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Original Article

Japanese Kawasaki Disease Scoring Systems: Are they Applicable to the Iranian Population?

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Abstract

Background: Kawasaki disease (KD) is the most frequent cause of coronary artery aneurysm (CAA) in children. This study tried to evaluate the accuracy of different KD scores developed for prediction of CAA, in an Iranian population.

Methods: This is a cross-sectional retrospective investigation on pediatric patients with a diagnosis of KD. Clinical manifestations, laboratory, and echocardiographic data were recorded. Five Kawasaki scores, including Kobayashi, Egami, Sano, Nakano, and Harada, were assessed and analyzed in relation to CAA and intravenous immunoglobulin (IVIG) resistance.

Results: During five years, we recruited 121 cases of KD under 13 years of age. The rates of CAA and IVIG resistance were 16.5%, and 13.2% respectively. The IVIG resistance group was significantly younger than responder patients. All five scores had low sensitivity in predicting CAA or IVIG resistant cases; the highest sensitivity pertained to the Harada score with 50% sensitivity and 59% specificity (the area under the curve: 0.545, with a 95% confidence interval: 0.423 to 0.667) in predicting CAA, which is lower than the usual acceptable criteria for a screening test. The specificity of all other scores were more than 85% in predicting CAA or IVIG resistance. Gender, fever before therapy and laboratory data showed no significant difference between the groups.

Conclusion: The Kobayashi, Egami, Sano, Nakano and Harada scores have limited usefulness in the Iranian population to predict high risk patients for coronary artery involvement or IVIG resistance; in our study, age under one year was a risk factor for IVIG resistance.

Keywords: Coronary aneurysm, Harada, IVIG

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Introduction

Kawasaki disease (KD) is the most frequent cause of medium size autoimmune vasculitis with coronary artery involvement, ranging from arterial wall brightness to giant aneurysms. Coronary complications, with a prevalence of 10% to 25% of untreated patients in different populations, are the most important long-term morbidity of KD.[1-3] Due to the importance of coronary involvement in KD and description of treatment protocol, many investigators have attempted to present a risk score for coronary artery involvement and criteria for intravenous immunoglobulin (IVIG) resistance.[4-7] The aim of these studies was determination of IVIG resistant in refractory cases, presuming that IVIG resistance might increase the risk of coronary artery involvement and mandate other treatment strategies or more aggressive therapy as the first step. These investigations have resulted in development of various KD scores.

Some of the well-known KD scoring systems are Kobayashi, Egami, Sano, Nakano and Harada scores from Japan.[5,7-11] These scoring systems are presented in the complementary section at the end of the article. All of these systems try to identify IVIG resistance cases, who are at high risk for coronary artery aneurysm (CAA), based on a combination of clinical and laboratory data.[10,12]

Each system chooses a specific combination of certain parameters such as age, ESR, CRP, WBC, sodium, platelet, aspartate aminotransferase and total bilirubin and then use the aggregate score to predict the risk for each patient. Most of the parameters are common among all of these systems.[10,12]

Nevertheless, studies in different populations have yielded controversial results in terms of the sensitivity and specificity of these scoring systems, suggesting that these systems do not seem to have the same predictive value across different populations. Therefore, previous studies have recommended them to be individually investigated in each country.[6,13,14]

The Iranian population has a relatively high rate of CAA in addition to early treatment with IVIG.[2,14-16] Some epidemiologic studies from Iran report a CAA rate of about 15% to 20%, which goes even as high as 47% in a few studies.[2] Thus, identifying the high risk group among these patients may change our treatment policy and decrease the rate of CAA.

This study tried to evaluate the accuracy of these

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well-known KD scoring systems in a southern Iranian population in predicting high risk patients.

Material and Methods

This is a cross-sectional retrospective investigation conducted from 2012 to 2017 on pediatric and adolescent patients with a diagnosis of KD or incomplete KD based on the American Heart Association guideline who were admitted to the hospitals of Shiraz University of Medical Sciences, Shiraz, Iran, the referral centers of pediatric diseases in southern Iran.[17] The patients' clinical data were reviewed and the relevant data were recorded for analysis. We checked the relevant data for each patient, including age and sex, clinical signs especially duration of fever before IVIG treatment, laboratory data such as CBC, ESR, LFT, BUN, Cr, Na, K, and urine analysis. We also evaluated echocardiography data for coronary artery involvement like wall brightness, thickening, aneurysm formation (number, size and location of the abnormalities), and other cardiac anomalies such as valvular regurgitation and alteration in left ventricular function. All patients were followed for 6 weeks based the on standard protocol for KD management.

