma exchange.

Table 1. Comparison between resistant and responder groups

	Resistant group $n = 37$	Responder group $n = 126$	*P*-value
Sex (male)	21 (56.8%)	58 (46.0%)	0.251
Age* (month)	28 (3-148)	22 (2-159)	0.064
Egami score*	2 (0-4)	1 (0-4) $n = 125$	< 0.001
Incomplete type	6 (16.2%)	15 (11.9%)	0.491
CRP before IVIG* (mg/dL)	8.66 (1.14-24.83)	6.36 (0.16-26.32) $n = 125$	0.018
Day of illness at sampling*	5 (4-9)	5 (3-16)	0.446

Initial IVIG			
Start day of illness*	5 (4-9)	5 (4-16)	0.237
Aspirin	17	74	
Flurbiprofen	20	52	0.169
Defervescence			
Day of illness*	9 (7-16)	6 (3-17)	< 0.001
Days after IVIG*	3 (2-9)	1 (-2-3)	< 0.001
Laboratory findings			
Day of illness at sampling*	8 (6-12)	8 (7-20)	0.149
Days at sampling after	3 (2-4)	3 (2-5)	0.523

IVIG*			
Leukocyte count* (/mm3)	11500 (4600 - 20600) *n* = 36	7000 (2500-17000)	< 0.001
Neutrophil count* (/mm3)	6448 (1449-16274) *n* = 35	2468 (59-11798) *n* = 125	< 0.001
Lymphocyte count* (/mm3)	2802 (856-7790) *n* = 35	3345 (799-8844) *n* = 125	0.014
NLR*	2.35 (0.33-12.65) *n* = 35	0.74 (0.01-4.42) *n* = 125	< 0.001
CRP after IVIG* (mg/dL)	4.89 (0.23-20.58)	1.54 (0.03-11.45)	< 0.001

		n = 125	
CRP ratio*	0.55 (0.20‑1.48)	0.25 (0.05‑1.49)	< 0.001
		n = 125	
CAL before	1 (2.7%)	1 (0.8%)	0.404
CAL after	1 (2.7%)	0 (0.0%)	0.227

* Median (minimum–maximum); CRP: C-reactive protein; IVIG: intravenous immunoglobulin therapy; NLR: neutrophil to lymphocyte ratio; CAL before: coronary artery lesions before 30 days of illness; CAL after: coronary artery lesions after 30 days of illness

Incomplete type: patients with fewer than five major symptoms.

Table 2. Comparison between the rescue and non-rescue groups

	Rescue group *n* = 13	Non-rescue group *n* = 24	*P*-value
Sex (male)	6 (46.2%)	15 (62.5%)	0.338
Age* (month)	24 (3–148)	34.5 (4—95)	0.279
Egami score*	3 (1–4)	2 (0–4)	0.016
Incomplete type	2 (15.4%)	4 (16.7%)	0.920
CRP before IVIG* (mg/dL)	9.76 (3.93–21.87)	7.925 (1.14–24.83)	0.139

Day of illness at sampling*	5 (4–7)	5 (4–9)	0.084
Initial IVIG			
Start day of illness*	5 (4–7)	5 (5–9)	0.107
Aspirin	5	12	
Flurbiprofen	8	12	0.501
Defervescence			
Day of illness*	10 (9–16)	8 (7–12)	0.001
Days after IVIG*	4 (4–9)	3 (2–5)	< 0.001
Laboratory findings			
Day of illness at sampling*	8 (6–11)	8 (7–12)	0.428
Days at sampling after IVIG*	3 (2–4)	3 (2–4)	0.676
Leukocyte	12400 (5100–	10000 (4600–19000)	0.118

count* (/mm3)	20600)		
		n = 23	
Neutrophil count* (/mm3)	9660 (1530–16274)	5752.5 (1449–9500)	0.008
		n = 22	
Lymphocyte count* (/mm3)	2548 (856–3553)	3001.5 (1260–7790)	0.037
		n = 22	
NLR*	5.42 (0.52–12.65)	1.645 (0.33–4.08)	0.003
		n = 22	
CRP after IVIG* (mg/dL)	9.33 (2.86–20.58)	3.945 (0.23–9.88)	0.001
CRP ratio*	0.76 (0.52–1.48)	0.455 (0.20–1.13)	< 0.001
CAL before	1 (7.7%)	0 (0.0%)	0.351
CAL after	1 (7.7%)	0 (0.0%)	0.351

* Median (minimum–maximum); CRP: C-reactive protein; IVIG: intravenous immunoglobulin therapy; NLR: neutrophil to lymphocyte ratio; CAL before: coronary artery lesions before 30 days of illness; CAL after: coronary artery lesions after 30 days of illness; Incomplete type: patients with fewer than five major symptoms.

