ORIGINAL ARTICLE

Clinical Characteristics and Outcomes in Children With Severe Multisystem Inflammatory Syndrome in Children in Malaysia: A Nationwide Cohort Study

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ABSTRACT

Introduction: Early identification of patients at risk for severe multisystem inflammatory syndrome in children (MIS-C) is essential for favourable clinical outcomes. This study aims to identify the clinical characteristics, factors and outcomes associated with severe MIS-C. **Materials and methods:** In this retrospective cohort study involving 14 major hospitals in Malaysia, children <15 years who met the United States Centres for Disease Control and Prevention case definition for MIS-C were included. Severe MIS-C was defined as children who required inotropic support, ventilatory support (invasive or non-invasive ventilation), or left ventricular ejection fraction of <55%. The factors investigated for severe MIS-C were demographic characteristics, the presence of comorbidities, clinical characteristics, and laboratory measures. Multivariable logistic regression was used to compute the adjusted odds ratio (aORs) of factors associated with severe MIS-C. **Results:** Among the 155 patients, 91 (58.7%) presented with severe MIS-C. Severe MIS-C was more likely in patients aged ≥5 years old (aOR 2.13, 95% confidence interval [CI] 1.08-4.21), with dehydration (aOR 3.80, 95% CI 1.53-9.45), lethargy (aOR 2.02, 95% CI 0.97-4.18), tachycardia (aOR 8.33, 95% CI 3.27-21.22), albumin <30g/L (aOR 3.36, 95% CI 1.58-7.13), creatine kinase >200U/L (aOR 3.68, 95% CI 1.57-8.64), D-dimer >3.0µg/mL (aOR 2.11, 95% CI 1.08-4.13), ferritin >500ng/mL (aOR 3.77, 95% CI 1.88-7.55), prothrombin time >12.7 seconds (aOR 3.22, 95% CI 1.61-6.43), and urea >6mmol/L (aOR 5.09, 95% CI 2.04-12.71). **Conclusion:** Identification of these associated factors of severity in MIS-C could aid in early recognition and prompt escalation of care, leading to better outcomes.
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Keywords: Coronary artery aneurysm, Outcomes, Mortality, Multisystem inflammatory syndrome in children (MIS-C), SARS-CoV-2

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INTRODUCTION

With the advent of the coronavirus disease 2019 (COVID-19) pandemic emerged an unprecedented

hyperinflammatory syndrome affecting children worldwide. It was first described in early 2020, involving clusters of children in Europe and North America, which showed a temporal association to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.[1, 2] There are several terminologies coined for this novel syndrome mainly multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 by the United States Centres for Disease Control and Prevention (CDC)[3] and the World Health Organization,[4] and paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 by the Royal College of Paediatrics and Child Health.[5] This severe disease phenotype has features closely mimicking Kawasaki disease (KD), Kawasaki disease shock syndrome (KDSS), toxic shock syndrome, and severe COVID-19 disease.[6]

Although MIS-C has been extensively reported in many parts of Europe and the United States, it is still less commonly described in Asia.[7] Furthermore, it has been increasingly recognised that MIS-C involves damage to multiple organ systems in predominantly previously healthy children and adolescents.[8] Despite being a life-threatening condition whereby up to 76% of children with MIS-C require intensive care, and 2% eventually die,[9] a knowledge gap exists in identifying the risk factors for severe disease. Early identification of factors associated with severe MIS-C allows appropriate intervention, thus preventing further complications or mortality.

Therefore, this study aims to compare the epidemiology, clinical characteristics, and outcomes between children hospitalised with severe and non-severe MIS-C in Malaysia. Our secondary objective is to identify factors associated with severe illness in MIS-C.

MATERIALS AND METHODS

Study setting and design

This is a multicentre, retrospective cohort study of paediatric patients (aged <15 years) who met the criteria for MIS-C, admitted from June 1, 2020, and December 31, 2021, to 14 major hospitals in 10 states in Malaysia. The investigations, treatment and follow-up varied according to individual centres, as there was no standardised national protocol for the management of MIS-C. This study was performed before COVID-19 vaccinations were available to children <12 years old in the country. A waiver of informed consent was obtained as all data were anonymised during data transfer and analysis.