Criteria of the CAA were defined as diameter more than 3 mm in patients aged under 5 years, diameter more than 4 mm in patients aged 5 years or more, or a localized coronary artery dilatation 1.5 times compared to the adjacent coronary segment.[17] Other forms of incomplete criteria for coronary involvement such as coronary artery dimension z-score between 2 and 2.5, coronary wall brightening, tubular dilatation and lack of tapering, also labeled as early stages of coronary artery involvement, and all patients with any coronary artery involvement were labeled as the high risk group in statistical analysis. The time of detection of CAA during 6 weeks of follow-up did not matter, and all patients with aneurysm at any time were categorized in the CAA group.

Echocardiographic assessments were done with 2-dimentional, M-mode and Doppler methods. M-mode data included the inter-ventricular septum, and left ventricular posterior wall diameter in systole and diastole and we evaluated ejection fraction and fractional shortening in long-axis view. We performed M – mode echocardiography for ejection fraction at the site of mitral valve leaflets.[18]

In addition, we investigated treatments including IVIG dosage and frequencies and use of steroids or Infliximab.

The IVIG resistant group was defined as patients who needed more than 2 g/kg IVIG to stop fever, recurrent fever and any patient who needed steroid or Infliximab to control the disease.

Then, we calculated the Kobayashi, Egami, Sano, Nakano, and Harada scores across the two groups (Resistant vs. Responder to IVIG and also No CAA vs. CAA) to investigate the accuracy of these scores in prediction of CAA formation and IVIG resistance. For details of these scores, refer to the complementary data at the end of the article.

We excluded patients who did not have a thorough follow-up.

The initial clinical and laboratory data were used to calculate the disease scores. Any CAA during the follow-up period was included in this study as a case with positive CAA. All data were analyzed using SPSS, IBM software windows version 24. We analyzed the sample using statistical tests including independent *t* test, chi-square test, ANOVA test and ROC curve.

Factors pertaining to each of these scores are presented in complementary data (Table S1) at the end of this article. The format of the table was imported from an article by Rigante et al reviewing these scores.[11]

Results

All the patients enrolled with impression of KD with complete follow-up for 6 weeks were 121 cases; the age range of all cases was 4 months to 13 years with 57% male and a M/F ratio of 1.3; while 101 patients had normal coronary arteries (83.5%), 20 patients developed coronary involvement (16.5%).

The most common involved coronary arteries were the left anterior descending with 60% involvement, followed by the left main coronary artery (50%) and then the right coronary artery (40%). Involvement of the left circumflex artery was not observed in this study. Coronary artery involvement persisted in three patients after the 6th weeks of follow-up in spite of IVIG therapy in the right time. One patient developed CAA one month after treatment: this case had no CAA during hospitalization and had undergone appropriate treatment.

Only one patient needed prednisolone in addition to two doses of IVIG to stop fever, while all the other patients were treated with only IVIG.

The patients were stratified based on normal coronary arteries and coronary involvement as shown in Tables 1-4; they were also categorized with regard to being IVIG responder or resistant, as illustrated in Tables 5-7.

We categorized our patients in three age groups and the rate of aneurysm in each group was determined. Chi-square test did not show any significant statistical difference in CAA among the three age groups.

Laboratory data are presented in Table 2, showing no difference between the two groups of CAA.

M-Mode data also showed no significant difference between the two groups of patients.

In the next step, we calculated the five scores for each of the two groups and analyzed the accuracy of each score in detecting high risk patients for CAA. These data are presented in Tables 3 and 4.

None of the scores could predict the high risk patients and all the results showed non-significant difference.

