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Electrocardiographic changes in non-hospitalised children with COVID-19

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Abstract

Objectives: Many children diagnosed with COVID-19 infections did not require hospitalisation. Our objective was to analyse electrocardiographic changes in children with asymptomatic, mild or moderate COVID-19 who did not require hospitalisation *Methods:* All children are seen in a paediatric cardiology clinic who had asymptomatic, mild or moderate COVID-19 that did not require hospitalisation and had at least one electrocardiogram after their diagnosis were included in this retrospective analysis. Records were reviewed to determine COVID-19 disease severity and presence of Long COVID. Rhythm assessment, atrial enlargement, ventricular hypertrophy, PR/QRS/QT interval duration and ST-T wave abnormalities were analysed by a paediatric electrophysiologist. Clinically ordered echocardiograms were reviewed for signs of myopericarditis (left ventricular ejection fraction and pericardial effusion) on any subject with an electrocardiographic abnormality. *Results:* Of the 82 children meeting inclusion criteria (14.4 years, range 1–18 years, 57% male), 17 patients (21%) demonstrated electrocardiographic changes. Ten patients (12%) had electrocardiogram of borderline significance, which included isolated mild PR prolongation or mild repolarisation abnormalities. The other seven patients (9%) had concerning electrocardiographic findings consisting of more significant repolarisation abnormalities. None of the patients with an abnormal electrocardiogram revealed any echocardiographic abnormality. All abnormal electrocardiograms normalised over time except in two cases. Across the entire cohort, greater COVID-19 disease severity and long COVID were not associated with electrocardiographic abnormalities. *Conclusions:* Electrocardiographic abnormalities are present in a minority of children with an asymptomatic, mild or moderate COVID-19 infection. Many of these changes resolved over time and no evidence of myopericarditis was present on echocardiography.

On March 11, 2020, the World Health Organization declared a global pandemic as coronavirus 2019 (COVID-19) became a global health crisis.[1] COVID-19, caused by the novel severe acute respiratory syndrome coronavirus 2, was first reported in December 2019 and tll date has infected over 27 million people and caused approximately 500,000 deaths in the United States alone.[1,2] In the adult literature, COVID-19 affects the heart more frequently than other viruses, with some studies reporting cardiac involvement in up to 28% of patients,[3–8] however data remains limited in the paediatric population. Initial reports indicated that children were typically asymptomatic or had mild-moderate courses of acute COVID-19.[9]

Beginning in April 2020, however, doctors began to recognise case clusters of hospitalised children with multi-system inflammatory syndrome in children in the setting of recent COVID-19 infection. Several studies have been published describing the common cardiovascular findings in multi-system inflammatory syndrome in children and in children hospitalised with acute COVID-19 infection.[10–15] Conduction disturbances were primarily low-grade atrioventricular block[10] with infrequent transient progression to more advance heart block that resolved by discharge.[11,13,16] Significant but typically transient ventricular dysfunction, coronary artery dilation and pericardial effusion are common echocardiographic findings in multi-system inflammatory syndrome in children[14,17] with elevated markers of cardiac involvement seen in most cases.

While our understanding of the paediatric impact of COVID-19 and multi-system inflammatory syndrome in children has improved over the last year, a knowledge gap remains surrounding the effects of milder forms of acute COVID-19 illness on the paediatric cardiovascular system, especially in Long COVID-19[18] cases where symptoms can remain for a prolonged course. A recent study noted the possibility of subclinical myocarditis found on echocardiogram in patients with mild COVID-19 infection.[19] Another recently published study that looked at paediatric patients referred to paediatric cardiology for abnormal electrocardiograms did not result in any patient being diagnosed with myocarditis or ventricular

dysfunction.[20] That being said, there remains limited paediatric data on the frequency and severity of electrocardiographic abnormalities, a commonly utilised cardiovascular screening test for children following COVID-19 infection. The primary aim of this study is to report the frequency and type of electrocardiographic abnormalities in a paediatric cohort seen in the outpatient cardiology clinic with no known pre-existing cardiac conditions following COVID-19 infection in the absence of multisystem inflammatory syndrome in children and/or hospitalisation.

