

ORIGINAL ARTICLE

Mild coronary artery dilatation developed in some children with mild COVID-19 but completely regressed within 3 months

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Abstract

Aim: We studied the incidence and time course of any coronary artery changes in children up to 2 years of age who were hospitalised with mild COVID-19.

Methods: This was a single-centre prospective study of 29 children (19 males) with a median age of 3 months and interquartile range (IQR) of 1.6–4.3 months. They were admitted to a Greek University hospital for mild COVID-19 from 1 March to 30 December 2021. Three echocardiographic evaluations were performed at a median (IQR) of 19 (16–24) days, 82 (75–89) days and 172 (163–197) after the first symptoms. The prevalence of coronary artery dilation, regression, and changes was documented.

Results: Coronary artery dilation was present in 3 (10.3%) cases at the first evaluation, with complete regression at the second. Regression was observed in 18/24 (75%) cases with follow-up data and 9 (31%) demonstrated significant z-score changes of >2. Coronary artery changes in any segment at any time were documented in 18/29 (62%) of the patients.

Conclusion: Cases of transient and very mild coronary artery dilatation following mild COVID-19 completely regressed within 3 months. Large-scale studies are needed to document the extent and time course of coronary artery dilation following paediatric COVID-19.

KEYWORDS

aneurysm, coronary artery, COVID-19, dilation, pandemic

1 | INTRODUCTION

The association between Kawasaki disease and coronary artery dilatation or aneurysms in children has been well established. Coronary artery changes in young febrile children without a source meet the American Heart Association's diagnostic criteria for incomplete Kawasaki disease.¹ Shortly after COVID-19 was declared a pandemic, Italy reported an unexpected, increased incidence of an inflammatory syndrome like Kawasaki disease in children.² This was followed by similar observations worldwide.^{3,4} Since then, clinical, laboratory

and imaging criteria have been established to better define the new syndrome and to differentiate it from Kawasaki disease.¹ The most commonly used term is now multisystem inflammatory syndrome in children (MIS-C),⁵ but paediatric inflammatory multisystem syndrome temporary associated with COVID-19 has also been used.⁶ MIS-C differs from Kawasaki disease in terms of the patients' ages, laboratory findings and a higher incidence of heart failure or shock at manifestation.⁵ However, a number of studies have reported that MIS-C was associated with similar coronary artery changes to Kawasaki disease.^{2-4,7-15} Most of these were transient dilations or

Abbreviations: IQR, interquartile range.; MIS-C, multisystem inflammatory syndrome in children; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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small aneurysms that tended to regress,^{7,10,12,15,16} but giant aneurysms have been also reported.^{3,11} The hypothesis that MIS-C and Kawasaki disease share common pathophysiology features that result in coronary changes in young children is being investigated.¹⁷ Despite this, there is a lack of data about whether milder forms of COVID-19^{18–20} are also associated with coronary artery changes. The aim of this study was to study the incidence, potential predictors and short-term time course of any coronary artery changes in patients up to 2 years of age who were hospitalised with mild symptomatic COVID-19.

2 | METHODS

This was a prospective cohort study carried out in a single tertiary referral centre, the University Hospital Heraklion, which is part of the University of Crete, Greece. The subjects were children up to 2 years of age who were admitted for mild symptomatic COVID-19 from 1 March to 30 December 2021. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was confirmed by a positive nasal reverse transcriptase polymerase chain reaction test on admission. We excluded COVID-19 patients who fulfilled the criteria for Kawasaki disease or MIS-C, based on established criteria,^{1,5} and patients with congenital heart disease. The type and duration of the children's symptoms were documented, based on the history provided by the children's parents and their inpatient medical records. Written informed consent was provided by the parents, and the study was approved by the Hospital's Ethics Committee.

2.1 | Laboratory evaluations

The standard laboratory evaluations on admission included a complete blood count, liver and renal function assessment, C-reactive protein and high sensitivity Troponin I levels. Further diagnostic testing was carried out on some children, according to clinical indications, to rule out alternative diagnoses, including MIS-C and Kawasaki disease. Troponin I and haemoglobin levels were compared with age-specific normative data to identify any increases in Troponin I levels or anaemia, respectively.²¹ We also documented the presence of thrombocytopenia or thrombocytosis (platelet counts of <150 and >450 K/ μ L, respectively), leucocytosis (white blood count >15 K/ μ L) and lymphopenia (absolute lymphocyte count <1.0 K/ μ L).

