Usefulness of Kawasaki disease risk scoring systems to the Turkish population

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Abstract

Objective: Kawasaki disease (KD) is the most common cause of coronary artery aneurysm (CAA) in children. The available risk scores to predict intravenous immunoglobulin (IVIG) resistance and CAA were developed in Asian populations in whom their effectiveness has been proven, but data on non-Asian children are limited. This study aimed to evaluate the ability of 5 risk scoring systems to predict IVIG resistance and CAA in Turkey patients with KD.

Methods: Patients with KD were retrospectively evaluated with clinical, laboratory, and echocardiographic findings. Data analyses were performed in 5 scoring systems (Harada, Kobayashi, Egami, Formosa, and Sano).

Results: A total of 259 patients (Male:Female, 1.7) were treated for KD in our hospital. The mean age of diagnosis in patients with KD, CAA, and IVIG resistance were 3.31, 2.19, and 2.06, respectively. CAA development and IVIG resistance were seen in 11.6% and 12.3% of cases, respectively. IVIG resistance was detected in 35.6% of patients with CAA. In our study, 5 risk scoring systems were applied to our patients. ROC analysis results were found highest in Kobayashi scoring system for IVIG resistance (AUC, 0.864) and in Harada scoring system for CAA development (AUC, 0.727).

Conclusion: Harada score was significant in predicting CAA risk, and Kobayashi score was significant in predicting the risk of developing IVIG resistance. It is necessary to determine more specific and sensitive risk scores that increase the risk of IVIG resistance and the development of CAA in Turkey. *(Anatol J Cardiol 2020; 24: 97-106)*

Keywords: Kawasaki disease, coronary aneurysm, IVIG resistance, Kobayashi, Harada

Introduction

Kawasaki disease (KD) is an acute febrile systemic vasculitis that mostly affects children <5 years of age, characterized by fever, bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rashes, and cervical lymphadenopathy (1-3).

About 15%–25% of patients with untreated KD develop coronary artery lesions (CALs), such as aneurysms or ectasia (3). KD can cause myocarditis and arrhythmias in the acute phase, and myocardial infarction and cardiac death due to coronary artery aneurysms (CAAs) and stenosis in the subacute and chronic phases. KD is considered an important health problem, and early diagnosis and treatment significantly reduce the risk of complications, morbidity, and mortality with coronary artery disease (1-4).

Complications that may develop due to coronary artery involvement are the most important factor affecting the morbidity of the disease in the long term. Therefore, some scientists have developed risk scores for KD that predict the development of CAAs and resistance to intravenous immunoglobulin (IVIG) treatment (5-12). Thus, we aimed to predict which patient will develop IVIG resistance and which patient will have coronary involvement and to select patients for the use of aggressive treatment methods in addition to standard primary therapy.

The best-known KD risk scores are the Harada (HS), Kobayashi (KS), Egami (ES), Formosa (FS), and Sano (SS) risk scores, and most of them are used in the Asian population (5, 9-12). Scoring

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system criteria are based on different combinations of clinical and laboratory data. When the scores were tested in different countries, the scores yielded different sensitivities and specificities; these differences were explained by ethnic variability in the populations (Table 1) (7, 13, 14).

This study aimed to determine the power and accuracy of scoring systems to predict high-risk patients in Turkey using our patients' recorded data. In addition, predictions were made for possible new scoring system criteria specific to Turkey by comparing comprehensive clinical and laboratory findings.

Methods

Between 2010 and 2019, a total of 259 patients were hospitalized and treated in our hospital with a diagnosis of KD according to the American Heart Association (AHA) guidelines [male (M), 162; female (F), 97; M:F, 1.7]. Our hospital is a reference center that accepts patients from all regions of the country. Our patients in the study have demographic characteristics that represent the Turkish population.

There are 2 types of KD diagnosis: typical KD (classic type/complete KD) and atypical KD (incomplete KD) (2). Complete (typical) KD is defined as the presence of ≥5 days of fever and ≥4 of the 5 principal clinical features (2). Incomplete (atypical) KD is defined as prolonged unexplained fever, <4 of the 5 principal clinical findings, and compatible laboratory or echocardiographic findings (2). Studies evaluating incomplete KD diagnostic algorithm first proposed in 2004 guidelines suggested its usefulness in identifying patients requiring treatment and in preventing CAAs (2, 3, 15). The study protocol was approved by the Local Ethics Committee and informed parental consent was obtained for all infants.

