Medium term health and quality of life outcomes in a cohort of children with MIS-C in Cape Town, South Africa

Submitted

By

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DECLARATION

I, Dr Frank Phoya……, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.
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Acknowledgements, format and contributions.

Acknowledgement

I would like to give thanks to my supervisor Dr Kate Webb for pushing me and all the encouragement and support she gave me during this process. I would also like to thank my co supervisor Professor Christiaan Scott for the support and introduction to the field of rheumatology. I would like to acknowledge the use of "Turnitin application" to check for plagiarisms. As this paper will also be submitted to the University of Cape Town as part requirement for my MPhil in paediatric rheumatology (the university requires the all papers submitted should undergo a Turnitin evaluation before submission). Some editing was done after the Turnitin report. A copy of the reports can be made available.

Contributions

As this work forms part of the ongoing paediatric rheumatology biorepository, I would like to thank Dr Kate Webb and her team for allowing me to join their research team and also build from the work they had started doing and also allowing me to add a different component to their research.

The initial recruitment of MIS-C participants into the paediatric rheumatology biorepository was done by Dr. Kate Webb and her research team.
The protocol for this study was written by Dr. Frank Phoya with supervision from Dr. Kate Webb.
The recruitment of MIS-C participants into the quality of life sub study was done by the Dr. Frank Phoya.
Dr. Frank Phoya did the data analysis, presentation and interpretation of the results under the supervision of Dr. Kate Webb.

Format

This thesis has been written in a ready to submit/publication format. Frontiers in Pediatrics is the journal I submitted to. The format/author guideline can be found here in the link below: https://www.frontiersin.org/guidelines/author-guidelines#figure-and-table-guidelines

This manuscript has been submitted, accepted and published in the journal of Frontiers in Pediatrics, in the pediatric rheumatology section. The full citation is found below:
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Abstract

Background: Multisystem inflammatory syndrome in children (MIS-C) is a disease that occurs after exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Its short term effects have been documented but little data exist on the longer term effects of MIS-C on the health and quality of life of patients. The objective of this study was to assess the long-term effects of MIS-C on the quality of life of children.

Methods: This study was a prospective, case control, cohort study. We included 24 participants with previous MIS-C and 20 children with juvenile idiopathic arthritis (JIA) as a positive comparator group. All children were examined and completed a paediatric quality of life (PedsQL) generic inventory score. This score was used to evaluate the school functioning, social, emotional, and physical domains of the two groups.

Results: All participants with previous MIS-C made a full recovery with normal physical examination after a median of 705 days after acute MIS-C. The PedsQL inventory revealed that 16.7% of the children with previous MIS-C showed a deficit in the physical domain compared to 60% of the children with JIA ($p<0.001$). There was a deficit in the psychosocial domain (which combines emotional, social and educational scores) in 12.5% children with previous MIS-C compared to 40% children with JIA ($p=0.035$)

Conclusions: In 24 children with previous MIS-C, after approximately 2 years, no medical complications were reported. A small proportion felt a prolonged effect on their quality of life even after making a full recovery, which was less severe than in children with JIA. This highlights the need to continue to follow up these patients and offer more comprehensive long-term care.

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List of abbreviations

CDC: Centers for Disease Control and Prevention
COVID 19: *Coronavirus disease 2019*
CYP: Children and young people
HRQOL: Health related quality of life
KD: Kawasaki disease
MIS-C: Multisystem inflammatory syndrome in children
PedsQL: Pediatric Quality of Life inventory
PCR: Polymerase chain reaction
RCWMCH: Red Cross War Memorial Children's Hospital
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
WHO: World Health Organization

Chapter 1: Published or Publication-ready Manuscript

Keywords

MIS-C (Multisystem inflammatory syndrome in children) and PedsQL (Pediatric Quality of Life Inventory)

Background

In 2020, a hyperinflammatory syndrome with multiorgan involvement, potentially linked to Coronavirus disease (COVID-19) emerged among clusters of children. This syndrome resembled Kawasaki disease, but with notable clinical and diagnostic distinctions(1). While data on this syndrome, Multisystem Inflammatory Syndrome in Children (MIS-C), remains rare in Africa, a cohort study done in Cape Town, South Africa helped to estimate its incidence and characteristics, estimating an incidence of 22 cases per 100,000 SARS-CoV-2 exposures (2-4). MIS-C presents with fever, inflammation, and involvement of multiple organ systems, often including gastrointestinal symptoms, with lower mortality rates compared to classic Kawasaki disease (4, 5).

Despite the relatively low mortality rates, concerns over long-term impacts on health and quality of life (QOL) post-MIS-C have emerged (6, 7)**.** Very few studies have investigated long term health and QOL in children after MIS-C. One study done by Penner et al reported that almost 20% of children with previous MIS-C had deficits in psychosocial quality of life (QOL) with persistent emotional and physical impairment in some children (8). It is not clear whether these findings are unique to MIS-C or have been suggested to reflect general responses to an episode of severe childhood illness. During this study the Pediatric Quality of Life Inventory (PedsQL) was used to access the long term effects of the disease on the child's quality of life. PedsQL is a 23-item generic health status instrument that is used to assess five domains of health (physical functioning, emotional functioning, psychosocial functioning, social functioning, and school functioning)(9).

There are no studies that compare the QOL of children with previous MIS-C to an unwell comparator group from the same setting, in order to contextualise the residual impairment. Research on the long-term effects of MIS-C, particularly on QOL, remains limited, especially in Africa.

Here, we aimed to describe the long-term effects of MIS-C on the health and QOL of a cohort of children in Cape Town, South Africa. We included children with juvenile idiopathic arthritis (JIA), a chronic disease with a known severe effect on QOL (10) as a positive comparator group in order to contextualise these findings.

Methods

We performed a prospective, case control, cohort study in which participants diagnosed with MIS-C between March 2020 and January 2022, who had been recruited into an existing biorepository were recalled and asked to attend a follow up research visit between January 2023 and December 2023. Children with JIA were recruited as a convenience comparator group during the same period. The study was conducted at Red Cross War Memorial Children's Hospital, which is a government-funded, tertiary-level referral hospital located in Cape Town, South Africa. This study was approved by the University of Cape Town Human Research Ethics Committee (HREC 112/2012; 599/2020).

Inclusion criteria included:

- Children and young people (CYP) aged between 1 and 18 years at the time of MIS-C diagnosis.
- Previous diagnosis of MIS-C between March 2020 and January 2022 (Diagnosed according to the WHO, MIS-C criteria) (11)(Supplementary Material Table 1)
- 6 months or more post-disease onset (MIS-C)
- CYP attending paediatric rheumatology clinics with a diagnosis of JIA according to the treating physician

The exclusion criteria were:

- Not willing to participate
- Age now above 18 years at the time of recruitment for this study
- Any chronic comorbidity that may affect the quality of life (e.g., HIV, malignancy)

CYP (or their caregiver where appropriate) who had previously been recruited into an ongoing paediatric database and biorepository study who had agreed to be contacted again by researchers and met the inclusion and exclusion criteria were contacted telephonically to return for a repeat clinical follow-up visit.
During the visit, the following variables were collected, demographics (sex, age) and current complaints (i.e., joint pain, recent infection). Clinical data was collected (weight, height, and vital signs [temperature, respiratory rate, heart rate and blood pressure]) and recorded in a case report form (CRF) (Supplementary material appendix C). A brief history was taken to screen for any complaints since their admission with MIS-C and since their last clinical visit. A general examination was done by the principal investigator (PI), reviewing the neurological, respiratory, cardiovascular, gastroenterology, and musculoskeletal systems and the findings were recorded in the CRF (Supplementary appendix C). After the history was taken and the clinical examination was completed, patients or caregivers were asked to complete the paediatric quality of life inventory questionnaire version 4.0 (PedsQL; Supplementary material Appendix B).

Briefly, the PedsQL tool can be used as a child self-report or parent (caregiver) proxy-report format. Child self-report includes ages 5–7 years, 8–12 years, and 13–18 years. Parent (caregiver) proxy report includes ages 2–4 years (toddler), 5–7 years (young child), 8–12 years (child), and 13–18 years (adolescent), and assesses parents (caregivers) perceptions of their child's health-related quality of life. A 5-point response scale is utilized across child

self-report for ages 8–18 years and parent (caregivers) proxyreport (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). To further increase the ease of use for the young child self-report (ages 5–7 years), the response scale is reworded and simplified to a 3-point scale (0 = not at all a problem; 2 = sometimes a problem; 4 = a lot of a problem). Items were reverse scored and linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0) so that higher scores indicate better health related quality of life (HRQOL). Scale scores were computed as the sum of the items divided by the number of items answered (to account for missing data). If more than 50% of the items in the scale are missing, the scale score was not computed. A score of less than 80% was indicative of a deficit in that particular domain. The psychosocial Score was computed as the sum of the items divided by the number of items answered in the school functioning, social, and emotional subscales (9)

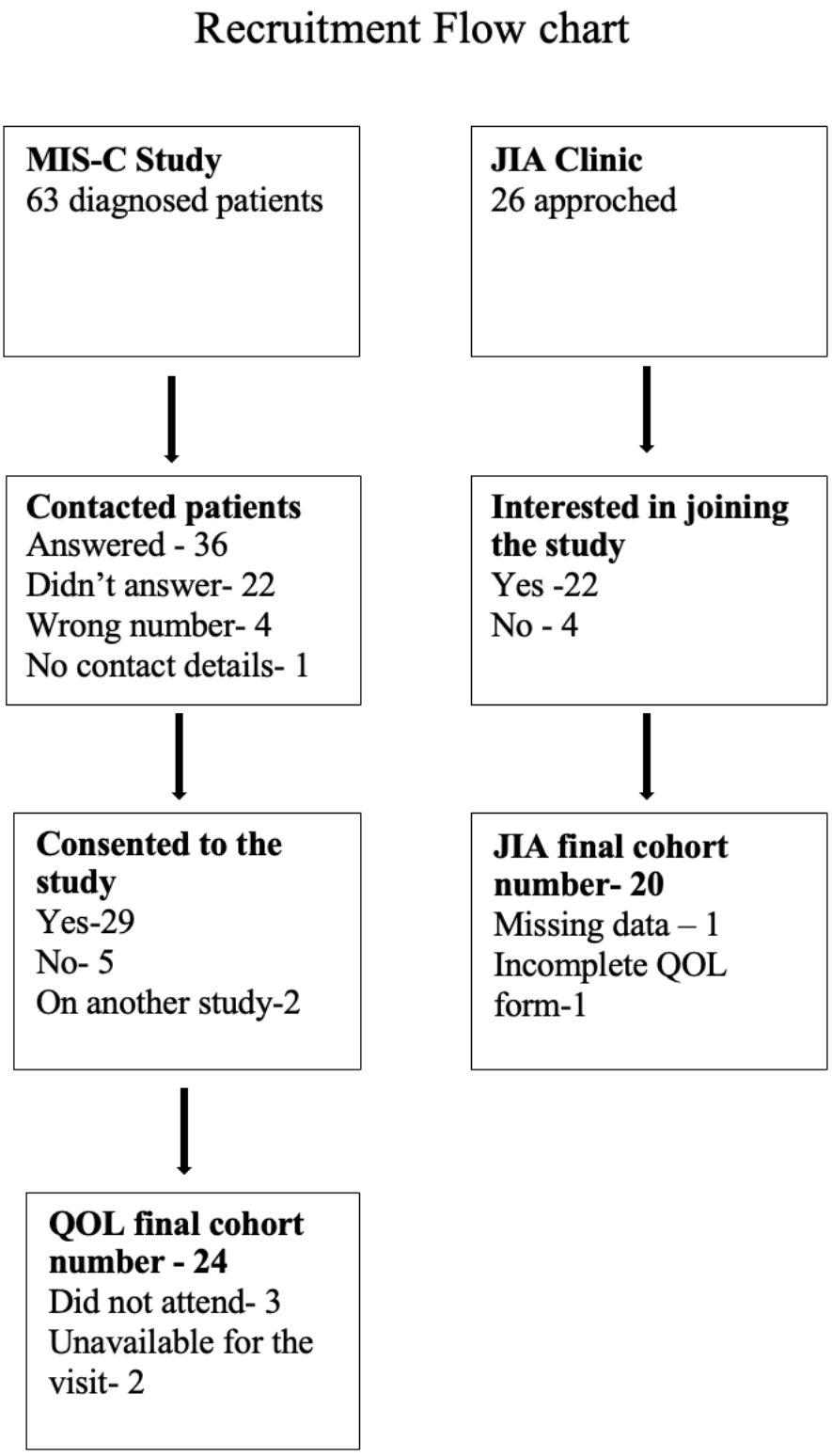
Where necessary the PI would help to clarify the questions in the questionnaire to the child or their caregiver. The questionnaire was administered in English and for those with difficulty with understanding English a translator was used.

