Clinical, laboratory and echocardiographic parameters suggestive of multi-system inflammatory syndrome in children at a tertiary hospital in South Africa

V Mammen,[1] FCPaed (SA), Cert Cardio (SA) Paeds; **K Thandrayen,**[2] FCPaed (SA), Cert Endocrine (SA) Paeds, PhD; **A Alharm,**[1] FCPaed (SA), Cert Cardio (SA) Paeds; **T David**[1], FCPaed (SA), Cert Cardio (SA) Paeds; **M Monareng,**[1] FCPaed (SA); Cert Cardio (SA) Paeds; **P Raphulu,**[1], FCPaed (SA), Cert Cardio (SA) Paeds; **W Sethomo,**[1] FCPaed (SA), Cert Cardio (SA) Paeds; **A Cilliers**,[1] FCPaed (SA)

[1] *Division of Paediatric Cardiology, Department of Paediatrics, Chris Hani Baragwanath Academic Hospital, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[2] *Division of Paediatric Endocrinology, Department of Paediatrics, Chris Hani Baragwanath Academic Hospital, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*

Corresponding author: *V Mammen (vijay.mammen@wits.ac.za)*

Background. Worldwide studies have described features and outcomes of multi-system inflammatory syndrome in children (MIS-C) to assist with the diagnosis and guide medical management, with few studies emanating from Africa.
Objective. To describe the clinical, laboratory and echocardiographic parameters suggestive of MIS-C.
Methods. The paediatric cardiology database identified all patients referred with suspected MIS-C at Chris Hani Baragwanath Academic Hospital (CHBAH), from 1 March 2020 until 31 December 2021. Patients were classified as 'MIS-C likely' or 'MIS-C unlikely' based on the 2020 Centers for Disease Control and Prevention (CDC) criteria for MIS-C.
Results. A total of 101 patients were analysed, with 60 in the 'MIS-C likely' group and 41 patients in the 'MIS-C unlikely' group. The significant clinical features differentiating between the 'MIS-C likely' and the 'MIS-C unlikely' groups were the presence of documented fever (p=0.018) and eye changes (p<0.001). Patients with a positive COVID antibody test that were referred for suspected MIS-C were most likely to present with MIS-C (p< 0.001). Laboratory parameters suggesting a greater likelihood of patients having MIS-C was a high troponin T (p=0.018) and a high C-reactive protein (CRP) (p=0.019). The main echocardiographic feature associated with a MIS-C diagnosis was left ventricular (LV) dysfunction at presentation (p=0.023). In the adjusted logistic regression analyses, the contributory findings associated with a greater risk of having MIS-C were fever and LV dysfunction (OR 6.52 (95% CI 2.31 - 18.45); p<0.001 and 6.70 (95% confidence interval (CI) 1.61 - 28.59); p =0.009, respectively).
Conclusion. Clinical features such as documented fever and eye changes together with a positive COVID antibody test suggest that patients had MIS-C in our setting. Laboratory findings of elevated CRP and troponin T in patients with suspected MIS-C assisted with the diagnosis. Patients with suspected MIS-C with LV dysfunction at presentation were more likely to have MIS-C.

Keywords. COVID-19; multi-system inflammatory syndrome in children; MIS-C; echocardiography in MIS-C.

S Afr J Child Health 2025;19(1):e1759. https://doi.org/10.7196/SAJCH.2025.v19i1.1759

The coronavirus disease of 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-COV-2), emerged towards the end of 2019 and was declared a global pandemic on 11 March 2020 by the World Health Organization (WHO).[1,2]

Unlike other viruses that cause significant respiratory symptoms, COVID-19 infection is generally associated with mild respiratory symptoms in children compared with adult patients.[3,4] However, COVID-19 is associated with a more severe disease named multi-system inflammatory syndrome in children (MIS-C), with some possibly having a poorer outcome.[5-7]

MIS-C was first described in the UK, in mid-April 2020, in a cluster of children with hyperinflammatory shock and features of typical and atypical Kawasaki disease, as well as toxic shock syndrome.[7] Other studies, including a study from Western Cape, South Africa (SA) in 2020, subsequently reported similar findings.[8,9]

Many researchers have attempted to describe features and outcomes of MIS-C to assist with the identification and guide the medical management of MIS-C, as this disease can have nonspecific findings and multi-system involvement mimicking other conditions.[7,10-12] There are also studies that have described the comorbidities, symptoms, biomarkers, echocardiographic features and outcomes in MIS-C.[10,11] However, few studies originate from Africa.

Recently, two studies from Egypt and Kenya, as well as two SA studies (in the Western Cape and KwaZulu-Natal (KZN) provinces) have published their findings;, highlighting a need for more local studies in similar resource settings.[13-16]

The present study aims to describe and compare the clinical, laboratory and echocardiographic parameters in patients referred for suspected MIS-C at a large tertiary referral centre in Johannesburg, SA.

