



# Coronary Artery Involvement Kawasaki Disease Versus Non-Kawasaki Febrile Diseases in Children Attending a Pediatric Hospital in Bandar Abbas

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Received 2018 November 26; Accepted 2018 November 26.

## Abstract

**Background:** Kawasaki disease (KD) is one of the main causes of acquired heart disease. Due to the fact that there is no prospective study regarding the involvement of coronary arteries in patients with non-KD febrile diseases.

**Objectives:** The aim of this study was to compare coronary artery changes between non-KD febrile children and patients with (complete) KD who were hospitalized.

**Methods:** This study was performed on 56 patients aged one month to eight years (26 KD cases and 30 non-KD febrile cases) admitted to the Bandar Abbas Pediatric Hospital. After obtaining parental or guardian consent, demographic data, coronary artery involvement, and lab tests were recorded. Chi-square and Student's *t*-test were used to compare the recorded data.

**Results:** We found that coronary artery involvement was significantly higher in KD cases (50% vs. 6.7%), especially left coronary artery (LCA) dilatation (30.8% vs. 3.3%) and right coronary artery (RCA) brightness (11.5% vs. 0%) were significantly higher in KD cases compared to non-KD febrile cases ( $P = 0.05$ ). Meanwhile, we found that in both non-KD febrile cases and KD cases with  $WBC \geq 15 \times 10^9/L$  the risk of abnormal findings increased.

**Conclusions:** These findings suggests that non-KD febrile children, especially those with  $WBC \geq 15 (10^9/L)$ , as well as all KD cases should undergo echocardiography five to six days after the onset of the illness.

**Keywords:** Kawasaki Disease, Cardiovascular Diseases, Coronary Artery, Vasculitis, Echocardiography, Coronary Aneurysm

## 1. Background

Kawasaki disease (KD) is an acute febrile vasculitis syndrome in children and the leading cause of acquired heart disease worldwide, which involves the coronary arteries (1, 2). KD is more common in boys than girls, in those of an Asian ethnicity than those of other ethnicities (3), and in children between six months and five years of age than any other age groups (4). Coronary artery involvement develops in up to 25% of untreated KD cases with 2% to 3% mortality rate due to coronary vasculitis (1). The etiology of coronary artery involvement is unknown, however, some studies demonstrated that acquired heart disease is associated with systemic inflammation, infectious agents, toxins, immune system activation, and increased cytokine production and is characterized by clinical manifestations and laboratory features (4). The diagnosis of complete KD requires a fever plus four other signs including conjunc-

tivitis, cervical lymphadenopathy, changes to lips or oral mucosa, rash, and changes to extremities-although not necessarily all at the same time (5). Thus, patients with less than the above four features, especially a fever with duration of five days or more, may be diagnosed with incomplete KD; in addition, treatment such as intravenous immunoglobulin (IVIG) is started for them, which is expensive (5). Prompt treatment with IVIG has been shown to treat all signs of KD and significantly decreases the risk for development of coronary artery aneurysms (6). Moreover, patients with incomplete presentation have a risk of coronary artery aneurysm formation, which is at least as high as the risk among patients with complete manifestations of KD (7, 8). Moreover, coronary artery dilatation has been known to occur in various other inflammatory diseases manifesting fever, such as Epstein-Barr virus infection, rickettsial infection, and systemic-onset juvenile

idiopathic arthritis (9-12). Therefore, evaluating coronary changes in both groups of patients with proved KD and fever without KD is needed. To the best of our knowledge, there are not enough prospective studies regarding this issue.

## 2. Objectives

We designed this study to evaluate and compare coronary artery involvement between non-KD febrile children and patients with (complete) KD who were hospitalized.