This study was an observational study, no intervention was done. Written informed consent was obtained from the guardians/parents so that we could use the data gathered. The participants above 12 years old were asked to give assent as well. Ethics approval was awarded by Red Cross War Memorial Children's Hospital Departmental Research Committee (DRC) and the University of Cape town Human Research Ethical Committee (HREC REF 452/2023)

The statistical analyses were performed using SPSS (version 28.0.1.1). Simple descriptive statistics were used to summarize variables. Data was coded appropriately e.g., scores as ordinal data (e.g., PedsQL) or scale numerical data (weight/ height etc.) as applicable before entering into the analytical program. As per PedsQL guidelines, ordinal scores were transformed into a numerical values (9). Numerical data such as age was presented as means (Standard Deviation) or median (Inter-Quartile Range) depending on data normality. Categorical variables were presented as proportions or percentages. Data from the two different groups (MIS-C and JIA) were compared by non-parametric comparator testing as appropriate, using Mann-Whitney U tests or Fisher's exact tests.

Results

Figure 1: Recruitment flow chart



Twenty four out of 63 (38%) patients diagnosed with MIS-C at Red Cross War Memorial Children's Hospital (RXWMCH) between May 2020 and March 2022 agreed to participate in the study. Twenty children diagnosed with JIA and currently followed up in the rheumatology clinic at RXWMCH also agreed to take part in the study.

Table 1: MIS-C and JIA demographics and clinical features

MIS-C	
Demographics at diagnosis	**n=24**
Gender (Male)	66 %(16)
Age (median)	8.2 years; min=1.4; max=14.2
Median time since diagnosis	705 days (min=255; max=1004)
Clinical features at diagnosis	
Fever	100%(24)
Rash	100%(24)
Abdominal pain	100%(24)
Tachycardia	91%(22)
Conjunctivitis	79%(19)
Hypotension	54%(13)
Headache	45%(11)
Diarrhoea	41%(10)
Arthritis	37%(9)
CNS disease	25%(6)
Lung disease	20%(5)
Renal disease	16%(4)
Bleeding	4%(1)
Coronary artery aneurysm present	4%(1)
Median ejection fraction	61% (min=32; max=70)
Median CRP	173 mg/dL (min=103; max=511)
Median white cell count	17.2 x 10^9/L (min=8.6; max=59.9)
Median Pro BNP	1319 pg/mL (min=24; max=48172)
Initial management and outcomes	
1st line antibiotics	87%(21)
IVIG 2g/kg first dose	70%(17)
IVIG 1g/kg first dose	16%(4)
IVIG 2g/kg second dose	4%(1)
Methylprednisone	58%(14)
ICU admission	29%(7)

Inotropes	33%(8)
Discharged	100%(24)
Duration of admission	7 days (min=5; max=21)
JIA	
Demographics at recruitment	**n=20**
Gender (male)	45% (9)
Age (median)	14.3 years (min=3.1; max=17.1)
Duration since diagnosis	1.6 years (min=0.4;max=10)
Median time since diagnosis	591 days (min=27; max=3693)
Type of JIA	
ERA	30% (6)
Oligo	20% (4)
Poly	20% (4)
PsJIA	20% (4)
Sys	10% (2)

CRP C-reactive protein; Pro-BNP, Pro-brain natriuretic peptide ; MIS-C, multisystem inflammatory syndrome in children; JIA, juvenile idiopathic arthritis; IVIG, intravenous immunoglobulin; ICU intensive care unit; ERA, enthesitis related arthritis; Oligo oligoarticular arthritis; Poly, polyarticular arthritis; PsJIA, psoriatic associated juvenile idiopathic arthritis

The clinical characteristics of acute MIS-C in the overall MIS-C cohort have been previously described (4). Of this cohort, 24 children were followed up in this study. Of these, 16 (66%) were male. At the time of diagnosis of MIS-C, the median age was 8.2 years (min=1.4; max=14.2) and fever, rash, conjunctivitis, tachycardia, hypotension, abdominal pain, diarrhoea, headache and arthritis were common features (Table 1). Summary of clinical laboratory data are supplied in Table 1. Central nervous system (CNS) disease and renal disease had been present in 6 (25%) and 4 (16%) of the patients respectively. Coronary artery dilatation was recorded in one patient with a median ejection fraction of 61% (min = 32; max = 70) in the cohort. During admission, 21 (87%) of the children received antibiotics, 17 (70%) received intravenous immunoglobulin (IVIG) at 2g/kg and 14 (58%) received IV methylprednisolone (30mg/kg per day for 3 days). Seven participants (29%) required ICU admission and 8 (33%) needed inotropic blood pressure support. All patients made a full recovery and were discharged home, with no deaths recorded. The average in-hospital stay was 8 days (SD- 3.7, min =5; max=21) (Table 1).

The median time to the study visit from the acute diagnosis of MIS-C was 705 days (min 255; max 1004). The minimum age at the time of the study visit was 3 years and the maximum was 16.5 years. All children had made a full recovery with no admissions or illnesses of note since discharge. They all had normal growth, normal vital signs and a normal clinical examination.

Out of the 20 recruited JIA participants in the comparator group, 11 (55%) were female. The median age was 14.3 years (min=3.1; max=17.3). The median time since the diagnosis of JIA was made was 591 days (min=27; max=3693). The most common type of JIA was enthesitis related arthritis (ERA), at 30% (Table 1). No other significant clinical problems apart from intermittent pain was reported at the time of recruitment.

Figure 2: Quality of life assessment MIS-C and JIA

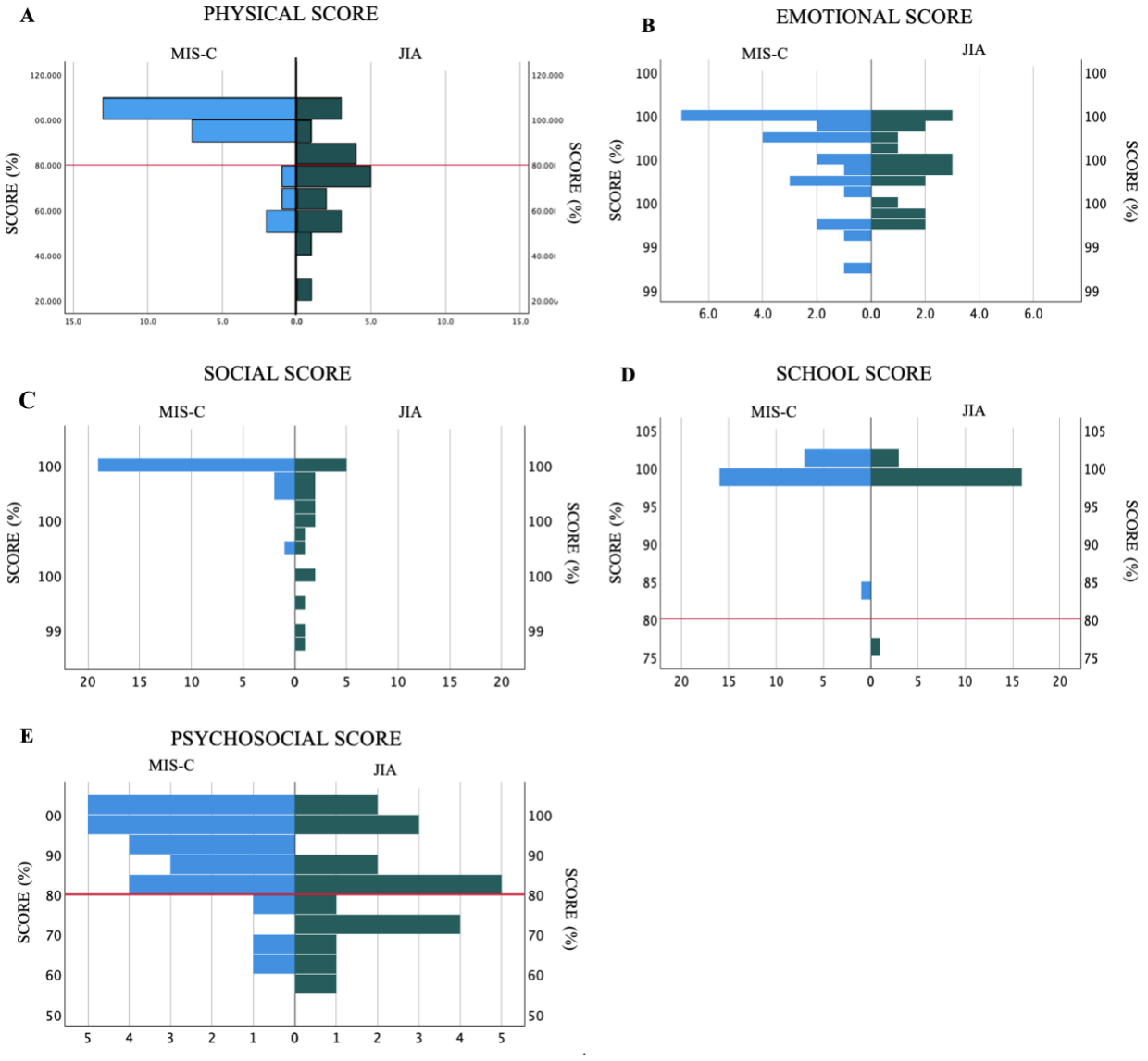


FIGURE 2
Quality of life assessments in children with previous MIS-C compared to children with JIA. (A) Physical domain score, (B) Emotional domain score, (C) Social functioning domain score, (D) School functioning domain score, (E) Psychosocial functioning domain score. The red line indicates 80%, scores below which indicate a deficit in that domain.

Physical domain
Four out of 24 (16%) participants with MIS-C showed an overall deficit (score of less than 80%) in the physical domain as compared to 12 (60%) of participants with JIA (p=0.001) (Figure 2A). These included problems with walking ('often'-3/24; 'almost always'- 1/24), running ('often'-1/24; 'almost always'- 1/24). Compared to participants with MIS-C, participants with JIA reported more difficultly participating in active play (p=0.001), doing chores (p=<0.001) and reported feeling tired (p=0.001) (Supplementary material Table 2).

Emotional domain
A summary percentage score for the emotional domain showed that no participant with previous MIS-C or JIA scored below 80%, showing no deficit in that field (Figure 2B) with no difference between the two groups (Supplementary material Table 3).

Participants with JIA more frequently reported feelings of anger about their condition than participants with MIS-C (p=0.022) and were also found to be more worried about what would happen to them due to their disease than participants who had MIS-C (p=0.004) (Supplementary material Table 3).

Social domain
In the social domain, participants with JIA showed more difficulties in 3 reported areas compared to participants with previous MIS-C. These areas revealed that participants with JIA had more difficulty getting along with other children (p=0.003), doing things that their peers can do (p=<0.001), and keeping up when playing with their peers(p=<0.001) (Supplementary material Figure 4).

