Risk factors of intravenous immunoglobulin resistance and coronary arterial lesions in Turkish children with Kawasaki disease

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ABSTRACT

Kawasaki disease (KD) is the most common cause of childhood coronary artery disease. The incidence of coronary artery lesions (CALs) has declined with the routine use of intravenous immunoglobulin (IVIG) treatment, but there is still considerable risk for resistance to IVIG treatment and development of CALs. The present study was aimed to determine the risk factors in Turkish children with IVIG resistant KD and coronary artery involvement. Clinical, laboratory and echocardiographic data were retrospectively analyzed in 94 Kawasaki patients. IVIG resistant and responsive groups were compared. The IVIG resistant group had a higher rate of CALs compared to the IVIG responsive group (p<0.05). Duration of fever ≥ 9.5 days, C-reactive protein (CRP) ≥ 88 mg/L and Neutrophil/lymphocyte ratio (NLR) ≥1.69 were the best cutoff values for predicting IVIG resistance before treatment. The criteria for at least two of these three predictors were considered to be statistically significant risk factors for detecting IVIG resistance in KD before treatment (76.47% sensitivity, 71.05% specificity and 95% CI were 50.1-93.19% and 59.51-80.89%, respectively). Based on the clinical and laboratory features, we established a new risk-scoring system for predicting IVIG resistance in a cohort of Turkish children with KD. This may be useful for choosing optimal treatment for KD to prevent coronary artery involvement.

Key words: Kawasaki disease, IVIG resistance, risk score.

Kawasaki disease (KD) is an acute, systemic, febrile vasculitis that occurs during infancy and is the most common cause of childhood coronary artery disease.[1] Although, its etiology has not been definitively determined, recent studies have focused on the increased inflammatory cytokines in KD pathology.[2-4] The clinical features include an existence of fever persisting more than five days with mucocutaneous and lymphatic manifestations that are commonly self-limiting. However, the most serious complication is the coronary artery involvement that can be mortal. With the routine use of intravenous immunoglobulin (IVIG) treatment, the incidence of coronary artery lesions (CALs) has declined from 23% to 8%.[5] On the other hand, some patients are at risk for resistance to IVIG treatment and development of CALs.[6] In Turkey, KD was reported as the second most common type of vasculitis in a nationwide study by Ozen et al.[7], despite the real prevalence being unknown. Previous studies about KD from Turkey reported higher prevalence of coronary arterial involvement than Japanese children based studies.[8-12]

Many studies have previously been conducted about the risk factors of KD, and patients with atypical age presentation, elevated acute phase reactants and liver function tests were reported as high risk.[10-12] The Japanese-based risk scoring systems such as that by Kobayashi, Egami, and Sano was reported as inadequate for fully determining the risks for IVIG resistance and CALs in Western populations living in North

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America, Israel and the UK.[13-15] We had a similar concern, when we tried to estimate the risk of IVIG resistance using the Japanese risk scoring systems for our patients in Turkey. The sensitivity and specificity were 17.65% and 92.11% for Egami[10], 40.00% and 89.66% for Kobayashi[11], and 40.00% and 94.44% for Sano[12], regarding our patients. Also, a recent paper by Yang et al.[16] had a different scoring system for Chinese children with KD. We also evaluated our patients using the related score, and found the sensitivity and specificity as 43.75% and 80.43%, respectively. These scoring systems have limited predictive capacity for IVIG resistance of KD in Turkish children.

The present study was aimed to determine the risk factors in Turkish children with IVIG resistant KD and coronary artery involvement for early effective treatment.

Material and Methods

This study was approved by Dokuz Eylul University Non-Interventional Research Ethics Committee (2018/21-07, 02.08.2018).

Subjects and Definitions of KD: This retrospective study was performed by reviewing the medical records of 94 Kawasaki patients who had received IVIG treatment in a tertiary center between 1996 and 2018. Patients were diagnosed with following six major clinical signs: i) fever persisting for five or more days (≥38.0 °C); ii) bilateral conjunctival congestion; iii) changes of the lips and oral cavity; iv) polymorphous exanthema; v) changes of peripheral extremities; and vi) acute non-purulent cervical lymphadenopathy.[17] Complete KD (cKD) was diagnosed when subjects had at least five of the six clinical signs, and incomplete KD (iKD) was defined as having four or fewer major signs, with or without cardiac lesions.[18] Laboratory findings including leukocytosis, anemia, elevation of erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), elevated alanine aminotransferase (ALT) levels, and sterile pyuria were considered while diagnosing iKD. According to these definitions, patients were classified as 61 cKD and 33 iKD. Demographic data including age and sex, and clinical information such as the duration of fever before IVIG treatment were noted.

