Original Article

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Paediatrics Section

Cardiovascular Complications in Patients with Kawasaki Disease in a Tertiary Care Hospital in West Bengal, Eastern India- A Prospective Clinical Study

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ABSTRACT

Introduction: Kawasaki Disease (KD) is an acute self-limiting systemic vasculitis involving medium and small sized arteries. It may soon replace rheumatic fever to become the most common cause of acquired heart disease in Indian children. Coronary Artery Aneurysm (CAA) which can develop in 15-25% of untreated children remains the most dreaded complication of KD. Predicting the risk of CAA and taking timely measures can help in reducing the fatality of the condition.

Aim: To study the spectrum of cardiovascular complications in patients with KD and also to assess associated risk factors for developing CAA in the patients under study.

Materials and Methods: The prospective clinical study was carried out in the Paediatric Medicine Ward, Burdwan Medical College and Hospital, West Bengal, Eastern India, from 1st January, 2020 to 31st May, 2021. A total of 52 children diagnosed with KD, aged between one month to 12 years, were included and followed-up for six months. Data regarding demographic variables, duration of fever, Intravenous Immunoglobulin (IVIG) resistance, hepatomegaly, neutrophilia, thrombocytopaenia, haematocrit, Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), hepatic transaminases (alanine transaminase, aspartate amino-transferase), hyponatraemia, hypoalbuminaemia, and N-terminal-brain natriuretic peptide (NT-proBNP) were collected. Univariate and multivariate regression analyses were done using these variables for assessment of risk factors.

Results: In the present study, out of 52 children, 28 (53.85%) were males and 24 (46.15%) were females with mean age of 3.74±2.55 years. Cardiovascular complications were observed in 27 (51.92%) patients, of whom 19 (35.54%) had CAA. Duration of fever ≥10 days, IVIG resistance, thrombocytopaenia, low haematocrit, Alanine Transaminase (ALT) ≥100 U/L, hypoalbuminaemia, and raised NT-proBNP were proven to be significant risk factors for development of CAA on univariate analysis. Thrombocytopaenia and raised NT-proBNP came across as significant on binary logistic regression analysis.

Conclusion: In this study, one or more types of cardiovascular abnormalities were present in 51.92% cases. Seven risk factors were identified to be significant in development of CAA on univariate analysis and among them two were proven significant in binary logistic regression.

Keywords: Aneurysm, Coronary arteries, Echocardiography, Risk factors, Vasculitis

INTRODUCTION

Kawasaki disease, an acute self-limiting systemic vasculitis involving medium and small-sized arteries, is the leading cause of acquired heart disease in children in most of the developed countries [1]. In India there has been a steady increase in the number of cases of KD since the mid-1990s [2]. There is anecdotal evidence that KD may soon replace rheumatic fever to become the most common cause of acquired heart disease in Indian children [3].

The primary concern in KD is coronary artery abnormalities, which can develop in 15-25% of untreated children [1]. Untreated CAA can lead to Myocardial Infarction (MI), ischaemic heart disease or even sudden death [4].

Several risk stratification models have been constructed to determine which patients with KD are at highest risk for CAA. Out of these, the Kobayashi Score is the most widely used and has high sensitivity and specificity [5]. Duration of fever has been consistently proven to be a powerful risk factor [6]. Younger age, particularly age less than one-year, male, delayed diagnosis and treatment have also been associated with development of CAA [1]. Laboratory detected conditions, including neutrophilia, thrombocytopaenia, elevated hepatic transaminases, elevated CRP, and lower serum albumin, are also prominent risk factors [7].

There is a possible difference in clinical presentation of KD in India [8]. Whether these differences are the reason that none of the published risk scores can accurately identify all the at-risk children in the Indian population is open to question. Although, there are a multitude of Indian studies on the epidemiology, clinicolaboratory features, and cardiovascular sequelae of KD [9-12], authors could not find any study particularly pertaining to the risk factors of developing CAA in KD in India.

