Rheumatology International (2019) 39:1343–1349
https://doi.org/10.1007/s00296-019-04336-2

Rheumatology
INTERNATIONAL

COHORT STUDIES

The factors affecting the disease course in Kawasaki disease

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Received: 9 April 2019 / Accepted: 23 May 2019 / Published online: 28 May 2019

Abstract

The aim of this study was to review the characteristics of patients with Kawasaki disease (KD) from Turkey and to assess the performance of the Kobayashi score (KS), Harada score (HS), Formosa score (FS), Egami score (ES) and other parameters in predicting intravenous immunoglobulin (IVIG) resistance and coronary artery involvement (CAI) in the Turkish population. Patients who were diagnosed as being in the acute phase of KD at Hacettepe University Faculty of Medicine (Ankara, Turkey) between June 2007 and January 2016 reviewed retrospectively, and those between January 2016 and February 2018 reviewed prospectively, were included in this cohort study. A total of 100 patients with KD were included in this study. Statistical Package for Social Sciences for Windows 22.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Eighty-five patients (85%) responded to IVIG treatment, whereas 15 (5 female, 10 male) were IVIG resistant. CAI was detected in echocardiography at diagnosis in 31 (31%) (9 female; 22 male) patients. For predicting IVIG resistance, KS, ES, FS, and HS had sensitivity of 82.1%, 26.7%, 30.8%, 69.2% and specificity of 35.7%, 94%, 51.2%, 45.8%, respectively. For the association with CAI occurrence, the sensitivities were 17.2%, 3.3%, 35.7%, 70.4% and the specificities were 78.5%, 88.4%, 49.3%, 49.3% for the aforementioned scores, respectively. The multivariate analysis showed white blood cell (WBC) count [Odd's ratio (OR) 4.1; 95% confidence interval (CI) 1.26–13.23; $p=0.019$] and hematocrit (OR 3.8; 95% CI 1.15–12.4; $p=0.028$), as independent predictors of CAI while gamma-glutamyl transferase (GGT) level (OR 5.7; 95% CI 1.73–27.51; $p=0.018$) was detected as the only independent predictor of IVIG resistance. This is the first study from Turkey in KD to evaluate the association of the scoring systems for IVIG resistance and CAI. The risk scoring systems in KD did not predict the risk for IVIG resistance and were not associated with CAI in Turkish population.

Keywords Coronary artery aneurysm · Echocardiography · IVIG resistance · Kawasaki disease · Predictive score

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00296-019-04336-2) contains supplementary material, which is available to authorized users.

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Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CAI	Coronary artery involvement
CRP	C-reactive protein
ES	Egami score
ESR	Erythrocyte sedimentation rate
FS	Formosa score
GGT	Gamma-glutamyl transferase
HS	Harada score
IL	Interleukin
IVIG	Intravenous immunoglobulin
IQR	Interquartile range
KD	Kawasaki disease
KS	Kobayashi score
MP	Methylprednisolone
OR	Odd's ratio
ROC	Receiver operating characteristic
SPSS	Statistical Package for Social Sciences
WBC	White blood cell

Introduction

Kawasaki disease (KD) is one of the most common vasculitides of childhood [1, 2]. It is an arteritis associated with the mucocutaneous involvement predominantly affecting the medium- and small-sized arteries; mainly coronaries [3–5]. Coronary artery involvement (CAI) is the most important complication of the disease and the major cause of the mortality [1]. In the vast majority of patients, fever improves with the first intravenous immunoglobulin (IVIG) treatment [1]. However, studies have shown that 10–20% of patients continue to have fever after the first IVIG treatment and these patients are at high risk for CAI [6–8]. IVIG resistance is defined as persisting or recurring fever at least 36 h after the end of IVIG infusion [1]. Although there are some risk scoring systems, it is not always possible to predict the IVIG resistance and CAI. Egami score (ES) [9], Kobayashi score (KS) [10], Harada score (HS) [11], and Formosa score (FS) [12] have been used for predicting IVIG resistance and CAI. The items of these scores and high-risk definitions are summarized in Table 1. All of these scores have been formulated in studies including only Asian patients [13]. The sensitivities of these scores range between 78 and 86% and the specificity between 67 and 76% among Japanese population [13]. However, these scores did not perform well in non-Japanese populations [13–19].