Data collection

Patient data and clinical outcomes were collected from the medical records through a standardised, secured data collection sheet. The data collected were patient demographics, clinical characteristics, laboratory measures, chest radiographic and 2d-echocardiographic findings, treatment received, and outcomes.

Definition

MIS-C was diagnosed based on the CDC criteria, i.e. fever in children with increased inflammatory markers, involvement of two or more organ systems, evidence of recent SARS-CoV-2 infection, and exclusion of alternative diagnoses[3] and the study did not include children with an acute severe COVID-19 infection. Laboratory evidence of COVID-19 was determined by either a positive SARS-CoV-2 serology or reverse transcription-polymerase chain reaction (RT-PCR) from respiratory samples. Then, MIS-C was categorised into severe and non-severe, adapting from the Yale New Haven Children's Hospital's disease severity classification.[10] Briefly, severe MIS-C was defined as children who required inotropic support, ventilatory support (either invasive or non-invasive ventilation), or had left ventricular ejection fraction (LVEF) of <55%. A coronary artery aneurysm was defined as a z-score >2.5 on a 2d-echocardiogram. Dehydration included any signs of dehydration evidenced by sunken eyes, drinking eagerly and acting thirsty, poor skin turgor, or impaired general condition (unconsciousness, restlessness or irritability).[11] Hypoxia was defined as oxygen saturation <92% via pulse oximetry. Tachycardia and hypotension were defined based on age standards.[12] For Kawasaki-like illness, the oral changes included fissured lips or oral ulcers, while the peripheral changes included peeling, oedema, or redness of the extremities. Acute kidney injury was defined as a creatinine level above the following values by age: (1) <4 weeks: 133µmol/L; (2) 4 weeks to <1 year: 53µmol/L; (3) 1 to 10 years: 93µmol/L; and (4) ≥11 years: >133µmol/L.[12]

Factors for severe MIS-C

The factors investigated for severe MIS-C were demographic characteristics (age, sex, and race), presence of comorbidities, clinical characteristics, and laboratory measures (coagulation profile, cardiac marker, haematology, inflammatory markers, and liver and renal functions). Clinical characteristics and laboratory measures were analysed as binary variables. Laboratory measures (D-dimer, fibrinogen, haemoglobin, absolute lymphocyte count, absolute neutrophil count, platelet count, C-reactive protein [CRP], ferritin, albumin, and alanine transaminase) were reclassified into binary variables based on the cut-off points used by Feldstein et al.[8] For the other laboratory measures without a cut-off point by Feldstein et al., the hospital cut-off points were used. No imputations were made for missing laboratory values.

Statistical analysis

Descriptive statistics were used to describe the cohort in this study. Median and interquartile ranges (IQR) were used to describe continuous variables that were not normally distributed, whereas frequency and

percentage were used to describe categorical variables. The chi-square test was used to compare the categorical variables, while the Mann-Whitney U test was used for the continuous variables.

Multivariable logistic regression analysis was performed to explore demographic, clinical and laboratory factors and their association with severe MIS-C. The adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated. Clinical characteristics and laboratory measures were assessed in separate regression models to identify the factors associated with severe MIS-C. Similarly, aORs and 95% CIs were calculated for each variable, adjusting to age group, sex, and race. Clinical characteristics were dichotomised into presence or absence, and laboratory values were dichotomised using the cut-off points mentioned above.

All data were analysed with SAS 9.4 statistical software (SAS Institute, Inc., Cary, North Carolina) and IBM SPSS Statistics for Windows, Version 28.0 (SPSS, IBM Corp., Armonk, NY, USA). A two-sided P value of <0.05 was considered statistically significant.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by The Medical Research and Ethics Committee, Ministry of Health, Malaysia (NMRR ID-21-02238-HST) on December 28, 2021.

