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Cardiac involvement in children with paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS): data from a prospective nationwide surveillance study

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Summary

BACKGROUND: Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) may occur 4 to 8 weeks after SARS-CoV-2 infection. The acute presentation of PIMS-TS has been well described, but data on longer-term outcomes, particularly cardiac, is scarce.

METHODS: This prospective nationwide surveillance study included children and adolescents less than 18 years of age who were hospitalised with PIMS-TS in Switzerland between March 2020 and March 2022. Data was collected from all 29 paediatric hospitals through the Swiss Paediatric Surveillance Unit (SPSU) during hospitalisation and approximately six weeks after discharge. The data was analysed after categorising the participants into three groups based on their admission status to the intensive care unit (ICU) (non-ICU, ICU-moderate) and the requirement for invasive ventilatory and/or inotropic support (ICU-severe).

RESULTS: Overall, 204 children were included of whom 194 (95.1%) had follow-up data recorded. Median age was 9.0 years (interquartile range [IQR] 6.0–11.5) and 142 (69.6%) were male. In total, 105/204 (51.5%) required ICU admission, of whom 55/105 (52.4%) received inotropic support and 14/105 (13.3%) mechanical ventilation (ICU-severe group). Echocardiography was performed in 201/204 (98.5%) children; 132 (64.7%) had a cardiac abnormality including left ventricular systolic dysfunction (73 [36.3%]), a coronary artery abnormality (45 [22.4%]), pericardial effusion (50 [24.9%]) and mitral valve regurgitation (60 [29.9%]). Left ventricular systolic dysfunction was present at admission in 62/201 (30.8%) children and appeared during hospitalisation in 11 (5.5%) children. A coronary artery abnormality was detected at admission in 29/201 (14.2%) children and developed during hospitalisation or at follow-up in 13 (6.5%) and 3 (1.5%) children, respectively. None of the children had left ventricular systolic dysfunction at follow-up, but a coronary abnormality and pericardial effusion were found in 12 (6.6%) and 3 (1.7%) children, respectively. School absenteeism at the time of follow-up was more frequent in children who had been admitted to the ICU (2.5% in the non-ICU group compared

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to 10.4% and 17.6% in the ICU-moderate and ICU-severe group, respectively) (p = 0.011).

CONCLUSION: Cardiac complications in children presenting with PIMS-TS are common and may worsen during the hospitalisation. Irrespective of initial severity, resolution of left ventricular systolic dysfunction is observed, often occurring rapidly during the hospitalisation. Most of the coronary artery abnormalities regress; however, some are still present at follow-up, emphasising the need for prolonged cardiac evaluation after PIMS-TS.

Introduction

Since the description of the first cases of paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in April 2020, this disease has affected thousands of children and adolescents worldwide. In the United States of America alone, the Centers for Disease Control and Prevention (CDC) reported more than 9000 cases on the COVID Data Tracker as of 3 October 2022. PIMS-TS usually occurs 4 to 8 weeks after SARS-CoV-2 infection [1, 2]. Clinical features include fever and multiple organ dysfunction, including cardiac involvement often requiring intensive care unit (ICU) admission [3, 4]. The pandemic has generated several successive waves of various intensities and SARS-CoV-2 will continue to circulate, with an ongoing risk of PIMS-TS. Due to the potential severe course of the disease, efforts must be maintained to understand how PIMS-TS affects the heart and what long-term consequences are to be expected. The acute presentation of PIMS-TS has been described exhaustively, but the short-, medium- and long-term manifestations are still poorly understood and rely on reports from a small number of children [5, 6]. This study provides a detailed description of cardiac involvement according to disease severity in a large cohort of children and adolescents with PIMS-TS. It focuses on the detailed short-term evolution during the hospital stay and in the first two months thereafter.

Methods

Study design and population

The prospective national observational cohort study included children and adolescents below 18 years of age who were hospitalised with PIMS-TS in Switzerland from 1 March 2020 to 31 March 2022.

PIMS-TS was defined according to national guidelines [7]:

- presence of fever;
- laboratory evidence of inflammation;
- single or multiorgan dysfunction;
- exclusion of an alternative diagnosis;
- evidence of current or recent SARS-CoV-2 infection or exposure to SARS-CoV-2.

Data was collected as part of a larger study on SARS-COV-2 infections in children through the Swiss Paediatric Surveillance Unit (SPSU, https://www.spsu.ch) [8, 9]. All 29 paediatric hospitals in Switzerland were asked to submit cases monthly using an electronic clinical report form through REDCap (Research Electronic Data CAPture) [10] (see supplementary data for the questionnaire). For each patient, detailed epidemiological and clinical data, laboratory values, transthoracic echocardiographic findings, treatment and outcome were recorded during hospitalisation and four to six weeks after hospital discharge. Normal values for troponin T and N-terminal pro B-type natriuretic peptide (NT-proBNP) were defined according to international normal ranges for age [11]. Coronary artery dimensions and left ventricular ejection fraction (LVEF) were taken from the echocardiography report, which was completed by a paediatric cardiologist. Coronary artery involvement was classified according to the AHA guidelines [12] and using the z-score system by Dallaire and Dahdah [13], which has the following categories: no involvement: z-score <2; dilation: z-score ≥2 to <2.5; small aneurysm: z-score ≥2.5 to <5; medium aneurysm: z-score ≥5 to <10; giant aneurysm: z-score ≥10. A normal LVEF was defined as an LVEF of 55% or higher. Mild systolic dysfunction was defined as LVEF ≥45% to <55%; moderate systolic dysfunction as LVEF >35% to <45%; and severe systolic dysfunction as LVEF ≤35%. Right ventricular systolic function and right or left ventricular diastolic function were deemed abnormal or not on the basis of the echocardiography report. For the analysis, children were stratified into three groups according to disease severity: “non-ICU”: children not admitted to the ICU; “ICU-moderate”: children admitted to the ICU but not requiring invasive ventilation or inotropic support; “ICU-severe”: children admitted to the ICU and requiring invasive ventilation and/or inotropic support.

Ethical approval

The study was approved by the Ethikkommission Nordwest- und Zentralschweiz (EKNZ 2020-01130).

Statistical analysis

Descriptive statistics were used to summarise the epidemiological and clinical data (median and interquartile range [IQR] for continuous data and proportions for categorical data). Categorical data were compared using the Chi-square test and comparisons between the three groups were assessed using the Kruskal-Wallis rank-sum test for non-normally distributed data. The Pearson and Spearman correlation coefficients were used for normally and non-normally distributed data, respectively, to assess the association between inflammatory biomarker values and coronary artery abnormalities or left ventricular systolic dysfunction. Missing data is mentioned in the tables summarising echocardiographic findings. To aid readability of tables, all other missing data are mentioned only in the supplementary data section. All analyses were performed with R software (version 2022.07.1).