The aim of this study was to analyze the characteristics of Turkish children with KD and to assess the association of the existing scores along with IVIG resistance and CAI in Turkish population.

Methods

Patients who were diagnosed as being in the acute phase of KD at Hacettepe University Faculty of Medicine, Ankara, Turkey were included in this study. The characteristics of the patients admitted between June 2007 and March 2016 were reviewed retrospectively while the patients admitted between March 2016 and February 2018 were evaluated prospectively.

The diagnosis of KD was made using the criteria of the American Heart Association [1]. According to this criteria set, a patient should have fever for at least 5 days, together with at least 4 of the five principal clinical features [changes in oral and pharyngeal mucosa, bilateral bulbar non-exudative conjunctival injection, skin rash, erythema and edema of the hands and feet, unilateral cervical lymphadenopathy (≥ 1.5 cm diameter)] to be diagnosed as having KD [1]. The patients were defined as being IVIG resistant if they had persistent or recrudescent fever at least 36 h after completion of the first IVIG infusion [1]. CAI was evaluated according to McCrindle *Z* score classification [1].

Clinical features, laboratory parameters, echocardiographic findings, response to IVIG treatment, and the KS, ES, FS, and HS were evaluated.

The study was approved by the ethics committee of Hacettepe University and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki (1964). All patients were anonymous. The parents signed a consent approving anonymous data use for academic purpose when the patients admitted to the hospital.

Statistical analysis

SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov–Smirnov) to determine whether or not they were normally distributed. Data were expressed as median (IQR) for continuous variables or as a percentage of patients in a given categorical variable.

The χ^2 test or Fisher's Exact test was used for comparison of categorical variables, and the Mann–Whitney *U* test to compare continuous variables in the two groups. The effects of different variables on IVIG resistance and CAI risk were calculated in univariate analysis for each. The variables for which the unadjusted p value was < 0.05 in the logistic regression analysis were identified as potential risk markers and included in the full model. We reduced

Table 1 Published risk scoring systems for intravenous immunoglobulin (IVIG) resistance and coronary artery involvement (CAI)

Score component	Point assignment
EGAMI SCORE (5 variables)	Low risk, 0–2; High risk ≥ 3
ALT ≥ 80 IU/L	2
Age < 6 months	1
CRP ≥ 8 mg/dL	1
Platelets < 300,000/mm^3	1
Fever < 4 days	1
HARADA SCORE (7 variables)	Low risk, 0–3; High risk ≥ 4
WBC count > 12,000/mm^3	1
Platelets < 350,000/mm^3	1
CRP > 3 mg/dL	1
Hematocrit < 35%	1
Albumin < 3.5 g/dL	1
Age ≤ 12 months	1
Male gender	1
KOBAYASHI SCORE (7 variables)	Low risk, 0–3; High risk ≥ 4
Sodium ≤ 133 mmol/L	2
Fever ≤ 4 days	2
AST ≥ 100 IU/L	2
Neutrophil ≥ 80%	2
CRP ≥ 10 mg/dL	1
Age ≤ 12 months	1
Platelets ≤ 300,000/mm^3	1
FORMOSA SCORE (3 variables)	Low risk, 0–2; High risk ≥ 3
Positive lymphadenopathy	1
Neutrophil ≥ 60%	2
Albumin < 3.5 g/dL	1

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *CRP* C-reactive protein, *WBC* white blood cell

the model using backward elimination multivariate logistic regression analyses. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off values. Hosmer–Lemeshow test was used for model fit. A p value < 0.05 was considered to be statistically significant.

Results

A total of 100 patients with KD were included in this study. 23 patients were evaluated prospectively, whereas 77 were evaluated retrospectively. The general characteristics of the patients are presented in Table 2. The median (IQR) age at diagnosis of KD was 38 (42) months, with an age range of 4–164 months. The median (min–max) number of febrile days at the time of diagnosis was 6.5 (3–32) days. All patients received IVIG (2 g/kg, infusion in 12 h) and aspirin (60 mg/kg/day). 18% of the patients also received oral corticosteroids because of IVIG resistance or high acute phase reactants. Of all patients, 75% received the first dose of IVIG within 10 days after disease onset. 6% received the second dose of IVIG, 11% received pulse methylprednisolone (MP), 6% received both of them, %1 received cyclosporine and 2% received infliximab. Eighty-five patients (85%) responded to IVIG treatment, whereas 15 (5 female, 10 male) were IVIG resistant. CAI was detected in echocardiography at diagnosis in 31 (31%) (9 female; 22 male) patients.

