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Changes in the cardiovascular system in children with pediatric multisystem inflammatory syndrome temporally associated with COVID-19 – A single center experience

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ABSTRACT

Background
Pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS) is a serious complication of a previous SARS-CoV-2 infection in the group of pediatric patients. Despite the fact that this disease affects only about 1 of 1000 children, it may be severe, and changes in the cardiovascular system may cause long-term complications and the need for longitudinal patient care.

Methods
It is a single-center retrospective study considering 51 patients with PIMS-TS. The aim of this study was to analyze patients with PIMS-TS, taking into account demographic data, clinical course, laboratory tests and cardiovascular system assessment (electrocardiography, echocardiography, etc.).

Results
From June 2020 to October 2021, 51 patients with PIMS-TS were hospitalized in our center. In the studied group, 26/51 children (51%) were girls. The mean age of patients was 7 years. Changes in electrocardiograms were found in 21/51 patients. Echocardiography revealed pericardial fluid in most patients. In addition, heart valve insufficiency was found. Changes in the coronary vessels in the form of dilatations and even aneurysms were found in 42 patients. Myocardial hypokinesis was visualized in more than 1/4 of the patients. Sixteen patients (31.3%) required transfer to the intensive care unit (ICU) due to severe hypotension. Laboratory tests revealed increased levels of markers of heart failure and enzymes of myocardial damage.

Conclusions
Changes in the cardiovascular system in the course of PIMS-TS are of various nature, but in most patients they require close cardiac supervision and long-term follow-up.

1. Introduction

Pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS), which is also referred to as multisystem inflammatory syndrome in children (MIS-C) in the literature is a new disease entity evolved during the COVID-19 pandemic [1]. According to worldwide guidelines among which WHO, American Academy of Pediatrics (AAP) and Royal College of Pediatrics and Child Health stated that PIMS-TS syndrome should be suspected in an individual aged <21 years presenting with fever, high markers of inflammation and multisystem (≥2) organ involvement, in which other infectious causes have been excluded and with a confirmed history of SARS-COV-2 infection in the last 4-8 weeks (positive RT-PCR test, antigen test or serology). Symptoms of the disease vary according to patient from self-limiting disease through gastrointestinal symptoms, Kawasaki disease-like symptoms to toxic shock symptoms. In laboratory tests, the outline of the disease includes leukocytosis with lymphopenia, anemia, ion disturbances, very high indicators of inflammation, coagulation disorder, and high

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1 This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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concentration of cardiac enzymes. Although this condition affects only about 1 in 1000 children, the literature emphasizes the risk of this disease in terms of the severity of its course, especially the involvement of the cardiovascular system. Treatment involves intravenous immunoglobulins (IVIG), systemic corticosteroids, acetylsaliclic acid and in severe cases immunomodulatory treatment (biologic drugs) [2–6].

2. Material and methods

The objective of this study was to evaluate changes in the cardiovascular system of patients with PIMS-TS, in particular changes in electrocardiography (ECG) and echocardiography. According to the guidelines, patients meeting the PIMS-TS diagnosis criteria require additional diagnostic tests, including echocardiography and ECG on the basis of which a list of changes in the circulatory system that accompany this disease was prepared. Information was acquired from database of patients hospitalized in the single Polish center (Department of Pediatric Cardiology and Rheumatology, Medical University of Lodz, Poland) from June 2020 to October 2021. The study has been performed according to the standard Helsinki Declaration. Legal guardians of patients consented to review of the medical records and to the use of the data.

Diagnosis was based on clinical and laboratory criteria according to WHO/AAP statements. Clinical features, laboratory results and treatment were evaluated. Besides imaging examinations, such as trans-thoracic echocardiography and ECG, laboratory parameter such as N-terminal pro-brain natriuretic peptide (NT-proBNP), troponin I, creatinine kinase MB (CK-MB) and lipoprotein profile were assessed in each child. All the laboratory tests were performed by the standard methods. All patients who were admitted to our hospital had laboratory tests performed within 1 h and echocardiographic examination within 24 h after admission. Some of the patients were transferred from different medical centers, so their testing time is not fully known. Each child had a full echocardiographic examination, however for the purpose of this study following parameters were taken into account: ejection fraction (EF), presence of pericardial fluid, degree of heart valve regurgitations (Vmax, gradient in mmHg), diameter of coronary arteries with reference to the Z-scores. Examinations were performed with Philips Epiq Elite echocardiograph. Three pediatric cardiologists took part in the examination.