Hence, the present study was undertaken to study the spectrum of cardiovascular complications in patients with KD and also to assess the risk factors for developing CAA in the Indian scenario.

MATERIALS AND METHODS

The present prospective clinical study was carried out in the Paediatric Medicine Ward, Burdwan Medical College and Hospital, West Bengal, India, from 1st January, 2020 to 31st May, 2021. Approval for the study was taken from the Institutional Ethics Committee (Memo no: BMC/Ethics/030). Informed consents were taken from the parents for use of anonymised data.

Inclusion criteria: Children aged between one month to 12 years, with KD (meeting the criteria for complete or incomplete KD) were included in the study. Complete KD was defined as persistent fever for atleast five days along with presence of atleast for out of the five principal features namely: (i) bilateral non exudative conjunctival injection with limbal sparing; (ii) erythema of the oral and pharyngeal mucosa with strawberry tongue and red, cracked lips; (iii) oedema

(induration) and erythema of the hands and feet; (iv) rash of various forms (maculopapular, erythema multiforme, scarlatiniform or less often psoriatic-like, urticarial or micro-pustular); and (v) nonsuppurative cervical lymphadenopathy, usually unilateral, with node size >1.5 cm. Atypical KD included patients who had persistent fever, fulfilled <4 of the five principal criteria but echocardiographic and laboratory finding were suggestive of KD [1].

Exclusion criteria: Patients who had pre-exiting heart disease, and whose guardians refused to provide consent were excluded from the study.

A total of 52 patients, who presented to the Department of Paediatric Medicine Ward, within the study duration, following the inclusion criteria, were enrolled in the study by convenient sampling.

Study Procedure

Once the diagnosis was confirmed, two-dimensional (2D) echocardiography was performed at diagnosis and on second week of the disease. The diameters of the Right Main Coronary Artery (RMCA), Left Main Coronary Artery (LMCA), the Left Anterior Descending coronary artery (LAD) and the Left Circumflex (LCX) coronary artery were measured with the help of 2D echocardiography.

All the patients were followed-up for six months after admission. If the initial results were normal, a repeat echocardiography was performed six weeks after onset of illness. Echocardiography study was repeated in these patients after three months and at the end of six months. If results of either of the initial studies were abnormal or the patient had recurrent fever or other symptoms of KD, then echocardiography was done monthly or tailored to the patient's coronary status.

As Body Surface Area (BSA) adjusted coronary artery dimensions (z-scores) on baseline echocardiography in the first 10 days of illness appear to be good predictors of involvement during follow-up and the American Heart Association (AHA) uses Z-score classification system for CAA in KD, serial Z-score assessment was done (with every echocardiographic study as mentioned previously) throughout the follow-up period [13]. The AHA z-score classification system is as follows:

i. No involvement: always <2
ii. Dilation only: 2 to <2.5; or if initially <2, a decrease in Z-score during follow-up ≥1
iii. Small aneurysm: ≥2.5 to <5
iv. Medium aneurysm: ≥5 to <10, and absolute dimension <8 mm
v. Large or giant aneurysm: ≥10, or absolute dimension ≥8 mm [1]

For assessment of risk factors for developing CAA, 17 independent variables (considering importance as per literature search) namely age, sex, religion, socioeconomic status, duration of fever, IVIG resistance (persistent or recrudescent fever 36 hours after completion of the initial IVIG infusion of 2 g/kg), hepatomegaly, neutrophilia (absolute neutrophil count/ANC >7,700/mm^3), thrombocytopaenia (Platelet count <1,50,000/mm^3), haematocrit, ESR, CRP, hepatic transaminases (alanine transaminase, aspartate aminotransferase, hyponatraemia (serum sodium <135 mEq/L), hypoalbuminaemia (serum albumin <3.5 g/dL), and N-terminal-brain natriuretic peptide (NT-proBNP) [14-19]. All these necessary investigations were sent to the Pathology, Biochemistry, and Radiology Department of the study institution on the first week upon diagnosis of the illness.

