IJMS
Vol 47, No 4, July 2022

Original Article

The Negative Predictive Value of Harada Scoring for Coronary Artery Dilatation or Aneurysm in Children with Kawasaki Disease: A Cross-sectional Study

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Received: 07 February 2021
Revised: 03 May 2021
Accepted: 05 June 2021

Abstract

Background: The most common cause of coronary artery aneurysms in children is Kawasaki disease (KD). One of the risk ratings used to predict coronary artery aneurysms is the Harada score. This study aims to assess the negative predictive value (NPV) of Harada scoring in children with KD.

Methods: This cross-sectional study was conducted in Mashhad (Iran) from January 2014 to December 2017. The Harada score was generated for each patient using demographic, laboratory, and echocardiography data retrieved from their medical records. The patients were divided into typical and atypical cases, and the sensitivity, specificity, positive predictive value (PPV), and NPV were calculated. The Chi square test, independent *t* test, Mann–Whitney U test, and Fisher exact test were used to analyze the data in SPSS software (version 23.0). $P \leq 0.05$ was considered statistically significant.

Results: The study involved 168 individuals with a mean age of 29.91±19.52 months, including 103 typical and 65 atypical cases. Regarding cardiac complications, the atypical group had a significantly greater rate of coronary artery tapering (P=0.030). Out of 101 patients with cardiac complications, the Harada score was positive in 57 cases, while it was falsely negative in the remaining 44 patients. The calculated sensitivity, specificity, PPV, and NPV were 56.44%, 53.73%, 64.77%, and 45%, respectively.

Conclusion: The findings revealed that the Harada scoring is ineffective in detecting coronary artery aneurysms or dilation in KD patients.

Please cite this article as: Malek A, Ghodsi AR, Hamedi A. The Negative Predictive Value of Harada Scoring for Coronary Artery Dilatation or Aneurysm in Children with Kawasaki Disease: A Cross-sectional Study. Iran J Med Sci. 2022;47(4):379-384. doi: 10.30476/IJMS.2021.90005.2079.

Keywords ● Mucocutaneous lymph node syndrome ● Coronary aneurysm ● Predictive value of tests ● Children

What's Known

- Various studies on the diagnostic accuracy of Harada scoring have indicated different results from the original study. One reason contributing to these changes is that racial variances may influence the results.
- Therefore, identifying a high-risk group among Iranian Kawasaki disease patients can help to adjust treatment policies and reduce the incidence of coronary artery aneurysms.

What's New

- Among Iranian children, the Harada scoring criterion did not have satisfactory sensitivity, specificity, positive and negative predictive values in predicting cardiac complications.
- The Harada criteria do not seem to be very efficient at predicting coronary artery lesions in children with Kawasaki disease.

Introduction

Kawasaki disease (KD) is an acute febrile, self-limiting, and systemic vasculitis, with an unknown etiology, which primarily affects children under the age of five years old.[1,2] Asian countries, particularly Japan, have the highest prevalence of KD.[3,4] The male-to-female ratio ranges from 1.5-1.7 to 1.[5] Fever, rashes, cervical lymphadenopathy, erythema of the lips and oral mucosa, bilateral nonexudative conjunctivitis, and changes in the extremities are

all symptoms of KD.[6]

KD is frequently associated with medium- and small-size autoimmune vasculitis, particularly in the coronaries. Coronary complications such as aneurysms or ectasia are the most common long-term morbidity of KD, affecting approximately 15-25% of untreated patients.[1] Myocarditis and arrhythmia, as well as myocardial infarction and cardiac mortality due to coronary artery aneurysms, can occur in the acute phase, while stenosis is common in the sub-acute and chronic phases.[1, 7] Echocardiography is the recommended modality for early cardiac imaging.[8]

Prompt treatment with intravenous immunoglobulin (IVIG) reduces the risk of developing coronary artery aneurysms in most patients.[1] However, 10-20% of patients who received their first IVIG treatment, still had a fever, and these patients were at a higher risk of coronary artery complications.[9-11] If the patient has a persistent or recurrent fever at least 36 hours following the end of the IVIG infusion, this condition is called IVIG resistance.[1] IVIG resistance and coronary artery involvement have been predicted using risk scores. The Harada score from Japan is one of the most well-known KD risk scores.[12, 13]