Materials and methods

Study design

This retrospective single-centre study included patients less than 21 years of age seen in outpatient cardiology clinic between February 2020 and February 2021 with a confirmed diagnosis of COVID-19 (positive COVID-19 PCR or antigen test). Exclusion criteria were history of CHD, known pre-existing dysrhythmia, presumed COVID-19 without confirmatory testing, multi-system inflammatory syndrome in children or hospitalised acute COVID-19. Referral indications varied, but included sports clearance, abnormal electrocardiographic findings or cardiac symptomatology. The study was approved by the Children's Mercy Kansas City Institutional Review Board.

COVID-19 data

Retrospective chart review was performed to collect demographic and clinical data. Patient demographics included gender, age, race and body mass index. Clinical data included dates (illness, COVID-19 test, clinic appointment and electrocardiograms), presence/absence and duration of acute COVID-19 symptoms and associated cardiovascular symptoms. Acute COVID-19 symptoms were defined as fever, myalgia, chills, lethargy, anosmia, nasal congestion and cough. Per American Academy of Pediatrics guidelines, patients were categorised as either asymptomatic, mild (less than 4 days of symptoms) or moderate (at least 4 days of symptoms without hospitalisation or multisystem inflammatory syndrome in children diagnosis) infection.[21] Long COVID-19-associated cardiovascular symptoms were defined as prolonged chest pain, palpitations, fatigue, dizziness or syncope following acute COVID-19 infection.

Electrocardiography

All subjects (82) had a standard 12-lead electrocardiogram obtained after their COVID-19 diagnosis, either at the cardiology visit or at a prior appointment with their primary care physician or urgent care. A minority of subjects had a pre-COVID-19 electrocardiogram (17) that was used as a baseline comparison or multiple electrocardiograms following COVID-19 diagnosis (8), which were included in this analysis. All the electrocardiograms were reviewed by a specialty trained paediatric electrophysiologist (LMW, CF) in either electronic (67 patients) (MUSE editor, GE Medical System Information Technologies, Inc.) or paper form (15 patients). Rhythm assessment, atrial enlargement, ventricular hypertrophy, PR/QRS/QT interval duration and ST-T wave abnormalities were reviewed. The QTc interval was corrected according to the Bazett's formula. An abnormal range greater than 465 milliseconds was chosen based on prior recommendations.[22] Abnormal PR and QRS intervals were based on age criteria.[22] The following repolarisation (ST-T) abnormalities were evaluated: (1) ST elevation or depression, (2) ST segment horizontal or downward sloping depression (doming) $\geq$ 0.05 mV plus T wave asymmetric inversion, (3) flat, inverted, biphasic or coved T waves and (4) changes in ST-T wave pattern compared to pre-COVID-19 electrocardiogram when available.

Electrocardiographic abnormalities of *borderline* significance were defined as diffuse T wave flattening, isolated T wave inversion in a single inferior or lateral lead, and PR prolongation above the 95th percentile for age but less than 250 milliseconds. *Concerning* electrocardiographic abnormalities were defined as ST segment elevation/depression including ST doming, abnormal T waves (inverted, biphasic or coved) in multiple leads, or any combination of abnormalities defined as borderline.

Echocardiography

For borderline and concerning cases, a limited analysis of the echocardiographic images obtained during the cardiology clinic visit was performed for left ventricular systolic function and pericardial effusion. Left ventricular ejection fraction was measured using the 5/6 Area-Length method.[23]

Statistical analysis

Characteristics of the study population were summarised as percentages, means ± standard deviation or as median, minimum and maximum, as appropriate depending on the normalcy of the data. Categorical data were compared using Chi-square test or Fischer exact test for smaller sample groups ($n < 5$). The independent t-test and Wilcoxon rank sum test was used to compare normally and non-normally distributed continuous variables. All statistical analyses were performed utilising SPSS 24 (IBM SPSS Statistics for Windows, Version 24.0. IBM Corp., Armonk, NY, USA, 2016) with p-value of $\leq$ 0.05 considered statistically significant.