Treatment and Definition of IVIG Resistance

All patients were treated with IVIG (2 gr/kg) and high dose acetyl salicylic acid (80-100 mg/kg/day). The IVIG resistance was defined as persistent fever (≥ 38.0 °C) 48 hours after administration of initial dose of IVIG.[19] Second dose of IVIG was given to IVIG resistant patients, and high dose steroids (IV methyl prednisolone 30 mg/kg dose) were administered in patients who were resistant to recurrent IVIG treatments.

Laboratory Assessment

Hemogram parameters such as white blood cell count (WBC), absolute neutrophil count (Neu), absolute lymphocyte count (Lym), hemoglobin count (Hb), absolute platelet count (Plt), mean platelet volumes (MPV), and acute phase reactants such as CRP and ESR were recorded prior to the IVIG treatment and 48-hours following the treatment. In addition, biochemical parameters such as serum albumin (Alb) and total bilirubin (T-bil), liver function tests (LFT), and electrolyte levels of sodium (Na^+), potassium (K^+) and calcium (Ca^{++}) were noted. Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratios (PLR) were calculated from the available data. The difference between the assessments related to ESR, CRP and WBC values were recorded as delta values (ΔWBC, ΔESR and ΔCRP).

Echocardiographic Assessment and Definition of CALs

Echocardiographic assessment was performed on all patients at the time of diagnosis and in the subacute phase (two weeks after IVIG). Coronary artery involvement was determined in 31 patients (33%) before initial IVIG treatment. Coronary artery lesions were

listed as perivascular echogenicity, ectasia/ dilatation and aneurysm, according to severity. Perivascular echogenicity was defined as echogenicity of pericoronary tissue minus blood pool. Coronary artery ectasia and dilatation were defined if the internal diameter was up to 1.5 times that of the adjacent coronary artery, and as presenting a luminal dilatation up to 3 mm in children under the age of 5 years or 4.0 mm in children 5 years of age or older. Coronary artery aneurysms were defined and classified according to the criteria established by the Japanese Ministry of Health and Welfare guidelines as follows: Small aneurysm: localized dilatation showing an inner diameter ≤ 4 mm (in children ≥5 years: the internal diameter of a segment < 1.5 times compared to an adjacent segment). Medium aneurysm: aneurysm showing an inner diameter > 4 mm and < 8 mm (in children ≥5 years: the internal diameter of a segment 1.5~ 4 times compared to an adjacent segment). Giant aneurysm: aneurysm showing an internal diameter ≥ 8 mm (in children ≥5 years: the internal diameter of a segment > 4 times compared to an adjacent segment).[20] The CALs were sorted according to this severity classification such that perivascular echogenicity 19.35%, ectasia and dilatation in coronary arteries 61.30% and coronary artery aneurysms 19.35%.

Statistical Analysis

Statistical analysis was performed using SPSS 20 software. Chi-square or Fisher's exact test (when expected count was below 5 in any of the cells) was used to compare categorical variables. Shapiro-Wilk test was performed to evaluate homogeneity of the values. Homogeneously distributed values were presented as mean±SD and heterogeneously distributed values were presented as median and interquartile ranges (25%-75%). Homogenous values were estimated by one-way ANOVA and independent T-test, while heterogeneous values were tested by nonparametric tests. Variables having statistically significant differences among

groups were evaluated by receiver operating characteristic (ROC) curves to determine the optimal cut-off values, and relevant odds ratios (OR) were calculated. *p*<0.05 was considered as statistically significant.

Results

Of the 94 patients included in the study, 55 (58.5%) were male and 39 (41.5%) were female and the ratio was 1.41. The median age at the time of diagnosis was 35 (19-52)* months. CALs were observed at echocardiographic evaluation in 31 patients (33%). Seventeen patients (18.1%) were IVIG resistant. 61 patients were evaluated as cKD (64.9%) and 33 patients as iKD (35.1%). No statistically significant difference was found between complete and iKD groups in terms of age, gender, laboratory and echocardiographic data (Table I).