Methods

We conducted a retrospective, descriptive study using the paediatric cardiology database at Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto, Johannesburg, Gauteng, to identify all patients with suspected or confirmed MIS-C that were referred to the paediatric cardiology unit from 1 March 2020 until 31 December 2021. Paper-based patient files were used to extract additional data.

Patients who were referred for echocardiography for suspected or confirmed MIS-C were further classified into 'MIS-C likely' or 'MIS-C unlikely' by a single paediatric cardiologist (after reviewing all the information relevant to each patient) and this was confirmed by a second paediatric cardiologist. The classification was based on the 2020 Centers for Disease Control and Prevention (CDC) criteria for MIS-C.[17] We used the label 'MIS-C likely' as there were cases where not all the information was available to fully confirm the diagnosis of MIS-C, based on the CDC criteria. During the pandemic, especially the early period, COVID-19 antibody tests were not available. Therefore, patients who matched all criteria for MIS-C with no other plausible diagnosis other than MIS-C and had no confirmatory evidence of MIS-C were included in the 'MIS-C likely' group. The 2020 CDC criteria[17] for MIS-C diagnosis may be accessed here (http://coding.samedical.org/file/2337).

Not all patients had a temperature recorded in their admission files. Therefore, documented fever for any duration was regarded as a positive finding for the purposes of the present study. Gastrointestinal complaints were broad and included signs and symptoms such as vomiting, diarrhoea, abdominal pain or abdominal tenderness. Skin and mucous membrane changes included polymorphous rash, fissured lips or strawberry tongue, similar to Kawasaki disease. Respiratory complaints included signs and symptoms such as cough, shortness of breath, crackles or signs of respiratory distress. Neurological signs and symptoms encompassed seizures, headaches, weakness or Guillain-Barre syndrome and neck stiffness or meningitis. Eye changes were mainly bilateral bulbar conjunctival injection, like those seen in Kawasaki disease.

The initial blood investigations performed at admission (or closest to admission) were analysed and included the following tests: full blood count (FBC); kidney function test; liver function test (LFT); inflammatory markers (C-reactive protein (CRP) and erythrocyte sedimentation test (ESR)), COVID tests (COVID polymerase chain reaction (PCR) nasopharyngeal swab and COVID antibodies), cardiac enzymes (creatinine kinase-myoglobin binding protein (CK-MB), troponin T (trop-T) and pro-*B*-type natriuretic peptide (Pro-BNP), *D*-Dimer, international normalised ratio (INR), lactate dehydrogenase (LDH) and ferritin.

The echocardiography assessments were done at initial presentation and at any follow-up visit. Coronary arteries were considered dilated if any of the origins of the right coronary artery, left coronary artery, left anterior descending or circumflex artery had a *Z*-score greater than +2.5 (Parameterz website, http://www.parameterz.com/sites/coronary-arteries).[18] Left ventricular (LV) function was abnormal if the ejection fraction was less than 55%. Patients who had coronary artery dilatation (CAD) and left ventricular dysfunction at any follow-up visit, either at 2 - 6 weeks or after 6 weeks were documented.

Statistical analysis was done using TIBCO Statistica (StatSoft, GmbH) and STATA (version 18) (StataCorp., USA). Chi-square or Fisher's exact test were used for categorical variables and Student's *t*-test was used for normally distributed continuous variables. Appropriate non-parametric tests using the Mann-Whitney *U*-test were conducted on continuous variables that were not normally distributed. The 95% confidence intervals were reported for parameters of interest and two-sided *p*-values <0.05 were considered statistically significant. Univariate and adjusted multiple logistic regression analysis were performed to assess contributory factors for the 'MIS-C likely' group. Significant variables on univariate logistic regression with a *p*-value <0.1 were analysed in the adjusted regression analysis.

Results

A total of 102 patients were referred to the Paediatric Cardiology unit for suspected MIS-C during the study period. One patient was excluded from the analysis because there were limited data available from the patient's file. Therefore, 101 patients were analysed, with 60 in the 'MIS-C likely' group and 41 patients in the 'MIS-C unlikely' group.

Age

The median (interquartile range (IQR)) age in the 'MIS-C likely' group was 7.0 (2 - 10) years. There were 42 (70%) males and 18 (30%) females (male: female ratio 2.3:1). The median (IQR) age in the 'MIS-C unlikely' group was 6.0 (1 - 11) years. There were 31 (76%) males and 10 (24%) females (male:female ratio 3.1:1).

There were no significant differences in the mean or median ages in the two groups (p=0.956 and p=0.915, respectively) and between the males and females in the two groups (p=0.536).

COVID status and clinical signs (Table 1)

Patients with a positive COVID antibody test referred for suspected MIS-C were most likely to present with MIS-C (p<0.001). Among the patients who had a COVID PCR nasopharyngeal swab in the 'MIS-C likely' group, 39% were positive. Ninety percent of the patients who had COVID antibodies done, were positive in the 'MIS-C likely' group. Forty-three patients (72%) who had either COVID PCR nasopharyngeal swab or antibody tests done, were positive in the 'MIS-C likely' group. Seven patients (12%) who had both COVID PCR nasopharyngeal swab and COVID antibodies done, were positive in the 'MIS-C likely' group.