2.2 | Echocardiography

Detailed expert echocardiographic studies were carried out at three time points after the patients first displayed symptoms of COVID-19. All evaluations included coronary artery internal diameter measurements, namely absolute values and body surface area adjusted z-scores. These were carried out shortly after the

Key notes

- This study examined the incidence and time course of any coronary artery changes in 29 children up to 2 years of age who were hospitalised with mild COVID-19 in 2021.
- Echocardiographic evaluations showed coronary artery dilation in 3 (10.3%) cases at a median of 19 days, but these had completely regressed within 3 months.
- Coronary artery changes in any segment at any time were documented in 18/29 (62%) children.

patients made a clinical recovery and were discharged from hospital. The second and third evaluations were scheduled for 2 and 6 months after the first symptoms. A high-frequency sector transducer (10 MHz) on a GE Vivid 3 Expert Ultrasound System (GE Healthcare) was used for optimal imaging. Established imaging protocols were used to cover the left main coronary artery, left anterior descending coronary artery, circumflex coronary artery, proximal and mid-segment of the right coronary artery.^{22,23} These were carried out in addition to a complete echocardiographic evaluation. A single expert sonographer performed all the studies for consistency and documented the internal diameter of each coronary segment, using the average of three measurements from the digitally stored images. The coronary artery segment z-score values were estimated based on Boston z-score reference data.²⁴ The presence of a z-score of ≥ 2 or ≥ 2.5 in any segment was documented as coronary artery dilation or an aneurysm, respectively.¹ Regression of a coronary artery segment was documented if there was a z-score reduction of >1 between the initial evaluation and any follow-up evaluation.^{1,25} Cases were documented as positive for coronary artery changes if there was dilation and/or regression in any segment.

2.3 | Statistical analysis

Repeated measurements of the coronary artery dimensions on the same subjects, namely absolute and z-score values, were evaluated for significant changes over time. This was done by using paired t-tests of the first and second and first and third evaluations. Appropriate tests were used to evaluate potential associations between demographic data, symptoms, admission laboratory tests, electrocardiogram and echocardiography findings, namely the presence of coronary artery dilation or coronary artery changes. These were carried using the chi-squared test, Fisher's exact test, Student's t-test and the Mann-Whitney U-test. The values are presented as means and standard deviations (SD) or medians and interquartile ranges (IQR). A sub-analysis that used an alternative recommended z-score indexing process was also performed. This tested the impact of the coronary artery z-score reference on the reported prevalence

TABLE 1 Demographic and laboratory data on admission for patients who were positive and negative for coronary artery dilation

Group	Age (months)	Weight (Kg)	Height (cm)	Fever peak (C)	Fever duration (days)	hsTnI (ng/mL)	CRP (mg/dL)	D-Dim (mg/L)	WBC (K/ μ L)	PMN (K/ μ L)	ALC (K/ μ L)	PLT (K/ μ L)	Hb (gr/dL)
Positive CAD ^a													
Median	4.3	7.0	66	39	3	6.2	0.35	1.2	5.2	1.4	1.34	343	10.5
Range	2.6–6.2	6.4–8	64–69	38.2–39.9	2–5	3.6–12	0.1–1.12	0.3–5.5	3–10.2	1.1–3.0	1.3–6.7	267–403	10–10.9
Negative CAD ^a													
Median	2.7	5.9	60.5	38.3	2	10.2	0.17	1.2	7.6	1.9	3.5	323	10.8
Range	0.7–24	4–14.5	51–86	37.7–39.2	1–4	0.1–331	0.3–0.83	0.3–9.3	4.4–17	0.4–4.9	1.3–13	44–586	8.7–13.4

Abbreviations: ALC, absolute lymphocyte cell count; CRP, C-reactive protein; D-Dim., D-dimer levels; hsTnI, high sensitivity Troponin I; PLT, platelet count; PMN, polymorphonuclear leukocytes cell count; WBC, white blood cell count; Hb, haemoglobin value.

^aCoronary artery dilation (CAD) defined as z-score of >2.

of coronary artery dilation.^{1,22} The statistical analysis was performed using SPSS 12 (SPSS Inc.).

3 | RESULTS

3.1 | Patients

During the study period, a total of 39 children (<16 years) have been admitted for acute COVID-19 disease, excluding MIS-C and KD cases. Of them 30 were infants <2 years.

