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Lukban, MLS, Garcia RDJ. Factors Associated with Poor Clinical Outcomes in Patients with Multisystem Inflammatory Syndrome in Children in a Tertiary Level Hospital: A retrospective, cross-sectional, descriptive study
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ORIGINAL ARTICLE

FACTORS ASSOCIATED WITH POOR CLINICAL OUTCOMES IN PATIENTS WITH MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN IN A TERTIARY LEVEL HOSPITAL: A RETROSPECTIVE, CROSS-SECTIONAL, DESCRIPTIVE STUDY

Marie Louise S. Lukban, MD, DPPS, Robert Dennis J. Garcia, MD, MHSA
Department of Pediatrics, Makati Medical Center

ABSTRACT

Introduction: Multisystem Inflammatory Syndrome in Children (MIS-C) is a delayed hyperinflammatory condition affecting multiple organ systems. Prominent symptoms include fever, skin rashes, and gastrointestinal symptoms, manifesting prior to critical signs such as cardiac involvement, hypotension, and shock.

Objective: To determine if certain demographic, clinical, and laboratory markers are predictive of poor outcomes in patients diagnosed with MIS-C.

Method: This is a retrospective, cross-sectional study (2020-2023) of children who met the 2020 CDC MIS-C criteria. Data on demographics, comorbidities, clinical course, outcomes, laboratory results and 2D Echocardiogram findings were obtained and analyzed.

Results: There were 28 patients with MIS-C, with a median age of 4.5 years. The majority of patients were male (64%). The percentage of neutrophils showed a significant association with hypotension/shock (OR 1.16). White blood cell count (WBC) and ferritin were significantly associated with ICU admission (OR 3.5 and 2.9, respectively). Pericardial effusion was observed in 71.4% while myocarditis was present in 67.9% of patients. The most notable risk factor was HIV infection, which was significantly associated with a more than 50-fold increase in the odds of developing ARDS and 165-fold increase in the odds of mortality; there was only one mortality, and only one patient with documented HIV infection.

Conclusions: The outcome was good in non-immunocompromised patients and the only recorded mortality was a patient not previously known to have HIV. We identified statistically significant factors that were associated with adverse outcome measures, with the limitation of a small sample, such as HIV infection and risk for ARDS and mortality; elevated neutrophil percentage and risk for hypotension/shock; elevated WBC and ferritin and risk for ICU admission; and saw a high prevalence of pericardial effusion and myocarditis in these patients, highlighting the critical role of hyperinflammation and cardiac involvement in disease progression and outcome.

KEYWORDS: *MIS-C, COVID-19, Inflammatory, Risk Factors*

Correspondence:
Dr. Marie Louise S. Lukban
mlslukban@gmail.com

The authors declare that the data presented are original material and have not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and that the authors have met the requirements for authorship.

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INTRODUCTION

COVID-19, more formally known as SARS-COV-2 infection, causes acute respiratory symptoms affecting patients all over the world.[1] In the earlier years of the pandemic, the population thought to be mostly at risk were the elderly and the immunocompromised. However, as more children became infected, more cases of its critical complications were reported.[1,2]

Multisystem Inflammatory Syndrome in Children (MIS-C), as coined by the World Health Organization and Centers for Disease Control and Prevention (CDC), is a severe complication seen in children and adolescents that usually manifests two to six weeks after a COVID-19 infection.[3] It is characterized as a delayed hyperinflammatory condition affecting multiple organ systems, which makes it difficult to distinguish from other conditions with heightened inflammation such as Kawasaki disease and toxic shock syndrome.[1] Clinical presentations vary, with more prominent symptoms like fever, skin rashes, and gastrointestinal symptoms manifesting prior to the development of more critical manifestations such as cardiac involvement, hypotension, and shock.[3]

This study aimed to determine if certain demographic, clinical, and laboratory/inflammatory markers were associated with poor outcomes in patients diagnosed with MIS-C. Specifically, this study aimed to: 1) determine the specific risk factors (age, co-morbidities) that may be related to complications and poor outcomes in patients with MIS-C; 2) determine the trends in the values of the WBC, platelet counts, CRP, ESR, ferritin, procalcitonin, D-dimer, troponin I, and IL-6, during the course of MIS-C; 3) determine an association between the increase or decrease of the above laboratory results, and complications and outcome measures, such as admission to the intensive care unit, acute respiratory distress syndrome (ARDS), hypotension/shock, myocarditis, bacteremia, death, and length of hospital stay; and 4) determine an association between 2D echocardiogram (2DE) findings and poor outcomes. By establishing a possible association between diagnostics done early on in the course of illness and poor clinical outcomes, practitioners may be guided on subsequent management and therapeutics needed.

METHODOLOGY

The study was a retrospective, cross-sectional study of pediatric patients with MIS-C. Data on demographics, comorbidities, clinical course, laboratory results, 2DE findings, and outcomes were obtained and analyzed.

The research investigated pediatric patients under 18 years old, admitted at a tertiary hospital in Metro Manila from January 1, 2020 to December 31, 2023, managed and discharged as a case of MIS-C.

Based on the study of Alam et al.,[4] the initial sample size calculation required a minimum of 80 patients for this study to achieve a 5% level of significance and 90% power. Subsequent adjustments to the sample size were made to accommodate specific conditions, resulting in an adjusted minimum sample size of 25. Due to the limited number of MIS-C cases seen in the institution, total enumeration of all cases admitted during the specified study period was done.

Individually identifiable research data was not shared with others outside of the research and analysis team. The authors obtained Good Clinical Practice (GCP) training on the responsible conduct of research with human data.

