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RISK STRATIFICATION AFTER INITIAL THERAPY FOR INTRAVENOUS IMMUNOGLOBULIN-RESISTANT KAWASAKI DISEASE

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ABSTRACT: Background: Effective rescue therapies and guidelines for intravenous immunoglobulin (IVIG)-resistant patients with Kawasaki disease (KD) have not yet been established. Objective: To ascertain the usefulness of risk stratification after an initial single IVIG infusion (2 g/kg). Materials and methods: This retrospective study included data from 50 consecutive patients with initial IVIG resistance. The data were divided into a group for cases with rescue therapy for resistance (rescue group, n = 22) and another group for cases without rescue therapy (non-rescue group, n = 28). The data on three variables including serum C-reactive protein (CRP), albumin levels, and neutrophil-to-lymphocyte ratio (NLR) were collected, and the ratios of the values of these variables after and before the initial therapy were calculated. Results: Three rescue group patients developed coronary artery lesions (CALs), which posed no stenosis risks. None of the patients in the non-rescue group received rescue therapies for resistance and they did not develop CALs. All of the values for the three variables and the ratios for each one were significantly different between the two groups after the initial therapy ($P < 0.05$). The CRP ratio cut-off value of 0.51 identified 95.5% of patients in the rescue group and 67.9% of patients in the non-rescue group. Conclusion: The risk stratification after an initial therapy for IVIG resistance was useful for prevention of KD coronary artery stenosis and for identification of the patients who did not require rescue therapy for resistance of an initial single IVIG infusion (2 g/kg). **Keywords:** Kawasaki disease, Intravenous immunoglobulin resistance, Coronary artery lesions, Intravenous immunoglobulin therapy, Inflammatory markers.

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1. INTRODUCTION

Kawasaki disease (KD) is an acute systemic vasculitis of unknown origin that majorly affects children [1]. Coronary artery lesions (CALs) are a severe KD complication. Intravenous immunoglobulin (IVIG) therapy resistance during the acute phase of KD has been implicated in CAL development [2]. IVIG resistance has been identified in patients when the fever either persists or reappears 24 h after the first-line KD treatment [3]. However, effective rescue therapies and guidelines for patients with IVIG resistance have not yet been established. The early identification of patients likely to develop IVIG resistance is also a challenge [4-8]. A risk stratification after initial IVIG therapy is important for appropriate rescue therapies and to prevent coronary artery stenosis in high-risk patients [9, 10]. However, a risk stratification system after initial IVIG therapy during the acute KD phase has not yet been established, in part because the clinical outcomes of patients with initial IVIG resistance are unclear. Two studies have demonstrated different subgroups of patients with initial IVIG resistance [11, 12]. Downie, et al. in their study divided non-responders into partial (axillary temperature decreased to <37.5 °C but the fever recurred) and complete non-responders (axillary temperature remained ≥ 37.5 °C throughout the IVIG treatment) [11]. They found that defervescence could be achieved with a second IVIG dose in 72% of partial non-responders and in 58% of complete non-responders (P = 0.001) [11]. The complete non-responders were more likely to develop CAL than the partial non-responders [11]. Another study with different subgroups regarding the absence of rescue therapy in patients with IVIG resistance found that two-thirds of those who were diagnosed 24 h after completion of the initial therapy did not develop CAL after 30 days of illness without rescue therapies [12]. The standard therapy for acute KD is IVIG therapy at 2 g/kg with the concomitant use of medium- or high-dose aspirin [3, 13]. However, the concomitant use of medium- or high-dose aspirin is now controversial [14-17]. A randomized controlled trial regarding the effectiveness of intravenous immunoglobulin alone and intravenous immunoglobulin combined with high-dose aspirin in the acute KD stage is ongoing [18]. Studies have suggested that aspirin may inhibit CAL prevention [19, 20]. The delayed use of aspirin (DUA) may be beneficial for coronary artery stenosis prevention during KD [21-23]. This study aimed to ascertain the usefulness of risk stratification after an initial therapy for patients with IVIG resistance who received an initial single IVIG therapy (2 g/kg) with DUA.

