Original Article

Coronary Complications of Kawasaki Disease: Novel Diagnosis Based on Z-score and Absolute Dimension

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Abstract

Background: Kawasaki Disease or KD (also known as mucocutaneous lymph node syndrome) is an acute, febrile, mucocutaneous condition accompanied by swelling of cervical lymph nodes in infants and young children. Regarding serious coronary complications of the disease, the coronary effects and consequences of the disease in KD diagnosed children were investigated at Ayatollah Mousavi Hospital of Zanjan during 2013 to 2017.

Methods: This is a cross-sectional study in which 40 diagnosed cases of KD were evaluated from 2013 to 2017. At the time of diagnosis and 2 to 4 years later, the necessary measures were taken to check cardiovascular complications. After documenting informed consent, the patients underwent follow up echocardiography and electrocardiography. The data analysis was performed by statistical software, SPSS-18.

Results: Totally, 21 patients participated in the follow up. The results were analyzed and compared based on coronary artery dimension and Z-score reference values. Next, left coronary artery size was calculated in primary echocardiography based on Z-score in terms of body surface area. In primary echocardiography, Left Coronary Artery (LCA) size was within the reference range in 36 patients (90%) and abnormalities were observed in 4 patients (10%). In the follow up echocardiography, 21 patients revisited (2 of the 4 patients with abnormal findings) and all of them were reported to be within the reference range (p=0.02). Regarding Right Coronary Artery (RCA), findings from primary echocardiography were normal in 38 patients (95%) and abnormal in 2 patients (5%), and based on follow up echocardiography, RCA sizes of all patients were in reference range (p=0.15). Interestingly, 2 patients were within the normal range based on coronary artery dimension, but were included in the dilation range using the Z-score; also, 2 patients who were in the dilated coronary artery range measured by the coronary artery dimension criterion, were included in the normal range by the Z-score.

Conclusion: To prevent missed diagnosis and further complications, it is recommended to use standard Z-score based on body surface area to diagnose coronary artery aneurysm in addition to merely measuring the diameter of the vessels.

Keywords: Coronary aneurysm, Echocardiography, Kawasaki disease, Mucocutaneous lymph node syndrome

Introduction

Kawasaki is an acute, self-limiting disease associated with multi-systemic vasculitis, which approximately in 90% of cases occurs in children under the age of 5 (1,2). This disease is a type of acute vasculitis and often involves medium-sized vessels, especially coronary arteries, and is considered the most common cause of acquired heart disease (3-5).

Coronary artery disease is one of the most common and major cardiovascular complications of Kawasaki Disease (KD), and the most common presentation of coronary artery complications is coronary aneurysms which can vary from mild dilation to giant Coronary Artery Aneurysms (CAA) and the morbidity and mortality of KD is commonly due to giant CAA. Coronary artery disease can be associated with rare but dangerous complications, including myocardial infarction, coronary artery dissection, and fatal dysrhythmias (4,6,7). Although the cardiac involvement can be presented as pancarditis, in 50-70 % of KD cases, myocarditis is the only complication associated with the disease. Pericarditis is another complication that is detected in 0.7% of the cases (4,6,8). Mild changes in the electrocardiogram are seen as P-R prolongation and ST changes (9,10). Coronary artery involvement is the most important complication of KD and is seen in approximately 15–20% of affected patients (11).

The clinical diagnosis of KD is based on the 5 principal clinical criteria. There are no specific para-clinical findings, however, nonspecific changes include leukocytosis, increased ESR and CRP, increased immunoglobulins, thrombocytosis, and anemia (12).

Classically, remittent and high spiking fever over 5 days and the presence of 4 of the following 5 symptoms are the signs of KD: (a) erythema of the oral and pharyngeal mucosa with strawberry tongue and cracking around the lips, (b) various forms of rash, (c) edema (induration) in hands and feet,(d) bilateral non-exudative conjunctival injection with limbal sparing, (e) nonsuppurative cervical lymphadenopathy (13,14).

If the patient did not fully meet the mentioned criteria, Kawasaki was considered incomplete or atypical (15,16).

Although aspirin and high-dose intravenous gamma globulin prescription within the first 10 days and before aneurysm formation and coronary artery involvement may decrease the complications of the disease, cardiac complications occur in 4 to 6% of patients, and approximately 1% of patients develop giant coronary artery aneurysm. It should be noted that the disease is not preventable, but early diagnosis and timely treatment is the best way to reduce further coronary artery complications. Therefore, in the present study, the prevalence of cardiac complications was evaluated in KD patients as well as the consequences of these complications during treatment with aspirin and IVIG (17-22).