The most common clinical feature at diagnosis was fever (100%) followed by conjunctival congestion (77%) and mucosal changes (74%). Apart from the features included in the diagnostic criteria, the most common clinical finding was perianal peeling (20%) followed by vomiting (17%) and sterile pyuria (14%) (Table 2).

The patients were most frequently diagnosed in the spring and winter months. Fifty-two (52%) patients had complete KD while 48% had incomplete KD. Atypical KD patients were not included.

When the patients were assessed with the previously suggested scores described above, five patients were determined to have high risk by KS (sensitivity 82.1%; specificity 35.7%), while ES identified only 4 patients as having high risk (sensitivity 26.7%; specificity 94%) for IVIG resistance. FS and HS predicted 4 and 9 patients, respectively as having high risk (sensitivity 30.8% and 69.2%; specificity 51.2% and 45.8%, respectively) for IVIG resistance. On the other hand, five patients were predicted as having high risk by KS (sensitivity 17.2%; specificity 78.5%) while ES identified only 1 patient as having high risk (sensitivity 3.3%; specificity 88.4%) for CAI. FS and HS predicted 10 and 19 patients, respectively as having high risk (sensitivity 35.7% and 70.4%; specificities 49.3%, respectively) for CAI. Thus, none of the aforementioned scores were associated with IVIG resistance and CAI with acceptable performance in our cohort.

Among patients with CAI, 2 (6.5%) had dilatation, 16 (51.6%) had small aneurysm, 6 (19.4%) had medium aneurysm, and 7 (22.5%) patients had giant aneurysm. Of the patients with CAI, 14 (42.2%) had incomplete KD. CAI was detected in nine patients (29%) with age of 0-12 months, 19 (61.3%) with 13–60 months, and 3 (9.7%) patients who were older than 60 months. The median time from disease onset to IVIG treatment was not significantly different between patients with and without CAI. The median time from disease onset to IVIG treatment with CAI was 7.00 (min–max: 4–32) days. The median time from disease onset to IVIG treatment without CAI was 6.00 (min–max: 3–30) days. Erythrocyte sedimentation rate (ESR) and white blood cell (WBC) were significantly higher; hematocrit was significantly lower among patients

Table 2 The general characteristics of the patients with Kawasaki disease (KD)

Characteristics	%
Sex	
Male	61
Female	39
Age	
≤ 12 months	11
13–60 months	60
> 60 months	29
Season at the time of diagnosis	
Spring	29
Winter	27
Summer	24
Autumn	20
Clinical presentation	
Fever	100
Conjunctival congestion	77
Mucosal changes	73
Rash	72
Cervical lymphadenopathy	69
Changes in hands and feet	68
Extracardiac findings	
Perianal peeling	20
Vomiting	17
Sterile pyuria	14
Abdominal pain	10
Arthritis	9
Diarrhea	9
Peribronchial and interstitial infiltration on chest X-ray	7
Arthralgia	6
Headache	4
Aseptic meningitis	2
Erythema and induration of the BCG site	2
Pleural effusion	1
Presentation	
Incomplete KD	48
Complete KD	52
CAI	31
Dilatation	2
Mild aneurysm	16
Moderate aneurysm	6
Giant aneurysm	7
IVIG responsiveness	
IVIG-resistant	15
IVIG-responsive	85
Laboratory parameters	
High ESR	100
High CRP	100
Anemia[a]	49
Leukocytosis[a]	48.5
Thrombocytosis[a]	47.4

BCG Bacillus Calmette-Guérin, *CAI* coronary artery involvement, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *IVIG* intravenous immunoglobulin, *KD* Kawasaki disease

[a]All variables were evaluated in all patients ($n = 100$) except anemia (checked in 98 patients), leukocytosis (checked in 97 patients), and thrombocytosis (checked in 97 patients)

who developed CAI (74 vs. 55, $p = 0.026$; 16,400 vs. 12,800, $p = 0.008$; 30.3 vs. 33.0, $p = 0.015$; respectively). On the other hand, sex, incomplete presentation, alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP), gamma-glutamyl transferase (GGT), hemoglobin, sodium, neutrophil, platelet, and albumin had no significant effect on the development of CAI ($p > 0.05$).

