

Original Research Article

Clinico-hematological profile and coronary artery changes detected at initial echocardiography in children with Kawasaki disease: a 12 years single centered experience from a tertiary care referral center of Bangladesh

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Received: 31 December 2024

Revised: 04 February 2025

Accepted: 06 February 2025

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ABSTRACT

Background: Kawasaki disease (KD) is the most common cause of acquired heart disease in childhood. Coronary artery abnormalities may occur in 15-25% of children with KD. Our study aimed to analyze the demographic, clinical, laboratory profile and initial echocardiographic changes of coronary arteries among KD patients admitted in a tertiary care center in Bangladesh.

Methods: This was a retrospective study of 66 children diagnosed with KD admitted in the Department of Paediatrics from July 2010 to March 2023 at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Results: We found that 51.5% patients had complete KD while 48.5% had incomplete KD. Clinical profile showed fever, extremity changes, oral mucosal changes, maculopapular rash, cervical lymphadenopathy and non-purulent conjunctivitis in 100%, 72.7%, 68.2%, 62.1%, 50% and 48.5% cases respectively. Echocardiography done at the time of diagnosis demonstrated coronary artery abnormalities among 48.5% cases. Overall, 15.2% cases had small aneurysms, 7.6% patients had medium aneurysms and 4.5% cases had large or giant aneurysms in our study. Majority of the patients had developed LCA abnormalities (42.4%) followed by RCA abnormalities in 21.2% cases and LCX abnormalities in 7.6% cases.

Conclusions: In this study, we observed a slightly higher frequency of the complete KD (51.5%) in comparison to incomplete KD patients. Fever was the most consistent clinical feature followed by extremity changes, oral mucosal changes, maculopapular rash, cervical lymphadenopathy and lastly non-purulent conjunctivitis. Initial echocardiography revealed 48.5% patients with KD had coronary artery abnormalities with a predilection towards left coronary artery.

Keywords: Kawasaki disease, Complete KD, Incomplete KD, Coronary artery aneurysm

INTRODUCTION

Kawasaki disease (KD) is one of the most frequent vasculitis among children below 5 years of age. The exact etiology of this disease is still unknown.¹ This disease was initially narrated by Dr. Tomisaku Kawasaki in 1967.² The incidence of KD is increasing day by day.³ It is 10-30 times more frequent among Northeast Asian countries including Japan, South Korea, China, and Taiwan than that in the

United States of America or European countries. In 2014, 308 per 100000 under 5 children were diagnosed as KD in Japan. In contrast, incidence of KD in United States is 19.1 per 100000 under 5-year-old children in 2015.⁴ The incidence rate of KD in Chandigarh, North India was 4.7/100,000 children in 2009 and 1.11/100,000 in 2012.⁵ KD is diagnosed clinically by the diagnostic criteria mentioned in 2017 American Heart Association (AHA) guidelines.⁶ Children with fever lasting for 5 or more days

along with 4 or more out of the 5 of the major features like conjunctival injection, cervical lymphadenopathy, oral mucosal changes, polymorphous eruption and swelling or redness of the extremities are labelled as complete KD. But patients with ≥ 5 days fever and at least 2 major features that can't be explained by other diseases are diagnosed as incomplete KD.⁶ KD can affect both small and medium sized vessels. Coronary artery abnormalities may occur in 15-25% of children with KD if proper treatment is delayed or not received.^{6,7} It has become the most frequent cause of acquired heart disease in childhood due to its predilection for coronary arteries.^{8,9} Myocarditis and pericarditis are commonly seen in acute phase of KD (initial 10-14 days of illness), whereas coronary artery aneurysm is commonly seen during 2 to 4 weeks of illness.¹⁰ Imaging like echocardiography is helpful for early diagnosis of coronary artery aneurysm, the major complication of KD.¹¹ Previous studies showed that children <12 months and >10 years with KD have more chance of developing coronary artery abnormality.^{12,13} Risk of coronary artery abnormalities highly increased with prolonged fever, initial low hemoglobin according to age and sex, raised neutrophil lymphocyte ratio, initial thrombocytopenia.¹⁴⁻¹⁶ Administration of IVIG within 10 days dramatically reduces the risk of cardiac complications.¹⁷⁻¹⁹ IVIG treatment given after 10 days increases the risk for coronary artery aneurysm by more than 2 folds.²⁰ The incidence of KD is in rising trend globally.²¹ But incident of KD among Bangladeshi children is not published yet through any study. There are only two published studies present on KD among children in Bangladesh.^{22,23} Pediatric rheumatology division in Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), a well renowned tertiary referral center in Bangladesh has been successfully treating children with KD over 12 years. This retrospective study aims to analyze the clinical and hematological profile and coronary artery changes detected at initial echocardiography in children with KD that had been admitted in BSMMU.