RESULTS

Baseline characteristics

One hundred fifty-five patients were included in the study with a male-to-female ratio of 2:1 (Table I). The median age and weight were 6.9 years (IQR 2.6-9.1) and 19.6 kg (IQR 14.0-30.0), respectively. Comorbidities were reported in 37 (23.9%) patients, with the respiratory system being the most reported (63/155, [40.7%]). Severe MIS-C was observed in 91 (58.7%) patients, of whom 21 (13.5%) had LVEF <55% and needed both inotropic and ventilatory support. One hundred and two patients (65.8%) were admitted into the paediatric intensive care unit (PICU). The median PICU stay was 6.0 days (IQR 4.0-9.0). Overall, nine (5.8%) patients died. Of these, four had underlying comorbidities (two haematological malignancies, two cardiac diseases), and three were complicated by viral or bacterial co-infections (varicella-zoster virus, dengue fever with haemorrhagic complications and methicillin-resistant *Staphylococcus aureus* ventilator-associated pneumonia). In those who died, the median time of death was 19.0 (IQR 5.0-45.0) days from the time of admission. Out of the 146 patients who survived, the median duration of hospitalisation was 9.0 days (IQR 6.0-14.0).

Table I: Baseline characteristics, treatment, and outcomes of patients with Multisystem Inflammatory Syndrome in Children

	N (%)
Total number of patients	155 (100)
Age categories, year	
< 1	22 (14.2)
1 to 4	37 (23.9)
5 to 9	72 (46.5)
10 to 14	24 (15.5)
Duration of hospital stay in days, median (IQR)	9.0 (6.0 - 15.0)
Sex	
Male	104 (67.0)
Female	51 (32.9)
Ethnicity	
Malay	96 (61.9)
Non-Malay	59 (38.1)
Presence of comorbidity	
Single	28 (18.1)
Multiple	9 (5.8)
Evidence of COVID-19 infection/exposure	
Positive serology for COVID-19 (n=115)	112 (97.4)
COVID-19 exposure within 4 weeks prior to onset of symptoms	77 (49.7)
Positive COVID-19 RT-PCR	65 (57.5)
[a]**Severe MIS-C**	91 (58.7)
Inotropic support	67 (43.2)
Invasive ventilatory support	36 (23.2)
Non-invasive ventilatory support	12 (7.7)
LVEF <55% (n=146)	32 (21.9)
Treatment	
Intravenous immunoglobulin	133 (85.8)
Steroid	125 (80.6)
Biologics	2 (1.3)
Aspirin	110 (71.0)
Anticoagulant	69 (44.5)
Clinical outcomes	
Coronary artery aneurysm (n=146)	37 (25.3)
Died	9 (5.8)

Some patients may have had more than one parameter for severe MIS-C.
Abbreviations: COVID-19, Coronavirus Disease 2019; IQR, interquartile range; LVEF, left ventricular ejection fraction; MIS-C, Multisystem inflammatory syndrome in children; RT-PCR, Reverse Transcriptase-Polymerase Chain Reaction.

Clinical findings

The most frequent presenting symptoms were fever (100.0%), tachycardia (78.1%), poor feeding (71.6%), and lethargy (67.1%). The clinical manifestations of cardiovascular and gastrointestinal systems were the most common organ systems, observed in 81.9% and 74.2% of patients, respectively (Table II). Kawasaki-like illness was observed in 110 (71.0%) patients, with 27 (24.5%) presented with complete KD (fever for ≥5 days and the presence of ≥four of the five principal clinical features)[13] and 15 (13.6%) presented with KDSS.

Table II: Clinical manifestations of patients with severe and non-severe Multisystem Inflammatory Syndrome in Children