The Egami scores and CRP values before initial IVIG therapy of the resistant group were significantly higher than those of the responder group (Table 1). The day of illness and days after initial IVIG therapy regarding defervescence of the resistant group were more than those of the

responder group (Table 1). The leukocyte count, neutrophil count, NLR, CRP value, and CRP ratio after initial IVIG therapy of the resistant group were significantly higher than those of responder group (Table 1). The lymphocyte count after initial IVIG therapy of the resistant group was significantly lower than that of the responder group (Table 1). The Egami score of the rescue group was significantly higher than that of the non-rescue group (Table 2). The day of illness and days after initial IVIG therapy regarding defervescence of the rescue group were more than those of the non-rescue group (Table 2). The neutrophil count, NLR, CRP value, and CRP ratio after initial IVIG therapy for the rescue group were significantly higher than those of the non-rescue group (Table 2, Figure 1). The lymphocyte counts after initial IVIG therapy in the rescue group were significantly lower than those of the non-rescue group (Table 2). The CRP ratio cut-off value of < 0.50 excluded all 13 patients in the rescue group and included 15 non-rescue patients from the 37 IVIG-resistant group (41%) (Figure 1). The NLR values, day of illness and days after initial IVIG therapy regarding defervescence as well as the CRP values after initial IVIG therapy were significantly different among the rescue, non-rescue, and responder groups according to the Kruskal-Wallis test ($P < 0.001$). Among the entire study population, only one patient in the rescue group had CAL after day 30 of illness (Tables 1 and 2), and she had the highest NLR value of 12.65 on day 8 of illness. This patient had CAL on day 8, and this 2-year-old girl received plasma exchange on day 9 at the hospital of Hirosaki University School of Medicine for 3 days. Her CAL diameters of the right proximal artery were 4.8 and 2.9 mm on days 21 and 40, respectively, of her illness.

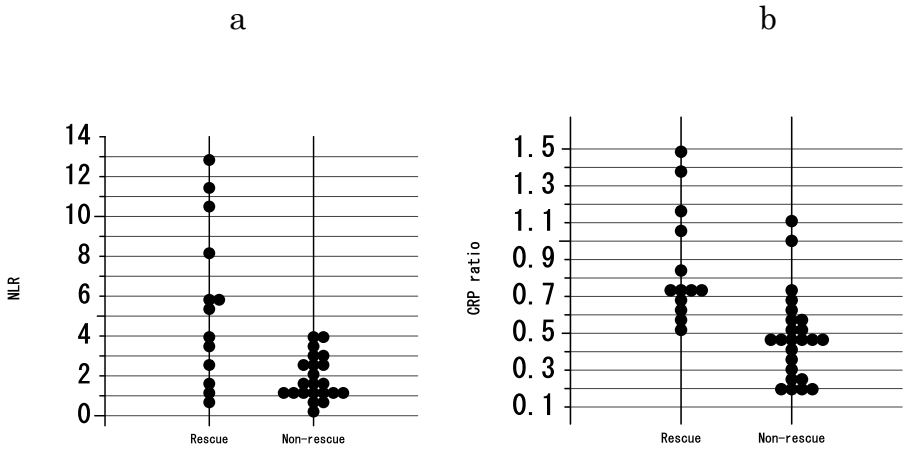

Figure 1. Neutrophil to lymphocyte ratio (NLR) (a) and C-reactive protein (CRP) ratio (b) in the rescue and non-rescue groups

However, echocardiography on day 52 of her illness showed regression of CAL and a normal internal coronary artery size. The selective coronary arteriogram performed at 7 months after disease onset revealed no abnormal findings. Thereafter, she was followed up without medication. Her clinical course was uneventful at 1 year and 3 months after disease onset [4].

