Clinical characteristics of Kawasaki disease in Polish children: A retrospective study

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ABSTRACT

Background: Kawasaki disease (KD), an acute, generalized vasculitis, is associated with an increased risk of coronary heart disease and is the most common cause of acquired heart disease in childhood. The incidence of KD is increasing worldwide.

Aims: Our study aims to analyze KD's clinical course in children and to evaluate risk factors for persistent changes in coronary vessels after 6–8 weeks of treatment.

Methods: The retrospective analysis included patients with KD hospitalized in a single tertiary care hospital. The diagnosis, as well as treatment, were based on the current worldwide treatment standards. The clinical course, selected laboratory parameters, the treatment effect, and following cardiac complications were analyzed in different age groups.

Results: In the years 2006–2019, 140 patients aged from two months to 16 years: 52 girls and 88 boys, were diagnosed with KD. Coronary artery aneurysms (CAA) at weeks 6–8 of disease were found in 16% of patients. Boys and infants were more likely to develop aneurysms at weeks 6–8 of the disease ($P = 0.045$; $P = 0.03$; respectively). The CAA frequency was related to the atypical course ($P = 0.02$), late diagnosis ($P = 0.04$), presence of changes in the coronary arteries at the time of diagnosis ($P < 0.001$), immunoglobulin resistance ($P = 0.002$), a lower hemoglobin concentration ($P < 0.001$), and a higher platelet count ($P = 0.02$). There were 28% of patients resistant to first-line time treatment. In this group, we found CAA in 31% of children.

Conclusions: We found that late diagnosis, low hemoglobin level, high platelet count, CAA presence at diagnosis, atypical course of KD, and resistance to intravenous immunoglobulins are predictors of CAA after 6–8 weeks in KD patients.

Key words: acquired heart disease, coronary artery aneurysm, Kawasaki disease, vasculitis

INTRODUCTION

Kawasaki disease (KD) is an acute, self-limiting, generalized, small to medium-sized vessel vasculitis, most commonly occurring in children under five years of age. It was described for the first time in 1967 by Tomisaku Kawasaki [1, 2]. This disease is presently the most common cause of acquired heart disease in childhood. It is associated with an increased risk of coronary heart disease [3–6]. The etiology of the disease remains unknown. It is suggested that in genetically predisposed persons, there is an incorrect activation of the immune system and oligoclonal immune response to bacterial, viral, or other unidentified environmental factors, which results in damage of vascular endothelial cells and necrotizing vasculitis [4]. The incidence in the Japanese population is 138 cases/100 000 children under the age of five years. In Great Britain, the number of new cases has doubled recently and is now 8.1/100 000 [7]. The disease is most common in young children, with most patients aged between six months and five years old, with a predominance in males (1.5:1) [4, 5, 7].

WHAT'S NEW?

Kawasaki disease (KD), an acute, generalized vasculitis, is the most common cause of acquired heart disease in childhood. Epidemiological data for KD in Poland are still unknown. Only a few single-center studies have been published. To our knowledge, this retrospective single-center study is based on the largest population of children with KD from Poland. Coronary artery aneurysms (CAA) are one of the main complications of KD. Literature data indicate that many predictors of CAA have been previously identified. We found three significant, independent risk factors for CAA after 6–8 weeks in KD patients: late diagnosis, low hemoglobin level, and the presence of CAA at diagnosis.

The diagnosis of KD is based on clinical criteria. The course of the disease is acute, three-phase, and self-limiting [4–6]. Since the inflammatory process affects all vessels, the clinical manifestation can involve many systemic symptoms. According to the American Society of Cardiology (ASC)/American Heart Association (AHA), the typical form of KD is defined as the occurrence of fever and at least four clinical symptoms that are the criteria for diagnosis [3, 4]. The incidence of atypical forms is increasing. Sometimes the only clinical sign may be fever and abnormalities in laboratory tests, which can cause diagnostic errors. The diagnosis of atypical KD can be also confirmed by the presence of changes in echocardiography.