Risk Factors and Predictive Tools for IVIG Resistance

The IVIG resistant group had a higher duration of fever before treatment, and a higher rate of CALs compared to the IVIG responsive group (p<0.05). There was no significant difference in the distribution of severity of coronary artery lesions between groups (Table I).

When two groups were compared prior to IVIG, neutrophil/lymphocyte ratio (NLR) and CRP parameters were statistically higher in the IVIG resistant group. Also in the same group, other inflammatory markers such as ESR, and Neu count were found to be higher, and Hb and Lym count values were lower than the IVIG responsive group (p>0.05). In further evaluations two days following initial IVIG administration, NLR values were still found to be statistically higher in the IVIG-resistant group; while the Lym count, Na, K, and Ca values were statistically lower (Table II). There was no significant difference between the two groups in terms of delta values including ΔWBC, ΔESR and ΔCRP.

Table I. Comparison of demographic, clinic and echocardiographic data between IVIG responsive and IVIG resistant groups.

	Parameters	IVIG responsive n= 77 (81.9%)	IVIG resistant n=17 (18.1%)	p value
Age	months	34 (21-54) *	36 (12-49) *	0.426
Gender	male/female	1.40	1.42	0.572
Clinic Type	(complete/incomplete)	1.75	2.4	0.466
Duration of fever before IVIG	days	7 (6-10) *	10 (7-20) *	0.039
CALs		21 (45.7%)	10 (54.4%)	0.009
Perivascular echogenicity		4 (5.2%)	2 (11.8%)	0.208
Coronary ectasia /dilatation		13 (35.3%)	6 (16.9%)	0.191
Aneurism		4 (5.2%)	2 (11.8%)	0.208

p<0.05, *median (25%-75%)
IVIG: intravenous immunglobulin, CALs: coronary artery lesions

The predictive value of the variables before initial IVIG treatment revealed duration of fever (*p*=0.039), CRP (*p*=0.017) and NLR (*p*=0.029) as independent predictors of resistance to treatment for KD. ROC curves applied to each variable revealed cut-off values as; duration of fever≥9.5 days, CRP≥88 mg/L and NLR ≥1.69. The criteria for at least two of the three predictors were considered to be statistically significant risk factors for detecting IVIG resistance in KD before treatment (76.47% sensitivity, 71.05% specificity and 95% confidence intervals were 50.1-93.19% and 59.51-80.89%, respectively). The predictive values and OR of each parameters are shown in Table III, and related ROC-curve is presented in Figure 1.
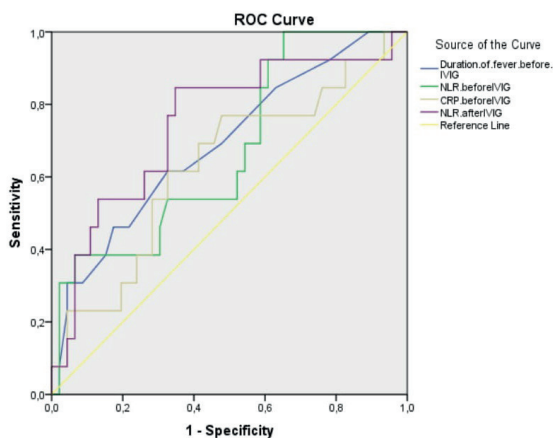
Risk Factors and Predictive Values of Coronary Arterial Lesions

Regarding demographic-clinical data and echocardiographic findings, increased duration of fever prior to IVIG treatment, and IVIG resistance were found as significant determiners in patients with CALs (p <0.05) (Table IV).