STATISTICAL ANALYSIS

The collected data was entered in Microsoft Excel worksheet (Microsoft, Redwoods, WA, USA) and double-checked. International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS), software version 26.0 for Windows software package (IBM SPSS Inc., Chicago, IL, USA) and statistical software, STATA (version 14.2) were used for recording the data and analysing the results. Means were compared by Chi-square test. The p-value of <0.05 was considered as statistically significant.

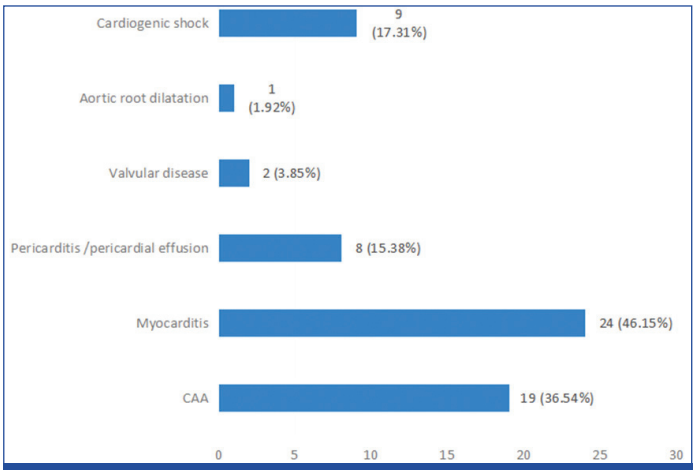
RESULTS

Out of the 52 KD patients, 28 (53.85%) were males, rest were females with a mean age of 3.74±2.55 years. In the present study, 32(61.54%) patients aged below four years and only 2 (3.85%) patients were more than eight years of age [Table/Fig-1].

Parameters	n (%)
Age	
0-4	32 (61.54%)
>4-8	18 (34.61%)
>8-12	2(3.85%)
Gender	
Male	28 (53.85%)
Female	24 (46.15%)

[Table/Fig-1]: Distribution of study population according to age and sex (n=52).

The most frequently encountered cardiac abnormality was myocarditis, found in 24 (46.15 %) patients, followed by CAA, were present in 19 (35.54%) patients. In the present study, 27 (51.92%) patients had developed more than one cardiac abnormality [Table/Fig-2]. Of total, 19 (36.54%) patients had myocarditis in the acute phase of the disease and developed CAA in the follow-up period. A total of 5 (9.62%) other patients developed pericarditis with myocarditis, pericarditis/pericardial effusion (15.38%) mitral regurgitation like valvular disease (3.85%) and mild aortic root dilatation (1.92%). Nine (17.31%) patients who had both CAA and myocarditis, suffered from cardiogenic shock in the acute phase of the disease. Three (5.77%) patients who had developed valvular disease and aortic root dilatation, also had associated CAA. Case fatality rate was zero.



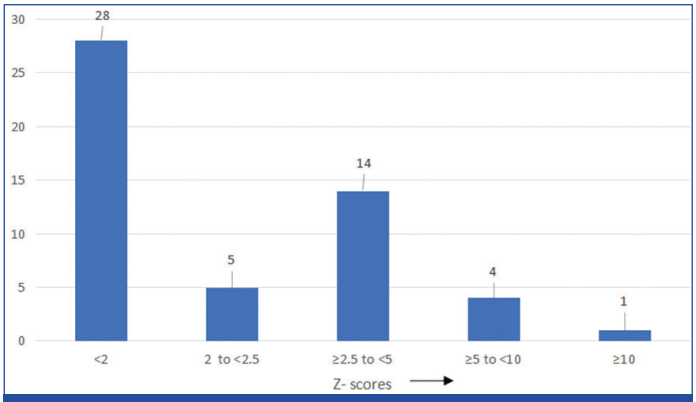
[Table/Fig-2]: Types of cardiovascular complications observed in the study subjects (n=52).