Table 1. Demographic Characteristics in Two Groups (with and without Coronary Artery Involvement) Based on Echocardiography

Variables	No Coronary Involvement n = 101	Coronary Involvement n = 20	*P* Value
Sex			0.430
Male	56 (55.4)	13 (65)	
Female	45 (44.6)	7 (35)	
Age (mean ± SD)	3.64 ± 2.7 (0.33–13)	2.8 ±1.9 (0.33–7)	0.211
Fever (range)	9.3 ± 6.4 (1–45)	8.5 ± 5.4 (1–60)	0.305
Age (y)			0.532
<1	11 (10.9)	4 (20)	
1 ≤ age <5	69 (68.3)	12 (60)	
≥5 age	21 (20.8)	4(20)	

Table 2. Laboratory Data and M-Mode Echocardiography Data in the Two Groups (with and without Coronary Artery Involvement)

Variables	No Coronary Involvement (Range or SD) n = 101	Coronary Involvement (Range or SD) n = 20	*P* Value
WBC	14300 (5300–22500)	10600 (6700–33000)	0.975
Neutrophil count	56.6 (17.5)	51.1 (19.8)	0.285
Hct	31.2 (23–38.5)	29.8 (23.7–35.6)	0.591
Plt	397477 (198197)	460150 (240087)	0.215
T.Bili	0.4 (0.2–4.3)	0.4 (0.2–1.57)	0.717
D.Bili	0.21 (0.35)	0.18 (0.14)	0.680
AST	35.44 (22.59)	36.94 (18.53)	0.791
ALT	20.5 (3–226)	25 (11–302)	0.736
Na	137.21 (3.62)	137.26 (3.51)	0.956
K	4.49 (0.75)	4.29 (0.71)	0.297
T.Pro	7.34 (1.37)	7.61 (1.42)	0.492
Alb	3.71 (0.66)	3.48 (0.52)	0.194
ESR	67.85 (30.94)	73.95 (31.31)	0.435
CRP	66.24 (46.80)	54.19 (52.37)	0.316
BS	97.57 (22.93)	92.33 (25.27)	0.390
M-Mode Echocardiography Data			
EF	69.38 (5.55)	68.50 (5.91)	0.528
FS	37.58 (7.33)	37.11 (4.68)	0.786

WBC, white blood cell; Hct, hematocrit; Plt, platelet; T.Bili, total bilirubin; D.Bili, direct bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Na, sodium; K, potassium; T.Pro, total protein; Alb, albumin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BS, blood sugar; EF, ejection fraction; FS, fractional shortening.

These analyses showed very low sensitivity for all of the scores in detecting high risk patients as well as low positive predictive value. The best specificity was pertained to the "Sano" score.

Furthermore, the IVIG resistance rate was also evaluated and reanalyzed with the five scores to evaluate the power of prediction of resistant cases in each system. Table 5 shows that we had 13.2 % resistant cases, defined as IVIG >2.0 g/kg or need for steroid therapy to control fever. In demographic data, age showed a significant statistical difference between the IVIG responsive and resistant groups (Table 5).

Table 3. Different Scores in the Groups with and without Coronary Artery Involvement

Scoring System	No Coronary Involvement, No. (%) (n = 101)	Coronary Involvement, No. (%) (n = 20)	*P* Value
Kobayashi			0.056
Low risk	80 (81.7)	18 (18.3)	
High risk	13 (93)	1 (7)	
Very high risk	0 (0)	1 (100)	
Egami			0.6
Low risk	90 (84)	17 (16)	
High risk	11 (78.6)	3 (21.4)	
Sano			0.989
Low risk	91 (83.5)	18 (16.5)	
High risk	10 (83.3)	2 (16.7)	
Harada			0.457
Low risk	59 (85.5)	10 (14.5)	
High risk	41 (80.4)	10 (19.6)	
Nakano			0.364
Low risk	89 (82.4)	19 (17.6)	
High risk	12 (92.3)	1 (7.7)	

Analysis of the five scores in terms of IVIG response is shown in Table 6. None of the scores could differentiate between resistant and non-resistant cases or predict resistance in our patients.

Sensitivity and specificity analysis in these settings also revealed low sensitivity and high specificity for all the scores in predicting IVIG resistance. The Kobayashi score had the highest specificity (100% positive predictive value).