Results

Patient characteristics

Eighty-four patients meeting criteria were seen in the cardiology clinic for evaluation after acute COVID-19 infection. After excluding one subject with a history of atrial fibrillation and one with pre-excitation, 82 subjects met criteria with a median age of 14.4 years (range 1–18 years) and a slight male predominance (n = 47, 57%). Most of the patients had a normal body mass index (n = 64, 78%) and were Caucasian (n = 62, 75%). Other races represented were African-American (n = 9, 11%), Hispanic (n = 6, 7%), Multiracial (n = 3, 4%) and of unknown ethnicity (n = 2, 2%). The indications for the cardiology clinic visit were persistent cardiovascular symptoms (n = 42, 51%), sports clearance (n = 35, 43%) and prior abnormal electrocardiogram performed post-COVID-19 infection (n = 22, 29%) either alone or in combination.

Acute COVID-19 illness severity

All subjects had laboratory confirmed acute COVID-19 infection with symptoms at time of acute infection including cough (n = 36, 44%), fever (n = 34, 42%), sore throat (n = 31, 38%), headache (n = 30, 37%), myalgia (n = 24, 29%) and anosmia (n = 22, 26%). This cohort was nearly evenly split between mild (46%) and moderate (51%) acute COVID-19 disease severity by American Academy of Pediatrics criteria[21] (Table 1). There was interval resolution of these acute COVID-19 symptoms in most

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Table 1. Acute COVID-19 disease severity and cardiovascular symptoms.

	Total cohort (82)	Normal electrocardiogram (64)	Abnormal electrocardiogram (17)
COVID-19 disease severity			
Asymptomatic	1 (1%)	1 (2%)	0 (0%)
Mild	37 (45%)	32 (50%)	5 (29%)
Moderate	42 (51%)	29 (45%)	12 (71%)
Indeterminate	2 (2%)	2 (3%)	0 (0%)
CV symptoms of long COVID			
Chest pain	42 (51%)	34 (53%)	8 (47%)
Shortness of breath	34 (42%)	25 (39%)	9 (53%)
Fatigue	33 (40%)	24 (38%)	8 (47%)
Palpitations	21 (26%)	15 (23%)	5 (29%)
Dizziness/Syncope	16 (20%)	12 (19%)	4 (24%)
Persistence of cardiovascular symptoms	53 (65%)	39 (61%)	13 (77%)

of the subjects by the time they were seen in cardiology clinic (n = 67, 82%). Moderate symptoms were not associated with any abnormal electrocardiographic findings (relative risk 2.2; p = 0.92).

Cardiovascular symptoms that arose following acute COVID-19 infection consistent with Long COVID-19 are reported in Table 1 and include chest pain (n = 42, 51%), shortness of breath (n = 34, 41%), fatigue (n = 33, 40%), palpitations (n = 21, 25%) and dizziness/syncope (n = 16, 19%). Fifty-three (65%) patients reported at least one of these cardiac symptoms remaining at the time of the cardiology visit (mean 44.5 ± 36.2 days following symptoms onset). This group did not have a significantly higher risk of having any abnormal electrocardiographic findings (relative risk 1.8; p = 0.25).

Electrocardiographic data

Normal electrocardiographic findings were present in 65 (79%) patients on their post-COVID-19 testing that occurred 34.6 ± 33.9 days following symptom onset. Electrocardiographic abnormalities were present in 17 (21%) subjects including three with PR prolongation for age and 14 with repolarisation abnormalities. There were no QRS abnormalities and all QTc intervals were less than 465 milliseconds. All electrocardiograms demonstrated sinus rhythm. There were 17 subjects who had a pre-COVID-19 electrocardiogram in the medical record that served as a baseline for comparison, and those electrocardiograms were all normal. Of those with a baseline electrocardiogram, five had a new electrocardiographic abnormality post COVID-19 infection (two PR prolongation for age and three repolarisation abnormalities).