The summary percentage score revealed no participant scored below 80% in both groups; however, there was still a significant difference between the two groups (p=<0.001) (Supplementary material Table 4).

School domain
No participants with MIS-C showed a deficit in the school domain and only 1 (5%) of participants with JIA showed a deficit, with no overall difference (p=0.31) (Figure 2D; Supplementary material Table 5). Participants with JIA more frequently reported missing school to go to the doctor (p=0.003) (Supplementary material Table 5; Supplementary material Figure 5)

Psychosocial domain
The psychosocial domain was made up of a combined score of the emotional, social and school domain summary percentage scores.

Twelve percent (3/24) of participants with MIS-C had a deficit in the psychosocial domain compared to 8 (40%) of children with JIA (p=0.035) (Figure 2E; Supplementary material Table 6).

Discussion

In this study, we recruited 24 participants with MIS-C and investigated their quality of life after a median of about 2 years from diagnosis. We compared these children to a group of children from the same setting with JIA, a known chronic inflammatory condition with expected deficits in multiple QOL domains (10).

All of the participants who had MIS-C previously made a full recovery and had no significant medical complications, which matches the good long-term outcomes in MIS-C reported elsewhere (6, 7).

Participants with previous MIS-C did however present with deficits in multiple quality of life domains, although these were universally less severe than the deficits seen in children with JIA. Sixteen percent of participants with previous MIS-C in this study had difficulty in the physical domain and 12% showed difficulty in the psychosocial domain. This was similar to the study done by Penner et al.(8) in the UK, who showed that 13% and 18% of participants had a deficit in the physical and psychosocial domain respectively. Surprisingly, the cohort in the current study showed no significant deficit in the emotional domain as was reported in the UK study, which showed that emotional lability was reported in 12 (26%) of 46 patients at 6 weeks and in seven (15%) of 46 patients at 6 months (8). This discrepancy may be explained by an emotional resilience in this cohort or could be due to the different time period between disease and recruitment in the two studies, with a longer period in this cohort, which may diminish the emotional burden of the acute event.

Sixteen percent of participants with MIS-C had a deficit in the physical domain, which was lower than in participants with JIA (60%) as would be expected since JIA affects primarily the musculoskeletal system (12). Future research may compare children with previous MIS-C to healthy children to get a truer reflection of whether the limitation in the physical domain is meaningful. It is known that children with JIA have low overall health related quality of life (HRQOL), in all aspects of physical health, psychosocial health, emotional functioning, and school functioning (10). Participants with JIA reported more anger and worry than participants with previous MIS-C, which may be expected due to the chronicity of the disease and therefore they may not have been the most optimal comparison group.

There were no differences in scores in the social and school domain. However, the small number of participants with JIA were more likely to find it difficult to get along with other children, with difficulty participating in activities that their peers were doing and difficulty keeping up when playing with their peers, as previously reported in JIA(12).

A small sample size was one of the major limitations of this study. There are however very few long-term outcome data reported in MIS-C, and none from Africa. Another limitation is the comparator group chosen; this study used only a “positive” control group, as it is known that children with JIA have low overall health-related QOL, in all aspects of physical health, psychosocial health, emotional functioning, and school functioning (10). Future research is needed to also compare the long-term QOL in children with MIS-C to a cohort that has recovered from a similar acute, monophasic disease and healthy children from the same

setting. As the COVID-19 pandemic abates, we believe it is vital to continue to monitor children with MIS-C in the long term.

Conclusions

In 24 children with previous MIS-C, after approximately 2 years, no medical complications were reported. A small proportion felt a prolonged effect on their quality of life even after making a full recovery, which was less severe than in children with JIA. This highlights the need to continue to follow up these patients and offer more comprehensive long-term care.

Data availability statement

Data gathered is available on request from the principal investigator via email. Case reporting forms are attached at the end of the document.

Ethics statement

Written informed consent was obtained from the guardians/parents so that we could use the data gathered. The participants above 12 years old were asked to give assent as well. Ethics approval was awarded by Red Cross War Memorial Children's Hospital and the University of Cape Town Departmental Research Committee (DRC) and Human Research Ethical Committee (HREC REF 112/2012; 599/2020)

Author contributions

FP: Writing – review & editing, Writing – original draft, methodology, investigation, formal analysis, data curation and conceptualization. CB: Writing – review & editing, resources and data curation. TS: Writing – review & editing, resources and data curation. HK: Writing – review & editing. HR: Writing – review & editing and data curation. CS: Writing – review & editing. KW: Writing – review & editing, supervision, resources, methodology and data curation.

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Conflict of interest

No competing interest

Abbreviations

COVID 19, Coronavirus disease 2019; CRP, C-reactive protein; CYP, children and young people; HRQOL, health-related quality of life; JIA, juvenile idiopathic arthritis; KD, Kawasaki disease; MIS-C, multisystem inflammatory syndrome in children; PedsQL, Pediatric Quality of Life Inventory; QOL, quality of life; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

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Appendices

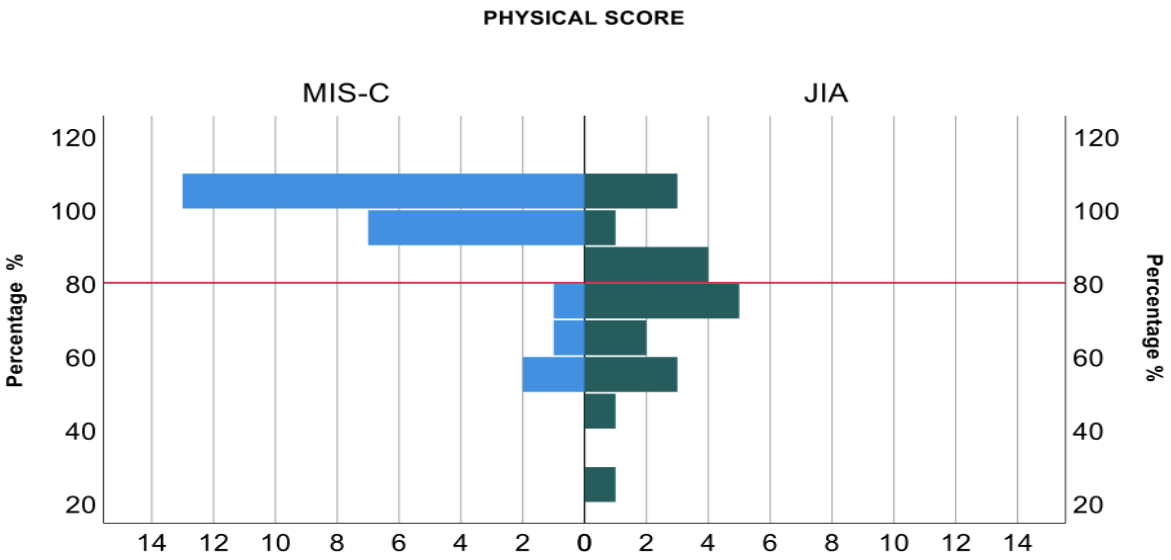
Appendix A: Supplementary material

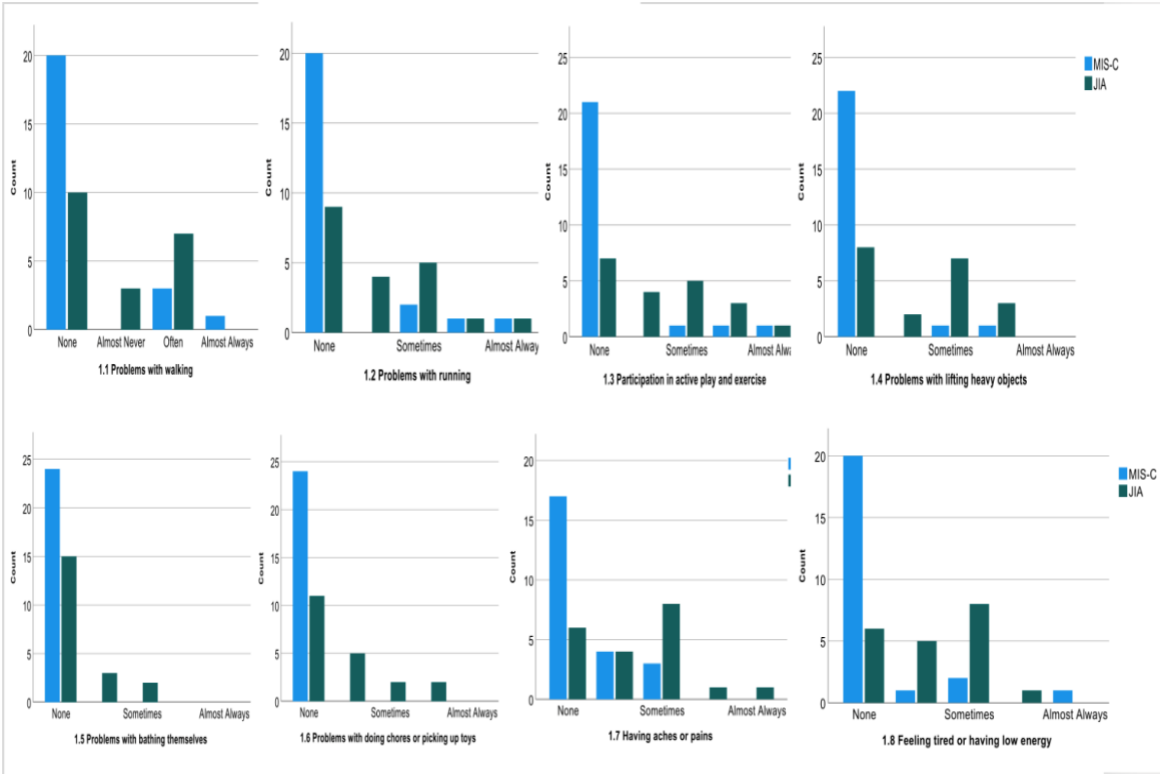
Table 1. MIS-C definition criteria (11)

Table 1: Essential components for the diagnosis of MIS-C	
	Description
1. Child	In the USA this includes adolescents up to 21 years of age.
2. Fever	> 38.5ºC
3. Single OR multiorgan dysfunction	Organ dysfunction includes: Shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder Feature may include: Hypotension, tachycardia confusion, headache, syncope, conjunctivitis, respiratory symptoms including cough or supplemental oxygen requirement, sore throat, mucous membrane changes lymphadenopathy, neck swelling abdominal pain, diarrhoea, vomiting, rash, swollen hands and feet
4. Clear evidence of inflammation	Laboratory parameters include features of an exaggerated inflammatory response and cytokine storm and include: Raised C-Reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), fibrinogen, d-dimer, ferritin, lactic acid dehydrogenase (LDH), neutrophils, troponin T and Pro BNP. Reduced lymphocytes and low albumin
5. No clear other cause	Consider: Bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice or management)
6. SARS-CoV2 PCR testing may be positive or negative if possible antibody test should be performed	

Table 2. Quality of life assessment physical functioning score comparison between MIS-C and JIA

Physical Score MIS-C n=24 JIA n=20	MIS-C	JIA	MIS-C	JIA	MIS-C	JIA	MIS-C	JIA	MIS-C	JIA	
	None		Almost Never		Sometimes		Often		Almost Always		P-value
Problems with walking	20	10	0	3	0	0	3	7	1	0	.043
Problems with running	20	9	0	4	2	5	1	1	1	1	.023
Problems participation in active play	21	7	0	4	1	5	1	3	1	1	.001
Problems lifting heavy objects	22	8	0	2	1	7	1	3	0	0	<.001
Problems with bathing self	24	15	0	3	0	2	0	0	0	0	.010
Problems with doing chores or picking toys	24	11	0	5	0	2	0	2	0	0	<.001
Having aches or pains	17	6	4	4	3	8	0	1	0	1	.003
Feeling tired or having low energy	20	6	1	5	2	8	0	1	1	0	.001
Converted total score to %											**<.001**