For statistical analysis the Shapiro-Wilk test were performed to test for normal distribution. Continuous variables are presented as median with the values of the lower and upper quartiles (25–75 percentile). The nonparametric Mann–Whitney test was used for comparison between two groups. The Kruskal–Wallis test (nonparametric ANOVA) was used for comparison between the three and more groups. Categorical variables are presented as numbers with an appropriate percentage. The chi-square test with appropriate corrections applied depending on the size of the subgroups was used for their analysis. Correlations were assessed using the Spearman's rank correlation coefficient. All p-values <0.05 were considered statistically significant. Statistically significant differences between the groups are presented graphically in the charts. Statistical analysis was performed using the Dell Statistica 13 data analysis software (StatSoft Polska, Krakow, Poland).

3. Results

From June 2020 to October 2021, 51 patients with PIMS-TS (26 boys and 25 girls) were hospitalized. The median age of the patients was 7 years, (min. 3 months; max. 17 years). Forty patients were diagnosed as a regular PIMS-TS, 9 as Kawasaki-like PIMS-TS and 2 as Macrophage Activation Syndrome (MAS) in the course of PIMS-TS. In our study we took into account age, sex, number of days of fever, certain laboratory parameters (i.e., peripheral blood count, markers of inflammation, heart enzyme levels), as well as echo- and ECG parameters (Table 1).

44/51 (86%) patients had positive antibodies for SARS-CoV-2 infection, whilst 7/51 (14%) patients had a positive result of RT-PCR

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Table 1

| Variable                          | Valid N | Median | 25th quartile | 75th quartile | Norms |
|-----------------------------------|---------|--------|---------------|---------------|-------|
| NT-pro BNP [pg/ml]                | 44      | 1579   | 348           | 9692          | < 125 |
| Troponin I [ng/ml]                | 45      | 0.014  | 0.002         | 0.145         | < 0.028 |
| CK MB-mass [ng/ml]                | 47      | 0.7    | 0.4           | 1.2           | 0.5-2 |
| Total cholesterol [ng/ml]         | 46      | 115    | 96            | 158           | 0-200 |
| Low density lipoprotein [mg/dl]   | 44      | 68     | 48            | 102           | < 100 |
| High density lipoprotein [mg/dl]  | 46      | 25     | 13            | 36            | > 55  |
| Triglycerides [mg/dl]             | 51      | 143    | 105           | 195           | 0-150 |
| Hemoglobin [g/dl]                 | 51      | 11     | 10            | 12            | < 2 years – 10.0-13.0 |
|                                  |         |        |               |               | 2.6 years – 11.0-13.8 |
|                                  |         |        |               |               | 6-12 years – 11.1-14.7 |
|                                  |         |        |               |               | 12-18 years: Female –12.1-15.1 |
|                                  |         |        |               |               | Male - 12.1-16.1 |
|                                  |         |        |               |               | < 2 years – 30.0-38.0 |
|                                  |         |        |               |               | 2.6 years – 32.0-40.0 |
|                                  |         |        |               |               | 6-12 years – 32.0-43.0 |
|                                  |         |        |               |               | 12-18 years: Female –35.0-44.0 |
|                                  |         |        |               |               | Male - 35.0-49.0 |
|                                  |         |        |               |               | 150-400 |
| Platelet count [thou/ul]          | 51      | 194    | 109           | 347           | 3.8-10.0 |
| Leukocytes [thou/ul]              | 51      | 10.4   | 5.7           | 15.5          | 1.5-6.0 |
| Neutrophiles [thou/ul]            | 51      | 7.2    | 4.5           | 12.2          | 4.5-12.0 |
| Lymphocytes [thou/ul]             | 51      | 1.3    | 0.6           | 2.4           | 1.5-4.0 |
| CRP [mg/l]                        | 51      | 187    | 92            | 256           | < 5    |
| ESR [mm/h]                        | 44      | 65     | 35            | 106           | < 10   |
| Procalcitonin [ng/ml]             | 51      | 1.8    | 0.5           | 6.7           | < 0.5  |
| pH                               | 49      | 7.4    | 7.4           | 7.4           | 7.35-7.45 |
| Lactate [mmol/l]                  | 43      | 2.1    | 1.3           | 2.9           | 0.5-1.6 |
| Sodium [mmol/l]                   | 51      | 137    | 134           | 140           | 135-145 |
| Potassium [mmol/l]                | 51      | 4.1    | 3.7           | 4.5           | 3.8-5.00 |
| vitamin D3-OH-25 [ng/ml]          | 30      | 17.4   | 11.4          | 25.7          | 30-100 |
| Phosphorus [mg/dl]                | 37      | 3.7    | 2.9           | 4.3           | 2.95-5.43 |
| Lactate Dehydrogenase [U/l]       | 47      | 264    | 214           | 318           | 120-300 |
| Ferritin [ug/l]                   | 50      | 304    | 180           | 1044          | 14-124 |
| Fibrinogen [mg/dl]                | 47      | 485    | 405           | 609           | 200-400 |
| D-Dimers [ng/ml]                  | 50      | 2441   | 1425          | 4908          | 0-500  |
| ALT [U/l]                         | 51      | 27     | 16            | 48            | 0-41   |
| Creatinine [mg/dl]                | 50      | 0.6    | 0.5           | 0.8           | 0.58-0.81 |
| Albumin [g/dl]                    | 49      | 3.1    | 2.9           | 3.6           | 3.8-5.4 |
| Number of days of fever           | 51      | 4      | 3             | 6             |       |
| Age [years]                       | 51      | 7      | 4             | 14            |       |

