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Original Article

## Predictors for coronary artery dilatation in Kawasaki disease

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### Abstract

**Background** Kawasaki disease (KD) is an acute, self-limited, febrile illness of unknown cause that predominantly affects children below 5 years of age. It has a high incidence of coronary complications such as aneurysms. The current treatment of choice is intravenous immunoglobulin, which is costly, with aspirin. Identifying the predictive factors for coronary artery dilatation or aneurysm is important in order to establish the indications for giving immunoglobulin, especially when resources are limited.

**Objective** To identify the predictors for the development of coronary artery dilatation in patients with Kawasaki disease

**Methods** This cross-sectional study was done between January 2003 and July 2013. Inclusion criteria were patients who fulfilled the *American Heart Association* criteria for acute Kawasaki disease, and had complete clinical, echocardiogram, and laboratory data [hemoglobin, leukocyte, platelet, albumin, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)]. All of them received immunoglobulin and aspirin.

**Results** Of 667 KD patients, 275 met the inclusion criteria. There were 185 (67%) males. Subjects' ages varied between 1 to 157 months. The frequency of coronary artery dilatation at the acute phase was 33.3%. Multivariate analysis showed that >7-day duration of fever and hypoalbuminemia were significant predictive factors for coronary artery dilatation.

**Conclusion** Predictive factors for coronary artery dilatation are duration of fever over 7 days and hypoalbuminemia, while age, gender, hemoglobin level, leukocyte count, and platelet count are not. Frequency of coronary artery dilatation at the acute phase is 33.3%. [Paediatr Indones. 2018;58:257-62; doi: <http://dx.doi.org/10.14238/pi58.5.2018.257-62>].

**Keywords:** coronary dilatation; Kawasaki disease; predicting factor

Kawasaki disease is an acute, self-limited, febrile illness of unknown cause that predominantly affects children below 5 years of age.<sup>1</sup> Coronary artery aneurysms occur in 15-25% of untreated cases, which may lead to myocardial infarction, sudden death, or ischemic heart disease.<sup>2</sup> The main current treatment to prevent coronary artery dilatation is high dose immunoglobulin and aspirin.

Considering the high cost of immunoglobulin, in cases with limited financial means and/or facilities, identifying risk factors for coronary artery dilatation may help physicians predict which patients are necessary to have immunoglobulin therapy. When the risk is high, then immediate treatment or referral would be mandatory.

Initial echocardiogram during the early days of the disease may not be useful to assess the need for immunoglobulin. Coronary artery dilatation is detectable from day 6 after onset, but commonly reaches its peak between 2-6 weeks from onset.<sup>3-6</sup> Furthermore,

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facilities and pediatric cardiologists are unavailable in most Indonesian hospitals. Therefore, it is of value to determine the predictors for coronary artery dilatation by other parameters that can be observed earlier.

Several scoring systems are available to assess the indications of giving immunoglobulin.<sup>7-9</sup> However, none are sensitive and specific enough to accurately detect the possibility of coronary aneurysm.<sup>10</sup> Thus, many experts in Japan who previously gave intravenous immunoglobulin only to the high risk patients, now give it to all Kawasaki patients in the acute phase.<sup>11</sup> Administering immunoglobulin to all KD patients in Indonesia would be financially prohibitive, and we do not know if the progression of the disease is the same in Indonesian patients.

It has been widely accepted that delayed administration of intravenous immunoglobulin is a major risk factor for coronary aneurysm.<sup>1,11</sup> Other risk factors are duration of fever,<sup>7,12-15</sup> age less than 1 year,<sup>7-9,16,17</sup> male sex,<sup>9,17</sup> and Asian/Hispanic race.<sup>7,17</sup> Laboratory examinations such as leukocytosis,<sup>7-9</sup> low albumin level,<sup>9,16,18</sup> high CRP level,<sup>7-9</sup> high ESR level,<sup>7,13</sup> anemia,<sup>3,7</sup> and thrombocytopenia<sup>3,9</sup> or thrombocytosis at acute phase<sup>8</sup> are also important risk factors.

Coronary artery dilatation was once determined using criteria from the Japanese Ministry of Health, but currently Z-score criteria is preferred.<sup>1</sup> The correlation between coronary artery dilatation and risk factors such as young age, male sex, leukocytosis, high neutrophil level, thrombocytopenia, high CRP level, high ESR level, low albumin, anemia, delayed treatment, and duration of fever using the Japanese Ministry of Health is inconsistent. In contrast, Z-score cutoff for coronary artery dilatation is relevant to young age, duration of onset to therapy, low IgM level, and low albumin level.<sup>18</sup> Until now, risk or predictive factors for coronary artery dilatation are diverse and sometimes contradict each other.

This study aimed to identify the predictors for the development of coronary artery dilatation in patients with Kawasaki disease.