Gender, age at the time of diagnosis, presence of diagnostic criteria, number of days with fever, and personal and family histories were recorded. Laboratory findings included hemogram parameters, erythrocyte sedimentation rate (ESR), acute phase reactants [C-reactive protein (CRP), procalcitonin, and ferritin], electrolytes (Na, K, Cl, Ca, Mg, and P), kidney and liver function tests (ALT, AST, GGT, LDH, albumin, ALP, total and direct bilirubin, urea, creatinine, and uric acid), lipid profile (total cholesterol, LDL, HDL, and triglycerides), coagulation parameters (PT, aPTT, and INR), urinalysis, and hemoculture.

All data were obtained from clinical and laboratory findings recorded at the time of diagnosis and echocardiographic examinations obtained at diagnosis and follow-up. Twenty-six cases with missing file data or with a diagnosis other than KD were excluded from the study at the beginning.

The patients had an echocardiographic examination at the time of diagnosis and in the subacute period for the presence of coronary involvement and risk of complications. Myocardial wall mobility, ejection fraction (%), diameters of coronary arteries, and z-scores (calculated according to AHA guidelines) were recorded. The following findings were indicated by the z-score calculation: dilation, z-score 2 to <2.5 or if initially <2 and a decrease in z-score during follow-up ≥1; small aneurysm, z-score 2.5 to <5; moderate aneurysm, z-score 5 to <10; and large or giant aneurysm, z-score ≥10 (2). 2D, M mode, CW, and PW Doppler examinations were performed by the same pediatric cardiologist. A Vivid S5 echocardiogram device with GE 3S and 6S probes (General Medical Electric Systems, Milwaukee, WI, USA) was used.

All patients were treated with high-dose IVIG (2 g/kg) as a single infusion according to the AHA criteria; 21 patients with KD who developed recrudescent or persistent fever received IVIG at a dose of 1 g/kg. Acetylsalicylic acid (ASA) was administered every 6 hours with a total daily dose of 80–100 mg/kg/day for 1–2 weeks. When high-dose ASA was discontinued, low-dose ASA (3–5 mg/kg/day) was initiated and continued for 6–8 weeks (2). IVIG resistance was defined as recurrent or persistent fever at least 36 hours after the end of IVIG infusion in 10%–20% of patients with KD (2, 16, 17).

Patients were grouped retrospectively as with and without CAAs and with response and resistance to IVIG treatment; 5 of the Japanese risk scoring systems were applied and comparisons were performed. KS, ES, and SS scores that predict resis-

Table 1. Differences among the clinical studies for 5 risk scoring systems

Clinical studies	Harada [7]	Kobayashi [5]	Egami [10]	Formosa [12]	Sano [11]
Year of publication	2014	2006	2006	2016	2007
Country	USA	Japan	Japan	Taiwan	Japan
Sample size	106 patients	750 patients	320 patients	248 patients	112 patients
Cutoff points	≥4 pts: high risk	≥4 pts: high risk	≥3 pts: high risk	≥3 pts: high risk	≥2 pts: high risk
Sensitivity	90%[a]	86%[b]	61%[a] 78%[b]	86%[b]	77%[b]
Specificity	51%[a]	68%[b]	81%[a] 76%[b]	81%[b]	86%[b]

[a]Referring to the identification of children at higher risk to develop coronary artery aneurysms
[b]Referring to the identification of children at higher risk to be nonresponders to the administration of intravenous immunoglobulin

tance to treatment in Japanese population and Farmosa score that predicts resistance to treatment in Taiwan population were studied in our population and in ethnic subgroups. HS scores (0 to 7 points) includes the presence of white blood cell count >12000/mm^3 (1 point), platelet count <35.10^4/mm^3 (1 point), CRP >3 mg/dL (1 point), hematocrit <35% (1 point), albumin <3.5 g/dL (1 point), age ≤12 months (1 point), and male sex (1 point) with cutoff value ≥4 (7). KS score (0 to 11 points) includes sodium level ≤133 mmol/L (2 points), illness days ≤4 days (2 points), aspartate aminotransferase (AST) level ≥100 IU/L (2 points), neutrophil count ≥80% (2 points), CRP level ≥10 mg/dL (1 point), age ≤12 months (1 point), and platelet count ≤30.10^4 IU/L (1 point) with cutoff value ≥4 points (5). ES score (0 to 6 points) includes age at diagnosis <6 months (1 point), illness days <4 days (1 point), CRP level ≥8 mg/dL (1 point), alanine aminotransferase (ALT) level ≥80 IU/L (2 points), and platelet count <30.10^4 IU/L (1 point) with cutoff value ≥3 (10). FS score (0 to 4) includes the presence of lymphadenopathy (1 point), neutrophil count ≥60% (2 points), and albumin <3.5 g/dL (1 point) with cutoff value ≥3 (12). SS score (0 to 3) includes CRP level ≥7 mg/dL (1 point), total bilirubin ≥0.9 mg/dL (1 point), and AST level ≥200 IU/L with cutoff value ≥2 (Table 2) (11).