(continued on next page)
test for SARS-Cov-2 infection. Only half of the patients (26/51) confirmed a known contact with a person with COVID-19 infection or a previous COVID-19 infection.

The most frequently presented clinical symptoms of PIMS-TS were: fever (51/51 = 100%), gastrointestinal symptoms such as abdominal pain or diarrhea (27/51 = 52.9%), rash (25/51 = 49%) neurological symptoms such as nystagmus or meningeal symptoms were present in 6/51 (11.8%) patients, and osteoarticular ailments, which were present in 7/51 (14%) children. Infectious changes in the lungs confirmed by chest X-ray or computed tomography were found in 38/51 (74.5%) patients. Features of myocarditis were found in 12/51 (23.5%) patients. Four children developed acute pancreatitis. Another etiological factor was found in 8/51 (15.7%) patients (co-infection) i.e.:

1. Four children developed acute pancreatitis. Another etiological factor was found in 8/51 (15.7%) patients (co-infection) i.e.:
2. Twenty-three of them required additional administration of systemic corticosteroids. Due to the severe course of the disease, two patients required administration of ciclosporin, and three required biological therapy with intravenous tocilizumab (humanized anti-interleukin-6 receptor antibody), and one patient received anakinra (anti-interleukin-6 receptor antibody and anti- IL-1 receptor antagonist anti-body) subcutaneously. Patients with co-infections received the same treatment as those without co-infections (empiric antibiotics and immunomodulatory treatment), and in children with M. pneumoniae infection, an appropriate antibiotic (macrolide) was added. In the absence of symptoms, patient with Salmonella infection appeared to be a carrier.
3. Patient with influenza received oseltamivir, however their condition improved after appliance of IVIG and systemic steroids. Six patients did not receive IVIG due to the good clinical condition and no changes in echocardiographic examination (good contractility of a heart muscle, no changes in coronary arteries).

Ciclosporin and biological agents were used as a second- or third-line therapy in patients with severe fever, elevated markers of inflammation and persistent circulatory or respiratory failure unresponsive to IVIG and systemic corticosteroids treatment. Three patients who received tocilizumab had elevated levels of IL-6 in the initial laboratory tests. The patient who received anakinra had severe heart failure, but low IL-6 levels.

According to guidelines each patient with suspicion of PIMS-TS had a twelve-lead ECG recording on admission. Changes in ECG were found in 21/51 (41.2%) patients (11/51 (21.6%) repolarization abnormalities (Fig. 1), 9/51 (17.6%) QTc interval prolongation, 3/51 (5.9%) ventricular arrhythmia, 1/51 (1.9%) 1st and 2nd degree atrioventricular block, 1/51 (1.9%) atrial tachycardia, 1/51 (1.9%) ECG changes resembling Brugada syndrome) (Fig. 2). A higher concentration of troponin I and creatinine, a lower concentration of leukocytes and lymphocytes, and higher age of a child were the parameters that influenced the changes in ECG recordings. The prolongation of the QTc interval in the ECG recordings was influenced by the higher concentration of NT-proBNP, troponin I, and lymphopenia. None of the studied parameters had a statistically relevant impact on the incidence of ventricular arrhythmias and atrio-ventricular blocks in patients with PIMS-TS however repolarization disorders were observed significantly more often in older children over 7 years of age.

