

# Risk Factors of Resistance to Intravenous Immunoglobulin in patients with Kawasaki: A Cross-Sectional Study Over a 10 Year Period (2006-2016)

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## Abstract

**Introduction:** Kawasaki is an acute vasculitis and is the most common cause of acquired heart disease in children. About 25% of patients remain infected and febrile despite receiving intravenous immunoglobulin and aspirin. The aim of this study was to investigate the clinical and laboratory predictive resistance factors for intravenous immunoglobulin in patients with Kawasaki hospitalized in Khorramabad Shahid Madani Hospital.

**Materials and Methods:** Patients were divided into two groups: a) responders to IVIG treatment, consisting of 47 patients (90/4 %); and b) resistant to treatment, consisting of 5 patients (9.6%), and the difference between clinical manifestations and laboratory findings of the two groups were examined and the results were statistically analyzed.

**Results:** 52 patients with Kawasaki diagnosis were gauged. In the treatment-resistant group (9.6%), the number of clinical symptoms was lower than that of KAU diagnosis criteria, but this difference was not statistically significant between the two groups. Laboratory tests evaluation showed that the mean of ESR and CRP were higher in the treatment-resistant group and the mean of serum sodium in this group was lower than that of the responder group.

**Discussion and Conclusion:** High ESR and CRP and lower serum sodium levels can be considered as predictors of resistance to intravenous immunoglobulin therapy in patients with Kawasaki.

**Key words:** Kawasaki disease, immunoglobulin resistance, acute vasculitis

## Introduction

Kawasaki disease is a self-limiting acute vasculitis with unknown etiology and is more predominant in children younger than 4 years, which was first described in 1967 by Tomisacu Kawasaki (1).

Diagnosis of the disease is based on the presence of at least 5 findings out of the six following clinical findings: 1. Stable fever 2. Cutaneous rash 3. Organ changes including erythema, edema and flatulence, 4. Bilateral non-viral conjunctivitis 5. Oral mucosa and lips changes including redness and lips fissure 6. Lymphadenopathy (2). Although some sources characterize this disease by continuous fever for at least 5 days and 4 signs out of 5 other symptoms (3). Occasionally, patients do not have all the diagnostic criteria or they appear later which is known as Kawasaki latent or incomplete Kawasaki. These patients are about 15 to 36.2 percent of the infected and are beyond the defined age range (less than one year and more than 5 years) (5, 4). Kawasaki disease is the main cause of childhood acquired cardiac disease in developed countries (6).

Coronary artery aneurysm is the most important problem of the disease that occurs in 15-25% of untreated patients and can lead to myocardial infarction, sudden death, or ischemic heart disease in children (7,8). The risk in case of early onset of treatment by Intravenous immunoglobulin and aspirin will be reduced to 5% (9). Although this treatment reduces the fever and risk of cardiac problems, about 10-20% of the patients remain febrile even after receiving the suitable treatment (11) and these patients are most at risk for coronary arteries problems (11). Late cardiac manifestations are reported with Kawasaki cases, with symptoms other than fever not yet improving for more than a month from the onset of the disease (12).

Recent studies have described some of the demographic characteristics links and laboratory findings with a variety of resistant Kawasaki treatments. These factors include age, sex, duration of disease before treatment, abnormal Primary echocardiography, ESR, CRP, sodium, lactate dehydrogenase, hemoglobin, eosinophil, neutrophil, lymphocyte, liver transaminases and serum albumin (13, 14). Kobayashi et al. calculated 13 variables in patients with Kawasaki, including the duration of the disease before treatment, gender, age, the percentage of neutrophils, platelet count, transaminase (ALT, AST), total bilirubin, sodium, chlorine, total protein, albumin, and CRP. This retrospective study was performed on 546 patients to confirm the predictive accuracy of resistant cases in a prospective study conducted on 204 cases. Primary treatment of IVIG (2 g / kg) was prescribed aspirin and dipyridamole for two consecutive days, and patients who remained febrile after 24 hours were considered as resistant to treatment. In this study, IVIG resistance was considered interrelated to serum sodium less than 133 mmol / L, the duration of the disease before treatment less than 4 days, AST > 133, neutrophil < 80%, CRP < 10mg / dl, age less than 12 months and platelets less than 300,000

(15). In Japan, Kobayashi grading is used to predict drug-resistant cases and initiate oral prednisone with IVIG from the very beginning of the diagnosis (3). Although the study of Davis et al. stated that Kobayashi grading has not been promising in the prediction of resistant cases (16). The aim of this study was identifying the demographic, clinical and laboratory factors of Kawasaki resistant to treatment and to use alternative remedies or additional therapies to reduce the cost of treatment and lethal and enervating problems of the disease.

