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ORIGINAL ARTICLE

Epidemiology, clinical characteristics, and immediate outcome of Kawasaki disease: a population-based study from a tropical country

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Abstract

Data on Kawasaki disease from tropical countries are scarce. Hence, this population-based study aims to determine the epidemiology, clinical characteristics, and outcome of Kawasaki disease in children enrolled in the Kawasaki disease registry between 2006 and 2019 in Southern Malaysia. Diagnosis of Kawasaki disease was made using standard criteria. Primary outcome measure was a coronary artery aneurysm. Multivariable logistic regression was used to analyze the associated risk factors for coronary artery aneurysm. There were 661 Kawasaki disease, with 27% incomplete and 11% atypical presentations. Male-to-female ratio was 2:1, and median age of diagnosis was 1.4 years (interquartile range 9 to 32 months). Incidence in children of less than 5 years was 14.8 (95% confidence interval [CI]: 13.6 to 16.0) per 100,000 population, higher in males (19/100,000) and Chinese (22/100,000), with a gradual increase from 5.7/100,000 in 2006 to 19.6/100,000 in 2019, $p < 0.001$. Incidence in children between 5 and 9 years old was 1.3 (95% CI: 0.9 to 1.6) per 100,000 population and remained stable over time. There was a seasonal pattern with peak incidence during the rainy season. Out of 625 intravenous immunoglobulins (IVIG)-treated Kawasaki disease, 7.4% were resistant, and 9% had coronary artery aneurysms. Atypical presentation, male sex, late diagnosis, and IVIG resistance were independent risk factors for coronary artery aneurysms.

Conclusions: Despite the tropical climate, Kawasaki disease epidemiology is similar to non-tropic regions with seasonal patterns and a rising incidence. Atypical presentation, male sex, late diagnosis, and IVIG resistance were significantly associated with coronary artery aneurysms.

What is Known:
- *Kawasaki disease predominantly occurs in males, children less than 5 years old, and the Asian population.*
- *Male sex, late diagnosis, incomplete Kawasaki disease, and IVIG resistance were associated with coronary artery aneurysms.*

What is New:
- *In multi-ethnic Asian countries such as Malaysia, ethnic Chinese have a higher prevalence of Kawasaki disease compared to other ethnicities.*
- *Kawasaki disease with atypical presentation can occur in both complete and incomplete Kawasaki disease and is significantly associated with a coronary artery aneurysm.*

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Keywords Registry · Intravenous immunoglobulin · Coronary aneurysm

Introduction

Kawasaki disease is an acute self-limiting vasculitis primarily seen in children [1]. It was first described in the English language by Tomisaku Kawasaki in 1974 [2]. Currently, the diagnosis is based on clinical criteria [3], and there are two subtypes, complete and incomplete. However, Kawasaki disease may also present with unusual signs and symptoms, described as atypical Kawasaki disease [1, 4–8]. One serious complication of Kawasaki disease is coronary artery aneurysms, which occurs in 4 to 20% of intravenous immunoglobulin (IVIG)-treated cases [7, 9–11]. Despite advances in medical science, the etiology of Kawasaki disease remains elusive. Among the possible etiologies are environmental toxins, infectious agents, and immune and genetic factors [12]. A seasonal variation in particular geographical areas [13] has been demonstrated, and several susceptibility genes [14–16] and immune complexes [17, 18] have been linked to Kawasaki disease.

Kawasaki disease occurs predominantly in the northeastern Asian population, with an incidence ranging from 28 to 330 per 100,000 children under 5 years of age and rising [9, 19–21]. Meanwhile, the incidence in Europe and the USA is much lower, ranging from 3.3 to 20 per 100,000 [7, 10, 11, 22, 23]. To date, there is no population-based epidemiological study from Malaysia, and data from tropical and southeastern Asian countries are limited [24]. As Malaysia is an Asian country, we hypothesize that the incidence of Kawasaki disease in this country is higher than that in Northern America and Europe. Furthermore, given the humid tropical climate in Malaysia, there should be no seasonal variation. Therefore, this work aimed at studying the epidemiology of Kawasaki disease and determining the prevalence and associated risk factors for coronary artery aneurysms. Hopefully, these data will shed some light on this intriguing disease.