Regarding the laboratory parameters, no statistically significant risk factor for coronary artery involvement was detected prior to IVIG treatment. On the other hand, after first IVIG treatment, lower hemoglobin and higher Plt were determined to increase the risk of CALs (p<0.05) (mean Hb count was 10.2±1.5 gr/dL and median Plt count was 583 (409-706) x10³/uL in

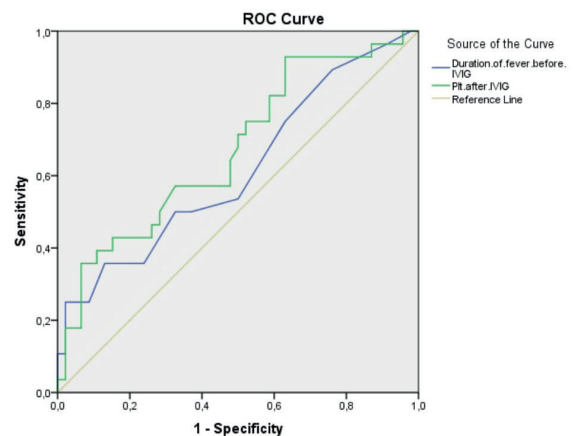**Fig. 1.** ROC-curve of the factors for predicting IVIG resistance.

Fig. 2. ROC-curve of the factors for predicting CALs.

Table II. Comparison of laboratory values between IVIG responsive and IVIG resistant groups. Evaluation of before and after IVIG values.

Parameters		Before IVIG			2 Days After IVIG		
		IVIG response n= 77 (81.9%)	IVIG resistant n=17 (18.1%)	P value	IVIG response n= 77 (81.9%)	IVIG resistant n=17 (18.1%)	P value
Hb	g/dL	11.2 ±1.5**	10.6 ±1.3**	0.109	10.98 ±1.29**	10.18 ±1.59**	0.047
WBC	10³/uL	14.75 ±6.15**	15.08 ±5.95**	0.838	10.4 (8.0-12.5) *	11.6 (7.0-15.1) *	0.671
Plt	10³/uL	395 (325-514) *	352 (284-649) *	0.551	458 (387-641) *	397 (298-502) *	0.064
Neu	10³/uL	8.2 (4.3-13) *	9.87 (7-15) *	0.065	4.4 (3.3-7.2) *	5.65 (3.80-10.20) *	0.191
Lym	10³/uL	3.6 (2.6-5.5) *	3.0 (1.6-3.82) *	0.137	4.40 (3.40-6.20) *	3.60 (2.50-4.50) *	0.045
NLR	Neu/Lym	1.69 (0.74-3.32) *	3.0 (2.0-7.13) *	0.029	1.07 (0.53-1.78) *	1.79 (1.27-3.38) *	0.023
PLR	Plt/Lym	101.76 (80.36-157.04) *	122.15 (98.89-361.11) *	0.097	104.56 (78.65-153.18) *	101.32 (80.67-161.36) *	0.774
MPV	fL	7.3 (6.7-8.0) *	7.9 (7.9-8.1) *	0.068	7.3 (6.9-7.7) *	7.7 (7.4-8.3) *	0.197
CRP	mg/L	54.50 (23.30-116.55) *	108.20 (86.0-158.0) *	0.017	13.3 (5.0-25.0) *	25.5 (4.0-84.3) *	0.191
ESH	mm/h	58 (38-82) *	73 (49-102) *	0.155	65.89±39.76**	72 ± 48.16**	0.239
ALT	U/L	25 (15-44) *	31 (24-59) *	0.173	26 (17-37) *	20 (12-121) *	0.954
AST	U/L	30 (21-43) *	25 (17-45) *	0.468	33 (19-42) *	29 (20-59) *	0.440
T. bil	mg/dL	0.32 (0.20-0.61) *	021 (0.20-1.00) *	0.946	0.30 (0.19-0.41) *	0.29 (0.20-0.80) *	0.571
Alb	g/dL	3.8 (3.4-4.1) *	3.7 (3.1-4.2) *	0.525	3.6 (3.4-3.9) *	3.5 (3.2-3.6) *	0.153
Na	mmol/L	137 (135-139) *	135 (132-137) *	0.066	138.04 ± 3.23**	135.64 ± 2.09**	0.012
K	mmol/L	4.47 ± 0.59**	4.48 ± 0.17**	0.428	4.68 ±0.59**	4.00 ± 0.64**	0.001
Ca	mg/dL	9.38 ± 0.07**	9.16 ± 0.17**	0.426	9.44 ± 0.56**	8.99 ± 0.58**	0.023

p <0.05, *Median (25%-75%), **Mean ± Standard deviation
Hb: hemoglobin, WBC: White blood cell, Plt: platelet count, Neu: absolute neutrophil count, Lym absolute lymphocyte count, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, MPV: mean platelet volume, CRP: C reactive protein, ESH: erythrocyte sedimentation rate, AST: aspartate aminotransferase, ALT: alanine aminotransferase, T. bil: total bilirubin, Alb: albumin, Na: sodium, K: potassium, Ca: calcium.