## 3. Methods

### 3.1. Participants

This case-control study was conducted in Bandar Abbas Pediatric Hospital, from January 2016 to March 2017. All cases were primarily hospitalized and evaluated by a pediatrician, and KD diagnosis was confirmed. Inclusion criteria for patients with the complete criteria of KD included fever (axillary temperature  $> 37.5$  °C) with duration of at least five days plus at least four of the other characteristics of the illness (including bilateral and non-suppurative conjunctivitis, large cervical lymphadenopathy ( $> 1.5$  cm and usually unilateral), polymorphous rash, changes in lips or oral mucosa and changes in extremities), age of one month to eight years, negative blood and urine culture as well as negative clinical findings for other infectious causes (measles, scarlet fever, adenovirus infection, Toxic Shock Syndrome, leptospirosis), and informed parental (or guardian) consent to participate in the study. Inclusion criteria for patients with non-KD febrile diseases included fever (axillary temperature  $> 37.5$  °C) with a duration of five days or more, age of one month to eight years, and informed consent to participate in the study.

Exclusion criteria consisted of cases with symptoms of measles, scarlet fever, adenovirus infection, toxic shock syndrome, leptospirosis, autoimmune diseases, Behcet's disease, juvenile idiopathic arthritis with systemic onset and congenital heart disease (structural or functional heart disease), family history of hypertrophic or dilated cardiomyopathy, preexisting systemic disorder, clinical conditions that made coronary artery imaging impractical, such as inability to change position, systemic hypertension, weight for height  $> 95$ th percentile or  $< 5$ th percentile, and lack of parental cooperation or consent to participate in the study.

For all patients, axillary temperature was obtained every six hours by a standard mercury thermometer. A blood sample was obtained from all patients in order to measure the WBC count and other laboratory variables needed for

the study including ESR and CRP (all measured by the same standardized laboratory kit).

Coronary artery involvement was assessed by means of echocardiography using the Vivid S5 Cardiovascular Ultrasound System manufactured by GE Healthcare in the United States. All the echocardiographic cardiovascular assessments were performed by a single specialist and the same aforementioned equipment.

### 3.2. Study Design

We evaluated 65 cases with KD and non-KD febrile diseases based on the inclusion and exclusion criteria whose diagnosis of KD had been confirmed by a pediatrician (Figure 1). The study received an ethics approval from the Ethics Committee of Hormozgan University of Medical Sciences.

Demographic data and disease information were recorded in a prepared questionnaire. We also extracted the variables including WBC count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and duration of fever (Table 1).

Coronary artery changes were evaluated by echocardiography (Table 2). Coronary artery changes and normal limits were based on BSA (coronary artery diameter matched to the surface area of the body) and the diameter of the coronary artery was measured in millimeters). Given that the best time to do the echocardiography is in the first 10 days of the disease, we performed the echocardiography in the fifth or sixth day of the disease (based on the inclusion criteria of persisting fever for five days or more).

### 3.3. Data Analysis

Statistical analysis of data was performed using SPSS software version 24 (SPSS Inc., Chicago, IL, USA). Chi-square test and Fisher's exact test were used to compare qualitative variables between groups. Kolmogorov-Smirnov test was used in order to evaluate the normal distribution of all quantitative parameters studied. Student's *t*-test was used to analyze variables with normal distribution, on the other hand Mann-Whitney and Wilcoxon tests were used for variables without normal distribution. The two-tailed *P* value less than 0.05 was considered significant.

## 4. Results

This study was performed on 56 patients (26 KD cases and 30 non-KD febrile cases). The mean age of the patients was  $3.22 \pm 2.32$  y (one months to eight y). We found that age ( $P = 0.861$ ), studied laboratory tests (WBC ( $P = 0.126$ ) and CRP ( $P = 0.12$ )) and fever duration ( $P = 0.926$ ) did not differ