Materials and methods

This cross-sectional observational population-based study was conducted among children (0 to 10 years) with Kawasaki disease diagnosed between January 2006 and December 2019 in the State of Johor, Malaysia. This study as registered with the National Medical Research Register (NMRR-19-2549-50342). The Medical Research and Ethics Committee, Ministry of Health Malaysia approved this study and waived written informed consent. All procedures performed in this study followed the institutional and national research committee's clinical standards and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

The state of Johor is in the southern part of peninsular Malaysia, with an average of six hundred thousand children who are less than 10 years of age. It has a characteristic hot and humid tropical climate with rainfall throughout the year and a rainy season from October to December [25]. Meanwhile, the population consists mainly of Malay (52%), followed by Chinese (30%), and Indian (6%) ethnic groups. Due to the high cost of IVIG, most Kawasaki disease cases are referred to government hospitals for management.

The diagnosis of Kawasaki disease was made according to the American Heart Association guidelines on Kawasaki disease [1, 3]. Briefly, all children with a fever for more than 5 days with at least four of five standard clinical criteria were diagnosed with complete Kawasaki disease. Meanwhile, children with less than four criteria were considered to have incomplete Kawasaki disease. As suggested by Newburger et al. [1], atypical Kawasaki disease was defined if the patient presented with unusual signs and symptoms or complications such as shock, neurological, abdominal, and renal involvement. All patients diagnosed with Kawasaki disease had a full clinical assessment, laboratory investigations, and cardiac assessment. All confirmed cases of Kawasaki disease in infants or children diagnosed within 10 days of the onset of the illness received a single high dose of IVIG (2 g/kg) [3, 26]. For a late diagnosis, IVIG was given if a patient still had a persistent fever or had increased inflammatory markers. Additionally, all patients received either 80 to 100 mg/kg/day or 30 to 50 mg/kg/day aspirin. They had at least one echocardiogram either at diagnosis or at 6 to 8 weeks after the onset of the illness. Subsequent echocardiograms and follow-up were performed depending on the clinical findings.

IVIG resistance was defined as the persistence or recurrence of fever occurring between 48 h and 2 weeks after the initial IVIG infusion [27]. The primary outcome measured was coronary artery aneurysm, defined according to the Japanese Ministry of Health [1]. Briefly, the coronary artery aneurysm diagnosis was made when the internal lumen diameter was > 3 mm in children younger than 5 years, or when the diameter was > 4 mm in children 5 years or older, when a segment was 1.5 times greater than the adjacent segment, or when there was a luminal irregularity. Coronary artery aneurysms were further divided into small (< 5-mm internal diameter), medium (5- to 8-mm internal diameter), and giant (more than 8-mm internal diameter) aneurysms.

Data were retrieved from the Kawasaki Disease Information System, a clinical registry developed in 2006

for of all children with Kawasaki disease diagnosed in Johor. For this study, the data retrieved included age, the timing of the diagnosis, the clinical criteria, the type of Kawasaki disease presentation, IVIG resistance, and the coronary outcome. Kawasaki disease cases diagnosed in other states of Malaysia were not included. Based on 4% of coronary artery aneurysms reported from a previous study [3] and an anticipated 7% in our cohort, a sample size of 389 patients was required to achieve 80% power of the study with a probability type 1 error of 0.05.