2. MATERIALS AND METHODS

The institutional ethics committee of our hospital approved the study protocol and waived the requirement for patient consent owing to the retrospective nature of the study. This retrospective study included data on 50 consecutive pediatric patients with initial IVIG resistance (28 boys and 22 girls; mean age, 3 years and 2 months, ranging from 3 months to 12 years 4 months) who received an initial 2 g/kg of IVIG therapy with DUA for KD from January 2004 to April 2019 at our department (Figure 1). The clinical data on these patients were collected retrospectively, and were

divided into two groups: one for cases with rescue therapy for resistance (rescue group, n = 22); and another one for cases without rescue therapy (non-rescue group, n = 28) (Figure 1). The KD diagnoses were established based on the Japanese criteria in the diagnostic guidelines for KD [24]. The data from patients with a first episode of KD were included and the data from patients who presented CAL prior to the therapy were excluded. Persistent fever during initial IVIG therapy was defined as axillary temperature at a consistent ≥37.5°C throughout IVIG treatment [11]. IVIG resistance was defined as fever that persisted or reappeared 24 h after the first-line treatment [3]. Defervescence was defined as a body temperature < 37.5 °C for 24 h, and the defervescence time was defined as the moment when the body temperature reached < 37.5 °C. The Egami score, a risk score for predicting IVIG resistance based on clinical findings such as age, days of illness, platelet count, alanine aminotransferase level, and C-reactive protein (CRP) level, was evaluated before the initial IVIG therapy [25]. The data on three variables including serum CRP, albumin levels, and neutrophil-to-lymphocyte ratio (NLR) were retrospectively extracted, and the ratios of each one, defined as the ratio of the values after and before the initial IVIG therapy were calculated. The NLR was defined as the ratio between the neutrophil and lymphocyte counts.

Initial therapy

During the study period, an initial single IVIG infusion of 2 g/kg, starting on day 5 of the illness, was used as first-line therapy, whenever possible. Between January 2004 and November 2017, anti-inflammatory drugs (aspirin or flurbiprofen) were initiated within 24 h after the end of the initial IVIG infusion. Aspirin was initiated at a dose of 30 mg/kg/day and decreased to 5−10 mg/kg/day once the patient became afebrile. Flurbiprofen was initiated at a dose of 3−5 mg/kg/day and decreased to 3 mg/kg/day once the patient became afebrile [19]. Each treating physician made a choice between aspirin and flurbiprofen after considering the patient's liver function and the risk of Reye syndrome during the influenza season. A regimen of initial IVIG therapy with delayed anti-inflammatory drug administration was used after 2004. Some patients received this therapy with delayed use of anti-inflammatory drugs between 2004 and 2008. The treating physicians chose between delayed use of anti-inflammatory drugs and concomitant use of anti-inflammatory drugs during this period. After 2009, all physicians prescribed initial IVIG therapy with delayed use of anti-inflammatory drugs for all patients until November 2017 [19, 22]. After December 2017, low-dose aspirin (5 mg/kg/day) was initiated on the 8th to 10th day of illness after completion of the IVIG infusion, including after the second therapy [23].