The main complication of the disease is coronary artery lesions. Risk factors for the development of coronary artery aneurysms (CAA) were previously reported in the medical literature. The risk of permanent changes in coronary arteries in untreated cases is up to 25%, and it decreases significantly (4%) if patients are adequately treated [9, 10]. Standard treatment for KD is based on an infusion of 2 g/kg immunoglobulin and orally administered acetylsalicylic acid optimally implemented before day 10 of the disease. Approximately 10%–20% of patients are resistant to this type of treatment (no resolution of fever, no or only slight decrease in inflammation parameters) [3, 4, 11]. In such cases, re-treatment of intravenous immunoglobulins (IVIG) and/or use of immunosuppressive drugs (glucocorticosteroids, cyclosporin, biological treatment) are considered [4–6, 12].

Our study aims to analyze KD's clinical course in patients hospitalized in our department and to evaluate risk factors for persistent changes in coronary vessels after 6–8 weeks of treatment.

METHODS

The retrospective analysis included patients with Kawasaki disease hospitalized in the Department of Pediatrics, Nutrition, and Metabolic Diseases of the Children's Memorial Health Institute in Warsaw from 2006 to 2019. Patients were referred to our hospital due to persistent fever with high parameters in the acute phase. In all patients, the diagnosis of KD was made based on the AHA criteria: classic KD was defined as the presence of fever for at least 5 days, together with at least 4 of the 5 following principal clinical features. The diagnosis of atypical KD was established in children with prolonged unexplained fever, fewer than 4 of the principal clinical findings, and compatible laboratory or echocardiographic findings [4]. At the time of diagnosis, all patients underwent basic laboratory tests, chest X-rays, and echocardiography (ECHO). ECHO included an assessment of cardiac function, measurements of internal diameters, and Z-scores of coronary arteries that were performed according to the methodology described by Lopez et al. [13]. CAA were defined using z-score classifications: coronary artery aneurysms (z-score >2.5), no coronary artery aneurysms (z-score <2.5). Dilatation of coronary aneurysm defined using the AHA criteria (2 <z-score <2.5) was not included in the analysis (detailed characteristic of coronary abnormalities is ongoing).

Differential diagnosis was performed in all children. Children with other causes of systemic inflammation were excluded from the study.

Our patients were divided into age groups (under 12 months of age, 1–5 years, over five years of age) and clinical type (atypical vs. typical).

All patients were treated with empirical antibiotic therapy and an infusion of intravenous immunoglobulins at a dose of 2 g/kg body weight with orally administered acetylsalicylic acid (ASA) at 30–100 mg/kg body weight/day. The lack of effect of the first-line treatment (resistance to IVIG) was defined as the persistence of fever and acute phase parameters elevation 36 hours after the end of IVIG infusion. In some patients with significant risk factors for resistance to IVIG (age less than one year, elevated inflammatory parameters, liver dysfunction, hypoalbuminemia, anemia, heart failure, dilation of the coronary arteries from baseline echocardiography), and in severely ill patients, glucocorticosteroids (GCS) were administered together with the first infusion of IVIG. Because using GCS in children with KD is still controversial and varies depending on individual recommendations [4–6, 12], the decision for treatment with GCS was made in each case based on the most recent recommendations. IVIG was re-transfused with or without GCS in patients with no effect of first-line treatment. Echocardiography at weeks 6–8 of disease was performed in all patients.

The clinical course, selected laboratory parameters, the treatment effect, and following cardiac complications were analyzed in different age groups.

Statistical analysis

Statistica v. 10 (StatSoft Inc., Tulsa, OK, US) was used for statistical calculations. The Shapiro-Wilk test was used for assessing departures of analyzed variables from the Gaussian distribution. Continuous variables were presented as median (interquartile range [IQR]). Categorical variables were presented as the number of patients. The Mann-Whitney test was used for quantitative variables to compare between two studied groups. The χ^2 test was used to examine differences between categorical variables. Univariable and multivariable logistic regression was performed to assess significant predictors of coronary artery aneurysms. Initially, all variables were included in the model. A backward stepwise procedure was carried out for the removal of nonsignificant factors. This model was adopted as the final one. A *P*-value of less than 0.05 was considered significant.

Institutional ethics committee approval was not required as this was a retrospective observational study.

RESULTS

In the years 2006–2019, 140 patients with KD aged from two months to 16 years (median 2.50 years), 52 girls and 88 boys, were hospitalized in our department. In the group of infants (under 12 months), there were 32 children, in the group between 1 and 5 years old — 79 children, over 5 years — 29 children.

The patients were also divided into a group with a typical disease course — 93 (75%), 39 girls, 54 boys, and a group with atypical patients — 47 (25%), 13 girls, 34 boys.