Descriptive statistics were used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for categorical variables (nominal/ordinal), mean and standard deviation for normally distributed interval/ratio variables, and median and range for non-normally distributed interval/ratio variables. Mann-Whitney U Test was used to compare two independent groups when the outcome was continuous and not normally distributed. Fisher's Exact Test was used for categorical data, particularly when sample sizes are small, to assess the association and the comparison between two categorical variables. Logistic regression was used to determine the odds ratios (ORs) and 95% confidence intervals (CIs) for various risk factors (e.g., age, comorbidities, laboratory values) associated with poor outcomes like ARDS, myocarditis, hypotension/shock, ICU admission, and mortality. Logistic regression was used to assess whether certain variables were predictive of binary outcomes, i.e., the presence or absence of a condition. Repeated-measures ANOVA was used to compare the changes in continuous variables (like WBC, platelet count, CRP) across different time points (upon admission, during the

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hospital stay, highest or lowest values recorded). Friedman test was used to assess changes in laboratory values across different time points, especially when data did not follow a normal distribution. Missing variables were neither replaced nor estimated. The null hypothesis was rejected at a significance level of 0.05α. R-4.1.3 was used for data analysis.

Operational Definitions

Multisystem Inflammatory Syndrome in Children (MIS-C)

At the time of admission, patients were diagnosed with MIS-C following the criteria by CDC (2020)[3]: Children and adolescents 0-19 years with fever > 3 days and two of the following: 1) rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs, 2) hypotension or shock, 3) features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities, 4) evidence of coagulopathy, 5) acute gastrointestinal symptoms; with elevated markers of inflammation (ESR, CRP, procalcitonin); and no other obvious microbial causes; and with evidence of COVID-19 infection (by RT-PCR, antigen test or serology). These criteria were updated by the CDC in 2023, with key parameters which included fever, elevated CRP, and new-onset cardiac manifestations; shock, mucocutaneous signs, gastrointestinal symptoms, and/or hematologic signs.[3]

The outcomes of interest included admission to the intensive care unit (ICU), length of hospital stay (in days), pediatric acute respiratory distress syndrome (PARDS), defined as respiratory failure not fully explained by cardiac failure or fluid overload, occurring within seven days of a known clinical insult, with chest imaging findings of new infiltrates consistent with acute pulmonary parenchymal disease; myocarditis, based on clinical and laboratory findings (e.g., elevated troponin-I levels, 2DE findings of pericardial effusion, decreased left ventricular ejection fraction (LVEF), dilated coronary artery/ies, and valvular regurgitation); hypotension/shock with blood pressure less than the 5th percentile for age, or < 90/50 mmHg in children 10 years and older; bacteremia, and death.

Laboratory markers measured were white blood cell count (WBC), percentage of neutrophils and lymphocytes, platelet count, C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), ferritin, interleukin-6 (IL-6), D-dimer, lactate dehydrogenase (LDH), pro-brain natriuretic peptide (pro-BNP), and troponin-I.

Ethical considerations

This protocol was submitted to the Institutional Review Board (IRB) for approval prior to conducting the study. No conflicts of interest nor financial disclosures were declared for this study. Informed consent for chart review was waived as there was no contact involved with the patients during the course of the study.

RESULTS

The clinico-demographic profile of twenty-eight (28) pediatric patients diagnosed with MIS-C is shown in Table 1. The median age of the population was 4.5 years, with 39.3% of patients aged between 1 to 4 years, 25.0% between 5 to 9 years, and 10.7% under 1 year. The majority of patients were male, representing 64.3%, while females accounted for 35.7%. The median weight of the patients was 20.6 kg, and the mean height was 113.7 cm. The median body mass index (BMI) was 15.9 kg/m². Nutritional status was categorized as follows: 57.1% were underweight, 25.0% had a normal BMI, 10.7% were overweight, and 7.1% were obese.

Comorbidities were present in some patients, with each occurring in 3.6% of patients except for dengue fever which occurred in 7.1% of patients. Regarding organ system involvement, the cardiovascular system was affected in majority of patients (82.14%), followed by the respiratory system (78.57%) and the integumentary system (64.29%). COVID-19 infection history revealed that 64.3% of patients had no known prior infection, 32.1% were mildly symptomatic, and one patient required hospitalization for COVID-19. Positive SARS-CoV-2 results were confirmed via RT-PCR in 46.4% and via electrochemiluminescence immunoassay (ECLIA) in 53.6%.

Four patients required intensive care unit (ICU) admission, with a mean ICU stay of 6.5 ± 3.7 days. Among these patients, 25% stayed less than 5 days, 50% stayed between 5 to 7 days, and 25% stayed more than 10 days. The median length of hospital stay for the overall population was 4 days. Regarding clinical complications, 67.9% developed myocarditis, 14.3% experienced hypotension or shock, while 7.1% of patients each

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developed ARDS and bacteremia. There was only one mortality (3.6%).

