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| RESEARCH ARTICLE

Risk Factors for Coronary Artery Aneurysm in Children with Kawasaki Disease: A Case-control Study

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| ABSTRACT
Coronary artery aneurysms (CAA) are common in children with Kawasaki disease (KD) who have delayed diagnosis. This can increase the high cardiovascular burden and cause acquired heart defects in adulthood. This study aims to investigate the risk factors for CAA in children with KD. An observational retrospective case-control study was carried out in Surabaya Tertiary Hospital. We collected the medical records in the child care installation, Pediatrics ward, from 2016 to 2019. The research participants were pediatric patients who were treated with KD. The exclusion criteria were incomplete medical record data regarding the risk factors studied. The risk factors studied included age, sex, duration of fever, haemoglobin, leukocytes levels, platelets levels, C-reactive protein (CRP), and albumin levels. Twenty-eight medical records of children with KD were collected in this study; only 17 eligible patients were observed. The confirmed CAA was found in 8 patients, while 9 patients were non-CAA aged ranging from 3-124 months. Almost 60% of patients had fever duration > 7 days, and 47.1% of patients had hemoglobin <10 g/dL. Platelets were the only risk factor that had a significant correlation for developing CAA in children with KD, with a p-value of 0.015 at a 95% confidence interval (CI), odds ratio (OR) of 24 (1.785 – 336.227). Almost half of KD patients in this study were at risk for developing CAA; platelet value was a risk factor that we could consider in the administration of aspirin and IVIG therapy, providing the follow-up results and evaluating aneurysm progression or regression after IVIG administration is needed to prevent poor long-term outcomes.

| KEYWORDS

Kawasaki disease, coronary artery aneurysms, risk factors, children

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1. Introduction

Kawasaki disease (KD) is a small-moderate inflammatory vascular disease (vasculitis) of unknown cause, occurring mainly in children under 5 years of age (Tang et al., 2018). The symptoms include fever for several days, red rash/spots, swelling of the hands and feet, red eyes, irritation and inflammation of the mucous membranes of the mouth, lips and throat, and swollen lymph nodes in the neck. In Japan in 2012, KD sufferers reached 15,442 men and 11,249 women (Makino et al., 2015). Research from a global perspective, KD in several countries experienced a significant increase, especially in the United Kingdom with as many as 2,009 cases in the period 1982 - 2005, United States of America showed 5,127 cases from several countries in the period 1976 – 2012 (Burns et al., 2013). In Indonesia alone, there were 1150 cases in the period 2003 – 2016 in 5 Hospitals in Jakarta and South Tangerang. The rest, there were approximately 5000 new cases in 1 year (Advani et al., 2018, 2019). However, due to the lack of medical personnel and the public who know the symptoms of this disease, it causes frequent errors and delays in diagnosis. Although most KD is self-limiting, in 25% of patients who are not treated properly, coronary artery aneurysms (CAA) will occur, which can cause coronary thrombosis, coronary stenosis, myocardial infarction, and mortality (Tang et al., 2018). Administration of Intravenous immune globulin (IVIG) and aspirin can reduce the prevalence of CAA by about 4% (McCrindle et al., 2017). However, some cases of persistent CAA despite standard therapy may lead to future acquired heart defects.

The severity of CAA in KD patients is classified according to the size of the coronary artery diameter that occurs in the acute phase up to 1 month of illness. There are three classifications, namely: small (<4 mm), medium (4–8 mm), and large (>8 mm). The degree of severity based on this classification can predict future coronary artery output (Liu et al., 2017). In patients with a history of KD, after growing up, late cardiovascular complications are seen in patients with persistent CAA, in the form of occlusion and stenosis. These may develop into ischemic heart disease and high cardiovascular risk, which can increase mortality, morbidity, and the burden of medical costs in the community (Núñez-Gil et al., 2020; Tang et al., 2018).

