Cardiac Events in Kawasaki Disease With Coronary Aneurysms Revisited, A Two-center Retrospective Cohort Study in Thailand

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Abstract

Kawasaki disease (KD) is a common vasculitis in children, which may be complicated with coronary artery aneurysms (CAAs). We aimed to report the rates of major adverse cardiac events (MACE) and determine the risks of MACE in children diagnosed with KD and CAAs in Thailand. Data of 170 children diagnosed with KD and CAAs in two centers of Thailand between 1994 and 2019 was retrospectively reviewed. The risks of MACE were analyzed using multivariate analysis. Of 170 patients, forty-nine patients (28.8%) had giant CAAs. During the median time of follow-up (5.4 years; ranging from 22 days to 23 years), 19 patients (11.1%) experienced MACE including 12 coronary artery bypass grafting, 2 percutaneous coronary intervention and 5 patients with evidence of coronary occlusion. Coronary interventions were performed at 4 years (ranging from 0.01 to 9.5 years) after the KD diagnosis. Independent risks of MACE in KD with CAAs were from the presence of giant aneurysms (HR 16.55; 95% CI 2.52 to 108.63; p=0.003) and lack of intravenous immunoglobulin (IVIG) treatment (HR 11.43; 95% CI 2.8 to 46.62; p=0.001). The intervention-free rate at 5 and 10 years in patients with giant CAAs was 78.7% and 52.2%, respectively.

Trial registration: TCTR20190125004

Introduction

Kawasaki disease (KD) is an acute febrile illness involving inflammation of medium-sized vessels, which commonly occurs in young children[1,2]. Without treatment, patients may develop complications such as coronary artery aneurysms (CAAs), occurring as frequently as 15% to 25%. [2,3] Initiating a treatment with intravenous immunoglobulin (IVIG) within 10 days of onset leads to a reduced incidence of CAAs (to 4-10%)[1-7]. Persistent CAAs subsequently lead to thrombosis and stenotic lesions that result in myocardial ischemia and infarction [3]. Aggressive management, such as thromboprophylaxis and revascularization intervention is sometimes required for patients with these complications[1,6,7].

In 2004 [2], the American Heart Association (AHA) released guidelines for the diagnosis and treatment of KD and more recently in 2017[1]. The criteria for diagnosing typical, suspicious KD and the risk classifications are widely recognized[1-6]. Long-term management especially in adults with a history of KD and coronary artery aneurysms has been described[6]. The latest AHA guideline stratified patients into five risk levels according to their relative risk of myocardial ischemia and infarction, with indications for the subsets of each risk level using the current status of the coronary artery and its Z-score. Serial myocardial stress tests are recommended in addition to regular echocardiography in the presence of CAAs[1-6].

Long-term outcomes and reports of MACE have been published. A large Japanese, nationwide survey between 1999 and 2010 identified 209 patients with giant CAAs having a 10-year survival rate of 94.3% and a total cardiac event-free rate of 0.68[8]. A large scaled retrospective study of 500 CAAs in 2,860 KD patients in the US population reported MACE in 24 patients (4.8%) [9]. In Thailand, the incidence of KD from 1998 to 2002 was reported to be 2.14 to 3.43 cases per 100,000 children aged 0-5 years, and 15.6%

of the patients had IVIG-resistant KD[10]. The prevalence of incomplete KD was reported to be 29% in a single-center study from Northern Thailand[11]. These may consequently have an increased risk of CAA in the Thai population. The long-term outcome of CAAs after treatment, however, has not been reported in the Thai population. We therefore conducted this surveillance study to revisit the natural history of patients with CAAs after KD and to identify factors associated with MACE in the Thai population using KD databases from two large cardiac centers (Siriraj Hospital and Srinagarind Hospital).

Results

Patient Characteristics

A total of 658 patients had been diagnosed with KD in the two centers from 1994 to 2019. 170 patients with CAAs following KD were included in the study (Fig. 1). Of these patients, 65% were male. MACE was reported in 19 patients (11.2%), comprised of 12 CABG, 2 PCI, and 5 with evidence of coronary occlusion. Demographic, clinical, and laboratory data, and KD treatments of the patients in this study are shown in Table 1. Of 170 patients, 52.9% (n=90) received IVIG treatment within 10 days of onset of fever, whereas 9.4% (n=16) did not receive IVIG. Retreatment of IVIG was reported of 14.7%. Adjunctive anti-inflammatory medications were prescribed for 9 patients; 8 with steroids and 1 with abciximab (GP IIb/IIIa inhibitors). All patients received 80-100 mg/kg/day of aspirin during the acute phase of KD followed by the standard low-dose aspirin (3-5 mg/kg/day). An additional anticoagulant such as warfarin was given with aspirin in 36 patients (21.2%). The initial Z-score for the coronary artery aneurysm dimensions was as high as 6.3 (ranging from 2.6 to 85.5) in the study.