Borderline electrocardiographic cases

There were 10 subjects (12% of the total study population) with electrocardiographic findings of borderline significance. This group included the three with isolated mild PR prolongation and seven with mild repolarisation abnormalities with details provided in Table 2. Only four borderline subjects had a follow-up electrocardiogram with a resolution of repolarisation abnormalities in three subjects (range 6–94 days to repeat electrocardiogram) and no resolution of the mild PR prolongation on follow-up electrocardiogram at 5 days in a 12-year-old. All 10 borderline subjects had an echocardiogram demonstrating normal left ventricular ejection fraction and no pericardial effusion. There was limited data regarding ambulatory heart rhythm monitoring in our cohort. Of these 10 patients, two underwent Holter monitoring, subjects #1 and #10 in Table 2. These Holter monitors were normal, defined by <1% premature atrial complexes or premature ventricular complexes with no pauses, couplets, triplets and runs of arrhythmia.

Concerning electrocardiographic cases

There were seven subjects (9% of the total study population) with concerning electrocardiographic findings (Table 3) all related to more significant repolarisation abnormalities. Five of these subjects had resolution of their electrocardiographic abnormality on repeat electrocardiogram within 30 days. One subject had no follow-up electrocardiogram as their clinical cardiologist decided one was not necessary in the setting of a normal echocardiogram. The one that did not have a resolution of electrocardiographic findings continues to show an abnormal repolarisation pattern with diffuse ST elevation and coved T waves (Concerning Subject 1 in Table 3, Fig 1). There was no pre-COVID-19 electrocardiogram for comparison. The second subject had diffuse ST segment abnormalities mimicking right bundle branch block (QRS duration normal, 100 milliseconds) and ST doming in the anterior leads (concerning subject 2 in Table 3, Fig 1). High precordial lead placement was negative for a Brugada pattern, and this was the only subject to have lab testing with normal troponin (<0.01 ng/ml) and normal NT-pro BNP (32 pg/ml). Follow-up electrocardiogram normalised 29 days later. For these seven subjects, all but one had echocardiograms, and they all demonstrated normal left ventricular ejection fraction and no pericardial effusion. One did not have an echo (concerning subject 7 in Table 3) as their electrocardiographic abnormality had normalised when seen in cardiology clinic. None of these patients underwent Holter or event recorder monitoring.

Discussion

Summary of results

In this population of children and adolescents presenting to paediatric cardiology clinic following COVID-19 infection that did not require hospitalisation, including a majority with symptoms of Long COVID-19, 79% of the total sample had a normal electrocardiogram. In those with an abnormal electrocardiographic result, 10/17 (59%) demonstrated an abnormality of borderline significance and 7/17 (41%) had a more concerning result, although none of these subjects had abnormal ventricular function or pericardial effusion on echocardiography. All follow-up electrocardiograms in the concerning group showed resolution of the abnormality except for one (concerning subject #1, Fig 1).

COVID-19 symptoms and severity

Based on the American Academy of Pediatrics guidelines,[21] this study population was split evenly between those with

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Table 2. Borderline electrocardiogram cases