Although the mortality rates caused by KD are low, the risk of long term cardiovascular and especially coronary outcome can be increased by missed diagnosis. For a timely and precise diagnosis, the present study was conducted to compare the common methods of assessing the coronary vessels complications.

Materials and Methods

This cross-sectional study was executed considering the ethical codes of Zanjan University of Medical Sciences and obtaining written consent forms from the patients. Forty patients based on the mentioned inclusion criteria who had been admitted to Ayatollah Mousavi Hospital in Zanjan during 2013-2017 were enrolled in the study. Patients included in the study were recalled for reevaluation.

Finally, 21 patients revisited the hospital and were evaluated by echocardiography. Unfortunately, from 4 patients with abnormal findings in Left Coronary Artery (LCA), 2 of them and all of the patients with RCA abnormal findings were evaluated.

Patients were assessed based on demographic data, type of Kawasaki Syndrome (typical or atypical), duration of aspirin use, previous and current echocardiography, previous and current Electrocardiography (EKG), and duration of fever. In echocardiography, coronary artery dimension, mitral and aortic valve insufficiency, presence of fluid in the pericardial cavity, and left ventricular ejection fraction were evaluated. The diagnostic criteria for coronary artery aneurysm were based on the internal diameter of the coronary arterial lumen. Aneurysms are defined as the ones with an internal diameter more than 3 *mm* in cases under 5 years of age and more than 4 *mm* in children over 5 years, or with the diameter of a segment of the artery 1.5 times more than that of an adjacent segment or with significant irregularities of coronary arterial lumen. Giant aneurysms are defined as those with an internal lumen diameter >8 *mm*, or if

the child is >5 years of age, and an internal diameter of a segment measuring 4 times more than that of an adjacent segment (7-9). In addition, information on the dimension of the coronary artery, in *mm*, was included in the Z-score table based on Body Surface Area (BSA) so that age as the confounding variable could be eliminated in coronary artery dimension. Data were analyzed by SPSS-16 software using chi-square and paired T-test ($p< 0.05$) to compare the mean sizes of the coronary arteries at the time of primary admission and follow up.

Results

In this study, 40 patients who had been admitted to Ayatollah Mousavi Hospital in Zanjan between 2013 and 2017 were studied and 21 patients were reevaluated after treatment during the follow up. Of the 40 patients with Kawasaki Syndrome, 21 cases were female and 19 cases were male. Typical KD cases were 32 (82%) and 8 cases (20%) were reported to be atypical. The mean diameters of left coronary artery in primary echocardiography and follow up echocardiography were 2.33±0.98 and 2.07±0.87 *mm*, respectively. The mean diameters of Right Coronary Artery (RCA) in primary echocardiography and follow up echocardiography were 2.01±1.88 and 1.9±0.91 *mm*, respectively (Table 1), (Figure 1).

As it is shown in figure 2, in this study, internal

Table 1. Patients' demographic information on first visit and observed changes following echocardiography

Type of Kawasaki Syndrome	Number (%)
Type of Kawasaki Syndrome Typical Atypical	Number (%) 32 (80%) 8 (20%)
Age at the time of primary admission (Average)	30.8±19.4 months (Minimum: 5, maximum: 101 months)
Age at the time of referral admission (Average)	60.8±10.3 months (Minimum: 11, maximum: 130 months)
Gender Female Male	Number (%) 21 (52.5) 19 (47.5)
Fever Less than 5 days 5-10 days 11-15 days More than 15 days	Number (%) 4 (10) 27 (67.5) 5 (12.5) 5 (10)
Onset of symptoms to initiation of IVIG therapy	9.45±1.2 days (Minimum:0, maximum: 32)
Mean LCA diameter in the first echocardiography	2.33±0.98 (Minimum:1.2, maximum: 5.4)
Mean LCA diameter in the follow up echocardiography	2.07±0.87 (Minimum:1.5, maximum: 3)
Mean RCA diameter in the first echocardiography	2.01±0.88 (Minimum:1.1, maximum: 5)
Mean RCA diameter in follow up echocardiography	1.9±0.91 (Minimum:1.1, maximum: 3.1)
Mean ESR levels	77.5±12.3 (Minimum:3, maximum: 131)
Mean CRP levels	48.1±18.9 (Minimum:0.2, maximum: 111)
Mean platelet levels	121000±512250 (Minimum:100000, maximum: 952000)
Mean primary ejection fraction	60±6.3% (Minimum:55, maximum: 70)
Mean follow up ejection fraction	62.3±3.4% (Minimum:45, maximum: 60)