All the patients were followed-up with utmost care and sincerity for six months after admission. In the present study, 14 (26.92%) patients had small aneurysms, 4 (7.69%) had moderate aneurysms and only 1 (1.92%) patient had a large aneurysm [Table/Fig-3].

On follow-up, 17 out of the 19 patients with CAA showed regression in Z-scores. In four patients Z-score reduced by >2, in six patients between ≥1 to 2 and in seven patients Z-score had decreased only slightly (<1). Two patients had no regression in Z-score and developed thrombi in coronary arteries (LMCA in both cases).

Risk Factor Assessment for Development of Coronary Artery Aneurysm (CAA)

Seventeen independent variables were considered while assessing risk factors for development of CAA. Among them, seven variables



[Table/Fig-3]: Maximum Z-score of coronary arteries on serial echocardiography (N=52).

i.e., duration of fever ≥10 days, IVIG resistance, thrombocytopaenia, haematocrit <35%, ALT ≥100U/L, hypoalbuminaemia, and NT-proBNP ≥1000 pg/mL, were found to have significant association with development of CAA [Table/Fig-4a,b].

	0 (negative), 1 (positive)	CAA		Chi-square	p-value	Odds ratio (OR)
		Present	Absent			
Duration of fever ≥10 days	1	12	4	14.74	**0.000015**	12.43
	0	7	29			
IVIG resistance	1	7	2	7.98	**0.004**	9.04
	0	12	31			
Hepatomegaly	1	5	3	2.75	0.09	3.57
	0	14	30			
Neutrophilia	1	12	16	1.04	0.31	1.82
	0	7	17			
Thrombocytopenia	1	9	3	9.95	**0.002**	9.00
	0	10	30			
Haematocrit <35%	1	12	11	4.35	**0.037**	3.43
	0	7	22			
ESR ≥40 mm/hour	1	12	12	3.48	0.062	3.00
	0	7	21			
CRP ≥30 mg/L	1	17	24	2.03	0.15	2.28
	0	2	9			
ALT ≥100 U/L	1	10	6	6.72	**0.01**	5.00
	0	9	27			
AST ≥100 U/L	1	8	6	3.50	0.06	3.27
	0	11	27			
Hyponatremia	1	11	13	1.66	0.20	2.12
	0	8	20			
Hypoalbuminaemia	1	12	6	10.78	**0.001**	7.71
	0	7	27			
NT-proBNP (≥1000 pg/mL)	1	11	3	14.60	**0.000133**	13.75
	0	8	30			

[Table/Fig-4a]: Risk factor assessment for development of Coronary Artery Aneurysm (CAA).
The p-value in bold font indicates statistically significant values

Parameters		CAA	No CAA	Chi-square	p-value
Age	0-4 years	14	18	2.46	0.29
	>4-8 years	4	14		
	>8-12 years	1	1		
Sex	Male	12	16	1.04	0.31
	Female	7	17		
Religion	Hindu	10	19	0.23	0.89
	Muslim	8	13		
	Sikh	1	1		
Socio-economic status	Lower	2	3	7.58	0.11
	Upper-lower	2	5		
	Lower-middle	5	19		
	Upper-middle	9	5		
	Upper	1	1		

[Table/Fig-4b]: Risk factor assessment for development of CAA.

On multivariate analysis using binary logistic regression, two variables: Thrombocytopaenia (p-value=0.02, OR=9.00), and NT-proBNP (p-value=0.02, OR=1.003) had p-value of <0.05. The model can collectively explain 60.1%-82.2% variability of development of CAA [Table/Fig-5].