Table 1. Clinico-demographic profile of pediatric patients diagnosed with MIS-C (n = 28)

	Mean ± SD; Median (IQR); Frequency (%)
Median age (IQR), in years	4.50 (2.00-8.50)
Age distribution	
<1	3 (10.71)
1-4	11 (39.29)
5-9	7 (25.00)
10-14	5 (17.86)
15-18	2 (7.14)
Sex	
Male	18 (64.29)
Female	10 (35.71)
Weight, kg	20.60 (11.75-32.275)
Height, cm	113.67 ± 31.20
BMI, kg/m^2	15.90 (14.45-19.90)
Underweight	16 (57.14)
Normal	7 (25.00)
Overweight	3 (10.71)
Obese	2 (7.14)
Comorbidities	
Dengue fever	2 (7.14)
Hemophagocytic lymphohistiocytosis (HLH)	1 (3.57)
Thalassemia trait	1 (3.57)
Disseminated tuberculosis (TB)	1 (3.57)
HIV	1 (3.57)
Bronchial asthma	1 (3.57)
DIC	1 (3.57)
Allergic rhinitis	1 (3.57)
Asthma	1 (3.57)
Sepsis	1 (3.57)
Bacteremia	1 (3.57)
Organ System Involvement	
Cardiovascular	23 (82.14)
Respiratory	22 (78.57)
Integumentary	18 (64.29)
Gastrointestinal	16 (57.14)
Renal	1 (3.57)
Neurologic	1 (3.57)
COVID-19 History	
No known infection	18 (64.29)
Mild symptomatic	9 (32.14)
Required hospitalization	1 (3.57)
SARS-COV-2 results	
(+) SARS-COV-2 ECLIA	15 (53.57)
(+) SARS-COV-2 RT-PCR	13 (46.43)
ICU admission	4 (14.29)
Admission to ICU, days (n=4)	6.50 ± 3.70
<5 days	1 (25.00)
5-7 days	2 (50.00)
8-10 days	0
>10 days	1 (25.00)
Length of hospital stay, days	4 (4-7)
<5 days	15 (53.57)
5-7 days	7 (25.00)
8-10 days	3 (10.71)
>10 days	3 (10.71)
Myocarditis	19 (67.86)
Hypotension/Shock	4 (14.29)
Acute Respiratory Distress Syndrome (ARDS)	2 (7.14)
Bacteremia	2 (7.14)
Outcome/Disposition	
Mortality	1 (3.57)
Alive/discharged	27 (96.43)

2DE findings are shown in Table 2. The median left ventricular ejection fraction (LVEF) was 72%. When stratified, patients with normal 2DE findings had a higher median LVEF of 76%, compared to those with abnormal findings, whose median LVEF was 72%. While analysis showed a statistically significant difference between these two groups, the LVEF values in both groups remained within normal pediatric thresholds, hence this difference is statistically significant but its clinical significance is unknown.

Wall motion abnormalities were largely absent, with 92.9% of patients showing normal wall motion and 7.1% having hypokinesia. Pericardial effusion was observed in 71.4% of all patients. Pulmonary artery pressure was normal in all patients.

Coronary artery abnormalities were also assessed. Various degrees of coronary dilatation were present, mostly involving the right coronary artery (RCA), followed by the left coronary artery (LCA), and, rarely, the left anterior descending artery (LAD) and right circumflex artery (RCx). Valvular abnormalities were common, with mild mitral regurgitation (MR) seen in 42.9% and tricuspid regurgitation (TR) in 25% of patients.

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Table 2. 2D Echo findings of pediatric patients diagnosed with MIS-C (n = 28)

	All (n=28)	Normal (n=3)	Abnormal (n=25)	p-value
	Median (IQR); Frequency (%)			
LVEF, %	72 (65.75-74)	76 (68.50-76.50)	72 (67-74)	**<.001**ψ
Wall Motion Abnormalities				>.999§
Normal	26 (92.86)	3 (100)	23 (92)	
Hypokinetic	2 (7.14)	0	2 (8.00)	
Akinetic	0	0	0	
Dyskinetic	0	0	0	
Pericardial Effusion	20 (71.43)	0	20 (80)	**.017**§
Pulmonary Artery Pressure				**<.001**§
Normal	28 (100)	3 (100)	25 (100)	
Coronaries				
Normal	11 (39.29)	3 (100)	8 (32.00)	**.050**§
Dilated RCA	9 (32.14)	0	9 (36.00)	.530§
Dilated LCA	7 (25.00)	0	7 (28.00)	.551§
Dilated LAD	2 (7.14)	0	2 (8.00)	>.999§
Dilated RCx	1 (3.57)	0	1 (4.00)	>.999§
Perivascular Brightness	6 (21.43)	0	6 (24.00)	>.999§
Valvular Abnormalities				
Normal	8 (28.57)	2 (66.67)	6 (24.00)	.188§
MR	2 (7.14)	0	2 (8.00)	>.999§
TR	7 (25.00)	0	7 (28.00)	.551§
Mild MR	12 (42.86)	0	12 (48.00)	.238§
Mild TR	1 (3.57)	0	1 (4.00)	>.999§
Moderate MR	1 (3.57)	0	1 (4.00)	>.999§
Moderate TR	0	0	0	-
Trivial MR	1 (3.57)	0	1 (4.00)	>.999§
Trivial TR	5 (17.86)	1 (33.33)	4 (16.00)	.459§
Pulmonic Regurgitation	1 (3.57)	0	1 (4.00)	>.999§

Statistical Analysis Used: ψ–Mann-Whitney U-Test; §–Fisher's Exact test

The association between 2DE and poor outcomes is shown in Table 3. Acute respiratory distress syndrome (ARDS) occurred in 7.1% of patients, all of whom had abnormal 2DE findings. However, the association between ARDS and 2DE findings was not statistically significant. Myocarditis was present in 67.9% of the population. Hypotension or shock occurred in 14.3% of the patients, all of whom had abnormal echocardiograms, but the association was not statistically significant. Similarly, bacteremia was observed in two patients, both of whom had abnormal 2DEs, but the association was not statistically significant.

Regarding patient outcomes, there was one mortality (3.6%) among the patients with abnormal 2DE. There was no statistically significant difference in outcome/disposition between those with normal and abnormal 2DE.