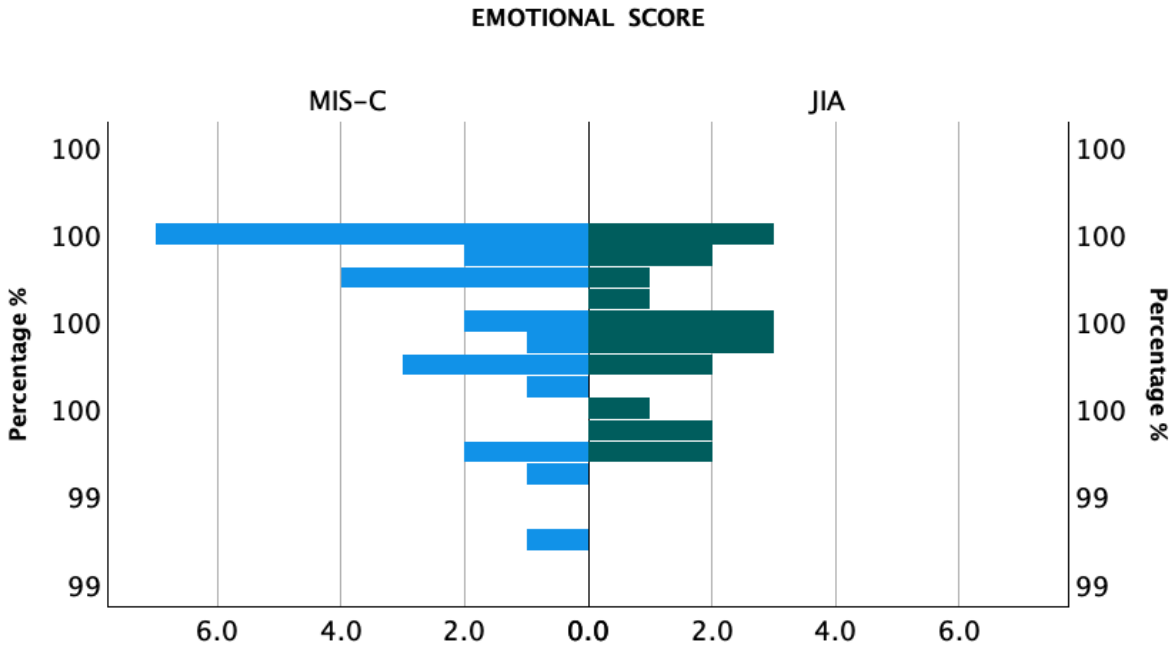


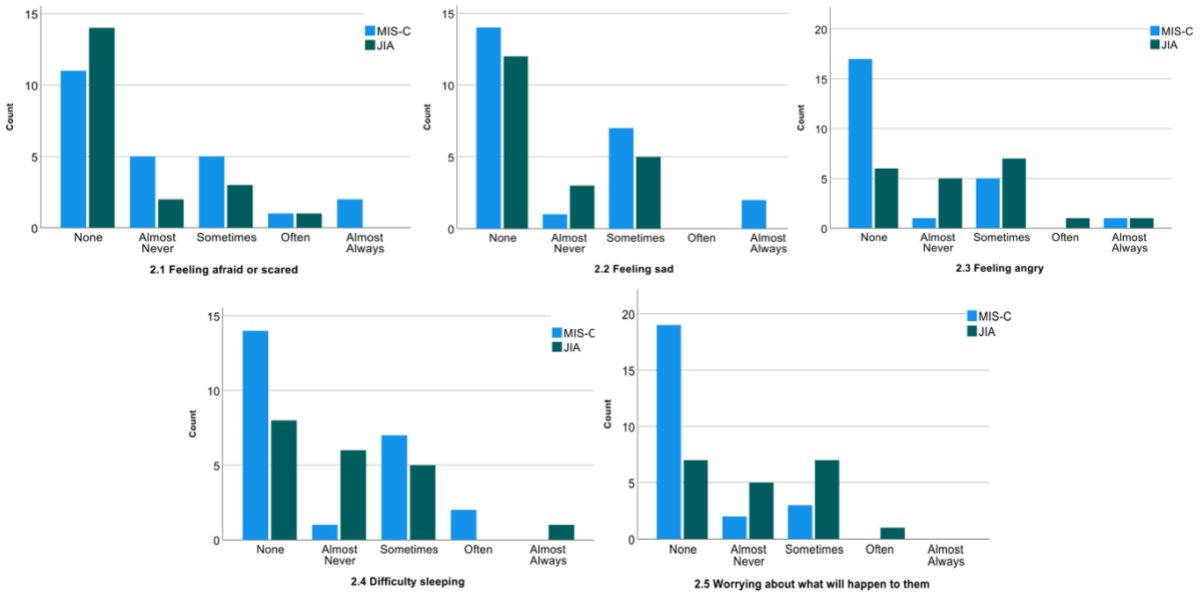


Quality of life assessment physical functioning score MIS-C and JIA
MIS-C- Blue, JIA-Green

Table 3. Quality of life assessment emotional functioning score comparison between MIS-C and JIA

Emotional MIS-C n=24 JIA n=20	MIS-C	JIA	MIS-C	JIA	MIS-C	JIA	MIS-C	JIA	MIS-C	JIA	
	None		Almost Never		Sometimes		Often		Almost Always		P-value
Feeling afraid or scared	11	14	5	2	5	3	1	1	2	0	.122
Feeling sad or blue	14	12	1	3	7	5	0	0	2	0	.592
Feeling angry	17	6	1	5	5	7	0	1	1	1	**.022**
Trouble sleeping	14	8	1	6	7	5	2	0	0	1	.618
Worrying about what will happen to them	19	7	2	5	3	7	0	1	0	0	**.004**
Converted total score to %											**.392**

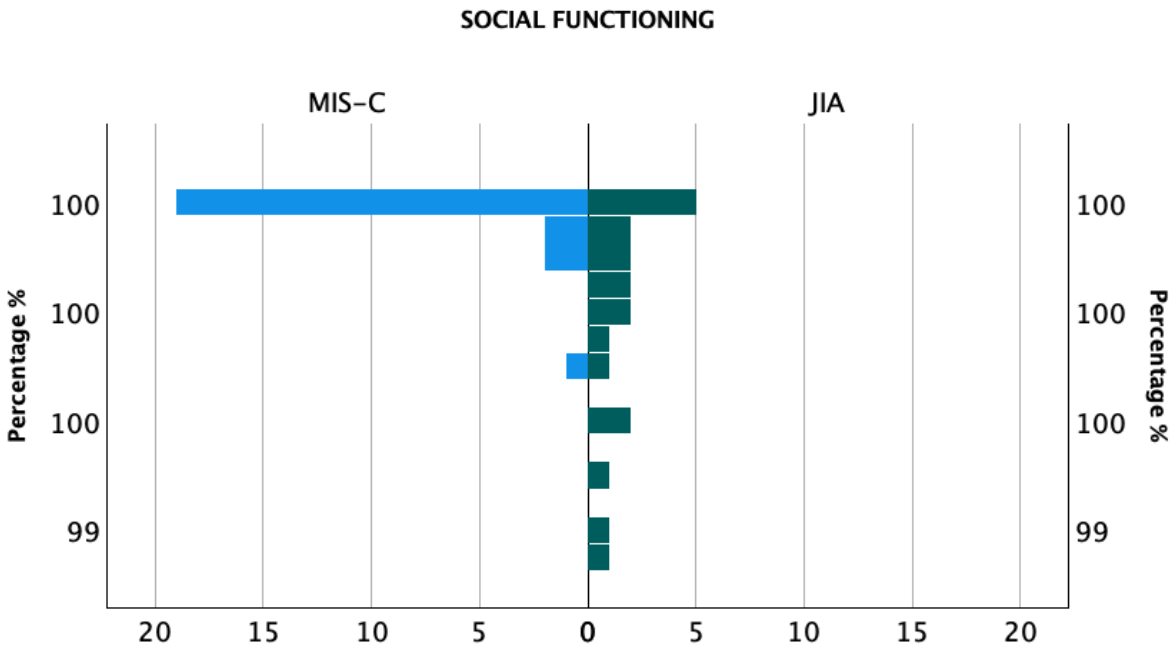


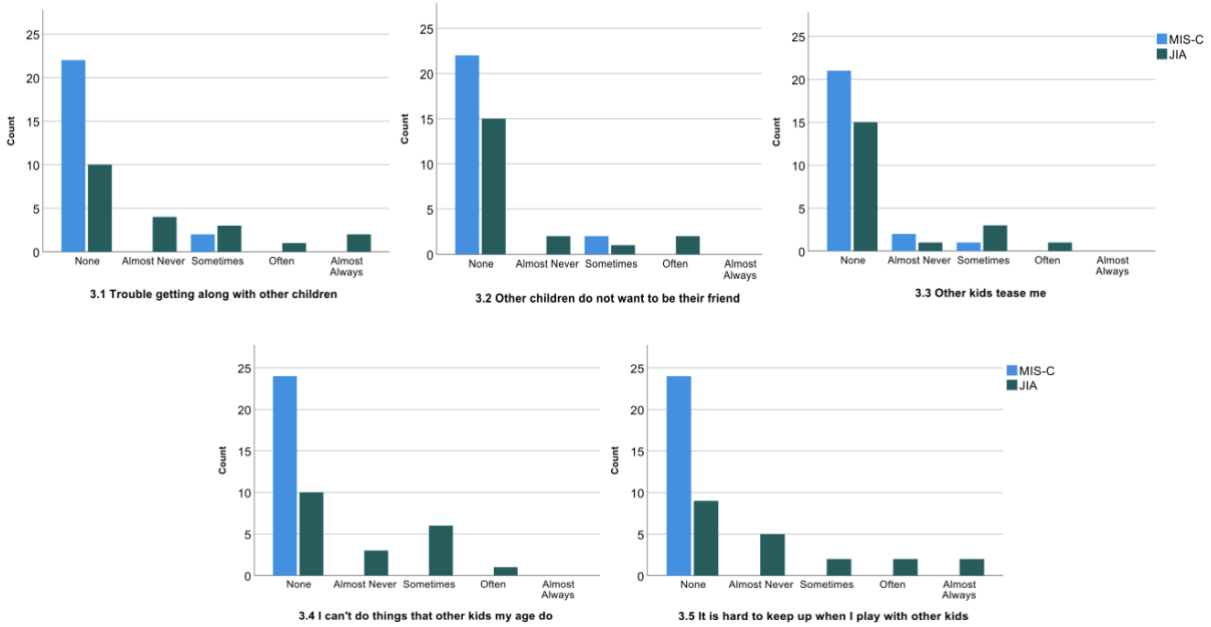


Quality of life assessment, emotional functioning score MIS-C and JIA
MIS-C- Blue, JIA-Green

Table 4. Quality of life assessment social functioning score comparison between MIS-C and JIA

Social MIS-C n=24 JIA n=20	MIS-C	JIA	MIS-C	JIA	MIS-C	JIA	MIS-C	JIA	MIS-C	JIA	
	None		Almost Never		Sometimes		Often		Almost Always		P-value
Getting along with other children	22	10	0	4	2	3	0	1	0	2	**.003**
Other kids not wanting to be his or her friend	22	15	0	2	2	1	0	2	0	0	.139
Getting teased by other children	21	15	2	1	1	3	0	1	0	0	.233
Not able to do things that other children his or her age can do	24	10	0	3	0	6	0	1	0	0	**<.001**
Keeping up when playing with other children	24	9	0	5	0	2	0	2	0	2	**<.001**
Converted total score to %											**<.001**