Apart from fever, the most common symptoms found in the whole group were skin lesions and conjunctivitis (85.7%), followed by mucosal lesions (79.3%), swelling of the hands and feet (62.9%), and lymphadenopathy (63.4%).

Tables 1–2 show that selected clinical and laboratory parameters in patients with coronary lesions persist at weeks 6–8 of disease compared to the group with normal echocardiography during this period. Boys and infants were more likely to develop aneurysms at weeks 6–8 of disease ($P = 0.045$; $P = 0.03$, respectively). Their frequency is also related to the atypical course ($P = 0.02$), late diagnosis ($P = 0.04$), presence of changes in the coronary arteries at the time of diagnosis ($P < 0.001$), immunoglobulin resistance ($P = 0.002$), a lower hemoglobin value ($P < 0.001$), and a higher platelet value ($P = 0.02$). Statistically significant differences were presented using box plots (Supplementary material, *Figures S1–S5*). Uni- and multivariable logistic regression analysis are presented in Tables 3 and 4.

In 16 patients with predisposing factors to IVIG resistance (4 girls, 12 boys), glucocorticosteroids were used together with the first infusion of IVIG (Figure 1). There were 39 (28%) patients with resistance to first-line treatment, 35 out of 124 treated with IVIG only (28%), and 4 out of 16 treated with IVIG plus GCS (25%). We found CAA in 12/39 (31%) children. There was no statistically significant relationship between the use of steroids and the occurrence of dilated coronary arteries at weeks 6–8 of disease in the whole group. All IVIG-resistant patients were re-infused with IVIG 2 g/kg, six patients received GCS with a repeated infusion of IVIG. At the time of diagnosis, an aneurysm of the coronary vessels (z-score >2.5) was found in 32 patients (22.9%), the highest rate was in the under-12-month-old group (14/32 — 43.8%). CAA at weeks 6–8 of disease was found in 22/140 (16%) patients. In patients treated only with IVIG infusions, changes in the coronary arteries were found in 18 out of 118 cases (15%). In the group in which GCS was added to the treatment (with the first or second IVIG), changes in the coronary arteries at weeks 6–8 were found in 4 out of 22 cases (18%) (Figure 1).

DISCUSSION

The incidence of KD is increasing worldwide [14–16]. Epidemiological data for KD in Poland are still unknown. Only a few single-center studies have been published [17–22]. Although it is a single-center retrospective study, to our knowledge, it is based on the largest population

Table 1. Comparison of clinical parameters in the group of patients with coronary artery aneurysms (CAA) persisting at 6-8 weeks of disease to the group with no CAA

		No CAA at weeks 6–8 (n = 118)	CAA at weeks 6–8 (n = 22)	*P*-value
Day of diagnosis	Median (IQR)	8.0 (6.0–10.0)	9.5 (8.0–12.0)	0.04
Age, years	Median (IQR)	2.5 (1.5–4.5)	1.3 (0.8–1.8)	0.004
IVIG	Sensitive, n (%)	91 (77)	10 (45)	0.002
	Resistant, n (%)	27 (23)	12 (55)	
GCS	No, n (%)	81 (69)	15 (68)	0.97
	Yes, n (%)	37 (31)	7 (32)	
Sex	Male, n (%)	70 (59)	18 (82)	0.04
	Female, n (%)	48 (41)	4 (18)	
Clinical course	Classical, n (%)	83 (70)	10 (45)	0.02
	Atypical, n (%)	35 (30)	12 (55)	
ECHO at diagnosis	Normal, n (%)	102 (86)	6 (27)	<0.001
	Z-score >2.5, n (%)	16 (14)	16 (73)	

Abbreviations: CAA, coronary artery aneurysms; other — see Figure 1

Table 2. Comparison of laboratory parameters in the group of patients with coronary lesions persisting at 6–8 weeks of disease to the group with no coronary artery aneurysms (CAA)