Seventeen patients (28%) in the 'MIS-C likely' group that did fit all the criteria for MIS-C but did not have a COVID antibody test done during admission, were analysed in the 'MIS-C likely' group. During the initial part of the pandemic, COVID antibodies were not available in our setting.

The main differentiating significant clinical features between the 'MIS-C likely' and the 'MIS-C unlikely' groups were the presence of documented fever (p=0.018) and eye changes (p<0.001). Gastrointestinal signs and symptoms (54%) and respiratory signs and symptoms (56%) were common in 'MIS-C likely' patients.

Six (10%) of the 'MIS-C likely' patients presented with signs of suspected appendicitis, with 4 patients undergoing laparotomies with negative findings. The remaining 2 patients were diagnosed as MIS-C and managed accordingly.

Echocardiography

'MIS-C likely' group

The main echocardiographic feature suggesting the diagnosis of MIS-C was LV dysfunction at presentation (p=0.023) (Table 1). Two patients (17%) continued to have LV dysfunction 6 weeks after presentation – only one of them was documented to receive intravenous immunoglobulin (IVIG). One patient who had normal LV function at presentation developed LV dysfunction

on follow-up echocardiography. Of the 11 'MIS-C likely' patients with LV dysfunction, 7 patients had an ejection fraction (EF) between 40 and 55%, 2 had EFs between 30 and 40% and 3 had EFs below 30%.

Although the 'MIS-C likely' group had more cases of CAD at presentation (44% in the 'MIS-C likely' group and 11% in the 'MIS-C unlikely' group), the difference was not statistically significant (p=0.113).

Twenty-six (43%) of the 60 patients in the 'MIS-C likely' group had CAD on initial presentation. Twenty-four (93%; n/N=24/26) of these 26 patients received 2 g/kg of IVIG after admission on suspicion of having MIS-C. Fifteen of these 26 patients (58%; n/N=15/26) continued to have CAD 6 weeks after presentation.

Six (10%; n/N=6/60) of the 60 patients in the 'MIS-C likely' group with no CAD on initial presentation were found to have CAD on follow-up echocardiographic studies 2 to 6 weeks after presentation. Five of the 6 patients were confirmed to have received IVIG at initial presentation.

'MIS-C unlikely' group

Eleven (29%; n/N=11/41) of the 41 patients had CAD, but the COVID PCR test and the COVID antibody test were both negative. The patients had the following problems: 3 patients with cardiac diseases (1 rheumatic heart disease, 1 pulmonary stenosis, 1 trisomy 21 with atrioventricular septal defect), 2 patients with malignancies (1 leukaemia, 1 lymphoma), 2 patients with systemic lupus erythematosus, 1 patient with an acute abdomen, 1 patient with bronchopneumonia, 1 patient with nephrotic syndrome and 1 patient with neonatal sepsis (Supplementary Table 1; http://coding.samedical.org/file/2336).

Laboratory parameters (Table 2)

Laboratory parameters suggestive of likely MIS-C were: an abnormal platelet count (p=0.045) (64% had thrombocytosis); an abnormal sodium (p=0.010) (85% had hyponatraemia); high urea (p=0.030); abnormal albumin (p=0.028) (95% had hypoalbuminaemia); high INR (p=0.004); high trop-T (p=0.018); and high CRP levels (p=0.019). A small number of pro-BNP tests were done in ICU in our setting. Therefore, a meaningful comparison could not be done between the groups.

Comorbidities

Twelve (20%) of the 'MIS-C likely' patients had a variety of comorbidities, including cardiac disease (7%), renal disease (5%) and malignancies (3%).

Intensive care and inotropes

Eleven (18%) of the 'MIS-C likely' patients required intensive care unit (ICU) admission and ventilation. Twelve (20%) of the 'MIS-C-likely' patients required inotropes. One patient received inotropes in the paediatric high care ward under the care of paediatricians owing to a lack of ICU beds. Most patients who were not on ventilatory support or inotropes were provided with treatment for shock and haemodynamic instability, as well as immunoglobulins in the paediatric high-care setting.

Mortality

Two patients (3.3%) demised in the 'MIS-C likely' group. A 5-year-old male who had suspected sepsis with shock received inotropes but demised soon after admission. The other patient was a 2-month-old female who also presented in shock, with a disseminated intravascular coagulopathy and gangrene of the hands and feet.

Contributory findings associated with MIS-C

In Table 3, the contributory factors in unadjusted logistics regression for 'MIS-C likely' were fever, eye changes, LV dysfunction and an elevated CRP level. In the adjusted logistic regression analyses, the patients with fever and LV dysfunction were 6 times more likely to have MIS-C (odds ratio (OR) 6.52 (95% confidence interval (CI) 2.31 - 18.45), p<0.001; and OR 6.70 (95% CI 1.61 - 28.59); p=0.009, respectively).