Results

Study population

Detailed data were collected for 223 children; 220 fulfilled the diagnostic criteria of PIMS-TS. Of these, 16 children were excluded from the analysis because of duplicate entry (patients referred to other hospitals). Of the 204 children included in the final analysis, 194 (95.1%) had follow-up data available at a median of 41.0 (IQR 28.0–50.0) days. Figure 1 illustrates the number of PIMS-TS cases report-

ed over time. Median age at presentation was 9.0 (IQR 6.0–11.5) years and 142 (69.6%) children were male (table 1).

Most children had a positive SARS-CoV-2 serology (175 [85.8%]). A positive nasopharyngeal polymerase chain reaction (PCR) was reported in 54 (26.5%) children. One (0.5%) child had a positive SARS-CoV-2 antigen test. Eight (3.9%) children had a negative PCR and/or serology but had a history of SARS-CoV-2 exposure. One (0.5%) child had no laboratory evidence of SARS-CoV-2 infection or exposure to an index case but fulfilled all other clinical criteria. None of the children had been vaccinated against SARS-CoV-2. Baseline characteristics are summarised in table 1. More than half of the children (105 [51.5%]) required ICU admission; 55 (52.4%) were classified into the ICU-severe group as they needed inotropic support, with 14 of them (13.3%) also needing mechanical ventilation.

Cardiac abnormalities

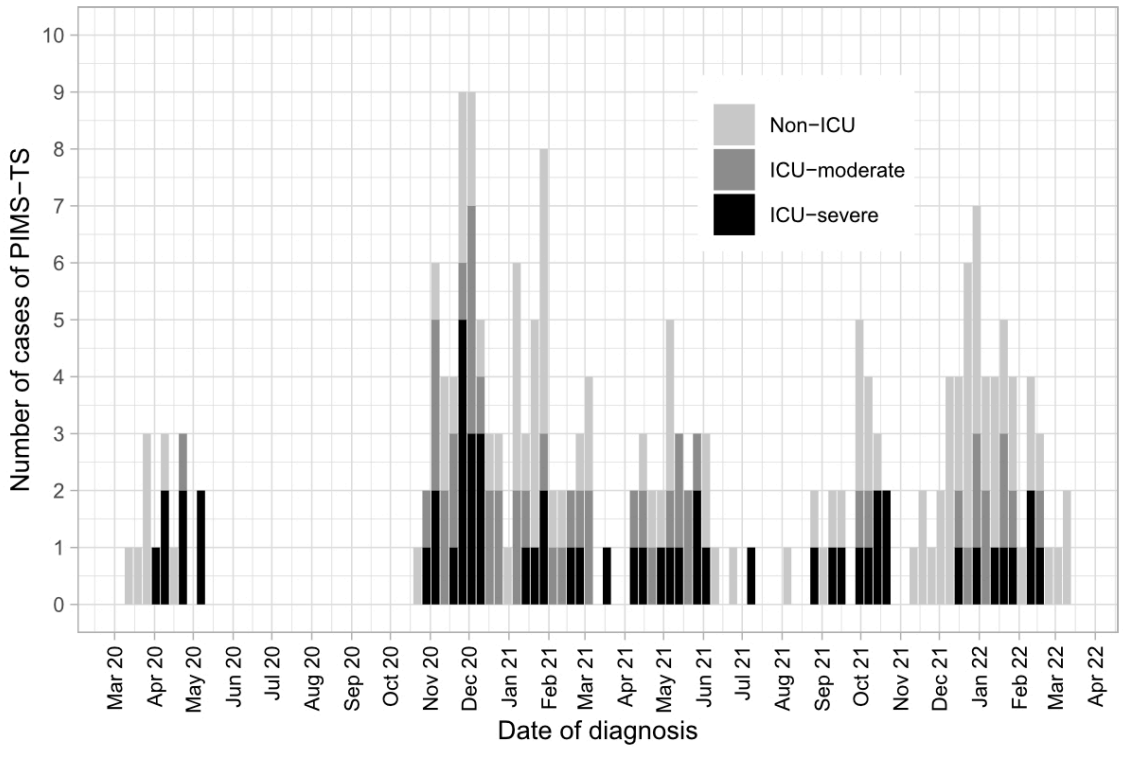
Echocardiography was done in 201 (98.5%) children. Of these, 132 (65.7%) had a novel cardiac abnormality recorded during hospitalisation or follow-up. Left ventricular systolic dysfunction was present in 73 (35.8%) children and was more common in those admitted to the ICU (21.5% in the non-ICU group compared to 42.9% and 58.2% in the ICU-moderate and ICU-severe group, respectively [p <0.001]). Among the 73 children with left ventricular systolic dysfunction, 43 (58.9%) had mild, 13 (17.8%) moderate and 7 (9.6%) severe dysfunction (table 2). The LVEF was not documented for ten children, therefore severity of left ventricular systolic dysfunction could not be assessed. Left ventricular systolic dysfunction was present at admission in 62 (31.5%) children and developed during hospitalisation in 11 (5.4%) children. Left ventricular systolic dysfunction resolved during hospitalisation in 67 (91.8%) children. In children not admitted to the ICU, rapid resolution occurred whereas in children admitted to the ICU left ventricular systolic dysfunction initially deteriorated in some cases. Full recovery at discharge or follow-up was observed in all children (figure 2).

Right ventricular systolic dysfunction was reported at admission in 14 (6.9%) children and resolved in all, except one (0.5%), before discharge. No child had persistent left or right ventricular systolic dysfunction at follow-up (table 3).

Left ventricular diastolic dysfunction was reported in 23 (11.9%) children at admission and developed in eight (3.9%) children during hospitalisation. Five (2.5%) children had left ventricular diastolic dysfunction at follow-up: two (1.0%) children from the ICU-severe group had persistent diastolic dysfunction and three (1.5%) children were newly diagnosed with diastolic dysfunction, one patient in each severity group.

Coronary artery abnormalities were reported in 45 (22.1%) children (20 [20.2%], 11 [22.0%] and 14 [25.5%] in the non-ICU, ICU-moderate and ICU-severe group, respectively) (detailed in table 2). The abnormalities were diagnosed in 29 (64.4%) children at admission, in 9 (20.0%) during hospitalisation, in 4 (8.9%) at discharge and in 3 (6.7%) at follow-up. The degree of coronary artery dilation was mild in 9 (9.4%), 4 (8.0%) and 3 (5.5%) children in the non-ICU, ICU-moderate and ICU-severe group, respectively. Among the 29 children who had a coronary artery abnormality at admission, 17 (58.6%) still had some dila-

Figure 1: Number of children with PIMS-TS according to ICU admission over time. ICU: intensive care unit; PIMS-TS: paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2.



tion during hospitalisation, and 5 (17.2%) and 4 (13.8%) had persistent coronary artery dilation at discharge and at follow-up, respectively.