The univariate and multivariate regression analyses for the CAI risk are presented in Supplementary Table 1. The multivariate analysis showed WBC count [Odd's ratio (OR) 4.1; 95% confidence interval (CI) 1.26–13.23; $p = 0.019$] and hematocrit (OR 3.8; 95% CI 1.15–12.4; $p = 0.028$), as independent predictors of CAI. If the hematocrit was ≤29.7%, the risk of CAI increased 3.8 times. The specificity of the hematocrit level in predicting CAI was 51.9% and the sensitivity was 83.8%. While the WBC count was ≥ 14,200/mm^3, the risk of CAI was 4.1 times higher. WBC count had a sensitivity of 78.6% and a specificity of 59.4% for predicting CAI.

For IVIG resistance, the only differentiating laboratory parameters were CRP and GGT (respectively 16.3 vs. 9.1, $p = 0.044$; 72.2 vs. 29.9, $p = 0.005$). However, sex, incomplete presentation, ALT, AST, WBC, ESR, hemoglobin, hematocrit, sodium, neutrophil, platelet, and albumin had no significant differences between IVIG responsive group and IVIG resistance group ($p > 0.05$).

The univariate and multivariate regression analyses for the IVIG resistance risk are presented in Supplementary Table 2. The multivariate analysis identified GGT level (OR 5.7; 95% CI 1.73–27.51; $p = 0.018$) as an independent predictor of IVIG resistance. The risk of IVIG resistance increased 5.7-fold with GGT ≥ 53.2 U/L. When GGT ≥ 53.2 U/L, it had a sensitivity of 79% and a specificity of 66% for predicting IVIG resistance (Fig. 1).

Discussion

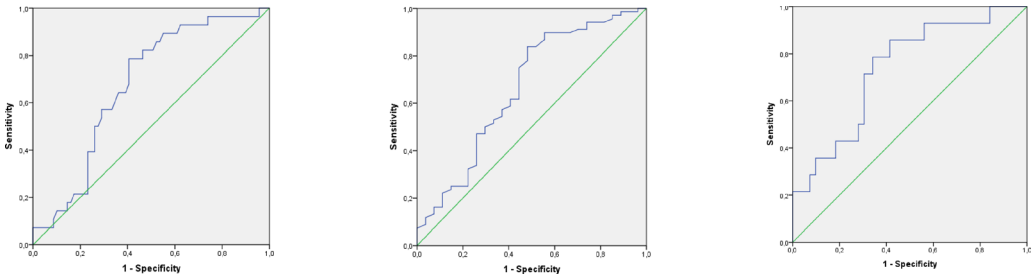
Turkey is an Eastern Mediterranean country with a Caucasian population where certain vasculitides such as Takayasu and Behcet's diseases are more common than European countries. This is the largest report of KD patients from the area. The previously suggested scores (namely FS, HS, KS, and ES) were not associated with IVIG resistance or CAI in our study group. The only independent predictive factor for IVIG resistance was high GGT, while high WBC and low hematocrit were associated with risk for CAI in our patients.

It is very important to predict IVIG resistance since the physician could modify the treatment (e.g., adding corticosteroids to IVIG) at disease onset in case of high risk [18]. There are different biomarkers such as interleukin (IL)-10, IL-6, IL-17A, ferritin, tenascin C, and CRP reported to be used for predicting IVIG resistance; however, none of these are validated in large multinational studies [20]. In addition, it is not appropriate to depend on one laboratory marker to predict the risk. Thus, several scores including different combinations of laboratory and clinical features have been designed such as KS, ES, FS, and HS for predicting IVIG resistance and CAI risk in KD patients [13]. These scores have been formed based on the characteristics of Japanese patients and their sensitivities range between 78 and 86% and specificities between 67 and 76% among Japanese patients [13]. However, in a few recent reports, these have not performed well in other populations. Here, we have shown that these scores had poor performance and did not predict IVIG resistance and were not associated with CAI among Turkish patients. Very recently, Fabi et al. demonstrated that KS, ES and FS were ineffective in predicting IVIG resistance and CAI among Italian patients, as well [14]. A study published from Israel found that Sano, KS and ES, which are highly effective in the Japanese population, were unreliable for predicting IVIG resistance in Caucasian Israeli children [21]. Shin et al. have demonstrated that these scores had good specificity but low sensitivity to predict IVIG resistance among Korean children with KD [17]. The difference in the performance of the risk scores among different countries may be attributed to ethnic differences.

