Cardiac outcomes in children with multi-system inflammatory syndrome associated with SARS-CoV-2 at Great Ormond Street Hospital

Dr Filip Kucera, MD[1]
Dr Craig Laurence, MBChB, MMed[1]
Dr Jacob Simmonds, MD (Res), MB BChir, MRCPCH[1]
Dr Javier Gavela, MD[1]
Dr Tetyana Bodnar, MD[1]
Prof Paul Brogan, BSc, MBChB, MSc, PhD[2,3]
Dr Aparana Hoskote, [degrees][4]
PICU - Dr Sophie Skellett MA MB BChir FRCPCH[5]
ID - Dr Karyn Moshal MBChB, MRCP(UK) MRCPCH, DTM+H[6]
ID - Dr Alasdair Bamford MBBS FRCPCH DTM+H PhD[6]
Dr Sachin Khambadkone, [degrees][1]

[1] Department of Cardiology, Great Ormond Street Hospital NHS Foundation Trust
[2] Department of Rheumatology, Great Ormond Street Hospital NHS Foundation Trust
[3] Institute of Child Health, University College London
[4] Cardiac Intensive Care Unit, Great Ormond Street Hospital NHS Foundation Trust
[5] Paediatric Intensive Care Unit, Great Ormond Street Hospital NHS Foundation Trust
[6] Infectious Diseases department, Great Ormond Street Hospital NHS Foundation Trust

Abstract

Objective

We describe a cohort of children referred with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), and compare this cohort with a 2019 cohort of children with Kawasaki Disease (KD).

Methods

We conducted a retrospective cohort study of the 2019 and 2020 referrals to the inflammatory cardiology service at Great Ormond Street Hospital for Children NHS Foundation Trust. We compared cardiac and inflammatory parameters of a sub-section of the 2020 cohort who presented with reduced left ventricular ejection fraction (LVEF) with the remainder of the cohort, since this cardiac feature was common in our cohort of PIMS-TS.

Results

Referrals to our service significantly increased between February and June 2020 compared to 2019 (19.8/30 days vs 3.9/30 days). Frequency of coronary artery aneurysms (13.9% vs 14.9%; p = 1.000) or severe coronary artery aneurysms (7.6% vs 6.4%; p = 1.000) was similar between 2020 and 2019 respectively. The 2020 cohort was older (p < 0.001), more likely to be of Black, Asian or other minority ethnic group (p = 0.032), more likely to have required intensive care admission (48.75% vs 0%; p < 0.001) and inotropic support (27.5% vs 0%; p < 0.001). One child in the 2020 cohort required ventriculo-arterial extracorporeal membrane oxygenation (VA ECMO) support. Apart from one child who died from diffuse arterial thrombosis, all children in the 2020 cohort with reduced LVEF

Commented [PB1]: I did not raise this point in the last draft but seeing as you highlight this now we need to be very careful here

If numerically you are seeing a big increase in the absolute numbers of patients being referred, but with no significant difference in the percentage of coronary artery aneurysms, that means you are seeing a disease that is associated with exactly the same coronary aneurysm rate as Kawasaki disease: so although the rate of CAA is not increased the absolute numbers of patients with CAA is increased purely by arithmetic

This result will be much clearer if you look at the absolute numbers 2019 vs 2020

So I think we need to change our message/wording as suggested in my edits

Commented [PB2]: Check ive got this the right way round and modify if needed

Commented [AB3]: Need to be slightly careful with this conclusion as the pathway was to admit through Dolphin even if they didn't require ICU level care

Commented [AB4]: We should be careful with this patient. This patient (if it's the one I think it is 3082257) should not

permanent coronary sequelae, indicating that the majority of children with PIMS-TS are unlikely to encounter long-term cardiac morbidity.

Commented [PB6]: You may need to further modify this statement when you consider the absolute numbers of CAA and their severity in 2020 as compared to 2019

Section Head
You will be asked to choose the most relevant topic area for your article from the list of sections published in *Heart*.

Keywords

Supply up to 5 keywords from the list provided.

COVID-19; PIMS-TS; MIS-C; Kawasaki Disease; hyper-inflammatory syndrome

Commented [AB7]: You may want to put MIS-C as a keyword too

Key Questions

- *What is already known about this subject?*

Children who experience SARS-CoV-2 infection predominantly experience a milder course than adults, with lower mortality. A subset of children, however, present with a multi-system inflammatory illness with varying degrees of decreased left ventricular systolic function, valvulitis, or coronary artery dilatation. The incidence and severity of cardiac pathology, and its potential recovery is incompletely described.

- *What does this study add?*

We describe one of the largest single-centre paediatric cohorts with PIMS-TS. Our findings support the hypothesis that the presentation is a novel inflammatory syndrome that is distinct from KD. Additionally, our findings suggest that recovery of LVEF is rapid and complete even in children with severe clinical presentations, and that the incidence of severe coronary artery abnormalities is low.

- *How might this impact on clinical practice?*

Our findings suggest that appropriate supportive care combined with anti-inflammatory treatments was associated with cardiac recovery even in children severely affected by PIMS-TS. Long-term cardiac follow-up is unlikely to be required in the majority of cases.