Permission for participation was withheld for one child who was eligible to take part in the study and 29 (19 male) were included. Their median age 3.03 months (IQR 1.6–4.3 months) and they ranged from 21 days to 24.5 months of age. The 29 subjects included 23 infants under 6 months of age and 13 of those were under 3 months of age.

3.2 | Symptoms and findings

The most common symptom was fever in 28 cases (96%), with a median temperature of 38.3°C (range 38–40°C) and a median duration of two days (range 1–5 days). The other symptoms were feeding difficulties and rhinitis, which both occurred in 13 cases (45%), coughing in 9 (31%) and gastrointestinal symptoms in 7 (24%), as shown in Table 1.

The laboratory values were recorded on admission. C-reactive protein was increased in 4/29 (14%) cases, and there were increased high sensitivity Troponin I levels for age in three cases (10%), anaemia for age in 11 (38%), thrombocytosis in 5 (17%), thrombopenia in 3 (10%) and one case of leucocytosis (Table 1).

Electrocardiogram abnormalities were detected during admission in 12 (41%) cases, corresponding to mild ST segment changes in 10 (35%) and/or mild QTc interval prolongation in 3 (10%). Normalised electrocardiogram findings were documented during follow-up in all cases.

Inpatient care included intravenous fluids in 14 cases (48%) and antibiotics in 20 (69%). None of the patients required oxygen.

The first detailed echocardiographic evaluation was performed on all 29 patients at a median of 19 (IQR16–24) days after their first symptoms. Coronary artery dilation of at least one segment was present in 3 (10%) cases. There was a single case of left main coronary artery, left anterior descending coronary artery and right coronary artery mild dilation (z-score ≥ 2.0 to <2.5). The prevalence of coronary artery dilation, in any segment, during the serial echocardiographic evaluations is presented in Table 2.

A second detailed echocardiographic study was carried out on 21/29 cases (72%) at a median time of 82 (IQR 75–89) days following the first symptoms. A third study was carried out at a median of 172 (IQR163–197) days on 11/29 cases (38%). Repeat evaluations were available in 24 cases (83%): 13 cases underwent the first and second evaluations, eight underwent all three evaluations, and three underwent the first and third evaluations.

TABLE 2 Coronary artery dilation during serial evaluations

	1st evaluation	2nd evaluation	3rd evaluation
Median time [IQR] in days ^a	19 [16-24]	82 [75-89]	172 [163-197]
Patients evaluated (n)	29	21	11
Maximum z-score	n (%)	n (%)	n (%)
<1	17 (58.6)	11 (100)	11 (100)
1-1.99	9 (31.0)	0	0
2-2.49	3 (10.3)	0	0
2.5-5	0	0	0

^aAfter appearance of symptoms.

Regression of all coronary artery segments to normal z-score values (<2) had already been observed in all cases during the second evaluation, with further reductions to lower z-scores during the third evaluation (Table 2 and Figure 1). A significant coronary artery size reduction in absolute and indexed z-score values was observed between the first and second evaluations and of indexed values between the first and third evaluations (Table 3).

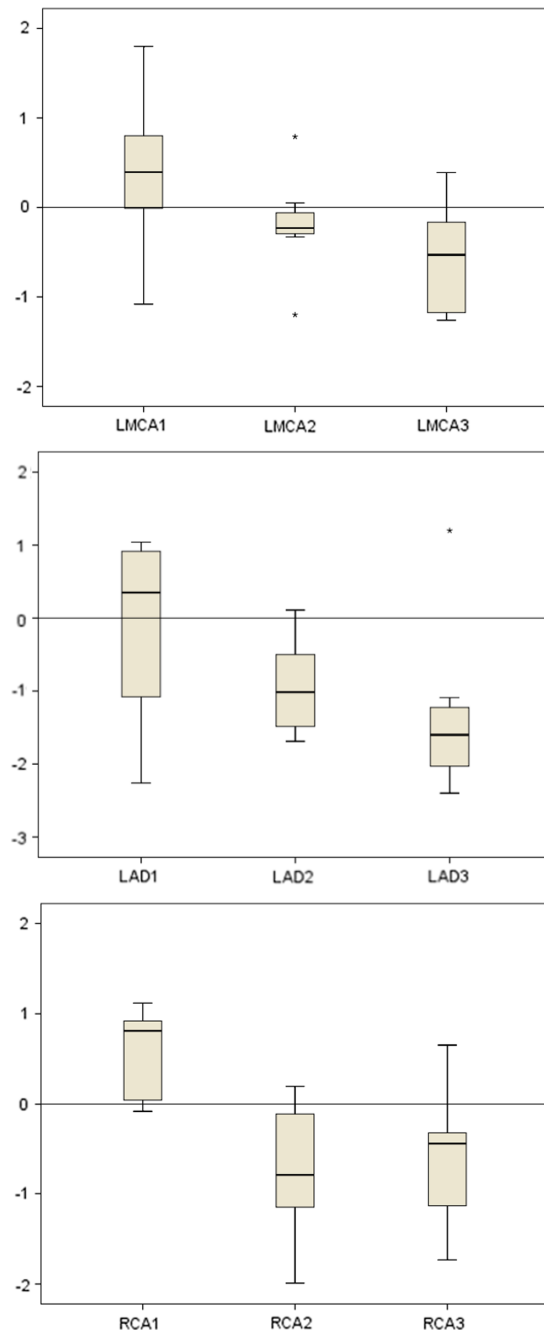
Regression of coronary artery size, defined as a z-score difference of >1, was observed in 18/24 (75%) cases with follow-up data. These comprised all three cases with coronary artery dilation, all eight cases with an initial z-score of 1.00-1.99 and 7/13 cases with z-scores of <1 at the first evaluation. Significant regression, defined as a difference in the z-score of >2, was observed in 9/24 (31%) cases with follow-up data. Coronary artery changes in any segment at any time were documented in 18/29 (62%) of cases.