We have shown that high GGT level increases the risk for IVIG resistance while high WBC and low hematocrit were significantly associated with CAI. In the same lines, Wang et al. showed that high GGT level was associated with IVIG resistance [22]. Their hypothesis was that elevated GGT levels may take role in blocking IVIG-induced neutrophil apoptosis, and consequently contribute to IVIG resistance [22]. High WBC and low hematocrit are associated with the severity of inflammation and, therefore, may be associated with CAI.

Previous studies have shown that IVIG resistance, male gender, and age under 12 months at diagnosis increase the risk for CAI [23, 24]. In this study, none of these correlated with CAI.

In our study, IVIG resistance was found in 15% of the patients. In other studies, IVIG resistance has been reported as 17% in Japan, 12.5% in Taiwan, 26.8% in Germany, and 17.1% in the US [12, 25–28].



WBC **Htc** **GGT**

	Sensitivity %	Specivicity %	AUC	p value	%95 CI	St errr
CAI						
WBC ≥ 14.200/mm³	59	79	0.673	0.002	0.570-0.760	0.06
Htc ≤ 29.7%	84	52	0.662	0.014	0.532-0.792	0.07
IVIG resistance						
GGT ≥ 53.2 U/L	79	66	0.735	0.001	0.635-0.820	0.07

Fig. 1 Area under the receiver operating characteristic (ROC) curves for white blood cell (WBC) count and hematocrit (Htc) for coronary artery involvement (CAI), and gamma-glutamyl transferase (GGT) for intravenous immunoglobulin (IVIG) resistance in patients with Kawasaki disease (KD). *AUC* area under the curve, *CAI* coronary artery involvement, *CI* confidence interval, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *Htc* hematocrit, *IVIG* intravenous immunoglobulin, *ROC* receiver operating characteristic, *St error* standard error, *WBC* white blood cell

Kawasaki disease with its most important complication CAI is the most common cause of acquired cardiac diseases in developed countries [29, 30]. CAI leads to enlargement, aneurysm, ischemic heart disease, and sudden death [1, 31]. In their study from USA ($n=392$), Clark et al. reported that 27% of KD patients had coronary ectasia or aneurysm, and 2.3% have giant coronary aneurysm [26]. Among Taiwanese children with KD, Lin et al. showed the rate of CAI as 5.3% [32]. In our study, 31% of patients had coronary dilatation or aneurysm and 2% had giant aneurysms. The high frequency of CAI (present in approximately one-third of patients) in our study is probably due to our hospital being a tertiary reference center. The median time from disease onset to IVIG treatment was not significantly different between patients with and without CAI in our study probably since most of the patients received IVIG treatment within the first 10 days after disease onset.

A limitation of our study is that some of patients were evaluated retrospectively while some of them were evaluated prospectively. However, all patients were evaluated thoroughly by the same two staff physicians ("attending physicians").

Conclusions

We have shown that published risk scores did not perform effectively among Turkish patients with KD. In our cohort, we demonstrated that high GGT was a risk factor for IVIG resistance while high WBC count and low hematocrit were associated with CAI. Future studies with larger number of patients from multiple centers of different countries could help for developing risk score systems and for identifying biomarkers that perform well among KD patients from different ethnicities.

Author contributions Manuscript EAA; literature search EAA, EDB, SO; figure EAA, SO; study desing EAA, SO; data collection EAA, EDB, HES, SD, ZSA, ES, İE, DA, YB, SO; data analysis EAA, SO; data interpretation EAA, YB, SO; writing EAA, EDB, SO. All authors read and approved the final manuscript.

Funding There is no funding source.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Research involving human participants and/or animals When the patients admitted to the hospital, the parents gave a general consent approving anonymous data use for academic purpose.

Informed consent The written consents from the patient families were obtained according to the Declaration of Helsinki (1964) and the study was approved by the ethics committee of Hacettepe University (GO-16/45-15; approval date, 1st March 2016).

Ethics approval and consent to participate The written consents from the patient families were obtained according to the Declaration of Helsinki (1964) and the study was approved by the ethics committee of Hacettepe University (GO-16/45-15; approval date, 1st March 2016).

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