Patients with CAAs were classified into three groups: small CAAs [74 patients (43.5%)], medium CAAs [47 patients (27.6%)], and giant CAAs [49 patients (28.8%)] (Fig. 1). Table 2 illustrates the management of patients including MPI, coronary angiography, and coronary intervention. Coronary artery bypass grafting (CABG) was a mainstay treatment for KD with coronary occlusion and myocardial infarction. Fourteen patients (1 medium-sized CAA and 13 giant CAAs) required coronary intervention (8.2%) in a study cohort. Importantly, four patients with giant CAAs required a second operation for CABG due to the re-stenosis of the coronary artery.

Clinical Outcomes and Survivals

During the follow-ups [median time of 5.4 years (range from 22 days to 23 years)], 19 patients (11.2%) experienced MACE. Fourteen patients required coronary intervention including 12 CABG and 2 PCI at 4 years (range from 0.01 to 9.5 years) after the diagnosis of KD. One patient who underwent CABG at 7 years-of-age had a car accident and died in 2019 at the age of 21 years. Five patients had evidence of chronic total occlusion of coronary artery with well-developed collateral circulation, no coronary intervention has yet been performed. Details of the 19 patients who experienced MACE are given as supplementary data (Table 1S). Notably, no MACE reports were found for patients with small CAAs. The

intervention-free survival of patients with giant CAAs was significantly lower than that in patients with small CAAs (Log rank *p*-value < 0.001) and medium CAAs (Log rank *p*-value = 0.001) (Fig. 2). The intervention-free rate at 1, 5, and 10 years in patients with giant CAAs was 93.8%, 78.7%, and 52.2%, respectively. Furthermore, the cardiac event-free rate at 1, 5, and 10 years in patients with giant CAAs was 87.6%, 72.1%, and 50.7%, respectively (Fig. 3). The progression and regression of CAAs is demonstrated in Fig. 4. Ninety-six patients (56.4%) had regression of CAAs to normal coronary artery. Of the small CAAs, 81% could regress to a normal size, and for medium aneurysms, 50% could regress to a normal size (Fig. 4).

Risk factors of MACE in KD with CAAs

Risk analyses of the factors associated with MACE in patients with CAAs following KD are shown in Table 3. A lack of IVIG treatment and the presence of giant aneurysms were identified as independent risks of MACE (adjusted HR 11.43; 95% CI 2.8-46.62; *p*-value=0.001 and adjusted HR 16.55; 95% CI 2.52-108.63; *p*-value= 0.003, respectively) (Table 3).

Discussion

This 2-center study describes the prevalence of MACE in children with KD and CAAs using a 25-year KD database from two large referral hospitals in Thailand. A quarter of patients with KD in two-center cohort had CAAs (n=170). During the median time of follow-up (5.4 years; ranging from 22 days to 23 years), MACE was reported in 19 patients (11.1%) comprised of 14 coronary interventions and 5 with evidence of coronary occlusion. Most of the patients experiencing MACE had giant aneurysms. No MACE was reported in patients with small CAAs. Fourteen patients underwent coronary interventions at 4 years (range from 0.01 to 9.5 years) after onset of the diagnosed KD. This study supports the current belief that cardiac events in KD with CAAs are significantly related to giant aneurysms and a lack of IVIG treatment. This is the first study reporting MACE in KD with CAAs using a cohort database in Thailand.

The proportion of CAAs in KD using the 2017 AHA criteria in this study was comparable to the proportions of 24.6% and 27.1% reported in previous studies by Kato and Dominguez, respectively [3,12]. Nevertheless, these values are higher than those in other studies where the prevalence of CAAs were found to vary from 3.6 to 17.4%[7,13-15]. Data from a Korean national survey on KD, showed differences in the prevalence of CAAs using AHA criteria (21-42%) and a Japanese guideline (18%) for the same sample population[16]. The use of different guidelines and Z-score formulas can lead to different CAA prevalence and diagnostic classification of KD. At our two centers; however, the physicians regularly practice with Z-scores and the AHA criteria, as used in this research. In addition, the lack of IVIG treatment and resistant IVIG KD, which has been associated with the occurrence of coronary artery lesions in KD[13] was found to be slightly higher at 9.4% and 14.7%, respectively, in this cohort.