DISCUSSION

This study showed that NLR may be useful for risk stratification after initial IVIG therapy with DUA in Kawasaki disease. The establishment of parameters to guide rescue therapy is important for suppressing CAL caused by Kawasaki disease. The NLR after initial IVIG therapy may be useful for guiding rescue therapy. The NLR has been reported to be a powerful biomarker of systemic inflammation [18]. Moreover, the NLR is believed to be predictive of the severity of coronary artery disease [19]. The day of illness and days after initial IVIG therapy regarding defervescence as well as the CRP values after initial IVIG therapy are parameters for the severity of Kawasaki disease [20]. The NLR values after initial IVIG therapy in the rescue, non-rescue, and responder groups were significantly different. Furthermore, only one patient with a coronary artery aneurysm had the highest NLR value. These findings are consistent with the results of recent studies [5, 6]. A recent study using multivariate analysis revealed that NLR after IVIG therapy independently predicted coronary artery aneurysm development and IVIG therapy resistance [5]. Another study showed that the NLR values in Kawasaki patients with CAL were significantly higher than in those without [6]. A previous study showed that coronary artery dilation alone and coronary artery aneurysms differ in the total duration of inflammation, as measured by the number of days from fever onset to defervescence [21]. Another study demonstrated that the most important predictor of coronary artery aneurysms in Kawasaki disease is a total fever duration of longer than 8 days [22]. Therefore, day 8 may be appropriate to identify high risk patients with coronary artery aneurysm development. In this study, the NLR values from a median of day 8 were useful for risk stratification of Kawasaki disease and identification of the patient with coronary artery aneurysm development. A recent study showed that rescue therapies, including plasma exchange before day 10, were useful for preventing large CAL caused by Kawasaki disease [23]. This finding was consistent with the clinical course of the patient with coronary artery aneurysms in this study. Identification of patients who have a risk of coronary artery aneurysms on day 8 according to the NLR and the following rescue therapies, including plasma exchange before day 10, may prevent large CAL caused by Kawasaki disease. The recent 22nd nationwide survey of Kawasaki disease in Japan showed that 1.09 % of patients have coronary artery aneurysms during the acute phase [24].

In this study, the prevalence of coronary artery aneurysm was 1/163 (0.6 %). The only patient with coronary artery aneurysm had the highest NLR value of > 12.00 (Figure 1). This NLR value may be a guide for choosing plasma exchange at day 8 after initial IVIG therapy with DUA. This value may be different according to the different initial therapies and ethnic population. The appropriate decision for rescue therapies contributes to the appropriate use of IVIG and to the avoidance of the need for rescue therapies. The recent 22nd nationwide survey of Kawasaki disease in Japan showed that 16 % of patients received rescue IVIG therapy for initial IVIG therapy resistance and 3 % of patients had associated CAL after 30 days of illness [24]. In this study, the prevalence of rescue IVIG therapy for initial IVIG therapy resistance was 8.0 % (13/163) and the prevalence rates of CAL after 30 days and after 7 months of illness were 0.6 % (1/163) and 0 %, respectively. These findings also suggested that a decision at day 8 might be useful for safe and effective rescue therapies for suppressing CAL. The CRP ratio might be useful for choosing to refrain from rescue IVIG therapy (Fig 1). On the other hand, the NLR values were useful for identifying high risk patients with coronary artery aneurysm development (Fig 1). The NLR value and CRP ratio at day 8 may be useful for appropriate choices of rescue therapies after initial IVIG therapy with DUA.This study showed the favorable outcome of CAL after initial IVIG therapy with DUA regarding prevention of large CAL. In addition to effective rescue therapies, including plasma exchange, removal of the negative impact of anti-inflammatory drugs during the initial IVIG therapy by DUA may be another factor for suppressing CAL. Twenty-four out of 37 IVIG-resistant patients recovered without rescue therapy for resistance and had no CAL. This finding suggested the efficacy of the initial IVIG therapy with DUA. A limitation of this study was the small number of IVIG-resistant patients. The retrospective nature of the study was another limitation. The efficacy and safety of the strategy of this study should be confirmed in a large study.

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CONFLICT OF INTEREST

There are no conflicts of interest to disclose.

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