3.3 | Predictors of coronary artery changes

There were no significant clinical and demographic predictors for coronary artery dilation development or coronary artery changes during the follow-up period (Table 1).

3.4 | Impact of coronary artery diameter indexing method

We applied an alternative z-score indexing reference,²² which enabled us to index all the coronary artery segments evaluated in the present study. This showed a higher incidence of coronary artery dilation in 10/29 patients (34%) during the first evaluation: five had a z-score of <2.5 and five had a z-score of 2.5-3.0. All 10 patients showed complete regression at the time of the second evaluation. Just over two-thirds of the cases (69%) had coronary artery changes during the follow-up period. Cases with coronary artery dilation had lower mean haemoglobin values (10.0 vs. 11.1 gr/dl, *p* = 0.018) than those without dilation and they were younger (2.3 vs. 3.5 months, *p* = 0.01), with higher platelet counts (382 vs. 260K/ μ L, *p* = 0.034).



LMCA, left main CA; LAD, left anterior descending CA; RCA, right CA

FIGURE 1 Box plots of coronary artery segmental z-scores according to evaluation time. LMCA, left main CA; LAD, left anterior descending CA; RCA, right CA

4 | DISCUSSION

Sufficient evidence has been reported that the SARS-CoV-2 virus has been associated with the development of coronary artery changes, namely dilation and aneurysms, in addition to acute myocardial dysfunction in children affected by MIS-C. A large registry study from the USA reported that the incidence of coronary dilation and aneurysms was 16.5%,¹⁴ and other studies have reported rates ranging from 9% to 38.6%.^{2-4,7-15} Most studies have reported

TABLE 3 Coronary artery size in serial evaluations, based on absolute size and z-scores

	Left main CA1	Left main CA2	Left main CA3	Left ant d CA1	Left ant d CA2	Left ant CA3	Left and t CA3	Circ. CA1	Circ. CA2	Circ. CA3	Right CA prox 1	Right CA prox 2	Right CA prox 3	Right CA dist 1	Right CA dist 2	Right CA dist 3
Absolute																
Mean	2.02	1.86 ^a	1.89	1.39	1.22 ^a	1.30	1.27	1.12 ^a	0.98	1.53	1.34 ^a	1.41	1.25	1.21	1.22	
Median	2.00	1.80	1.80	1.50	1.20	1.30	1.20	1.10	1.00	1.60	1.35	1.40	1.40	1.20	1.20	
z-score																
Mean	0.38	-0.27 ^a	-0.50 ^a	-0.24	-1.36 ^a	-1.30 ^a	n.a	n.a	n.a	0.31	-0.47 ^a	-0.54 ^a	n/a	n/a	n/a	
Median	0.28	-0.26	-0.50	-0.54	-1.42	-1.60	n.a	n.a	n.a	0.53	-0.26	-0.38	n/a	n/a	n/a	

Note: Coronary artery (CA) internal diameter absolute (mm) and z-score²⁵ value. Left ant d, left anterior descending; circ, circumflex; right coronary artery prox (proximal)/med (median) segment; n/a not available.