Some laboratory parameters influenced the severity of changes in echocardiographic examinations. Myocardial hypokinesis was found in 14/51 (27.5%) patients. The lowest EF measured in the initial echocardiographic examination equaled 35%. The EF values correlated negatively with the concentration of NT-proBNP, troponin I, tri-glycerides, ferritin, D-dimers, creatinine and positively with the concentration of leukocytes, lymphocytes, PLT, albumin, and low-density lipoprotein (LDL) (Fig. 3). Lymphopenia correlated negatively with the presence of aortic regurgitation which was stated in 9/51 (17.6%) children. Tricuspid valve regurgitation was found in 49/51 (96.1%) patients (trace in 8 children (15.7%), mild in 27 children (52.9%) and moderate in 14 (27.5%) children). Statistical significance was stated between the severity of tricuspid valve regurgitation and the concentration of NT-proBNP, troponin I, fibrinogen, platelets, as well as lymphopenia and hypokalemia. Mitral valve regurgitation was found in 49/51 (96.1%) patients (trace in 29 children (56.9%), mild in 11 children (21.6%) and moderate in 9 children (17.6%). Concentration of serum PLT correlated with the degree of mitral regurgitation. Pulmonary valve regurgitation was found in 37/51 (72.5%) patients (trace in 15 children (29.4%), mild in 17 children (33.3%) and moderate in 5 children (9.8%)). The concentration of NT-proBNP and hypertriglyceridemia correlated with the degree of pulmonary valve insufficiency. The prevalence of fluid in the pericardium was found in 42/51 (82.35) children. The concentration of NT-proBNP and PCT was statistically significant in this group in comparison to children without pericardial fluid.

Table 2

| Variable | Valid N Group 1 | Median | 25% quartile | 75% quartile | Variable | Valid N Group 2 | Median | 25% quartile | 75% quartile |
|----------|---------------|--------|--------------|--------------|----------|---------------|--------|--------------|--------------|
| NT-pro BNP [pg/ml] | 16 | 17,194 | 3770 | 28,837 | 28 | 787 | 270 | 1981 | 0.0001 |
| Troponin I [ng/ml] | 17 | 0.14 | 0.02 | 0.44 | 29 | 0.01 | 0.00 | 0.03 | 0.0012 |
| Triglycerides [mg/dl] | 17 | 184 | 123 | 259 | 34 | 12 | 120 | 160 | 0.0115 |
| Hematocrit (%) | 17 | 29.4 | 27.9 | 31.2 | 34 | 32.9 | 28.8 | 34 | 0.0272 |
| Platelet count [thou/ul] | 17 | 94 | 71 | 115 | 34 | 293 | 181 | 394 | 0.0000 |
| Lymphocytes [thou/ul] | 17 | 0.77 | 0.55 | 1.33 | 34 | 1.81 | 1.04 | 2.62 | 0.0240 |
| CRP [mg/l] | 17 | 241 | 187 | 289 | 34 | 140 | 76 | 233 | 0.0132 |
| Procalcitonin [ng/ml] | 17 | 8.32 | 4.59 | 18.54 | 34 | 1.51 | 0.42 | 2.65 | 0.0001 |
| Ferritin [ug/l] | 17 | 1047 | 333 | 2069 | 33 | 244 | 147 | 396 | 0.0006 |
| D-Dimers [ug/ml] | 17 | 4240 | 2638 | 7160 | 33 | 1728 | 826 | 3700 | 0.0022 |
| Creatinine [mg/dl] | 17 | 0.75 | 0.53 | 1.04 | 34 | 0.51 | 0.47 | 0.69 | 0.0128 |
| EF (%) | 17 | 58 | 51 | 65 | 34 | 68 | 65 | 71 | 0.0001 |

Group 1 - children with cardiovascular failure, who presented hypotension and/or required catecholamines and hospitalization in the ICU (overall 17/51).
Group 2 - children without cardiovascular failure (overall 34/51).

CRP C-reactive protein, EF ejection fraction.
Hyperechoic walls of the coronary arteries were found in 28/51 (54.9%) patients (left coronary artery (LCA) 7 patients (13.7%), right coronary artery (RCA) 12 patients (23.5%), both in 9 patients (17.6%)). Dilation of the coronary arteries was found in 13/51 (22.8%) patients (LCA 5 patients (9.8%), RCA 7 patients (13.7%), both in 1 patient (1.9%)). One patient (1.9%) had an aneurysm of the RCA (Fig. 4). None of the tested laboratory parameters, age, gender, or the number of days of fever influenced the risk of developing coronary aneurysms.