Regarding coronary dimensions over time, a regression of CAAs to normal coronary artery in this study was 56.4% and an overall regression in size of CAAs was 72%. This finding is consistent with Friedman's report that demonstrated a regression in CA aneurysms for 75% of the KD patients[9]. Nonetheless, some patients still have a progressive sized CAA over time, which indicates the need for caution and further follow-up[9,13].

In this study, the incidence of MACE was as high as 11.1%, which is greater than what has been previously reported for the US population in 2016 (4.8%) [9] but less than what Tsuda and colleagues reported (21%)[17]. Most of the patients with MACE had giant aneurysms and no MACE was found in patients with small CAAs. These findings are consistent with previous publications[5,9,17]. Friedman and colleagues[9] reported no MACE in 313 patients with a coronary artery Z-score < 5, and 23% MACE occurred in patients with a coronary Z-score > 10. Similarly, the recent 34-institution international registry of 1,651 KD patients with CAAs showed no MACE in patients with small CAAs, while the patients with giant aneurysms had a cumulative incidence of significant luminal narrowing (20±3%), coronary artery thrombosis (18±2%), and composite MACE at 10 years (14±2%)[5].

In 19 patients with MACE, 14 underwent coronary interventions (12 CABG, 2 PCI) at a median time of 4 years after KD diagnosis (range from 0.01 to 9.5 years). These included our anecdotal five-case series that had been institutionally published in 2006[18]. Overall, the 10-year cardiac event-free rate in patients with giant CAAs in the current study was 50.7%, which is less than that reported (65-75%) in prior studies[8,17,19]. The independent risks of MACE in KD with CAAs in this study were the presence of giant aneurysms (HR 16.55; 95% CI 2.52-108.63; p=0.003) and a lack of IVIG treatment (HR 11.43; 95% CI 2.8-46.62; p=0.001). Aneurysm size, a higher CAA Z-score, and a greater number of coronary artery branches being affected in KD patients have been shown to be an important risk of MACE, luminal narrowing, and thrombosis in many reports[5,8,9,17,19]. Beyond the larger size of CAAs, age less than 60 months, recurrent KD, parental history of KD, delayed admission, and IVIG-resistant KD have been reported to lead to worse coronary outcomes at >30 days following the diagnosis[13] while hypoalbuminemia was said to be an additional risk of progressive coronary dilatation at one-year post KD diagnosis[20].

Study Limitations

This study has several limitations. First, this study is retrospective in its nature. Selective bias is inevitable. The authors therefore have carefully explored and included only patients with KD who had evidence of CAAs by echocardiographic studies and had been in a follow-up at either of the centers. Echocardiographic data and clinical outcomes at a recent follow-up in October 2020 were recorded, and patients who had a recent follow-up prior to 2020 were phone-contacted to assess their MACE and clinical status. At the end of study, 87 patients (51.2%) had their recent clinical status assessed in October 2020. Of the 83 patients who had no record in 2020, their status at the recent follow-up was based on the available medical database. Another concern was the minimal variability for the investigations, especially the cardiac stress test, treatment with adjunctive anti-inflammation medication,

and the time to follow-up at the two centers. Lastly, the small sample population was a confounding factor that affected the MACE correlations and the power of the analysis.

Conclusion

The major adverse cardiac event rate was 11.1% for KD with CAAs. A lack of IVIG treatment and the presence of giant aneurysms are independent risk factors for major adverse cardiac events. Patients with giant CAAs following KD had an intervention-free survival rate that was lower than that for patients with small and medium CAAs. The cardiac event and intervention-free rate at 10 years in patients with giant CAAs was approximately 50%. Once medium to giant aneurysms develop, cautious surveillance and early recognition of cardiac complications is recommended.