Table 1. COVID-19 status, HIV status, clinical features, echocardiography and treatment in the 'MIS-C likely' and 'MIS-C unlikely' groups

Variable	'MIS-C likely' (N=60), n/N (%)	'MIS-C unlikely' (N=41), n/N (%)	p-value
Positive COVID PCR nasopharyngeal swab	23/59 (39)	15/41 (37)	0.81
Positive COVID Ab	27/30 (90)	1/12 (8)	<0.001
Positive HIV status	2/52 (4)	0/32 (0)	0.26
Fever	38/57 (67)	17/40 (43)	0.02
Gastrointestinal signs and symptoms	32/59 (54)	15/41 (37)	0.08
Skin and mucous membranes changes	19/59 (32)	13/41 (32)	0.96
Respiratory signs and symptoms	33/59 (56)	16/41 (39)	0.10
Neurological signs and symptoms	19/59 (32)	10/41 (24)	0.40
Eye changes	18/59 (31)	1/41 (2)	<0.001
CAD	26/59 (44)	11/39 (28)	0.11
LV dysfunction	12/54 (22)	2/39 (5)	0.02
CAD later at any follow-up visit	21/53 (40)	8/30 (27)	0.23
LV dysfunction later at any follow-up visit	3/34 (9)	2/21 (10)	0.93
IVIG	49/55 (89)	12/33 (36)	<0.001
Steroids	18/55 (33)	7/33 (21)	0.25
Aspirin	43/50 (86)	11/28 (39)	<0.001

PCR = polymerase chain reaction; Ab = antibodies; CAD = coronary artery dilatation; LV = left ventricular; IVIG = intravenous immunoglobulin.

Table 2. Laboratory results comparing the 'MIS-C likely' and the 'MIS-C unlikely' groups

Category	Parameter (normal values)	'MIS-C likely', median (IQR)		'MIS-C unlikely', median (IQR)		*p*-value
Haematology	WCC (3.9 - 10.2), ×109/L	60	11.0 (8.6 - 18.1)	41	9.8 (7.1 - 13.6)	0.05
	Hb (10.5 - 13.7), g/dL	60	11.0 (9.8 - 12.6)	41	10.9 (8.9 - 12.9)	0.92
	HCT (0.34 - 0.48), L/L	58	0.3 (0.3 - 0.4)	41	0.4 (0.3 - 0.4)	0.72
	MCV (70 - 86), fL	60	77.3 (77.4 - 85.9)	41	83.7 (78.6 - 86.4)	0.05
	PLT (180 - 440), ×109/L	60	264.5 (179.0 - 334.5)	41	361.0 (218.0 - 450.0)	0.05
Kidney function, mmol/L	Na+ (136 - 145), mmol/L	59	136.0 (130.0 - 139.0)	41	139.0 (134.0 - 141.0)	0.01
	K+ (3.4 - 4.7), mmol/L	58	4.5 (4.1 - 4.9)	40	4.4 (3.9- 5.1)	0.76
	Cl– (98 - 107), mmol/L	59	96.0 (91.0 - 100.0)	41	98.0 (94.0 - 102.0)	0.09
	HCO3– (23 - 29), mmol/L	58	16.0 (12.0 - 20.0)	39	15.0 (12.0 - 20.0)	0.80
	Urea (1.8 - 5.7), mmol/L	59	5.0 (3.5 - 10.1)	41	3.4 (2.7 - 5.1)	0.03
	Creatinine (2 - 57), mmol/L	59	45.0 (28.0 - 77.0)	41	36.0 (28.0 - 65.0)	0.68
Liver function	Total protein (57 - 89), g/L	51	63.0 (56.0- 69.0)	30	62.0 (57.0 - 71.0)	0.45
	Albumin (32 - 47), g/L	53	33.0 (27.0- 37.0)	31	35.0 (31.0 - 43.0)	0.03
	Total bilirubin (5 - 21), umol/L	51	6.0 (4.0 - 9.0)	31	5.0 (4.0 - 7.0)	0.14
	Conjugated bilirubin (0 - 5), umol/L	51	3.0 (2.0 - 6.0)	29	3.0 (2.0 - 4.0)	0.05
	ALT (5 - 20), U/L	55	34.0 (17.0 - 79.0)	32	20.5 (13.5 - 44.5)	0.09
	AST (0 - 37), U/L	53	47.0 (33.0- 115.0)	32	39.0 (25.5 - 74.5)	0.13
	ALP (69 - 325), U/L	52	165.5 (135.0 - 208.5)	32	211.0 (115.5 - 324.0)	0.06
	GGT (3 - 22), U/L	52	24.5 (18.0 - 56.0)	32	28.0 (22.0 - 54.5)	0.22
Cardiac enzymes	CK-MB (0 - 4.8), ug/L	38	3.9 (1.8 - 8.2)	24	2.0 (1.2 - 10.9)	0.20
	Trop-T (0 - 14), (ng/L)	50	28.5 (7.0 - 70.5)	28	10.5 (5.0 - 28.0)	0.02
	Pro-BNP (0 - 300), ng/L	17	2074.0 (393.0- 18616.0)	11	788.0 (124.0 - 1232.0)	0.11
Inflammatory markers	CRP (0 - 10), mg/L	57	135.0 (34.0 - 239.0)	35	53.0 (4.0 - 172.0)	0.02
	ESR (0 - 10), mm/hr	11	72.0 (34.0 - 109.0)	6	14.0 (7.0 - 120.0)	0.35
Other	INR (0.9 - 1.1)	44	1.3 (1.1 - 1.4)	24	1.1 (1.0 - 1.2)	0.004
	D-dimers (0 - 0.25), mg/L	52	2.1 (1.5 - 4.2)	26	2.1 (0.8 - 10.7)	0.78
	LDH (180 - 430), U/L	38	478.5 (407.0 - 768.0)	23	460.0 (297.0 - 739.0)	0.56
	Fibrinogen (1.7 - 4.2), g/L	29	5.9 (3.5 - 7.5)	13	3.7 (2.8 - 4.9)	0.16
	Ferritin (14 - 124), ug/L	45	320.0 (185.0 - 718.0)	25	328.0 (80.0 - 591.0)	0.39