4. Discussion

We present a single center retrospective study considering a group of 51 patients with PIMS-TS with a special focus on changes in the cardiovascular system.

Despite the fact that most children usually undergo SARS-CoV-2 infection mildly or asymptotically, the post infectious complications in the form of a new disease entity called the PIMS-TS may be life threatening condition to pediatric patients [7]. PIMS-TS initially appeared to be a similar disease to the well-known Kawasaki disease (KD) due to the fact that some patients present symptoms such as fever, rash, enlargement of peripheral lymph nodes, dermal and mucosal changes, and severe changes in the cardiovascular system that may lead to serious complications [8]. In one of the largest studies on PIMS-TS, changes in the digestive and circulatory systems were most frequently described. The average age of children suffering from PIMS-TS is 8 years, although it can affect a child at any age, male gender seems to be slightly more predisposing [9]. In the study group, the mean age of the patients was 7 years, and the gender distribution was equal. In our study we decided to separately identify patients with the KD phenotype of PIMS-TS (these are patients with rash, conjunctivitis, enlarged lymph nodes,
dry, red lips, swelling of the palms and feet), but not meeting the KD criteria (older age, different characteristics of changes in laboratory tests, changes in the myocardium, symptoms from other systems, confirmed SARS-CoV-2 infection). We also extinguished patients with MAS in the course of PIMS-TS due to their severe course of the disease. These patients presented splenomegaly, persistent fever, exceptionally high levels of ferritin, pancytopenia, coagulopathy, hypertriglyceridemia and liver dysfunction. The etiology of this syndrome is not yet fully understood, but it seems that genetically susceptible patients develop PIMS-TS as a result of a cytokine storm approximately 4–6 weeks after the infection [7,10]. The most frequently mentioned inflammatory cytokines in the etiopathogenesis of PIMS-TS are i.e., interleukin 1, 6, and tumor necrosis factor (TNF) [11,12]. It is known from many years of research that over-expression of interleukin 6 is associated with inflammatory responses in endothelial cells, leading to endothelial dysfunction and further with atherosclerosis, myocardial infarction or heart failure [13].

A feature differentiating PIMS-TS syndrome from KD is the involvement of other systems, i.e., the digestive and nervous systems. Also, the involvement of the cardiovascular system is much greater in children with PIMS-TS than KD. It is reported in the literature that cardiac involvement occurs in over 50% of children with PIMS-TS, in the form of elevated markers of myocardial damage and markers of heart failure, myocardial damage, systolic or diastolic myocardial dysfunction, changes in coronary arteries, hypotension and bradycardia leading to shock [8,11]. Due to the multiplicity of the systems involved, the important role of interdisciplinary teams of doctors participating in the diagnosis and treatment of PIMS is emphasized [8]. In our study group, symptoms from the digestive system were dominant, 9 patients met the criteria of KD. We observed cardiovascular involvement in all of our patients with PIMS-TS in the form of changes in echocardiography, ECG, or increased cardiac enzymes levels.

Based on the data collected so far, it is assumed that myocardial damage in PIMS syndrome most likely results from complex mechanisms consisting of immune disorders (cytokine storm) in response to a previous viral infection, damage to muscle tissue leading to its swelling, myocardial blood supply and microcirculation disturbances, as well as anomalies in in the coagulation system (i.e., D-dimers) [8,10]. Children with co-infection with another pathogen did not present a more severe...
course of the disease in the study group.

The worldwide guidelines regarding PIMS-TS recommend that in every patient with suspected PIMS syndrome biochemical markers of myocardial damage (troponin, CK-MB mass) and heart failure (NT-proBNP) should be performed, and a 12-lead ECG recording and echocardiography should be performed as soon as possible. If any disturbances are found in the ECG recordings, it is also recommended to perform a 24-h ECG record [6]. ECG recordings should be made every 48 h, or daily if any abnormalities are found. Echocardiography should be repeated according to the patient’s condition and severity of symptoms [8,10]. It is suggested that patients with a history of PIMS-TS and any form of cardiac involvement should undergo cardiological evaluation once a year [10].