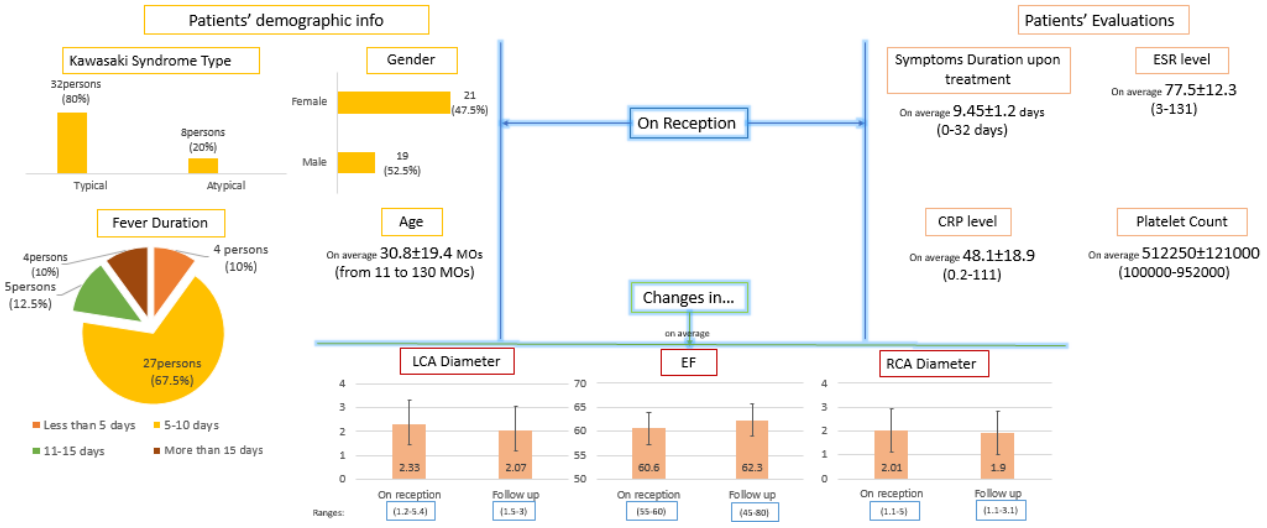

Figure 1. Patients' demographic information, on reception evaluation and changes observed following echocardiography.

diameters of the left coronary artery in terms of size and Z-score were compared in primary and follow up echocardiography. LCA diameter in primary echocardiography examination was normal in 36 patients (90%) and abnormal in 4 patients (10%) based on Z-score and BSA. The internal diameter of the LCA in follow up echocardiography was normal in all patients. However, one of the patients had a LCA diameter greater than 3 *mm* and was reported to be in the dilation range in terms of dimension, but the Z-score, which was less than 2, was within the normal range. In another patient, the diameter of the LCA was less than 3 *mm*, which was normal in terms of dimension, but the Z-score, which was more than 2, was in the dilation range. By Friedman test, Z-scores of the LCA size in the follow up echocardiography were compared with the LCA dimension in the primary echocardiography, which showed a statistically significant difference between the size of the coronary artery before and after the treatment (p=0.02) (Figure 3).

RCA size was assessed in primary echocardiography on the basis of Z-score by BSA, with 38 cases (95%) in the normal range and 2 cases (5%) in the abnormal range. The size of the RCA was also evaluated in the follow up echocardiography based on Z-score in BSA, with all 21 patients in the normal range. Also, 39 cases (97.5%) had a normal RCA diameter in primary echocardiography while RCA diameter of 1 case (2.5%) was in dilation range in terms of size. However, based on the Z-score, 38 cases (95%) were normal and 2

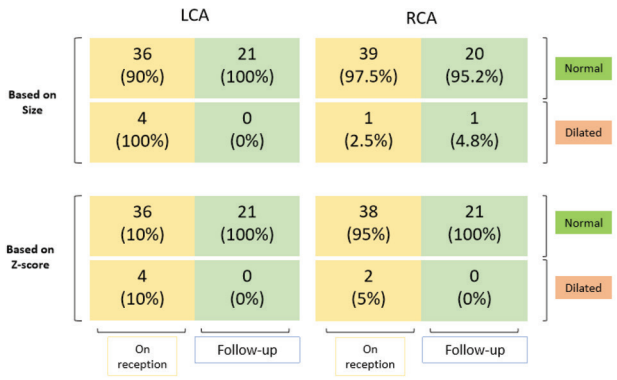

Figure 2. Coronary artery changes (Based on size and Z-score) in primary and follow up echocardiography.

cases (5%) were in dilation range, indicating that RCA diameter of one case was less than 3 *mm* in size but the Z-score suggested the dilatation of RCA (more than 2). Friedman test showed that there was no significant difference between the size of the RCA diameter in follow up echocardiography compared to the RCA diameter in the primary echocardiography on the basis of Z-score (p=0.15).