At follow-up, coronary artery abnormalities were reported in 12 (5.9%) children. Details on coronary artery involvement and treatment during hospitalisation are summarised in the supplementary data (table S6).

Pericardial effusion was present in 50 (25.0%) children, occurring more frequently in children admitted to the ICU (p = 0.035). Three (1.7%) children with pericardial effusion during hospitalisation had persistent pericardial effusion at follow-up (table 3). No child had pericardial effusion that required an intervention.

Mitral valve regurgitation was reported in 60 children (29.4%) and was classified as mild in most (93.3%) cases (table 3).

An abnormal NT-proBNP peak value was reported in 182 (97.8%) children and an abnormal troponin T value in 183 (69.4%) (table S5). The median troponin T and NT-proBNP values were higher in the ICU-severe group than in the ICU-moderate and non-ICU groups (table S5). There was no correlation between coronary artery involvement and inflammatory markers (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR] or ferritin) (Pearson *r* coefficient of 0.0 for CRP; Spearman *r* coefficient of -0.2 and -0.1 for ESR and ferritin, respectively). However, a trend of increased CRP values and left ventricular systolic dysfunction was found (Pearson *r* coefficient of 0.22). No correlation was found between ESR or ferritin values and left ventricular systolic dysfunction (Spearman *r* coefficient of 0.1 and 0.04, respectively). Figure 3 summarises the key echocardiographic and laboratory abnormalities documented during hospitalisation and follow-up according to disease severity.

Electrocardiogram (ECG) abnormalities were noted in 37 (18.1%) children (table S2). Ten (4.9%) children had atrioventricular (AV) block (1st degree n = 7; 2nd degree n = 1; 3rd degree n = 2), which was significantly more frequent in children admitted to the ICU (1 [1.0%], 2 [4.0%] and 7 [12.7%] in the non-ICU, ICU-moderate and ICU-severe group, respectively) (p = 0.005). At follow-up, three (1.5%) children had persistent ECG abnormalities (right axis deviation n = 2; abnormal ST- and T-wave segment n = 1).

Among the six children who had a pre-existing cardiac comorbidity, four were admitted to the ICU. Two children, one with left heart hypoplasia and one with atrial septal defect, presented with ventricular systolic dysfunction and one required inotropic support.

Table 1:
Baseline characteristics of children with PIMS-TS, by disease severity group. (Non-ICU: child not admitted to the ICU; ICU-moderate: child admitted to the ICU without need for mechanical ventilation and/or inotropic support; ICU-severe: child admitted to the ICU with need for mechanical ventilation and/or inotropic support.)

	Total	**Non-ICU**	**ICU-moderate**	**ICU-severe**	**p-value**
	n (%)	**n (%)**	**n (%)**	**n (%)**	
	204 (100)	**99 (48.5)**	**50 (24.5)**	**55 (26.9)**	
Age category (years)					0.135
0–2	9 (4.4)	6 (6.1)	3 (6.0)	–	
2–5	30 (14.7)	18 (18.2)	4 (8.0)	8 (14.5)	
5–10	80 (39.2)	39 (39.4)	23 (46.0)	18 (32.7)	
10–15	78 (38.2)	33 (33.3)	20 (40.0)	25 (45.5)	
15–18	7 (3.4)	3 (3.0)	–	4 (7.3)	
Female	62 (30.4)	33 (33.3)	12 (24.0)	17 (30.9)	0.502
Ethnicity					0.466
Caucasian	128 (62.7)	68 (68.7)	30 (60.0)	30 (54.5)	
Black	22 (10.8)	5 (5.1)	8 (16.0)	9 (16.4)	
Asian	5 (2.5)	3 (3.0)	1 (2.0)	1 (1.8)	
Hispanic	5 (2.5)	3 (3.0)	1 (2.0)	1 (1.8)	
Other or Unknown	39 (19.1)	17 (17.2)	10 (20.0)	12 (21.8)	
Pre-existing medical conditions					
Respiratory disease*	9 (4.4)	5 (5.1)	1 (2.0)	3 (5.5)	0.629
Cardiovascular disease**	6 (2.9)	2 (2.0)	2 (4.0)	2 (3.6)	0.747
Other disease***	23 (11.3)	12 (12.1)	7 (14.0)	4 (7.3)	0.516
SARS-CoV-2 PCR**					0.367
Positive	54 (26.5)	31 (31.3)	9 (18.0)	14 (25.5)	
Negative	134 (65.7)	61 (61.6)	38 (76.0)	35 (63.6)	
Not done	16 (7.8)	7 (7.1)	3 (6.0)	6 (10.9)	
SARS-CoV-2 serology					0.373
Positive	175 (85.8)	80 (80.8)	45 (90.0)	50 (90.9)	
Negative	6 (2.9)	4 (4.0)	2 (4.0)	–	
Not done	21 (10.3)	14 (14.1)	3 (6.0)	4 (7.3)	

* Asthma 8; obstructive sleep apnoea 1.

** Atrial septal defect 3; right aortic arch 1; left heart hypoplasia after Glenn surgery 1; partial anomalous pulmonary venous connection 1.

*** Grade V vesicoureteral reflux 1; PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis) syndrome 1; PCDH-19 encephalopathy 1; polymalformative syndrome 1; varicella infection one week prior 1; obesity 7; Osgood Schlatter disease 3; neurofibromatosis type 1 1; unilateral multicystic dysplastic kidney 1; mild developmental delay 1; glucose-6-phosphate dehydrogenase deficiency 1; attention deficit hyperactivity disorder 3; congenital anomalies of the kidney and urinary tract 1.

**** Result of first nasopharyngeal PCR test.

ICU: intensive care unit; PCR: polymerase chain reaction; PIMS-TS: paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2.

One child with partial abnormal pulmonary venous return presented with hypotensive shock requiring inotropic support. One child with right aortic arch presented with coronary artery dilation and mild mitral valve regurgitation.

Drug treatment

Acetylsalicylic acid and intravenous immunoglobulin (IVIG) were the most frequently used treatments (161 [82.1%] and 155 [77.9%], respectively). The combination of IVIG and corticosteroids was used in 124 (60.8%) children. In total, 31 (15.2%) and 30 (14.7%) children, respectively, received either IVIG or corticosteroids as single treatment. Children admitted to the ICU were more likely to receive corticosteroids, anti-coagulation treatment and anakinra (p <0.001) (table S1). Thirty-two children (15.7%) had been recruited into the Swissped-Recovery Trial for randomised treatment with methylprednisolone or immunoglobulin (non-ICU n = 16; ICU-moderate n = 6; ICU-severe n = 10) [14].