Commented [AB8]: Can not say results in as we don't have RCT evidence that anti-inflammatories make a difference yet and this data is observational

Introduction

Although the majority of patients affected by novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) present with primarily respiratory pathology, cardiac injury was described in a minority in the initial phase of the pandemic[1]. Children predominantly experience a milder course than adults, with lower mortality.[2,3] (as reviewed by Alsaied et al.[4]) However, a subset of children present with a multi-system inflammatory illness with a variable degree of cardiac involvement.[3,5–7] The Royal College of Paediatrics and Child Health (RCPCH) provided a pragmatic interim case definition in May 2020[8]. This was closely followed by (slightly more restrictive) case definitions from the Centres for Disease Control (CDC) in the USA[9] and World Health Organization (WHO) [10]. The RCPCH refers to it as paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), whereas in the US it is labelled multisystem inflammatory syndrome in children (MIS-C). These case definitions are broad, and permit phenotypic overlap with many infectious and non-infectious hyperinflammatory conditions of childhood. The rapidity of spread between countries has precluded the development of internationally validated management guidelines. However, the majority of children have been treated with intravenous immunoglobulin (IVIg) with or without corticosteroids,[4] consistent with therapy for Kawasaki Disease (KD). Fortunately, most affected children have made excellent short term recovery[6,7,11].

From a cardiac perspective, there is overlap between the case definitions described above, KD[6] and acute myocardial injury without classical features of KD [7]. Although the term 'Kawasaki-like' has been used for these patients, there appear to be significant discrepancies between PIMS-TS and classical KD in terms of both clinical and laboratory features as well as demographics.[3,12,13] It is more likely that PIMS-TS represents a clinically distinct immune mediated inflammatory disorder, akin to that already described in some adults with cytokine storm.[14] Additionally, several authors have commented on coronary artery involvement, with a wide discrepancy in incidence[3,15–17]

Commented [AB9]: Have you seen this review?:

https://pubmed.ncbi.nlm.nih.gov/33166178/

would be useful to refer to this at the appropriate points in the paper – especially as it's likely to be sent to them for review – can cite as (reviewed in X)

Commented [AB10]: This is a ref from China – maybe better to include a UK relevant ref : https://pubmed.ncbi.nlm.nih.gov/32960186/ and https://pubmed.ncbi.nlm.nih.gov/32796006/

Deleted: [2]

Deleted: .

Deleted:

Deleted: [5–7].

Commented [AB12]: Needs a ref – maybe the US CDC document?

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7346765/

Deleted: [12,13].

Deleted: [14,15] A

Deleted: [15–17]

We describe a cohort of children referred to the paediatric inflammatory cardiology service at Great Ormond Street Hospital for Children NHS Foundation Trust (GOSH) from the end of February 2020. This service accepts referrals for KD and other inflammatory diseases of children associated with cardiac involvement. We have compared the clinical and laboratory features of this cohort, with particular emphasis on clinical characterisation based on proposed PIMS-TS definitions, SARS-CoV-2 exposure status, and cardiac involvement including rates of coronary artery abnormalities (CAA), with historic referrals to our service spanning comparable calendar months in 2019. We additionally present the first published data regarding follow-up of cardiac pathology in children affected by PIMS-TS.

Deleted: , both quantitatively and qualitatively,

Commented [AB17]: It's usual to make a statement about what is unique about this study in this para. Could mention that this is the first longer term clinical outcome data as I think that is a USP

METHODS

Commented [AB18]: Need a comment on study setting: GOSH is a large tertiary/quaternary children's hospital in London UK which receives referrals from a large catchment area from the London region and beyond.

Patients

This study includes all patients referred to the KD service at GOSH from 20/02/2020 until 20/06/2020 (the 2020 study cohort). GOSH is a large tertiary/quaternary children's hospital in London, UK, which receives referrals from a large catchment area from the London region and beyond. A proportion of the cohort of patients have been previously reported in case series,[3,16] but this is the first detailed analysis of acute and medium term cardiac outcomes. The starting point reflects the first referral of an inflammatory condition with atypical features after the first recognised case of COVID-19 in the UK (31/1/2020). Mean follow-up was 103 days. For the purposes of comparison to previous referrals, our institutional database was used to identify all new referrals to the service in 2019 (2019 cohort); prior to this date, KD referrals were not centralised and therefore not comparable to the 2020 study cohort. In both instances, in-patient and out-patient referrals were reviewed retrospectively; as such, formal ethical approval was waived (in accordance with institutional guidelines). Data included demographics, clinical features and radiological and laboratory investigations; datasets were limited due to the retrospective nature of the study, and numbers of patients with specified values (n) are given throughout. Because we have included all referrals to our inflammatory cardiology service

within the timeframe given, the 2020 cohort contains patients who did not meet criteria for a diagnosis of either PIMS-TS or KD. No patients from either cohort were excluded.

SARS-CoV-2 exposure status

Patients and family members were considered affected with COVID-19 if they had a positive test (PCR or serum IgG) for SARS-CoV-2 infection; in addition, family members who had not been tested were considered positive if they demonstrated strong clinical evidence of infection (pyrexia, new continuous cough, anosmia or alteration in sense of smell or taste).