Table 3. Association between 2DE findings and poor outcomes in pediatric patients diagnosed with MIS-C (n = 28)

	All (n=28)	Normal (n=3)	Abnormal (n=25)	p-value
	Frequency (%)			
Acute Respiratory Distress Syndrome (ARDS)	2 (7.14)	0	2 (8.00)	>.999§
Myocarditis	19 (67.86)	0	19 (76.00)	**.026**§
Hypotension/Shock	4 (14.29)	0	4 (16.00)	>.999§
Bacteremia	2 (7.14)	0	2 (8.00)	>.999§
Disposition				>.999§
Mortality	1 (3.57)	0	1 (4.00)	
Alive/Discharged	27 (96.43)	3 (100)	24 (96.00)	

Statistical Analysis Used: ψ–Mann-Whitney U-Test; §–Fisher's Exact test

Laboratory findings upon admission and during the course of hospital stay are shown in Table 4. The median WBC count was 10 x 10^9/L. During the hospital stay, the lowest median WBC count was 5.87 x 10^9/L, while the highest median WBC count increased to 12.91 x 10^9/L, with a statistically significant difference between the values. The percentage of lymphocytes upon admission was at a median of 23%, decreasing to a median of 18% at the lowest during the hospital stay, and increasing to a median of 31.5% at its highest point. This difference was statistically significant. The percentage of neutrophils was at a median of 65% on admission; was at a median of 58% during the lowest point, and rose to 72.5% at its highest, with a significant change noted. Platelet counts changed significantly during the hospital stay. The mean platelet count on admission was 350.9 x 10^9/L, dropping to a mean of 283.7 x 10^9/L during the lowest point before rising to 467.6 x 10^9/L during the highest point.

CRP was at a median value of 60.6 mg/L upon admission, which decreased to 30.0 mg/L, before significantly decreasing to 6.0 mg/L during the lowest value recorded in the hospital stay. Procalcitonin levels were measured in a small number of patients, and the difference between the level on admission and the subsequent lowest level was significant. Ferritin levels were markedly elevated, with a median of 74.1 ng/mL on admission, increasing to a median of 1053.0 ng/mL during the hospital stay, and further increasing to 2156.6 ng/mL at its highest level. Interleukin-6 (IL-6) levels showed considerable variation throughout the hospital stay, but changes were not statistically significant. D-dimer levels were elevated throughout the hospital stay and variations did not show any statistical significance. Lactate dehydrogenase (LDH) showed a significant change over the hospital stay, with a median of 672.7 U/L

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on admission, progressively decreasing to a median of 302.6 U/L. This change was statistically significant. Brain natriuretic peptide (BNP) levels also fluctuated, with a median of 479.6 pg/mL on admission, and a marked increase to 3032.7 pg/mL at its highest value, though this increase was not statistically significant.

Table 4. Laboratory findings of patients with MIS-C upon admission and during hospital stay

	Upon Admission	Hospital Stay		p-value
		Lowest	Highest	
	Mean ± SD; Median (IQR)			
White blood cell count	(n=27) 10 (5.76-17.80)	(n=21) 5.87 (3.15-10)	(n=20) 12.91 (8.47-18.80)	**<.001§**
Percentage lymphocytes	(n=27) 23 (14.50-34)	(n=21) 18 (8-28)	(n=20) 31.50 (23-49)	**<.001§**
Percentage neutrophils	(n=27) 65 (56.50-76.50)	(n=21) 58 (38-65)	(n=20) 72.50 (64.25-85.25)	**<.001§**
Platelet count	(n=27) 350.93 ± 211.06	(n=21) 283.71± 220.72	(n=20) 467.55± 230.54	**.001ψ**
C-reactive protein	(n=23) 60.61 (8.86-85.01)	(n=20) 5.97 (1.49-11.20)	(n=19) 30.02 (8.84-80.32)	**<.001§**
Procalcitonin	(n=5) 1.69 ± 1.98	(n=6) 1.98 ± 2.37	(n=2) 3.12 ± 0.86	**<.001ψ**
Erythrocyte sedimentation rate	(n=8) 61.50 ± 45.57	(n=3) 46.33 ± 39.70	(n=1) 52 ± NA	-
Ferritin	(n=10) 74.10 (121.60-335)	(n=13) 1053 (454.30-1584.10)	(n=6) 2156.60 (1784.90-4363.20)	-
Interleukin-6	(n=4) 279.43 ± 362.60	(n=4) 92.45 ± 120.70	(n=3) 1896.54 ± 3182.61	.498ψ
D-dimer	(n=13) 1480.77 ± 949.94	(n=14) 2279.57 ± 2245.57	(n=8) 4229.75 ± 3312.04	.235ψ
Lactate dehydrogenase	(n=7) 672.70 (292.20-708.60)	(n=12) 302.60 (235.50-434)	(n=8) 514.70 (438.80-681.30)	**.039§**
Troponin I	(n=12) 0.004 (0.002-0.08)	(n=12) 0.0025 (0-0.009)	(n=5) 0.03 (0.009-0.08)	.223§
Brain natriuretic peptide	(n=12) 479.56 (161.72-932.51)	(n=12) 482.94 (179.05-1188.21)	(n=5) 3032.70 (672.20-3272)	.135§

Statistical Analysis Used: ψ–Repeated Measures ANOVA; §–Friedman Test.