According to the data from 40 patients, normal echocardiographic values were reported in 24 (60%) patients, comorbid aortic or mitral valve insufficiency in 5 (12.5%) patients, and coronary artery diseases in 10 patients (25%) out of which 5 (12.5%) cases had perivascular brightness in their RCA, 4 (10%) cases had left coronary aneurysm and 1 (2.5%) patient had right coronary aneurysm. One patient also had valvular disorders and left coronary aneurysm at the same time.

After 6 months, only 21 cases referred for

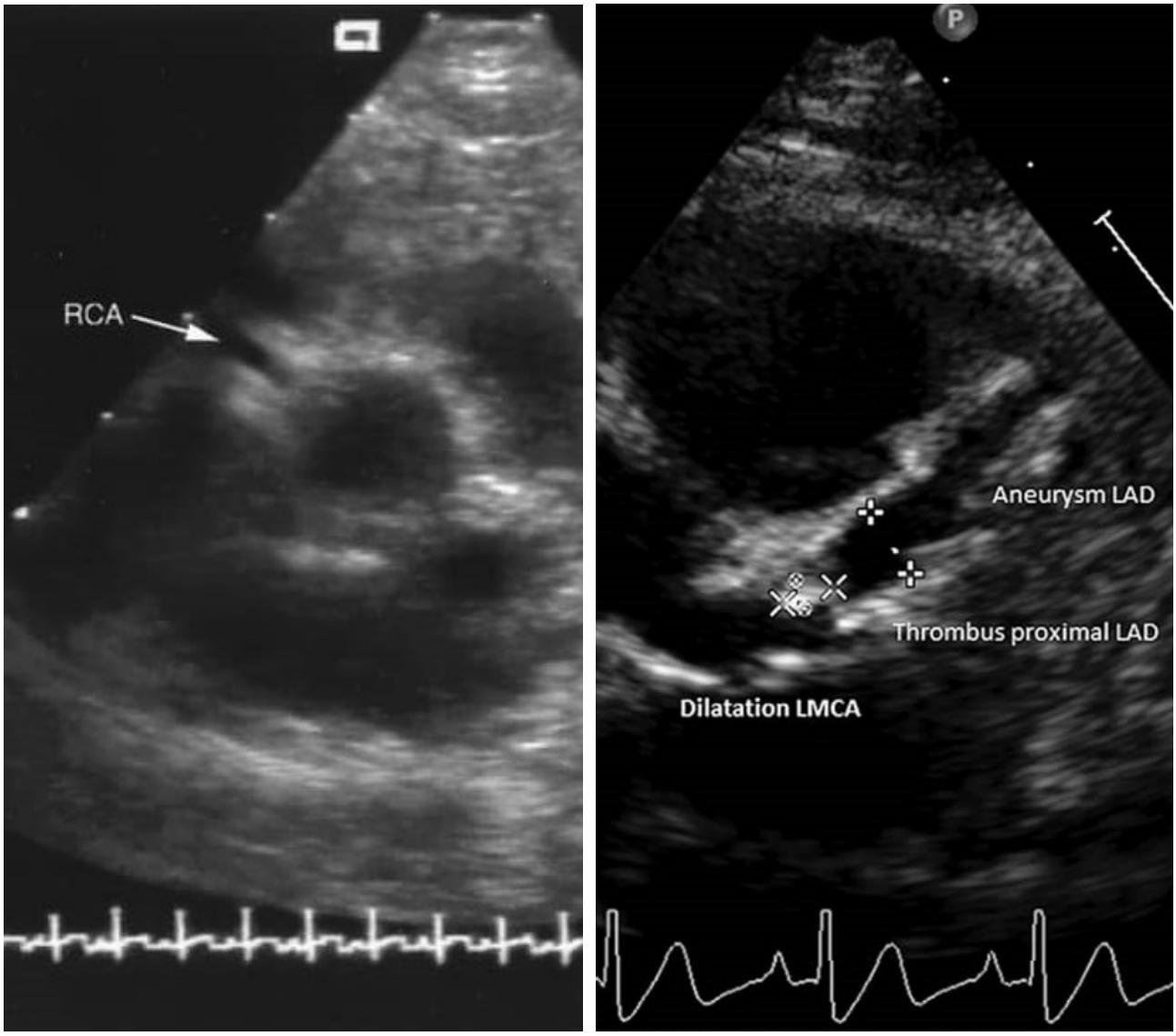

Figure 3. Echocardiography for sizing coronary artery. Internal diameter is measured.