Statistical analysis

All data were analyzed with the Statistical Package for the Social Sciences (SPSS) version 23 (IBM Corp., Armonk, NY, USA). Cases of Kawasaki disease with and without coronary artery aneurysm were compared using Student's t-test for normally distributed continuous data and a nonparametric test for nonnormally distributed continuous data. Meanwhile, Pearson's chi-square test was used for categorical data. A p-value < 0.05 was considered statistically significant. Univariable and multivariable binary logistic regression was used to identify risk factors associated with coronary artery aneurysms in IVIG-treated Kawasaki disease cases. The variables included in the analysis were sex, ethnicity, age group, hospital type, clinical criteria, clinical presentation, year of diagnosis, timing of the diagnosis, and IVIG responsiveness. The odds ratios were statistically significantly different from the reference category if their 95% confidence intervals excluded one.

The annual incidence of Kawasaki disease was calculated as the sum of all new Kawasaki disease episodes in that particular year divided by the total population in the same year. The incidence of Kawasaki disease was calculated for different ages (0–4 years and 5–9 years), sexes (male and female), and ethnic groups (Malay, Chinese, and Indian). Linear regression was used to determine the trend of the Kawasaki disease incidence over time.

Results

There were 661 cases of Kawasaki disease detected with a median age of onset of 1.4 years (interquartile range 9 to 32 months), with 177 (26.8%) incomplete Kawasaki disease, 236 (35.7%) were less than 1 year old, and 439 (66.4%) were male (Table 1). Seventy patients (10.6%) had atypical presentations, with 34 (48.6%) having at least four diagnostic clinical criteria for Kawasaki disease. Fifteen (2.3%) presented with Kawasaki disease shock syndrome, 41 (6.2%) with gastrointestinal manifestations, 32 (4.8%) with neurological manifestations, and 17 (2.6%) with musculoskeletal manifestations. Overall, three patients required ventilatory support, and no mortality was recorded.

The incidence of Kawasaki disease among children less than 5 years old and between 5 and 9 years old was 14.8 (95% confidence interval [CI]: 13.6 to 16.0) and 1.3 (95% CI: 0.9 to 1.6) per 100,000 population, respectively. There was a statistically significant change over time in Kawasaki disease incidence among children less than 5 years ($p < 0.001$) but not in children between 5 and 9 years of age (Fig. 1). In children less than 5 years old (Supplement 1), a higher incidence of Kawasaki disease was observed in males compared to females (19.1/100,000 versus 10.3/100,000, $p < 0.001$) and in ethnic Chinese compared to other ethnicities (21.8/100,000 versus 13.2/100,000, $p < 0.001$). Monthly case numbers remained stable throughout the year, except from October to December (Fig. 2). This pattern was observed every year throughout the study duration.

IVIG infusion was administered to 625 (94.6%) of the Kawasaki disease patients, of which, 46 (7.4%) were resistant. Forty-three of the IVIG resistant group showed a positive response after a second course of IVIG and three required a third course of IVIG. None of them received steroids or immunosuppressive therapy. Among the 36 who did not receive IVIG, 28 (77.8%) had a late diagnosis, and 8 (22.2%) had a fever that had subsided at the time of diagnosis without any increased inflammatory markers.

Overall, 9.5% (63/661) had coronary artery aneurysms, with 8.9% (56/625) in IVIG-treated patients and 19.4% (7/36) in non-IVIG-treated patients developing coronary artery aneurysms ($p = 0.07$). Of 56 coronary artery aneurysms in IVIG-treated Kawasaki disease, 10 (17.8%) were late IVIG therapy (5 complete and 5 incomplete), 35 (62.5%) were complete (25 classics and 10 atypical presentations), and 11 incomplete (6 classics and 5 atypical presentations) Kawasaki disease. Among 63 coronary artery aneurysms, 44 (69.8%) were small, 14 (22.2%) were medium, and five (7.9%) were giant. Meanwhile, small transient coronary ectasia was noted in 57 (8.6%). In IVIG-treated Kawasaki disease, a multivariable binary logistic regression model showed that atypical presentation, male sex, IVIG resistance, and a late diagnosis were independent risk factors for coronary artery aneurysms (Table 2).