Several studies have been conducted to assess the prognosis of KD patients in the short, medium, or long term, but research on risk factors for CAA has not been done much (Friedman et al., 2016; Holve et al., 2014). If the risk factors for CAA can be identified earlier in KD patients, it will be more profitable. A 3-year observational study in Northern China in patients with KD reported that age, time to start IVIG therapy, and response to IVIG were risk factors for CAA (Tang et al., 2018). Meanwhile, a retrospective study in Taiwan reported that early coronary dilatation and hypo albumin were significant risk factors for persistent CAA in KD patients after one year (Liu et al., 2017). In Indonesia, a study by Advani et al. (2018) reported that fever > 7 days and hypoalbuminemia were predictive factors for the occurrence of CAA in children with KD (Advani et al., 2018). Research on risk factors for the occurrence of CAA in KD patients in Indonesia will be able to provide a more comprehensive picture than the results of previous studies abroad. So that it can predict and provide early IVIG therapy to prevent persistent CAA and the onset of acquired heart defects in adulthood.

2. Methods

An observational retrospective case-control study was carried out in Surabaya Tertiary Hospital. We collected the medical records from January 2016 – January 2019 in the child care installation, Pediatrics ward. The research participants were pediatric patients who were treated with KD. The exclusion criteria were incomplete medical record data regarding the risk factors studied. In the case of CAA, the patient had an echocardiographic examination that met the following criteria: 1) internal lumen diameter >3 mm in children <5 years or >4 mm in children ≥5 years, 2) internal diameter of coronary artery segments >1.5 times that of a coronary artery segment adjacent, and/or 3) irregular coronary lumen. This research has obtained ethical feasibility issued by the Ethics Committee of Dr. Soetomo General Academic Hospital Surabaya in February 2019, Ethics Number 0970/KEPK/II/2019.

Data were analyzed using IBM SPSS Statistics Version 25. Bivariate analysis of risk factors for CAA was tested using the Pearson Chi-square test and/or the Fisher Exact test as appropriate. The results of the analysis were considered significant if the p-value was < 0.05. The risk factors that will be studied include age, sex, duration of fever, hemoglobin, leukocytes levels, platelets levels, C-reactive protein (CRP), and albumin levels.

3. Results

Twenty-eight medical records of children with KD are collected in this study. However, only 17 patients with complete medical records regarding risk factor data were observed, including duration of fever, age, sex, hemoglobin, leukocytes, CRP, serum albumin levels, and platelets. The confirmed CAA was found in 8 patients, while 9 patients were non-CAA. The study participants were aged between 3 and 124 months. The majority of patients were under 5 years of age, as many as 13 (76.5%), with the highest incidence between 1 to 2 years. A total of 58.8% of patients were male. Patients with fever duration > 7 days were 10 (58.8%). There were 8 patients (47.1%) with hemoglobin < 10 g/dL. A total of 10 (58.8%) patients with leukocyte values > $16x10^3/\mu L$ and 9 (52.9%) patients with platelet values > $500x10^3/\mu L$. Patients with CRP values > 10 mg/L were 14 (82.4%). Patients with serum albumin values < 3.5g/dL were 10 (58.8%). The characteristics of the study patients are shown in Table 1.

Table 1. The characteristics of the pediatric patients with KD

Characteristics	Value
Age (years old)	
< 5	13 (76.5)
≥ 5	4 (23.5)
Sex	
Male	10 (58.8)
Female	7 (41.2)
Fever duration (days)	
≤ 7	7 (41.2)
> 7	10 (58.8)
Hemoglobin (g/dL)	
< 10	8 (47.1)
≥ 10	9 (52.9)
Leukocytes ($10^3/\mu L$)	

≤ 16	7 (41.2)
> 16	10 (58.8)
Platelets (10^3/µL)	
≤ 500	8 (47.1)
> 500	9 (52.9)
CRP (mg/L)	
≤ 10	3 (17.6)
> 10	14 (82.4)
Albumin (g/dL)	
< 3.5	10 (58.8)
≥ 3.5	7 (41.2)

Data were viewed as number and percentage.