follow up echocardiography, of which 17 (81%) cases were normal and 4 (19%) cases had aortic or mitral valve abnormalities. All 21 patients under observation were also treated with ASA for 6 months.

Discussion

In the present study, patients with KD and coronary artery involvement were assessed. Forty patients, who had been admitted to Ayatollah Mousavi Hospital in Zanjan between 2013 and 2017 were investigated and finally 21 patients were evaluated after follow up. Some measures were taken to decrease the age-related interference of coronary artery size; the results showed that patients can benefit from being evaluated by Z-score besides vascular dimension.

In this study, in addition to demographic variables, type of Kawasaki Syndrome (typical or atypical), duration of ASA use, initiation of IVIG therapy after symptom onset, initial and follow up echocardiography, cardiac ejection fraction, current and previous electrocardiography, and duration of fever were also investigated. The mean age of the patients in first visit was 30.8 months, which was approximately the same as other similar studies. The mean age of patients diagnosed with KD in Holman *et al*'s study was 36 months (23). Among 40 patients, 21 cases (52.5%) were males and 19 cases (47.5%) were females with an approximate ratio of one to one. However, in similar studies, males' rate of infection has been higher than the one in females. In Massibey *et al*'s study, the ratio was 1.75:1 and in Amirimoghadam *et al*'s study was 2:1; also the rate in Huang *et al*'s study in Taiwan was 1.62:1 (8, 24, 25).

Thirty two patients (80%) were diagnosed as typical and 8 patients (20%) as atypical KD cases. In Shamsizadeh *et al*'s study, 61.5% of patients had Kawasaki Symptoms and were considered typical and 38.5% were considered atypical (26). In Manlhiot *et al* study, 77% of cases had typical and 23% had atypical KD (27).

According to our study and previous studies, the majority of patients develop a typical type of disease depending on genetic, physician, and referral system characteristics. ECG was normal for all patients, either typical or atypical KD. Previous studies did not investigate ECG and its course, but this finding may indicate that KD usually does not involve cardiac conduction system (28). The data from the patients' records in our study indicated a normal ejection fraction in all cases. Since studies have not reported any changes in the ejection fraction, and generally compared it with its normal rate in children which is 68% (49 to 86%), it can be concluded that the ejection fraction was relatively reduced.

Given that the patients in our study were children and the mean coronary artery size is significantly different in different age groups, BSA was calculated in this study to eliminate the effect of age-related interference with coronary artery size. Newburger *et al* in 2004, in an effort to modify the recommendations of the American Heart Association on the diagnosis, treatment, and long-term follow up of KD, introduced methods for normalizing coronary artery luminal dimensions of RCA and LCA diameter in echocardiography. Patients with normal coronary artery size in echocardiography were considered abnormal using the Z-score. Thus, Z-score was calculated, using the available tables of the Z-score for determining coronary artery size based on each child's BSA, and the Z-score of more than 2 indicated occurrence of aneurysm (29).

Interestingly, in the present study, 2 patients with normal coronary artery dimension were included in the dilation range using the Z-score. Also, 2 patients who were in the dilated coronary artery range considering coronary artery dimension were included in the normal range by the Z-score. Thus, it can be partly concluded that the coronary artery size is not a reliable parameter for diagnosing coronary artery aneurysm in children.

In this study, the dimension of LCA in primary echocardiography was evaluated based on Z-score and BSA and LCA diameter was reported to be abnormal in 4 cases (10%) in the first echocardiography. But at follow up echocardiography, all 21 (100%) cases were normal. The Friedman test showed that the dimension of the LCA based on the Z-score in the follow up echocardiography was significantly different compared to the dimension of the LCA in the first echocardiography. Coronary artery size decreased after treatment (p=0.02). Of the 4 patients with LCA aneurysm at the first visit, only 2 patients were followed up in our study and both were within the normal range of coronary artery dimension after treatment.