Discussion

This is the first population-based study to describe the epidemiology, clinical features, and outcomes of Kawasaki disease in Malaysia. Most of the population-based epidemiology studies of Kawasaki disease are from northeastern Asian, North American, and European regions [28]. In this study, the mean annual incidence of Kawasaki disease among children less than 5 years of age was 14.8 per 100,000 population and

Table 1 The characteristics and coronary artery aneurysm of children with Kawasaki disease

Variables	Total N (%)	Coronary artery aneurysm		p-value
		Yes n†(%)	No n†(%)	
Sex				
Male	439 (66.4)	54 (12.3)	385 (87.7)	**0.001**
Female	222 (33.6)	9 (4.1)	213 (95.9)	
Ethnicity				
Chinese	247 (37.4)	25 (10.1)	222 (89.1)	0.690
Malay and others	414 (62.6)	38 (9.2)	376 (90.8)	
Age group				
0 to 12 months	236 (37.7)	19 (8.1)	217 (91.9)	0.134
1 to 4 years	372 (56.3)	35 (9.4)	337 (90.6)	
5 to 9 years	53 (8.0)	9 (17.0)	44 (83.0)	
Hospital type				
Private	119 (18.0)	12 (10.1)	107 (89.9)	0.821
Government	542 (82.0)	51 (9.4)	491 (90.6)	
Clinical criteria				
Incomplete	177 (26.8)	20 (11.3)	157 (88.7)	0.350
Complete	484 (73.2)	43 (8.9)	441 (91.1)	
Kawasaki disease presentation				
Atypical	70 (10.6)	23 (32.8)	47 (67.2)	**<0.001**
Classic	591 (89.4)	40 (6.8)	551 (93.2)	
Year diagnosis				
2006–2009	104 (15.7)	9 (8.7)	95 (91.3)	0.568
2010–2014	263 (39.8)	22 (8.4)	241 (91.6)	
2015–2019	294 (44.5)	32 (10.9)	262 (89.1)	
Timing of diagnosis				
Late diagnosis, > 10 days	66 (10.0)	17 (25.8)	49 (74.2)	**<0.001**
Early diagnosis, ≤10 days	595 (90.0)	46 (7.7)	549 (92.3)	
Received IVIG				
Yes	625 (94.6)	56 (9.0)	569 (91.0)	0.070
No	36 (5.4)	7 (19.4)	29 (80.6)	
Timing of IVIG‡				
Late, after 10 days	38 (6.1)	10 (26.3)	28 (73.7)	**0.001**
Early, before 5 days	51 (8.2)	4 (7.8)	47 (92.2)	
Appropriate, within 5–10 days	536 (85.8)	42 (7.8)	494 (92.2)	
IVIG resistant‡				
Yes	46 (7.4)	11 (23.9)	35 (76.1)	**<0.001**
No	579 (92.6)	45 (7.8)	534 (92.2)	
Total	661 (100)	63 (9.5)	598 (90.5)	

† (%) represents the percentage within the variables

IVIG, intravenous immunoglobulin

‡ of 625 who received IVIG

Statistically significant if p-value < 0.05 (in bold)

was statistically significantly among ethnic Chinese compared to other ethnicities. Our annual incidence was two to three times higher than that in Thailand [24] and India [29]. However, our rate was 10 to 30 times lower than that in Japan [19], Korea [20], China [9], and Taiwan [21]. This could be due to the ethnic distribution, with a relatively low number of people with Chinese or Japanese origins in Malaysia, Thailand, and India compared to northeastern