Statistical analysis

IBM SPSS Statistics for Mac (version 24.0; IBM Corp., Armonk, NY, USA) was used for statistical analyses. Categorical variables were summarized using frequencies (%). Continuous variables were expressed as mean±standard deviation. Normality was assessed for continuous data using the Kolmogorov–Smirnov test. Student's t-test and Mann-Whitney U tests for continuous data and χ^2 test for categorical data were used to compare variables between groups. P<0.05 was considered statistically significant. Results and significance values are summarized in the relevant tables.

Results

A total of 259 patients (M, 162; F, 97; M:F, 1.7) with KD were treated in our hospital. The age range was 3 months to 9.8 years. The frequency of clinical findings were as follows: changes in the lips and oral mucosa (79%), polymorphic rash (69%), conjunctivitis (65%), changes in the extremities (54%), and cervical lymphadenopathy (48%). According to the diagnostic criteria, 31% were treated as typical KD and 69% as atypical KD. The frequencies of clinical findings in diagnostic types are summarized in Table 3.

In our study, CALs were noted in 45 patients. Coronary ectasia/dilation was detected in only 15 patients [5.8% (z-score to 2<2.5)] and the coronaries were completely normal in 214 patients (82.6%). CAA development and IVIG resistance occurred in 11.6% (n=30) and 12.3% (n=32) of cases, respectively.

The mean age at the time of diagnosis of KD, CAA, and IVIG resistance was 3.31, 2.19, and 2.06 years, respectively. IVIG resistance was more common in infants and hospitalization times were longer in this group. Coronary involvement rate in our patients was 17.3%. CAA development occurred in 12.8% of the IVIG-responsive group and 50% in the IVIG-resistant group. Involving with the right coronary artery (RCA) only affected 20% of cases, left coronary artery (LCA) affected 44.5%, and RCA and LCA together affected 35.5%. In the patient group in which the left coronary artery (LCA) was involved with the left main coronary artery (LMCA), 20 cases were affected, the left anterior descending artery (LAD) affected 9 cases (45%), the left circumflex artery (LCx) affected 2 cases (10%), and the LAD and LCx together affected 2 cases (10%). Of the patients with coronary artery involvement, 53.3% were <1 year of age and 83.3% were <5 years of age. IVIG resistance was detected in 35.6% of patients with CAAs.

In our study, the HS, KS, ES, FS, and SS risk scoring systems were analyzed. These risk score values were calculated for all patients. The results were compared in the 2 groups according to CAA development and IVIG treatment response.

The frequencies of criteria in the whole patient group and in both subgroups were summarized in Table 2. The levels of statistical significance of the observed differences were presented (Table 2). Especially when the scoring criteria were evaluated independently for both variables (IVIG resistance vs CAA development), those with significant differences were observed: leukocytosis (HS), being in the infant age group (<6 and/or <12 months) (HS, KS, ES), and white blood cell to leukocyte ratio ≥80% (in KS). The criteria that were significant in predicting IVIG resistance were hyponatremia (≤133 mmol/L) (KS) and hematocrit <35% (HS). The only criterion found more frequently significant in the CAA group was serum AST ≥200 IU/L (SS). However, although p values of thrombocytopenia (HS, KS, ES) and lymphadenopathy criteria (FS) were <0.05, CAA did not make a positive contribution to scoring because it was seen at a lower frequency in developing patients (Table 2). Some scoring criteria were found to negatively affect the predictive power of the scores. The most notable among these was the CRP level criterion, which took place in 4 different scoring (HS, KS, ES, and SS). The fact that the cutoff value presented for CRP in these criteria was very low negatively affected the specificity of 4 scores (Table 2).

Sensitivity, specificity, positive and negative predictive values, and statistical significance are summarized in Table 4 with respect to CAA development and Table 5 with respect to IVIG response. Based on these analyses, combining the sensitivity and specificity did not predict high-risk patients in any scoring system; however, sensitivity predicted the IVIG resistance using KS (84.4%) and the risk of CAA using HS (83.3%).

All patients were treated with standard primary therapy, IVIG, and ASA. ASA was discontinued in 29 patients (11%) due to salicylic acid poisoning. Two patients were given pulse steroid therapy, 8 patients needed intensive care, and 1 patient was treated with plasmapheresis.