The Harada score identifies the cases who are at high risk for coronary artery aneurysms due to IVIG resistance.[12] The characteristics of the Harada score are presented in table 1. Possessing four out of seven criteria indicates a positive score and necessitates IVIG treatment.[12]

Table 1: Characteristics of the Harada score, the cutoff for high Risk≥ 4

1. WBC count>12 000 /µL
2. Hematocrit<35% (our cutoff Hemoglobin<11.6 g/dL)
3. Platelets<350 000 /µL
4. CRP>3 mg/dL
5. Albumin<3.5 g/dL
6. Age≤12 months
7. Male sex

CRP: C-reactive protein; WBC: White blood cell

Although the Harada score has been around for decades, various studies on its diagnostic accuracy, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), have reported results that differ from the original study. One of the factors contributing to these differences is that the initial study was conducted on Japanese children, which may have been biased by racial disparities.[14] The Harada risk score has been proven to be 90% sensitive in identifying children at risk for coronary artery aneurysms in the United States population, however, it has a poor PPV (19%) and low specificity (51%).[15] Despite early treatment with IVIG, a relatively high rate of coronary artery aneurysms has been reported in various research on the Iranian population.[16, 17] A rate of 15% to 20%, with the possibility of reaching 47%, has been reported among Iranian children.[16] Therefore, identifying a high-risk group among Iranian KD patients can help to modify the treatment policies and reduce the incidence of coronary artery aneurysms. The purpose of this study was to see if the Harada score could be used to predict coronary artery dilatation or aneurysms in KD patients, with a focus on NPV.

Materials and Methods

From January 2014 to December 2017, all patients with a diagnosis of KD or incomplete KD in the pediatric wards of Imam Reza and Akbar Hospitals (Mashhad, Iran), which were the pediatric referral centers in the northeast of Iran, were included in this cross-sectional retrospective study. The study included all patients, who had an echocardiogram performed by a pediatric cardiologist and were diagnosed with KD or incomplete KD, according to the American Heart Association guideline.[1] Patients, whose hospitalization records were insufficient to calculate the Harada score, were excluded from the research.

Written informed consent was obtained from the participants' parents or guardians, who agreed to participate in the study. The data were coded and recorded to ensure complete confidentiality. Furthermore, all steps of this study complied with the Helsinki Declaration and were approved by the Ethics Committee of Mashhad University of Medical Sciences (#IR.MUMS.fm.REC.1396.687).

The main purpose of this research was to compare major cardiac complications in patients with a Harada score≤4 and to see whether cardiac complications were more likely in patients with a Harada score of less than four during the course of the disease and subsequent follow-up. Data on demographics, laboratory tests, and echocardiography were retrieved from the participants' files and documented separately. The Harada score was then computed using table 1. The physician who performed the patient's echocardiogram, was unaware of the patient's Harada score. A coronary artery aneurysm was defined as a diameter greater than 3 mm in children under the age of five, greater than 4 mm in children over the age of five, or a localized coronary

artery dilatation of 1.5 times the adjacent coronary segment.[1] Patients were divided into two groups: atypical (incomplete) and typical (complete). The cardiac problems and laboratory findings of the two groups were then compared. To exclude age as a confounding factor, patients were divided into two age groups, including less than and greater than 12 months, and then the cardiac problems were compared between the two groups. Finally, the sensitivity, specificity, PPV, and NPV values were computed.

Data were analyzed using SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics, such as central indices, dispersion, and frequency distribution, were used to indicate the patients' characteristics. In the case of normal distribution of data, an independent *t* test was used to compare quantitative variables between the two groups (positive and negative Harada score), and otherwise, a Mann-Whitney test was utilized. To compare the qualitative variables between the two groups, the Chi square test and, if necessary, Fisher's tests were used. P≤0.05 was considered statistically significant.

Results

A total of 168 individuals (105 boys and 63 girls) were enrolled in the study. The mean age of children was 29.91±19.52 months, and the minimum and maximum ages were two and 114 months, respectively. In the typical group, there were 105 (62.5%) patients, and 63 (37.5%) patients were in the atypical group. In terms of age, gender, birth order, parent-child connection, and type of delivery, there was no statistically significant difference between the typical and atypical groups (table 2).