Material And Methods

The present study was a two-center retrospective study using hospital databases from large tertiary cardiac centers in Thailand: Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok and Faculty of Medicine Srinagarind Hospital, Khon Kaen University, Khon Kaen. Following approval from the institutional ethics committees of both institutes, all patients who were diagnosed with KD with CAAs between January 1, 1994 and June 30, 2019 were retrospectively reviewed. Patients who had only a single echocardiography or angiography without any follow-up were considered as incomplete data and were excluded from the study. The requirement for informed consent from patients was waived and the process for protecting patient confidentiality was guaranteed. Permission for the study protocol to waive the informed consent process was approved by the Siriraj Institutional Review Board, Faculty of Medicine, Siriraj Hospital, Mahidol University [Study number 294/2561 (EC1)] and Srinagarind Hospital, Khon Kaen University [Reference No.HE611289]. All methods were performed in accordance with the relevant guidelines and regulations. Demographic, clinical, initial laboratory, and echocardiographic findings of CAAs and KD treatment were explored. Demographic data was collected for gender, age at diagnosis of KD, clinical presentation, and criteria of diagnosis. The laboratory data was recorded, including erythrocyte sedimentation rate (ESR), white blood cell (WBC), and platelet count. The echocardiographic findings of CAAs were collected at the time of diagnosis, 6-8 weeks following diagnosis, and from recent follow-up data. The dimensions of the right coronary artery (RCA), left main coronary artery (LMCA), left anterior descending artery (LAD), and left circumflex artery (LCx) were recorded with their Z-scores. The maximal dimension of CAAs was used to categorize the patients as having small, medium, or giant aneurysms. Based on the 2017 AHA criteria[1], CAAs were classified as small aneurysms (Z-score 2.5 to <5), medium aneurysms (Z-score 5 to <10), or large or giant aneurysms (Z-score 10 or an absolute dimension > 8 mm). Treatment of KD included receiving IVIG, onset of fever that received IVIG (within 10 days or after 10 days), retreatment with IVIG, and receiving adjunctive anti-inflammation medications. Coronary angiographic findings and data of stress from myocardial perfusion imaging (MPI) consisted of stress nuclear imaging, stress cardiac cardiovascular magnetic resonance (CMR), and exercise stress test. Long-term outcomes were examined, including MACE and mortality using either the current

hospitals' databases or phone contact. MACE was identified if the patients had cardiovascular-related illness including total coronary artery occlusion, heart failure, clinical or imaging evidence of myocardial ischemia (MI), requirement of coronary artery bypass grafting (CABG), or percutaneous coronary intervention (PCI) following a diagnosis at the most recent follow-up in 2020.

Statistical Methods

Statistical analyses were performed with SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Demographic, clinical, laboratory, cardiac imaging data, and KD treatment data were presented as a frequency with percentages for the categorical variables and mean ± SD or median with range for the continuous variables. Factors associated with MACE were analyzed using univariate and multivariate analyses; cox regression. The Kaplan-Meier method was used to analyze intervention-free rates for CABG or PCI in patients after being diagnosed with KD at a recent follow-up. A statistically significant difference was considered to be a p-value < 0.05.

Declarations

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Author Contributions Statement

C.V. conceptualized the study, collected and analyzed the data for this research and wrote the manuscript. K.S. collected and analyzed the data and prepared the initial reports. Y.S facilitated the data collection and edited the manuscript. Sa.K collected and analyzed the data. P.C., M.P., P.C, K.D, P.C., S.K., and J.S. provided critical feedback and edited the manuscript. All authors contributed to the manuscript, and read and approved the final submission.

Competing Interests

The authors declare no competing interests.

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Ethics Approval and Consent to Participate

Permission for the study protocol to waive the informed consent process was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University [Study number 294/2561 (EC1)] and Srinagarind Hospital, Khon Kaen University [Record No.3.4.05: 27/2561, Reference No.HE611289].

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available due to patient confidentiality, but they are available from the corresponding author upon reasonable request.

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Tables

Table 1. Baseline characteristics

Variable	Total (n=170)	MACE (n=19)	No MACE (n=151)
Age at diagnosis (years)	1.68 (0.2-12.5)	2.72 (0.3-12.5)	1.65 (0.2-9.9)
Site			
- Siriraj Hospital	135 (79.4%)	18 (94.7%)	117 (77.5%)
- Srinagarind Hospital	35 (20.6%)	1 (5.3%)	34 (22.5%)
Male sex	111 (65.3%)	17 (89.5%)	94 (62.3%)
Typical KD	66 (38.8%)	7 (36.8%)	59 (39.1%)
Atypical KD	88 (51.8%)	9 (47.4%)	79 (52.3%)
Uncertain typical or atypical KD	16 (9.4%)	3 (15.8%)	13 (8.6%)
Lack of IVIG treatment	16 (9.4%)	5 (26.3%)	11 (7.3%)
Timing of IVIG treatment			
- ≤10 days of fever	90 (52.9%)	5 (26.3%)	85 (56.3%)
- >10 days of fever	51 (30%)	8 (42.1%)	43 (28.5%)
- Unknown timing	29 (17.1%)	6 (31.6%)	23 (15.2%)
Onset of fever received IVIG (day)	9 ± 4	12 ± 5	9 ± 4
Retreatment with 2nd IVIG	25 (14.7%)	4 (21.1%)	21 (13.9%)
Receiving adjunctive anti-inflammatory medication	9 (5.3%)	1 (5.3%)	8 (5.3%)
WBC (/mm^3)	17,851 ± 7,550	19,651 ± 7,466	17,732 ± 7,571
Platelet (/mm^3)	512,076 ± 189,334	652,250 ± 172,609	502,885 ± 187,376
ESR (mm/hr)	80 ± 29	93 ± 22	79 ± 29
Degree of coronary artery			
- Small aneurysm	74 (43.5%)	-	74 (49%)
- Medium aneurysm	47 (27.6%)	2 (10.5%)	45 (29.8%)
- Giant aneurysm	49 (28.8%)	17 (89.5%)	32 (21.2%)
Initial Z-score of coronary dimension	5.4 (0.2-85.5)	23.2 (1.8-85.5)	4.6 (0.2-34.9)
Maximal Z-score of coronary dimension	6.3 (2.6-85.5)	24.2 (6.7-85.5)	5.4 (2.6-34.9)
Location of coronary artery aneurysm			