	No CAA at weeks 6–8	Median (IQR)	CAA at weeks 6–8	Median (IQR)	*P*-value	Median difference
PCT, ng/ml	n = 81	0.79 (0.35–2.29)	n = 18	0.815 (0.200–5.510)	0.55	-0.025
ESR, mm/h	n = 104	68.5 (48–92)	n = 18	70 (48–118)	0.40	–1.5
CRP, mg/dl	n = 117	9.95 (5.61–15.3)	n = 21	13.5 (4.56–19.80)	0.59	–3.56
Leukocytosis, 10^3/µl	n = 118	16.1 (11.2–20.5)	n = 22	16.1 (14.2–20.5)	0.36	0
% of neutrophils	n = 108	59 (48–67)	n = 22	49 (45–64)	0.09	10
Hb, g/dl	n = 118	10.45 (9.6–11)	n = 22	9.3 (8.7–10.2)	<0.001	1.15
PLT, K/µl	n = 118	425 (315–518)	n = 22	528 (356–818)	0.02	–103
Na, mmol/l	n = 113	138.0 (136–140)	n = 22	137 (136–140)	0.56	1
Albumin, g/l	n = 104	34 (30–37)	n = 22	32.3 (29.8–34.8)	0.15	1.7
NT-proBNP, pg/ml	n = 37	1202 (352–3110)	n = 9	2104 (521–4223)	0.78	–902

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; NT-proBNP, N-terminal pro-B natriuretic peptide; PCT, procalcitonin; PLT, platelets; other — see Figure 1 and Table 1

Table 3. Univariable logistic regression analysis

	OR (95% CI)	*P*-value
Age, years	0.736 (0.550–0.986)	0.04
Day of diagnosis	1.115 (1.002–1.241)	0.04
Hemoglobin, g/dl	0.358 (0.203–0.632)	<0.001
Platelets, K/µl	1.003 (1.000–1.005)	0.02
Female sex	0.528 (0.278–1.006)	0.05
cKD, typical	0.557 (0.339–0.915)	0.02
CAA at admission, presence	4.865 (2.640–8.966)	<0.001
IVIG, resistance	1.925 (1.168–3.170)	0.01

Abbreviations: CI, confidence interval; cKD, classical Kawasaki disease; OR, odds ratio; other — see Figure 1

Table 4. Multivariable logistic regression analysis

	OR (95% CI)	*P*-value
Hemoglobin, g/dl	0.386 (0.184–0.808)	0.01
Day of diagnosis, days	1.159 (1.011–1.330)	0.04
CAA at admission, presence	4.280 (2.211–8.285)	<0.001