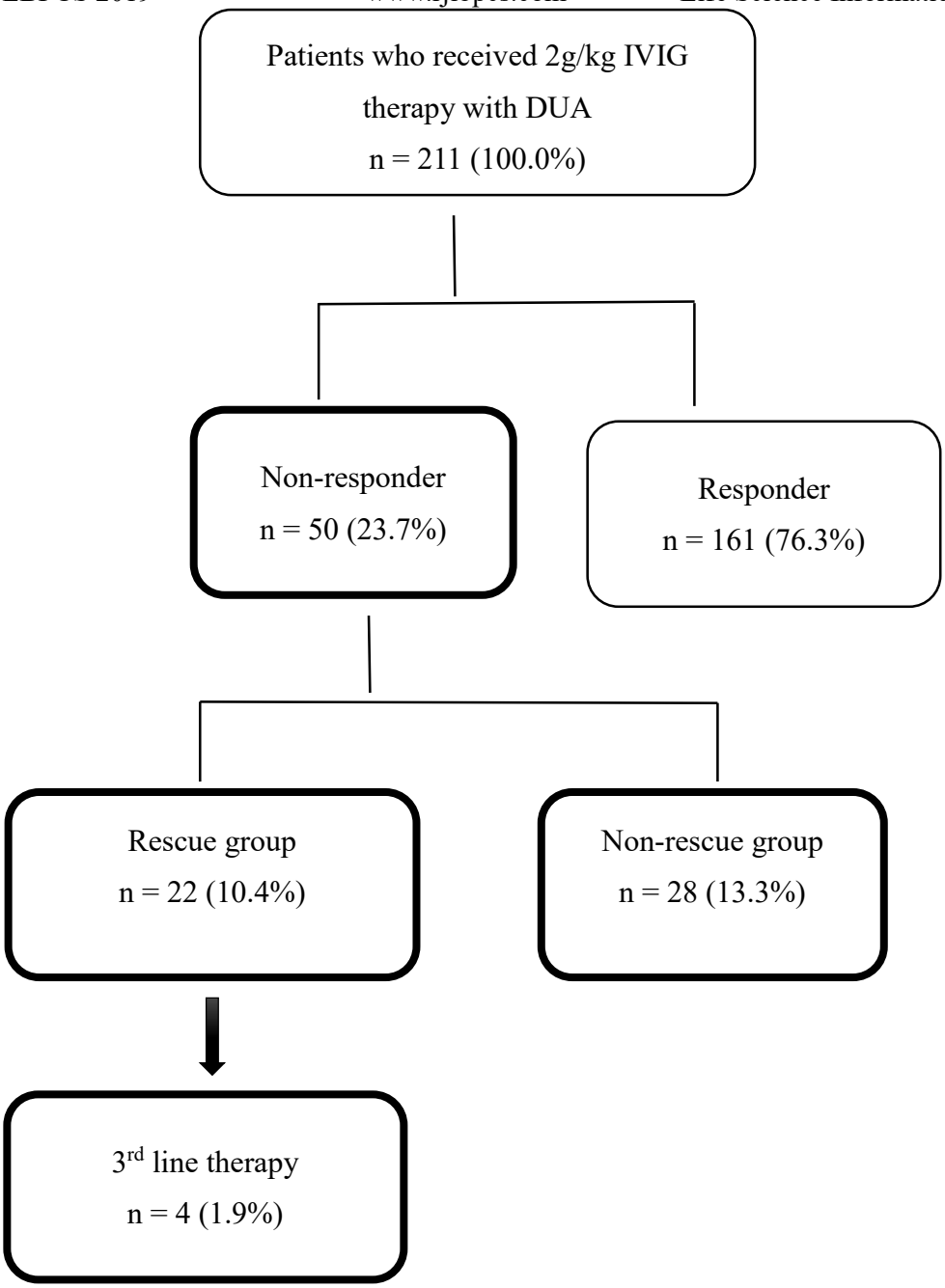

Figure 1. Clinical courses of the 211 patients who received 2g/kg IVIG with DUA

IVIG, intravenous immunoglobulin; DUA, delayed use of aspirin.

Rescue therapy

The decision to use rescue therapies in patients with resistance was made between 48 and 72 h after the completion of initial IVIG therapy. The decision was made comprehensively according to individual clinical variables that included body temperature, major KD symptoms, general condition, and laboratory data. The second-line therapy was rescue IVIG therapy at 2 g/kg, and the third-line therapy consisted of ulinastatin infusion, third IVIG therapy, or plasma exchange [23].

Diagnosis of CAL

CAL was diagnosed using echocardiography based on the Japanese criteria according to the study by Kobayashi et al [2]. CAL was diagnosed if any of the examinations showed an internal lumen

diameter ≥ 3 mm in a patient younger than 5 years or a diameter ≥ 4 mm in a patient older than 5 years, if the internal diameter of a segment was at least 1.5 times that of an adjacent segment, or if the lumen appeared irregular. Transient CAL was defined as the disappearance of CAL within 30 days of the illness.

Statistical analysis

Statistical analyses were performed using Stat Flex version 6 for Windows (Artech, Osaka, Japan). Chi-square, Fisher's exact, and Mann–Whitney U tests were used as appropriate, with sample size considerations. A value of $P < 0.05$ was considered statistically significant.

3. RESULTS AND DISCUSSION

Fifty patients among 211 patients (23.7 %) were resistant to the initial IVIG therapy with DUA (Figure 1). All 22 patients in the rescue group received a second round of 2 g/kg IVIG therapy. Four of 22 patients received the third-line therapy (plasma exchange for two, a third 2 g/kg IVIG therapy for one, and ulinastatin infusion for another one) (Figure 1). Three patients in the rescue group developed CALs (Table 1). Two of them developed medium sized CALs (5.3 and 4.8 mm maximal diameters) and one of them had a small CAL (3.6 mm maximal diameter) [23]. The small and medium-sized CAL of two of the patients regressed at 30 and 60 days post onset of illness. The selective coronary arteriogram one year after KD onset in the third patient with a medium-sized CAL revealed a solitary medium-sized aneurysm without stenosis in the mid-portion of the right coronary artery (Figure 2). None of the patients in the non-rescue group received rescue therapies for resistance. All of them recovered without further treatment. None of the patients in this group developed CALs (Table 2). Gender, age at onset, and the prevalence of incomplete type patients (those with fewer than five major symptoms of KD) were not significantly different between the two groups (Table 1). KD severity before initial IVIG therapy (as evaluated using the Egami score), rate of persistent fever during initial IVIG therapy, and fever duration were significantly different between the two groups (Table 1). The patients in the rescue group were more severely ill than those in the non-rescue group (Table 1). However, the rates of CAL were similar between the patients of the two groups (Table 1). The CRP and NLR values were similar and only the albumin levels were significantly different between the patients in the rescue and non-rescue groups before the initial IVIG therapy (Table 2). However, all these variables were significantly different between the two groups after the initial therapy (Table 2). Moreover, the CRP, albumin, and NLR ratios were all significantly different between the two groups at that point (Table 2). A CRP ratio cut-off value of 0.51 identified 95.5% of the patients in the rescue group and 67.9% of patients in the non-rescue group (Figure 3).