Cardiac status

Echocardiograms were reviewed offline by a single observer (FK), and z-scores calculated based on the Boston dataset.[18] CAA was defined as a z-score of 2.5 or more, and severe CAA as z-score of 5 or more.[19] Left ventricular ejection fraction (LVEF) was determined by single-plane parasternal short axis M-Mode evaluation. In a subsequent analysis, the 2020 cohort was divided into two groups based on those with normal left ventricular systolic function (defined as a worst LVEF of ≥ 55%) versus those with reduced left ventricular systolic function (defined as worst LVEF < 55%), and compared in terms of clinical features, requirement for intensive care and invasive support, anti-inflammatory or disease modifying therapy, SARS-CoV-2 laboratory status and coronary artery pathology. Serial electrocardiograms were obtained. For the purpose of the QTc interval analysis, we used the Bazett formula. QTc interval exceeding 450 ms in males and 460 ms in females was considered as prolonged. Significant QTc prolongation was defined as QTc > 500ms.

Statistical methods

Statistical analysis was performed with SPSS Statistics 22 (IBM, Armonk, NY, USA). All continuous data was tested for normality with the Shapiro-Wilk test; data is given as mean (+/- S.D.) or median (IQR)

Commented [CL19]: May need to state one patient who was excluded if we remove the patient who died.

Commented [AB20]: Need a comment on children from the PIMS cohort having been previously reported in other publications – suggest something like: A proportion of the cohort of patients with a diagnosis of PIMS-TS have been previously reported in case series (give some examples – see below) but this is the first detailed analysis of acute and longer term cardiac outcomes.

https://pubmed.ncbi.nlm.nih.gov/32511692/
https://pubmed.ncbi.nlm.nih.gov/32653054/
https://pubmed.ncbi.nlm.nih.gov/32553126/
https://pubmed.ncbi.nlm.nih.gov/32609336/

Also need a statement that this will include children ultimately diagnosed as PIMS or KD or neither. The message is slightly confusing because the paper's inclusion criteria is patients referred to your service irrespective of ultimate diagnosis. The two cohorts are separated by date of referral only.

Deleted: COVID-19

Deleted: COVID

Deleted: *s*

accordingly. Two-group comparisons of means of normally distributed data was analysed with the unpaired Student's t-test, and non-normally distributed data with Mann-Whitney U test. Categorical data was analysed using Fisher's exact test. A p-value of < 0.05 was considered significant.

Commented [AB21]: Any correction for multiple comparisons? No problem if not but need to state.

RESULTS

A. General overview of the 2020 study cohort

1) Referral rates

In the four-month study period, 80 patients were referred to the service, at a rate of 19.8 patients/30 days. This represented a five-fold increase compared to 2019 (47 patients; 3.9 patients/30 days) (**Figure 1**). Since KD is a seasonal disease with peaks in winter and spring,[20] the rate of referral was also calculated for the three months with the highest rate in 2019, which at 19 referrals from January to March (6.3 referrals/30 days) represented a frequency of approximately one-third that of the 2020 cohort.

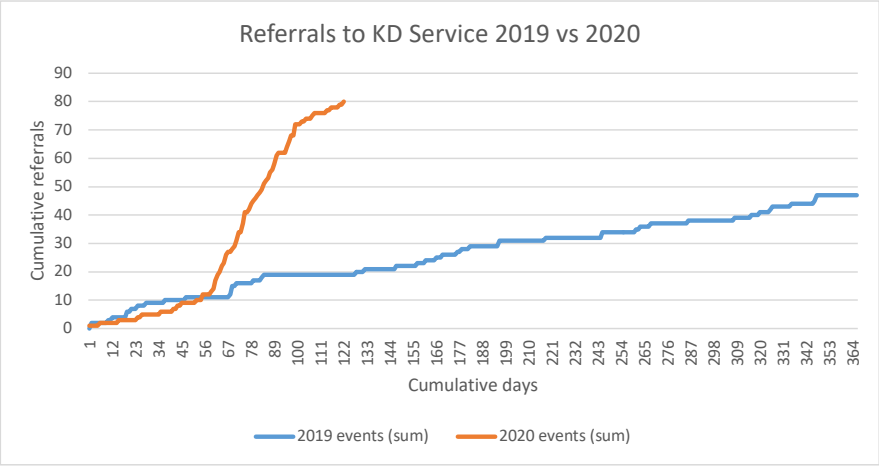


Figure 1: Comparison of number of referrals to KD service in 2019 vs 2020.

Commented [AB22]: Need to label the axes

2) *Baseline demographics*

The baseline demographics of the cohort are represented in **Table 1**. The 2020 study cohort was significantly older than the 2019 cohort, and more likely to be of Black, Asian or minority ethnic group (BAME) origin; there was no difference in sex distribution.

Parameter	2019	2020	P
Age in years	2.38 (0.98, 5.06)	9.07 (4.29, 12.00)	0.000
Sex (Male)	29/47 (61.7%)	54/80 (67.5%)	0.564
BAME	25/42 (59.5%)	60/76 (78.9%)	0.032

Table 1: Demographics and phenotype of the 2020 study cohort versus the 2019 cohort.

Commented [AB23]: Need to explain why the denominator is different for sex and ethnicity columns

Deleted: group

Deleted: referrals in 2019

3) *Clinical status*

Of the 2020 cohort, 52 (65%) required admission to hospital, with a median length of stay of 8 days. The median duration of fever was 7 days. Twenty-seven (34%) patients required supplemental oxygen, 19 (23.75%) required respiratory support (defined as high flow supplemental oxygen, continuous positive pressure or mechanical ventilation), 39 (48.75%) were admitted to intensive care, and 22 (27.5%) required inotropic support. One patient required V-A ECMO.