The cardiac problems in the typical and atypical groups were compared and reported in table 3. The coronary artery ectasia and lack of coronary artery tapering were significantly higher in the atypical group (P=0.007, P=0.021). To eliminate the confounding factor of the age variable, the patients were divided into two age groups of less than 12 months and more than 12 months. In the typical group, 15 (14.4%) of the patients were under the age of 12 months, and 89 (85.6%) were older. In the atypical group, 23 (36.5%) of the patients were under 12 months old, while 40 (63.5%) of the patients

Table 2: Demographic information and comparison of typical and atypical groups

Variable		Total (N=168) N (%)	Typical group (N=105) N (%)	Atypical group (N=63) N (%)	P value
Age (month, mean±SD)		29.91±19.52	32.12±18.12	26.23±21.14	0.057*
Gender	Male	105 (62.5%)	65 (61.9%)	40 (66.2%)	0.837**
	Female	63 (37.5%)	40 (63.5%)	23 (36.5%)	
Birth order	1st	60 (38.2%)	43 (43.9%)	17 (28.8%)	0.308**
	2nd	62 (39.5%)	37 (37.8%)	25 (42.4%)	
	3rd or more	35 (22.3%)	18 (18.3%)	17 (28.8%)	
Family relationship of parents	Yes	15 (22.7%)	6 (14.6%)	9 (36.0%)	0.068**
	No	51 (77.3%)	35 (85.4%)	16 (64.0%)	
Type of delivery	NVD	66 (43.7%)	46 (47.9%)	20 (36.4%)	0.168**
	C/S	85 (56.3%)	50 (52.1%)	35 (63.6%)	

C/S: Cesarean section; NVD: Normal vaginal delivery; *Independent samples *t* test was used for comparison. **Chi square test was used for comparison. P<0.05 was considered significant.

Table 3: Cardiac clinical findings, and comparison of typical and atypical groups

Variable		Total (N=168) N (%)	Typical group (N=105) N (%)	Atypical group (N=63) N (%)	P value*
Pericardial effusion	Yes	8 (4.76)	7 (6.67)	1 (1.59)	0.261
	No	160 (95.24)	98 (93.33)	62 (98.41)	
Coronary artery ectasia	Yes	22 (13.10)	8 (7.62)	14 (22.22)	0.007
	No	146 (86.90)	97 (92.38)	49 (77.78)	
Coronary artery dilation	Yes	12 (7.14)	5 (4.76)	7 (11.11)	0.134
	No	156 (92.86)	100 (95.24)	56 (88.89)	
Aneurysm	Yes	10 (5.95)	5 (4.76)	5 (7.94)	0.504
	No	158 (94.05)	100 (95.24)	58 (92.06)	
Perivascular brightness of coronary artery	Yes	49 (29.17)	25 (23.81)	24 (38.09)	0.055
	No	119 (70.83)	80 (76.19)	39 (61.91)	
Lack of coronary artery tapering	Yes	11 (6.55)	3 (2.86)	8 (12.70)	0.021
	No	157 (93.45)	102 (97.14)	55 (87.30)	

*Chi square test was used for comparison. P<0.05 was considered significant.

Table 4: Frequency distribution of the Harada score by study groups

Harada score	Total N (%)	Typical group N (%)	Atypical group N (%)
<4	80 (47.62)	54 (51.43)	26 (41.27)
≥4	88 (52.38)	51 (48.57)	37 (58.73)

Table 5: Frequency distribution of true positive, false positive, true negative, and false-negative cases

Harada score	Has a cardiac complication	N	No cardiac complication	N	Total	
Positive	True positive	57	False positive	31	True positive+False positive	88
Negative	False-negative	44	True negative	36	False-negative+True negative	80
Total	True positive+False-negative	101	False positive+True negative	67	-	

were older than 12. After eliminating the age confounding factor, the difference in coronary artery ectasia between the two groups was no longer statistically significant (P=0.063), while the lack of coronary artery tapering, which was significant (table 3), was still significant (P=0.030). Moreover, among the children under the age of 12 months, pericardial effusion complication was more common in the typical group than in the atypical group, which became statistically significant (P=0.030). The frequency distribution of patients per Harada score was summarized in table 4. The percentage of patients with a Harada score≥4 in the typical and atypical groups was equal to 48.57% and 58.73%, respectively.