Table 2 present the correlation between several risk factors for CAA, including duration of fever, age, sex, hemoglobin, leukocytes, CRP, serum albumin levels, and platelets. Bivariate analysis with Pearson Chi-square test or Fisher Exact test showed that male sex, duration of fever > 7 days, leukocytes > 16x10^3/µL, and platelets > 500x10^3/µL had a p-value of <0.25. However, only platelets were statistically significant as a risk factor for coronary artery aneurysm in KD with a p-value of 0.015 at a 95% confidence interval (CI), odds ratio (OR) of 24 (1.785 – 336.227).

Table 2. The correlation of risk factors and CAA (bivariate analysis)

Variables	CAA N= 8	Non-CAA N = 9	OR (95% CI)	p-value
Age (years old)				0.576
< 5	7 (87.5)	6 (66.7)	3.5	
≥ 5	1 (12.5)	3 (33.3)	(0.284-43.161)	
Sex				0.153
Male	3 (37.5)	7 (77.8)	0.171	
Female	5 (62.5)	2 (22.2)	(0.020-1.436)	
Fever duration (days)				0.050
≤ 7	1 (12.5)	6 (66.7)	14	
> 7	7 (87.5)	3 (33.3)	(1.135-172.64)	
Hemoglobin (g/dL)				0.637
< 10	3 (37.5)	5 (55.6)	0.48	
≥ 10	5 (62.5)	4 (44.4)	(0.069-3.352)	
leukocytes (10^3/µL)				0.050
≤ 16	1 (12.5)	6 (66.7)	14	
> 16	7 (87.5)	3 (33.3)	(1.135-172.642)	
Platelets (10^3/µL)				0.015*
≤ 500	1 (12.5)	7 (77.8)	24	
> 500	7 (87.5)	2 (22.2)	(1.785-336.227)	
CRP (mg/L)				0.576
≤ 10	2 (25)	1 (11.1)	0,375	
> 10	6 (75)	8 (88.9)	(0.027-5.169)	
Albumin (g/dL)				1.000
< 3.5	5 (62.5)	5 (55.6)	1.33	
≥ 3.5	3 (37.5)	4 (44.4)	(0.191-9.311)	

Data were presented as numbers and percentages; Fisher Exact test; *a p-value ≤ 0.05 was significant.

4. Discussion

Cardiovascular symptoms and complications are the leading causes of KD-related morbidity and mortality. The most serious complication of KD is CAA. KD is the major cause of acquired heart disease in children, especially in developed countries, and a risk factor for myocardial infarction in early adulthood (Mossberg et al., 2021). In this study, there were more pediatric patients aged less than 5 years, males sex with fever > 7 days and hemoglobin level > 10 g/dL. In a 10-year observational study, risk factors for coronary artery dilatation in KD patients included: age < 1 year, male sex, age 9-17 years, Asia-Pacific, and Hispanic race (Belay et al., 2006).

In this study, 87.5% aged < 5 years with CAA were found, and it was not statistically significant. However, quantitatively, the results of aneurysms were positive, mostly < 5 years old. Another study showed that the incidence of CAA, especially in incomplete KD, was highest in infants (45%), followed by ages 1-5 years (30%), and the remaining 17.6% aged over 5 years (Mossberg et al., 2021). A meta-analysis study stated that male sex was associated with the incidence of CAA (Yan et al., 2019). In contrast to that study, our study found that the male gender was not a risk factor for CAA. In general, more patients with KD were male, but there were more female pediatric patients in the group of confirmed CAA.