Although we were unable to capture the same degree of descriptive data with respect to hospital admissions for the 2019 cohort, none of them required intensive care admission, inotropic support, or ECMO support.

Deleted: None of the 2019 referrals required any of the above therapies. …

Additionally, a significant proportion of children in the 2020 cohort had severe symptoms not commonly experienced in patients with KD. These included encephalopathy in 14 (18%), and gastrointestinal symptoms in 57 (71%).

Deleted: Again, none of the 2019 cohort experienced these symptoms. …

4) Biochemical parameters

a) Cardiac biomarkers

Cardiac biomarkers were elevated in a significant proportion of the 2020 cohort **(Table 2)**. Peak N-terminal pro B-type natriuretic peptide (NT-proBNP) was over 1000 pg/ml in 34 of 52 (65.3%) patients tested, and exceeded 10000 pg/ml in 12 (23.1%) (median 2858 pg/ml). Troponin I was raised in 37 of 68 (54.4%), with 26 (38.2%) patients having a level over 100 ng/l, and 6 (8.8%) with a level over 1000 ng/l (median 21 ng/l).

Commented [AB26]: 2020?

Commented [AB27]: Need a comment that not all were tested. Also were these admission measurements or peak measurements?

b) Inflammatory markers and other parameters

C-reactive protein and D-Dimer were markedly elevated in the cohort, with a more modest overall increase in serum ferritin. The white blood count and neutrophil count were also significantly elevated, with only a modest increase in the platelet count and reduced lymphocytes. Renal and hepatic function was largely unimpaired (**Table 2**).

Commented [AB28]: This comtradicts the renal paper https://pubmed.ncbi.nlm.nih.gov/32553126/

Parameter	N	Mean/Median	SD/IQR
Cardiac Biomarkers			
NT-proBNP max (pg/ml)	52	2858	724 - 9639
Troponin I max (ng/l)	68	21	12 - 206.5
Other Laboratory parameters			
CRP max (mg/l)	76	248.5	131.8 - 300.0
Ferritin max (µg/l)	67	603	356 - 1557
D-Dimer (µg/l)	63	2595	1181 - 5603
WBC max (x10^9/l)	69	15.6	11.3 - 23.1

Commented [AB29]: Fibrinogen has turned out to be more of a correlate of inflammation and D-Dimer is proving less and less useful – it would be good to include if possible

Lymphocyte min (x10^9/l)	65	1.89	1.16 - 3.79
Neutrophil max (x10^9/l)	67	11.87	7.00 - 16.63
Platelet max (x10^9/l)	69	469	299 - 682
Hb at CRP max (g/l)*	**69**	100	±14
Na min (mmol/l)	58	136	134 - 138
ALT max (U/l)	62	74	38 - 145
Bilirubin max (µmol/l)	56	7	5 - 12
INR max	56	1.2	1.1 - 1.4
Creatinine max (µmol/l)	55	44	29 - 68
Urea max (mmol/l)	55	5.0	3.6 - 8.1
Albumin min (g/l)	61	26	23 - 30
Echocardiographic parameters			
LVEF% (minimum)	80	63.5	58 - 68
LVFS% (minimum)	79	34	30 - 37
LVIDd z-score (minimum)*	77	+0.48	± 1.79
LVIDs z-score (minimum)*	77	+0.70	± 1.93
TAPSE z-score (minimum)*	56	+0.51	± 3.07
LVEF% (at follow-up)*	61	67.6	± 6.3
LVFS% (at follow-up)*	61	37.4	± 4.7
LVIDd z-score (at follow-up)*	60	-0.24	± 1.46
LVIDs z-score (at follow-up)	60	-0.40	-1.28 - 0.60
TAPSE z-score (at follow-up)*	42	+0.27	± 1.85

Table 2: Objective parameters of the 2020 study cohort. The majority of the data was non-normally distributed. Parameters marked with an * were normally distributed. Key: SD – standard deviation; IQR – inter-quartile range; max – maximum; min – minimum; NT-proBNP – n terminal pro B-type natriuretic peptide; CRP – C-reactive protein; WBC – white blood cell count; Hb – serum haemoglobin; Na – serum sodium; ALT – alanine transferase; INR – International normalised ratio; LVEF – left ventricular ejection fraction; LVFS – left ventricular fractional shortening; LVIDd – left ventricular internal diameter in diastole; LVIDs – left ventricular internal diameter in systole; TAPSE – tricuspid annular plane systolic excursion

5) Assessment of cardiac function

a) General overview of the 2020 study cohort

The majority of the cohort did not demonstrate echocardiographic evidence of significant LV dilatation or systolic dysfunction. Only 13 patients (16.25%) had an LVEF < 55% at any time during the study period. Likewise, there was no significant evidence of LV dilatation, with only 16 patients

Commented [AB30]: A lot of them had low platelets – can you include plt min?

Commented [AB31]: Not clear why you've chosen this time point ? more consistent to use minimum?

Commented [AB32]: Cautious with this as the ALT ULN changes with age and I think most of them were abnormal at one point or other in their journey

Commented [AB33]: I think a significant proportion of them had AKI (according to the renal paper from GOSH). Reporting these summary statistics will miss that …

Commented [PB34]: I presume you mean the 2020 Cohort; so you need to specify this in the title and legend

Commented [AB35R34]: Agree needs clarification

Commented [PB36]: throughout this narrative you must specify if you are talking about the 2020 cohort because you also looked at 2019 cohort

Commented [AB37R36]: agree

Deleted: *in*

demonstrating a worst LV diastolic diameter (LVIDd) z-score of > 2, and only 6 patients > 3. The median LVIDd z-score was 1.79. RV systolic function was similarly preserved, with only 12 patients demonstrating a lowest TAPSE z-score of < -2, and only 9 patients < -3. The median TAPSE z-score for the cohort was 1.85. (**Table 2**).