## Materials and Methods

This cross-sectional study included all the patients admitted to Shahid Madani Hospital of Khorramabad (West of Iran) with the diagnosis of Kawasaki over a ten year period from 2006 to 2016. The sampling method was census-based and at that time all patients were hospitalized with full Kawasaki (fever and 4 signs out of 5 disease symptoms), as well as atypical or incomplete cases of fever less than 5 days or with fewer symptoms were examined. Patients who did not register their demographic information, clinical findings during hospitalizing, the desired tests, or the course of the disease in their records were excluded. The patients were then divided into two groups, (A) responding to the first dose of intravenous immunoglobulin and aspirin, and (b) not responding to the first dose of intravenous immunoglobulin and aspirin, and demographic characteristics, clinical signs, laboratory findings such as complete blood cell count, liver transaminases (ALT, AST), serum sodium level, ESR and CRP and problems related to each of them were recorded and compared in two groups. The criterion for treatment response was fever breakdown at 48 hours after treatment. Data were examined using t-test and chi-square tests. To determine the severity of the relationship, the odds ratio (OR) was calculated with a confidence interval of 90%.

## Findings

In total, 52 patients with final Kawasaki diagnosis were observed. 26 (50%) patients had the fever for more than 5 days and 17 patients (32.7%) with fever had 4 out of 5 signs of Kawasaki, and the other 35 patients (3 / 67%) were considered as incomplete or atypical Kawasaki. Out of 52 children with Kawasaki, 47 (90.4%) responded to the first dose of intravenous immunoglobulin (group A) and 5 children (9.6%) did not respond to initial treatment (group B).

35 (67.3%) patients were male and 17 (32.7%) were female. 30 male patients (85.7%) and all female patients responded to the first dose of intravenous immunoglobulin, but the frequency of gender distribution in the two groups was not statistically significant ( $P = 0.1$ ).

Most children responded to the first dose of intravenous immunoglobulin and all single-dose resistant children were in the age of 12-60 months. The age distribution of the two groups was not statistically significant ( $P = 0.29$ ) (Table 1)

**Table 1: Frequency Distribution of age in two groups**

Studied groups	Age				P-Value
	Under 12 months	60-12 months	over 60 months	Total	
	N (%)	N (%)	N (%)	N (%)	
Receiving 1 dose of IVIG	7 (14.9)	31 (66)	9 (19.1)	47 (100)	0.29
Receiving more than 1 dose of IVIG	0 (0)	5 (100)	0 (0)	5 (100)	

The mean weight of children receiving the intravenous immunoglobulin dose was between  $15.5 \pm 5.2$  Kg and the mean weight of children resistant to treatment was  $14.2 \pm 1.48$  kg and based on t-test the difference was not statistically significant ( $P = 0/59$ )

Differences in the distribution of oral lesions, conjunctivitis, neck lymphadenopathy, edema and cutaneous rash were not statistically significant. (Table 2)

**Table 2: Frequency distribution of clinical symptoms on admission in two studied groups**

Clinical symptoms	Group A	Group B	P-Value
	Responding to treatment	No response to treatment	
	N (%)	N (%)	
Skin rash	27 (57.4)	4 (80)	0.32
Terminal lesions	19 (40.9)	33 (60)	0.4
Neck lymphadenopathy	21 (44)	2 (40)	0.84
Mucosal lesions	37 (78.7)	4 (80)	0.94
Conjunctivitis	33 (70.2)	4 (80)	0.66

33.3% of the respondents to the initial treatment with IV immunoglobulin had fever along with 4 other disease signs, while most of the resistant children to the treatment had 3 symptoms, but according to Fisher's exact test, the difference in the number of symptoms associated with fever on admission between the two groups was not statistically significant ( $P = 0.04$ ) (Table 3)

**Table 3: Frequency distribution of the number of symptoms associated with fever on admission in studied groups**

Studied groups	The number of symptoms associated with the fever on admission					P-Value
	1 sign	2 signs	3 signs	4 signs	Total	
	N (%)	N (%)	N (%)	N (%)	N (%)	
Receiving 1 dose of IVIG	2 (4.4)	14 (31.1)	14 (31.1)	15 (33.3)	45 (100)	0.4
Receiving more than 1 dose of IVIG	0 (0)	0 (0)	3 (60)	2 (40)	5 (100)	