Outcome and follow-up

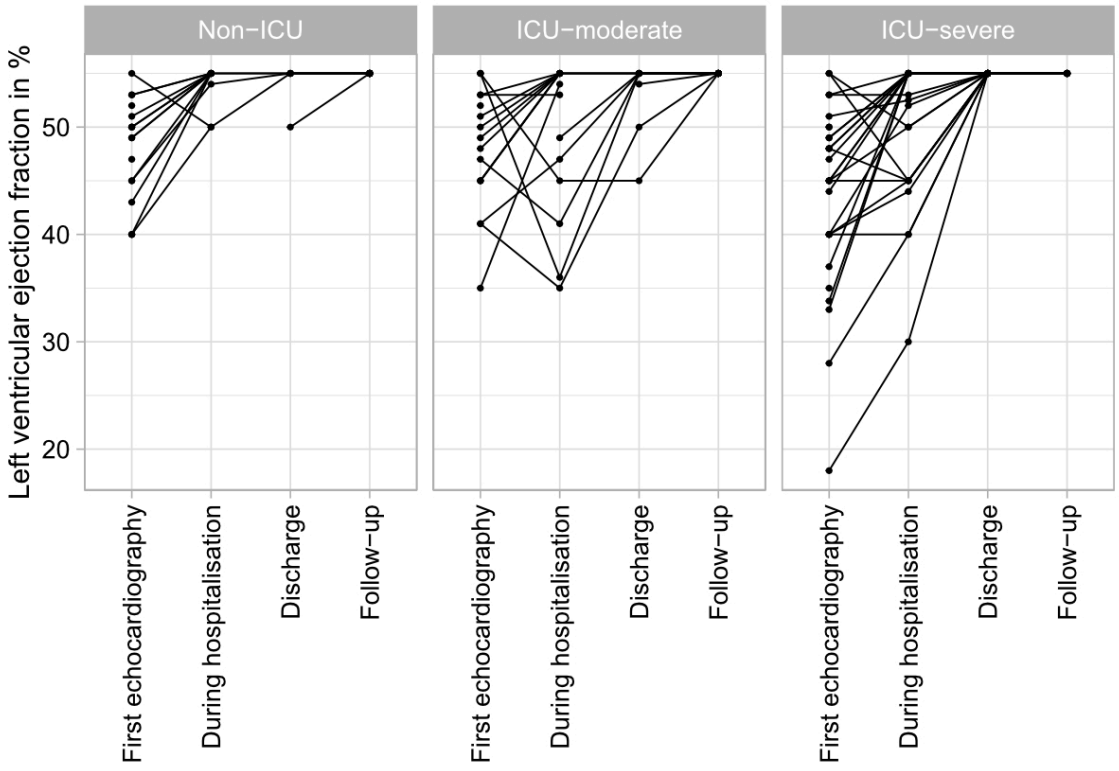
The median length of hospitalisation was 6.0 (IQR 5.0–8.0) days and the duration of ICU admission was 2.0 (1.5–5.0) days. No child required treatment with extracorporeal membrane oxygenation and no deaths occurred. Follow-up data were available from 194 (95.1%) children (table 4). Limitation in daily life activities because of fatigue was reported in 15 (7.9%) children without differences according to initial disease severity (p = 0.189). School or kindergarten attendance was disrupted in 16 (8.9%) children: 4 (2.1%) complained of difficulty concentrating, 7 (3.6%) were attending school only part-time and 5 (2.6%) had not been able to return to school. Children admitted to the ICU were more likely to experience limitations in school attendance (p = 0.011). Physical activity was restricted in most children (106 [58.6%]) according to local recommendations. Few children complained of persisting symptoms at 6-week follow-up, with headache, abdominal pain and rash being the most frequently reported (10 [5.3%], 8 [4.2%] and 6 [3.1%], respectively). The frequency of these symptoms was reported regardless of initial disease severity (p >0.05).

Discussion

This large multicentre national study presents detailed cardiological data and follow-up from active surveillance of children diagnosed with PIMS-TS during the first two years of the COVID pandemic in Switzerland. The overall epidemiological data are comparable with that of other European and North American studies, including the rate of cardiac involvement [15–19]. Although the number of children of Black ethnicity is not available in Switzerland, they were likely overrepresented in our cohort, a finding that is in line with data from a previous meta-analysis [20].

Left ventricular systolic dysfunction was one of the key cardiac findings in this cohort of children with PIMS-TS,

Figure 2: Evolution of left ventricular systolic dysfunction over time, by disease severity. To make trends visible, we assigned a value of 55% (= normal) when a patient with left ventricular systolic dysfunction had recovered at the next echocardiography. (Non-ICU: child not admitted to the ICU; ICU-moderate: child admitted to the ICU without need for mechanical ventilation and/or inotropic support; ICU-severe: child admitted to the ICU with need for mechanical ventilation and/or inotropic support.) For discharged the closest echocardiography before discharge was used.



reported in approximately one in three children. This finding is also frequently reported in other studies ranging from 13% to 80% [15, 16, 21–24]. Most commonly, detection of left ventricular systolic dysfunction has been described on admission with rapid resolution before discharge [25], as documented in most of our patients. One novel finding in our cohort is a decrease in left ventricular systolic dysfunction several days after admission, which has rarely been seen previously [24]. This deterioration of cardiac function after admission emphasises the need for regular echocardiographic assessment during hospitalisation in patients presenting with PIMS-TS as left ventricular systolic dysfunction, particularly in children with more severe disease.

In our cohort, coronary artery involvement occurred regardless of the severity of illness. Interestingly, there was no correlation between coronary artery involvement and anti-inflammatory markers like CRP, ferritin and ESR**.** However, children with coronary artery aneurysm were more likely to be admitted to the ICU. One novel finding in our study is that coronary artery involvement can occur several days after admission. This has only rarely been reported previously: one study described a series of three children who presented with coronary artery dilation after initial presentation and treatment with IVIG [26].

We found that few children with coronary artery aneurysms had persistent aneurysms at follow-up. Most studies with short-term follow-up of coronary artery abnormalities in PIMS-TS patients describe a rapid regression to normal size of the coronary arteries — as was seen in our cohort [27–32]. Only a few coronary aneurysms persisted in our short-term follow-up; most regressed to normal size. However, regression to normal size does not equate to resolution and absence of long-term coronary artery sequelae. The pathophysiology of coronary artery aneurysms in PIMS-TS is not well understood. The occurrence may be caused by vasodilation in a highly proinflammatory milieu as described in febrile children [33]. Alternatively it may

Table 2:
Echocardiographic findings in children with PIMS-TS at admission. (Non-ICU: child not admitted to the ICU; ICU-moderate: child admitted to the ICU without need for mechanical ventilation and/or inotropic support; ICU-severe: child admitted to the ICU with need for mechanical ventilation and/or inotropic support.)