METHODS

This retrospective study was performed at in-patient Department of Paediatric Rheumatology Division, Department of Paediatrics, BSMMU, Bangladesh from July 2010 to March 2023. A total of 66 children below the age of 18 years clinically diagnosed as KD according to diagnostic criteria of American Heart Association (AHA) guidelines admitted at in-patient Department of Paediatric Rheumatology Division, Department of Paediatrics, BSMMU during the study period were enrolled as cases in this study.⁶ Children with fever for ≥ 5 days along with ≥ 4 of the major features like conjunctival injection, cervical lymphadenopathy, oral mucosal changes, polymorphous eruption and swelling or redness of the extremities were diagnosed as complete KD. But patients with ≥ 5 days fever and at least 2 major features that can't be explained by other diseases were enrolled as patient with incomplete KD in this study. Meanwhile, KD patients with evidence

of infection, other vasculitis, inflammatory disease or known cases of cardiac disease were excluded from the study.

The study was performed by the ethical standards stated in the 1964 Declaration of Helsinki and its later amendments. Because of the study's retrospective nature, obtaining written informed consent from the patients was not required. The study protocol was reviewed and approved by the ethical committee of BSMMU. All the relevant data were collected from the electronic database and written records of patient's profile of Paediatric Rheumatology division, Department of Paediatrics, BSMMU. A data collection sheet was developed containing demographic information, initial clinical presentation, hematological parameters, and echocardiographic findings. Demographic variables included total number of cases, gender, mean age and distribution of disease onset among different age categories and seasonal variation. Clinical variables comprised of duration of fever, maculopapular rash, oral mucosal changes, conjunctivitis, cervical lymphadenopathy, extremity changes like edema, peeling, other systemic involvements, complications and type of KD (complete or incomplete KD). Relevant laboratory findings included complete blood count with ESR, CRP, ALT, urine RE were recorded also in data collection sheet. Echocardiography was performed by GE Echo Machine Model Vivid E95 at the Department of Paediatric Cardiology, BSMMU. Patients were examined in supine and lateral position. All standard echocardiographic views: apical 4 chamber and 5 chamber, parasternal long axis, short axis, ductal, suprasternal and subcostal views were recorded in all patients and 4 MHZ (4s), 5 MHZ (5s) and 6 MHZ (6s) probes were used. Left coronary artery (LCA), left circumflex artery (LCX) and right coronary artery (RCA) diameters were measured and Z score was calculated using age, sex, weight, height and body surface area of the patients. According to AHA guideline 2017 Z-score classification of coronary artery is as follows: no involvement: always <2 , dilation only: 2 to <2.5 , small aneurysm: ≥ 2.5 to <5 , medium aneurysm: ≥ 5 to <10 or an absolute dimension of >4 mm to <8 mm and large or giant aneurysm: ≥ 10 or an absolute dimension of ≥ 8 mm.⁶ Appropriate statistical test were used to analyze the data of demographic, clinical, laboratory and echocardiographic findings. Non-normally distributed quantitative variables were expressed by median with interquartile range and frequency distribution were calculated by percentages.

RESULTS

A total of 66 patients diagnosed and admitted as KD at in-patient department of Paediatric Rheumatology Division, Department of Paediatrics, BSMMU were considered as case in this retrospective study. Table 1 demonstrated the median age of the cases at the time of diagnosis was 5 years. Majority of the cases (57.6%) were among 0-5 years age group, followed by 6-10 years age group (39.4% cases). Only 3% patients were above 10 years old. We observed male gender predominance (74.2%) in this study.