Table 1. Comparison of clinical findings between the rescue and non-rescue groups

Variables	Rescue group (n = 22)	Non-rescue group (n = 28)	P value
Gender (male)	11 (50.0%)	17 (60.7%)	0.449
Age (months)	28.0 (21.0-60.0)	34.0 (20.5-53.0)	0.784
Incomplete type	2 (9.1%)	4 (14.3%)	0.683
Egami score	3.0 (2.0-4.0)	2.0 (1.0-3.0)	0.004
Aspirin/Flurbiprofen			0.975
Low-dose aspirin	5 (22.7%)	3 (10.7%)	
Medium-dose aspirin	6 (27.3%)	13 (46.4%)	
Flurbiprofen	11 (50.0%)	12 (42.9%)	
Timing of initial IVIG therapy with regard to day of illness	5.0 (5.0-5.0)	5.0 (5.0-6.0)	0.012
Persistent fever during initial IVIG therapy	13 (59.1%)	4 (14.3%)	< 0.001
Defervescence: days of illness	10.0 (9.0-12.0)	8.0 (8.0-9.5)	< 0.001
Defervescence: days after initial IVIG therapy	5.0 (4.0-7.0)	3.0 (2.5-3.0)	< 0.001
CAL before 30 days of illness	3 (13.6%)	0 (0.0%)	0.079
CAL at 30th day of illness	2 (9.1%)	0 (0.0%)	0.189

Data are presented as n (%) or median (interquartile range).

IVIG, intravenous immunoglobulin; CAL, coronary artery lesions.

Incomplete type: patients with fewer than five major symptoms of Kawasaki disease.

Table 2. Laboratory findings comparison between the rescue and non-rescue groups

Variables	Rescue group (n = 22)	Non-rescue group (n = 28)	P value
Before initial IVIG therapy			
Sampling day of illness	5.0 (4.0-5.0)	5.0 (5.0-6.0)	0.019
CRP (mg/dL)	9.59 (5.93-15.50)	7.93 (5.80-10.40)	0.261
Albumin (g/dL)	3.20 (2.90-3.30)	3.35 (3.20-3.70)	0.009
NLR	5.58 (4.03-11.00) (n = 20)	4.52 (2.93-7.24) (n = 25)	0.089
After initial IVIG therapy			
Sampling day of illness	8.0 (8.0-8.0)	8.0 (8.0-9.0)	0.217
Days after initial IVIG therapy	3.0 (3.0-3.0)	3.0 (2.5-3.0)	0.504
CRP (mg/dL)	8.27 (5.05-22.97)	3.78 (1.75-5.09)	< 0.001
Albumin (g/dL)	2.45 (2.10-2.70)	2.90 (2.73-3.20) (n = 27)	< 0.001
NLR	3.80 (2.36-5.81) (n = 22)	1.29 (0.92-2.48) (n = 26)	< 0.001
CRP ratio	0.76 (0.64-1.15)	0.44 (0.30-0.54)	< 0.001
Albumin ratio	0.79 (0.72-0.84)	0.86 (0.79-0.93) (n = 27)	0.004
NLR ratio	0.60 (0.27-0.92) (n = 20)	0.28 (0.18-0.54) (n = 23)	0.045

Data are presented as median (interquartile range).

IVIG, intravenous immunoglobulin; CRP, C-reactive protein;

NLR, neutrophil-to-lymphocyte ratio; Ratio, the ratio of the values after/before initial IVIG therapy.