Table 5 provides a consolidated overview of factors associated with acute respiratory distress syndrome (ARDS), myocarditis, hypotension or shock, bacteremia, ICU admission, and mortality in pediatric patients with MIS-C. Notably, HIV infection was a significant risk factor for both ARDS (OR: 53.00, 95% CI: 2.01–9409.70, p = .018) and mortality (OR: 165.00, 95% CI: 4.21–58946.59, p = .006). However, it is important to clarify that only one patient had HIV in the entire cohort—a 15-year-old female who was diagnosed with HIV infection during the admission, later developed ARDS and eventually died. Prolonged hospital stay (>10 days) was significantly associated with ICU admission (OR: 16.11, 95% CI: 1.33–328.44, p = .029). Other variables such as age, sex, BMI category, and comorbidities like sepsis, thalassemia trait, and disseminated tuberculosis showed elevated odds across various outcomes, though these were not statistically significant.

Increased odds of ARDS were observed in adolescents (ages 15–18) and female or overweight patients, though not reaching statistical significance. Comorbidities such as HLH, thalassemia trait, and disseminated TB showed strong associations with bacteremia (OR: 53.00, 95% CI: 2.01–9409.70, p = .018), which suggest that underlying infections may heighten susceptibility. Hypotension or shock was more frequent in older children and those with multiple comorbidities, while no statistically significant predictors for mortality aside from HIV were identified.

Table 6 presents the associations between peak inflammatory markers and adverse clinical outcomes among MIS-C patients, including ARDS, myocarditis, hypotension/shock, bacteremia, ICU admission, and mortality. A higher neutrophil percentage was significantly associated with hypotension/shock (OR: 1.16, 95% CI: 1.01–1.61, p = .021), while elevated WBC count (OR: 3.49, 95% CI: 1.26–13.67, p = .030) and ferritin level (OR: 2.92, 95% CI: 1.19–9.32, p = .019) were significantly associated with ICU admission. Most inflammatory markers did not show statistically significant associations with ARDS, myocarditis, or mortality. Although Troponin I had a notably high odds ratio for ARDS (OR: 778.22, 95% CI: 0.36–1.58e+08, p = .092), this result was not statistically significant. Similarly, common inflammatory markers such as WBC, CRP, ferritin, interleukin-6, and procalcitonin showed no significant correlation with myocarditis or mortality. This suggests that while elevated levels may reflect systemic inflammation, they may not independently predict these specific outcomes.

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Table 5. Risk Factors associated with ARDS, myocarditis, hypotension/shock, bacteremia, ICU admission, and mortality in MIS-C Patients