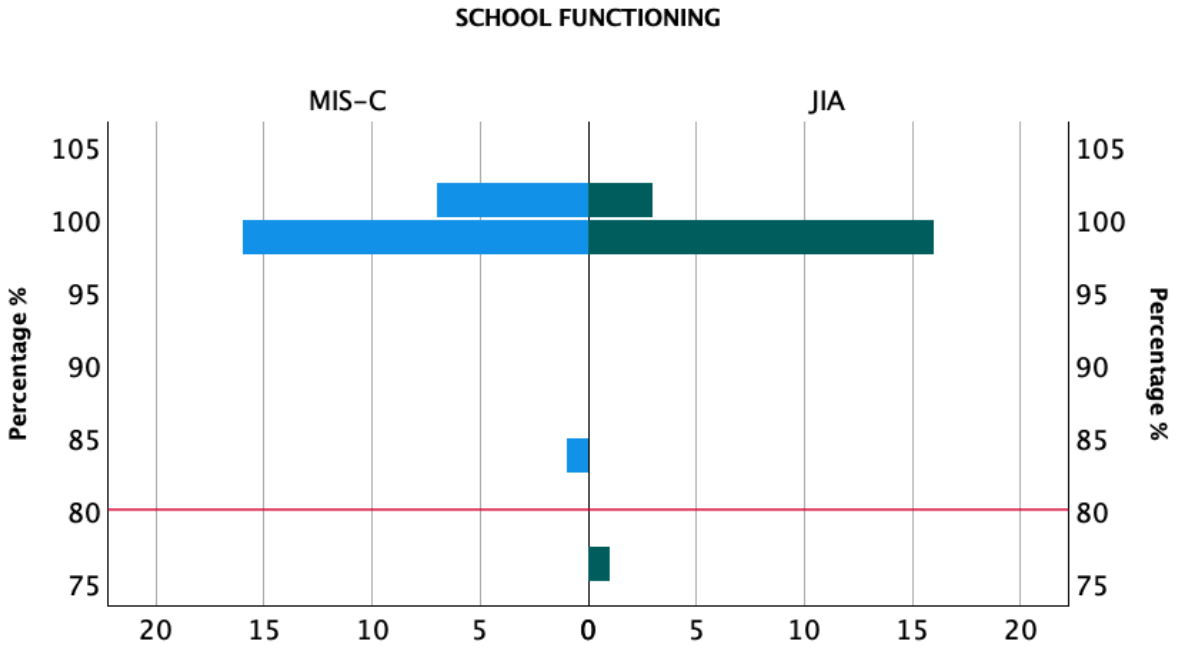


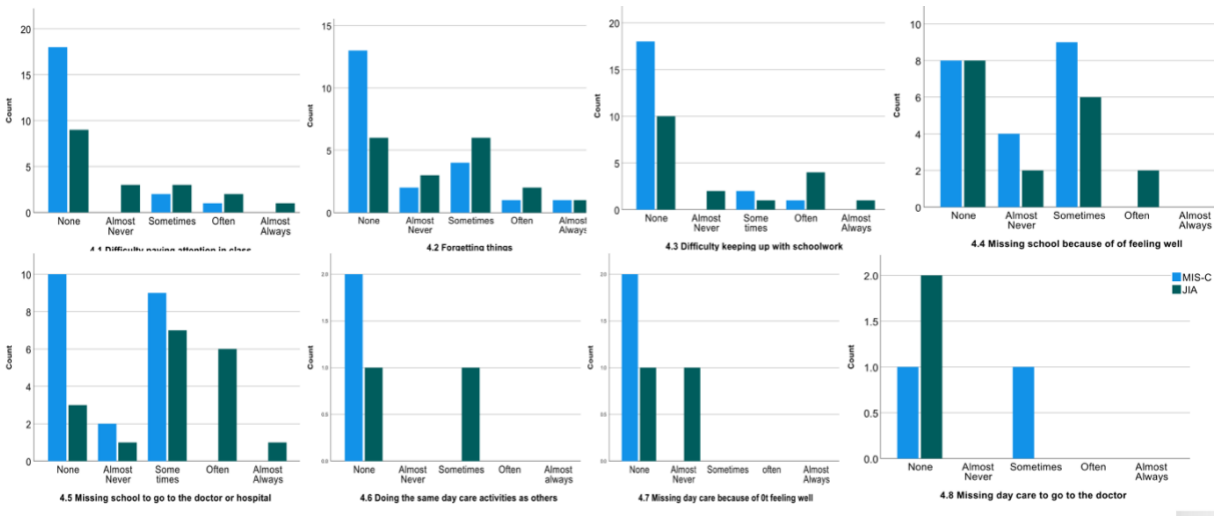


Quality of life assessment, social functioning score MIS-C and JIA
MIS-C- Blue, JIA-Green

Table 5. Quality of life assessment school functioning score comparison between MIS-C and JIA

School MIS-C n=24 JIA n=20	MIS-C	JIA	MIS-C	JIA	MIS-C	JIA	MIS-C	JIA	MIS-C	JIA	
	None		Almost Never		Sometimes		Often		Almost Always		P-value
Difficulty paying attention in class	18	9	0	3	2	3	1	2	0	1	.069
Forgetting things	13	6	2	3	4	6	1	2	1	1	.133
Difficulty keeping up with schoolwork	18	10	0	2	2	1	1	4	0	1	.100
Missing school because not feeling well	8	8	4	2	9	6	0	2	0	0	.922
Missing school because has to go to the doctor	10	3	2	1	9	7	0	6	0	1	.004
Difficulty doing the same daycare activities (younger kids)	2	1	0	1	0	0	0	0	0	0	1.0
Missing daycare because not feeling well(younger kids)	2	1	0	1	0	0	0	0	0	0	1.0
Missing daycare because has to go see the doctor (younger kids)	1	2	0	0	1	0	0	0	0	0	.667
Converted total score to %											.031

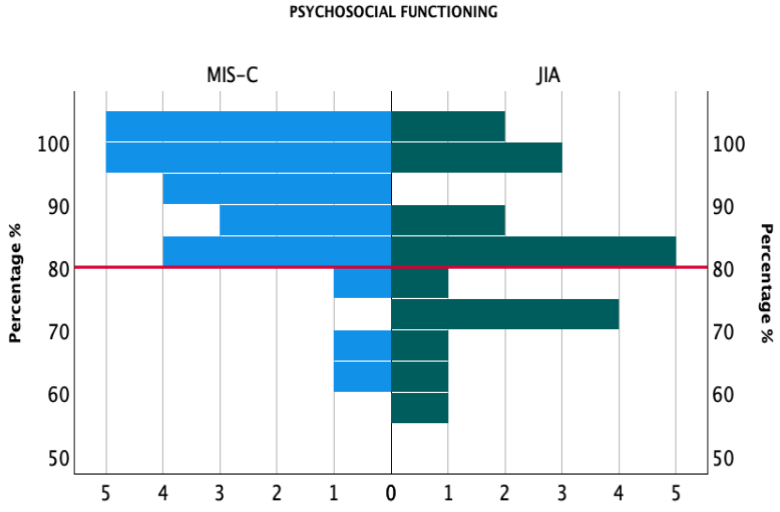




Quality of life assessment, school functioning score MIS-C and JIA
MIS-C- Blue, JIA-Green

Table 6. Quality of life assessment psychosocial functioning score comparison between MIS-C and JIA

Psychosocial MIS-C n=24 JIA n=20	MIS-C	JIA	MIS-C	JIA	P-value
	Yes (<80%)		No (>80%)		
Deficit	3	8	21	12	.035



Quality of life assessment, psychosocial functioning score MIS-C and JIA
MIS-C- Blue, JIA-Green

Appendix B.Quality of life inventory questionnaire

ID#_____

Date:_____

TM

PedsQL

Paediatric Quality of Life Inventory

Version 4.0 – UK English

PARENT REPORT for **TODDLERS** (ages **2-4**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **PAST MONTH** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the **PAST MONTH**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Sometimes	Often	Almost Always
1. Walking	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in active play and exercise	0	1	2	3	4
4. Lifting heavy things	0	1	2	3	4
5. Bathing	0	1	2	3	4
6. Helping to pick up his or her toys	0	1	2	3	4
7. Having aches or pains	0	1	2	3	4
8. Feeling tired	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Sometimes	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Having trouble sleeping	0	1	2	3	4
5. Worrying	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Sometimes	Often	Almost Always
1. Playing with other children	0	1	2	3	4
2. Other children not wanting to play with him or her	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

****Please complete this section if your child attends nursery or day care***

NURSERY/DAY CARE FUNCTIONING *(problems with…)*	Never	Almost Never	Sometimes	Often	Almost Always
1. Doing the same nursery/day care activities as peers	0	1	2	3	4
2. Missing nursery/day care because of not feeling well	0	1	2	3	4
3. Missing nursery/day care to go to the doctor or hospital	0	1	2	3	4

ID# _____

Date: _____

PedsQL™

Paediatric Quality of Life Inventory

Version 4.0 English (United Kingdom)

PARENT REPORT for YOUNG CHILDREN (ages 5-7)

INSTRUCTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **ONE month**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Sometimes	Often	Almost Always
1. Walking 100 metres	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activities or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores, like picking up his or her toys	0	1	2	3	4
7. Having aches or pains	0	1	2	3	4
8. Feeling tired	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Sometimes	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Sometimes	Often	Almost Always
1. Getting on with other children	0	1	2	3	4
2. Other children not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not being able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Sometimes	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with school activities	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

ID#
_____

Date:_____
_

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

CHILD REPORT (ages 8-12)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **ONE month**, how much of a **problem** has this been for you …*

ABOUT MY HEALTH AND ACTIVITIES ***(problems with…)***	**Never**	**Almost Never**	**Sometimes**	**Often**	**Almost Always**
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS ***(problems with…)***	**Never**	**Almost Never**	**Sometimes**	**Often**	**Almost Always**
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS ***(problems with…)***	**Never**	**Almost Never**	**Sometimes**	**Often**	**Almost Always**
1. I have trouble getting along with other kids	0	1	2	3	4
2. Other kids do not want to be my friend	0	1	2	3	4
3. Other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age can do	0	1	2	3	4
5. It is hard to keep up when I play with other kids	0	1	2	3	4

ABOUT SCHOOL ***(problems with…)***	**Never**	**Almost Never**	**Sometimes**	**Often**	**Almost Always**
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

ID#
_____

Date:_____
_

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for CHILDREN (ages 8-12)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **ONE month**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Sometimes	Often	Almost Always
1. Walking more than one block	0	1	2	3	4

2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING ***(problems with…)***	**Never**	**Almost Never**	**Sometimes**	**Often**	**Almost Always**
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING ***(problems with…)***	**Never**	**Almost Never**	**Sometimes**	**Often**	**Almost Always**
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING ***(problems with…)***	**Never**	**Almost Never**	**Sometimes**	**Often**	**Almost Always**
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

Appendix C. Case reporting form

Version 1 (QUALITY OF LIFE FOR MIS-C PATIENTS POST DISEASE AT THE RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL) (March 2023)

Case reporting form 1:

Study number:
Date:
Gender:

DOB	Clinical complaint	BP	HR	Weight	Height	Abnormal exam findings	ECHO done

Appendix D. Ethics approval letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone (021) 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/home/human-research-ethics

03 July 2023

HREC REF: 452/2023

Dr K Webb
Division of Paediatric Rheumatology
Red Cross War Memorial Children's Hospital
Email: kate.webb@uct.ac.za
Student: frankphoya@yahoc.com

Dear Dr Webb

PROJECT TITLE: QUALITY OF LIFE OF MIS-C PATIENTS POST DISEASE AT THE RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL-SUB STUDY LINKED TO 112/2012 & 599/2020- (MPHIL CANDIDATE-DR FRANK PHOYA)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study, subject to Form A being provided.