Abbreviations: see Figure 1 and Table 3

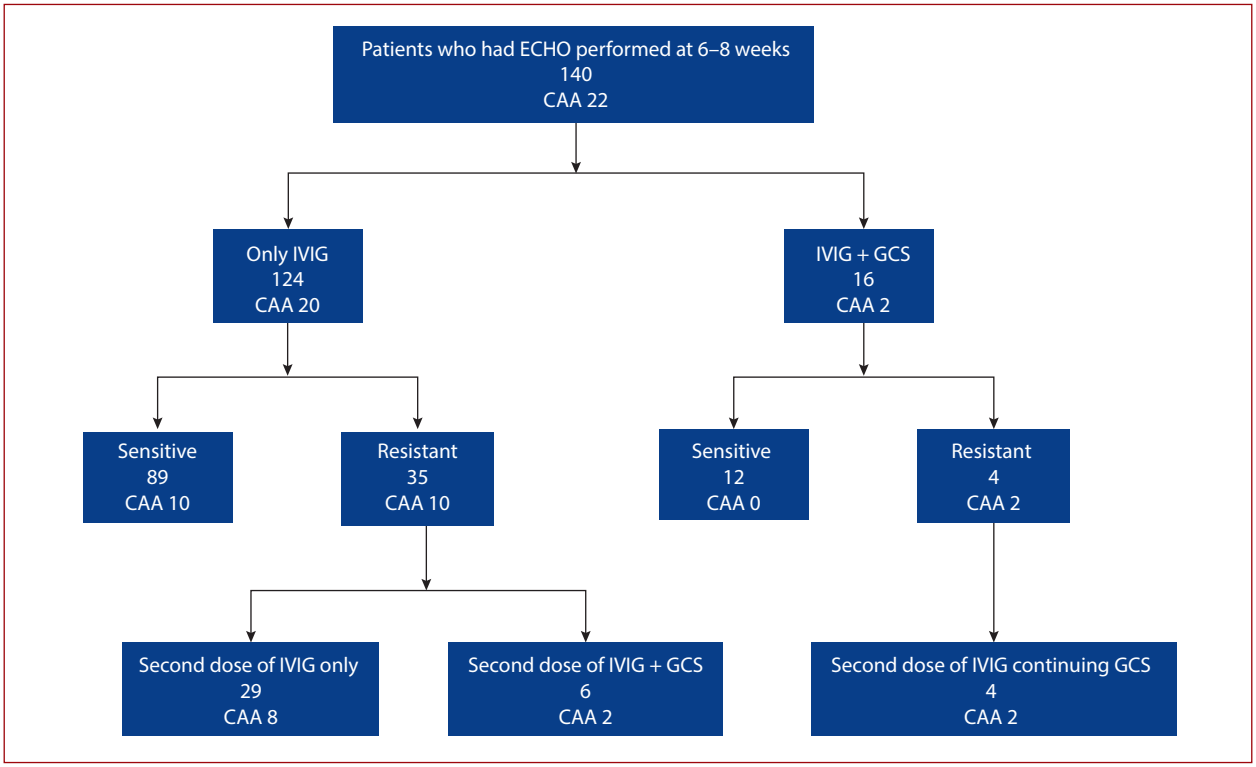

Figure 1. Treatment regimen in patients who underwent echocardiography at weeks 6–8

Abbreviations: CAA, coronary artery aneurysms; ECHO, echocardiography; IVIG, intravenous immunoglobulins; GSC, glucocorticosteroids

of children with KD from Poland. It is worth emphasizing that all patients came from Poland (particularly the Masovian Voivodeship), and there were no ethnic differences (homogeneous Caucasian population). Our genetic studies revealed that polymorphisms of genes *KIF25*, *PTRPJ*, *SPECC1L*, and *RNP2* might be linked with KD incidence in Polish children [23].

Our data confirm a higher incidence in males patients and in children under 5 years of age, which is consistent with literature data. We found that classical KD is more common than atypical in each age group. Atypical KD mainly occurs in infants. Our data suggest that the most common symptoms of KD are fever (99%), skin lesions, conjunctivitis (85.7%), followed by mucosal lesions (79.3%), swelling of the hands and feet (62.9%), and lymphadenopathy (63.4%). In infants, fever could be a sole clinical symptom.

In our study, coronary artery aneurysms were found in nearly 22.9% of KD at the time of diagnosis and in 16% at weeks 6–8 in children treated with IVIG. In other countries, the development of CAA despite IVIG treatment ranges from 19 to 42% [24, 25]. Boys and infants are statistically more likely to develop aneurysms at weeks 6–8 of the disease. This finding is consistent with previous studies.

Literature data indicate that many predictors of CAA have been previously identified. Yan et al. [8] performed a meta-analysis confirming that sex, IVIG resistance, IVIG treatment beyond ten days after the onset of symptoms, and increased C-reactive protein (CRP) levels are significant risk factors for CAA. Zheng X et al. [26] performed the first meta-analysis that revealed the strongest association between the incidence of CAA and IVIG resistance. In our study, we identified seven factors: age, atypical course, late diagnosis, presence of changes in the coronary arteries at the time of diagnosis, IVIG resistance, low hemoglobin level, and high platelet count. Berdej-Szczot et al. [27] found similar independent risk factors in Polish children: prolonged fever, late diagnosis, poorly symptomatic course of the disease, and a high platelet count.

Among seven risk factors found in univariable analysis, multivariable analysis showed only three of them as significant, and independent: low hemoglobin concentration, late diagnosis, and the presence of aneurysms in the first ECHO examination.

In the preliminary analyzes, there was a relationship between sex and the occurrence of CAA (using the χ^2 test), while in the univariable logistic regression model, no such relationship was shown, and the *P*-value was slightly higher than 0.05.

However, Yan et al. [8] in their meta-analysis cannot deny a potential connection between platelet count and CAA development. Further studies are needed to investigate the association between CAA and previously identified factors.

All patients received IVIG together with ASA. In 16 patients, glucocorticosteroids (GCS) were used with the first infusion of IVIG.

In the population under study, 28% of patients were resistant to first-line time treatment, with no differences between groups treated with IVIG infusion only and treated with IVIG plus GCS. This proportion is higher than the 10%–20% reported in previous studies [4].