Table 5 indicated the frequency of true positive, false positive, true negative, and false-negative cases. The Harada score was positive in 57 of 101 individuals with cardiac complications, which indicated a true positive. However, the Harada score was erroneously negative in the remaining 44 individuals, indicating a false negative. Similarly, the Harada score was erroneously positive in 31 patients out of 67, who did not have cardiac complications, indicating false positives. Finally, for 36 patients, who did not have complications, the Harada score was correctly negative.

According to the Harada scoring criterion, the probability of an accurate diagnosis of the disease (sensitivity) was 56.44%. In cases without cardiac complications, the probability of a proper diagnosis (specificity) was 53.73%. When the Harada test results were positive (PPV), the probability of having the disease was 64.77%. Furthermore, the probability of the absence of the disease when the result of the Harada test was negative (NPV) was 45%. The overall probability of correctly classifying a patient (accuracy) was 55.36%.

Discussion

According to this scoring criterion, the findings of the study indicated a sensitivity of 56.44%, a specificity of 53.73%, PPV of 64.77%, and NPV of 45%.

In a study, Tewelde and others investigated the predictive value of the Harada scoring criterion in 105 children with KD in the United States (64% of them were typical).[15] Despite IVIG treatment, 10 patients developed coronary artery aneurysms, and patients with an atypical presentation had a higher risk of developing coronary artery aneurysms (20% vs. 5%, P=0.03).[15] They reported sensitivity, specificity, PPV, and NPV of 90%, 51%, 19%, and 98%, respectively.[15] However, contrary to their findings, our study found no significant difference in the formation of coronary artery aneurysms between the typical and atypical groups. The obtained sensitivity in their study was much higher than in ours (90% vs. 56.44%). In addition, the NPV in that study was substantially higher than in ours (98% vs. 45%).

In an Iranian population, Edraki and others investigated the accuracy of five KD risk scores established for coronary artery aneurysms.[18] They studied 121 children with KD for five years and found that all five risk scores had low sensitivity, with the Harada score having the highest sensitivity, with 50% sensitivity and 59% specificity (95% confidence interval=0.423 to 0.667, the area under the curve=0.545) in detecting coronary artery aneurysms, which was lower than the normal appropriate criterion for a screening test. Moreover, they reported Harada score PPV and NPV of 19.61% and 85.5%, respectively.[18] These findings were in line with our study, as we reported the sensitivity, specificity, PPV, and NPV of 56.44%, 53.73%, 64.77%, and 45%, respectively.

Mori and colleagues investigated coronary artery aneurysms formation and the predictive value of Harada score in 193 Japanese children for 30 days.[19] At the end of the research, 12.2% of patients had coronary artery aneurysms. The sensitivity and specificity mentioned in that study were 90% and 51%, respectively.[19] In a similar

study, Kobayashi and others found that the sensitivity and specificity of predicting coronary artery disease were 46% and 86%, respectively.[20] Racial differences seemed to have an impact on the outcomes, as the results differed among races.

In addition, the preliminary study by Harada and others reported 100% sensitivity and 60% specificity for the criteria that they set to predict cardiac complications in KD, which were much higher than other studies.[12] Such a high sensitivity and specificity have not been reported in any other studies.

Other risk scores for indicating IVIG treatment and predicting cardiac complications were suggested. Egami and others proposed a risk score for predicting cardiac complications in KD with 61% sensitivity and 81% specificity.[21] In other studies, Sano[22] and Kobayashi[23] presented two different risk scores. The study risk score developed by Kobayashi had a sensitivity of 77% and a specificity of 86%,[23] whereas the Sano scoring criterion had a sensitivity of 86% and a specificity of 67%.[22] In general, the new risk scores appear to have a higher sensitivity and specificity in predicting coronary artery aneurysms in KD patients than the Harada score. Although our study provided valuable findings regarding the applicability of the Harada score, it was limited to an Iranian population and cannot be generalized to other ethnicities.

Conclusion

The present study on Iranian children found that the Harada scoring criterion had insufficient sensitivity, specificity, and positive and negative predictive values for predicting cardiac complications. Apart from the original study by Harada, no other studies have achieved positive results. Therefore, the Harada criteria do not seem to be very suitable for predicting coronary artery lesions in KD. Thus, a review and investigation of other new criteria are recommended.

Acknowledgment

We would like to express our gratitude to Mashhad University of Medical Sciences Research Vice-Chancellor for approving this research project (Research No: 960367). We would also appreciate Dr. Elham Kargozar for her assistance with the study.

Conflict of Interest: None declared.

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