A significant proportion of patients with PIMS-TS have significantly elevated levels of NT-proBNP and troponin. The normalization of the levels of heart markers lasts from a few days to several weeks, sometimes after the patient is discharged home. Serum concentration of cardiac markers may even correlate with subclinical changes in the echocardiographic image. Some patients have only myocardial dysfunction, which may persist for several weeks. The most frequently reported changes in the echocardiographic image in patients with PIMS in the literature are abnormalities of myocardial contractility, trace amounts of fluid in the pericardium and mitral regurgitation [8]. The most common findings in the acute phase of the disease are echocardiographic images similar to myocarditis resulting from the ongoing inflammatory process, hypoxia, and vascular endothelial dysfunction and permeability, which lead to edema within the myocardial tissue. In the majority of patients with preserved EF, it usually remains subclinical [10,14,15]. In most patients, the abnormalities of myocardial contractility resolve about a week after the initiation of treatment [10]. In our group of patients, we found that 27% of patients had an impaired EF in the initial echocardiography. Myocardial contractility abnormalities resolved within one week of treatment initiation.

Due to the changes in the myocardium, the initial question was the usefulness of computed tomography and magnetic resonance imaging (MRI) in the evaluation of the heart after PIMS-TS syndrome. In the study conducted by Bartoszek et al. in which MRI was performed 3 months after PIMS, no abnormalities were found in any of 19 patients, despite the fact that the heart muscle contraction was abnormal at first. This may prove that the changes in the myocardium are transient and do not leave long-term effects [16].

In our analysis we found that children with higher NT-proBNP, troponin I, triglycerides, CRP, PCT, D-dimers, ferritin, and creatinine and lower lymphocytes, PLT, hematocrit and EF more often presented with circulatory failure, hypotension, and required hospitalization in the intensive care unit (ICU) and appliance of catecholamines. A higher concentration of troponin I and creatinine, a lower concentration of leukocytes and lymphocytes, and higher age of a child were the parameters that influenced the changes in ECG recordings. Changes in ECG recordings were more common in older children, but age was not statistically significant in children with heart failure. There are several theories related to the underlying pathophysiology of those changes in heart. Importance of myocardial edema, which might appear after the initial SARS-CoV-2 infection and increase due to PIMS-TS, as well as activation of inflammatory cytokines are crucial and, in some patients, can lead to cardiovascular failure [10]. Not all of the mechanisms underpining pathophysiology of PIMS-TS and origin of changes in the circulatory, as well as other systems is known yet.

Similarly to KD, one of the most serious complications of PIMS-TS are coronary aneurysms, which can even result in a myocardial ischemia. It is reported in the literature that changes in the coronary vessels occur in 8–50% of patients with PIMS-TS [8,10,17]. The pathogenesis of this phenomenon is not fully understood yet, but it is likely that changes in the coronary vessels occur in the course of a cytokine storm and the deposition of immunological complexes in the vascular walls [9]. In PIMS, coronary aneurysms can develop even during the recovery phase, so it is important to regularly perform echocardiography in these children [8,10,17]. Dilation of the coronary arteries was most often found in the left main coronary artery trunk [17]. In the study group 43 patients had changes in the coronary arteries, dilations were found in 13 patients, most of them occurred in the RCA. One patient had an aneurysm, which also occurred in the RCA. Less severe changes like hyperechoic coronary walls resolved within 4–6 weeks form the onset of the disease. Children with dilatation and an aneurysm of the lumen of the coronary vessels remain under constant cardiological control and require acesulbic acid therapy (antiplatelet dose) for a longer period of time.

The most frequently observed abnormalities in ECG recordings in patients with PIMS-TS were repolarization disorders, prolongation of the QTc interval, or arrhythmias in the form of premature supraventricular /ventricular beats, as well as more complex arrhythmias such as atrial fibrillation [8]. In a study conducted in the United States on a large group of patients, arrhythmia was found in 12% of children with PIMS-TS [18]. Exact data on the incidence of arrhythmias in children with PIMS and their follow-up are unknown [10]. In our study group, the most frequently detected ECG abnormalities were repolarization abnormalities, QT interval prolongation, ventricular arrhythmia, 1st and
2nd degree atrioventricular block, atrial tachycardia, and ECG changes resembling Brugada syndrome. Several cases of adults with Brugada syndrome-like post-covid ECG recording have been reported in the literature, most likely due to disturbances in ion channels (hypotension, hypophosphatemia), changes in the myocardium and fever [19]. In a study conducted by Clark et al. electrocardiographic abnormalities occurred in 6 patients and included atrioventricular block, sinus tachycardia, ventricular tachycardia, non-specific T wave changes [20]. Most of the changes in ECG recordings resolved after 4–6 weeks from the onset of the disease, in some patients the repolarization abnormalities persisted in the ECG recordings up to 6 months.