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Table 2. Scoring criteria and frequencies in patients

Risk score	Criterion	Frequencies of occurrence				
		All patients n=259 % (n)	IVIG nonresponders n=32 % (n)	P_1[a]	CAA (+) n=30 % (n)	P_2[a]
Harada						
	White blood cell count >12000/mm^3	61.4% (159)	84.4% (27)	**0.004**	86.7% (26)	**0.003**
	Platelet count <350000/mm^3	42.1% (109)	46.9% (15)	0.558	20% (6)	**0.009**
	C-reactive protein >3 mg/dL	99.2% (257)	100% (32)	0.595	100% (30)	0.608
	Hematocrit <35%	73.4% (190)	93.8% (30)	**0.005**	86.7% (26)	0.080
	Albumin <3.5 g/dL	25.9% (67)	18.8% (6)	0.327	33.3% (10)	0.322
	Age ≤12 months	18.5% (48)	46.9% (15)	**<0.001**	53.3% (16)	**<0.001**
	Male sex	62.5% (162)	65.6% (21)	0.701	73.3% (22)	0.195
Kobayashi						
	Na ≤133 mmol/L*	25.5% (66)	43.8% (14)	**0.011**	26.7% (8)	0.874
	Disease duration at the start of treatment ≤4 days*	15.1% (39)	31.3% (10)	**0.006**	6.7% (2)	0.173
	AST ≥100 IU/L*	6.2% (16)	12.5% (4)	0.113	13.3% (4)	0.084
	Neutrophil to white cell ratio ≥80%*	17% (44)	37.5% (12)	**0.001**	33.3% (10)	**0.011**
	C-reactive protein ≥10 mg/dL	93.1% (241)	96.9% (31)	0.364	96.7% (29)	0.408
	Age ≤12 months	18.5% (48)	46.9% (15)	**<0.001**	53.3% (16)	**<0.001**
	Platelet count ≤300000/mm^3	32% (83)	34.4% (11)	0.763	10% (3)	**0.006**
Egami						
	Age <6 months	7.7% (20)	25% (8)	**<0.001**	33.3% (10)	**<0.001**
	Disease duration at the start of treatment <4 days	3.5% (9)	9.4% (3)	0.052	3.3% (1)	0.964
	C-reactive protein ≥8 mg/dL	94.6% (245)	96.9% (31)	0.543	96.7% (29)	0.594
	ALT ≥80 IU/L*	16.2% (42)	25% (8)	0.151	26.7% (8)	0.099
	Platelet count <300000/mm^3	31.7% (82)	34.4% (11)	0.725	10% (3)	**0.007**
Formosa						
	The presence of lymphadenopathy	47.9% (124)	43.8% (14)	0.618	16.7% (5)	**<0.001**
	Neutrophil to white cell ratio ≥60%*	52.9% (137)	59.4% (19)	0.434	53.3% (16)	0.959
	Albumin <3.5 g/dL	25.9% (67)	18.8% (6)	0.327	33.3% (10)	0.322
Sano						
	C-reactive protein ≥7 mg/dL	95.4% (247)	96.9% (31)	0.665	96.7% (29)	0.719
	Total bilirubin ≥0.9 mg/dL	3.5% (9)	6.3% (2)	0.361	3.3% (1)	0.964
	AST ≥200 IU/L	3.1% (8)	6.3% (2)	0.271	10% (3)	**0.020**

*Marked criteria scores are 2 points. Others are 1 point.
[a]The Mann-Whitney U test was used to compare differences between 2 independent groups. Values found significant are written in bold.
P_1, Significance value for predicting intravenous immunoglobulin resistance.
P_2, Significance value for predicting the development of coronary artery aneurysm

The patients were grouped and the response to IVIG treatment and development of CAA are shown in Table 6. Gender, age range, number of febrile days before admission, duration of hospitalization, and diagnosis types were compared. In our study, in the laboratory findings of the group in which CAAs were detected in patients with KD, leukocyte and platelet counts and CRP, troponin T, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were significantly increased, whereas albumin level was decreased.

The frequency of CAAs increased in IVIG-resistant patients, and the frequency of IVIG resistance increased in patients who developed CAA; this association was statistically significant

Table 3. Frequency of diagnosis criteria in patients

Clinical findings	Total (n=259) (%)	Typical KD (n=80) (%)	Incomplete KD (n=179) (%)
Changes of the lips and oral mucosa	**206 (79.5%)**	75 (93.8%)	131 (73.2%)
Conjunctival congestion	**168 (64.9%)**	70 (87.5%)	98 (54.7%)
Cervical lymphadenopathy	**124 (47.9%)**	57 (71.3%)	67 (37.4%)
Rash	**179 (69.1%)**	72 (90%)	107 (59.8%)
Peripheral extremity changes	**140 (54.1%)**	58 (72.5%)	82 (45.8%)