Of the 13 patients with reduced LV systolic function, one died 6 days after admission from thrombotic complications. Due to the temporal association with the SARS-CoV-2 pandemic, this patient was referred to our service, and is therefore included in our cohort. However, on retrospective review, this patient did not fulfil criteria for a diagnosis of PIMS-TS or KD. The other 12 all demonstrated complete resolution of systolic dysfunction within 10 days (mean 5.25 days +/- 2.7). This coincided with a rapid reduction of CRP in all patients (median CRP fell from 333.5 to 15.5; p = .002) (**Figure 2**).

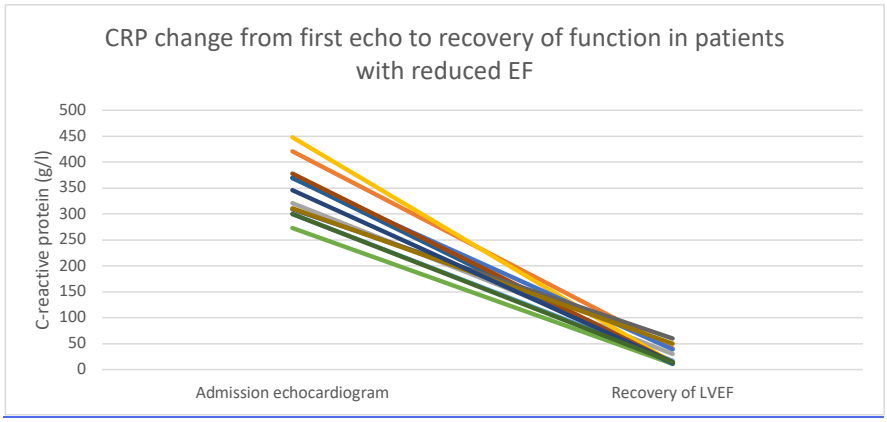
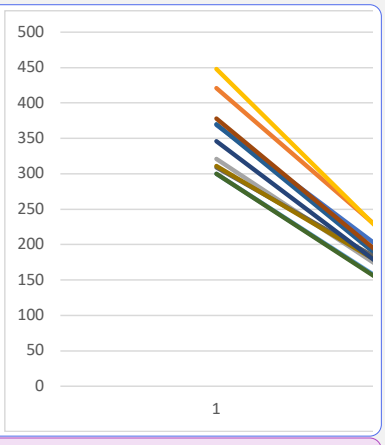


Figure 2: CRP change from first echocardiogram to recovery of function in patients with reduced LVEF

b) Comparison of patients with reduced versus normal LV systolic function

Commented [AB38]: This patient can't be included as a PIMS patient.



Deleted:

Commented [PB39]: need to label the y-axis in this graph and also provide a more informative X axis. If you leave as 1 and 2 on the x-axis you must define what this is in the legend

Commented [AB40R39]: Would it be worth having a similar graph for cardiac enzymes (perhaps in the supplementary data?)

Deleted: Change the data labels on X axis (something like Admission and FU rather than 1, 2?)¶

Commented [PB41]: suggest use bold font for the parameters with the p value that was statistically significant in all these tables as I have done in this table

Commented [AB42R41]: Would also include a 0 before the decimal point as is standard format

Parameter	LVEF < 55%	LVEF ≥ 55%	p
Demographics			
Age	9.02 (8.71, 11.75)	9.32 (2.57, 12.25)	0.423
Height	135.0 (93.0, 151.7)	135.0 (133.0, 148.0)	0.584
Weight	40.5 (30.1, 49)	31.4 (14.7, 45.6)	0.161
BMI	18.6 (16.52, 24.31)	17.65 (16.15, 20.51)	0.248
Clinical parameters consistent with KD			
Rash	9/13	40/65	0.757
Red Eyes	9/13	35/64	0.376
Oedema	4/13	20/63	1.000
Lymphadenopathy	3/13	15/63	1.000
Red lips/tongue	7/13	27/65	0.543
Cardiac biomarkers			
Raised NT-proBNP >1 000 pg/ml	**12/12 (100%)**	**22/40 (55%)**	**0.004**
Raised NT-proBNP >10 000 pg/ml	**9/12 (75%)**	**3/40 (7.5%)**	**0.000**
Raised troponin I > 34 ng/l	**13/13 (100%)**	**24/55 (43.6%)**	**0.000**
Raised troponin I > 100 ng/l	**11/13 (84.6%)**	**15/55 (27.3%)**	**0.000**
Raised troponin I > 1 000 ng/l	3/13 (23.0%)	3/55 (54.5%)	0.079
Inflammatory biomarkers			
Highest ferritin (ug/l)	**1529 (990, 4851)**	**545 (346, 1156)**	**0.010**
Highest D-Dimer (ug/l)	**5869 (2826, 8082)**	**2172 (976, 4581)**	**0.001**
Max CRP (mg/l)	**321 (300, 370)**	**203 (119, 287)**	**0.000**
Lowest albumin (g/l)	**24 (23, 26)**	**27 (23, 32)**	**0.048**
SARS-CoV-2 status			
PCR positive	**4/13**	**4/56**	**0.036**
Serology positive	7/12	29/50	1.000
Any positive test	9/13	30/58	0.358
Coronary artery dimensions			
Any coronary z-score > +2	2/13	9/66	1.000
Any coronary z-score > +2.5	2/13	9/66	1.000
Any coronary z-score > 5	1/13	5/66	1.000