	Total	**Non-ICU**	**ICU-moderate**	**ICU-severe**	**p-value**
	n (%)	**n (%)**	**n (%)**	**n (%)**	
	204 (100)	**99 (48.5)**	**50 (24.5)**	**55 (26.9)**	
Coronary involvement					0.469
Normal (z-score <2)	156 (76.5)	76 (76.8)	39 (78.0)	42 (76.4)	
Dilation (2≤ to <2.5)	16 (7.8)	9 (9.1)	4 (8.0)	2 (3.6)	
Small aneurysm (2.5≤ to <5)	27 (13.2)	11 (11.1)	6 (12.0)	10 (18.2)	
Medium aneurysm (5≤ to <10)	2 (1.0)	–	1 (2.0)	1 (1.8)	
Missing data	3 (1.5)	3 (3.0)	–	–	
Pericardial effusion	50 (24.5)	16 (16.2)	15 (30.0)	19 (34.5)	**0.026**
Missing data	4 (2.0)	4 (4.0)	–	–	
Right ventricular systolic dysfunction	18 (8.8)	6 (6.1)	3 (6.0)	9 (16.4)	0.079
Missing data	3 (1.5)	3 (3.0)	–	–	
Left or right ventricular diastolic dysfunction	34 (16.7)	11 (11.1)	12 (24.0)	11 (20.0)	0.115
Missing data	3 (1.5)	3 (3.0)	–	–	
Left ventricular systolic dysfunction					**<0.001**
Normal (LVEF ≥55%)	124 (60.8)	73 (73.7)	28 (56.0)	23 (41.8)	
Mild (LVEF ≥45% to <55%)	43 (21.1)	13 (13.1)	13 (26.0)	17 (30.9)	
Moderate (LVEF <35% to <45%)	13 (6.4)	4 (4.0)	3 (6.0)	6 (10.9)	
Severe (LVEF ≤35%)	7 (3.4)	-	2 (2.0)	5 (9.1)	
LVEF not specified	10 (4.9)	3 (3.0)	3 (6.0)	4 (7.3)	
Missing data	7 (3.4)	6 (6.1)	1 (2.0)	–	
Mitral valve regurgitation					0.149
None	135 (66.2)	70 (70.7)	33 (66.0)	32 (58.2)	
Mild	56 (27.5)	22 (22.2)	15 (30.0)	19 (34.5)	
Moderate	3 (1.5)	–	1 (2.0)	2 (3.6)	
Severe	1 (0.5)	–	–	1 (1.8)	
Missing data	9 (4.4)	7 (7.1)	1 (2.0)	1 (1.8)	

LVEF: left ventricular ejection fraction

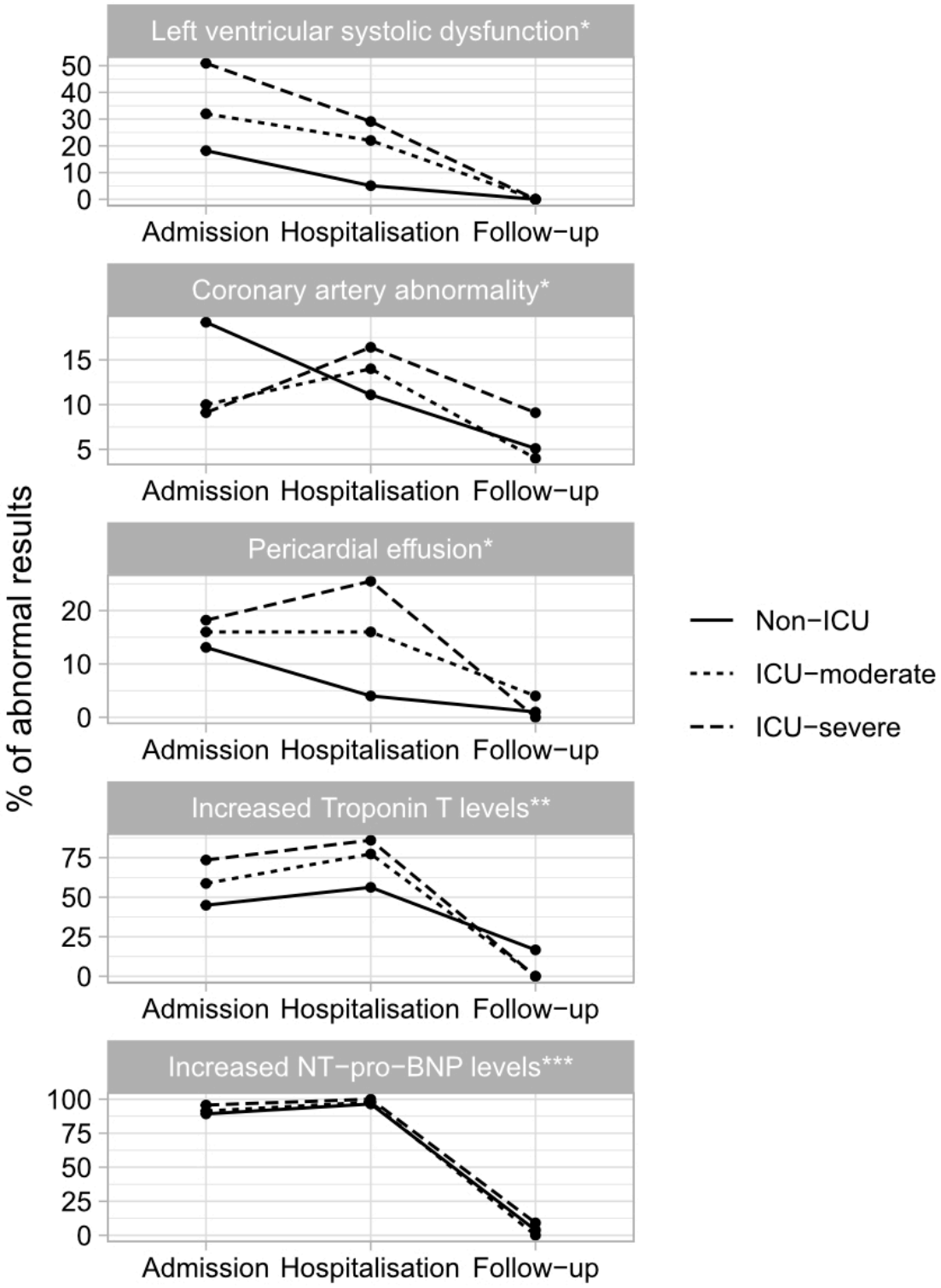
Table 3:
Echocardiography findings during hospitalisation and follow-up (n represents an abnormal echocardiographic finding at each timepoint, not necessarily a newly diagnosed abnormality).