	ARDS		Myocarditis		Hypotension/ Shock		Bacteremia		ICU Admission		Mortality	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age, years												
<1	reference	-	reference	-	reference	-	reference	-	reference	-	reference	-
1-4	0.30 (0.002-61.35)	.577	0.35 (0.002-5.26)	.482	0.07 (0.00-1.76)	.106	0.07 (0.00-1.76)	.106	0.07 (0.00-1.76)	.106	0.30 (0.002-61.35)	.578
5-9	1.62 (0.07-262.26)	.780	0.18 (0.001-2.98)	.255	0.11 (0.01-2.79)	.182	0.11 (0.011-2.79)	.182	0.38 (0.02-6.50)	.487	0.47 (0.002-95.20)	.719
10-14	0.64 (0.003-131.47)	.831	0.10 (0.001-1.83)	.130	0.56 (0.001-9.86)	.674	0.56 (0.03-9.86)	.674	0.15 (0.00-3.92)	.259	0.64 (0.003-131.47)	.831
15-18	7.00 (0.23-1317.30)	.273	0.71 (0.003-155.64)	.877	8.33 (0.33-1520.62)	.211	0.33 (0.002-10.12)	.538	8.33 (0.33-1520.62)	.211	7.00 (0.23-1317.30)	.273
Sex												
Male	reference	-	reference	-	reference	-	reference	-	reference	-	reference	-
Female	10.88 (0.78-566.89)	.079	2.55 (0.46-20.26)	.313	0.56 (0.03-5.13)	.633	0.31 (0.002-4.38)	.423	2.00 (0.21-19.36)	.525	5.84 (0.28-887.100	.253
Weight, kg	1.03 (0.94-1.11)	.462	0.97 (0.92-1.01)	.161	1.04 (0.98-1.10)	.192	1.00 (0.90-1.08)	.913	1.03 (0.97-1.09)	.338	1.03 (0.90-1.15)	.609
Height, cm	1.03 (0.98-1.10)	.242	0.98 (0.95-1.01)	.219	1.03 (1.00-1.07)	.073	1.00 (0.95-1.05)	.993	1.02 (0.99-1.06)	.209	1.07 (0.99-1.28)	.253
BMI, kg/m²												
Underweight	reference	-	reference	-	reference	-	reference	-	reference	-	reference	-
Normal	0.69 (0.004-14.61)	.821	9.29 (0.86-1281.17)	.070	2.64 (0.33-21.64)	.347	2.38 (0.17-33.88)	.489	1.34 (0.11-12.31)	.799	0.69 (0.004-14.61)	.821
Overweight	6.20 (0.39-107.14)	.181	0.37 (0.03-3.43)	.379	0.83 (0.01-13.88)	.908	1.48 (0.01-34.87)	.827	3.48 (0.24-42.08)	.327	1.48 (0.01-34.87)	.827
Obese	2.07 (0.01-53.43)	(-)	0.62 (0.04-8.89)	.704	1.16 (0.01-21.89)	.931	2.07 (0.01-53.43)	.696	1.16 (0.01-21.89)	.931	2.07 (0.01-53.43)	.696
Comorbidities												
HLH	3.40 (0.02-86.70)	.524	1.54 (0.07-233.77)	.791	21 (0.94-3334.12)	.055	53.00 (2.01-9409.70)	.018	1.74 (0.01-38.77)	.756	5.89 (0.03-192.34)	.387
Thalassemia trait	3.40 (0.02-86.70)	.524	1.54 (0.07-233.77)	.791	21 (0.94-3334.12)	.055	53.00 (2.01-9409.70)	.018	1.74 (0.01-38.77)	.756	5.89 (0.03-192.34)	.387
Disseminated TB	3.40 (0.02-86.70)	.524	1.54 (0.07-233.77)	.791	21 (0.94-3334.12)	.055	53.00 (2.01-9409.70)	.018	1.74 (0.01-38.77)	.756	5.89 (0.03-192.34)	.387
HIV	53 (2.01-9409.70)	**.018**	1.54 (0.07-233.77)	.791	21 (0.94-3334.12)	.055	3.40 (0.02-86.70)	.524	21.00 (0.94-3334.12)	.055	165.00 (4.21-58946.59)	.006
Bronchial asthma	3.40 (0.02-86.70)	.524	1.54 (0.07-233.77)	.791	1.74 (0.01-38.77)	.756	3.40 (0.02-86.70)	.524	1.74 (0.01-38.77)	.756	5.89 (0.03-192.34)	.387
Dengue	1.96 (0.01-36.33)	.705	2.71 (0.19-389.61)	.496	6.71 (0.45-104.05)	.152	1.96 (0.01-36.33)	.705	6.71 (0.45-104.05)	.152	3.40 (0.02-86.70)	.524
Allergic rhinitis	3.40 (0.02-86.70)	.524	1.54 (0.07-233.77)	.791	21 (0.94-3334.12)	.055	3.40 (0.02-86.70)	.524	21.00 (0.94-3334.12)	.055	5.89 (0.03-192.34)	.387
Asthma	3.40 (0.02-86.70)	.524	1.54 (0.07-233.77)	.791	1.74 (0.01-38.77)	.756	3.40 (0.02-86.70)	.524	1.74 (0.01-38.77)	.756	5.89 (0.03-192.34)	.387
COVID History												
No known infections	reference	-	reference	-	reference	-	reference	-	reference	-	reference	-
Mild symptomatic	0.35 (0.002-4.89)	.469	0.38 (0.07-1.96)	.244	0.78 (0.07-5.75)	.815	0.35 (0.002-4.89)	.469	0.78 (0.07-5.75)	.815	0.61 (0.004-12.73)	.764
Required hospitalization	2.20 (0.01-56.76)	.672	0.10 (0.001-2.29)	.150	1.48 (0.01-34.87)	.827	2.20 (0.01-56.76)	.672	1.48 (0.01-34.87)	.827	3.89 (0.02-128.26)	.496
SARS-COV 2 Results												
(+) RT-PCR	reference	-	reference	-	reference	-	reference	-	reference	-	reference	-
(+) SARS-COV ECLIA	0.86 (0.03-23.26)	.916	1.72 (0.35-9.03)	.507	0.85 (0.09-8.02)	.877	0.86 (0.03-23.26)	.916	3.00 (0.33-65.57)	.370	0.27 (0.002-5.50)	.399
Length of hospital stay, days												
<5 days	reference	-	reference	-	reference	-	reference	-	reference	-	reference	-
5-7 days	0.64 (0.004-13.70)	.789	0.88 (0.15-5.18)	.884	2.23 (0.16-31.78)	.523	7.15 (0.34-1102.82)	.206	0.64 (0.004-13.70)	.789	0.64 (0.004-13.70)	.789
8-10 days	1.38 (0.009-32.70)	.856	4.79 (0.37-686.34)	.260	5.80 (0.36-100.48)	.198	4.43 (0.02-893.36)	.490	5.80 (0.36-100.48)	.198	1.38 (0.01-32.70)	.856
>10 days	5.80 (0.36-100.48)	.198	4.79 (0.37-686.34)	.260	5.80 (0.36-100.48)	.198	18.60 (0.77-3066.61)	.071	16.11 (1.33-328.44)	**.029**	1.38 (0.01-32.70)	.856

Statistical Analysis Used: Logistic Regression
ARDS - Acute Respiratory Distress Syndrome; HLH – Hemophagocytic Lymphohistiocytosis

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Table 6. Association of peak inflammatory markers with ARDS, myocarditis, hypotension/shock, bacteremia, ICU admission, and mortality in MIS-C patients