WCC = white cell count; Hb = haemoglobin; HCT = haematocrit; MCV = mean cell volume; PLT = platelets; Na+ = sodium; K+ = potassium; Cl– = chloride; HCO3– = bicarbonate; ALT = alanine transaminase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase; CK-MB = creatinine kinase myoglobin-binding protein; Trop-T = troponin T; Pro-BNP = N-terminal pro-B-type natriuretic peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; INR = international normalised ratio; LDH = lactate dehydrogenase.

Table 3. Contributory findings associated with MIS-C

Risk factor	uOR (95% CI)	*p*-value	aOR (95% CI), *N*=82	*p*-value	aOR (95% CI), *N*=90	*p*-value
Fever, *n*=97	4.23 (1.79 - 9.98)	0	5.58 (1.86 - 16.7)	0.002	6.52 (2.31 - 18.45)	<0.000
Eye changes, *n*=100	3.33 (1.10 - 10.11)	0.03	2.46 (0.71 - 8.52)	0.16	-	-
LV dysfunction, *n*=93	2.99 (0.86 - 10.33)	0.08	4.21 (0.82 - 21.6)	0.08	6.70 (1.61 - 28.59)	0.009
An elevated CRP level, *n*=92	3.02 (0.96 - 9.57)	0.06	1.59 (0.39 - 6.55)	0.52	-	-

uOR = unadjusted odds ratio; CI = confidence interval; aOR = adjusted odds ratio; LV = left ventricular; CRP = C-reactive protein.

Discussion

The present study aimed to describe clinical, laboratory and echocardiographic parameters to assist in the diagnosis of MIS-C in children at a tertiary hospital, in SA. We showed that the clinical features of MIS-C of documented fever and eye changes, together with a positive COVID antibody test, suggest that patients had MIS-C in our setting. Laboratory findings of high CRP and trop-T levels assisted with the diagnosis. Patients presenting with LV dysfunction were 6 times more likely to have MIS-C.

Regarding age of presentation of MIS-C, international studies showed a higher probability of MIS-C in older children, while African (including SA) data showed a slightly younger age of presentation. A European study comprising 35 children had shown an older age at presentation of 10 years (range 2 - 16 years).[11] A systematic review also showed a median (IQR) age of 9 (5.5 - 12.5) years.[19] Similarly, another large systematic review of 783 MIS-C cases showed a median (IQR) age of 8.6 (7 - 10) years.[20] In comparison, Egyptian[13], and Kenyan[14] studies reported much lower median (IQR) age values of 4 (1.25 - 10) years and 3.98 (1.71 - 7.44) years, respectively. Comparing the SA studies, the KZN study also found a lower mean (SD) age of 55 (45) months) while the Western Cape study found a median (IQR) age of 7.0 (3.6 - 9.9) years, similar to our study of a median (IQR) age of 7.0 (2 - 10) years.[15,16]

Male predominance in patients with MIS-C is a common theme in many studies. Two smaller studies done early in the COVID-19 pandemic also showed a male predominance of 63% and 70% respectively.[7,8] Similarly, a Spanish study assessing outcomes of children admitted to ICU showed a male predominance with 66.7%,[21] while a study in Turkey documented a male majority in their patients with MIS-C (57.7%; $p<0.001$).[22] This finding of male predominance in MIS-C patients was also reported in the Egyptian (53.3%), Kenyan (70%), a Western Cape study (52.9%), as well as in our study (70%).[13,14,16] Regarding age and gender, we found no significant difference between the 2 groups to help to identify 'MIS-C likely' patients.