Recently, many recommendations for the diagnosis and treatment of Kawasaki disease have been published. The most important ones include the scientific statement of the AHA in 2017, the guidelines of the Italian Pediatric Society (2018), and the European rheumatological guidelines (2018) [4–6, 12]. While the diagnosis of KD is consistent in most respects, there are controversies in therapeutic management. The most controversial is the risk scales of IVIG resistance and using GCS. In recent years, the usefulness of the most common IVIG resistance risk scales for European populations has been verified. Researchers from Poland, Germany, and Italy showed that Kobayashi, Sano, and Egami scales are not reliable for identifying patients resistant to IVIG in the European population [27–29]. Because of these findings (and the small size of the patient group), we did not perform such analyses in this study.

Glucocorticosteroids have been used for decades to treat systemic vasculitis but are not yet widely used as an initial treatment for KD. The authors of meta-analyses showed that the frequency of abnormalities in the coronary arteries was significantly lower in children who received GCS with IVIG than only in IVIG therapy [30]. Other researchers suggest that long-term steroid treatment should be considered in all children diagnosed with the disease [31]. Otherwise, Yang et al. [32] showed that GCS treatment, combined with IVIG, reduces the incidence of coronary aneurysms, but only in Japanese patients, which was not observed in other nations' patients. Opposing opinions are also presented. Some believe that conclusions from these studies should not be extrapolated to non-Asian populations due to the possible influence of various environmental, genetic, and economic factors on the effects of therapy [33]. Others state that the use of GCS is an independent risk factor for the development of coronary aneurysms, especially giant aneurysms (child population from China), and may interfere with vessel remodeling (study on a group of 80 patients) [34, 35].

The lack of reliable risk scales for IVIG resistance for the European population may limit using glucocorticosteroids due to doubts about treatment indications and potential side effects.

In our study, we did not find a relationship between the use of GCS and the presence of coronary abnormalities at weeks 6–8 of disease. Further research is required to provide evidence of the effectiveness of GCS and IVIG as first-line treatments.

Interestingly, no CAA was found in patients treated with initial therapy IVIG and GCS with positive effect (without a necessity of second-line treatment) vs children treated only with IVIG not requiring a second-line treatment. Be-

cause of the small sample size, we did not find a statistically significant correlation.

Furthermore, in children treated with GCS and IVIG as initial therapy, CAA developed less often than in a group of children treated with GCS as a second-line treatment (together with the second dose of IVIG). This finding is consistent with the results of the meta-analysis performed by Chen et al. [29]. Still, we cannot confirm it.

In our opinion, treatment with GCS, especially in children with the presence of multi-organ failure resulting from systemic vasculitis (not only medium-sized vessels) should not be avoided. Because of the lack of reliable studies on this topic, GCS treatment decisions should be made individually, based on clinical experience.

Our study ended in 2019, but it is worth mentioning that since 2020 we found an increasing incidence of Kawasaki-like disease after the beginning of the SARS-CoV-2 epidemic. The new entity was proposed so-called pediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C; an alternative name proposed in the US and adopted by the World Health Organization (WHO) [36–38]. Whether this is a form of KD triggered by SARS-CoV-2 or a different entity is still a matter of debate. Children with PIMS-TS are usually older, mucocutaneous symptoms are less common, while gastrointestinal and respiratory symptoms are more frequent. Patients are at higher risk of developing myocarditis with acute heart failure and may require longer time in the hospital and admittance to an intensive care unit. Recently, Lam Y et al. [39] proposed an algorithm (KIDMATCH) for screening patients for MIS-C, KD, or other febrile illness. Many treatment protocols recommend using IVIG and aspirin with/without GCS as first-line therapy. Indications for using GCS and dosing depend on the phenotype of the disease and differ in many medical centers. PIMS-TS remains the diagnostic and therapeutic challenge, the effect of immunomodulatory therapy needs further evaluation in both observational and trial settings [40–42].

The main limitation of our study is the small sample of the examined population. A central case reporting system to report and monitor all KD cases in the Polish pediatric population is ongoing, it belongs to the MultiOrgan Inflammatory Syndromes COVID-19 Related Study (MOIS-CoR) that reports patients diagnosed with PIMS-TS and KD. The detailed characteristic of coronary abnormalities in patients included in our study is of interest to our cardiologists and is unfinished. Follow-up of patients is continuing to provide additional data.

CONCLUSIONS

We found six predictors of CAA after 6–8 weeks in KD patients, all of them are consistent with previous studies. The late diagnosis, low hemoglobin level, and the presence of CAA at diagnosis were identified as significant and independent risk factors.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska

Article information

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