KD - Kawasaki disease

Table 4. Analysis results of Kawasaki risk scoring related to the development of coronary artery aneurysm

Scores	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	ROC curve (AUC)	*P* value
Harada	83.3	46.7	17	95.5	51	**0.727 (0.631–0.823)***	**<0.001**[a]
Kobayashi	30	74.7	13.4	89.1	69.5	0.582 (0.486–0.679)	0.103[a]
Egami	33.3	81.7	19.2	90.3	76.1	0.595 (0.483–0.706)	**0.015**[a]
Formosa	23.3	69	9	87.3	63.7	0.467 (0.353–0.58)	0.579[a]
Sano	10	95.2	21.4	89	85.3	0.559 (0.452–0.666)	0.063[a]

[a]Pearson chi-square analysis was used.
*Values found significant are written in bold.
AUC - area under the curve; CAA - coronary artery aneurysm; NPV - negative predictive value; PPV - positive predictive value; ROC - receiver operating characteristic

Table 5. IVIG resistance related analysis results of Kawasaki risk scoring

Scores	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	ROC curve (AUC)	*P* value
Harada	84.4	47.1	18.4	95.5	51.7	0.773 (0.685–0.861)	**0.001**[a]
Kobayashi	71.9	80.6	34.3	95.3	79.5	**0.864 (0.815–0.912)***	**<0.001**[a]
Egami	46.9	83.7	28.8	91.8	79.2	0.729 (0.633–0.824)	**<0.001**[a]
Formosa	40.6	71.4	16.7	89.5	67.6	0.589 (0.491–0.686)	0.166[a]
Sano	15.6	96	35.7	89	861	0.606 (0.504–0.709)	**0.006**[a]

[a]Pearson chi-square analysis was used.
*Values found significant are written in bold.
AUC - area under the curve; CAA - coronary artery aneurysm; IVIG - intravenous immunoglobulin; NPV - negative predictive value; PPV - positive predictive value; ROC - receiver operating characteristic

(p<0.001). In our study, IVIG resistance was detected in 12.3% of patients. When the group developing CAAs was examined, IVIG resistance was shown to be 46.9% in infants <1 year of age and IVIG resistance increased the length of hospital stay.

There was a statistically significant difference between age groups with respect to CAA development and IVIG resistance and no significant difference based on gender. There was a high risk of developing CAAs and IVIG resistance in infants (p<0.001). The laboratory findings of patients with KD were compared according to the presence of coronary artery involvement and IVIG resistance (Tables 7 and 8). When laboratory findings of patients with coronary artery involvement were examined, it was found that the hematocrit and total protein and albumin levels were decreased, while the leukocyte and platelet counts and CRP, troponin T, and NT-proBNP levels were increased.

Discussion

KD is an acute, self-limiting, systemic vascular inflammatory disorder that primarily affects the small arteries, especially the coronary arteries (18). CALs are the most severe complication of

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Table 6. Comparison of demographic and clinical data of patients

Variable	Development of CAA			IVIG responsiveness		
	Normal (n=229)	CAA (n=30)	*P* value	IVIG responders (n=227)	IVIG nonresponders (n=32)	*P* value
Sex						
Male	140 (86.4%)	22 (13.6%)	0.194[a]	141 (87%)	21 (13%)	0.701[a]
Female	89 (91.8%)	8 (8.2%)		86 (88.7%)	11 (11.3%)	
Age at diagnosis (months)	35.3 (1.3–118.8)[d]	8.5 (2.3–117.4)[d]	**<0.001**[b]	36.7 (1.9–118.8)[d]	13.4 (1.3–117.4)[d]	**0.002**[b]
Age group						
<1 year	32 (66.7%)	16 (33.3%)	**<0.001**[a, c]	33 (68.8%)	15 (31.2%)	**0.001**[a, c]
1≤ and <5 years	141 (94%)	9 (6%)		136 (90.7%)	14 (9.3%)	
≥5 years	56 (91.8%)	5 (8.2%)		58 (95.1%)	3 (4.9%)	
Total fever days	6 (1–20)[d]	6 (2–15)[d]	0.896[b]	5 (1–20)[d]	6 (1–20)[d]	0.174[b]
Hospitalization time	10 (3–35)[d]	13 (6–35)[d]	**0.003**[b]	10 (3–34)[d]	15 (5–35)[d]	**<0.028**[b]
Type of diagnosis						
Typical KD	80 (92%)	7 (8%)	0.206[a]	69 (79.3%)	18 (20.7%)	0.796[a]
Incomplete KD	149 (86.6%)	23 (13.4%)		134 (77.9%)	38 (22.1%)	
IVIG resistance frequency	16 (7%)	16 (53.3%)	**<0.001**[a]	-	- -	
Coronary involvement	-	-	-	29 (12.8%)	16 (50%)	**<0.001**[a]