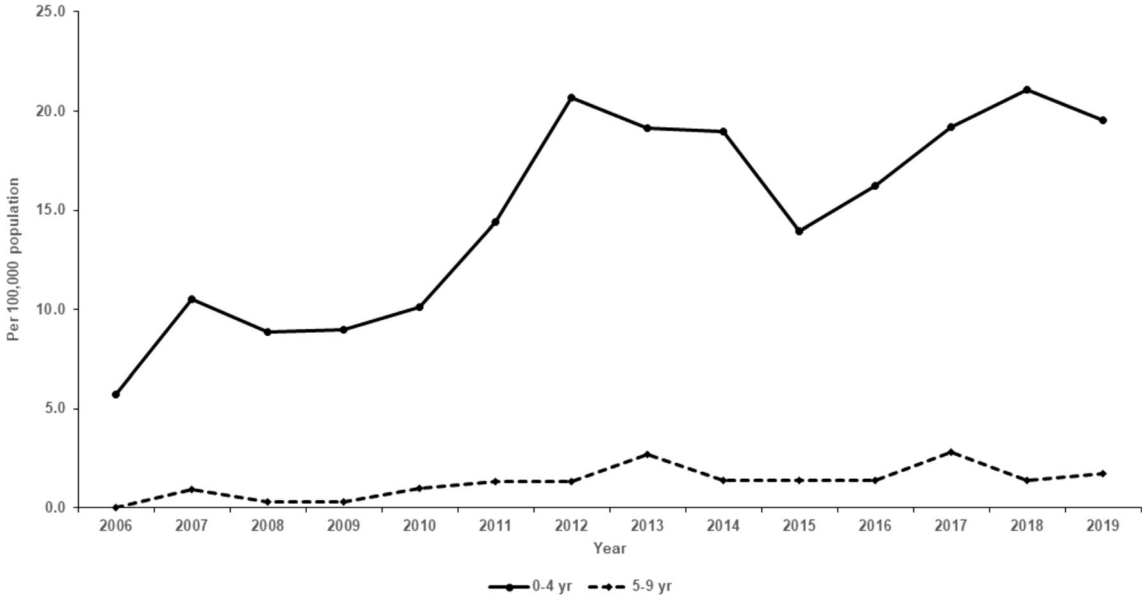

Fig. 1 Incidence of Kawasaki disease among children in Johor, Malaysia, from 2006 to 2019

Asian countries. Another reason could be differences in study design. Furthermore, we only studied a selected state rather than a national population.

The incidence found in the present study is comparable to the reported incidence in the USA [22] and Canada [11]. A higher incidence of Kawasaki disease among ethnic Chinese individuals was also observed in studies from the UK and Ireland [7] and in the USA [22]. These findings suggest that genetic factors play a significant role in the etiology and pathogenesis of Kawasaki disease. A recent meta-analysis showed that the H131R polymorphism in the FCGR2A gene is associated with an increased risk of Kawasaki disease in Asian children but not in Caucasians [16]. As in other studies [7, 19, 20, 30], a male predominance was detected in this study. This could be due to the presence of a susceptible male-specific FCGR2A His167Arg polymorphism in the male sex [15].

Certain pediatric diseases are associated with seasonal variation [31] which may provide clues to its etiologic agents. Burns et al. [13] noted a substantial seasonal variation in Kawasaki disease incidence in the Northern Hemisphere extratropical regions but only a weak association in tropical and Southern Hemisphere extratropical regions. Despite a humid tropical climate throughout the year, this study showed a higher incidence of Kawasaki disease during the rainy season from October to December. This result adds to the current evidence of a seasonal variation in Kawasaki disease in a tropical country. Similar to other studies [7, 19, 21, 23, 32], the incidence of Kawasaki disease in Malaysia is rising,