Abnormal electrocardiogram subject	Age (year)	M/F	COVID-19 Severity	Persistent cardiovascular symptoms	Electrocardiogram abnormalities	Time to electrocardiogram resolution	Left ventricular ejection fraction (%)
1	16	M	Mild	CP, DOE, F	T wave inversion in inferior leads	6 days	55.5
2	15	F	Moderate	DOE, F	T wave inversion and flattening in inferior leads	No follow up electrocardiogram	60.6
3	16	F	Mild	DOE, F	Diffuse T wave flattening in limb leads	No follow up electrocardiogram	56.6
4	14	M	Moderate	CP, P, DOE	T wave flattening in lead III and lateral leads	94 days	56.4
5	15	F	Moderate	CP	Late peaking/biphasic T waves in lead III and lateral leads	76 days	56.3
6	15	M	Moderate	CP, P, F, DOE	T wave inversion in inferior leads	No follow up electrocardiogram	62.9
7	4	M	Moderate	CP, DOE	T wave inversion in inferior leads	No follow up electrocardiogram	64.6
8	18	M	Moderate	DOE, F	PR prolongation (216 ms)	No follow up electrocardiogram	65.8
9	16	M	Mild	P, D, CP, F, DOE	PR prolongation (210 ms)	No follow up electrocardiogram	60.0
10	10	M	Moderate	CP, F	PR prolongation (190 ms)	No resolution on 5 day follow up electrocardiogram	62.5

CP, chest pain; D, dizziness/syncope; DOE, dyspnoea on exertion; electrocardiograms, electrocardiogram; F, fatigue; F, female; LVEF, left ventricular ejection fraction; M, male; ms, milliseconds; P, palpitations.

Table 3. Concerning electrocardiograms cases

Abnormal electrocardiogram subject	Age (year)	M/F	COVID-19 severity	Persistent CV symptoms	Electrocardiogram abnormalities	Time to electrocardiogram resolution	Left ventricular ejection fraction (%)
1	17	M	Mild	None	Diffuse ST segment elevation with coved T waves in anterior precordial leads	Remains > 90 days	57.6
2	14	M	Moderate	None	Diffuse ST-T wave abnormality mimicking RBBB with ST doming in anterior precordial leads	29 days	72.4
3	17	F	Moderate	None	T wave inversion in inferior and mid-precordial leads	No follow up electrocardiogram	63.4
4	13	M	Moderate	P	Biphasic T waves in anterior and mid leads	15 days	62.6
5	13	F	Moderate	D	Infero-lateral T wave inversion with borderline ST segment depression	26 days	65.5
6	15	M	Mild	None	T wave inversion in inferior leads with T wave flattening in lateral leads	18 days	73.7
7	16	M	Moderate	CP	T wave inversion in inferior leads, diffuse T wave flattening in lateral precordial leads, and mild ST elevation in anterior leads	20 days	No Echo

CP, chest pain; CV, cardiovascular; D, dizziness/syncope; F, female; LVEF, left ventricular ejection fraction; M, male; P, palpitations; RBBB, right bundle branch block.

asymptomatic or mild COVID-19 versus moderate COVID-19 disease severity with nearly two-thirds having prolonged cardiovascular type symptoms of Long COVID-19.[18] Neither severity of acute COVID-19 disease nor symptoms of Long COVID-19 were significantly associated with a higher risk of electrocardiographic abnormality, although the sample size of these subgroups with an electrocardiographic abnormality is small and this should be confirmed in a larger study. While disease severity in