Disease onset was mostly observed in Winter season followed by Spring, Summer and Autumn respectively.

Table 1: Demographics features of children with KD (n=66).

Patient's characteristics	n=66 (%)
Age in years, median (IQR)	5 (3-7)
Age (years)	
0-5	38 (57.6)
6-10	26 (39.4)
>10	2 (3)
Gender	
Male	49 (74.2)
Female	17 (25.8)
Seasonal variation	
Winter	28 (42.4)
Autumn	7 (10.6)
Summer	15 (22.7)
Spring	16 (24.3)

Table 2: Clinical features of children with KD (n=66).

Clinical features	Number of cases, N (%)
Presence of fever	66 (100)
Fever duration (days)	
1-5	7 (10.6)
6-10	33 (50)
>10	26 (39.4)
Mean±SD	10.12±5.57
Maculopapular rash	41 (62.1)
Conjunctivitis	32 (48.5)
Cervical lymph node	33 (50)
Oral mucosal changes	
Overall	45 (68.2)
Cracked lip	35 (53)
Strawberry tongue	31 (47)
Erythema of throat and pharynx	14 (21.2)
Extremity changes	
Overall	48 (72.7)
Erythema of palm and sole	5 (7.6)
Periungual peeling	39 (59.1)
Oedema of hands and feet	7 (10.6)
Arthritis	9 (13.6)
Gastrointestinal manifestations	
Abdominal pain, vomiting and diarrhoea	1 (1.5)
Neurological manifestation	
Convulsion	1 (1.5)
Complications	
Heart failure	1 (1.5)
Macrophage activation syndrome	1 (1.5)
Type of KD	
Complete	34 (51.5)
Incomplete	32 (48.5)

Our study revealed that all the patients had fever (100%) and mean duration of fever was 10.12 days. Mostly (50%) patients had suffered from fever for 6 -10 days. 39.4% cases experienced fever for more than 10 days and 10.6% had fever for less than 5 days (Table 2). In this retrospective study, we observed extremity changes, oral mucosal changes, maculopapular rash, cervical lymphadenopathy and non-purulent conjunctivitis in 72.7%, 68.2%, 62.1%, 50% and 48.5% cases respectively. We observed in this study that, 13.6% patients had developed arthritis, 1.5% cases had GI manifestations and 1 patient (1.5%) had experienced seizure. Heart failure and Macrophage activation syndrome were the other two serious complications observed among 1.5% cases respectively in the study. We found that 51.5% patients had complete KD while the remainder (48.5%) had been diagnosed as incomplete KD in this study.

In this study we observed that median values of Hb% 10.95 g/dl, total leucocyte count 13,600/mm³, total platelet count 450,000/mm³, ESR 50 mm in 1st hour, CRP 48.49 mg/l and serum ALT 31.5 U/l. Sterile pyuria was observed in 16.7% patients in our study (Table 3).

Table 3: Laboratory findings of children with KD (n=66).

Investigations	Median (range)
Haemoglobin (g/dl)	10.95 (7.6, 13.9)
White blood cell count (cells/mm³)	13600 (2000, 35000)
Platelet count (cells/mm³)	450000 (70000, 1200000)
ESR (mm in 1st hour)	50 (4,126)
CRP (mg/l)	48.49 (6, 320)
Serum ALT (U/l)	31.5 (5, 407)
Sterile pyuria, n (%)	11 (16.7%)

Table 4 revealed that coronary artery abnormalities were present in 48.5% cases during the first echocardiography at the time of initial diagnosis of KD in this study. Presence of at least one coronary artery dilatation only (Z score 2-<2.5) were observed in 31.8% and at least one coronary artery aneurysm was seen in 16.7% patients.

Total number of coronary artery changes comprised of 43.9% coronary artery dilatation only and 27.3% coronary artery aneurysms signifying that some patients had coronary artery abnormalities in more than one coronary arteries simultaneously (changes in either 2 or all 3 coronary arteries measured LCA, LCX and RCA diameters).