Discussion

KD is a medium-sized vasculitis of unknown etiology, which is most probably due to infectious and immunologic etiology; and it is the leading cause of CAA in the pediatric age group.[1,19] The main problem is coronary artery involvement and many investigators have tried to evaluate the patients to find the risk of coronary artery involvement and identify patients at high risk of complications.[12,20-22] The Japanese scoring systems are the most well-known criteria for finding high risk patients.[10,12] However, since the applicability of these scores in different countries is unknown, researchers have recommended to evaluate the scores in other countries individually.[13,14] This study aimed to evaluate these scores in an Iranian population.

In the present study, the rate of aneurysm in spite of appropriate treatment was relatively high (16.5%); this finding has been reported in some other studies on Iranian populations.[2,15,16] In comparison to other countries, Iranian studies have a higher rate of coronary artery involvement.[1,3,19] This may be related to the multi-factorial nature of KD and the genetic background in

Table 4. Calculation of Sensitivity, Specificity and Predictive Values of Different Scores in Predicting Coronary Artery Involvement Based on Five Scores

Risk Scores	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC -- 95% Confidence Interval
Kobayashi	5	86	100	81.63	71.68	0.5 -- 0.42 to 0.531
Egami	15	89.1	21.43	84.11	76.86	0.521 -- 0.435 to 0.606
Sano	10	91.1	16.67	83.49	75.21	0.5 -- 0.427 to 0.574
Harada	50	59	19.61	85.5	57.5	0.545 -- 0.423 to 0.667
Nakano	5	88.12	7.7	82.40	74.38	0.5 -- 0.41 to 0.523

PPV, positive predictive value; NPV, negative predictive value; AUC, area under curve.

Table 5. Demographic Data of the Patients in Terms of IVIG Resistance

Variables	IVIG Response		*P* Value
	Responder n = 105 (86.8%)	Resistance n = 16 (13.2%)	
Sex			0.122
Male	57 (54.3%)	12 (75.0%)	
Female	48 (45.7%)	4 (25.0%)	
Age (range)	3.66 ± 2.6 (0.33–13)	2.53 ± 2.5 (0.33–8)	0.02
Fever (range)	10 ± 6 (1–45)	8 ± 5 (1–20)	0.3
Age category			
<1 years	10 (9.5%)	5 (31.3%)	0.046[a]
1 ≤ age <5	73 (69.5%)	8 (50.0%)	
≥5 age	2 (15.2%)	3 (18.8%)	

IVIG, intravenous immune globulin.
[a] Under-1-year group had a different proportion.

Table 6. IVIG Resistance and Kawasaki Disease Scores

Scoring system	IVIG Response		*P* value
	Responder, No. (%) (n = 105)	Responder, No. (%) (n = 16)	
Kobayashi	97	16	
Low risk	84 (86.6)	14 (87.5)	
High risk	13 (13.4)	1 (6.3)	0.036
Very high risk	0 (0.0)	1 (6.3)	
Egami	105	16	
Low risk	94 (89.5)	13 (81.3)	0.41
High risk	1 (10.5)	3 (18.8)	
Sano	105	16	
Low risk	94 (89.5)	15 (93.8)	0.6
High risk	11 (10.5)	1 (6.3)	
Harada	104	16	
Low risk	59 (56.7)	10 (62.5)	0.56
High risk	45 (43.3)	6 (37.5)	
Nakano	105	16	
Low risk	9 (89.5)	14 (87.5)	0.6
High risk	11 (10.5)	2 (12.5)	

IVIG, intravenous immune globulin.

Iranian populations.[1,23] Regarding this finding, we tried to evaluate our patients for the risk of coronary artery disease and IVIG resistance based on other investigations in KD score.

Most studies indicate that the age under 1 year or above 5 years is a risk factor for development of CAA,[7,24,25] although in our study there was not any difference in the incidence of CAA among infants and older patients. However, patients with lower age had more IVIG resistance (mean age 3.66 ± 2.6 vs 2.53 ± 2.5 in responders vs. non-responders; *P* value: 0.046, Table 5). This result has been confirmed by some other investigators.[8,10,26] Thus, this age group might be prone to IVIG resistance.

Non-significant age difference for CAA may be related to the paucity of case numbers or to the awareness of pediatricians regarding KD and prompt therapy. In the past, some patients with age under 1 year had delayed diagnosis of KD due to nonspecific or atypical presentation in this age group; so, they were at risk of delayed treatment and increased complications. Nowadays, the pediatricians usually consider KD as a differential diagnosis of prolonged fever in infancy and childhood.

