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ABSTRACT
Background Despite the life-threatening presentation of multisystem inflammatory syndrome in children (MIS-C), the overall prognosis is favourable in centres with access to appropriate supportive care. In this study, we investigate the short-term outcomes in children with MIS-C in Cape Town, South Africa.

Methods This prospective observational cohort study included children <13 years who fulfilled the WHO case definition of MIS-C and were admitted to Tygerberg Hospital in Cape Town, South Africa between 1 June 2020 and 31 October 2021. Clinical features were recorded at baseline and at follow-up at the 6-week cardiology and 3-month rheumatology-immunology clinics, respectively.

Findings Fifty-three children with a median age of 7.4 years (IQR 4.2–9.9) were included. There was a slight male predominance (30/53; 56.6%) and the majority was of mixed ancestry (28/53; 52.8%) or black African ancestry (24/53; 45.3%). Fourteen children (14/53; 26.4%) had comorbid disease. The median length of hospital stay was 8 days (IQR 6–10). All children had an echocardiogram performed at baseline of which 39 were abnormal (39/53; 73.6%). All children were discharged alive. The median days from discharge to cardiology follow-up was 39 days (IQR 33.5–41.5) and for rheumatology-immunology clinic was 70.5 days (IQR 59.5–85.0). Eleven children (11/41; 26.8%) had a persistently abnormal echocardiogram at cardiology follow-up. Systemic inflammation and organ dysfunction resolved in most.

Interpretation Although the short-term outcomes of MIS-C in our cohort were generally good, the cardiac morbidity needs further characterisation and follow-up.

BACKGROUND
Multisystem inflammatory syndrome in children (MIS-C) is temporally associated with SARS-CoV-2 infection. The syndrome is characterised by fever, mucocutaneous features, hypotension, gastrointestinal symptoms and features of myocardial inflammation.1–3 MIS-C was first reported in Europe in March 2020.4–7 The first case in Cape Town, South Africa was noted in early May 2020.8

Fifty to 80% of children with MIS-C required intensive care admission for haemodynamic instability.6 9 In a cohort from Lagos, Nigeria, only 10.7% (3/28) of patients were admitted to intensive care with no deaths reported.10 A systematic review of 16 case series including 655 children with MIS-C reported a mortality rate of 1.7%.11 Mortality appears to be higher in older children and those with comorbid diseases.12 In a recent report from KwaZulu Natal, South Africa, the mortality was reported much higher at 20.6%, similar to the 20% mortality in Pakistan.13 14 The mortality rate was 11.2% in a multicentre cohort including 135 children from India.15

There are no randomised data on the management of children with MIS-C but large observational studies found clinical benefit in giving both intravenous immunoglobulin (IVIG) and glucocorticoids as compared with IVIG alone.16–18 The Best Available Treatment Study consortium evaluated the use of IVIG, glucocorticoid or combination therapy in a propensity-weighted cohort study including 2101 children from 39 countries.19 They
concluded that glucocorticoids appears to be a safe alternative to IVIG or combined therapy.\textsuperscript{19}

The available information on long-term outcomes from North America and Europe suggests good cardiac prognosis, with systolic dysfunction recovering in the convalescent phase and most children making a full clinical recovery at 6-month follow-up.\textsuperscript{20} Children with cardiac dysfunction showed recovery of ventricular function and resolution of coronary artery aneurysms.\textsuperscript{22,23}

We previously reported that the clinical presentation and early outcomes of South African children with MIS-C managed at Tygerberg Hospital (TBH) and Red Cross War Memorial Children’s Hospital in Cape Town are similar to European and North American children and adolescents.\textsuperscript{8,9,24} However, there are limited data on postdischarge outcomes of children with MIS-C from Africa. We aimed to evaluate the outcomes of children with MIS-C managed at TBH up to 3 months after diagnosis and beyond as indicated clinically.

METHODS

Study design and population

This single-centre prospective observational study of children and adolescents <13 years diagnosed with MIS-C at TBH between 1 June 2020 and 31 October 2021 describes the clinical progress from diagnosis until approximately 3 months after diagnosis. Where children with abnormal echocardiograms were followed beyond 3 months, those data are reported up to 6 months after diagnosis.

Locally, all children and adolescents diagnosed with MIS-C are managed with supportive care, IVIG and/or intravenous or oral steroids and low-dose aspirin. All children have echocardiography on admission and follow-up. The coronary artery diameter Z-score derived from the Paediatric Heart Network Z-score system, and left ventricular ejection fraction (LVEF) measured qualitatively and quantitatively and calculated using the M-mode method are recorded.\textsuperscript{25} All children and adolescents are given dates for review approximately at 6 weeks after diagnosis at cardiology and at rheumatology-immunology clinic within 6 weeks to 3 months after diagnosis. The evaluation at follow-up includes a detailed clinical assessment, repeat echocardiogram and repeating inflammatory markers, COVID-19 serum antibody, renal function, liver enzymes and other investigations as indicated.