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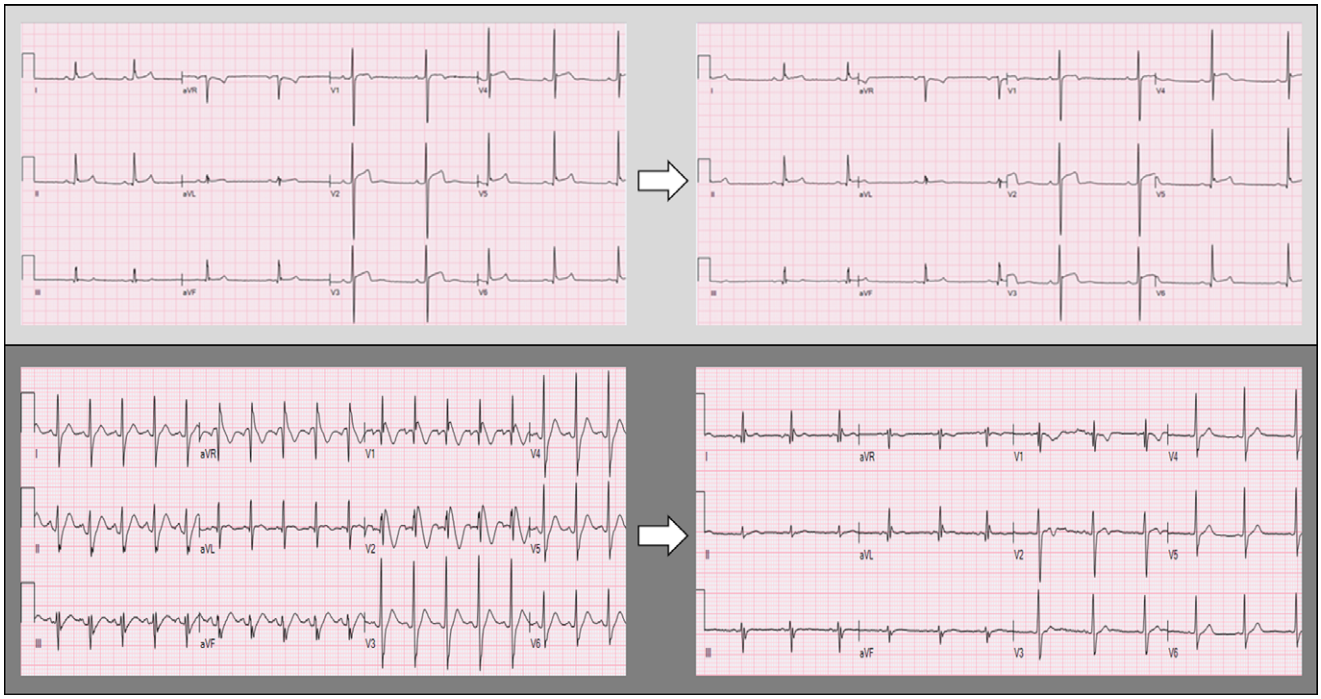

Figure 1. Concerning Subject 1 (top panels): Electrocardiographic findings in a 17-year-old male. Initial Post COVID-19 electrocardiogram (top left) demonstrating diffuse ST segment elevation; Coved T waves in anterior precordial leads. Persistent changes >60 days post COVID-19 (top right). Concerning Subject 2 (lower panels): Electrocardiographic findings in a 14-year-old male. Initial Post COVID-19 electrocardiogram (lower left) demonstrating Diffuse ST-T wave abnormality mimicking right bundle branch block with ST doming in anterior precordial lead. Complete resolution ~29 days post COVID-19 (lower right).

multisystem inflammatory syndrome in children is linked to cardiovascular involvement,[13,14] the pathogenesis of acute COVID-19 infection is quite different with significantly less of an inflammatory cascade than multi-system inflammatory syndrome in children.

Borderline electrocardiographic abnormalities following COVID-19 infection

Cardiac involvement is common in multi-system inflammatory syndrome in children including sinus bradycardia, varying degrees of heart block, repolarisation abnormalities, ventricular dysfunction and pericardial effusion.[10,11,13,24] In our cohort without multi-system inflammatory syndrome in children, electrocardiographic abnormalities were present in 21%, which may be higher than expected considering the limited prior evidence of cardiac involvement in children following acute COVID-19 infection. However, more than half of these abnormalities were considered of borderline significance. The abnormalities in the borderline group are mild and potentially normal variants and/or pre-existing minor abnormalities of no clinical consequence, given that most patients did not have pre-COVID-19 electrocardiogram studies. In a recent study by Gartenberg et al,[20] paediatric patients referred to cardiology clinic for abnormal electrocardiograms were noted to have benign variants or abnormalities with no significant clinic consequence and normal echocardiographic evaluation. In our study, there were 10 (12%) children with borderline electrocardiographic abnormalities (Table 2) all of whom had normal ventricular function and no pericardial effusion on the echocardiogram. The mild PR prolongation is a frequently observed normal variant in the adolescent population. The repolarisation abnormalities in this group may also represent physiologic variants in children.[25–27] In a study of children undergoing preparticipation sports physicals in Italy, only 2.5% of those with T wave inversions had an underlying cardiomyopathy.[28] The higher incidence of abnormal electrocardiographic findings in this cohort is at least partially related to increased screening and use of electrocardiogram for mild-moderate acute COVID-19 infections as per recommendations made by the American Academy of Pediatrics.[21] However, at least some of these repolarisation abnormalities appear to be a consequence of the illness as three subjects who had repeat electrocardiograms between 1 and 14 weeks showed normalisation of their repolarisation abnormality. While some of the abnormalities found in this borderline group appear related to the COVID-19 infection, they likely do not have any physiologic consequence.