Explanatory variables	Coef. (β)	Std. error	Z†	p-value	(95% confidence interval)		dy/dx*	Exp (B)#
Duration of fever	0.560	0.349	1.610	0.10	-0.123	1.244	0.090	1.402
IVIG resistance	-0.143	4.191	-0.030	0.97	-8.358	8.072	-0.022	9.042
Thrombocy topenia	6.436	2.797	2.300	**0.02**	0.954	11.917	0.919	9.000
Haematocrit	-0.133	0.103	-1.300	0.19	-0.334	0.068	-0.021	0.925
ALT	-0.031	0.032	-0.960	0.33	-0.095	0.033	-0.005	1.024
Hypoalbum inemia	2.372	1.666	1.420	0.15	-0.892	5.637	0.444	7.714
NT-proBNP	0.010	0.005	2.180	**0.02**	0.001	0.020	0.002	1.003
Constant	-4.899	4.492	-1.090	0.27	-13.703	3.906		

[Table/Fig-5]: Probability of getting CAA based on selected variables.
*dy/dx-Marginal effects after logit, dy/dx is for discrete change of dummy variable from 0 to 1; #Exp(B)-odds ratio; †z-ratio between the coefficient and standard error

DISCUSSION

The study aimed to diagnose various cardiovascular manifestations of KD and identify the risk factors for development of CAA. Majority of the children (61.54%) were aged below four years and only two children were more than eight years of age. One or more type of cardiovascular abnormalities was present in 51.92% cases. The major cardiovascular manifestations observed were myocarditis (46.15%), CAA (36.54%), cardiogenic shock (17.31%), pericarditis/pericardial effusion (15.38%), mitral regurgitation like valvular disease (3.85%) and mild aortic root dilatation (1.92%). On univariate analysis, we found that duration of fever ≥10 days, IVIG resistance, thrombocytopaenia, haematocrit <35%, ALT ≥100 U/L, hypoalbuminaemia, and NT-proBNP ≥1000 pg/mL were significantly associated with development of CAA. Thrombocytopaenia (p-value=0.02, OR=9.00), and NT-proBNP (p-value=0.02, OR=1.003) were proven to be significant in binary logistic regression model.

One study by Kato H et al., demonstrated CAA in 7 (35%) out of 20 KD patients [20]. This finding is similar to the present study where there was development of CAA in 36% patients. Various studies by Newburger JW et al., Rowley AH and Shulman ST, and Burns JC have estimated the incidence to be between 15-25% [21-23]. Anderson MS et al., found the incidence of CAA to be 24% when diagnosis of KD was delayed [24]. The higher incidence of CAA in the present study might indicate their rising incidence in KD, or it may be owed to delayed presentation by the patient at the hospital, delay in diagnosis or due to the mysterious link between Multisystem inflammatory Syndrome in Children (MIS-C) and KD. All the present cases, however tested negative for both Coronavirus Disease-2019 (COVID-19) Real-Time Reverse Transcription Polymerase Chain (RT-PCR) and antibody.

Authors did serial echocardiography to diagnose as well as document the progression of CAAs. On follow-up, 17 out of the 19 patients with CAA showed regression in Z-scores. In four patients Z-score had reduced by >2, in six patients between ≥1 to 2 and in seven patients Z-score had decreased only slightly (<1).

Two patients on the other hand, had no regression in Z-score and developed thrombi in coronary arteries (LMCA in both cases). Hörl M et al., studied 94 patients with KD between 2002 and 2018 and concluded that a significant progression of patients' coronary artery Z-scores in serial echocardiographic measurements may be helpful to ensure diagnosis of CAA early even if Z-scores are within the normal range [25].

Gowin E et al., did a retrospective analysis in 2008-2014 with 30 KD patients [26]. Cardiac involvement was detected in 18 (60%) patients, including CAA in 10 (33.3%). During 12 months of follow-up, coronary artery dilatation resolved in five children, and one patient developed aneurysm. They concluded that KD should be considered in the differential diagnosis of children with prolonged fever. During the acute stage of the disease, children with KD require regular cardiac evaluation, and long-term care is needed when cardiovascular complications occur and the present study had similar results.