[a]Pearson chi-square analysis was used.
[b]Mann-Whitney U test was used.
[c]Significant difference was observed in the <1 year age group.
"Median" and "lowest to highest values" in parentheses were specified for nonnormally distributed data.
CAA - coronary artery aneurysm; IVIG - intravenous immunoglobulin; KD - Kawasaki disease

KD, which develop in 15%–25% of patients with untreated KD (19, 20). In this study, the frequency of developing CALs in patients was 17.6% [CAAs (11.6%)+coronary dilation (6%)].

It is believed that administering large doses of immunoglobulin during the acute period can reduce the risk of damage to the coronary arteries. The risk of developing coronary artery disease in patients who respond to IVIG has been reported to be 19.6% (20). In this study, the risk of developing CALs who respond to IVIG was 12.8%. It is important to identify risk factors that increase the risk of developing CALs. Over the years, researchers have developed various scoring methods to predict the risk of complications and aggressive treatment in patients with KD (5, 9-12, 21).

All of the best-known risk scoring systems introduced for this purpose were developed by the Japanese, the first of which was the HS system which was introduced in 1991 (sensitivity=90%) (9). Few scoring models to predict the risk of CAA have been formulated (12, 19, 21). The risk of CALs has been evaluated using 5 scoring systems in our study. Indeed, the HS system was the most sensitive scoring (83.3%) in predicting the risk of coronary artery involvement.

Between 10% and 20% of patients with KD have persistent or recurrent fever after primary therapy with IVIG plus ASA (2, 22, 23). Because the probability of coronary artery damage associated with IVIG-resistant KD is higher than IVIG-sensitive KD, the probability of damage to the coronary arteries would decrease, as well as the cost and hospitalization time, if patients with IVIG-resistant KD can be detected and appropriately treated before additional IVIG treatment (24).

Researchers have focused on improving the recognition of early predictors of IVIG resistance with the hope of developing risk scoring algorithms and estimating the probability of a successful response to IVIG (6). Son et al. (22) reported that 13%–21% of KD patients were resistant to IVIG. The prediction of IVIG resistance has also been evaluated using 5 more recent risk scores.

This study aimed to determine the appropriate risk score by defining the clinical features and laboratory factors that predict IVIG-resistant KD in Turkey. We found that the rate of developing IVIG resistance was 12.3%. Of IVIG-resistant patients, 46.9% were <1 year of age, the number of febrile days and the length of hospital stay were significantly longer than IVIG-sensitive patients, and 50% of patients had coronary artery involvement.

Scoring system criteria are a combination of clinical and laboratory data. KD has no specific diagnostic laboratory mark-

Table 7. Central tendency and variability measures of laboratory data according to coronary involvement

Variable	Normal (n=214)	Coronary involvement (n=45)	*P* value
Sedimentation	67.35 (27.47)[c]	66.64 (28.86)	0.880[a]
WBC	13 000 (1 000–49 570)[d]	14 950 (5 290–36 800)[d]	**0.002**[b]
NEU (%)	61.74 (16.88)[c]	59.70 (19.12)[c]	0.504[a]
Hb	10.54 (1.42)[c]	10.08 (1.58)[c]	0.065[a]
Hematocrit	32.19 (4.14)[c]	30.65 (4.47)[c]	**0.032**[a]
PLT	374 000 (51 000–2 099 000)[d]	482 000 (162 000–1 395 000)[d]	**0.001**[b]
CRP	67.9 (1–417.4)[d]	93.5 (3.1–369)[d]	**0.044**[b]
Total protein	7.1 (1.16)[c]	6.53 (0.8)[c]	**0.001**[a]
Albumin	3.68 (0.51)[c]	3.49 (0.46)[c]	**0.037**[a]
AST	34 (4–628)[d]	38 (15.3–1 230)[d]	0.642[b]
ALT	24 (4–705)[d]	26 (8–704)[d]	0.307[b]
Na	135.03 (3.25)[c]	135.33 (3.23)[c]	0.591[a]
K	4.46 (0.59)[c]	4.76 (0.75)[c]	**0.020**[a]
Urea	18 (1–95)[d]	14 (1–57)[d]	**0.003**[b]
Creatinine	0.3 (0.09–1.03)[d]	0.27 (0.13–0.8)[d]	**0.006**[b]
Troponin	0.003 (0.003–0.03)[d]	0.007 (0.003–0.127)[d]	**0.034**[b]
NT-proBNP	241 (55–35 000)[d]	1 248 (196–35 000)[d]	**0.016**[b]
INR	1.06 (0.76–3.78)[d]	1.13 (0.87–2.33)[d]	0.176[b]

