Research Article

Role of Kobayashi Risk Scoring for Determining Refractory Kawasaki Disease

Seyed-Reza Raeeskarami[1,2], Fatemeh Tahghighi[1], Amir Hossien Ziaee Bigdeli[1], Raheleh Assari[3], Vahid Ziaee[1,4], Yahya Aghighi[1,4] and Payman Sadeghi[1,2,5,*]

[1]Pediatric Rheumatology Research Group, Rheumatology Research Center, Tehran University of Medical Sciences, Tehran, Iran
[2]Bahrami Children's Hospital, Tehran University of Medical Sciences, Tehran, Iran
[3]Vali-Asr Hospital, Imam Khomeini Complex, Tehran University of Medical Science,Tehran, Iran
[4]Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
[5]Department of Pediatrics, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran

*Corresponding author: Pediatric Rheumatology Research Group, Rheumatology Research Center, Bahrami Children's Hospital, Tehran University of Medical Sciences, Tehran, Iran. Tel: +98-9196050335, Email: p-sadeghi@tums.ac.ir

Received 2018 February 04; Revised 2018 September 22; Accepted 2018 October 07.

Abstract

Background: Coronary complications are common in children with Kawasaki disease (KD). Administration of intravenous immunoglobulin (IVIG) during the first 10 days will result in lower coronary complications. It is useful to predict if a patient will develop coronary complications or not.
Objectives: We designed this study to evaluate the role of Kobayashi risk scoring for determining refractory KD.
Methods: Medical records of all cases with KD were reviewed and demographic data, previous history, coronary artery involvement, laboratory findings, and days with fever were extracted for all cases. Kobayashi score was calculated.
Results: A total of 168 cases enrolled. There was no significant difference regarding Kobayashi score in different groups regarding coronary involvement. In cases without coronary involvement, 93.5% were classified as low risk, in one and two vessels involvement groups, all were categorized as low risk, and among three vessels involvement cases, 75% were known as low risk.
Conclusions: Kobayashi score is not useful for predicting severity of coronary involvement in Kawasaki disease.

Keywords: Kobayashi, Kawasaki, Iran

1. Background

Kawasaki disease (KD) is an acute, febrile, and systemic vasculitis with unknown etiology while special infections and super-antigens are considered to have roles in disease development (1, 2). Its prevalence in Asian countries was estimated as 239 cases per 100000 children less than five years old (3, 4).

High grade fever, rash, redness of the lips and a typical strawberry tongue, cervical lymph node enlargement, and swelling over the hands/feet are common presentations of the disease (5, 6). One of the most common complications of KD is cardiac complications, which is present with coronary artery disease, myocarditis, and pericarditis (2). Coronary artery disease remains as the most prevalent cardiac complication presenting in one fourth of untreated children (7, 8).

Administration of intravenous immunoglobulin (IVIG) during the first 10 days after symptoms detection will result in lower coronary artery aneurysm between 10% - 21% of cases could show drug resistance (9, 10).

2. Objectives

Recently, researchers focus on the predictors of IVIG resistance in children with KD to add additional therapies. We designed this study to evaluate the role of Kobayashi risk scoring for determining refractory KD.

3. Methods

This retrospective study conducted in the children wards of all affiliated hospitals of TUMS (Tehran University of Medical Sciences) between October 2014 and October 2016.

Medical records of all cases with KD were reviewed and demographic data, previous history, coronary artery involvement, valvular diseases, laboratory findings, and days with a fever were extracted for all cases. Then, Kobayashi

score was calculated. Patients divided into low and high-risk groups due to Kobayashi score: low risk, Kobayashi score less than four, and high-risk group (Kobayashi score more than four).

Data analysis was conducted by means of SPSS software version 22 (IBM, Chicago, IL, USA).

Data were presented as mean $\pm$ SD for continuous variables and frequencies for categorical ones. ANOVA was used for comparing continuous variables. P value less than 0.05 was considered to be significant.

4. Results

A total of 168 cases were enrolled. Fifty-six (33%) were female and 112 (67%) were male. Four cases (2.4%) had pulmonary diseases, four (2.4%) had hypertension, and five (3.1%) had a family history of Kawasaki disease. The most common echocardiographic finding was mitral regurgitation (Table 1).