Overall, 15.2% cases had small aneurysms, 7.6% patients had medium aneurysms and 4.5% cases had large or giant aneurysms in our study. Here we observed that majority of the patients had developed LCA abnormalities (42.4%) followed by RCA abnormalities in 21.2% cases and LCX abnormalities in 7.6% cases.

Table 4: Coronary artery changes detected by echocardiography at initial diagnosis in children with KD (n=66).

Coronary artery changes at diagnosis	Number of cases, N (%)
No coronary artery abnormalities	34 (51.5)
Coronary artery abnormalities present	32 (48.5)
At least one coronary artery dilatation only	21 (31.8)
At least one coronary artery aneurysm	11 (16.7)
RCA normal	52 (78.8)
RCA abnormal	14 (21.2)
RCA dilatation only	9 (13.6)
RCA aneurysm	5 (7.6)
RCA aneurysmal changes	
Small aneurysm	2 (3)
Medium aneurysm	2 (3)
Large/giant aneurysm	1 (1.6)
LCA normal	38 (57.6)
LCA abnormal	28 (42.4)
LCA dilatation only	17 (25.8)
LCA aneurysm	11 (16.6)
LCA aneurysmal changes	
Small aneurysm	7 (10.6)
Medium aneurysm	2 (3)
Large/ Giant aneurysm	2 (3)
LCX normal	61 (92.4)
LCX abnormal	5 (7.6)
LCX dilatation only	3 (4.6)
LCX aneurysm	2 (3)
LCX aneurysmal changes	
Small aneurysm	1 (1.5)
Medium aneurysm	1 (1.5)
Large/giant aneurysm	0 (0)
Total number of coronary artery abnormalities	
Dilatation only	29 (43.9)
Overall aneurysms	18 (27.3)
Small aneurysm	10 (15.2)
Medium aneurysm	5 (7.6)
Large/giant aneurysm	3 (4.5)

Table 5: Treatment modalities of children admitted with KD (N=66).

Medication name	Number of cases, N (%)
IVIg received as 1 st line therapy	57 (86.3)
Non responder to 1 st dose of IVIg	5 (7.6)
IV methylprednisolone	14 (21.2)
Aspirin	66 (100)
Infliximab	1 (1.5)

Our study demonstrated that all the patients (100%) had received aspirin and majority of the patients (86.3%) had received IVIg as a 1st line therapy in this study. 7.6% cases were non responder to 1st dose of IVIg infusion.

Other therapies included IV methylprednisolone pulses followed by high dose oral prednisolone in 21.2% and IV infusions of Infliximab in 1.5% cases in our study (Table 5).

DISCUSSION

KD is one of the most common causes of childhood acquired heart disease. Though KD is diagnosed clinically, relevant laboratory investigations and echocardiographic changes helps to support the diagnosis, evaluate the ongoing coronary artery status and predict the cardiac outcome of a patient with KD. Our study aimed to observe the demographic, clinical, laboratory profile and initial echocardiographic changes of coronary arteries among KD patients admitted in department of Paediatrics, BSMMU, which is a well renowned tertiary care center in Bangladesh.

In this study, the median age of the cases at the time of diagnosis was 5 years. Sharma et al observed a median age of 3 years and Sakina et al showed a median age of 3.6 years in their study.^{24,25} Majority of the cases (57.6%) were among 0-5 years age group, followed by 6-10 years age group (39.4% cases). Only 3% patients were above 10 years old. Sharma et al found that most of the patients (72%) were <5 years old and rest of the cases (28%) were ≥5 years old. This variation in disease onset may be geographical, racial, genetic inheritance or lack of strong suspicion among clinicians about this rare disease. In this study, we observed that majority (74.2%) of the patients were male with a male female ratio of 2.9:1. A study performed in North India observed a male female ratio of 3.9:1, whereas a study in Taiwan observed a male female ratio of 1.84:1.^{5,26} KD is more commonly found in boys than in girls.⁶ This disparity in sex could be due to disease process and its pathogenesis, but such a higher male to female ratio in Bangladesh might also reflect the fact that boys were getting more care due to socio-cultural context of our country. In this study, we found that disease onset was mostly observed in Winter season followed by Spring, Summer and Autumn respectively. A study performed at New Delhi; India also showed similar observations which is consistent with our study findings.²⁷