•	RCA			
•	LAD+RCA	32 (18.8%)	1 (5.3%)	31 (20.5%)
•	LMCA+LAD+RCA	33 (19.4%)	6 (31.6%)	27 (17.9%)
•	LAD	31 (18.2%)	4 (21.1%)	27 (17.9%)
•	LMCA	22 (12.9%)	1 (5.3%)	21 (13.9%)
•	LAD+RCA+LCx	13 (7.6%)	-	13 (8.6%)
•	LMCA+LAD	4 (2.4%)	3 (15.8%)	1 (0.7%)
•	LMCA+RCA	8 (4.7%)	1 (5.3%)	7 (4.6%)
•	LMCA+LAD+RCA+LCx	22 (12.9%)	2 (10.5%)	20 (13.2%)
		3 (1.8%)	1 (5.3%)	2 (1.3%)

Data presented as n (%), mean ± SD and median (range)

MACE=major adverse cardiac event; KD=Kawasaki disease; IVIG=intravenous immunoglobulin; LMCA=left main coronary artery; LAD=left anterior descending artery; RCA=right coronary artery; LCx=left circumflex artery; WBC=white blood cell; ESR=erythrocyte sedimentation rate

Table 2. Management of CAAs at different risk levels

	Small CAAs (n=74)	Medium CAAs (n=47)	Giant CAAs (n=49)
Coronary angiography	9 (12.2%)	13 (27.7%)	35 (71.4%)
Myocardial perfusion imaging	5 (5.5%)	13 (27.7%)	35 (71.5%)
· Radionuclear stress MPI	1	4	16
· Stress CMR	4	7	16
· EST	-	2	3
Coronary intervention			
· CABG	-	-	12 (24.5%)
· PCI	-	1 (2.1%)	1 (2%)
· None	74 (100%)	46 (97.9%)	36 (73.5%)

Data is shown as n (%). CAAs=coronary artery aneurysms; MPI=myocardial perfusion imaging; CMR=cardiovascular magnetic resonance; EST=exercise stress test; PCI=percutaneous coronary

intervention; CABG=coronary artery bypass grafting

Table 3. Risk analysis of major adverse cardiac events (MACE) in Kawasaki disease with coronary aneurysms (CAAs)

Variable	Crude HR (95%CI)	P-value	Adjusted HR (95% CI)	P-value
Age at diagnosis <1 year	0.71 (0.26-1.98)	0.518		
Male sex	4.27 (0.99-18.49)	0.052	5.09 (1.04-25.02)	0.046
Atypical KD	1.05 (0.39--2.82)	0.924		
Lack of IVIG treatment	4.62 (1.66-12.86)	0.003*	11.43 (2.8-46.62)	0.001*
Retreatment with 2nd IVIG	1.76 (0.58-5.33)	0.315		
Received adjunctive anti-inflammatory medication	0.95 (0.13-7.10)	0.957		
Referral from other hospitals	2.93 (0.68-12.67)	0.151	0.63 (0.1-3.93)	0.622
Elevated ESR (mm/hr)	1.01 (0.99-1.03)	0.281		
Presence of giant CAAs	20.6 (4.76-89.26)	<0.001*	16.55 (2.52-108.63)	0.003*
Maximal Z-score of coronary involvement	1.14 (1.09-1.19)	<0.001*		
Location of coronary artery aneurysm				
• RCA				
• LAD	0.57 (0.06-5.51)	0.630		
• LAD+RCA	0.70 (0.73-6.81)	0.761		
	3.26 (0.93-11.42)	0.064	1.93 (0.44-8.5)	0.383