Table 1. Echocardiographic Findings[a]

Variable	Valvular Involvement
MR	36 (21.4)
TR	12 (7.1)
MR + TR	20 (11.9)
MR + TR + PI	4 (2.4)
Kobayashi score	
Low risk	156 (92.9)
High risk	12 (7.1)

Abbreviations: MR, mitral regurgitation; PI, pulmonary insufficiency; TR, tricuspid regurgitation.
[a] Values are expressed as No. (%).

There was no significant difference regarding the Kobayashi score in different groups regarding coronary involvement (Table 2).

Table 2. Kobayashi Score in Different Coronary Group

Coronary Involvement	Kobayashi Score	P Value
No involvement	1.9 $\pm$ 1.1	
One vessel involvement	2.3 $\pm$ 0.9	
Two vessels involvement	1.7 $\pm$ 0.8	0.6
Three vessels involvement	2 $\pm$ 1.9	

In cases without coronary involvement, 93.5% were classified as low risk, in one and two vessels involvement groups, all were categorized as low risk and among three vessels involvement cases, 75% were known as low risk.

5. Discussion

The results of the current study showed that Kobayashi score is not proper for predicting coronary involvement in children with Kawasaki disease.

In Japan, Kobayashi score is well established and valuable. Sleeper et al., in 2011, found that the Kobayashi scoring system is not useful for children with KD who live in North America (10).

Previous studies conducted in the USA and UK to determine predictive values of Kobayashi score for IVIG resistance found that the sensitivities were 42% and 58% while the specificities were 87% and 35% (10, 11). In another study in China, Fu et al., reported sensitivity and specificity of Kobayashi score for IVIG resistance as 49% and 72% (12).

KD is a vasculitis with incidence of 7.3 per 100000 in Iranian children (13), which occurs mostly in cases under 5 years (the peak incidence is three to five months for girls and three to five months and at nine to 11 months for boys) (2, 14).

One of the most complications of KD is coronary artery aneurysm while longer duration of fever is strongly associated with coronary artery aneurysm (15).

In one fourth of untreated children, coronary aneurysm occurs while IVIG treatment reduces this rate to 5% (8, 16).

Although timely administration of IVIG will reduce complications, between 10% to 20% of children do not respond to treatment who are at a higher risk of coronary complications (17).

Determining cases who are at a higher risk of developing coronary complications is valuable to protect against ongoing problems. Kobayashi scoring system is helpful in predicting IVIG resistance cases to initiate suitable treatment (18).

In this study, coronary involvement was detected in 26% and Kobayashi score was not predictive of severity of coronary involvement. In a previous study conducted by Zhao et al. (19), the prevalence of coronary artery complications in KD patients was reported as 36%, while this rate was 31.7% in the study of Deng et al. (20).

More studies are needed to evaluate the role of Kobayashi scoring system for predicting severity of coronary artery lesions in Iranian children with KD.

5.1. Conclusions

Kobayashi score is not useful for predicting severity of coronary involvement in children with Kawasaki disease.

Footnotes

data, wrote the manuscript, and is guarantor. The others contributed to the development of the protocol, abstracted data, and prepared the manuscript.

Ethical Considerations: All parents filled informed consent forms.

References

1. Council on Cardiovascular Disease in the Young; Committee on Rheumatic Fever Endocarditis and Kawasaki Disease; American Heart Association. Diagnostic guidelines for Kawasaki disease. *Circulation*. 2001;**103**(2):335–6. doi: 10.1161/01.cir.103.2.335. [PubMed: 11208699].

2. Sepahi MA, Miri R, Ahmadi HT. Association of sterile pyuria and coronary artery aneurysm in Kawasaki syndrome. *Acta Med Iran*. 2011;**49**(9):606–11. [PubMed: 22052144].

3. Makino N, Nakamura Y, Yashiro M, Ae R, Tsuboi S, Aoyama Y, et al. Descriptive epidemiology of Kawasaki disease in Japan, 2011-2012: From the results of the 22nd nationwide survey. *J Epidemiol*. 2015;**25**(3):239–45. doi: 10.2188/jea.JE20140089. [PubMed: 25716368]. [PubMed Central: PMC4341001].

4. Malekzadeh I, Ziaee V, Sadrosadat T, Moardinejad MH, Sayadpour-Zanjani K. Kawasaki disease and peripheral gangrene in infancy. *Iran J Ped*. 2015;**25**(6). doi: 10.5812/ijp.3309.