Comorbidities in MIS-C patients were non-specific in various studies. Twenty percent of the 'MIS-C likely' patients in our study had a variety of comorbidities, including cardiac disease (7%), renal disease (5%) and malignancies (5%). In contrast, in a European study, Belhadjer *et al.*[11] showed a slightly higher percentage of patients with comorbidities, with 28% having a different profile such as being overweight (17%), having asthma (8.5%) and lupus (3%). A Turkish study reported underlying illnesses in 11.8% of their patients of whom 3.1% were immunocompromised from autoimmune diseases, 2.8% had neurometabolic diseases, 1.6% had respiratory diseases and 1.1% had cardiac disease.[22] The KZN study[15] reported comorbidities in 28% of children, with the majority having moderate acute malnutrition (10%) and obesity (7%).

More than two-thirds (72%) of patients in the 'MIS-C likely' group in our study had either COVID PCR nasopharyngeal swab or antibody tests that were positive. In contrast, 88% of patients tested positive for SARS-CoV-2 infection using either nasopharyngeal swab PCR or serology in a European study.[11] Another large systematic review reported a 59% positivity for SARS-CoV-2 infection using both serology and PCR.[20] The KZN study also showed a high percentage (93%) of laboratory evidence of SARS-CoV-2 infection.[15] The Western Cape study also showed high (91%) SARS CoV-2 antibody positivity test results.[16] This was similar to our study in the 'MIS-C likely' patients, with a significant finding of 90% antibody positivity in patients who had antibody testing.[16]

Fever and gastrointestinal signs and symptoms are a common theme in patients with MIS-C, including in our study.[7,11,19,20,23] Suspected appendicitis as a presenting feature is also described in the literature in MIS-C patients, with negative laparotomy findings.[11,15,16] In the present study, there was a higher percentage of respiratory symptoms (56%) in 'MIS-C likely' patients. Respiratory findings is not a common feature of MIS-C as reported in a large systematic review.[20] African studies, however, did show higher levels of respiratory involvement: 29.4% in the Western Cape study;[16] 64.4% in the Egyptian study;[13] and 41% in the KZN study.[15] Conjunctivitis is a major and common symptom in patients with MIS-C.[15,16] We found that documented fever and eye changes were useful to differentiate between 'MIS-C likely' and 'MIS-C unlikely' patients.

Laboratory parameters differed between the 'MIS-C likely' and 'MIS-C unlikely' groups, with significant differences in inflammatory markers (trop-T and CRP) and in other biochemical parameters such as platelets, sodium, urea, albumin and INR results. Similar findings were present in a systematic review with 17 patients with MIS-C, evidenced by a marked inflammatory state (with an elevated CRP and procalcitonin (PCT)), as well as liver dysfunction, acute kidney injury and coagulopathy.[19] Another systematic review[20] documented a high CRP in 94% of cases and a Spanish study[21] demonstrated higher levels of CRP, PCT and trop-T. Raised CRP and *D*-dimers were also noted in the SA studies.[15,16] The changes in the other biochemical parameters in our study may be related to the general condition of the patients with MIS-C with multi-system involvement, as evidenced by abnormal albumin levels in the KZN study,[15] and low albumin and sodium levels in the Western Cape study.[16] Markedly raised inflammatory markers, such as CRP and trop-T levels, are likely to help identify MIS-C patients, as seen in our study.

CAD (or aneurysms) can occur in 6 to 24% of critically ill MIS-C patients and has also been described in asymptomatic patients with previous COVID-19 infection (coronary dilatation with a diameter *Z*-score >2.5).[24] A systematic review showed that 23.4% of patients had CAD or aneurysms associated with KD-like symptoms.[23] Our study had a higher percentage of CAD in the 'MIS-C likely' group (43%) although not statistically significant compared with the 'MIS-C unlikely' group. A Kenyan study[14] also showed CAD in 2 (33.3%) patients, although only 6 patients had echocardiography. However, the Egyptian[13] and Western Cape[16] studies showed much lower percentages of CAD of 2.2% and 5.9%, respectively. Interestingly, the KZN study[15] showed no CAD during early or late echocardiography.[13,15,16] Differences in these findings may be related to resource constraints in the other centres that could not perform echocardiography or had them done at a later stage.[14,15] All patients included in the present study had echocardiographies done and we found that a number of patients in our 'MIS-C unlikely' group had CAD.

Other studies have reported various causes of CAD, including infections, autoimmune/inflammatory processes, idiopathic causes and other febrile exanthematous illnesses.[25,26] Incidental findings of CAD with minimal or no symptoms in patients with a history of COVID-19 have been described above.[24] Further studies may be warranted to investigate the causes of CAD in our setting.