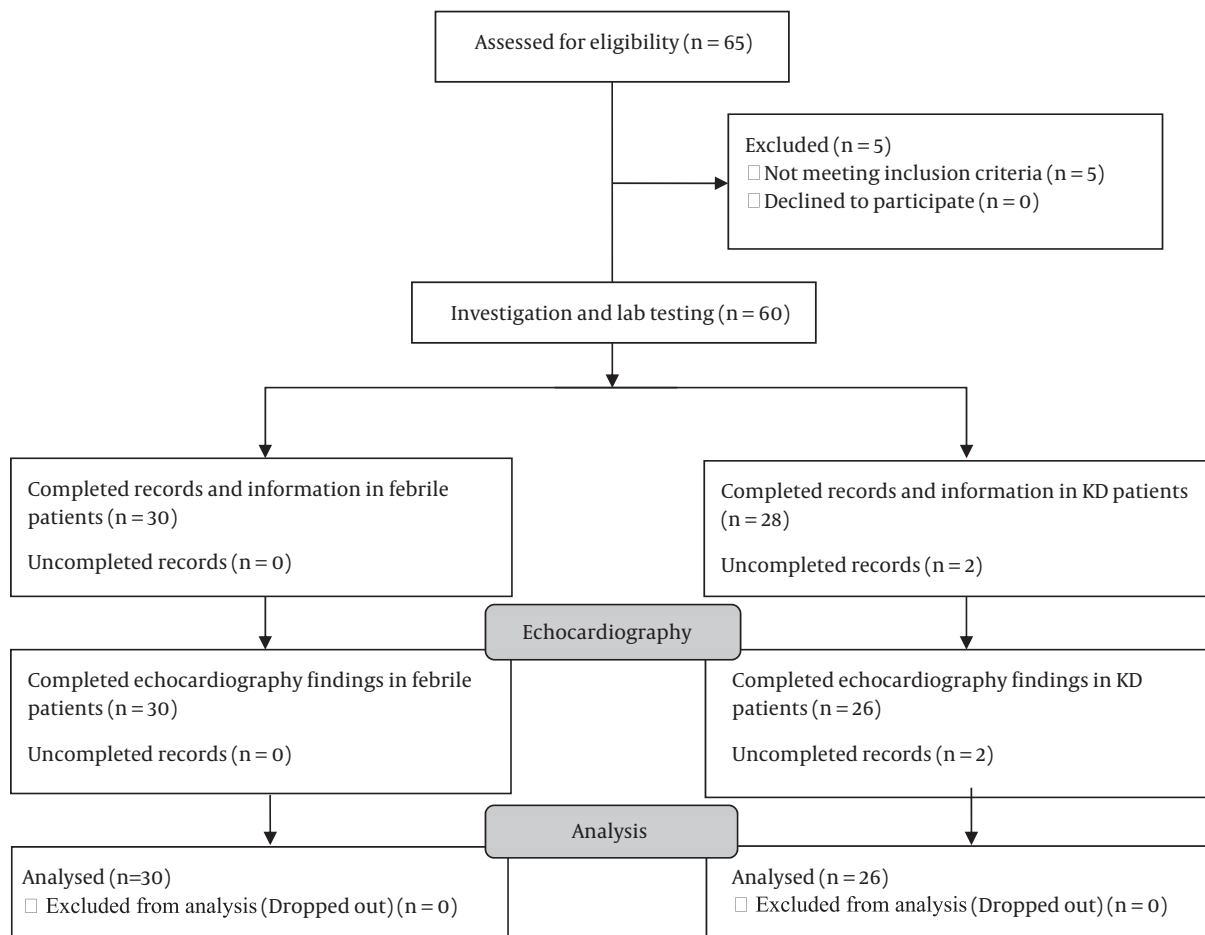


Figure 1. Study flowchart

Table 1. Demographic Data and Laboratory Findings in Both KD and Non-KD Febrile Patients

Variables	KD Group (n = 26)	Febrile Non-KD Group (n = 30)	P Value
Age (y)	3.44 ± 2.91	3.03 ± 1.68	0.861
Sex (male)	21 (80.8%)	15 (50%)	0.017
WBC (10 <sup>9</sup> /L)	14107.69 ± 4700.97	12023.33 ± 5255.58	0.126
ESR (mm/h)	71.65 ± 28.6	53.1 ± 31	0.031
CRP (mg/L)	53.42 ± 31.49	42.1 ± 34.34	0.12
Fever duration (d)	7.11 ± 1.98	7.23 ± 2.35	0.926

significantly between the two groups. While, male gender was significantly higher in KD cases compared to non-KD febrile cases (80.8 % vs. 50%) (P = 0.017). Moreover, ESR was significantly higher in KD subjects (71.65 ± 28.6 vs. 53.1 ± 31 mm/h) (P = 0.031).

Evaluating the echocardiography findings, we found that the total percentage of abnormal findings was signif-

icantly higher in KD cases (50% vs. 6.7 %), especially left coronary artery (LCA) dilatation (30.8 % vs. 3.3%) and right coronary artery (RCA) brightness (11.5% vs. 0%) were significantly higher in KD cases compared to non-KD febrile cases (P = 0.05).