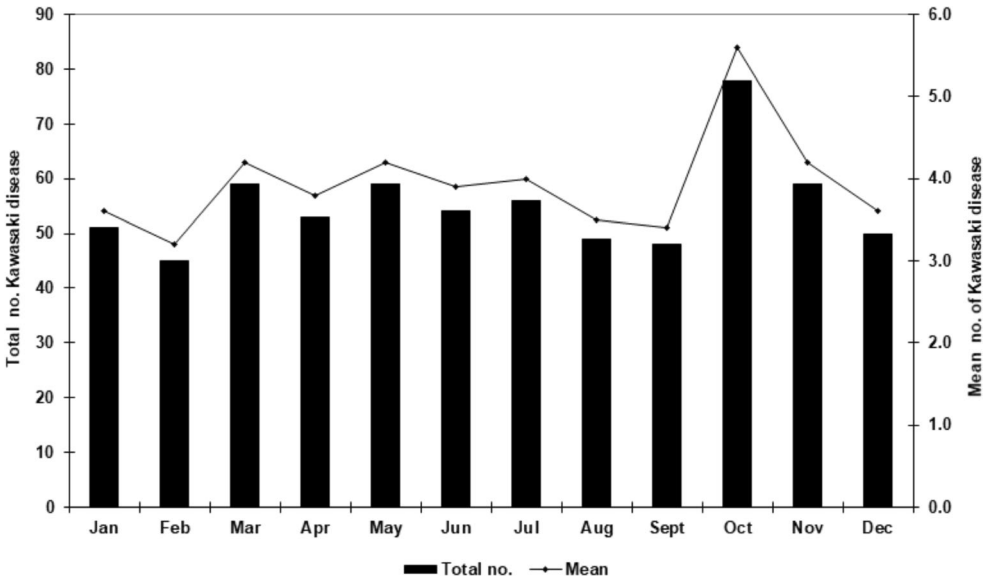

Fig. 2 The total and mean number of Kawasaki disease patient by month for each year from 2006 to 2019

Table 2 Risk factors for coronary artery aneurysm among 625 Malaysian children with Kawasaki disease treated with intravenous immunoglobulin

Variables	Total	CAA, n (%)	Crude OR (95% CI)	P-value	†Adjusted OR (95% CI)	P-value
Gender						
Male	412	49 (11.9)	3.97 (1.77, 8.93)	0.001	4.12 (1.82, 9.69)	0.001
Female	213	7 (3.3)	1 .00 (reference)		1.00 (reference)	
Timing of diagnosis						
Late diagnosis, > 10 days	38	10 (26.3)	4.20 (1.92, 9.18)	< 0.001	3.08 (1.24, 7.66)	0.01
Early diagnosis, ≤ 10 days	587	46 (7.8)	1.00 (reference)		1.00 (reference)	
IVIG responsiveness						
IVIG resistant	46	11 (23.9)	3.73 (1.77, 7.84)	0.001	3.22 (1.41, 7.33)	0.005
IVIG responder	579	45 (7.8)	1.00 (reference)		1.00 (reference)	
Clinical presentation						
Atypical	66	20 (30.3)	6.32 (3.38, 11.79)	< 0.001	4.88 (2.45, 9.72)	< 0.001
Classic	559	36 (6.4)	1.00 (reference)		1.00 (reference)	

(%) represent the percentage of coronary aneurysm of various variable

†Analyzed with multivariable binary logistic regression, Enter Method, corrected for age and ethnic group

Odds ratios are considered statistically different from the reference category if their 95% confidence intervals excluded one

CI, confidence interval; *OR*, odds ratio; *IVIG*, intravenous immunoglobulin; *CAA*, coronary artery aneurysm

reaching 19.6 per 100,000 population in 2019. This could be due to increased awareness and recognition of Kawasaki disease among medical practitioners or perhaps an actual increase in incidence.

Coronary artery aneurysm may cause significant long-term cardiovascular disease [30, 33]. Despite IVIG usage, the coronary artery aneurysm rate in this study was still high at 9%. However, this is within the range of recent population studies [7, 9–11]. A high coronary artery aneurysm prevalence could be due to a high number of late diagnosis of Kawasaki disease with late IVIG therapy, incomplete Kawasaki disease, and atypical presentations in this cohort.