LV dysfunction has also been described in a European study that showed a low ventricular ejection fraction of <30% in a third of patients with 80% requiring inotropes.[11] LV function was restored in 71% of those discharged from the ICU,[11] as in our study where the majority had their EF restored within 6 weeks of presentation. Studies have reported myocardial involvement with a prevalence of 26.7% and 50% of myocarditis.[13,15] The Western Cape study reported an estimated median (IQR) EF of 47% (39 - 60).[16] LV dysfunction was a significant finding in our study to help identify those patients at risk of presenting with MIS-C.

Our patients had a much lower percentage of ICU admissions (18%) and need for inotropes (20%). The lower number of ICU admissions might be related to the lack of resources in our setting, as ventilated patients are often accepted to ICU. In comparison, all 8 patients in a report from London with hyperinflammatory shock were admitted to the Paediatric ICU of whom all patients required inotropes for haemodynamic support and seven required mechanical ventilation for cardiovascular stabilisation.[7] The majority of patients from a systematic review (68%) required ICU admission, 63% requiring inotropic support.[20] Kaushik *et al.*[23] in their systematic review of MIS-C patients, found that 68% of patients also required intensive care. The African studies showed very different outcomes with an Egyptian study having 57.8% of patients who required vasopressor support and 51.1% who required mechanical ventilation;[13] and a Kenyan study showed 20% of patients required ICU and only 5% required inotropic support.[14] Other SA studies had a higher percentage of ICU admissions and need for inotropes compared with our setting. The KZN study[15] showed 38% of patients required ICU and 52% of patients needed inotropes, while 39.7% of patients required ICU admission and 38.2% required inotropes in the Western Cape study.[16] The differences in ICU admission numbers may be related to admission criteria and resources in different settings.

Two patients (3.3%) in the 'MIS-C likely' group demised. A low mortality rate has been observed in other studies[20,23] as well. Two systematic reviews showed that the majority of patients recovered, with 1.7% and 1.5% of patients reported to have demised, respectively.[20,23] The European study showed that no patients demised in their cohort.[11]

Study limitations

The major limitation of the present study was that some patients were classified as 'MIS-C likely', despite not completely fulfilling the MIS-C CDC criteria. This is because some patients did not have an antibody test, especially early in the pandemic and some patients had missing information, such as presence or absence symptoms of fever, in their medical records, owing to the retrospective nature of the study. We used MIS-C CDC classification system to differentiate the patients into two groups. As we only used one classification system, this may pose as a potential bias. Another limitation is that it was difficult to differentiate Kawasaki disease from MIS-C clinically. However, the clinicians were guided by a positive COVID PCR or antibodies to confirm the diagnosis when available.

Conclusion

The diagnosis of MIS-C in children is difficult due to variability in the clinical and biochemical presentation. Clinical features of MIS-C, especially documented fever and eye changes together with a positive COVID antibody test suggests that patients have MIS-C in our setting. Laboratory findings of a higher CRP and Trop-T assisted with the diagnosis in patients with suspected MIS-C. In addition, patients with LV dysfunction at presentations are more likely to have MIS-C. Further prospective and large-scale meta-analysis studies are warranted to further investigate and confirm these findings.

Declaration. None.

Acknowledgements. None.

Author contributions. VM and AC conceptualised the study. VM, KT and AC contributed to the study design. AA, TD, MM, PP and WM did the data collection and entry, assisted with the write-up and contributed to the final manuscript. KT analysed the data. VM, KT AND AC reviewed the final manuscript.

Funding. None.

Conflict of interest. None.

1. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res 2020;24:91-98. https://doi.org/10.1016/j.jare.2020.03.005
2. World Health Organization. WHO Director-General's Opening Remarks at the Media Briefing on COVID-19 – 11 March 2020. Geneva: WHO, 2020. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-COVID-19---11-march-2020 (accessed 27 November 2023).
3. Shi T, McAllister DA, O'Brien KL, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: A systematic review and modelling study. Lancet 2017;390(10098):946-958. https://doi.org/10.1016/s0140-6736(17)30938-8
4. Otto WR, Geoghegan S, Posch LC, et al. The epidemiology of severe acute respiratory syndrome Coronavirus 2 in a pediatric healthcare network in the United States. J Pediatric Infect Dis Soc 2020;9(5):523-529. https://doi.org/10.1093/jpids/piaa074
5. Pierce CA, Preston-Hurlburt P, Dai Y, et al. Immune responses to SARS-CoV-2 infection in hospitalised pediatric and adult patients. Sci Transl Med 2020;12(564):eabd5487. https://doi.org/10.1126/scitranslmed.abd5487
6. Viner RM, Whittaker E. Kawasaki-like disease: Emerging complication during the COVID-19 pandemic. Lancet 2020;395(10239):1741-1743. https://doi.org/10.1016/S0140-6736(20)31129-6
7. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395(10237):1607-1608. https://doi.org/10.1016/s0140-6736(20)31094-1
8. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: An observational cohort study. Lancet 2020;395(10239):1771-1778. https://doi.org/10.1016/S0140-6736(20)31103-X
9. Webb K, Abraham DR, Faleye A, McCulloch M, Rabie H, Scott C. Multisystem inflammatory syndrome in children in South Africa. Lancet Child Adolesc Health 2020;4(10):e38. https://doi.org/10.1016/S2352-4642(20)30272-8