Table 3: Comparison of demographics, clinical and objective parameters between children with reduced versus normal left ventricular systolic function. Key: LVEF – left ventricular ejection fraction; BMI – body mass index; KD – Kawasaki disease; NT-proBNP – N terminal pro B-type natriuretic peptide; CRP – C-reactive protein; SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus-2; PCR – polymerase chain reaction. Bold indicates statistically significant differences.

There was no statistically significant difference in the baseline demographics between patients with normal versus reduced LV systolic function in terms of age, height, weight or BMI. **(Table 3)**. Only one out of 15 patients of White ethnicity had LVEF <55% (7.7%), whereas 12 of 48 patients of BAME ethnicity (20%) were affected. The proportions were not statistically different (Pearson's Chi Square 1.684 [p = 0.194]).

Formatted: Line spacing: 1.5 lines

Formatted: Font: Not Bold

Deleted: Was there any difference in ethnicity? If not, that is an important finding too.

There was no statistically significant difference in the prevalence of clinic symptoms associated with KD; specifically rash, red eyes, oedema, lymphadenopathy, or red lips or tongue. With regards to symptoms not usually seen in KD, there was a statistically significant increase in the prevalence of abdominal symptoms in the cohort of children with reduced LV systolic function. Increases in the prevalence of neurologic symptoms and encephalopathy did not reach statistical significance.

There was no statistically significant difference between the groups in terms of duration of fever or length of hospital stay. However, there were significant differences in need for supplementary oxygen, need for PICU admission, need for respiratory support, and need for inotropic support.

Children in the group with reduced LV systolic function were more likely to have significantly elevated serum NT-proBNP and troponin I. Median peak NT-proBNP and troponin I in the group with reduced LV systolic function were significantly elevated compared to the latter group (**Table 3**). Children with reduced LV systolic function had evidence of more significant elevation of biochemical markers of systemic inflammatory response (CRP, D-dimer, ferritin) than their peers with normal LV systolic function. They also demonstrated more significant hypoalbuminaemia (**Table 3**).

Deleted: ¶

The cohort of children with reduced LV systolic function were more likely to have elevated white blood cell (and neutrophil counts as per age-related reference ranges). The median WBC and neutrophil counts were significantly elevated in the group with reduced LV systolic function compared to those with normal LV systolic function. The lymphocyte count, platelet count and haemoglobin level were not statistically significantly different between the two groups.

There was no statistically significant evidence of worse renal or hepatic dysfunction between the two groups. Although children with reduced LV systolic function had higher median urea values than children with normal function, neither group demonstrated evidence of significant renal dysfunction.

There was a higher proportion of positive SARS-CoV-2 PCR (from upper respiratory swab) in the group with reduced LV systolic function. However, there was no statistically significant difference between the groups in terms of the proportion of children with positive serum SARS-CoV-2 specific IgG, or the proportion who had any positive SARS-CoV-2 test (**Table 3**).

A higher proportion of children with reduced LV systolic function received corticosteroid therapy. However, there was no statistically significant difference in the proportion of children in either group receiving any other immunomodulating therapy. No children in the cohort received remdesivir (**Table 4**).

Therapy	LVEF < 55%	LVEF ≥ 55%	p
IVIG	13/13	53/64	0.194
High dose aspirin	2/13	21/66	0.326
Corticosteroid	**13/13**	**45/66**	**0.016**
Anakinra	2/13	4/66	0.255
Infliximab	0/13	2/66	1.000
Remdesivir	0	0	n/a

Table 4: Comparison of therapeutic strategies between group with reduced left ventricular systolic function and group with normal left ventricular systolic function. Key: LVEF – left ventricular ejection fraction; IVIG – intravenous immunoglobulin.

6) *Coronary artery abnormalities*

The absolute numbers of patients with CAA is shown in **Table 5**. The proportion of patients with coronary artery dilatation was 13.9% in the 2020 cohort in comparison to 19.1% in the 2019 group: a

Commented [AB43]: From upper respiratory sample? Need to state

Deleted: Interestingly, t

Deleted: incidence

Deleted: serology

Deleted: Children with

Deleted: were more likely to

Formatted: Line spacing: 1.5 lines

Commented [AB44]: It's quite confusing jumping from the comparisons within the 2020 group and the comparisons between the 2019 and 2020 group – suggest try to separate

result that did not reach statistical significance. Similar observations were made in the proportions of coronary artery aneurysms and severe coronary artery aneurysms.

Commented [AB45]: What proportion of the 2020 group were ultimately given a disagnosis of KD, how many a diagnosis of PIMS and how many neither diagnosis? I presume all of the 2019 cohort were given a diagnosis of KD?

Coronary z-score	2019	2020	P
> 2	9/47 (19.1%)	11/79 (13.9%)	0.458
≥ 2.5	7/47 (14.9%)	11/79 (13.9%)	1.000
≥ 5	3/47 (6.4%)	6/79 (7.6%)	1.000

Table 5: Comparison of coronary artery dilatation in the 2020 study cohort versus 2019 cohort

There was no significant difference in the prevalence of coronary artery dilatation, aneurysms or severe aneurysms between patients with reduced versus normal LV systolic function. (**Table 3**).