	N (%)	Severity		*P* value
		Severe n (%)	Non-severe n (%)	
Total number of patients	155 (100.0)	91 (58.7)	64 (41.3)	–
Constitutional				
Dehydration	38 (24.5)	31 (81.6)	7 (18.4)	<0.001
Lethargy	104 (67.1)	69 (66.4)	35 (33.7)	0.006
Poor feeding	111 (71.6)	62 (55.9)	49 (44.1)	0.252
Gastrointestinal	**114 (73.6)**	**65 (57.0)**	**49 (42.3)**	**0.476**
Vomiting	83 (53.5)	49 (59.0)	34 (41.0)	0.929
Diarrhoea	68 (43.9)	38 (55.91)	30 (44.1)	0.527
Abdominal pain	42 (27.1)	30 (71.4)	12 (28.6)	0.050
Respiratory	**63 (40.7)**	**46 (73.0)**	**17 (27.0)**	**0.003**
Cough	29 (18.7)	16 (55.2)	13 (44.83)	0.668
Dyspnoea/ Shortness of breath	24 (15.5)	21 (87.50)	3 (12.50)	0.002
Rhinorrhoea	14 (9.0)	9 (64.29)	5 (35.71)	0.657
Hypoxia	30 (19.4)	28(93.3)	2 (6.7)	<0.001
Neurology	**31 (20.0)**	**20 (64.5)**	**11 (35.5)**	**0.463**
Irritability	28 (18.1)	19 (67.9)	9 (32.1)	0.277
Encephalopathy	5 (3.2)	4 (80.0)	1(20.0)	0.326
Seizures	12 (7.7)	10 (83.3)	2 (16.7)	0.071
Headache/Dizziness	5 (3.2)	2 (40.0)	3 (60.0)	0.388
Kawasaki-like illness	**110 (71.0)**	**64 (70.3)**	**46 (71.9)**	**0.834**
Conjunctivitis	86 (55.5)	48 (55.8)	38 (44.2)	0.414
Rash	71 (45.8)	41 (57.8)	30 (46.9)	0.823
Oral changes	54 (34.8)	27 (29.7)	27 (42.2)	0.107
Cervical lymphadenopathy	44 (28.4)	23 (52.3)	21 (47.7)	0.306
Peripheral changes	26 (16.8)	15 (57.7)	11 (42.3)	0.908
Musculoskeletal				
Joint pain	4 (3.2)	3 (75.0)	1 (25.0)	0.50
Cardiovascular	**127 (81.9)**	**87 (68.5)**	**40 (31.5)**	**<0.001**
Tachycardia	121 (78.1)	84 (69.4)	37 (30.6)0	<0.001
Hypotension	71 (45.8)	67 (94.4)	4 (5.6)	<0.001
Chest pain	3 (1.9)	2 (66.7)	1 (33.3)	0.777
Renal involvement				
Acute kidney injury	14 (9.0)	13 (8.4)	1 (1.6)	0.007

Laboratory findings

All patients manifested biochemical evidence of inflammation. The median CRP and ferritin levels were 118.2mg/L and 653ng/mL, respectively (Table III). The median white blood count was 10.0 x103/µL, and 86 (55.5%) had lymphocytopenia. Ninety-four patients (70.7%) had either a prolonged prothrombin time or activated partial thromboplastin time, and 81 (66.7%) patients had elevated D-dimer levels. Forty-three patients had high urea (27.7%), with 11 (7.1%) associated with high creatinine levels (Table IV).

Table III: Laboratory findings in patients with Multisystem Inflammatory Syndrome in Children

Variables, units (normal range)	N	Median (IQR)
Haematology		
White blood cell count, x10^3/µL (5.0-13.0)	155	10 (6.7-14.3)
Absolute neutrophil count, x10^3/µL (2.0-8.0)	155	6.7 (4.1-11.4)
Absolute lymphocyte count, x10^3/µL (1.0-5.0)	155	1.5 (0.9-2.7)
Haemoglobin, g/dl (11.5-15.5)	155	11.1 (9.9-12.1)
Platelet count, x10^3/µL (170-450)	155	175 (120-276)
Liver and renal function		
Albumin, g/L (38-54)	155	33 (27-39)
Urea, mmol/L (2.5-6.0)	155	4.1 (2.9-6.6)
Creatinine, µmol/L (64-111)	154	44 (33-57)
Alanine transaminase, U/L (0-55)	153	37 (22-67)
Aspartate aminotransferase, U/L (18-36)	135	44 (31-87)
Inflammatory markers		
C-reactive protein, mg/L (≤5.0)	148	118.2 (55.0-177.6)
Ferritin, ng/mL (22-275)	138	653 (359-1377)
Lactate dehydrogenase, U/L (125-220)	140	356 (295-486)
Creatine kinase, U/L (30-200)	127	101 (44-280)
Coagulation		
Prothrombin time, s (9.6-12.7)	133	14.0 (12.3-16.3)
Partial thromboplastin time, s (29.5-44.9)	133	34.7 (31.1-43.0)
D-dimer, µg/mL (<0.5)	127	4.4 (1.7-9.7)
Fibrinogen, g/L (2.38-4.98)	125	4.3 (3.7-5.7)

Abbreviations: IQR, interquartile range.