Echocardiography findings	**At admission**	**During hospitalisation**	**At discharge**	**At follow-up**
	n/total (%)	**n/total (%)**	**n/total (%)**	**n/total (%)**
Pericardial effusion	31/195 (15.9)	26/138 (18.8)	18/113 (15.9)	3/181 (1.7)
Right ventricular systolic dysfunction	14/194 (7.2)	9/137 (6.6)	1/112 (0.9)	0/183 (–)
Left ventricular systolic dysfunction	62/197 (31.5)	32/139 (23.0)	6/113 (5.3)	0/183 (–)
Diastolic dysfunction	23/193 (11.9)	10/137 (7.3)	5/113 (4.4)	5/183 (2.7)
Coronary involvement	29/197 (14.7)	27/139 (19.4)	13/113 (11.5)	12/183 (6.6)

n/total: abnormal results/total; %: percentage of abnormal results

occur as a result of the destruction of the arterial wall by inflammatory cells as is known to occur in Kawasaki disease [34]. It is supposed that coronary artery dilation, as it is mostly seen in children with PIMS-TS, resolves without consequences whereas coronary artery aneurysms caused by the destruction of the arterial wall are known to increase the long-term risk of thrombosis, coronary artery steno-

Figure 3: Summary of echocardiographic and laboratory findings during admission, hospitalisation and follow-up according to disease severity. (Non-ICU: child not admitted to the ICU; ICU-moderate: child admitted to the ICU without need for mechanical ventilation and/or inotropic support; ICU-severe: child admitted to the ICU with need for mechanical ventilation and/or inotropic support.)* Non-ICU n = 99; ICU-moderate n = 50; ICU-severe n =55.** Troponin T reference value <14 ug/l; percentage calculated using n abnormal/total.*** NT-proBNP reference value according to age [11]; percentage calculated using n abnormal/total.



sis due to vascular remodelling or endothelial dysfunction even in case of regression to normal diameter [12].

In our cohort, pericardial effusion was present in one in four children but was not haemodynamically relevant and did not require intervention. In the literature, pericardial effusion is generally reported as mild and has been described in 23% to 31% of patients with PIMS-TS with rapid resolution during hospitalisation [15, 16, 35]. In contrast, in our cohort the pericardial effusion was still present at discharge in some cases, with resolution at follow-up echocardiography in most cases. Mitral valve regurgitation was frequently reported but most commonly classified as mild, which was also seen in another study [15]. Moderate or severe mitral valve regurgitation was rare and only seen in patients admitted to the ICU. One study demonstrated that the resolution of mitral valve regurgitation, which follows the development of the myocardial dysfunction, lags the resolution of the left ventricular dysfunction. But almost all patients showed a complete resolution of the mitral valve regurgitation within six months [36].

We found cardiac markers including troponin T and NT-proBNP to be higher in children admitted to the ICU. Cardiac biomarkers are frequently elevated in children with PIMS-TS [37]. One study reported that NT-proBNP values were higher in children with cardiac involvement compared to those without [38]. Similarly, further studies found an association between the severity of left ventricular systolic dysfunction and higher values of troponin T and NT-proBNP [39, 40]. The rapid resolution of the left ventricular systolic dysfunction and the cardiac biomarker levels documented in our study lends weight to the hypothesis that the myocardial injury results from a temporary myocardial oedema caused by severe inflammation rather than from direct virus-mediated myocardial damage [41].

ECG abnormalities were less commonly reported in our cohort with one in five children having an abnormal ECG. In the literature, abnormal ST- and T-wave segments are more frequently noted, up to 46%, as is atrioventricular block, up to 25% [15, 24, 42, 43]. One study found that an atrioventricular block was more frequent in children admitted to the ICU [43]. In our cohort, children with atrioventricular block were also more frequently admitted to the ICU but the reason for ICU admission was most likely related to left ventricular systolic dysfunction and/or shock requiring inotropic support. Moreover, the atrioventricular conduction abnormalities were usually present at admission or prior to corticosteroid treatment, except for two children who developed atrioventricular block two days after initiation of treatment with corticosteroids. The proposed mechanism of such atrioventricular conduction abnormalities is that the hyperinflammatory response leads to widespread myocardial injury as well as oedema of the conduction tissue [44].

The diversity of treatment regimens observed in our study reflects the absence of evidence-based recommendations regarding PIMS-TS treatment. Observational study and expert consensus recommendation had guided treatment strategy [45, 46]. The results of a recent randomised controlled trial comparing methylprednisolone and IVIG treatment are expected soon and will potentially influence the future management of children with PIMS-TS [14].

The high rate of sport limitation in our study was mainly due to physical activity being advised against for three to six months if cardiac involvement was documented, as suggested by national and international guidelines [45, 47]. Children without a cardiac abnormality were recommended to stop physical activity for two weeks only [7]. Interestingly, persisting clinical symptoms on follow-up did not correlate with initial disease severity.

Strengths and limitations

The strengths of this study are a relatively large number of children included with detailed clinical data available. Moreover, almost all children included had complete follow-up data available. Despite the active and established surveillance system, some cases might not have been captured in our study. Our classification of disease severity may not be applicable to other countries as the decision to admit apatient to the ICU instead of a standard ward might be determined by local practices and therefore differ between centres. However, the definition of severe cases is

Table 4:
General activity and symptoms at follow-up. Missing data is not included in this table; for further details on missing data, see table S4.

(Non-ICU: child not admitted to the ICU; ICU-moderate: child admitted to the ICU without need for mechanical ventilation and/or inotropic support; ICU-severe: child admitted to the ICU with need for mechanical ventilation and/or inotropic support.)

	Total	Non-ICU	ICU-moderate	ICU-severe	p-value
	n (%)	n (%)	n (%)	n (%)	
	194 (100)	92 (47.4)	49 (25.3)	53 (27.3)	
Daily life limitation					
General activity	15 (7.9)	8 (9.0)	1 (2.0)	6 (11.3)	0.189
School/kindergarten	16 (8.9)	2 (2.5)	5 (10.4)	9 (17.6)	**0.011**
Sport	106 (58.6)	44 (52.4)	30 (63.8)	32 (64.0)	0.291
Persisting symptoms					
Headache	10 (5.3)	8 (9.1)	–	2 (3.8)	0.068
Abdominal pain	8 (4.2)	6 (6.7)	–	2 (3.8)	0.176
Rash	6 (3.1)	1 (1.1)	1 (2.0)	4 (7.7)	0.084
Fever	3 (1.6)	1 (1.1)	–	2 (3.8)	0.279
Respiratory distress	3 (1.6)	–	1 (2.1)	2 (3.8)	0.204
Cough	3 (1.6)	2 (2.2)	1 (2.1)	–	0.556
Hypertension	2 (1.1)	–	1 (2.1)	1 (2.0)	0.402
Hepato-/splenomegaly	1 (0.5)	–	1 (2.0)	–	0.238

ICU: intensive care unit.

likely comparable as ventilation and inotropic support are clear definitions. ECG abnormalities were reported according to medical record and not all ECG were reviewed by a cardiologist, therefore we might have underestimated the rate of abnormalities. Coronary artery involvement in children is mostly assessed by transthoracic echocardiography; cardiac MRI was rarely done, therefore this data was not included for analysis.