Abnormal echocardiography findings were significantly higher in both age groups in the KD group (P = 0.004

**Table 2.** Echocardiography Findings in Both KD and Febrile Patients

Echocardiography Findings	KD Group (n = 26) <sup>a</sup>	Febrile Non-KD Group (n = 30) <sup>a</sup>	P Value
Normal	13 (50)	28 (93.3)	
Pericardial effusion	1 (3.8)	1 (3.3)	
LCA dilatation	8 (30.8)	1 (3.3)	0.05
TR	1 (3.8)	0	
RCA brightness	3 (11.5)	0	

<sup>a</sup> Values are presented as No. (%).

for < 5 y and  $P = 0.021$  for  $\geq 5$  y)(Table 3). In addition, abnormal echocardiography findings were significantly higher in the KD group based on gender ( $P = 0.011$  for males and  $P = 0.032$  for females), ESR ( $P = 0.044$  for  $ESR < 40$  mm/h and  $P = 0.017$  for  $ESR \geq 40$  mm/h), and duration of fever ( $P = 0.027$  for fever < 7 d and  $P = 0.014$  for fever  $\geq 7$  d). Similarly, abnormal findings were significantly higher in the KD group for  $WBC < 15000/\mu L$  ( $P < 0.001$ ) and  $CRP \geq 3$  mg/L ( $P = 0.001$ ); however, for  $WBC \geq 15000/\mu L$  there was no significant difference between the two groups regarding abnormal echocardiography findings ( $P = 0.323$ ). In general, by grouping individuals based on demographic features (age and sex) and lab tests (except  $WBC \geq 15$  ( $10^9/L$ )), we found that the total percentage of abnormal echocardiography findings in KD cases was significantly higher than febrile cases ( $P < 0.05$ ).

## 5. Discussion

The results of this study showed that abnormal findings of echocardiography in KD subjects were significantly higher compared to non-KD febrile subjects, while in non-KD febrile cases with  $WBC \geq 15$  ( $10^9/L$ ), we found that the risk of abnormal findings increased and was the same as KD cases.

In a study performed by Muniz et al., it was demonstrated that the mean coronary artery dimension in children with non-KD febrile disorders was larger than control subjects, however, smaller than patients with KD (13). They found that abnormal findings of echocardiography, especially LCA dilatation, were significantly higher in KD cases and were higher than the normal population in children with non-KD febrile illness. On the other hand, Sarkar et al. showed that among the children with non-KD febrile illness, 76% were from extremes of ages and 19.2% had coronary involvement, moreover myocarditis (38.1%) was the most common non-coronary finding (14). Vijayan et al. demonstrated that coronary involvement was more common in incomplete KD patients (91.6%) compared to KD cases (41.1%) and they concluded that children presenting

with incomplete Kawasaki criteria are at a higher risk of coronary artery involvement (15). However, we found that only 6.7% of non-KD febrile cases had coronary involvement. The differences in frequency of coronary involvement may be due to different sample size, different inclusion and exclusion criteria, and different demographic features of the studied samples.

Sudo et al. showed that the prevalence of coronary artery lesions development was higher in classic KD and the proportion of patients receiving initial IVIG treatment was significantly smaller in patients with incomplete KD compared to classic KD. Moreover, a fever more than seven days was significantly associated with the development of coronary artery lesions in all the patients in the incomplete KD group (16). However, we found that  $WBC \geq 15$  ( $10^9/L$ ) is the most important risk factor for coronary artery development in non-KD febrile cases.

In another study performed by Kuwabara et al., it was reported that KD patients are at a higher risk of coronary dilatation, giant coronary aneurysms, coronary aneurysms, valvular lesions, and coronary narrowing; moreover, they demonstrated that male gender, older age, high platelet levels, lower albumin serum levels, and higher CRP levels are the risk factors for cardiac lesions in KD patients (17). While, we found that ESR levels were higher in KD subjects compared to children with non-KD febrile illness, and more subjects in the KD group were of the male gender in comparison with the non-KD febrile illness group; both of which may play an important role in finding abnormal changes in coronary arteries via echocardiography.