MACE=major adverse cardiac event; KD=Kawasaki disease; IVIG=intravenous immunoglobulin; LMCA=left main coronary artery; LAD=left anterior descending artery; RCA=right coronary artery; WBC=white blood cell; ESR=erythrocyte sedimentation rate; CAAs=coronary artery aneurysms

Figures

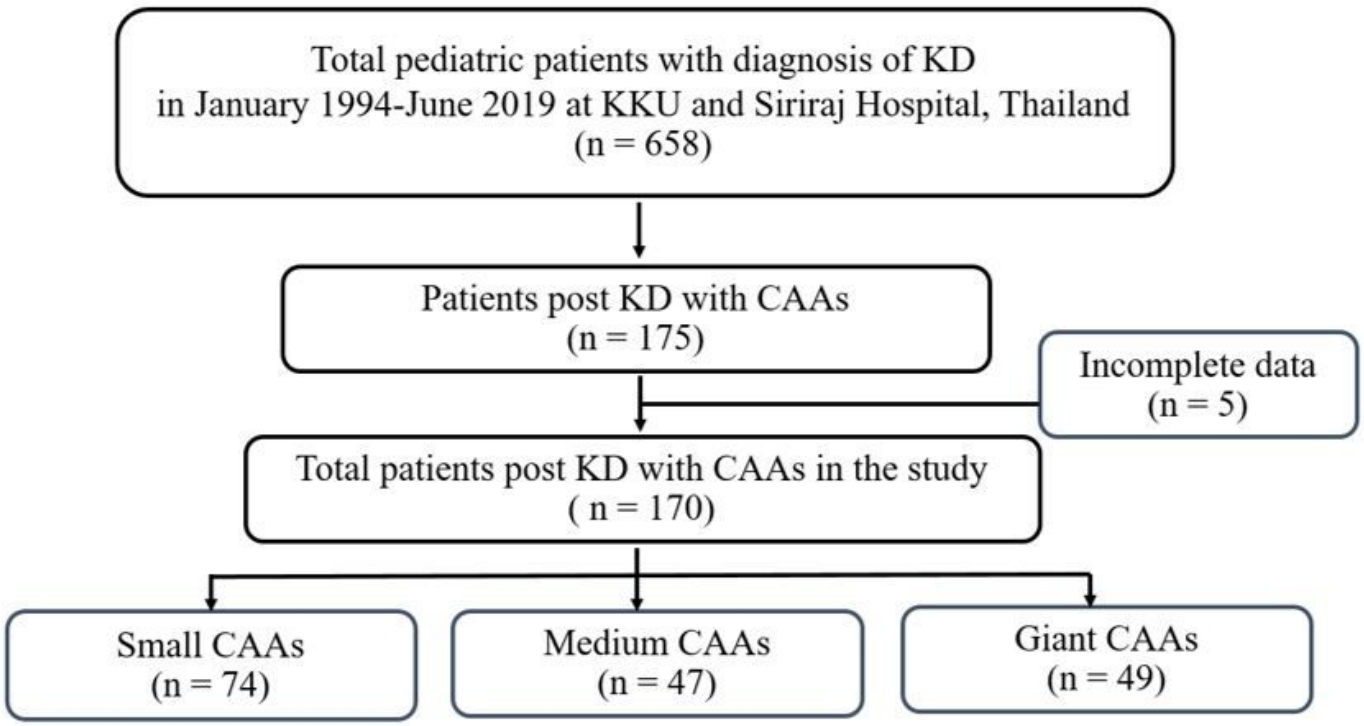
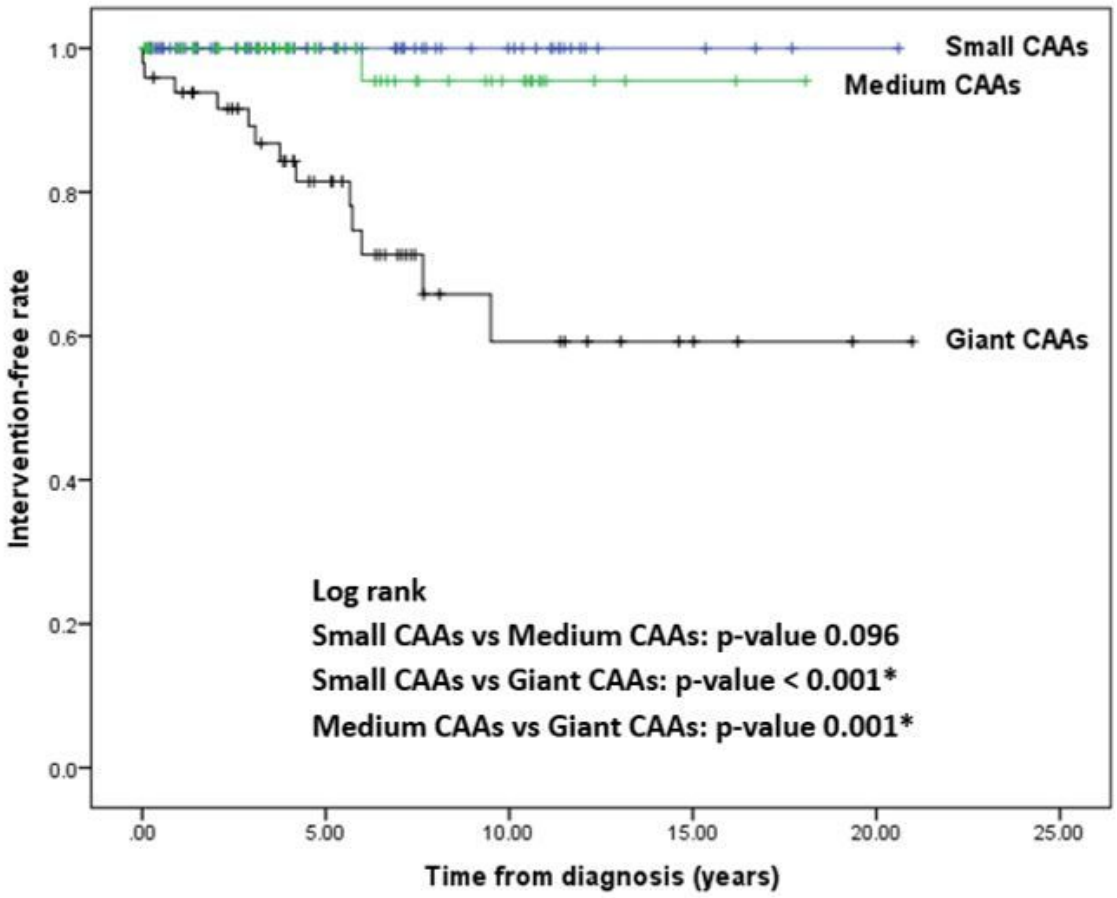