Conclusion

Our study shows that cardiac involvement occurs in the majority of children and adolescents with PIMS-TS, the extent of which is central to the course of the disease. In the acute stage, ventricular dysfunction is most prominent, which increases the risk for ICU admission. For the longer-term consequences, coronary artery aneurysms are more important as they carry an increased risk of coronary artery stenosis and thrombosis. With a timely diagnosis and adequate therapy of PIMS-TS, recovery was documented in a few weeks. Close monitoring and regular follow-ups of children with PIMS-TS particularly those with coronary artery changes is required due to the possibility of long-term cardiac consequences.

Data sharing statement

Data collected for the study and the study protocol will be made available to others on request.

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Author contributions: The study was designed by PZ and NR. Data analysis and interpretation were done by AU, PZ and NR. DW and SB critically reviewed cardiological data. Regular online meetings were conducted with all authors for critical review of the analysis. The first draft was written by AU; all authors have read and approved the final manuscript.

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Potential competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix: supplementary tables

Table S1:
Treatment according to disease severity.

	Total	Non-ICU	ICU-moderate	ICU-severe	p-value
	n (%)	n (%)	n (%)	n (%)	
	204 (100)	**99 (48.5)**	**50 (24.5)**	**55 (26.9)**	
IVIG	155 (76.0)	69 (69.7)	42 (84.0)	44 (80.0)	0.233
Missing data	5 (2.5)	2 (2.0)	1 (2.0)	2 (3.6)	
Methylprednisolone	122 (59.8)	42 (42.4)	33 (66.0)	47 (85.5)	**<0.001**
Missing data	6 (2.9)	4 (4.0)	1 (2.0)	1 (1.8)	
Prednisolone	122 (59.8)	46 (46.5)	36 (72.0)	40 (72.7)	**0.001**
Missing data	9 (4.4)	5 (5.1)	–	4 (7.3)	
ASA (high dose)*	42 (20.6)	26 (26.3)	9 (18.0)	7 (12.7)	0.287
Missing data	12 (5.9)	4 (4.0)	4 (8.0)	4 (7.3)	
ASA (low dose)**	161 (78.9)	74 (74.7)	43 (86.0)	44 (80.0)	0.428
Missing data	8 (3.9)	6 (6.1)	1 (2.0)	1 (1.8)	
Anakinra	20 (9.8)	3 (3.0)	2 (4.0)	15 (27.3)	**<0.001**
Missing data	7 (3.4)	3 (3.0)	1 (2.0)	3 (5.5)	
Tocilizumab	4 (2.0)	1 (1.0)	–	3 (5.5)	0.207
Missing data	8 (3.9)	4 (4.0)	1 (2.0)	3 (5.5)	
Unfractionated heparin	57 (27.9)	2 (2.0)	18 (36.0)	37 (67.3)	**<0.001**
Missing data	9 (4.4)	4 (4.0)	1 (2.0)	4 (7.3)	
LMWH	49 (24.0)	11 (11.1)	12 (24.0)	26 (47.3)	**<0.001**
Missing data	9 (4.4)	4 (4.0)	1 (2.0)	4 (7.3)	
Oxygen support	60 (29.4)	9 (9.1)	20 (40.0)	31 (56.4)	**<0.001**
Missing data	–	–	–	–	

* 50 to 80 mg/kg/day

** 2 to 5 mg/kg/day

ASA: acetylsalicylic acid; ICU: intensive care unit; IVIG: intravenous immunoglobulin; LMWH: low-molecular-weight heparin

Table S2:
ECG findings during hospitalisation and follow-up.

	Total	Non-ICU	ICU-moderate	ICU-severe	p-value
	n (%)	n (%)	n (%)	n (%)	
During hospitalisation	**204 (100)**	**99 (48.5)**	**50 (24.5)**	**55 (26.9)**	
ECG normal	142 (69.6)	74 (74.7)	35 (70.0)	33 (60.0)	0.162
ECG not done	25 (12.3)	15 (15.2)	1 (2.0)	9 (16.4)	0.554
ECG AV block	10 (4.9)	1 (1.0)	2 (4.0)	7 (12.7)	0.005
ECG Prolonged QT interval	6 (2.9)	3 (3.0)	3 (6.0)	–	0.191
ECG Tachyarrhythmia	1 (0.5)	1 (1.0)	–	–	0.587
ECG Other abnormality *	20 (9.8)	5 (5.1)	9 (18.0)	6 (10.9)	0.041
During follow-up	**194 (100)**	**92 (47.4)**	**49 (25.3)**	**53 (27.3)**	
ECG normal	164 (84.5)	78 (84.8)	43 (86.0)	43 (78.2)	0.514
ECG not done	27 (13.9)	13 (14.1)	6 (12.0)	8 (14.5)	0.896
ECG abnormality **	3 (1.5)	1 (1.1)	–	2 (3.6)	0.263

* abnormal ST-and T wave segment 9, new bundle branch block 4, supraventricular extrasystole 2, junctional rhythm 2, biphasic P wave in V1-V2 1, sinus bradycardia 1, low voltage 1

** axis deviation 2, abnormal ST- and T wave segment 1

AV: atrioventricular; ECG: electrocardiography; ICU: intensive care unit

Table S3:
Treatment on-going at follow-up.

	Total	Non-ICU	ICU-moderate	ICU-severe	p-value
	n (%)	n (%)	n (%)	n (%)	
	194 (100)	**92 (47.4)**	**49 (25.3)**	**53 (27.3)**	
Low-dose ASA (2 to 5 mg/kg/day)	150 (77.7)	68 (74.7)	36 (73.5)	46 (86.8)	0.174
Missing data	–	–	–	–	
Prednisone	26 (13.5)	13 (14.3)	6 (12.2)	7 (13.2)	0.906
Missing data	2 (1.0)	1 (1.1)	–	1 (1.9)	
LMWH	1 (0.5)	1 (1.1)	–	–	0.887
Missing data	4 (2.1)	2 (2.2)	1 (2.0)	1 (1.9)	

ICU: intensive care unit; ASA: acetylsalicylic acid; LMWH: Low-molecular-weight heparin

Table S4:
General activity and symptoms at follow-up.