Table III. ROC analyses and odds ratios for best cut-off values of variables for predicting IVIG resistance before treatment.

Variable	Value	Sensitivity	Specificity	Discriminative ability	Odds ratio
Duration of fever before IVIG	9.5 days	58.8%	72.7%	0.667±0.080 (95% CI: 0.510-0.824, p=0.032)	3.809 (95% CI: 1.28-11.31, p=0.016)
CRP before IVIG	88.0 mg/L	70.0%	64.7%	0.669±0.076 (95% CI: 0.520–0.817, p=0.032)	4.40 (95% CI: 1.38-13.97 p=0.012)
NLR before IVIG	1.69	93.3%	43.4%	0.679±0.070 (95% CI: 0.541–0.817, p=0.031)	4.40 (95% CI: 1.38-13.97 p=0.012)

p<0.05
IVIG: intravenous immunglobulin, CRP: C-reactive protein, NLR: neutrophil/lymphocyte ratio

CALs (+) group, and 11.2±1.2 gr/dl and 453 (342-511) x10³/uL in CALs (-) group, respectively).

The predictive value of the variables revealed duration of fever before initial IVIG treatment (*p*=0.050) and Plt counts two days after IVIG treatment (*p*=0.014) as independent predictors of coronary artery involvement. ROC curves applied to each variable revealed cut-off values

Table IV. Comparison of demographic-clinical data and echocardiographic findings.

	Parameters	CALs (-) 67.01% (n=63)	CALs (+) 32.9% (n=31)			p value
			Perivascular echogenicity 19.35% (n=6)	Ectasia/ Dilatation 61.30% (n=19)	Aneurism 19.35% (n=6)	
Age	months	36 (27-57)*	29 (14-40)*	33 (16-54)*	23 (6-42)*	0.367
Gender	m/f	1.07	5	2.16	1	0.337
Clinic	(cKD/iKD)	1.54	2	3.75	5	0.413
Duration of fever before IVIG	days	7 (5-10)*a	13 (5-25)*b	8 (7-14)*b	21 (10-25)*b	0.050
IVIG resistance	%	12.5a	33.3b	31.6b	33.3b	0.021

p <0.05, *Median (25%-75%)

IVIG: intravenous immunglobulin, CALs: coronary artery lesions, iKD: incomplete Kawasaki disease, cKD: complete Kawasaki disease.

as; duration of fever ≥9.5 days before IVIG, which had an OR 3.41 (51.6% sensitivity and 71.4% specificity), and Plt count after IVIG ≥ 670x10³/ uL which had an OR 5.5 (35.7% sensitivity and 95.3% specificity) for CALs. ROC-curve of the factors for predicting CALs is presented in Figure 2 for predicting CALs.

Discussion

Recent literature about KD in children reports better morbidity and mortality rates related with decreased incidence of coronary arterial disease. On the other hand, there is still a significant number of patients with IVIG resistance, and 15-25 % of them have CALs.[1,21] In the literature, there are many risk-scoring systems from different countries to predict IVIG resistance and CALs. However, using the same parameters for all countries is inadequate due to differences in genetic and environmental factors. There is no risk-scoring system of KD in Turkish children to the best of our knowledge. In the current study, we designed a risk-scoring system to predict IVIG resistant cases with 76.47% sensitivity, and 71.05% specificity.