Approval is granted for one year until the 30 July 2024.

You are required to submit a progress report form, using the standardised Annual Report Form (FHS016) if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Frank Phoya will also be involved in this study.

Please quote HREC REF 452/2023 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research

HREC/ref 452.2023

Appendix E. Research information sheet and consent form

Research Information Sheet/Consent Form v.3June 2019

What are we doing?

- We wish to perform research that aims to help find new treatments for rheumatic diseases like arthritis and lupus in young people. We would like to offer you the opportunity to help us do this research. We need information, blood and possible other tissues (like joint fluid and urine) from you or your child with a rheumatic disease. In addition, we are asking for healthy people to volunteer so that we can compare them with patients to try and find out what is causing disease.
- We are seeking permission to
    - 1. Store your or your child's blood, urine or synovial (joint) fluid or tissue for use in research. When you or your child has blood, urine or synovial fluid or tissue taken for clinical reasons, we request taking an additional sample for research. In addition, if you are above the age of 13, you may volunteer to donate blood for research even if you are not having blood taken anyway. 2. Collect information about your or your child.
- We are requesting permission for use of these specimens and information both in current research as well as future research that may occur. We do not yet know the nature of this research and wish to explain that in signing these forms, you are entitling us to use your child's tissue in any ethical manner that does not put you or your child, your family or your community at increased social, psychological or economic risk. Any future research would have to be reviewed by the Human Ethics Research Committee and agreed upon by Prof Chris Scott, who will be in charge of the repository.
- If other researchers from other centres would like to use the data or specimens for research, Prof Chris Scott would have to give written permission and the researchers would have to gain approval from their local and UCT's ethics committees.
- An example of how the samples may be used is to find out the cause of arthritis in patients with TB. We may look at the different type of cells in the joint fluid and blood of patients with TB and compare it to the joint fluid and blood of patients without TB.
- If you or your child has already had an HIV test, we will be recording whether your child is HIV positive or negative and we may be testing for HIV in the joint fluid and the blood. If your child has not been tested for HIV, we will not do an HIV test on your child without your permission and without you having been counselled.
- We may use your or your child's specimens for genetic research in the future. This would be subject to the approval of the Human Research Ethics Committee.
- We may use your or your child's specimens to aid in the discovery of drug therapy.
- If there is anything clinically significant in the specimen that we find, we do have an obligation to contact you or your child and offer treatment, for example, if we find TB on a sample of joint fluid, we will attempt to contact you or your child and offer treatment
- Patients or parents will not be charged for having the specimens stored or researched, and similarly you will have no monetary benefit if you agree to having the specimens stored or researched.
- The following clinical data may be collected: Name, hospital number, date of birth, demographics (age, gender, race) admission date, discharge date, area they live, type of rheumatological disease, disease activity and disease course, clinical condition, treatment, HIV status, TB status, family history, laboratory data and clinical data, address, contact details and images if clinically relevant.

• Why are we doing it?

- There will be benefits in the storage and use of your or your child's specimens. Very little is known about connective tissue disease in African patients. There is also very little known about the exact nature of joint disease in the setting of TB and HIV which are very common in South Africa. We hope that by looking at the samples from our patients and healthy volunteers, we will better be able to understand the biological mechanism of these diseases and ultimately improve the treatment that we can offer to patients.

• Will my /my child's identity be protected?

- When we take your or your child's samples, they will be stored under a unique research identifier. This will be able to link the researchers back to your name in a database that will be kept by the researchers. These links are only available to the researchers and your identity will be kept anonymous if any research was to be published or presented.

- Your or your child's personal information will only be available to researchers and your or your child's name, date of birth or other identifying features will never be published or presented without your permission.

What if I don't want to be involved?

- If you would not like your or your child's blood or joint fluid to be stored or if you would like to put restrictions on the storage or research of the specimens, we will continue to treat you as normal and you will not be disadvantaged in any way.
- You or your child may withdraw permission at any time –all you need to do is contact Prof Chris Scott at 0216585191 or chris.scott@uct.ac.za.
- You can contact the UCT human research ethics committee at 0214066338/6626.

Why do I have to sign?

- Any research that aims to store or research human specimens must be approved by the Human Research Ethics Committee.
- In accordance with ethical guidelines, patients and parents of patients must be informed of and consent to the storage and use of any biological specimens.

Consent

I consent to the following for myself/my child (tick ONE choice from each of the following boxes):

☐ I want my/my child's data collected and stored anonymously
AND

☐ I give permission for my/my child's blood/synovial fluid/urine sample to be stored indefinitely.
☐ I do not want my/my child's blood/synovial fluid/urine sample to be collected and stored
☐ I want my/my child's blood/synovial fluid/urine sample destroyed after ___ years

AND if the sample is to be stored:
☐ I give permission for my/my child's blood/synovial fluid/urine sample to be stored and used in future research of any type which has been approved by the HREC
☐ I give permission for my/my child's blood/synovial fluid/urine sample to be stored and used in future research but only for rheumatological diseases
☐ I give permission for my/my child's blood/synovial fluid/urine sample to be stored and used in future research except for research about _____

AND

☐ I am willing to be re-contacted by the researcher about possible future use of my tissue samples in future research.
☐ I do not want to be re-contacted to ask me to give more tissue samples in the future or to take part in future studies.

I have read the information, or it has been read to me. I have had the chance to ask questions about it and I am satisfied with the answers I was given. I consent voluntarily and understand that I have the right to withdraw my consent without this affecting the research I am currently taking part in or my medical care.

Signed

Parent/Subject:	Investigator:
Signature: Date:	Signature: Date:

Appendix F. List of co-authors and contributions

Author

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Medium term health and quality of life outcomes in a cohort of children with MIS-C in Cape Town, South Africa

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Background: Multisystem inflammatory syndrome in children (MIS-C) is a disease that occurs after exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Its short-term effects have been documented but little data exist on the longer term effects of MIS-C on the health and quality of life (QOL) of patients. The objective of this study was to assess the long-term effects of MIS-C on the QOL of children.
Methods: This study was a descriptive prospective study. We included 24 participants with previous MIS-C and 20 children with juvenile idiopathic arthritis (JIA) as a positive comparator group. All children were examined and completed a paediatric quality of life (PedsQL) generic inventory score. This score was used to evaluate the School Functioning, Social, Emotional, and Physical QOL domains.
Results: All participants with previous MIS-C made a full recovery, with no medical complaints, and normal physical examinations after a median of 705 days post acute diagnosis. The PedsQL inventory revealed that 16.7% of the children with previous MIS-C showed a deficit in the physical domain compared to 60% of the children with JIA ($p < 0.001$). 12.5% of the children with previous MIS-C had a deficit in their psychosocial domain which included emotional, social, and educational scores, compared to 40% of the children with JIA ($p = 0.035$).
Conclusions: In a cohort of 24 South African children with previous MIS-C, no medical complications were reported. A small proportion felt a prolonged effect on their QOL even after making a full recovery, although this was not as severe as children with JIA, a known chronic disease that affects QOL. This highlights the need to continue to follow up these patients and offer more comprehensive long-term care.

KEYWORDS

MIS-C (multisystem inflammatory syndrome in children), quality of life, juvenile idiopathic arthiritis, South Africa, physical deficits

Abbreviations
COVID 19, Coronavirus disease 2019; CRP, C-reactive protein; CYP, children and young people; HRQOL, health-related quality of life; JIA, juvenile idiopathic arthritis; KD, Kawasaki disease; MIS-C, multisystem inflammatory syndrome in children; PedsQL, Pediatric Quality of Life Inventory; QOL, quality of life; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

Background

In 2020, a hyperinflammatory syndrome with multiorgan involvement, potentially linked to Coronavirus disease (COVID-19) emerged among clusters of children, resembling Kawasaki disease, but with notable clinical and diagnostic distinctions (1). While data on this syndrome, Multisystem Inflammatory Syndrome in Children (MIS-C), remains rare in Africa, a cohort study done in Cape Town, South Africa helped to estimate its incidence and characteristics, estimating an incidence of 22 cases per 100,000 SARS-CoV-2 exposures (2–4). MIS-C presents with fever, inflammation, and involvement of multiple organ systems, often including gastrointestinal symptoms, with lower mortality rates compared to classic Kawasaki disease (4, 5).

Despite the relatively low mortality rates, concerns over long-term impacts on health and quality of life (QOL) post-MIS-C have emerged (6, 7). Very few studies have investigated long-term health and QOL in children after MIS-C. In the UK, Penner et al. reported that almost 20% of children with previous MIS-C had deficits in the psychosocial QOL with persistent emotional and physical impairment in some children (8). There are no studies that compare the QOL of children with previous MIS-C to an unwell comparator group from the same setting, in order to contextualise the residual impairment. Research on the long-term effects of MIS-C, particularly on QOL, remains limited, especially in Africa.

Here, we aimed to describe the long-term effects of MIS-C on the health and QOL of a cohort of children in Cape Town, South Africa. We included children with juvenile idiopathic arthritis (JIA), a chronic disease with a known severe effect on QOL (9) as a positive comparator group in order to contextualise these findings.

Methods

We performed a descriptive prospective longitudinal cohort study in which participants diagnosed with MIS-C between March 2020 and January 2022 were recalled and offered participation between January 2023 and December 2023. Children with JIA were recruited as a convenience comparator group during the same period. The study was conducted at Red Cross War Memorial Children's Hospital, which is a government-funded, tertiary-level referral hospital located in Cape Town, South Africa. This study was approved by the University of Cape Town Human Research Ethics Committee (HREC 112/2012; 599/2020).

Inclusion criteria included:

- Children and young people (CYP) aged less than 18 years.
- Previous diagnosis of MIS-C between March 2020 and January 2022 (Diagnosed according to the WHO, MIS-C criteria) (Supplementary Table 1)
- 6 months or more post-disease onset (MIS-C)
- CYP attending paediatric rheumatology clinics with a diagnosis of JIA according to the treating physician

The exclusion criteria were:

- Alternative diagnoses (e.g., Systemic lupus erythematous)
- Chronic, co-morbid diagnosis that may affect the QOL (e.g., HIV, malignancy)

CYP (or their parents where appropriate) who had agreed to be contacted again by researchers during their initial consent for a paediatric biorepository study and met the inclusion and exclusion criteria were contacted telephonically to return for a repeat clinical follow-up visit.

During the visit, variables were collected, including demographics (i.e., sex, age) and current complaints (i.e., joint pain, recent infection). Clinical data was collected [weight, height, and vital signs (temperature, respiratory rate, heart rate and blood pressure)] and recorded in a case report form (CRF) (Supplementary Appendix B2). A brief history was taken and a follow-up on their health since the last clinical visit was performed. A general examination was done reviewing the neurological, respiratory, cardiovascular, gastroenterology, and musculoskeletal system and recorded in the CRF (Supplementary Appendix B2). At the end of the visit, patients or guardians were asked to fill in a paediatric QOL Inventory/questionnaire (PedsQL; Supplementary Appendix B1). "PedsQL is a 23-item generic health status instrument that is used to assess five domains of health (physical functioning, emotional functioning, psychosocial functioning, social functioning, and school functioning)" (10). "The tool can be used as a child self-report or parent proxy-report format. Child self-report includes ages 5–7, 8–12, and 13–18 years. Parent proxy report includes ages 2–4 (toddler), 5–7 (young child), 8–12 (child), and 13–18 (adolescent), and assesses parents' perceptions of their child's health-related quality of life (HRQOL)". "A 5-point response scale is utilized across child self-report for ages 8–18 and parent proxy-report (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem)". "To further increase the ease of use for the young child self-report (ages 5–7), the response scale is reworded and simplified to a 3-point scale (0 = not at all a problem; 2 = sometimes a problem; 4 = a lot of a problem)". "Items were reverse scored and linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0) so that higher scores indicate better HRQOL". "Scale scores were computed as the sum of the items divided by the number of items answered (to account for missing data). If more than 50% of the items in the scale are missing, the scale score was not computed". "A score of less than 80% was indicative of a deficit in that particular domain". The Psychosocial Score (15 items), the mean was computed as the sum of the items divided by the number of items answered in the School Functioning, Social, and Emotional Subscales (10).