Table IV: Laboratory measures' numerators and denominators for patients with severe and non-severe Multisystem Inflammatory Syndrome in Children

	All	Severe	Non-severe	*P* value
	n/N (%)	n/N (%)	n/N (%)	
Total number of patients	155 (100)	91/155 (58.7)	64/155 (41.3)	–
Coagulation				
[a]D-dimer >3.0 µg/mL	76/145 (66.7)	52/76 (68.4)	24/76 (31.6)	0.016
[a]Fibrinogen >5.0g/L	42/125 (33.6)	27/42 (64.3)	15/42 (35.7)	0.229
Partial thromboplastin time >44.9s	27/133 (20.3)	20/27 (74.1)	7/27 (25.9)	0.188
Prothrombin time >12.7s	90/133 (67.7)	64/90 (71.1)	26/90 (28.9)	0.006
Cardiac Marker				
Troponin I ≥34.2pg/mL	43/76 (56.6)	39/43 (90.7)	4/43 (9.3)	<0.001
Haematology				
[a]Haemoglobin <9g/dL	15/155 (9.7)	10/15 (66.7)	5/15 (33.3)	0.510
[b]Lymphocytopenia	86/155 (55.5)	51/86 (59.30)	35/86 (40.7)	0.867
[a]Neutrophilia (ANC >7700/µL)	67/155 (43.2)	45/67 (67.2)	22/67 (32.8)	0.062

CONTINUE

Table IV: Laboratory measures' numerators and denominators for patients with severe and non-severe Multisystem Inflammatory Syndrome in Children. (CONT.)

	All	Severe	Non-severe	*P* value
	n/N (%)	n/N (%)	n/N (%)	
Haematology				
[a]Platelet <100,000/µL	25/155 (16.1)	17/25 (68.0)	8/25 (32.0)	0.303
[a]Platelet <150,000/µL	62/155 (40.0)	41/62 (66.1)	21/62 (33.9)	0.126
Total white blood count >1300/µL	50/155 (32.3)	33/50 (66.0)	17/50 (34.0)	0.203
Inflammatory Markers				
[a]C-reactive protein >30 mg/L	152/155 (98.1)	88/152 (57.9)	64/152 (42.1)	0.142
Creatine kinase >200 U/L	43/127 (27.7)	34/43 (79.1)	9/43 (20.9)	0.001
[a]Ferritin >500ng/m	87/138 (63.0)	64/87 (73.6)	23/87 (26.4)	<0.001
Lactate dehydrogenase >220 U/L	131/140 (93.6)	80/131 (61.1)	51/131 (38.9)	0.101
Liver and Renal Function				
[a]Albumin ≤ 30g/L	56/155 (36.1)	42/56 (75.0)	14/56 (25.0)	0.002
[a]Alanine transaminase ≥40 U/L	51/155 (32.9)	33/51 (64.7)	18/51 (35.3)	0.288
Aspartate aminotransferase >36U/L	69/141 (48.9)	45/69 (65.2)	24/69 (34.8)	0.181
Creatinine >111µmol/L	11/154 (7.1)	10/11 (90.9)	1/11 (9.1)	0.026
Urea >6 mmol/L	43/155 (27.7)	36/43 (83.7)	7/43 (16.3)	<0.001

[a] Cut-off points used by Feldstein et al.
[b] Lymphocytopenia was defined as an absolute lymphocyte count <1500/µL in patients ≥8 months old and <4500/µL in patients <8 months old.
Abbreviations: ANC, absolute neutrophil count; n, numerator; N, denominator.