Data sources and definitions

Children and adolescents <13 years who met the WHO case definition of MIS-C were enrolled. We excluded children and adolescents in whom another plausible diagnosis was apparent; we also excluded children with typical and atypical Kawasaki disease with negative SARS COVID-2 PCR and antibody tests. Routine access to SARS-CoV-2 antibody testing against the nucleocapsid protein only became available in August 2020. Cases with MIS-C prior to August 2020 that were SARS-CoV-2 PCR negative were included if the full case definition was met and there was a positive history of exposure to a likely source case. None of these children and adolescents was vaccinated against COVID-19. South Africa only approved the use of two doses of the Pfizer-BioNTech COVID-19 vaccines for those aged 12–17 years in October 2021.\textsuperscript{12–17}

Demographic data and clinical characteristics were reported at admission and follow-up. Care interventions including the need for intensive care intervention, IVIG and steroids were documented.

The laboratory parameters included white blood cell count, absolute lymphocyte count, absolute neutrophil count, haemoglobin, platelets, C reactive protein, ferritin, pro-brain natriuretic peptide (pro-BNP) and troponin T.

All data including echocardiograms and blood tests were performed as needed for routine care. All echocardiograms were performed or reviewed by a paediatric cardiologist. We classified coronary artery Z-scores as follows: normal (<2, dilation 2 to <2.5, aneurysm ≥2.5. Left ventricular (LV) systolic dysfunction was defined as an LVEF<53% and graded as mild (LVEF 43%–54%), moderate (LVEF 33%–44%) or severe (LVEF <33%) as previously described.\textsuperscript{15}

The WHO weight-for-age Z-scores were calculated for children younger than the age of 5 years and the WHO body mass index Z-score for children over the age of 5 years using the AnthroCalc application V.2.1.

Statistical analysis

Basic demographic data, clinical features on presentation, management and echocardiogram findings at baseline and follow-up was described using standard summary statistics. Continuous variables are summarised as mean, SD or median and IQRs where appropriate. Comparative data were analysed using IBM SPSS Statistics, V27. Fisher’s exact test and $\chi^2$ test were used for dichotomous variables and Mann-Whitney U test for non-parametric continuous variables.

RESULTS

We identified 64 children and adolescents <13 years with suspected MIS-C between 1 June 2020 and 31 October 2021; we excluded 11 cases that did not meet the case definition (figure 1). The median age of the 53 patients was 7.4 years (IQR 4.3–9.9) and 30/53 (56.6%) were male (table 1). Symptoms on presentation, findings on initial clinical examination, hospital course and management are summarised in table 1.

The median length of hospital stay was 8 days (IQR 6–8). Twenty-four (45.3%) patients required intensive care admission, 22 (41.5%) patients required inotropic support and 7 (13.2%) intubation and ventilation. The majority received both IVIG and methylprednisolone (56.6%) with 18 patients (34%) receiving IVIG only.

At baseline, 39 of the 53 children (73.6%) had an abnormal echocardiogram report (table 2). The majority (29, 54,7%) had 64 patients referred to paediatric rheumatology/immunology with suspected MIS-C (1 June 2020 – 31 October 2021)

53 patients meet WHO MIS-C criteria

44 patients presented for follow-up

Cardiology clinic follow-up: 41/53

Rheumatology clinic follow-up: 30/53

Figure 1 Follow-up of children and adolescents <13 years with confirmed multisystem inflammatory syndrome in children (MIS-C) at cardiology and rheumatology-immunology clinic. KD, Kawasaki disease.
Table 1  Demographic and clinical characteristics, hospital course and management