Figure 1

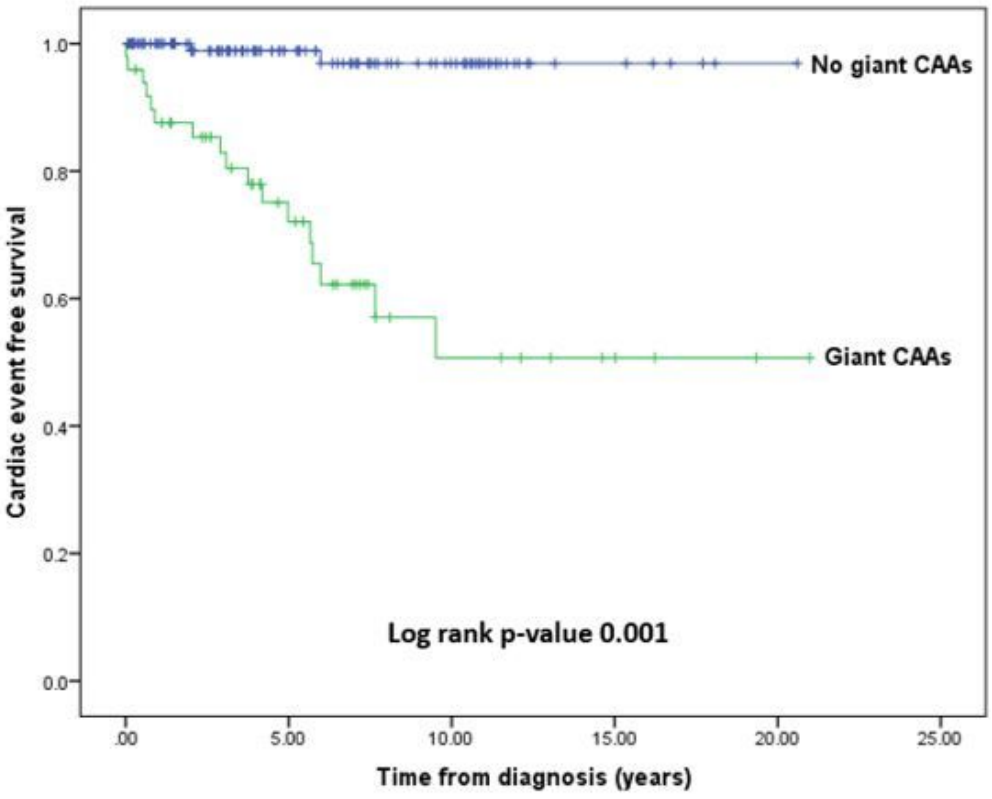
Flow diagram of pediatric patients included in the analysis (n=170)