Chest radiography and echocardiography

Chest radiography was available for 131 out of the 155 (84.5%) patients hospitalised for MIS-C, and 55 (42.0%) had abnormal findings. During the hospitalisation, 146 (94.1%) patients had a 2d-echocardiogram performed at a median of 6.0 days (IQR 4.0-7.0) of illness, of whom 26 (17.8%) had pericardial effusion, 32 (21.9%) had LVEF <55% and 37 (25.3%) had coronary artery aneurysms. Twenty-five (67.6%) of the patients with coronary artery aneurysms did not demonstrate complete features of KD, and 14 (27.8%) showed persistence of coronary artery aneurysm during the follow-up 2d-echocardiogram. Eighty-nine (57%) patients received a follow-up 2d-echocardiogram at a median of 34.0 days (IQR 20.0-46.0). Thirty-one (96.9%) of the 32 patients with LVEF <55% regained normal left ventricular function during follow-up.

Management and outcomes

Overall, 48 (30.9%) patients needed ventilatory support, and 42 (27.1%) required oxygen supplementation (10 high-flow masks, eight high-flow nasal cannulas, and 24 nasal oxygen). One hundred and forty-five (93.5%) patients received intravenous antibiotics. A combination of both steroids and intravenous immunoglobulin (IVIG) was given to 107 (69%) patients, whereas 18 (11.6%) received steroids only, and 26 (16.8%) received IVIG only. Of 125 patients who received steroids, 29 (23.2%) received dexamethasone, 92 (73.6%) received methylprednisolone, and four received a combination of both medications. Biologics were used in two (1.3%) patients, while eight (5.2%) patients required renal replacement therapy through continuous veno-venous hemofiltration or peritoneal dialysis. Meanwhile, 69 (44.5%) patients received anticoagulation agents due to high D-dimers.

Factors associated with severe MIS-C

Table V shows aOR for the association between the factors and severe MIS-C. Compared with non-severe MIS-C patients, severe MIS-C was more likely in patients aged ≥5 years old (aOR 2.13, 95% CI 1.08-4.21, *P*=0.030). There were no associations between sex, race and presence of comorbidities with severe MIS-C. Hypotension was not an independent risk factor for severe MIS-C because it is a diagnostic criterion for severe MIS-C.

Table V: Factors related to severe Multisystem Inflammatory Syndrome in Children

	Odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)	*P* value
Age Group (5-14 years old *vs* 0-4 years old)	2.11 (1.09-4.10)	0.032	[a]2.13 (1.08-4.21)	0.030
Presence of Comorbidities (Yes *vs* No)	2.28 (1.01-5.13)	0.047	[a]2.13 (0.93-4.88)	0.073
Race (Malay *vs* non-Malay)	0.68 (0.35-1.33)	0.260	[a]0.63 (0.32-1.27)	0.195
Sex (Male *vs* Female)	0.99 (0.50-1.96)	0.984	[a]0.94 (0.47, 1.90)	0.865
Clinical characteristics				
Tachycardia	8.76 (3.50-21.90)	<0.001	[b]8.33 (3.27-21.22)	<0.001
Dehydration	4.21 (1.72-10.31)	0.002	[b]3.80 (1.53-9.45)	0.004
Lethargy	2.00 (0.98-4.06)	0.007	[b]2.02 (0.97-4.18)	0.059
Abdominal pain	2.13 (0.99-4.58)	0.053	[b]1.78 (0.80-3.95)	0.159
[c]**Laboratory measures**				
Ferritin >500ng/mL	4.23 (2.14-8.34)	<0.001	[b]3.77 (1.88-7.55)	<0.001
D-Dimer >3.0µg/mL	2.22 (1.16-4.28)	0.017	[b]2.11 (1.08-4.13)	0.029
Prothrombin time >12.7s	3.46 (1.77-6.78)	<0.001	[b]3.22 (1.61-6.43)	0.001
Albumin <30g/L	3.06 (1.49-6.30)	0.002	[b]3.36 (1.58-7.13)	0.002

CONTINUE

Table V: Factors related to severe Multisystem Inflammatory Syndrome in Children (CONT.)

	Odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)	*P* value
[c]**Laboratory measures**				
Creatine kinase >200U/L	3.65 (1.60-8.30)	0.002	[b]3.68 (1.57-8.64)	0.002
Urea >6mmol/L	5.33 (2.19-12.98)	<0.001	[b]5.09 (2.04-12.71)	<0.001

[*] All patients (variables preceding to severe MIS-C);
[b] Adjusted for age group, sex, and race;
[c] Troponin I was excluded from the analysis as results were only available in 76/155 patients. Creatinine was excluded from the analysis due to the low number of observed events per variable in the non-severe group.
Abbreviations: CI; confidence interval

After adjusting for age group, sex and race, severe MIS-C was associated with dehydration (aOR 3.80, 95% CI 1.53-9.45, *P*=0.004), lethargy (aOR 2.02, 95% CI 0.97-4.18, *P*=0.059), tachycardia (aOR 8.33, 95% CI 3.27-21.22, *P*<0.001), albumin <30g/L (aOR 3.36, 95% CI 1.58-7.13, *P*=0.002), creatine kinase >200U/L (aOR 3.68, 95 CI 1.57-8.64, *P*=0.002), D-dimer >3.0µg/mL (aOR 2.11, 95% CI 1.08-4.13, *P*=0.029), ferritin >500ng/mL (aOR 3.77, 95% CI 1.88-7.55, *P*<0.001), prothrombin time >12.7 seconds (aOR 3.22, 95% CI 1.61-4.63, *P*=0.001), and urea >6mmol/L (aOR 5.09, 95% CI 2.04-12.71, *P*<0.001).

DISCUSSION

We described the clinical manifestations and risk factors for severe MIS-C based on a nationwide multicentre study conducted across 14 major hospitals in Malaysia. We found that the factors associated with severe MIS-C were age ≥5 years, dehydration, lethargy, tachycardia, albumin <30g/L, creatine kinase >200U/L, D-dimer >3.0µg/mL, ferritin >500ng/mL, prothrombin time >12.7 seconds, and urea >6mmol/L.

The prevalence of MIS-C among the Asian population is lower than that reported in the West, with only a few published reports from Asian countries.[14-18] The reasons for this are unclear but intriguing, considering the equally high burden of SARS-CoV-2 infection among children in Asia. Based on the latest statistics, Malaysia has an estimated population of 32.7 million, of which 23% are children <15 years old.[19, 20] During the study period, the incidence of reported COVID-19 cases was 5,954 cases per 100,000 children aged 0-17 years.[21] A case report of a pair of siblings in this study who developed MIS-C in close temporal proximity was published earlier.[22]

In our study, the males outnumbered the females by a ratio of 2:1, contrary to other studies, which reported only a slight male preponderance.[8, 23, 24] However, our ratio of males to females was almost similar to a published cohort from India.[16] Most patients tested positive for SARS-CoV-2 antibodies rather than for the virus using RT-PCR, which was in line with the current understanding that MIS-C is a post-infectious phenomenon rather than the result of an acute viral infection.[25]

MIS-C displays a broad spectrum of manifestations, with patients often presenting with fever and symptoms involving the gastrointestinal, dermatological and cardiovascular systems.[8, 23] We observed similar manifestations in our study, with the cardiovascular system being the most common organ system involved. Kawasaki-like features were present in 110 (71.0%) patients with MIS-C, notably higher than reported in the previous literature.[23, 26] Coronary artery aneurysms were present in one of every four patients in this study, which was remarkably higher than those reported elsewhere.[27-29] Furthermore, more than two-thirds of patients with coronary artery aneurysms did not demonstrate complete features of KD, which underscored the importance of echocardiograms in patients with MIS-C. The prominent cardiovascular system involvement was also observed in the sizable proportion of patients presenting with hypotension and LVEF <55%. Nevertheless, in line with the rapid myocardial recovery rates in past studies, most patients with left ventricular dysfunction recovered on follow-up echocardiograms.[24, 29]

Besides KD, MIS-C may also mimic another severe autoinflammatory disorder, i.e. macrophage activating syndrome secondary to systemic juvenile idiopathic arthritis (sJIA-MAS).[18, 30, 31] The Turkish nationwide cross-sectional study found that cardiovascular and gastrointestinal involvements were more common in MIS-C patients compared to those with KD and sJIA-MAS.[18] These findings align with our results, where both manifestations were predominant clinical features. While CRP values were reportedly elevated in MIS-C patients, ferritin levels were higher in those with sJIA-MAS. [18, 30, 31]