<table>
<thead>
<tr>
<th>Value</th>
<th>Table 1  Continued</th>
</tr>
</thead>
</table>
| **Table 1** continued  
| **Any biological** | 0 |
| Numbers are presented with percentages in brackets. Median values are presented with IQR. |  |
| BMI, body mass index; IVIG, intravenous immunoglobulin; PICU, paediatric intensive care unit; WAZ, weight for age Z-score. |  |
|mitral or tricuspid regurgitation at baseline, 8 of the 15 patients with coronary abnormalities had brightness of the artery and although 19 (29.3%) had abnormalities of LV function only, 10 of the patients had moderate or severe dysfunction. |  |
|In the acute phase, all patients had elevated markers of systemic inflammation. The majority had lymphopenia, anaemia, renal impairment, hypoponeraemia and elevated cardiac enzymes on admission. In the convalescent phase, C reactive protein and ferritin remained raised in 33 of 45 (73.3%) of children and 28/28 (100%) of children, respectively (online supplemental table 1). |  |
|**Follow-up** |  |
|By 28 February 2022, follow-up data for at least one cardiology outpatient review was available for 41/53 (77%) cases and 30/53 (56.6%) cases had at least one rheumatology follow-up (figure 1). The median days from discharge to cardiology follow-up was 39 days (IQR 33.5–41.5) and for rheumatology-immunology clinic was 70.5 days (IQR 59.5–85.0). |  |
|**Cardiology follow-up** |  |
|Thirty-three patients (33/41, 80.5%) had an initial repeat echocardiogram within 6 weeks, four patients (4/41, 9.8%) within 3 months and the remaining four (4/41, 9.8%) patients within 6 months. Eleven (11/41, 26.8%) patients had persistent abnormal findings on echocardiography at follow-up (table 3). In eight children, the persistent manifestation was due to an endocardial dysfunction manifesting as mitral or tricuspid regurgitation. Three patients had abnormalities that persisted at 6-month follow-up (patients 2, 3 and 4, table 3). Patients 2 and 3 had moderate and mild LV dysfunction, respectively and patient 4 had a dilated coronary artery (Z-score=2). We found that |  |
|**Table 2**  
| **Echocardiogram report (baseline and first follow-up)** |  |
| **Echocardiogram findings** | **Acute** (n=53) | **Follow-up** (n=41) |
| Normal echo, n (%) | 14 (26.4) | 30 (73.2) |
| Any left ventricular systolic dysfunction, n (%) | 19 (35.8) | 2 (4.9) |
| LVEF, mean (SD) | 55.2 (±11.6) | 62.3 (±8.4) |
| Mild (LVEF 45%–54%), n (%) | 9 (17.0) | 2 (4.9) |
| Moderate (LVEF 35%–44%), n (%) | 8 (15.1) | 0 |
| Severe (<35%), n (%) | 2 (3.8) | 2 (4.9) |
| Any coronary artery abnormality, n (%) | 15 (28.3) | 1 (2.4) |
| Dilated coronary artery (Z-score >2.5), n (%) | 5 (9.4) | 1 (2.4) |
| Coronary artery aneurysm (Z-score ≥2.5), n (%) | 5 (9.4) | 0 |
| Coronary artery eohbributy, n (%) | 6 (11.7) | 0 |
| Mitral or tricuspid regurgitation, n (%) | 29 (54.7) | 8 (19.5) |
| *Three patients reported to have a ‘dilated coronary artery’ did not have a Z-score documented. Acute echocardiogram was performed at presentation and follow-up echocardiogram at the first cardiology outpatient review. Numbers are presented with percentages in brackets. LVEF, left ventricular ejection fraction. |  |
SARS-CoV-2 diagnosed papular urticarial pustulosis, association with chronic arthritis or impaired mobility. Her symptoms resolved completely at 8-month follow-up. The second patient had mild intermittent urticarial rash, dermatology diagnosed papular urticarial pustulosis.

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Four patients (4/30, 13.3%) had ongoing clinical concerns.

Rheumatology-immunology follow-up

Four patients (4/30, 13.3%) had ongoing clinical concerns. The first patient had an intermittent urticarial rash, dermatology diagnosed papular urticarial pustulosis, association with SARS-CoV-2 infection could not be excluded. On subsequent follow-up, the rash had resolved. The second patient had mild conjunctival injection unrelated to MIS-C. The third patient was diagnosed with myasthenia gravis shortly after admission that was temporally associated with SARS-CoV-2. She was treated with pyridostigmine and methotrexate. Nine months after initial diagnosis, she had normal function and muscle strength and all medication was successfully stopped. The fourth patient complained of headache, ankle pain and stiff legs. She had no objective clinical signs or inflammatory markers suggestive of chronic arthritis or impaired mobility. Her symptoms resolved completely at 8-month follow-up.