Concerning electrocardiographic abnormalities following COVID-19 infection

Seven children (9%) had more concerning electrocardiographic findings that were all repolarisation abnormalities (Table 3) including: T-wave inversions in multiple leads, ST segment changes and one patient with diffuse ST segment elevations and coved T waves. Considering that >95% of children with T wave inversions do not have an underlying myocarditis,[28] these electrocardiographic findings are unlikely to represent myocarditis in most of this group. However, there appear to be a couple of these cases with significant electrocardiographic repolarisation abnormalities that normalised on follow-up electrocardiogram that are difficult to rule out as mild myocarditis (normal left ventricular ejection fraction on echocardiogram). Concerning subjects 1 and 2 (Table 3; Fig 1) had the most significant ST and T wave changes. The electrocardiographic pattern for subject 1 is likely reflective of an exaggerated but physiologic early repolarisation versus a slowly resolving inflammation of myocardial tissue that remains on a

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follow-up electrocardiogram 3 months after the initial study. The electrocardiographic changes on subject 2 prompted the clinician to draw troponin and NT-pro-BNP that were normal suggesting this abnormality is likely not related to myocarditis. Troponin and other cardiac labs were not drawn on other subjects in this cohort as their clinician had a low index of suspicion for significant cardiac involvement. Overall, while it is difficult to rule out subtle cardiac inflammation, there appear to be no cases in the entire cohort of myocarditis with significant myocardial or pericardial dysfunction.

Limitations

Our study is limited by its retrospective, single-centre design and relatively small sample size. In addition, it only includes patients who were seen in the cardiology clinic. Any patients with mild to moderate acute COVID-19 infection who had normal electrocardiograms and no cardiac symptoms were likely not referred as they could be cleared by their general physician resulting in a selection bias that inflates the frequency of electrocardiographic abnormality in this sample versus the general paediatric population. Echocardiograms were ordered by the clinical cardiologist during the clinic visit and were not deemed necessary on some patients. As this study is focused on electrocardiographic abnormalities, only left ventricular ejection fraction and the absence of pericardial effusion are reported in the abnormal electrocardiogram group to confirm that significant myocardial and/or pericardial dysfunction was absent. There were only two subjects who had clinically ordered ambulatory testing performed. Future prospective studies should include this testing. Cardiac MRI, the gold standard imaging modality to identify myocarditis, was not performed.

Conclusions

This study helps to continue to fill a knowledge gap in the paediatric literature by reporting frequency and types of electrocardiographic abnormalities in those with asymptomatic, mild or moderate COVID-19 infections seen in paediatric cardiology clinic. Fewer than 10% of these children and adolescents had concerning abnormalities on electrocardiogram (all during repolarisation) and nearly all resolved on follow-up testing with normal left ventricular ejection fraction and no pericardial effusion on echocardiography. Therefore, these abnormalities are unlikely to represent significant cardiac involvement although it is challenging to completely rule out mild myocardial involvement in a small number of cases. There were no significant patient characteristics or disease severity type that were associated with an abnormal electrocardiographic finding. Future larger studies without selected cohorts are needed to better inform clinical decision-making for children following COVID-19 infection.

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Conflict of interest. None.

Ethical standards. The study was approved by the Children's Mercy Kansas City Institutional Review Board.

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