	ARDS		Myocarditis		Hypotension/Shock		Bacteremia		ICU Admission		Mortality	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
WBC	1.86 (0.48-7.52)	.328	2.40 (0.92-10.09)	.133	2.02 (0.76-5.78)	.153	2.39 (0.81-9.26)	.111	3.49 (1.26-13.67)	**.030**	0.81 (0.01-3.26)	.799
Lymphocyte percentage	0.93 (0.79-1.02)	.276	1.00 (0.95-1.05)	.886	0.99 (0.93-1.04)	.742	0.99 (0.90-1.06)	.854	0.98 (0.92-1.04)	.606	0.92 (0.60-1.04)	.321
Neutrophil percentage	1.25 (1.00-2.23)	.248	1.02 (0.97-1.08)	.398	1.16 (1.01-1.61)	**.021**	1.18 (0.99-1.85)	.251	1.23 (1.04-1.78)	.103	1.09 (0.95-10.34)	.408
Platelet count	1.00 (0.99-1.01)	.483	1.00 (1.00-1.01)	.110	1.00 (0.99-1.00)	.521	1.00 (0.99-1.00)	.892	0.99 (0.99-1.00)	.934	1.00 (0.99-1.00)	.689
C-reactive protein	0.99 (0.91-1.01)	.537	1.00 (0.99-1.02)	.619	0.99 (0.97-1.01)	.507	1.00 (0.98-1.01)	.998	0.98 (0.92-1.00)	.356	1.00 (0.93-1.01)	.908
Procalcitonin	1.00 (0.01-98.35)	>.999	6.15 (0.21-884.04)	.306	6.15 (0.21-884.04)	.306	1.00 (0.01-98.35)	>.999	6.15 (0.21-884.03)	.306	1.00 (0.01-98.35)	>.999
Erythrocyte sedimentation rate	1.00 (0.01-98.35)	>.999	-	-	-	-	-	-	-	-	-	-
Ferritin	1.00 (0.99-1.00)	.118	1.00 (0.99-1.00)	.546	1.00 (0.99-1.00)	.075	1.00 (0.99-1.00)	.270	2.92 (1.19-9.32)	**.019**	1.00 (0.99-1.00)	.270
Interleukin-6	1.00 (0.99-1.00)	.182	1.00 (0.99-1.00)	.571	1.00 (0.99-1.00)	.572	1.00 (0.99-1.00)	.821	1.00 (0.99-1.00)	.572	1.00 (0.99-1.00)	.182
D-dimer	1.00 (0.99-1.00)	.897	1.00 (0.99-1.07)	.120	1.00 (0.99-1.00)	.066	1.00 (0.99-1.00)	.062	1.00 (0.99-1.00)	.182	1.00 (0.99-1.00)	.617
Lactate dehydrogenase	1.00 (0.99-1.00)	.656	1.00 (0.99-1.00)	.343	1.00 (0.99-1.00)	.805	1.00 (0.99-1.00)	.549	1.00 (0.99-1.00)	.482	1.00 (0.99-1.00)	.946
Troponin I	778.22 (0.36-1.58e+08)	.092	0.11 (0.00-30761.22)	.633	0.39 (0.00-583.99)	.810	8.78 (0.00-6.14e+05)	.633	33.98 (0.03-2.19e+06)	.318	8.78 (0.00-6.14e+05)	.633
Brain natriuretic peptide	1.00 (0.99-1.00)	.091	1.00 (0.99-1.00)	.628	1.00 (0.99-1.00)	.834	1.00 (0.99-1.00)	.628	1.00 (0.99-1.00)	.305	1.00 (0.99-1.00)	.628

Statistical Analysis Used: Logistic Regression; ARDS - Acute Respiratory Distress Syndrome

DISCUSSION

Multisystem inflammatory syndrome in children (MIS-C) emerged as a critical post-infectious complication associated with COVID-19, warranting extensive investigation into its clinical manifestations and outcomes. Our study highlighted several significant findings regarding the severity of MIS-C. With limited generalizability due to the small sample size, we report significant differences in hematological parameters, including WBC, percentage of lymphocytes and neutrophils, platelet counts, CRP, and LDH levels throughout the hospitalization period, which may serve as vital indicators of severity of inflammation. Conditions found to be associated with poorer outcomes were: 1) elevated percentage of neutrophils, significantly associated with the incidence of hypotension or shock, 2) higher WBC and ferritin levels, significantly associated with the need for ICU admission, and 3) the presence of HIV, as a significant risk factor for ARDS and mortality. Finally, pericardial effusion and myocarditis were prevalent among affected patients, emphasizing the cardiovascular implications of this syndrome.

In our study, there were notable variations in inflammatory markers throughout the hospitalization period. Specifically, levels of WBC, lymphocyte and neutrophil percentages, platelet counts, CRP, and LDH were significantly elevated during admission, but these decreased substantially as the patient received treatment. Several studies have reported significantly elevated WBC counts and CRP levels in MIS-C patients, compared to those with COVID-19 without MIS-C, indicating a distinct inflammatory profile.[2,5] Elevated LDH has also been associated with more severe disease presentations, reflecting tissue damage and a heightened inflammatory response.[6,7]

In the current study, PCT measured in a few patients was found to be increased; however, only two out of six patients were documented to be bacteremic. This finding was also reported in numerous studies [1,4,8,9]

wherein PCT was markedly higher in patients with MIS-C, despite the absence of bacteremia. In clinical practice, PCT is used for early detection of bacterial sepsis, but other conditions may cause its increase. PCT is the prohormone of calcitonin, which is responsible for calcium metabolism.[10] Its synthesis is increased, beyond homeostasis, when circulating endotoxins are present, or endogenous cytokines are increased, which in most cases would be due to bacterial infection.[10] Thus, in non-bacterial conditions associated with hyperinflammation and cytokine storm, PCT synthesis may be elevated even in the absence of bacterial infection.[10]

This study found neutrophil percentage to be significantly associated with hypotension/shock. According to Lin et. al., autoantibodies that target multiple antigens from various organ systems are elevated in patients with MIS-C; this includes a glycoprotein called endoglin, which is expressed in vascular endothelium.[22] DiStasi and Ley explained that activated neutrophils contribute to increased gaps between endothelial cells, leading to enhanced vascular permeability and promoting cutaneous vasodilation, both of which can result in hypotension in severe cases.[12]