In children less the 12 years old, the questionnaire was completed by their guardian/parent. We asked children older than 12 years old to fill out the questionnaire independently.

The statistical analyses were performed using SPSS (version 28.0.1.1). Simple descriptive statistics were used to summarize variables. Data was coded appropriately e.g., scores as ordinal data (e.g., PedsQL) or scale numerical data (weight, height, etc.) as applicable before entering into the analytical program. As per PedsQL guidelines, ordinal scores were transformed into

numerical values (11). Numerical data such as age were presented as mean (Standard Deviation) or median (Inter-Quartile Range) depending on data normality. Categorical variables were presented as proportions or percentages. Data between groups (MIS-C and JIA) were compared by non-parametric comparator testing as appropriate, such as Mann-Whitney U tests or Fisher's exact tests.

Disease definitions

MIS-C (Multisystem inflammatory syndrome in children).

Results

Of the 64 MIS-C cases diagnosed at Red Cross War Memorial Children's Hospital between 2020 and 2022, 24 children with previous MIS-C and 20 children with JIA agreed to take part in the study.

The clinical characteristics of the larger cohort have been described (4). Of the 24 MIS-C participants who were followed up in this study, 66.7% were male. At the time of diagnosis of MIS-C, the median age was 8.2 years (min = 1.4; max = 14.2) and fever, rash, conjunctivitis, tachycardia, hypotension, abdominal pain, diarrhoea, headache and arthritis were common features (Table 1). Summary clinical laboratory data are supplied in Table 1. Central nervous system (CNS) and renal disease were present in 25% and 16.7% of the patients respectively. Coronary artery dilatation was recorded in one patient, with a median ejection fraction of 61% (min = 32; max = 70) in the cohort. During admission, 87.5% of the children received antibiotics, 70.8% received intravenous immunoglobulin (IVIG) at 2 g/kg and 58.3% received IV methylprednisolone (30 mg/kg per day for 3 days). One third (29.2%) required ICU admission or inotropic blood pressure support (33.3%). All patients made a full recovery and were discharged home, with no deaths recorded. The average in-hospital stay was 8 days (SD- 3.7, min = 5; max = 21) (Table 1).

The median time to the study visit from the acute diagnosis of MIS-C was 705 days (min 255; max 1,004). The minimum age at the time of the study visit was 3 years and the maximum was 16.5 years. All children were well at study visit, with no admissions or illnesses of note since their admission with MIS-C, normal growth, normal vital signs and a normal clinical examination.

Out of the 20 recruited JIA participants in the comparator group, 55% were female. The median age was 14.3 years (min = 3.1; max = 17.3). The median time since the diagnosis of JIA was made was 591 days (min = 27; max = 3,693). The most common type of JIA was enthesitis related arthritis (ERA), at 30% (Table 1). No other significant clinical problems apart from pain were reported at the time of recruitment.

TABLE 1 MIS-C and JIA demographics and clinical features.

MIS-C	
Demographics at diagnosis	***n* = 24**
Gender	66.7% (16)
Age (median)	8.2 year (min = 1.4; max = 14.2)
Median time since diagnosis	705 days (min-255; max = 1,004)
Clinical features at diagnosis	
Fever	100% (24)
Rash	100% (24)
Abdominal pain	100% (24)
Tachycardia	91.7% (22)
Conjunctivitis	79.2% (19)
Hypotension	54.2% (13)
Headache	45.8% (11)
Diarrhoea	41.7% (10)
Arthritis	37.5% (9)
CNS disease	25% (6)
Lung disease	20.8% (5)
Renal disease	16.7% (4)
Bleeding	4.2% (1)
Coronary artery aneurysm present	4.2% (1)
Median ejection fraction	61% (min = 32; max = 70)
Median CRP	173 mg/dl (min = 103; max = 511)
Median white cell count	17.2×10^9/L (min = 8.6; max = 59.9)
Median Pro BNP	1,319 pg/ml (min = 24; max = 48,172)
Initial management and outcomes	
1st line antibiotics	87.5% (21)
IVIG 2 g/kg first dose	70.8% (17)
IVIG 1 g/k first dose	16.7% (4)
IVIG 2 g/kg second dose	4.2% (1)
Methylprednisone	58.3% (14)
ICU admission	29.2% (7)
Inotropes	33.3% (8)
Discharged	100% (24)
Median duration of admission	7 days (min = 5; max = 21)
JIA	
Demographics at recruitment	***n* = 20**
Gender (male)	45% (9)
Age (median)	14.3 year (min = 3.1; max = 17.1)
Duration since diagnosis	1.6 years (min = 0.4; max = 10)
Median time since diagnosis	591 day (min = 27; max = 3,693)
Type of JIA	
ERA	30% (6)
Oligo	20% (4)
Poly	20% (4)
PsJIA	20% (4)
Sys	10% (2)

CRP, C reactive protein; Pro BNP, Pro brain natriuretic peptide; MIS-C, multisystem inflammatory syndrome in children; JIA, juvenile idiopathic arthritis; IVIG, intravenous immunoglobulin; IUC, intensive care unit; ERA, enthesitis related arthritis; Oligo, oligoarticular arthritis; Poly, polyarticular arthritis; PsJIA, psoriatic associated juvenile idiopathic arthritis; Sys, systemic arthritis.

Quality of life assessment MIS-C and JIA

Physical domain

Four out of 24 (16.6%) participants with MIS-C showed an overall deficit (score of less than 80%) in the physical domain as compared to 12/20 (60%) of participants with JIA ($p = 0.001$) (Figure 1A). These included problems with walking ("often"-3/24; "almost always"- 1/24), running ("often"-1/24; "almost always"- 1/24). Compared to participants with MIS-C, participants with JIA reported more difficulty participating in

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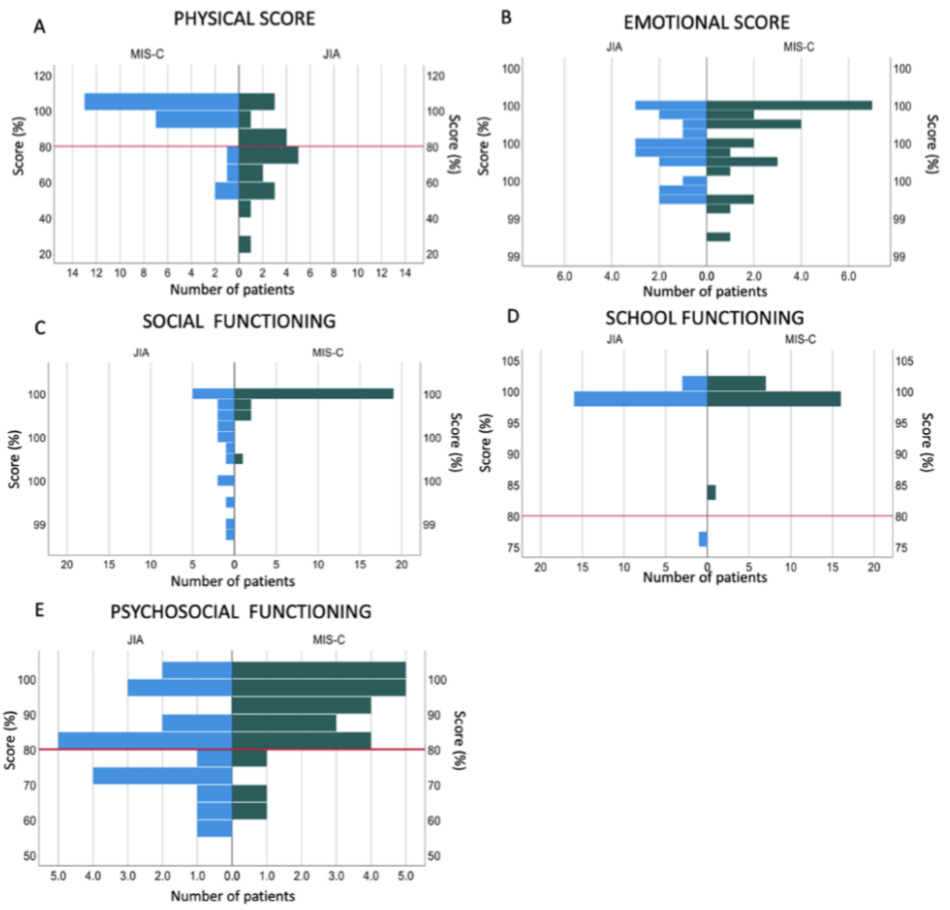

FIGURE 1
Quality of life assessments in children with previous MIS-C compared to children with JIA. (A) Physical domain score, (B) Emotional domain score, (C) Social functioning domain score, (D) School functioning domain score, (E) Psychosocial functioning domain score. The red line indicates 80%, scores below which indicate a deficit in that domain.

active play ($p = 0.001$), doing chores ($p = <0.001$) and reported feeling tired ($p = 0.001$) (Supplementary Table 2).

Emotional domain

A summary percentage score for the emotional domain showed that no participant with previous MIS-C or JIA scored below 80%, showing no deficit in that field (Figure 1B) with no difference between the two groups (Supplementary Table 3).

Participants with JIA more frequently reported feelings of anger due to their condition than participants with MIS-C ($p = 0.022$) and were also found to be more worried about what would happen to them due to their disease than participants with previous MIS-C ($p = 0.004$) (Supplementary Table 3).

Social domain

In the social domain, participants with JIA showed more difficulties in all the 4 reported areas than participants with previous MIS-C. Participants with JIA had more difficulty getting along with other children ($p = 0.003$), doing things that their peers can do ($p = <0.001$), and keeping up when playing with their peers ($p = <0.001$) (Supplementary document Figure 4).

The summary percentage score revealed no participant scored below 80% in both groups; however, there was still a significant difference between the two groups ($p = <0.001$) (Supplementary Table 4).

School domain

No participants with MIS-C showed a deficit in the school domain and only 1/20 (5%) of participants with JIA showed a

deficit, with no overall difference ($p = 0.31$) (Figure 1D; Supplementary Table 5). Participants with JIA more frequently reported missing school to go to the doctor ($p = 0.003$) (Supplementary Table 5; Supplementary Figure 5).

Psychosocial domain

The psychosocial domain was made up of a combined score of the emotional, social and school domain summary percentage scores.

Twelve percent (3/24) of participants with MIS-C had a deficit in the psychosocial domain compared to 40% of children with JIA ($p = 0.035$) (Figure 1E; Supplementary Table 6).

Discussion

In this study, we recruited 24 participants with previous MIS-C and investigated their health and QOL after a median of 2 years from diagnosis. We compared these children to a group of children from the same setting with JIA, a known chronic and painful disease with expected deficits in multiple QOL domains (9).

All of the participants who had MIS-C previously made a full recovery and had no significant medical complications, which matches the good long-term outcomes in MIS-C reported elsewhere (6, 7).

Participants with previous MIS-C did however present with deficits in multiple QOL domains, although these were universally less severe than the deficits seen in children with JIA. Sixteen percent of participants with previous MIS-C in this study had difficulty in the physical domain and 12% showed difficulty in the psychosocial domain. This was similar to the study done by Penner et al. (8) in the UK, who showed that 13% and 18% of participants had a deficit in the physical and psychosocial domain respectively. Surprisingly, the cohort in the current study showed no significant deficit in the emotional domain as was reported in the UK study (8), which may reflect an emotional resilience in this cohort or could be due to the different time period between acute disease and study visit in the two studies.