7) ECG changes

In the 2020 study cohort, 75 patients had at least one ECG performed. Arrhythmia was recorded only in 4 patients (3 patients had first degree AV block, 1 patient had junctional rhythm). 16 patients developed transient T wave flattening/inversions, which subsequently normalized. QTc interval prolongation occurred in 9 patients and was likely to be due to QTc prolonging drugs in 2 cases. In 2 children, the QTc interval was > 500ms. The QTc interval normalised in all 9 patients over the follow up period.

Discussion

Commented [AB46]: Usually start discussion with a statement of the main findings and the reason why they are unique. E.g.

This is the first published data on longer term outcomes of children referred to a tertiary cardiology service with a probable diagnosis of PIMS-TS. We have shown X, Y and Z.

We present unique medium-term cardiac follow up data on children referred to our inflammatory cardiac service during the SARS-CoV-2 pandemic. Our retrospective analyses confirmed our initial hypothesis that referrals to our inflammatory cardiac service at GOSH significantly increased from the end of February 2020 (**Figure 1**), a service which was designed in 2019 to predominantly to accept referrals with acute KD. We observed approximately three times as many referrals as the busiest months in 2019. There was no statistically significant difference in the frequency of CAA and severe

CAA, indicating a degree of phenotypic overlap with KD. However, the frequency of LV systolic dysfunction, inotropic support requirement, and other symptoms including encephalopathy and gastrointestinal symptoms, are not consistent with KD. PIMS-TS may therefore represent a novel inflammatory syndrome distinct from true KD. Additionally, there were several important differences between the two cohorts. The 2020 cohort were older, with a male and BAME predominance similar to the 2019 cohort. Objective data demonstrated significantly increased illness severity in the 2020 cohort, in terms of need for hospital and intensive care admission, ventilatory and inotropic support requirements, and inflammatory marker profile.

Thus, although children with PIMS-TS displayed significant phenotypic overlap with typical or atypical KD, we postulate that the presentation is sufficiently different to consider it a distinct clinical entity. The broad case definitions are unlikely to accurately distinguish PIMS-TS (or MIS-C) from KD, and we therefore emphasise the importance of considering the differential diagnosis of KD (and other infectious and non-infectious causes of hyperinflammation in the young) and an urgent need for improved case definition and diagnostic criteria for PIMS-TS/MIS-C. If KD is suspected clinically, this should be treated as per standard, contemporaneous, evidence-based, European guidance.[21]

Our data suggest that most children referred to our unit for assessment of PIMS-TS did not demonstrate significant systolic dysfunction. In the small proportion of patients with clinically significant LV systolic dysfunction, the mechanism of dysfunction was likely myocardial stunning from pro-inflammatory cytokine storm rather than direct viral myocarditis. This hypothesis is supported by our observation that all 12 surviving patients with LV dysfunction had rapid and complete normalization of their left ventricular systolic function, in parallel with resolution of systemic inflammation: echocardiographic normalization of left ventricular function coincided with a rapid reduction of biochemical markers of inflammation. This contrasts with our clinical experience and published literature regarding viral myocarditis,[22] which demonstrates longer recovery times as well

Deleted: , however this was not mirrored by a similar increase in CAA in our patients, strongly suggesting that the PIMS-TS cases referred represent a novel inflammatory syndrome distinct from KD. However, there was no statistically significant difference in the frequency of CAA in 2020, compared with 2019.

Deleted: ethnicity

Commented [AB48]: Confusing sentence

Deleted: presenting

Deleted: with

Deleted: important

as and non-universal recovery. Lastly, one of our patients underwent an endomyocardial biopsy, which failed to show evidence of lymphocytic myocarditis[23]. This is consistent with reports from adult literature,[24] and suggests cytokine-mediated hyperinflammatory myocardial depression rather than direct viral infection of myocardium.

Severe coronary artery dilatation, as opposed to mild coronary dilatation or perivascular echo-brightness, was overall less commonly observed than in other reports of PIMS-TS. This contrasts with recent UK literature,[16,17] which has suggested significantly higher incidence of coronary artery involvement. However, in both cases, authors did not adequately discriminate between genuine coronary artery aneurysms and coronary artery prominence or perivascular echo-brightness. This distinction is important because perivascular echo brightness[25] has been shown to be poorly discriminatory of KD, and – along with mild ectasia – may occur in other conditions such as juvenile idiopathic arthritis[26] and sickle cell disease.[27]

Our study has several important limitations, including its retrospective nature and relatively small numbers. In addition, the broad inclusion criteria and the opportunistic sampling method render the cohort prone to bias.

We have therefore demonstrated that the majority of patients with PIMS-TS are unlikely to encounter long-term cardiac sequelae, based on the low incidence of severe coronary artery pathology and complete recovery of myocardial dysfunction in even the most severely affected patients.

Acknowledgements

We would like to acknowledge the teams of physicians, nurses and nurse specialists, and allied health workers at GOSH who have responded tirelessly and selflessly to the SARS-CoV-2 pandemic. Without their expert care for these children, this paper would not have been possible. Collaboration between

Commented [AB49]: This should be in the results section too.