In the current study, all the patients (100%) had suffered from fever. Several studies done by Jindal et al, Banoo et al and Kuo showed that 100% of their study population had experienced fever.^{13,27,28} The simplest explanation to this is that the diagnostic criteria of KD require presence of history of fever as a mandatory criterion.⁶ In the present study, mean duration of fever was 10.12 days. Here, majority (50%) of the patients had suffered from fever for 6-10 days, whereas 39.4% cases experienced fever for more than 10 days and 10.6% had fever for less than 5

days. A study conducted in North India observed mean duration of fever in KD was 10.3 days which was consistent with findings in our study.²⁹ Sakina et al showed that 80% of their cases suffered from fever >5 days which is similar to our study findings.²⁵ In this retrospective study, we observed extremity changes, oral mucosal changes, maculopapular rash, cervical lymphadenopathy and non-purulent conjunctivitis in 72.7%, 68.2%, 62.1%, 50% and 48.5% cases respectively. A study conducted by Sharma et al observed 79 % extremity changes and 60% cervical lymphadenopathy among KD patients.²⁴ Jindal et al found oral mucosal 78.3% of KD cases.¹³ A study done in PGIMER, Chandigarh, India showed 60.9% had conjunctivitis and 62.3% had maculopapular rash among KD patients.²⁹ All these findings were almost similar to that of our study. Several studies have revealed some degree of variations among frequency of clinical features observed which could result from differences in geographical location, race, genetic inheritance and environmental variations. We observed 13.6% arthritis, 1.5% GI involvement and 1.5% seizure among KD patients in this study. We also recorded 1.5 % cases with heart failure and another 1.5% cases with macrophage activation syndrome (MAS). Banoo et al observed 29% arthritis among KD patients whereas Bhattad et al demonstrated 9.4% GI manifestation, 6.2% neurological features and 6.2% cases of heart failure among KD patients in his study.^{12,27} A study performed in China on 2015 observed 1.11% cases of MAS among KD patients.³⁰ MAS is a relatively frequent complication of rheumatic diseases and there have been several cases reported among children with KD.³¹ In the present study, we found that 51.5% patients had complete KD while the remainder (48.5%) had been diagnosed as incomplete KD. A study done at Bengaluru, India also observed 56.3% cases of complete KD and 43.7% cases of incomplete KD.¹² These findings were similar and consistent with observations in our study.

In this current study, we observed that median value of Hb% was 10.95 g/dl, total leucocyte counts 13,600/mm³, total platelet count 450,000/mm³, ESR 50 mm in 1st hour, CRP 48.49 mg/l, and serum ALT 31.5 U/l. Sterile pyuria was observed in 16.7% patients in our study. Sakina et al demonstrated a median Hb% of 10.24 g/dl whereas Sharma et al.²⁴ observed a median value of total count of WBC of 14,600/mm³ and total platelet count of 4,03,000/mm³.^{24,25} In another studies, Sakina et al found median value of ESR 59.5 mm in 1st hour and Cameron et al showed a median value of serum ALT of 33 U/l.^{25,32} Bhattad et al observed a mean ESR of 56.18 mm in cases with coronary artery abnormalities and 67.28 mm in cases without coronary artery abnormalities patients.¹² These observations are quite similar and consistent to the findings in our current study. Although these values may differ in various studies, but like other rheumatic diseases all these studies observed mild anaemia, leucocytosis, thrombocytosis, raised ESR and CRP levels reflecting underlying inflammatory process. In our study, we found sterile pyuria in 16.7% cases of KD. This is similar to the

observation of a study done in Northwest India where they found sterile pyuria in 14.3% cases of KD.¹³