Many studies on CAA in KD reported that the duration of fever > 7 days and hypo albumin were significant risk factors for the occurrence of CAA in KD patients (Advani et al., 2018; Jeon et al., 2019). In our case, the duration of fever was not significantly significant as a risk factor for CAA in KD. But quantitatively, it was found in the group with confirmed CAA, patients with fever > 7 days more than patients with fever < 7 days. We also did not find hemoglobin as a risk factor for CAA in KD patients, but this is different from the study reported by Fernandez-Cooke et al. in 2019 stated that hemoglobin levels <10.2 mg/dL had a 2.2 times greater risk of developing coronary aneurysms (Fernandez-Cooke et al., 2019). Our study also did not find leukocytes as a risk factor for CAA in children with KD. However, 87.5% of patients with confirmed CAA in this study tended to have leukocytes > $16x10^3/\mu L$.

Platelets are a significant risk factor for CAA, with platelet values > $500x10^3/\mu L$. This is in line with the results of a previous study by Santy et al. in 2019 which stated that a significant risk factor for coronary artery dilatation was platelets > 444000/µL (Santy et al., 2019). Another study reported that there was a correlation between the duration of fever and thrombocytosis, the occurrence of coronary artery dilatation, and unresponsiveness to IVIG administration in KD patients whose platelet count and activation increased (Park & Choi, 2021). In the acute phase of KD, there is an increase in platelet-derived microparticles (PDMP), a useful biomarker for platelet activation, rapidly decreasing after treatment with IVIG. In addition, PDMP levels positively correlated with levels of soluble CRP, IL-6, and IL-2 but did not correlate with an erythrocyte sedimentation rate (ESR), procalcitonin levels, and levels of tumor necrosis factor-α (TNF-α). These results suggest that platelet activation may be an inflammation marker for KD. Platelet activation is also a major determinant of a variety of KD-related complications, including sensorineural hearing loss, peripheral gangrene, and CAA (Park & Choi, 2021). On the other hand, thrombocytopenia is included in the scoring system criteria for IVIG administration in KD patients and the risk of developing CAA by the Harada score (Tewelde et al., 2014). If 4 of the 7 criteria are met within 9 days of the onset of fever, IVIG is recommended. Risk factors for CAA include leukocytes >12,000/µL, CRP >3+, hematocrit <35%, platelets <350,000/µL, serum albumin <3.5 g/dL, age <12 months, and male sex (Tewelde et al., 2014). In addition, thrombocytopenia causes increased morbidity and mortality in severe KD cases. The pathogenesis of thrombocytopenia in KD includes the use of coagulation-mediated platelets, macrophage activation syndrome (MAS), and immunoglobulin-induced platelet destruction (Park & Choi, 2021).

CRP and albumin were not found as risk factors for developing CAA. However, CRP values > 10 mg/L were more dominant in both groups, both in confirmed and non-confirmed CAA cases. This study found in 5 patients with CAA (62.5%) who had hypoalbuminemia <3.5 g/dL. According to the American Heart Association (AHA), resistance to IVIG is specified as the presence of fever persisting 36 hours after the first IVIG administration (Friedman et al., 2016; McCrindle et al., 2017; Song, 2019). To evaluate the progression or regression of the aneurysm, echocardiography can be performed after 6-8 weeks (Gargiulo et al., 2015; Wei et al., 2016). In this study, observations of aneurysm progression or regression by echocardiographic evaluation were not performed. We realize that this study still has several limitations, especially in the number of research participants and the short study time, so many of the risk factors observed do not provide a statistically meaningful picture. However, we believe that this study can make a good contribution in terms of monitoring patient treatment to prevent the risk of CAA in KD patients.

5. Conclusion

Almost half of KD patients in this study were at risk for developing CAA, although the platelet value was a risk factor that we could consider in the administration of aspirin and IVIG therapy. This study has its limitation, specifically, the small number of samples and the short duration of the research. This condition could affect the results, which makes them slightly different from previous studies. Only thrombocytosis has been shown to be a risk factor for the occurrence of CAA. Further research to investigate the risk factors for developing CAA in KD should be done multicentered in a longer research duration, Thereby providing the follow-up results and evaluating aneurysm progression or regression after IVIG administration to prevent poor long-term outcomes.

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