[a]Independent sample t-test was used from parametric tests.
[b]Mann-Whitney U test was used from nonparametric tests.
[c]"Average" and "standard deviation" values in parentheses were specified for normally distributed data.
[d]"Median" and "lowest to highest values" in parentheses were specified for nonnormally distributed data.
ALT - alanine transaminase; AST - aspartate aminotransferase; CRP - C-reactive protein; Hb - hemoglobin; INR - international normalized ratio; K - potassium; Na - sodium; NEU (%) - neutrophil to leukocyte ratio; PLT - platelet count; NT-proBNP -N-terminal pro-B-type natriuretic peptide; WBC - white blood cell

ers. Recent studies have investigated factors for predicting IVIG resistance and CAL development (12-14, 17, 19, 21). These data include duration of fever, polymorphonuclear neutrophil (PMN) cell count, hemoglobin concentration, platelet count, and CRP, transaminase, total bilirubin, NT-proBNP, albumin, and sodium levels (19).

Inflammatory parameters can facilitate confirmation of a clinical diagnosis of KD, but none are pathognomonic of KD. Elevation of acute phase reactants, such as ESR, neutrophil to white cell ratio, and CRP, is nearly universal; the degree of elevation of ESR and CRP may be discrepant. CRP normalizes more quickly than ESR during resolution of inflammation.

Myocardial involvement in acute KD is universal from histologic and functional perspectives; hence, the role of NT-proBNP as a potential biomarker has been extensively studied (25, 26). Kim et al. (27) described cardiac troponin I (cTnI) in relation to KD and showed a significant increase in cTnI level in the acute stage of KD.

The cause of hyponatremia is still unknown in patients with KD. Lim et al. (28) found that there is a strong negative correlation between the level of serum sodium and inflammatory factors, including CRP and interleukin-6 (IL-6) in children with KD. The most probable pathophysiologic mechanism underlying hyponatremia is the nonosmotic secretion of antidiuretic hormone (ADH). It has been confirmed that IL-6 and tumor necrosis factor-alpha (TNF-α) promote ADH release during inflammation (29). IL-6, TNF-α, and other cytokines participate in inflammation of KD patients in the acute phase (30), suggesting that hyponatremia may be associated with the inappropriate release of ADH. The marked increase in plasma IL-6 and TNF-α in IVIG-resistant infants compared with IVIG-responsive patients (31, 32) may explain the significant hyponatremia in IVIG nonresponders. In our study, it was observed that hyponatremia and hypoalbuminemia correlated with an increase in acute phase reactants in IVIG-resistant patients (33-37).

Thrombocytosis was detected in patients with CAL and IVIG resistance in our study. This increase was statistically significant in CAL patients. Although some studies have recognized both thrombocytopenia and significant thrombocytosis as predictors of CAAs or IVIG resistance (25, 38), another study showed no association (24). The exact mechanism underlying thrombocytosis is unclear. It has been suggested that elevated thrombopoietin level caused by acute inflammatory responses can lead to thrombocytopoiesis (25, 38).

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Table 8. Central tendency and variability measures of laboratory data according to IVIG resistance

Variable	Responders (n=227)	Nonresponders (n=32)	*P* value
Sedimentation	66.9 (27.18)[c]	69.44 (30.97)	0.629[a]
WBC	13 000 (1 000–49 570)[d]	18 000 (6 320–33 230)[d]	**<0.001[b]**
NEU (%)	60.62 (17.27)[c]	65.07 (17.55)[c]	0.190[a]
Hb	10.51 (2.08)[c]	10.07 (1.51)[c]	0.110[a]
Hematocrit	32.15 (4.23)[c]	30.38 (4.07)[c]	**0.029[a]**
PLT	399 000 (51 000–2 099 000)[d]	409 500 (195 000–1 356 000)[d]	0.621[b]
CRP	67 (1–417.4)[d]	107.2 (4.8–369)[d]	**0.015[b]**
Total Protein	7.03 (1.16)[c]	6.63 (0.89)[c]	0.183[a]
Albumin	3.65 (0.51)[c]	3.53 (0.45)[c]	0.298[a]
AST	34 (11–604)[d]	38.5 (4–1 230)[d]	0.245[b]
ALT	24 (4–527)[d]	35 (5–705)[d]	**0.033[b]**
Na	135.35 (3.18)[c]	133.83 (3.29)[c]	**0.010[a]**
K	4.48 (0.61)[c]	4.72 (0.73)[c]	0.051[a]
Urea	18 (1–95)[d]	16.5 (5–57)[d]	0.895[b]
Creatinine	0.3 (0.09–1.03)[d]	0.25 (0.16–0.8)[d]	**0.030[b]**
Troponin	0.005 (0.003–0.17)[d]	0.068 (0.008–0.127)[d]	**0.026[b]**
NT-proBNP	329 (55–35 000)[d]	19 792 (4584–35 000)[d]	**0.014[b]**
INR	1.02 (0.91–1.24)[d]	1.34 (1.18–1.49)[d]	0.105[b]