Commented [AB50]: Be careful with the wording as again these authors may be invited to peer review..

Commented [AB51]: Need a paragraph on study limitations:

Retrospective, small numbers, broad inclusion criteria, echo only rather than more detailed cardiac imaging, opportunistic sample, prone to bias etc

Just suggestions… take your pick or add

the cardiology, intensive care, rheumatology and infectious diseases was vital in the care of such complex patients, and in the creation and revision of this work.

Deleted: Need an acknowledgements section:¶
¶
Suggest PICU and general paeds teams specifically and then perhaps a broad acknowledgement of the clinicians/nurses and AHPs in the PIMS-TS MDT working group (list gets very long if you do everyone by name but there is a lead person for each and Karyn can give you that – I'm a fan of being as inclusive as possible in the acknowledgements section so no-one feels left out. ¶

References

1. Wang, D. *et al.* Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA* **323**, 1061 (2020).
2. Dong, Y. *et al.* Epidemiology of COVID-19 Among Children in China. *Pediatrics* e20200702 (2020) doi:10.1542/peds.2020-0702.
3. Whittaker, E. *et al.* Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. *JAMA* **324**, 259 (2020).
4. Alsaied, T. *et al.* Review of Cardiac Involvement in Multisystem Inflammatory Syndrome in Children. *Circulation* CIRCULATIONAHA.120.049836 (2020) doi:10.1161/CIRCULATIONAHA.120.049836.
5. Riphagen, S., Gomez, X., Gonzalez-Martinez, C., Wilkinson, N. & Theocharis, P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* **395**, 1607–1608 (2020).
6. Verdoni, L. *et al.* An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* **6736**, 1–8 (2020).
7. Belhadjer, Z. *et al.* Acute Heart Failure in Multisystem Inflammatory Syndrome in Children in the Context of Global SARS-CoV-2 Pandemic. *Circulation* **142**, 429–436 (2020).
8. RCPCH. *Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19*. (2020).
9. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). *CDC Heal. Alert Netw.* **14 May 202**, (2020).
10. Freedman, S. *et al.* Multisystem inflammatory syndrome in children and adolescents with COVID-19: Scientific Brief. *World Heal. Organ.* 1–3 (2020).
11. Toubiana, J. *et al.* Outbreak of Kawasaki disease in children during COVID-19 pandemic: a prospective observational study in Paris, France. 1–21 (2020) doi:10.1101/2020.05.10.20097394.
12. Shekerdemian, L. S. *et al.* Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. *JAMA Pediatr.* **2019**, 1–6 (2020).
13. Shulman, S. T. Pediatric Coronavirus Disease-2019–Associated Multisystem Inflammatory Syndrome. *J. Pediatric Infect. Dis. Soc.* 2019–2020 (2020) doi:10.1093/jpids/piaa062.
14. Consiglio, C. R. *et al.* The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. *Cell* **183**, 968-981.e7 (2020).
15. Capone, C. A. *et al.* Characteristics, Cardiac Involvement, and Outcomes of Multisystem Inflammatory Disease of Childhood (MIS-C) Associated with SARS-CoV-2 Infection. *J. Pediatr.* 2–6 (2020) doi:10.1016/j.jpeds.2020.06.044.
16. Davies, P. *et al.* Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. *Lancet Child Adolesc. Heal.* **4**, 669–677 (2020).
17. Ramcharan, T. *et al.* Paediatric Inflammatory Multisystem Syndrome: Temporally Associated with SARS-CoV-2 (PIMS-TS): Cardiac Features, Management and Short-Term Outcomes at a UK Tertiary Paediatric Hospital. *Pediatr. Cardiol.* **2**, (2020).
18. McCrindle, B. W. *et al.* Coronary Artery Involvement in Children With Kawasaki Disease. *Circulation* **116**, 174–179 (2007).

19. McCrindle, B. W. *et al.* Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. *Circulation* **135**, e927–e999 (2017).
20. Burns, J. C. *et al.* Seasonality of Kawasaki Disease: A Global Perspective. *PLoS One* **8**, e74529 (2013).
21. de Graeff, N. *et al.* European consensus-based recommendations for the diagnosis and treatment of Kawasaki disease – the SHARE initiative. *Rheumatology* **58**, 672–682 (2019).
22. Canter, C. E. & Simpson, K. E. Diagnosis and Treatment of Myocarditis in Children in the Current Era. *Circulation* **129**, 115–128 (2014).
23. Laurence, C. *et al.* Endomyocardial Biopsy in a Pediatric Patient With Cardiac Manifestations of COVID-19. *Circ. Hear. Fail.* **13**, (2020).
24. Peretto, G., Sala, S. & Caforio, A. L. P. Acute myocardial injury, MINOCA, or myocarditis? Improving characterization of coronavirus-associated myocardial involvement. *Eur. Heart J.* 1–2 (2020) doi:10.1093/eurheartj/ehaa396.
25. Yu, J. J. *et al.* Perivascular Brightness of Coronary Arteries in Kawasaki Disease. *J. Pediatr.* **159**, 454-457.e1 (2011).
26. Binstadt, B. A. Coronary Artery Dilation Among Patients Presenting With Systemic-Onset Juvenile Idiopathic Arthritis. *Pediatrics* **116**, e89–e93 (2005).
27. Nicholson, G. T. *et al.* Coronary Artery Dilation in Sickle Cell Disease. *J. Pediatr.* **159**, 789-794.e2 (2011).