Pilania RK et al., concluded in their study that while CAAs are the most well-recognised complications of this condition, other affectations like myocarditis, KD shock syndrome, valvular abnormalities, and endothelial dysfunction are also being increasingly recognised [27]. Studies by Kao CH et al., and Rinder CS et al., have documented myocardial inflammation in 50% to 70% of patients using 67Ga citrate scans (planar or single photon emission CT) and 99mTc-labeled white blood cell scans [28,29]. However, the severity of myocarditis does not appear to be associated with the risk of CAA [30]. In the current study, myocarditis was found in 46.15% and 21.15% had both myocarditis and CAA. These findings corroborated with findings of the studies mentioned above.

Over the years, a handful of scoring systems have been developed to identify children at highest risk for coronary artery abnormalities mostly from Japan and the United States (US). In some centres in Japan, a risk scoring system developed by Harada K is used to determine whether IVIG treatment will be used [17]. IVIG is given to children who fulfil four of the following criteria, assessed within nine days of onset of illness: 1) white blood cell count >12000/mm^3; 2) platelet count <350000/mm^3; 3) CRP >3+; 4) haematocrit <35%; 5) albumin <3.5 g/dL; 6) age ≤12 months; and 7) male sex. Bai L et al., conducted a decade-long study from the year 1998 to 2008 in north-west and central China in order to provide early intervention for coronary artery lesions caused by KD and observed that the KD patients with CRP higher than 30 mg/L, ESR higher than 40 mm/h, hepatomegaly and IVIG ineffectiveness, had higher incidence of CAA development [19]. Son MBF et al., designed a practical risk score assigning points to each variable like baseline Z score of LAD or RMCA ≥2.0, age less than six months, Asian race, and CRP ≥13 mg/dL and created low, moderate, and high-risk groups. The odds of CAA were 16-fold greater in the high versus the low-risk groups in the development cohort [31]. Various other studies by Kaneko K et al., Honkanen VE et al., and Nakamura Y et al., concluded prolonged duration of fever, thrombocytopaenia, raised ESR, hypoalbuminaemia, and age less than one year to be associated with higher chance of development of CAA [32-34]. Dionne A and Dahdah N concluded that patients with resistance to IVIG treatment and CAA had higher levels of NT-proBNP, suggesting a prognostic role [35]. The present study also mirrored these results.

In the present study, authors found seven independent risk factors for occurrence of CAA in KD. Giving special attention to patients with any of these features and subsequently following them up with serial echocardiography will help in early diagnosis of CAA and prevent grave consequences.

Although several Japanese risk scoring systems (Kobayashi, Egami, Sano, and Harada K risk scores) are available for prediction of CAA in KD, unfortunately, none of them are properly applicable on Indian population [13]. In one of the first initiatives in this country, authors have tried to identify the risk factors of development of CAA in KD and have able to delineate quite a few of them. The present study is a small step towards devising an Indian risk scoring system for CAA, but there is a need for more studies from other parts of the country to formulate that.

Limitation(s)

This is a single-centre hospital-based study conducted on a predominantly homogenous ethnic population that limits its generalisation. Though, authors could find several statistically significant risk factors of CAA in this population, to formulate a risk score, large-scale multi-center studies conducted over a larger geographical area with diverse ethnic composition. Also, following up the patients beyond six months was not done.

CONCLUSION(S)

In this study, one or more type of cardiovascular abnormalities was present in 51.92% cases. Seven risk factors were identified to be significant in development of CAA on univariate analysis and among them two were proven significant in binary logistic regression. In one of the first initiatives in this country, authors have tried to identify the risk factors of development of CAA in KD and have able to delineate quite a few of them. Further studies on these parameters with larger number of patients might be helpful in devising an Indian risk scoring system for CAA, so that it becomes possible to assess the probability of CAA early in the course of the disease and take necessary measures to minimise the fatality of this condition.

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