	Total	Non-ICU	ICU-moderate	ICU-severe	p-value
	n (%)	n (%)	n (%)	n (%)	
	194 (100)	**92 (47.4)**	**49 (25.3)**	**53 (27.3)**	
Daily life limitation					
General activity	15 (7.8)	8 (8.8)	1 (2.0)	6 (11.3)	0.229
Missing data	2 (1.0)	2 (2.2)	–	–	
School/kindergarten	16 (8.3)	2 (2.2)	5 (10.2)	9 (17.0)	**0.007**
Missing data	13 (6.7)	10 (11.0)	1 (2.0)	2 (3.8)	
Sport	106 (54.9)	44 (48.4)	30 (61.2)	32 (60.4)	0.522
Missing data	12 (6.2)	7 (7.7)	2 (4.1)	3 (5.7)	
Persisting symptoms					
Headache	10 (5.2)	8 (8.8)	–	2 (3.8)	0.119
Missing data	5 (2.6)	3 (3.3)	2 (4.1)	–	
Abdominal pain	8 (4.1)	6 (6.6)	–	2 (3.8)	0.447
Missing data	3 (1.6)	1 (1.1)	1 (2.0)	1 (1.9)	
Rash	6 (3.1)	1 (1.1)	1 (2.0)	4 (7.5)	0.213
Missing data	2 (1.0)	1 (1.1)	–	1 (1.9)	
Fever	3 (1.6)	1 (1.1)	–	2 (3.8)	0.462
Missing data	2 (1.0)	1 (1.1)	1 (2.0)	–	
Respiratory distress	3 (1.6)	–	1 (2.0)	2 (3.8)	0.375
Missing data	2 (1.0)	1 (1.1)	1 (2.0)	–	
Cough	3 (1.6)	2 (2.2)	1 (2.0)	–	0.695
Missing data	2 (1.0)	1 (1.1)	1 (2.0)	–	
Hypertension	2 (1.0)	–	1 (2.0)	1 (1.9)	0.757
Missing data	7 (3.6)	3 (3.3)	2 (4.1)	2 (3.8)	
Hepato-/splenomegaly	1 (0.5)	–	1 (2.0)	–	0.327
Missing data	4 (2.1)	3 (3.3)	–	1 (1.9)	

ICU: intensive care unit

Table S5:
Cardiac biomarkers values during hospitalisation and at follow-up according to disease severity

	Non-ICU		ICU-moderate		ICU-severe		p-value
	n abnormal/total (%)	median (IQR)	n abnormal/total (%)	median (IQR)	n abnormal/total (%)	median (IQR)	
Troponin T in µg/l (ref <14)							
Admission	40/89 (44.9)	11.0 (5.0, 35.0)	27/46 (58.7)	23.0 (11.5, 39.0)	36/49 (73.5)	31.0 (13.8, 130.3)	**<0.001**
Peak value	50/89 (56.2)	19.5 (7.0, 40.0)	34/44 (77.3)	32.0 (17.0, 65.0)	43/50 (86.0)	55.0 (28.5, 168.8)	**<0.001**
At discharge	31/86 (36.0)	10.0 (5.0, 19.0)	15/43 (34.9)	8.5 (5.8, 21.5)	29/49 (59.2)	17.0 (8.0, 41.0)	**0.002**
At follow-up	3/18 (16.7)	4.0 (3.0, 8.3)	0/7 (0.0)	3.0 (3.0, 3.5)	0/15 (0.0)	3.0 (3.0, 3.5)	0.271
NT-pro-BNP in pg/ml*							
Admission	74/83 (89.2)	1630 (528, 4505)	42/46 (91.3)	1871 (1142, 5693)	45/47 (95.7)	6035 (2431, 11224)	**<0.001**
Peak value	83/86 (96.5)	3435 (1772, 5930)	45/46 (97.8)	5711 (2521, 11990)	50/50 (100)	10925 (7217, 23998)	**<0.001**
At discharge	71/82 (86.6)	1213 (398, 2652)	37/45 (82.2)	804 (274, 1808)	41/50 (82.0)	1025 (367, 2430)	0.252
At follow-up	1/26 (3.8)	42.2 (26.8, 59.8)	0/13 (0.0)	50.0 (31.6, 60.0)	2/22 (9.1)	40.0 (23.1, 50.0)	0.437

* NT-pro-BNP reference value according to age[11]

ICU: intensive care unit; IQR: interquartile range; PIMS-TS: Paediatric inflammatory multisystem syndrome-temporally related to severe acute respiratory syndrome coronavirus 2

Table S6:
Details of coronary artery involvement during hospitalisation and follow-up.

Patient characteristics				Coronary artery involvement (z-score)			
Age*	**Sex**	**Severity group**	**Treatment**	**At admission**	**During hospitalisation**	**Before discharge**	**At follow-up**
4/3	M	Non-ICU	IVIG, Pred, high**- and low-dose*** ASA	LAD (3.8)	LAD (3.8)	LAD (2.5)	LAD (4.1)
8/0	F	Non-ICU	IVIG, low-dose ASA	LMCA (3.7), LAD (2.7)	LMCA (2.8)	None	LMCA (2.2)
11/3	F	Non-ICU	IVIG, MP, Pred, low-dose ASA	LAD (2.5)	Not done	Not done	LMCA (2.3)
5/6	M	Non-ICU	IVIG, high- and low-dose ASA	RCA (2.2), LMCA (4.7), LAD (2.7), LCX (2.3)	Not done	Not done	RCA (2.1)
0/5	F	Non-ICU	IVIG, high- and low-dose ASA	None	Not done	None	LMCA (2.5)
10/8	M	ICU-moderate	IVIG, Pred, high- and low-dose ASA, clopidogrel	RCA (5.3)	RCA (5.3)	RCA (5.3)	RCA (3.5)
7/5	M	ICU-severe	IVIG, MP, Pred, low-dose ASA	None	Not done	Not done	LMCA (2.3), LAD (2.5)
8/6	M	ICU-severe	IVIG, MP, Pred, low-dose ASA	None	None	LMCA (2.8)	LMCA (2.7)
2/11	M	ICU-severe	IVIG, MP, Pred, high- and low-dose ASA	None	None	LAD (3.4)	LAD (2.0)
12/11	M	ICU-severe	IVIG, MP, Pred, low-dose ASA	None	None	RCA (5.5)	LAD (2.7), LCX (2.4)
10/3	M	ICU-severe	IVIG, PM, anakinra, low-dose ASA	None	RCA (3.3), LAD (4.5)	RCA (4.0), LAD (4.5)	LAD (2.3), LCX (2.5)
4/10	M	ICU-severe	MP, high-dose ASA	None	None	Not done	RCA (2.4)

* years/months

** 50 to 80 mg/kg/day

*** 2 to 5 mg/kg/day

ASA: acetylsalicylic acid; IVIG: intravenous immunoglobulin; MP: methylprednisolone; Pred: prednisolone