Time	At Diagnosis	1 year	5 years	10 years
Small CAAs	74	61	33	16
Medium CAAs	47	41	24	11
Giant CAAs	49	45	27	9

Figure 2

Kaplan-Meier estimates of the intervention-free rate of patients with Kawasaki disease who had coronary artery aneurysms (CAAs) (n=170); small CAAs (n=74; blue line), medium CAAs (n=47; green line), and giant CAAs (n=49; black line) from the time of initial diagnosis



Time	At Diagnosis	1 year	5 years	10 years
No giant CAAs	121	102	56	27
Giant CAAs	49	42	24	8

Figure 3

Kaplan-Meier estimates of the cardiac event-free survival of patients with Kawasaki disease who had coronary artery aneurysms (CAAs) (n=170); patients without giant CAAs (n=121; blue line), and with giant CAAs (n=49; green line) from the time of initial diagnosis

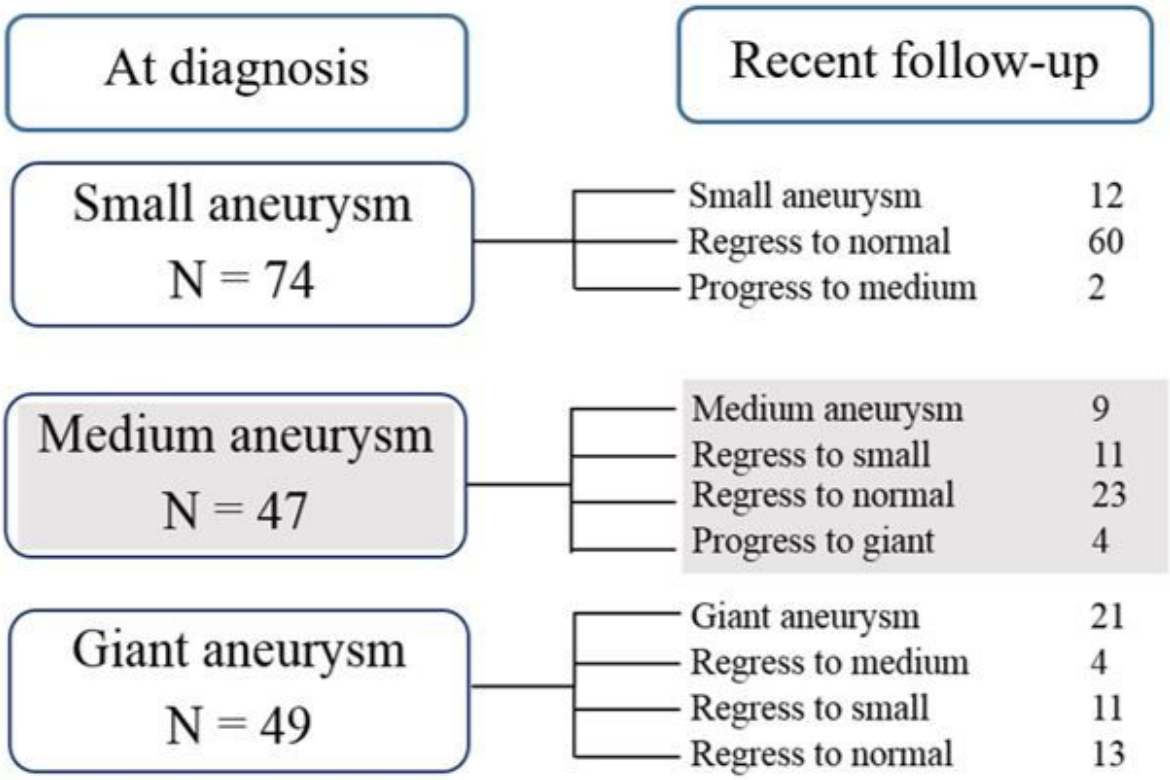


Figure 4

Progression and regression of coronary artery aneurysms (CAAs) at a recent follow-up (n=170)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementarydatatableS1SciRep.docx