A'rabi Moghadam et al. showed that 69% of KD cases did not have any signs of cardiac involvement; meanwhile, coronary artery aneurysm was detected in 13% of subjects, pericardial effusion in 11%, EKG changes and cardiomegaly in 8% of patients, and mild mitral regurgitation was observed in 10% of KD cases (18). These results were in accordance with our findings and they prove the fact that classic KD illness is a risk factor for coronary artery involvement. On the contrary, coronary artery involvement was signifi-

**Table 3.** Abnormal Echocardiography Findings in Both KD and Febrile Non-KD Patients Based on Age, Sex, WBC Count, ESR, CRP, and Duration of Fever

Variables	Total in KD Group	Total in Non-KD Febrile Group	Abnormal Echo in KD Group <sup>a</sup>	Abnormal Echo in Non-KD Febrile Group <sup>a</sup>	P Value
Age < 5 y	18	22	9 (50)	2 (9.1)	0.004
Age ≥ 5 y	8	8	4 (50)	0	0.021
<b>Sex</b>					
Male	21	15	10 (47.6)	1 (6.7)	0.011
Female	5	15	3 (60)	1 (6.7)	0.032
WBC count < 15 (10 <sup>9</sup> /L)	14	20	9 (64.3)	1 (5)	< 0.001
WBC ≥ 15 (10 <sup>9</sup> /L)	12	10	4 (33.3)	1 (10)	0.323
ESR < 40 (mm/h)	4	13	2 (50)	0	0.044
ESR ≥ 40 (mm/h)	22	17	11 (50)	2 (11.8)	0.017
CRP < 3 (mg/L)	0	3	0	0	-
CRP ≥ 3 (mg/L)	26	27	13 (50.0)	2 (7.4)	0.001
Fever duration < 7 d	11	16	5 (45.5)	1 (6.2)	0.027
Fever duration ≥ 7 d	15	14	8 (53.3)	1 (7.1)	0.014

<sup>a</sup> Values are presented as No. (%).

cantly lower in febrile non-KD cases and the only risk factor for developing cardiac involvement in this group was WBC ≥ 15 (10<sup>9</sup>/L).

One of the limitations of our study was it being conducted in a single center, which makes external validation of our study prone to controversy. Another limitation of our study was that although the definition of some of the coronary artery involvements, such as the perivascular brightness of the coronary arteries was consensual among all cardiologists of our hospital, it remains a rather subjective criterion; therefore, a more objective criterion, for instance Z-scores, should be considered in future studies.

Our results suggest that performing echocardiography in non-KD febrile patients with high WBC counts and all patients suspicious of KD should be taken into consideration to be able to timely administrate an adequate amount of IVIG in order to avoid the development of coronary artery lesions or further exacerbation of such lesions if already present.

### 5.1. Conclusion

Our results showed that that abnormal echocardiography findings in KD subjects was significantly higher than non-KD febrile subjects, while in non-KD febrile cases with WBC ≥ 15 (10<sup>9</sup>/L) the risk of abnormal findings increased and was the same as KD cases. Our findings suggest that non-KD febrile children, especially those with WBC ≥ 15 (10<sup>9</sup>/L), and all KD cases should undergo echocardiography five to six days after the onset of the illness. Future studies should be performed on larger samples and should assess

the value of using subjective echocardiography findings, in addition to standardized measurements (Z-scores), for risk stratification purposes.

### Supplementary Material

Supplementary material(s) is available [here](#) [To read supplementary materials, please refer to the journal website and open PDF/HTML].

### Acknowledgments

We gratefully acknowledge the dedicated efforts of the investigators, the coordinators, the volunteer patients who participated in this study, and the Clinical Research Development Unit (CRDU) of Bandar Abbas Pediatric Hospital.

### Footnotes

**Conflict of Interests:** The authors have indicated that they have no conflicts of interest regarding the contents of this article.

**Ethical Considerations:** The study received the ethics approval from the Ethics Committee of Hormozgan University of Medical Sciences.

**Funding/Support:** This study was financially supported by Hormozgan Medical Sciences University, Hormozgan, south of Iran.

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