Indicator type	Hb (g/dl) $\mu \pm SD$	Hct (%) $\mu \pm SD$	ESR (mm/hr) $\mu \pm SD$	CRP (g/dl) $\mu \pm SD$	ALT (IU/L) $\mu \pm SD$	AST (IU/L) $\mu \pm SD$	WBC ( $\times 10^3/\mu$ ) $\mu \pm SD$	Pit ( $\times 10^3/\mu$ ) $\mu \pm SD$	Na (meq/l) $\mu \pm SD$	PMN (%) $\mu \pm SD$	Lymph (%) $\mu \pm SD$
Responding to 1 dose of IVIG	10.6 $\pm$ 1.39	31.4 $\pm$ 3.6	82.5 $\pm$ 31.2	1.26 $\pm$ 0.99	48.2 $\pm$ 65.97	45.3 $\pm$ 53.1	487149 $\pm$ 16167	487149 $\pm$ 185344	13.9 $\pm$ 5.2	59.1 $\pm$ 15.1	40.1 $\pm$ 15.2
Resistance to 1 dose of IVIG	10.3 $\pm$ 0.72	31.2 $\pm$ 1.8	10.3 $\pm$ 10.3	2.25 $\pm$ 0.5	31.8 $\pm$ 18.3	30.4 $\pm$ 6.7	30860 $\pm$ 36910	483600 $\pm$ 126074	129.2 $\pm$ 3.5	62.4 $\pm$ 13.8	37 $\pm$ 14.4
T statistics	0.45	0.12	-3.18	-3.44	0.55	0.62	-0.95	0.042	3.26	0.46	0.43
P Value	0.65	0.89	0.002	0.017	0.2	0.079	0.39	0.95	0.017	0.63	0.66

**Table 4: The Comparison of mean and standard deviation of laboratory indices in the two groups**

In comparing the laboratory indices between the two groups, the results showed that there was no significant difference between the mean values of hemoglobin and hematocrit percentage, liver enzymes, the number of leukocytes, the percentage of polymorphonuclears and lymphocytes and the number of platelets in the two groups.

Nevertheless, the mean values of ESR (P = 0.002) and CRP (P = 0.011) in the group resistant to the first dose of intravenous immunoglobulin was higher than that of the responder group, and this difference was statistically significant based on t-test. Also, the difference in serum sodium levels was statistically significant on the basis of t-test between the two groups (p = 0.017) (Table 4 - left).

In four responder patients (8.9%) to the first dose of intravenous immunoglobulin a heart disease was recorded; this rate was 60% in children who were resistant to treatment and this difference was statistically significant based on t-test (P = 0/002) (Table 5).

**Table 5: Frequency Distribution of cardiac complication possibility in the studied groups**

Studied group	Cardiac Complication			P-Value
	Has	Has not	Total	
	N (%)	N (%)	N (%)	
Receiving 1 dose IVIG	4 (8.9)	41 (91.1)	45 (100)	0.002
Receiving more than 1 dose IVIG	3 (60)	2 (40)	5 (100)	

\* Type of test: T test

## Discussion and Conclusion

Kawasaki disease is an engaging vasculitis in multiple organs, of unknown etiology and the main cause of acquired heart disease in developed countries (9).

Diagnosis is based on fever for more than 5 days and at least 4 out of the five main symptoms of the disease such as cutaneous rash, non-puerperal bilateral conjunctivitis, neck lymphadenopathy, oral mucosal lesions, and edema or scaling of the organs (8). Some patients may not have the necessary diagnostic criteria from the beginning, which are recognized as atypical or, preferably, incomplete Kawasaki, since many patients' symptoms will appear in the course of the disease or echocardiographic findings confirm the disease (3). Incomplete types are more common in children of lesser age, and their timely identification and treatment to prevent cardiac problems are essential. Distinct differential diagnoses include streptococcal infections, measles, rheumatoid arthritis, and drug reactions (16). Prescribing of an intravenous immunoglobulin dose (2 g / kg) plus oral aspirin leads to improved symptoms and signs of disease and reduces the risk of cardiac problems from 20% to about 5% (17). Unfortunately, about 10-20% of patients do not respond to classical treatment and need recurrence doses or other treatments (18).

These patients are classified as resistant to intravenous immunoglobulins. These patients are at greater risk for heart problems (19). Identifying predictive factors for treatment-resistant types, considering other treatments or the probability of problems occurrence will allow them to be treated in a timely manner. Therefore, this study was conducted to identify these factors.

In this study, demographic factors including age, sex, weight, and laboratory and clinical symptoms were compared in the two groups of responders to the first dose of intravenous immunoglobulin (A) and non-responders to the first dose of intravenous immunoglobulin (B).

A total of 52 patients were diagnosed with Kawasaki's final diagnosis. 47 (90.4%) patients responded to intravenous immunoglobulin (group A), and 5 patients (9.6%) remained febrile 48 hours after receiving treatment and were classified as resistant (group B). There was no significant difference in age, sex, and weight between the two groups A and B.