## Methods

This cross-sectional study using retrospective data was done between January 2003 and July 2013. Subjects

were children with Kawasaki disease from 5 hospitals in the Jakarta area. Data of eligible subjects were taken from medical records, consisting of clinical presentation, therapy, laboratory studies (hemoglobin, leukocytes, platelets, albumin, CRP, and ESR) and echocardiography examination.

The minimum required sample size for studying coronary artery dilatation was estimated using an incidence of 20% and acceptable standard deviation of 5% ( $N = Z\alpha 2PQ/d^2 = 1.962 \times 0.2 \times 0.8 / 0.052 = 246$ ). The minimum required sample size for risk factors of coronary dilatation was calculated based on the rule of thumb: >400 subjects (large), 200-400 subjects (intermediate), and <200 subjects (small).

Inclusion criteria were patients who fulfilled the *American Heart Association* diagnostic criteria for complete/incomplete KD in the acute phase,<sup>1,10</sup> were treated with immunoglobulin (2 g/kg BW) and oral aspirin (80-100 mg/kg), and had complete laboratory and echocardiogram data. Complete Kawasaki disease is diagnosed in the presence of fever for at least of 5 days with at least 4 of the 5 clinical findings: erythema of lips and tongue, bilateral conjunctivitis, rash, palmar/plantar erythema and cervical lymphadenopathy, while incomplete Kawasaki is diagnosed when fever is accompanied by less than 4 clinical findings in the presence of coronary artery dilatation or other laboratory criteria.<sup>1</sup> Subjects with congenital heart disease, history of other acquired heart disease, or incomplete/missing data were excluded. Independent variables were gender, age, duration of fever, hemoglobin, leukocytes, platelets, albumin, ESR, and CRP. The dependent variable was coronary artery dilatation. All clinical and echocardiographic examinations were done by the author (NA) before immunoglobulin and aspirin administration.

For assessment of coronary artery dilatation, we measured the lumen dimensions and used a z-score based on body surface area for the right, left main, and left anterior coronary arteries.<sup>19</sup> Coronary dilatation was defined as z-score  $\geq 2.5$  mm of any of the right, left main, or left anterior descending vessels. This study was approved by the Ethics and Research Committee of Universitas Indonesia Medical School.

## Results

A total of 667 KD patients were found during the study period, 503 of whom were hospitalized during the acute phase. Coronary artery dilatation at this phase was seen in 168 patients (33.3%). Of the 503 subjects, 275 had complete medical records for risks factors (duration of fever, hemoglobin (Hb), leukocyte, platelets, ESR, CRP and serum albumin level). The majority of patients had complete Kawasaki disease (86.7%). There were 185 (67%) male and 90 (33%) female subjects. Subjects' ages ranged from 1 to 157 months. The majority of subjects were under 5 years (71%), with the highest incidence between 1 to 2 years.

**Table 1** shows correlations between predictors and coronary artery dilatation. Bivariate analysis revealed that duration of fever, hemoglobin, platelet, ESR and serum albumin level had P values < 0.25. Subsequent multivariate analysis of these

factors revealed that >7-day duration of fever and hypoalbuminemia were statistically significant as predictors for coronary artery dilatation (**Table 2**).

## Discussion

Cardiovascular manifestations and complications are the major contributors to morbidity and mortality related to KD, with coronary aneurysms as the main complication. In our study, we use the term 'dilatation' rather than 'aneurysm,' as we measured at the acute stage, meaning the dilatation may be transient. Aneurysm is considered to be a sequela that persists beyond 30 days.<sup>20</sup> The long-term outcomes of these patients have been published elsewhere.<sup>21</sup>

The predictors for coronary artery dilatation in our study were duration of fever >7 days and hypoalbuminemia. We used the cut-off point of 7 days

**Table 1.** Correlations between predictors and coronary artery dilatation (bivariate analysis)

Dependent variables	Coronary dilatation (n=119)	No coronary dilatation (n=156)	OR (95%CI)	P value
Mean age (SD), months	39.2 (30.2)	37.5 (27.4)		0.62*
Gender, n			1.22 (0.73 to 2.04)	0.45**
Male	83	102		
Female	36	54		
Duration of fever, n			2.76 (1.66 to 4.58)	<0.001***
> 7 days	58	40		
≤ 7 days	61	116		
Mean Hb (SD), g/dL	10.63 (1.5)	10.86 (1.16)		0.15*
Mean leukocytes (SD), /μL	16,683 (7,653)	16,108 (5803)		0.48*
Mean platelets (SD), /μL	526,264 (207,582)	444,029 (161,868)		<0.001*
Mean ESR (SD), mm	76.4 (39.9)	69.5 (37.8)		0.15*
Mean CRP (SD), mg/L	92.9 (63.9)	93.5 (68.8)		0.94*
Mean albumin (SD), g/dL	3.25 (0.57)	3.47 (0.53)		0.001*

\*unpaired T-test, \*\* Chi-square, Hb=hemoglobin

**Table 2.** Logistic regression test for coronary artery dilatation predictors (multivariate hypothesis test with cut-off P<0.25)