The findings in this study are in line with a recent meta-analysis by Yang et al. [34], which showed that male sex, late diagnosis, and IVIG resistance were significantly associated with coronary artery aneurysm. In addition, this is the first population study that showed that an atypical presentation is statistically significantly associated with coronary artery aneurysm. In this study, an old terminology of "atypical Kawasaki disease" following 2004 guidelines [1] but different from current guidelines [3] was consistently reserved only for patients who presented with an unusual symptom or complication [1, 6]. Infants or children with atypical presentations were five times more likely to develop coronary artery aneurysms than those with classical presentations. Kawasaki disease would be less likely to be listed in the differential diagnosis when patients present with shock, seizure, or joint pain. For many of these presentations, patients are initially treated for infectious diseases, leading to a delayed diagnosis of Kawasaki disease and later coronary artery aneurysm development [4, 6]. These results may suggest that a reintroduction of the old terminology, differentiating incomplete from atypical Kawasaki disease, might be considered.

In contrast with the findings by Sudo et al. [35], this study showed that there is no significant difference in the prevalence of coronary artery aneurysm between complete and incomplete Kawasaki disease. This supports the suggestion by Manlhiot et al. [5] that incomplete and complete Kawasaki disease is just different sides of the same coin.

Limitations

There are several limitations to this study. First, laboratory tests were not recorded in the registry between 2006 and 2009. Thus, this prevents further analysis of laboratory factors associated with coronary artery aneurysm. Second, the Z-score for coronary artery aneurysm, which has been shown to be a possible predictor of coronary artery aneurysm in Asian countries [36], and which is recommended for coronary aneurysm definition and classification in current Kawasaki disease guidelines [3], was not used in this study. Obviously, this represents a major limitation of our study. However, this was unfortunately unavoidable, because patient height was not recorded in this registry between 2006 and 2017, which prevented reanalysis of the Z-scores. Third, these data may or may not represent the national data. A national survey, such as the one conducted in Japan [19], is needed to determine the true incidence of Kawasaki disease in Malaysia. Finally, the definition of "atypical Kawasaki disease" used in this study, followed the old Kawasaki disease guidelines [1]. While this may obviously render our study surpassed, we believe that a discussion on the opportunity to re-introduce the differentiation between incomplete and atypical Kawasaki disease should start.

Conclusions

Similar to other parts of the world, the incidence of Kawasaki disease is rising in Malaysia. Kawasaki disease occurred predominantly in males and the ethnic Chinese and showed a seasonal pattern. These epidemiological findings support the hypothesis that Kawasaki disease pathogenesis is multifactorial, with both environmental and genetic factors probably playing some role. Atypical presentation of Kawasaki disease, male sex, late diagnosis, and IVIG resistance were significantly associated with the development of coronary artery aneurysms.

This work is original and has not been published or presented elsewhere, nor is it currently under consideration for publication elsewhere.

Abbreviations *IVIG,* Intravenous immunoglobulin

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Code availability Not applicable

Authors' contributions MNMB contributed to the study conception and design, carried out the echocardiogram, wrote the first draft, performed data analysis and revised the manuscript. MHS contributed to the study conception and design, carried out the echocardiogram and performed data collection. FFH contributed in the study conception and design, and performed data collection. HR contributed in the study design, data analysis, reviewed and revised the manuscript. EYA contributed in the study design, critically reviewed and revised the manuscript. NA contributed in the study design and critically reviewed the manuscript. All authors read and approved the final manuscript.

Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval All procedures performed in studies involving human participants were following the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was registered with the National Malaysian Research Registry with the identification number NMRR-19-2549-50342. It was approved by the Ministry of Health Research and Ethics Committee.

Consent to participate Malaysian Ministry of Health Research and Ethics Committee waived the written informed consent.

Consent for publication Not applicable

Conflict of interest The authors declare no competing interests.

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