10. Malik P, Patel U, Mehta D, et al. Biomarkers and outcomes of COVID-19 hospitalisations: Systematic review and meta-analysis. BMJ Evid Based Med 2021;26(3):107-108. https://doi.org/10.1136/bmjebm-2020-111536
11. Belhadjer Z, Méot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. Circulation 2020;142(5):429-436. https://doi.org/10.1161/CIRCULATIONAHA.120.048360
12. Balasubramanian S, Sankar J, Dhanalakshmi K, et al. Differentiating multisystem inflammatory syndrome in children (MIS-C) and its mimics – a single-center experience from a tropical setting. Indian Pediatr 2023;60(5):377-380.
13. Abdelaziz TA, Abdulrahman DA, Baz EG, et al. Clinical and laboratory characteristics of multisystem inflammatory syndrome in children associated with COVID-19 in Egypt: A tertiary care hospital experience. J Paediatr Child Health 2023;59(3):445-452. https://doi.org/10.1111/jpc.16311
14. Migowa A, Samia P, Del Rossi S, et al. Management of Multisystem Inflammatory Syndrome in Children (MIS-C) in resource-limited settings: The Kenyan experience. Pediatr Rheumatol Online J 2022;20(1):110. https://doi.org/10.1186/s12969-022-00773-9
15. Chinniah K, Bhimma R, Naidoo KL, et al. Multisystem inflammatory syndrome in children associated with SARS-CoV-2 infection in KwaZulu-Natal, South Africa. Pediatr Infect Dis J 2023;42(1):e9-14. https://doi.org/10.1097/INF.0000000000003759
16. Butters C, Abraham DR, Stander R, et al. The clinical features and estimated incidence of MIS-C in Cape Town, South Africa. BMC Pediatr 2022;22(1):241. https://doi.org/10.1186/s12887-022-03308-z.
17. Centers for Disease Control and Prevention. Information for Healthcare providers about Multisystem Inflammatory Syndrome in Children (MIS-C). Atlanta: CDC, 2023. https://www.cdc.gov/mis/mis-c/hcp/index.html (accessed 6 August 2023).
18. Dallaire F, Dahdah N. New equations and a critical appraisal of coronary artery Z scores in healthy children. J Am Soc Echocardiogr. 2011 Jan;24(1):60-74. https://doi..org.10.1016/j.echo.2010.10.004
19. Yasuhara J, Kuno T, Takagi H, Sumitomo N. Clinical characteristics of COVID-19 in children: A systematic review. Pediatr Pulmonol 2020;55(10):2565-2575. https://doi.org/10.1002/ppul.24991
20. Radia T, Williams N, Agrawal P, et al. Multi-system inflammatory syndrome in children and adolescents (MIS-C): A systematic review of clinical features and presentation. Paediatr Respir Rev 2021;38:51-57. https://doi.org/10.1016/j.prrv.2020.08.001
21. García-Salido A, de Carlos Vicente JC, Belda Hofheinz S, et al. Severe manifestations of SARS-CoV-2 in children and adolescents: From COVID-19 pneumonia to multisystem inflammatory syndrome. A multicentre study in pediatric intensive care units in Spain. Crit Care 2020;24(1):666. https://doi.org/10.1186/s13054-020-03332-4
22. Yilmaz Ciftdogan D, Ekemen Keles Y, Cetin BS, et al. COVID-19-associated multisystemic inflammatory syndrome in 614 children with and without overlap with Kawasaki disease-Turk MIS-C study group. Eur J Pediatr 2022;181(5):2031-2043. https://doi.org/10.1007/s00431-022-04390-2
23. Kaushik A, Gupta S, Sood M, Sharma S, Verma S. A systematic review of multisystem inflammatory syndrome in children associated with SARS-CoV-2 infection. Pediatr Infect Dis J 2020;39(11):e340-346. https://doi.org/10.1097/INF.0000000000002888
24. Khalid A, Patel N, Yusuf Ally Z, Ehsan S. Incidental finding of coronary artery dilatation in children with history of COVID-19 having minimal or no symptoms: Raising red flag. Cureus 2022;14(4):e24348. https://doi.org/10.7759/cureus.24348
25. Kawsara A, Núñez Gil IJ, Alqahtani F, Moreland J, Rihal CS, Alkhouli M. Management of coronary artery aneurysms. JACC Cardiovasc Interv 2018;11(13):1211-1223. https://doi.org/10.1016/j.jcin.2018.02.041
26. Reyna J, Reyes LM, Reyes L, et al. Coronary artery dilation in children with febrile exanthematous illness without criteria for Kawasaki Disease. Arq Bras Cardiol 2019;113(6):1114-1118. https://doi.org/10.5935/abc.20190191

Received 28 November 2023. Accepted 21 January 2025.