In the course of changes in the cardiovascular system and peripheral vasodilation, a significant proportion of patients develop hypotension and shock, which most often does not respond to intravenous fluid therapy and is an indication for hospitalization in the ICU and the administration of catecholamines [1]. In our study group 31% of children required a transfer to the ICU. None of the available studies presents any clear correlations between clinical features, laboratory tests and treatment, with the risk of having coronary artery abnormalities or necessity of hospitalization in the ICU [9].

Cardiological follow-up depends on the patient’s condition and changes in the cardiovascular system, however, in patients with changes in the coronary vessels, follow-up is recommended as in KD, i.e., echocardiographic examination at the beginning of the diagnosis, 1–2 weeks after the diagnosis and 4–6 weeks after the diagnosis and then according to the patient’s condition. For patients with coronary artery dilation / aneurysm it is suggested to repeat echocardiogram every 2–3 days until the coronary size is stable and then follow-up according to the severity of the aneurysm. Every patient with PIMS-TS must absolutely undergo echocardiographic examination at the beginning of the diagnosis and before discharge home [8,10].

In a 6-week follow-up of our patients results of laboratory tests normalized in all children. Only 2/51 children (3.9%) had persistent repolarization disorders in ECG. Echocardiography showed persistent trace regurgitation of the heart valves in 25/51 patients (49%) (mitral regurgitation in 21 patients, tricuspid regurgitation in 7 patients, atrial regurgitation in 4 patients, and pulmonary regurgitation in 5 patients). Pericardial fluid persisted in 24/51 patients (47%). Coronary artery lesions were found in 10/51 children (19.6%), who required further administration of acetylsalicylic acid. Borderline EF was found in 2/51 patients (3.9%). Completely normal echocardiographic and electrocardiographic images were found in 13/51 patients (25.5%) (Fig. 5).

Physical activity after PIMS-TS should be forbidden for 2 weeks after discharge from the hospital if no changes in the cardiovascular system were found and markers of myocardial damage have normalized, and for 3–6 months if changes in the cardiovascular system were found. Resumption of physical activity should be preceded by ECG recording, Holter ECG, echocardiography and exercise test [8].

Returning to physical activity is a very important aspect as more and more patients report impaired exercise tolerance after suffering from PIMS-TS. This may be due to the inflammatory process in the course of the disease, the severity of the disease itself, complications after treatment, or myopathy and weight gain during the recovery period. Penner, et al. report in their study that patients with a history of PIMS-TS have worse tolerance of exercise, even 6 months after the onset of the disease [21].

Most of the patients in the study group had abnormalities in the lipid profile, most often in the form of high triglyceride levels and low high-density lipoprotein (HDL) levels [22]. It is worth emphasizing that among the ionic disturbances in children with PIMS, there are also visible disturbances in vitamin D3 concentration. Most patients in the study group had a very low concentration of vitamin D3-OH-25. The role of vitamin D3 as a protective factor for the circulatory system has been emphasized in the literature for many years. The long-term effects of low vitamin D3 levels and the abnormalities in the lipid profile found in PIMS-TS syndrome may predispose to the earlier development of atherosclerosis or heart failure in these patients [22,23].

4.1. Study limitations

The main limitation of the study is a relatively small group of patients, thus any outcomes of the study cannot be used as recommendations. Due to the novel nature of the disease, there are no large comparative studies. There is no long-term follow up of the presented patients.

5. Conclusions

Abnormalities in the cardiovascular system in children with PIMS-TS are of various nature, from changes in the echocardiographic image, through arrhythmias, to heart failure. Despite the fact that most of these changes are withdrawn after the implementation of appropriate treatment, close cardiac supervision over these patients is necessary. Certain laboratory parameters (low hemoglobin, hematocrit, lymphocytes, PLT; high CRP, PCT, ferritin, D-dimers, triglycerides, creatinine, NT-pro BNP, troponin I) seem to influence the severity of changes in the cardiovascular system.

![Fig. 5. Echo- and electrocardiographic changes, which persisted in a 6-week follow-up of study group patients.](image-url)
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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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