5. Singh S, Kansra S. Kawasaki disease. *Natl Med J India*. 2005;**18**(1):20–4. [PubMed: 15835487].

6. Nabavizadeh SH, Safari M, Amin R. Hair loss as a sign of Kawasaki disease. *Iran J Allergy Asthma Immunol*. 2006;**5**(4):199–200. [PubMed: 17237574].

7. Ozen S, Orhan D. *Renal involvement in children with vasculitis*. Berlin, Heidelberg: Springer; 2014.

8. Han RK, Sinclair B, Newman A, Silverman ED, Taylor GW, Walsh P, et al. Recognition and management of Kawasaki disease. *CMAJ*. 2000;**162**(6):807–12. [PubMed: 10750471]. [PubMed Central: PMC1231277].

9. Kibata T, Suzuki Y, Hasegawa S, Matsushige T, Kusuda T, Hoshide M, et al. Coronary artery lesions and the increasing incidence of Kawasaki disease resistant to initial immunoglobulin. *Int J Cardiol*. 2016;**214**:209–15. doi: 10.1016/j.ijcard.2016.03.017. [PubMed: 27070994].

10. Sleeper LA, Minich LL, McCrindle BM, Li JS, Mason W, Colan SD, et al. Evaluation of Kawasaki disease risk-scoring systems for in-

11. travenous immunoglobulin resistance. *J Pediatr*. 2011;**158**(5):831–5. doi: 10.1016/j.jpeds.2010.10.031. [PubMed: 21168857]. [PubMed Central: PMC3075321].

11. Davies S, Sutton N, Blackstock S, Gormley S, Hoggart CJ, Levin M, et al. Predicting IVIG resistance in UK Kawasaki disease. *Arch Dis Child*. 2015;**100**(4):366–8. doi: 10.1136/archdischild-2014-307397. [PubMed: 25670405].

12. Fu PP, Du ZD, Pan YS. Novel predictors of intravenous immunoglobulin resistance in Chinese children with Kawasaki disease. *Pediatr Infect Dis J*. 2013;**32**(8):e319–23. doi: 10.1097/INF.0b013e31828e887f. [PubMed: 23446442].

13. Saffar MJ, Reshidighader F. Kawasaki disease in East Mazandaran, Islamic Republic of Iran, 1997-2002. *East Mediterr Health J*. 2005;**11**(1-2):28–35. [PubMed: 16532668].

14. Marcdante K, Kliegmen R, Macdante K, Jenson H, Behramn R, Robert M, et al. *Nelson essentials of pediatrics*. 5th ed. Philadelphia: WB Saunders; 2006.

15. Yeo Y, Kim T, Ha K, Jang G, Lee J, Lee K, et al. Incomplete Kawasaki disease in patients younger than 1 year of age: A possible inherent risk factor. *Eur J Pediatr*. 2009;**168**(2):157–62. doi: 10.1007/s00431-008-0722-1. [PubMed: 18478263].

16. Kiani A, Rafieyian S, Roodpeyma S, Sefidgarnia M. The relationship between coronary artery aneurysm and QT interval dispersion in acute phase of Kawasaki disease. *Iran J Pediatr*. 2011;**21**(2):220–4. [PubMed: 23056791]. [PubMed Central: PMC3446150].

17. Shin J, Lee H, Eun L. Verification of current risk scores for Kawasaki disease in Korean children. *J Korean Med Sci*. 2017;**32**(12):1991–6. doi: 10.3346/jkms.2017.32.12.1991. [PubMed: 29115081]. [PubMed Central: PMC5680498].

18. Kobayashi T, Inoue Y, Takeuchi K, Okada Y, Tamura K, Tomomasa T, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation*. 2006;**113**(22):2606–12. doi: 10.1161/CIRCULATIONAHA.105.592865. [PubMed: 16735679].

19. Zhao CN, Du ZD, Gao LL. Corticosteroid therapy might be associated with the development of coronary aneurysm in children with Kawasaki disease. *Chin Med J (Engl)*. 2016;**129**(8):922–8. doi: 10.4103/0366-6999.179801. [PubMed: 27064036]. [PubMed Central: PMC4831526].

20. Deng YC, Wang X, Tang XC, Huang CZ, Yang J, Mo LY. [Risk factors for coronary artery lesions secondary to Kawasaki disease in children]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2015;**17**(9):927–31. Chinese. [PubMed: 26412172].