[a]Independent sample t-test was used from parametric tests.
[b]Mann-Whitney U test was used from nonparametric tests.
[c]"Average" and "standard deviation" values in parentheses were specified for normally distributed data.
[d]"Median" and "lowest to highest values" in parentheses were specified for nonnormally distributed data.
ALT - alanine transaminase; AST - aspartate aminotransferase; CRP - C-reactive protein; Hb - hemoglobin; INR - international normalized ratio; K - potassium; Na - sodium; NEU (%) - neutrophil to leukocyte ratio; PLT - platelet count; NT-proBNP - N-terminal pro-B-type natriuretic peptide; WBC - white blood cell

In this study, in laboratory findings of the group in which CAAs were detected in patients with KD, leukocyte and platelet counts and CRP, troponin T, and NT-proBNP levels were significantly increased, whereas albumin level was decreased.

Several previous studies have demonstrated that a higher percentage of PMNs and NT-proBNP, total bilirubin, CRP, AST, and ALT levels were considered predictive factors for KD patients resistant to IVIG treatment (19, 39-41).

Widely used risk scoring systems for predicting IVIG nonresponsiveness come from studies in Asian populations (5, 11, 24), which are based on demographic, clinical, and laboratory parameters. In these populations, the scores were effective in identifying KD patients who could benefit from additional anti-inflammatory therapy to reduce CALs. Risk scoring studies in the European region showing the risk of developing CAAs and IVIG resistance are limited (42-46).

In one study, patients who were resistant to KD treatment were evaluated with ES risk scoring. Of the 365 patients enrolled in the study, 71 (19.4%) were resistance to the treatment. It demonstrated the use of ES risk scoring in determining treatment resistance in Japanese children with KD. This scoring system may not show treatment resistance in KD children in Europe and the USA (43).

One Italian study showed that KS, ES, and FS systems were not effective screening tools to predict IVIG unresponsiveness or CALs among Italian patients with KD (21). Recently, in another study conducted in Germany, it was shown that KS, ES, and SS in the Caucasian population do not have a good prognostic value in demonstrating IVIG resistance (43). It was shown that only the SS score can be used to show the risk of developing CALs with low sensitivity 4 weeks after the onset of KD (43).

In cohort studies, Jakob et al. (43) and Sánchez-Manubens et al. (44) found that IVIG resistance and the risk of developing CAAs were not assessed with Asian risk scores in German and Spanish cohorts (95% of the German cohort and 81.1% of the Spanish cohort).

In an English study evaluating children of Caucasian origin diagnosed with KD, Asian risk factors were evaluated in assessing the risk of developing CAAs and IVIG resistance. It was determined that risk scoring was not sensitive enough to demonstrate the risk of developing IVIG resistance and CAAs (43).

Studies conducted in North America (45, 46), Midwestern USA (42), Spain (44), and the UK (13) evaluated risk scores in non-Japanese populations and demonstrated low sensitivity and specificity for the risk of developing IVIG resistance and CAAs.

In one recent study, the KS system was compared to ES and SS systems to show IVIG resistance in French children. Of 425 patients with KD, 55% were Caucasian, 12% were North African/Middle Eastern, 10% were African/Afro-Caribbean, 3% were Asian, and 11% were of mixed ethnic origin. Low performance was observed in all patients in whom Japanese risk scores were administered (sensitivity=14%–61%). Therefore, a new risk scoring with better sensitivity and acceptable specificity was applied in a non-Asian country with IVIG resistance (47).

In recent years, new scoring systems studies have been carried out due to insufficiency in the sensitivity and specificity of risk scoring systems in non-Asian populations. We believe that there is a need for new risk scoring studies in our country that will be more sensitive and sensitive.

Study limitations

Twenty-six cases with missing file data or with a diagnosis other than KD were excluded from the study at the beginning.

Conclusion

Turkish patients with KD are at higher risk of developing coronary complications. In our study, it was found that the sensitivity and specificity values showing coronary artery involvement and IVIG resistance were lower than acceptable normal values in 5 scoring systems; therefore, a more sensitive and specific scoring system specific to Turkey is needed.

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