Our study also revealed that elevated WBC and ferritin levels were predictive of an ICU admission. Consistent with the retrospective study of Savorgnan et al., elevated levels of WBC and ferritin, along with creatinine, international normalized ratio (INR), respiratory rate (RR), and albumin distinguish those with mild versus severe MIS-C, requiring admission to the ICU, and mechanical ventilation, with or without vasoactive-inotropic support.[13] Chinniah et al. reported that elevated ferritin level with a mean of 1593 ng/mL was associated with shock and the need for mechanical ventilation, entailing close monitoring at the ICU.[14] Similar to the studies of Merckx et al. and Tran et al., initial serum ferritin levels of > 500 ng/mL and > 300 ng/mL, respectively were predictive of ICU admission and prolonged hospital stay.[15,16] Both WBC and ferritin are markers of inflammation that reflect the body's response to the viral stimulus. Elevated WBCs reflect the immune system's drive against the ongoing viral infection in MIS-C. Ferritin, aside from being a direct measure of stored iron in the body, has also been used as a marker of inflammation in the context of MIS-C. According to Kell and Pretorius, high levels of ferritin correlate with increased radical formation resulting in oxidative damage.[17] Thus, levels of WBC and ferritin both reflect the overwhelming infection and hyperinflammatory response, and at markedly increased levels, place patients at higher risk for complications.

While the statistical analysis showed a significant association between HIV infection and both ARDS and mortality, this finding should be interpreted with caution due to the limited sample size – specifically the fact that there was only one mortality case and only one patient with documented HIV infection. The observed statistical significance may not reflect a true effect, but rather a result of data sparsity. Nonetheless, the clinical relevance remains noteworthy. This finding is consistent with the study of Chinniah et al. in associating unidentified co-morbidities, including HIV and malnutrition, with an increased mortality rate among MIS-C by at least seven-fold among South African children.[14] The lone adolescent patient with HIV developed ARDS and died shortly after MIS-C diagnosis, highlighting the potential vulnerability of immunocompromised children. Even prior to the COVID-19 pandemic, Kohn and Flori reported that immunocompromised patients have a higher risk of developing ARDS, and the most common childhood immunodeficiency now is HIV infection.[18]

Cardiac involvement in MIS-C has garnered significant attention in recent research. In our study, pericardial effusion, myocarditis, and coronary artery abnormalities were the most commonly observed cardiac findings in patients with MIS-C. A study by Hoseininasab et al. [19] found pericardial effusion to be the most prevalent sign of cardiac involvement, which can manifest alone, or may be accompanied by varying degrees of myocardial inflammation, valvular abnormalities, coronary artery dilatation, and rarely, heart failure. Myocarditis, characterized by inflammation of the heart muscle, is also frequently reported, contributing to the overall cardiovascular morbidity associated with MIS-C. Furthermore, coronary artery abnormalities, including dilatation and aneurysm formation, have been documented in several studies. A local study [11] found that 50% of 36 MIS-C patients had mild to moderate pericardial effusion, and that coronary artery dilatation was present in 39% of patients. The study also noted that patients with cardiac involvement had higher levels of inflammatory markers, indicating a potential association between inflammation and cardiovascular complications.[11] Additionally, a report by

Alsaied et al.[20] found that coronary artery dilation occurred in 14% to 48% of MIS-C cases. The same study also reported some degree of left ventricular dysfunction in 31% to 58% of patients, detected either by 2DE or by elevated BNP levels.[19] There have been varying results in studies with regard to troponin levels. Dufort, et al.[21] concluded that elevated troponin levels were associated with cardiac complications, while Zhao et al. [1], and Zhao et al.,[2] reported that there was no significant difference in the levels of troponin in MIS-C patients, in comparison to COVID-19 patients without MIS-C. These findings underscore the significant cardiac compromise in this disease, possibly resulting from the hyperinflammatory state, and viral infiltration of cardiomyocytes, both leading to cellular damage and ischemic injury.[20]

Despite the numerous findings on poor clinical outcomes, all patients, except for one, recovered well with appropriate treatment, and were discharged with minimum residual morbidity.

CONCLUSION

With the limitation of a small population of MIS-C patients, we found HIV infection to be the only clinical parameter that is significantly associated with the occurrence of ARDS and mortality. There were no other clinical and demographic parameters found to be associated with poor outcomes such as age or nutritional status.

In terms of laboratory markers, a high percentage of neutrophils was found to be associated with hypotension/shock, and elevated WBC and ferritin levels were each found to be associated with an ICU admission. Myocarditis was seen in 68%, hypotension/shock and ICU admission each occurred in 14%; and ARDS and bacteremia were each seen in 7% of patients. The outcome was generally good in non-immunocompromised patients, with the lone (3%) mortality having an immunocompromising condition.

LIMITATIONS

While we identified strong associations with certain factors, the relatively small sample size and retrospective nature of the study limit the precision of our estimates, especially for rarer outcomes like mortality. Not all included patients had the same battery of laboratories upon admission, hence not all patients had baseline values for specified markers. Selection bias could have occurred if the study population was not representative of the broader MIS-C population, and information bias could have arisen from incomplete or inaccurate medical records. Confounding remains a possibility, particularly from factors such as underlying immunocompromise or prior SARS-CoV-2 exposure, which were not fully accounted for in the analysis. The lack of control for confounding variables, such as the use of immunomodulatory therapies or differing clinical management strategies, may have also influenced the observed relationships between inflammatory markers and clinical outcomes. As such, these constraints have limited the study to represent a descriptive analysis rather than an analytic one as a basis for predictive modeling.

RECOMMENDATIONS

For future studies, we recommend including a larger sample size involving multiple centers to enhance the study's generalizability. Considering the declining incidence of MIS-C in the current times, a retrospective descriptive study can still likely be employed.

CONFLICT OF INTEREST

None declared.

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