More than half of the patients (58.7%) in this cohort fulfilled the criteria for severe MIS-C, indicating a substantial proportion of patients with MIS-C who presented with severe disease. The definition of severe MIS-C varies in the literature, with studies using PICU admission as the criterion for severity.[32, 33] Our definition was justifiable, considering the decision for PICU admission varied by site. The proportion of our patients requiring mechanical ventilation and inotropes was almost comparable to the case series reported by Feldstein et al.[8] However, our study's mortality rate was higher than published studies from the United States, United Kingdom, and India, ranging from 0 to 3.3%.[16, 28, 34] The higher mortality rate was unlikely due to the low usage of biologic agents or the lack of extracorporeal membrane oxygenation (ECMO), as none of the Indian cohort published by Mehra et al.[16] received biologics, and only 0.8% received ECMO therapy. Instead, many

MIS-C mortalities in our cohort had cardiovascular complications, underlying comorbidities, or co-infections. Comparatively, a much higher mortality of 20% was reported in a case series from KwaZulu-Natal, South Africa, due to poor socioeconomic circumstances with high rates of tuberculosis and malnutrition.[35]

We found that age >5 years was associated with an increased risk of severe MIS-C, consistent with other studies that identified older age as a risk factor.[27, 36] Both of these studies stratified patients into three age groups, with maximum age ranges extending to 18 and 20 years. However, the maximum age in our cohort was only 14 years. Therefore, categorising our patients into the age groups 0-4 and 5-14 years is more appropriate for our analysis.

Also, our results identified three clinical parameters (tachycardia, dehydration and lethargy) and six abnormal laboratory values (ferritin, albumin, creatine kinase, D-dimer, prothrombin time, and urea) that were factors associated with severe MIS-C. A recent study from Pakistan, a middle-income country, showed that increased inflammatory markers such as lactate dehydrogenase, ferritin, D-dimer, and pro-B-type natriuretic peptide were associated with higher mortality risk.[37] Although raised inflammatory markers such as CRP, ferritin, and D-dimer were predictors of severity of MIS-C in past studies,[27, 32, 36] elevated CRP was not found to be significant in our study. We observed that the proportion of patients with elevated troponin I was significantly higher in the severe group. However, it was excluded from the analysis as the test was unavailable for more than half of our patients. Renal complications were reported in a considerable proportion of critically ill patients with MIS-C,[38] which concurred with our findings of high urea as a predictor of severity. These results might have significant clinical utility in identifying patients likely to have severe outcomes during hospitalisation.

A significant strength of the study was the inclusion of patients from 10 different states in the country, providing a comprehensive overview of the diversity of demographic and clinical manifestations of MIS-C among the Malaysian paediatric population. Nevertheless, our study has several limitations. Firstly, the differences in clinical practice across the study sites i.e. treatment protocols and criteria for PICU admission could have affected the findings and clinical outcomes. Secondly, as the 14 participating centres in the study were major hospitals in the country, our study could have introduced selection bias. We may not have captured non-severe MIS-C cases in other minor centres, which may explain a spuriously high mortality rate in our study. Thirdly, due to our study's retrospective nature, we could not collect complete data for all laboratory parameters as not all investigations were routinely carried out in the hospitals. Lastly, we were also unable to comment on the management and outcomes of the patients with coronary artery aneurysms post-MIS-C. Despite those limitations, this study provides a broad overview of MIS-C among Malaysian children.

CONCLUSION

Our study adds to the growing understanding of MIS-C as a potentially life-threatening condition presenting in a spectrum of overlapping clinical symptoms. In particular, cardiovascular system involvement was a prominent feature for most patients. Furthermore, a substantial proportion of patients hospitalised with MIS-C presented with severe disease, leading to a higher mortality rate than in other studies. Therefore, identifying risk factors associated with the severity shown in this study could aid early recognition and prompt escalation of care for patients with MIS-C.

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