In the present study, coronary artery abnormalities were present in 48.5% cases during the first echocardiography at the time of initial diagnosis of KD in this study. Presence of at least one coronary artery dilatation only (Z score 2 to <2.5) were observed in 31.8% and at least one coronary artery aneurysm (Z score ≥ 2.5) were seen in 16.7% patients. Total number of coronary artery changes comprised of 43.9% coronary artery dilatation only and 27.3% coronary artery aneurysms signifying that some patients had coronary artery abnormalities in more than one coronary arteries (changes in either 2 or all 3 coronary arteries measured LCA, LCX and RCA diameters). Overall, 15.2% cases had small aneurysms, 7.6% patients had medium aneurysms and 4.5% cases had large or giant aneurysms in our study. Here we observed that majority of the patients had developed LCA abnormalities (42.4%) followed by RCA abnormalities in 21.2% cases and LCX abnormalities in 7.6% cases. Bhattad et al demonstrated 43.6% cases of KD had coronary artery abnormalities in initial echocardiogram.¹² They observed 59% LCA abnormalities and 12.8% RCA abnormalities in cases with KD which is consistent with our study findings. Another study performed in North India showed 6.5% dilatation only, 32.3% small aneurysm, 12.9% medium aneurysm and 3.2% large or giant aneurysm in coronary arteries which resembles the coronary artery changes observed in our study.²⁷

In this retrospective study, all the patients (100%) had received aspirin and majority of the patients (86.3%) had received IVIg as a 1st line therapy in this study. 7.6% cases were non responder to 1st dose of IVIg infusion. Other therapies included IV methylprednisolone pulses followed by high dose oral prednisolone in 21.2% and IV infusion of infliximab in 1.5% cases in our study. Sharma et al showed that 93% of the cases diagnosed with KD had received IVIg as a 1st line therapy.²⁴ Other studies performed in France and India had demonstrated that 100% KD patients got IVIg as a first line therapy. Slightly less use of IVIg in our study mostly reflects the poor socio-economic condition of our country. A study done in Chicago, USA observed 16% IVIg resistance among KD patients. Bhattad et al showed 23% IVIg resistance in their study.¹² They used injection methylprednisolone in 10.3% cases and infliximab in 15.4% cases of KD. This disparity signifies that other centers use infliximab more commonly than methylprednisolone in IVIg resistant KD cases whereas the opposite scenario exists for IVIg resistance cases in our study which might also be due to poor socio-economic condition in our country.

Our study has several limitations. First, there is no standardized method to diagnose incomplete KD when it is not accompanied by coronary artery abnormalities (CAA). The diagnostic algorithm for incomplete KD suggested by the AHA in 2004 does not completely eliminate the risk of misdiagnosis. A thorough

understanding of the pathogenesis of KD is necessary, as identifying pathogenic markers rather than relying solely on clinical manifestations may enable more accurate diagnoses. Additionally, the higher risk of CAA in cases of incomplete KD may result from the tendency to select more severe cases when the full diagnostic criteria are not met. Second, the studies included in our analysis were non-randomized, retrospective case-control studies that tracked patients over a 12-year period. There have been changes in disease recognition, therapeutic approaches, and protocols for incomplete KD, which remain non-standardized. As a result, the significant heterogeneity among the studies limits the reliability of the findings. There is also a potential for sampling errors and publication bias. Given these limitations, the results of our study should be interpreted with caution. Future prospective cohort studies may help address these issues and provide clearer insights beyond those inherent in this retrospective study.

CONCLUSION

In this study, we observed a slightly higher frequency of the complete KD (51.5%) in comparison to incomplete KD patients. Fever was the most consistent clinical feature followed by extremity changes, oral mucosal changes, maculopapular rash, cervical lymphadenopathy and lastly non-purulent conjunctivitis. Mild anaemia, leucocytosis along with high ESR and CRP were usually observed during the acute stage of KD. Initial echocardiography done at the time of diagnosis revealed 48.5% patients with KD had coronary artery abnormalities with a predilection towards left coronary artery. At least one coronary artery dilatation only was observed in approximately one-third and at least one coronary artery aneurysm was seen in almost one-sixth of the KD patients during initial echocardiography.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Ali MA, Haque M, Islam MR, Talukder MK. Clinico-hematological profile and coronary artery changes detected at initial echocardiography in children with Kawasaki disease: a 12 years single centered experience from a tertiary care referral center of Bangladesh. *Int J Contemp Pediatr* 2025;12:343-9.