In this study, based on Z score, RCA was normal in 38 cases (95%) and abnormal in 2 cases (5%). RCA dimension in follow up echocardiography was evaluated by Z-score based on BSA, and all 21 cases were in normal range. Friedman test reported no significant difference in RCA size between primary and follow up echocardiography (p=0.15). Of the 2 patients with RCA aneurysm at the first echocardiography, only one patient was included in our study for follow up, who was within the normal range of coronary artery size after treatment. Of the 21 patients referred for follow up, only 2 patients showed coronary artery involvement at the time of diagnosis. One of the patients had RCA and LCA aneurysm at the same time. Both patients' coronary artery dimension was in normal range after treatment and follow up.

Kato *et al* conducted a study with 594 KD patients for 10 to 21 years and 146 cases (24.6%) revealed to have coronary artery aneurysm. After 2 years, all patients with coronary artery aneurysm were evaluated by angiography showing recovery of 72 cases (49.3%). During the 10 to 21 years of follow up, 28 cases of coronary aneurysm developed stenosis, 11 cases developed myocardial infarction, and 5 of them died. Of the 26 cases of giant coronary artery aneurysm, stenosis was observed in 12 patients (18).

In our study, all patients with aneurysm recovered, and no case of myocardial infarction, stenosis, or death was reported, which could be due to the small number of patients, short-term follow up, race, and genetic factors. In this study, following the results of echocardiography, 24 patients (60%) were reported as normal, 5 patients (12.5%) had aortic or mitral valve insufficiency and 10 cases (25%) had coronary artery disease. Among these 10 cases, 5 patients (12.5%) had perivascular brightness in RCA, 4 patients (10%) had left coronary aneurysm and 1 patient (2.5%) had RCA aneurysm.

In Kato *et al* study, 146 patients (24.6%) had coronary artery aneurysm at primary angiography and 448 cases had no abnormal cardiac findings at the moment of diagnosis and during the follow up. This study showed that the prevalence of coronary aneurysm in KD patients was 25% and the recovery rate was 55% (8).

In a study conducted by A'rabi Moghadam *et al* on 61 patients with KD, 42 patients (69%) had no cardiac involvement. Coronary artery aneurysm was detected in 8 patients (13%). Pericardial fluid accumulation was also seen in 11%, cardiomegaly in 8%, and mild mitral valve insufficiency in 10% of cases (30). In a similar study by Huang *et al*, coronary artery aneurysms occurred in 7.2% of cases (25).

As can be seen, the rate of coronary aneurysm incidence, although varying in different studies, is not more than 25% in any of them, indicating a low probability of coronary involvement and valvular involvement, which is also confirmed in our study. However, the incidence of heart disease can be influenced by various factors, such as the interval between the diagnosis and treatment of the disease, treatment protocol, access to standard treatments, racial and genetic characteristics, and so on. More studies are needed to reduce complications and morbidity rate of KD. If all patients had revisited for follow up, it would have been possible to make accurate judgment about the course of the heart disease. However, it can be concluded that in general, cardiac involvement rate declined among the patients with KD, confirming the results of previous studies. In other words, patients with cardiac complications of KD may partly recover with timely and standard treatment over time. In our study, the incidence rate of valvular disorders did not change significantly. On the other hand, valvular abnormalities in the patients studied in our survey were mild and none of them had cardiac symptoms; also, some patients may have had valvular involvement prior to KD. Also, no cases of myocardial infarction, stenosis or death were reported. It is recommended that a large scale study with longer follow up period be performed to evaluate the course of cardiac involvement and to compare the course of coronary and valvular disorders.

Conclusion

The results of this study show that patients with LCA involvement had a significant improvement. Also, the mean development of RCA decreased in the studied patients but was not statistically significant. Also, coronary artery dimension alone cannot be a reliable criterion to assess coronary artery aneurysm in KD in children, and using a Z-score based on BSA chart can provide more accurate information on the extent of coronary artery involvement. By evaluating the vascular dimension criterion alone, which is routinely utilized, normal-sized coronary artery in KD may be considered abnormal using the Z-score criterion, thereby, further complications can be prevented in children by eliminating missed diagnosis. Thus, utilization of Z-score besides artery dimension is recommended. However, due to the small number of the cases and short follow up period, the results of this study cannot be generalized to general population of the patients and further studies can clarify the optimal combination of these methods for clinical applications.

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Conflict of Interest

Authors declare that they have no conflict of interest.

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