^aSignificant differences against initial measurement in paired comparison.

that small aneurysms regressed within three months.^{7,10,11,13,15,16} Similar incidence rates of coronary changes were reported for Kawasaki disease cases during^{3,4,7,11} and before the COVID-19 pandemic,^{7,11,15,25} with 21%–40% of children with MIS-C also meeting the diagnostic criteria for Kawasaki disease.^{3,4,8,9} The exact mechanism for the development of coronary artery dilation in Kawasaki disease and MIS-C is still being investigated. However, the association between both diseases and the SARS-CoV-2 infection during the COVID-19 pandemic raises questions. These include whether SARS-CoV-2 is a cardio-tropic virus,²⁶ which could also be associated with coronary changes during milder forms of COVID-19 disease in children.²⁷

To our knowledge, this was the first study to evaluate the incidence and time course of coronary artery changes in young children with mild COVID-19. One study used echocardiography to compare children with MIS-C with those with severe acute COVID-19. This showed a very low incidence of coronary changes, of less than 1%, in the subset of paediatric patients with severe acute COVID-19.⁹ Another study found no coronary artery changes in children with COVID-19 pneumonia.²⁸ Our study used the same coronary artery indexing method as most of the MIS-C and COVID studies.²⁴ We found that 10% of our patients developed very mild coronary artery dilation, defined as a z-score of ≤ 2.5 , in the first month after their symptoms and that dilation regressed completely within 3 months. Two factors could account for the differences in the reported incidence of coronary artery dilation in our study and other studies.^{9,28} These were the prospective design of our study and the fact that most of our subjects were under 6 months of age, which was much younger than the other studies. Infants under 6 months of age with incomplete Kawasaki disease face a high risk for coronary artery dilation.¹ Infants under 1 year of age with MIS-C have a 13.9% incidence of coronary artery dilation, despite a milder disease course.¹⁰ We included cases with a z-score reduction of >1 during follow-up,¹ and this resulted in a higher incidence of coronary artery changes (62%), which was similar to observations during Kawasaki disease.²

Although the incidence of coronary artery dilation in our study approached the incidence reported for Kawasaki disease^{1,25} and MIS-C,^{2-4,7-16} the observed dilatation was very mild and always transient. We found that coronary artery dilation showed complete regression to normal size within 3 months of the first symptoms of COVID-19. That was similar to the time scale in MIS-C and Kawasaki disease.^{1,13,16} Due to the small sample size, and the low prevalence of coronary artery dilation, no significant predictors for this condition could be detected in the present study. This has also been an issue with MIS-C studies.^{3,16} The impact of the indexing method on the prevalence of coronary artery dilation, and on detecting potential predictors, should be further evaluated. This is because a higher prevalence of coronary artery dilation and potentially significant predictors were documented in our study by using an alternative indexing reference.²² These predictors included anaemia, higher platelet counts and younger age.

Coronary artery dilation is considered a specific finding for Kawasaki disease. However, it has been observed in up to 5% of

patients, as a transient finding during the acute phase of other infectious and inflammatory diseases. The z-scores for other diseases have tended to be lower than for Kawasaki disease, with most cases displaying values of <2.5.^{1,29} Coronaviruses had already been discussed as potential triggers for Kawasaki disease, together with other infectious and environmental factors, well before COVID-19 pandemic.^{1,30} The mild and transient coronary artery changes we observed shortly after our patients recovered from COVID-19 could also have been due to transient vasodilation in the course of the SARS-CoV2 acute infection.²⁹ This is more likely than the acute vasculitis that is characteristic of Kawasaki disease and possibly MIS-C.

Our study had some limitations. The small sample resulted in low power for evaluating potential predictors of coronary artery changes and identifying the strongest predictors with clinical relevance. Because only infants were included, the generalisability of our findings to older children needs to be confirmed. We cannot rule out that Crete, which has links to other Mediterranean basin populations, has a genetic predisposition for increased coronary artery dilation. Genetic predisposition to coronary artery changes in both Kawasaki disease and MIS-C have been noted.^{1,11}

5 | CONCLUSION

This study found an increased incidence of transient and very mild coronary artery changes in infants with mild COVID-19. However, the findings do not support the routine use of echocardiography, unless clinically indicated or for research purposes. Large-scale prospective cohort studies are needed to define the clinical and laboratory predictors of coronary artery dilation in young patients with mild COVID-19. These should also describe the magnitude, natural course and benign prognosis of coronary artery dilation.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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