Resistance to the initial IVIG treatment is a high-risk factor for CALs.[22] Kobayashi et al.[11] showed that each of the variables indicating IVIG resistance was also a risk factor for CALs. The current study determined the rate for developing CALs as 33%, and there was a positive correlation with IVIG resistance. The rate was similar to other Turkish studies, but more frequent than Japanese studies.[8-11,23]

Duration of fever before IVIG was found to be significantly higher in IVIG resistant and CALs (+) groups, in this study. This period was ≥ 9.5 days, which had an OR of 3.8 for IVIG resistance (58.8% sensitivity and 72.7% specificity) and 3.4 for CALs (51.6% sensitivity and 71.4% specificity). On the other hand, Egami[10] and Kobayashi's[11] risk scoring systems reported early administration of IVIG to be a strong predictor for IVIG resistance and coronary artery involvement. They defined fever ≤ 4 days before IVIG as a risk factor. They speculated that, patients who were earlier diagnosed and treated were probably sicker and had greater inflammation. However, Chantashiriwan et al.[24] reported duration of fever ≥ 8 days before IVIG as a predictor of coronary artery aneurism, similar with our results. Also, Gulhan et al.[22] suggested administrating initial IVIG treatment within 7 days of illness to prevent cardiac complications. We considered that delayed diagnosis and treatment may cause prolonged inflammation of vessel walls before IVIG treatment, which may create a high risk for IVIG resistance and CALs.

In the literature, CRP ≥ 100 mg/L (Kobayashi et al.[11]) and ≥ 70 mg/L (Sano et al[12]) was defined as a risk factor for IVIG resistance. Regarding IVIG resistant cases which had higher CRP values, we compared the related values with IVIG resistant and IVIG responsive groups in the current study. CRP values ≥ 88 mg/L had an OR 4.4 (70% sensitivity and 64.7% specificity) for IVIG resistance. In a recent study, Yang et al.[16] reported this cut-off value as 90 mg/L, which was similar to our results.

Studies about prognostic factors of many infectious and inflammatory disorders suggested that instead of WBC count, using absolute neutrophil and lymphocyte counts (Neu and Lym) and neutrophil/lymphocyte ratio (NLR) might be more predictive for IVIG resistance in KD.[25-27] Zahorec et al.[27] reported that higher Neu and NLR with lower Lym were associated with severe inflammatory response. Kawamura et al.[28] reported that NLR value before IVIG ≥3.83 and one day after IVIG ≥1.27 were the best cut-off values for predicting IVIG resistance. Similarly, a study by H-J Cho et al.[29] reported that higher NLR values before initial IVIG treatment were associated with increased risk for IVIG resistance and lower NLR changes before and 2 days after IVIG were a predictive tool for coronary artery abnormalities. In current study, we reported best cut-off values of NLR value for IVIG resistance as NLR ≥1.69 before IVIG which had an OR of 4.40 (93.3% sensitivity and 43.4% specificity) and ≥1.25 two days after IVIG which had an OR of 11.29 (85.7% sensitivity and 65% specificity) for IVIG resistance.

Increased pro-inflammatory cytokines stimulate megakaryocyte proliferation leading to an increase in platelet counts. Plt during the acute phase tend to decrease in patients with severe KD.[30] Egami[10] and Kobayashi[11] speculated

that it might be related with intravascular consumption, reflecting greater inflammation. They also stated that Plt ≤300x10³/mm³ was a predictor for IVIG resistance. We found no statistically significant difference in the IVIG resistant group. Patients had lower Plt both before and after IVIG. However, Plt two days after first IVIG was ≥ 670x10³ /uL (OR: 15.5) in CALs (+) group, which was significantly higher than CALs (-) group. This cut-off value had a 35.7% sensitivity and 93.5% specificity.

Hyponatremia has been associated with increased vascular permeability and inappropriate antidiuretic hormone secretion due to increased inflammatory cytokine levels, in the course of KD.[31] Sodium values under 133 mmol/L and 135 mmol/L was defined as a risk factor for Kobayashi[11] and Yang[16], respectively. In our study, lower sodium levels were detected in the IVIG resistant group, both before and after IVIG treatment, without significance.

This study defined three criteria for IVIG resistance in KD prior to treatment: Duration of fever before IVIG ≥ 9.5 days, CRP ≥ 88 mg/L and NLR value ≥ 1.69. Following initial therapy with IVIG, if NLR value was ≥ 1.25, it also predicted ongoing IVIG resistance, possibly implying a need for steroid therapy instead of IVIG.

In summary, based on the clinical and laboratory features, we established a new risk-scoring system for predicting IVIG resistance in KD. This may be useful for choosing optimal treatment for KD before coronary artery involvement. Our findings should be supported by multicenter studies in Turkey.

Acknowledgement

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