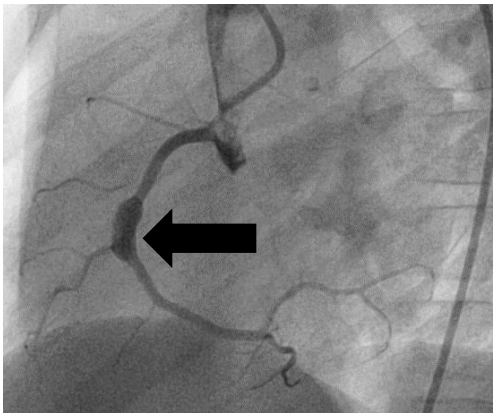

Figure 2. Selective coronary arteriogram one year after Kawasaki disease onset

The selective coronary arteriogram one year after Kawasaki disease onset in the patient with a medium-sized coronary artery lesion revealed a solitary medium-sized aneurysm without stenosis in the mid-portion of the right coronary artery (⬅).

DISCUSSION

This study showed that the patients with initial IVIG resistance belonged to two different subgroups (a rescue and non-rescue group), and that both the clinical findings (including the fever pattern during the initial IVIG therapy) and the laboratory findings after the initial therapy were significantly different. Moreover, a risk stratification after the initial therapy for IVIG-resistant patients was useful for KD coronary artery stenosis prevention and to identify patients not requiring rescue therapy (non-rescue group). Early identification of patients likely to develop IVIG resistance is a challenge [4-8]. On the other hand, identifying patients with initial IVIG resistance after the initial therapy is easier. This study showed that the differences in the clinical and laboratory findings between the patients in the rescue and the non-rescue groups were clearer during and after the initial therapy than they were before the initial therapy. The patients with initial IVIG resistance belonged to two different subgroups according to the severity of illness and risk stratification after the initial therapy, and this was useful for identifying the patients with initial IVIG resistance who did not require rescue therapy for resistance. Therefore, a risk stratification after initial IVIG therapy is appropriate for effective and safe rescue therapies. The Japanese guidelines for the acute-phase KD treatment recommended the initiation of rescue therapies 24 h after completion of the initial IVIG therapy [3]. However, a study showed that fever in the first 36 h following completion of initial IVIG therapy was not predictive of CALs and recommended refraining from rescue therapies until 36 h after completion of the initial IVIG therapy [26]. Another study defined IVIG resistance as that manifesting with persistent fever which failed to disappear within 48 h after completion of the initial IVIG therapy [27].