In a study conducted by Sungho et al., 51 patients were evaluated, 33 of whom responded to treatment with IVIG (64.7%) and 13 patients (35.3%) classified in the treatment-resistant group. The percentage of people resistant to treatment in this study was higher than our study. In the study of Sungho et al., there was no significant difference between the two groups in terms of gender and age (10). In another study conducted by Young and colleagues on 82 Kawasaki patients, 16 (19.5%) patients were resistant to treatment, and here as well there was no difference in terms of sex, age and weight between the responders and those who were resistant to treatment (9).

In our study, due to the low number of patients, especially the cases resistant to treatment comparing to Sungho et al. and Tremoulet et al. were lack of high sensitivity concerning other studies (10, 11).

In our study, there was no significant difference in the amount of hemoglobin, hematocrit, liver transaminases, and the number of leukocytes and neutrophils and lymphocytes in the liver.

In the study of Sundel et al. and Wallace et al., there was no difference in the demographic characteristics and clinical manifestations in the two groups while hospitalized (20, 23). In the Sungho study, laboratory tests were administered on two groups and compared to the time of admission and after IVIG. Hemoglobin, hematocrit, albumin, ESR, and the number of blood leukocytes were not significantly different between the two groups, while the percentage of polymorphonuclears (PMNs) and bilirubin and AST in the resistant group were significantly higher, and albumin and platelet count in the resistant group were significantly low. After prescription of IVIG, hemoglobin and hematocrit values, total protein and albumin were lower in the resistant group, and the number of leukocytes, the percentage of PMNs, ESR and total and direct bilirubin in the resistant group were higher and there was not a significant difference in the levels of transaminases and CRP (10).

In our study, the mean values of hemoglobin, hematocrit, liver transaminases, the number of leukocytes and platelets, and the percentage of poly-Moreno cells and blood lymphocytes were not significantly different in the two groups.

Though, the mean values of ESR ( $P = 0.002$ ) and CRP ( $P = 0.017$ ) were significantly higher in the treatment-resistant group. Correspondingly, mean serum sodium was lower in the treatment-resistant group ( $P = 0.017$ ). Serum albumin and bilirubin value were not included in our study due to the lack of record values in the files. Also in our study, laboratory tests were considered when the patients were hospitalized since none of the patients had not undergone laboratory tests again after receiving IVIG. In the study of Uehara et al., the relationship between high hepatic transaminases and the incidence of cardiac problems in patients with Kawasaki has been described (22). In the study of Sungho et al., the high levels of transaminases were associated with resistant varieties and Kawasaki referral, but in our study, there was no relationship between the level of liver transaminases and treatment resistance.

Tetsuya et al. have reported high levels of bilirubin, transaminases of the liver, and CRP as independent predictors of resistance to IVIG (25). In our study, there was a correlation between high CRP level and treatment resistance. Bilirubin values were not recorded in the files and liver transaminases were not included in predictor factors. In our study, the percentage of cardiac problems in the treatment-resistant group was significantly higher than the response group ( $p = 0.002$ ) (Table 5).

In a study conducted by Uehara et al., the incidence of cardiac problems was significantly higher in the IVIG-resistant group. In this study, male gender, the onset of treatment before the fifth day of the disease and recurrence of the disease were also known as factors related to resistance to IVIG (26). Although in the study of Taraguchi et al., there was no significant difference in the incidence of cardiac problems in patients who were resistant to primary treatment with IVIG and prednisolone treatment (24). In sum, in a large number of studies, some of the demographic and laboratory factors such as low age, the onset of treatment before the fifth day of the disease (which may indicate the severity of the disease), low platelet levels, sodium and albumin levels, raised liver transaminases, and Neutrophils were also associated with resistance to treatment and the incidence of cardiac problems (25). Further studies are needed to define the diagnostic criteria for incomplete Kawasaki type to initiate timely treatment (25). Currently, the recommended dose for Kawasaki disease is high doses of intravenous immunoglobulin and aspirin, but in the case of primary resistance cases, a second dose of intravenous immunoglobulin is also prescribed. Considering the predictive factors for treatment resistance, the second dose of intravenous immunoglobulin may be avoided due to its high cost and other adjunctive treatments.

Sonoda et al. have considered plasma replacement with infliximab prescription as effective factors in reducing the symptoms of patients who have been resistant to the second dose of intravenous administration of IVIG (28). In our study, high levels of ESR and CRP and low sodium levels were recognized as predictive factors for treatment resistance. Among the limitations of this study, we can point out the inadequacies of the records, which led to the elimination of a number of patients from the study and consequently the small size of samples. These deficiencies included the incompleteness of the cases' summary, the miscarriage to record the results of experiments, the absence of infection course, and the lack of patients' following up in terms of echocardiographic findings.

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