Follow-up laboratory parameters are summarised in online supplemental table 1. Of the 32 patients that had repeat SARS-CoV-2 antibody test at follow-up, 40.6% (13/32) remained seropositive. All patients were discharged alive from hospital.
**DISCUSSION**

This study adds to expanding data on the outcomes of African children with MIS-C. As in the cohort from Nigeria\(^1\) and Kenya,\(^2\) overall outcomes were good, and no children required a biologic agent. It is, however, in contrast with data recently published from KwaZulu Natal, South Africa,\(^3\) Pakistan\(^4\) and Egypt,\(^5\) where the mortality was reported to be very high (20.6%, 20% and 33.3%, respectively). Critical shortage of intensive care beds is reported from Nigeria and KwaZulu Natal. In KwaZulu Natal, limited intensive care space and delay in access to specialised care may have contributed to the high mortality. In addition, African children may have more aggressive inflammation.\(^1\) We note that children from both the cohorts from Egypt and KwaZulu Natal had a median age <5 years. It is not clear whether young age contributed to the higher mortality.

**Table 4** Determinants associated with abnormal echocardiogram at follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal echocardiogram</th>
<th>Abnormal echocardiogram</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in months (median, IQR)</td>
<td>70 (49.3–125.5)</td>
<td>106 (96.6–125.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Chronic illness (n, %)</td>
<td>8 (19.0%)</td>
<td>3 (27.2%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Duration of fever in days (median, IQR)</td>
<td>4 (2–5)</td>
<td>5 (3.5–5)</td>
<td>0.41</td>
</tr>
<tr>
<td>Days from symptom onset to diagnosis (median, IQR)</td>
<td>7 (4–8)</td>
<td>6.5 (5.3–8)</td>
<td>0.67</td>
</tr>
<tr>
<td>Highest C reactive protein (median, IQR)</td>
<td>232 (120.8–294.5)</td>
<td>237 (152–265)</td>
<td>0.94</td>
</tr>
<tr>
<td>Highest NT-pro-BNP (median, IQR)</td>
<td>5777 (1388–27 386)</td>
<td>7485 (3582.5–27 175.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Highest troponin T (median, IQR)</td>
<td>22.5 (9–64.3)</td>
<td>25 (18–67)</td>
<td>0.93</td>
</tr>
<tr>
<td>PICU admission (n, %)</td>
<td>20 (47.6%)</td>
<td>4 (36.6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Inotropic support (n, %)</td>
<td>17 (40.5%)</td>
<td>5 (45.5%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Methylprednisolone only</td>
<td>2 (4.8%)</td>
<td>0 (0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>IVIG only</td>
<td>17 (40.5%)</td>
<td>1 (9.1%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Both methylprednisolone and IVIG</td>
<td>20 (47.6%)</td>
<td>10 (90.1%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Strengths and limitations**

Follow-up studies of children with MIS-C are limited and our study adds to the growing knowledge base. Our cohort had substantial loss to follow-up, which limits some of our findings. In addition, our cohort did not include children older than 13 years, which is important, as mortality is reported to be higher in older children. Most echocardiograms in this cohort were performed and interpreted by a single operator and not verified and discussed by a few.
The preponderance of regurgitation in this cohort could thus be operator-dependent.

CONCLUSIONS AND RECOMMENDATIONS
Our findings are important as it adds to the limited data available on cardiac outcomes in children living in Africa. This is only the second study from Africa looking at the cardiac outcomes of children with MIS-C. Despite low mortality in this cohort, there are some concerns about mid-term cardiac morbidity and the possible implication on long-term cardiovascular health. Further research is needed to inform targeted interventions and ensure adequate long-term follow-up services.

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Contributors JL: joint first author. Responsible for conceptualisation, project administration and methodology of study. Responsible for data collection. Responsible for data curation and analysis. Had access to data and were responsible for writing the original draft. Responsible for draft review and editing. DRA: joint first author. Responsible for conceptualisation, project administration and methodology of study. Responsible for data collection and rheumatology-immunology follow-up of patients. Had access to data and were responsible for writing the original draft. Responsible for draft review and editing. BF: responsible for data collection and performing echocardiograms and cardiac follow-up of patients. Responsible for draft review and editing. NAY: responsible for data collection and rheumatology-immunology follow-up. Responsible for draft review and editing. AR: responsible for drafting the review and editing. MMVDZ: responsible for data curation and analysis. Responsible for draft review and editing. HR: responsible for conceptualisation, project administration and methodology of study. Had access to data and were responsible for writing the original draft. Responsible for draft review and editing. JL is guarantor.

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Disclaimer The content and findings reported/illustrated are the sole deduction, view and responsibility of the researcher and do not reflect the official position and sentiments of the SAMRC, NIH or National Treasury.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study was approved under Stellenbosch University Health Research Ethics Committee (HREC number N20/04/013_COVID-019; N20/07/041). The aim of the study was to describe standard practice without any additional intervention. Data were obtained from patient records, the laboratory system and the PACS system. There is minimal risk for breach of patient confidentiality.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available.

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