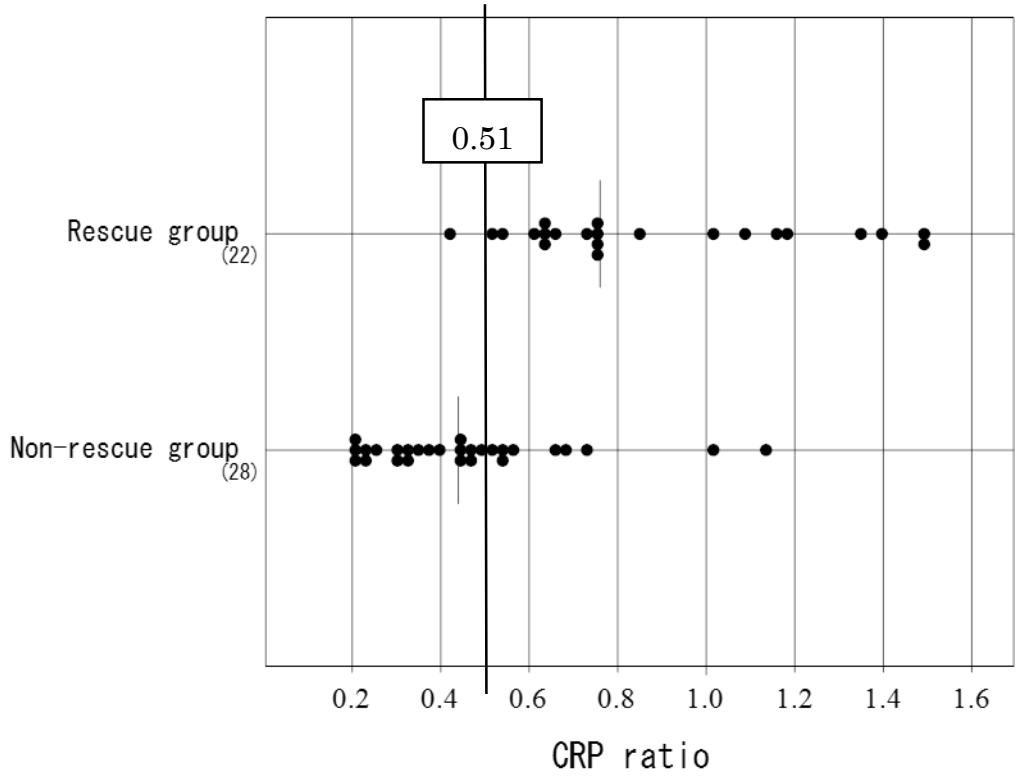

Figure 3. CRP ratio between the rescue and non-rescue group

A CRP ratio cut-off value of 0.51 identified 95.5% of the patients in the rescue group and 67.9% of patients in the non-rescue group. CRP ratio, the ratio of the C-reactive protein values after and before initial intravenous immunoglobulin therapy.

In this study, the 28 patients in the non-rescue group (56%) with IVIG resistance diagnosed 24 h after completion of the initial IVIG therapy with DUA did not develop CALs although they did not receive rescue therapies. Therefore, the rescue therapy at this time may lead to overtreatment. In the present study, the decision to use rescue therapies in resistant patients was made between 48 and 72 h after the initial IVIG therapy was completed. Both the favorable outcomes of the patients and the low frequency of the rescue therapies suggest that the decision and the timing were appropriate. Judicious use of IVIG therapies avoids unnecessary rescue therapy risk. IVIG, corticosteroids, infliximab, and plasma exchange have been applied as rescue therapies [3]. However, these therapies pose risks of anaphylaxis, possible CAL development, infusion-associated reactions, and shock, respectively [3, 28]. The 22nd nationwide KD survey in Japan showed that 16% of patients received rescue IVIG therapy for initial IVIG therapy resistance and that 3% had associated CALs after 30 days of illness [29]. In the present study, the rates of rescue IVIG therapy for initial IVIG therapy resistance and of CALs at 30 days of illness were 10.4 % (22/211) and 0.9% (2/211), respectively. Those findings suggest that the risk stratification after an initial therapy for patients with IVIG resistance is useful for CAL suppression and effective rescue therapy for resistant patients.

A study showed that rescue therapies, including plasma exchange before day 10, were useful for

preventing large KD CALs [30]. This finding was consistent with the clinical courses of the two patients who received plasma exchange in the present study. The rescue therapies, including plasma exchange before day 10, may prevent large KD CALs. A study on patients with KD, who were predicted to be unresponsive to IVIG and who received initial IVIG with concomitant medium-dose aspirin, showed that the incidence of CAL using the Japanese criteria was 31% [31]. The rate was significantly higher than that of the patients with IVIG resistance who received IVIG with DUA in this study; 31% [27/87] in that study [31] vs. 6% [3/50] in this study, $P < 0.001$. The use of IVIG therapy with DUA may be beneficial for suppressing CAL development and in order to prevent coronary artery stenosis in patients with KD [19, 23]. The delayed use of low-dose aspirin has been shown to reduce the incidence of large KD CALs [21]. The concomitant use of an anti-inflammatory drug may exert an inhibitory effect on the initial 2 g/kg IVIG therapy [22]. Thus, patients receiving an initial IVIG with delayed use of anti-inflammatory drugs may delay that inhibitory effect deemed adverse during the initial stages, and the combination order and timing of the initial IVIG therapy with anti-inflammatory drugs may be important to achieve the best outcome and inhibit CAL development [23]. The major goal of acute-phase KD treatment is prevention of large and stenotic CALs that may lead to myocardial ischemia. The cut-off values for CAL, within the first 100 days after the onset of KD leading to late-period stenotic lesions, have been defined as a diameter ≥ 6.1 mm in patients with a body surface area < 0.50 m^2, and as a diameter ≥ 8.0 mm in those patients with a body surface area ≥ 0.50 m^2 [32]. Three patients in the rescue group developed CALs, which posed no stenosis risks. The use of IVIG therapy with DUA may explain the favorable CAL outcomes in this study. The limitations of this study include the small number of the patients studied and the retrospective nature of the study.

4. CONCLUSION

The patients with initial IVIG resistance were assigned to two different subgroups according to resistance severity. The clinical findings (fever pattern during initial IVIG therapy) and the laboratory findings after the initial therapy were significantly different between the two groups. Moreover, a risk stratification after an initial therapy for IVIG resistance was useful for prevention of KD coronary artery stenosis and to identify patients who did not require rescue therapy for resistance.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this research are available within the article.

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CONFLICT OF INTEREST

None

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