Sixteen percent of participants with MIS-C had a deficit in the physical domain, which was lower than in participants with JIA (60%) (12). Participants with JIA reported more anger and worry than participants with previous MIS-C, which may be expected due to the chronicity of the disease.

There were no differences in scores in the social and school domain. Participants with JIA were more likely to find it difficult to get along with other children, the also found it difficult doing things that their peers were doing and difficult to keep up when playing with their peers, as expected (12).

A small sample size was one of the major limitations of this study. There are however very few long-term outcome data reported in MIS-C, and even fewer from Africa. Another limitation is the comparator group chosen; this study used only a "positive" control group, as it is known that children with JIA have low overall health-related QOL, in all aspects of physical health, psychosocial health, emotional functioning, and school functioning (9). Future research is needed to also compare the long-term QOL in children with MIS-C to a cohort that has recovered from a similar acute, monophasic disease and healthy children from the same setting. As the COVID-19 pandemic abates, we believe it is vital to continue to monitor children with MIS-C in the long term.

Conclusions

In a cohort of 24 African children with previous MIS-C, no medical complications were reported. A small proportion felt a prolonged effect on their QOL even after making a full recovery, which was less severe than in children with JIA. This highlights the need to continue to follow up these patients and offer more comprehensive long-term care.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Red Cross War Memorial Children's Hospital and the University of Cape Town Departmental Research Committee (DRC) and Human Research Ethical Committee (HREC REF 112/2012; 599/2020). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

FP: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal Analysis, Data curation, Conceptualization. CB: Writing – review & editing, Resources, Data curation. TS: Writing – review & editing, Resources, Data curation. HK: Writing – review & editing. HR: Writing – review & editing, Data curation. CS: Writing – review & editing. KW: Writing – review & editing, Supervision, Resources, Methodology, Data curation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2024.1465976/full#supplementary-material

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Appendix H. Turnitin report

thesis turnitin submission 4.docx

by Frank Phoya

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Word count: 2820
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A PROSPECTIVE STUDY AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL'S

Background: Multisystem inflammatory syndrome in children (MIS-C) is a disease that occurs after exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)". Its short term effects have been documented but little data exist on the longer term effects of MIS-C on the health and quality of life of patients. The objective of this study was to assess the long-term effects of MIS-C on the quality of life of children .

Methods: This study was a descriptive prospective study. We included twenty-four participants who were previously diagnosed with MIS-C. Twenty children with juvenile idiopathic arthritis (JIA) were recruited as a comparison group. We examined and had them complete a paediatric quality of life (PedsQL) generic inventory score. This score was used to evaluate the, School Functioning, Social, Emotional, and Physical domain of the two groups.

Results: All participants with previous MIS-C made a full recovery, with no medical complaints, and all had a normal physical examination median of 705 days after their diagnosis. The PedsQL inventory revealed that 16.7% of the children with previous MIS-C showed a deficit in the physical domain compared to 60% of the children with JIA ($p<0.001$) and 12.5% of the children with previous MIS-C had a deficit in their psychosocial domain which included emotional, social, and educational scores, compared to the children with JIA where 40% showed a deficit in this domain ($p=0.035$).

Conclusions: Even though children who previously had MIS-C showed no obvious long term medical effects, a prolonged effect on the quality of life was very evident in our group.

Keywords

MIS-C (Multisystem inflammatory syndrome in children) and PedsQL (Pediatric Quality of Life Inventory)

Background

In 2020, a hyperinflammatory syndrome with multiorgan involvement, potentially linked to Coronavirus disease (COVID-19) emerged among clusters of children, resembling Kawasaki Disease, but with notable clinical and diagnostic distinctions(1). While data on this syndrome, Multisystem Inflammatory Syndrome in Children (MIS-C), remains rare in Africa, a cohort study done in Cape Town, South Africa helped to estimate its incidence and characteristics, estimating an incidence of 22 cases per 100,000 SARS-CoV-2 exposures (2, 3). MIS-C presents with fever, inflammation, and involvement of multiple organ systems, often including gastrointestinal symptoms, with lower mortality rates compared to classic Kawasaki disease (4, 5).

Despite the relatively low mortality rates, concerns over long-term impacts on health and quality of life post-MIS-C have emerged (6, 7). Studies indicate varying degrees of physical, emotional, and psychosocial impairment among affected children (8). It is not clear whether these findings are unique to MIS-C or reflect general responses to severe childhood illness. Research on the long-term effects of MIS-C, particularly on their quality of life, remains limited, especially in the African regions . Here, we describe the long-term effects of MIS-C on children in Cape Town, and compare these to a group of children with juvenile idiopathic arthritis (JIA), another autoimmune/autoinflammatory condition.

Methods

We performed a descriptive prospective longitudinal cohort study in which participants diagnosed with MIS-C between March 2020 and January 2022 were recalled and offered participation between January 2023 and December 2023. Children with JIA were recruited

In children less the 12 years old, the questionnaire was completed by their guardian/parent. We asked children older than 12 years old to fill out the questionnaire independently.

The statistical analyses were performed using SPSS (version 28.0.1.1). Simple descriptive statistics were used to summarize variables. Data was coded appropriately e.g., scores as ordinal data (e.g., PedsQL) or scale numerical data (weight/ height etc.) as applicable before entering into the analytical program. As per PedsQL guidelines, ordinal scores were transformed into a numerical values (10). Numerical data such as age was presented as means (Standard Deviation) or median (Inter-Quartile Range) depending on data normality. Categorical variables were presented as proportions or percentages. Data between groups (MIS-C and JIA) were compared by non-parametric comparator testing as appropriate, such as Mann-Whitney U tests or Fisher's exact tests.

Results

Out of 64 MIS-C cases diagnosed at Red Cross War Memorial Children's Hospital between 2020-2022, 24 children with previous MIS-C and 20 children with JIA agreed to take part in the study.

Of the 24 MIS-C participants , 66.7% were male and 62.6% were of coloured ethnicity. At diagnosis of MIS-C, the median age was 8.2 years (min=1.4; max=14.2) and fever, rash, conjunctivitis, tachycardia, hypotension, abdominal pain, diarrhoea, headache and arthritis were common features (Table 1). CNS disease and renal disease had been present in 25% and 16.7% of the patients respectively. Coronary artery dilatation was recorded in one patient. During admission, 87.5% received antibiotics, 70.8% received intravenous immunoglobulin (IVIG) at 2g/kg and 58.3% received IV methylprednisolone (30mg/kg per day for 3 days). One third (29.2%) required ICU admission or inotropic blood pressure support (33.3%). All patients made a full recovery and were discharged home, with no deaths recorded. The average in-hospital stay was 8 days (SD- 3.7, min =5; max=21) (Figure 1).

Twenty-four participants with MIS-C were followed up for this study at a median of 705 days after their admission with MIS-C (min 255; max 1004). The minimum age at f follow up was 3 years and the maximum was 16.5 years. All children were well at follow up with no admissions or illnesses of note since their admission with MIS-C, normal growth, normal vital signs and a normal clinical examination.

Out of the 20 recruited JIA participants in the comparator group, 55% were female. The median age was 14.3 years (min=3.1; max=17.3). The median time since the diagnosis of JIA was made was 591 days (min=27; max=3693). The most common type of JIA was enthesitis related arthritis (ERA), at 30% (Figure 1). No other significant clinical problems apart from on and off pain were reported at the time of recruitment.

Quality of life assessment MIS-C and JIA

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Quality of life assessment MIS-C and JIA

Physical domain
Four out of 24 (16.6%) participants with MIS-C showed an overall deficit in the physical domain on follow up as compared to 12/20 (60%) of participants with JIA (p=0.001) (Figure 2). These included problems with walking ('often'-3/24; 'almost always'- 1/24), running ('often'-1/24; 'almost always'- 1/24). Compared to participants with MIS-C, participants with JIA reported more difficultly participating in active play (p=0.001), doing chores (p=<0.001) and reported feeling tired (p=0.001) (Table 2).

Emotional domain
A summary percentage score for the emotional domain showed that no participant with previous MIS-C or JIA scored below 80%, showing no deficit in that field (Figure 3) with no difference between the two groups (Table 3).

Participants with JIA more frequently reported feelings of anger due to their condition than participants with MIS-C (p=0.022) and were also found to be more worried about what would happen to them due to their disease than participants who had MIS-C (p=0.004) (Table 3).

Social domain
In the social domain, participants with JIA showed more difficulties in all the 4 reported areas than participants with previous MIS-C. Participants with JIA had more difficulty getting along with other children (p=0.003), doing things that their peers can do (p=<0.001), and keeping up when playing with their peers(p=<0.001) (Figure 4).

The summary percentage score revealed no participant scored below 80% in both groups; however, there was still a significant difference between the two groups (p=<0.001) (Table 4).

School domain
No participants with MIS-C showed a deficit in the school domain and only 1/20 (5%) of participants with JIA showed a deficit, with no overall difference (p=0.31) (Table 5). Participants with JIA more frequently reported missing school to go to the doctor (p=0.003) (Table 5) (Figure 5)

Psychosocial domain
The Psychosocial domain was made up of a combined score of the emotional, social and school domain summary percentage scores.

Twelve percent (3/24) of participants with MIS-C had a deficit in the psychosocial domain compared to 40% of children with JIA (p=0.035) (Table 6; Figure 6).

Discussion

In this study, we recruited 24 participants with MIS-C and investigated their quality of life after a median of 2 years from diagnosis, and compared them to a group of participants with JIA, a chronic and painful disease.

All of the participants who had MIS-C previously made a full recovery and had no significant medical complications, which matches the good long-term outcomes in MIS-C reported elsewhere (6, 7).

Participants with previous MIS-C did however present with deficits in multiple quality of life domains. Sixteen percent of participants with previous MIS-C in this study had difficulty in the physical domain and 12% showed difficulty in the psychosocial domain. This was similar to the study done by Penner et al.(8) in the UK, who showed that 13% and 18% of participants had a deficit in the physical and psychosocial domain respectively. Surprisingly, the cohort in the current study showed no significant deficit in the emotional domain as was reported in the UK study (8), which may reflect an emotional resilience in this cohort or could be due to the different time period between disease and recruitment in the two studies.

Sixteen percent of participants with MIS-C had a deficit in the physical domain, which was lower than in participants with JIA (60%)(12). Future research may compare children with previous MIS-C to healthy children to get a truer reflection of whether the limitation in the physical domain is meaningful. It is known that children with JIA have low overall health-related quality of life (HRQOL), in all aspects of physical health, psychosocial health, emotional functioning, and school functioning (13). Participants with JIA reported more anger and worry than participants with previous MIS-C, which may be expected due to the chronicity of the disease.

There were no differences in scores in the social and school domain. Participants with JIA were more likely to find it difficult to get along with other children, the also found it difficult doing things that their peers were doing and difficult to keep up when playing with their peers. This could be attributed to the deficit in the physical domain which can be expected and has been reported in JIA(12).

A small sample size was one of the major limitations of this study. There are however very few long-term outcome data reported in MIS-C, and even fewer from Africa. Another limitation is the comparator group chosen; participants with JIA have already been shown to have a poor quality of life due to the chronicity of the disease (13). The use of a cohort that has recovered from an acute disease or healthy children from the same setting may better reflect the true long-term outcome deficits associated with MIS-C. As the COVID-19 pandemic abates, we believe it is vital to continue to monitor children with MIS-C in the long term.

Conclusions

In a cohort of 24 African children who previously had MIS-C, no medical complications were reported. A small proportion felt a prolonged effect on their quality of life even after making a full recovery. This highlights the need to continue to follow up these patients and offer more comprehensive long-term care.

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