Predictor variables	Bivariate analysis		Multivariate analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
Duration of fever > 7 days	2.76 (1.66 to 4.58)	<0.001	2.02 (1.15 to 3.53)	0.014
Hemoglobin level		0.151	1.06 (0.86 to 1.3)	0.610
Platelets count		<0.001	1 (1 to 1)	0.010
ESR		0.149	1 (0.99 to 1.01)	0.862
Serum albumin level		0.001	0.53 (0.32 to 0.87)	0.012

due to the majority of coronary artery dilatation onset occur in the late first week to early second week after disease onset. An epidemiological study by Belay *et al.* involving 3,115 subjects during a 10-year observation showed that predictors or risk factors for coronary dilatation were age < 1 year, age 9-17 years, male, as well as Asia-Pacific and Hispanic races.<sup>17</sup> However, laboratory parameters were not mentioned.

Many studies agreed that delayed immunoglobulin administration is a major contributing factor for coronary artery dilatation.<sup>7,12-14</sup> A study on 130 KD patients reported that risk factors for coronary artery dilatation were duration of fever >14 days or 10-13 days, plus 2 or more criteria such as age <1 year, Hb  $\leq 10$  gr/dL, leukocyte count  $\geq 14,000/\mu\text{L}$ , and serum albumin  $\leq 3.5$  gr/dL.<sup>22</sup> Hypoalbuminemia was a risk factor for coronary artery dilatation, similar to our findings. Other parameters such as hemoglobin level, ESR, and leukocyte counts were not associated with coronary artery dilatation, also similar to the results of our study. Nevertheless, duration of fever >14 days differed from our study.<sup>22</sup>

Harada *et al.* evaluated a scoring system for immunoglobulin administration, recommending it if 4 out of 7 criteria were fulfilled within 9 days of fever onset. Other risk factors for coronary dilatation were leukocyte count  $> 12,000/\mu\text{L}$ , platelets count  $< 350,000/\mu\text{L}$ , CRP  $> 3+$ , hematocrit  $< 35\%$ , serum albumin  $< 3.5$  g/dL, age  $< 12$  months, and male sex.<sup>9</sup> However, the only similarity to our study was the hypoalbuminemia as a risk factor for coronary artery dilatation.

A previous study in 78 subjects with Kawasaki disease showed that CRP  $+6$ , age  $< 1$  year, and thrombocytosis were risk factors for coronary artery dilatation. Nakano recruited subjects on days 4 to 7 after fever onset, so fever itself was not stated to be a risk factor for coronary artery dilatation.<sup>8</sup> Another study used z-scores for measurements of the right coronary artery (RCA) and left anterior descending (LAD), without the left main coronary artery (LMCA), and concluded that risk factors for coronary dilatation were duration of fever, hypoalbuminemia, young age, and low immunoglobulin M level.<sup>18</sup> Fever and hypoalbuminemia were risk factors, similar to our findings.

In light of our findings, we suggest that every patient with fever  $> 7$  days and hypoalbuminemia be

referred to a medical center with echocardiography facilities and supported by a pediatric cardiologist. If referral is not possible, it is advisable to immediately give immunoglobulin and aspirin to reduce the possibility of coronary artery dilatation. This recommendation can be applied generally for all Kawasaki patients regardless of their risk factor status.

Duration of fever before immunoglobulin administration is a risk factor for coronary artery dilatation due to progressing inflammation. The pathophysiology of hypoalbuminemia and coronary dilatation is unclear. During acute phase, vascular endothelial growth factor (VEGF) plays a role in increasing vascular permeability,<sup>23</sup> which leads to vascular leakage and results in hypoalbuminemia and edema.<sup>24</sup> Therefore, low serum albumin is a marker for high VEGF. Increased vascular permeability due to VEGF also causes inflammatory cells to enter the intima via coronary artery endothelium, resulting in intimal hyperplasia and proliferation of smooth muscle cells.<sup>25</sup>

In a developing country such as Indonesia, where immunoglobulin cost is high while purchasing power is low, careful selection of patients who receive intravenous immunoglobulin based on predictors of coronary artery dilatation would be quite prudent, especially for those with limited funding.

However, it is not easy to accurately determine risk of coronary artery involvement, although some laboratory markers may provide helpful information for parental counseling and clinical follow up. Future identification of novel biomarkers and host predispositions may improve our knowledge of coronary artery risk factors and help personalize therapy for Kawasaki disease.

In conclusion, the predictors for coronary artery dilatation are duration of fever over 7 days and hypoalbuminemia, while age, gender, hemoglobin level, platelets count, leukocytes count, ESR, and CRP are not. The frequency of coronary dilatation at the acute phase of KD is 33.3%. All patients should be treated with immunoglobulin before day 7 of onset and those with hypoalbuminemia should be treated immediately to prevent coronary complications. When resources are limited, those with hypoalbuminemia and fever over 7 days should be prioritized for immunoglobulin treatment.

## Conflict of Interest

None declared.

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