Some related para-clinical data such as albumin, hemoglobin and urine analysis are useful for diagnosis of KD.[1] However, in our study, analysis of these lab data did not reveal any predictive value for patients regarding either CAA or IVIG resistance (Table 2). Some investigators use these factors in combination with other data to predict complications and a few studies have proposed a relationship between them and disease complications.[5,7,27] It seems that a combination of these factors along with clinical data would be a more acceptable method to categorize the risk of complications.

Therefore, a combination of para-clinical and clinical data in five KD score systems was calculated in our study.[4,5,7-9,28] We evaluated all these scores for each patient, but we could not find good sensitivity for any of them in predicting either CAA or IVIG resistance. The low sensitivity of these factors has been reported by some investigators.[12,14,29] It seems that there is conflicting data regarding the efficacy of these scores in predicting KD complications which may be dependent on many factors such as race and genetic background.[22,23] Most Southeast Asian articles are in consensus with these scores and at least one of these scores has been useful in their population; but other areas have reported greater controversies.[3,26,29] In the Iranian population, few studies have focused on evaluating these scores' sensitivity and specificity. Raeeskarami et al evaluated the Kobayashi score in an Iranian population and concluded that these scores could not predict the high risk group for CAA.[14] Our study evaluated multiple scores for the first time in an Iranian population and found very low sensitivity for all scores in finding high risk patients

Table 7. Sensitivity and Specificity of the Five Kawasaki Scores in Predicting IVIG Resistant Cases

Risk Scores	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC -- 95% Confidence Interval
Kobayashi	6.25	97.53	100	84.95	75.47	0.5 -- 0.405 to 0.595
Egami	18.75	89.54	21.43	87.73	78.57	0.541 -- 0.438 to 0.644
Sano	6.25	89.58	8.3	86.2	77.67	0.521 -- 0.453 to 0.589
Harada	37.5	56.74	11.7	85.5	52.25	0.529 -- 0.397 to 0.660
Nakano	12.5	89.5	15.3	87	79.36	0.510 -- 0.421 to 0.599

PPV, positive predictive value; NPV, negative predictive value; AUC, area under curve.

for either CAA or IVIG resistance. On the other hand, the analysis showed good specificity for all scores, which has been confirmed in some similar studies.[12-14] Good specificity means that these scores could find actual negatives, but they miss many high risk patients with low sensitivity. This leads to limited usefulness of the score for screening in our population, especially when we wish to identify the few high risk patients from among many patients.

Among all of the mentioned scores, Harada had the highest sensitivity for predicting CAA. This score was initially introduced to find patients who might benefit from IVIG treatment, at the time when IVIG was not used for all cases of KD. It includes two clinical (age, gender) and five para-clinical items to categorize the patients as low risk or high risk for CAA. In this study, Harada score had the best combination of sensitivity (50%) and specificity (59%) and it may be the most reliable scoring system for the Iranian population to predict CAA and, with less sensitivity, IVIG resistance. Nevertheless, the sensitivity and specificity of this score are lower than the usual acceptable criteria for a screening test in clinical settings.

In conclusion, the Iranian people have a high rate of coronary artery involvement with KD. The Japanese KD scores have limited usefulness in the Iranian population and cannot be used to predict high risk patients for coronary artery involvement or IVIG resistance. Age under 1 year is a risk factor for IVIG resistance and should be considered in management of KD.

Authors' Contribution

Main idea and proposal prepration: MRE, HM, HA and NM; Data gathering and data entering: MG, NM, ED and KK; Data analysis: MRE, HM, NM, GA and MB; Writing: HM, MG, HA, MRE and RB; Finalization and review: MB, GA, MRE and RB.

Conflict of Interest Disclosures

There no conflict of interest to declare.

Ethical Statement

This research was evaluated by ethics committee of Shiraz University of Medical Sciences and was found to be in accordance to the ethical principles and the national norms and standards for conducting Medical Research in Iran and was registered with Approval ID IR.SUMS.MED.REC.1397.253.

Supplementary Materials

Supplementary file 1 contains Table S1.

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