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Role of Macrophage Migration Inhibitory Factor in Prediction of Cardiac Affection in Multisystem Inflammatory Syndrome in Children

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Abstract

Background: Multisystem inflammatory syndrome in children (MIS-C) is a dysregulated immune response to viral infection by COVID-19 accompanied by systemic manifestations. Macrophage migration inhibitory factor (MIF) exerts inhibitory effects on macrophage migration and is raised in adult cardiac critical illness

Aim of Study: To identify the role of MIF as a marker of cardiac affection in MIS-C patients.

Patients and Methods: This case-controlled study was conducted on 24 MIS-C children and 24 apparently healthy controls. Clinical and laboratory data were compared between both groups. Echocardiography was done for all participants.

Results: Myocardial injury markers as troponins, CK-MB and liver injury markers were significantly (p>0.05) elevated among MIS-C patients than controls. MIF expression was also significantly higher (p>0.05) among MIS-C patients. Impaired LV function and valve regurgitation were the main echocardiographic findings among MIS-C patients. MIF correlated significantly with age, lymphocytic count, ferritin, LDH, D-dimer, CK-MB, EF%, LVESD, LVEDD, Z-score RCA and Z-score LCA.

Conclusion: Myocardial injury is common in MIS-C patients. Impaired LV function is the most prominent echocardiographic finding. MIF could be considered as a biomarker for MIS-C and correlated significantly with myocardial affection among those patients.

Key Words: *Multisystem Inflammatory Syndrome – COVID-19 in Children.*

Introduction

CORONAVIRUS disease 2019 (COVID-19) is caused by the seventh member of the Corona virus family. It was declared a public health emergency of international concern on January 30, 2020, and was identified as an outbreak in March 2020 **[1].**

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In mid-May 2020, the Centers for Disease Control and Prevention (CDC) published a case definition for MIS-C for disease surveillance. Pediatric Multi-System Inflammatory Syndrome (PMIS) involves primary symptoms that consist of persistent fever, extreme systemic inflammation, and evidence that one or more that organs are not functioning properly. In serious cases, MIS-C can cause heart champers enlargement and damage; fever with many symptoms, including rash; conjunctivitis; redness in the lips, tongue, and mucous membranes of the mouth and throat; swollen hands or feet; and sometimes enlarged lymph nodes on one side of the neck **[2].**

Immune dysregulation of MIS-C has been suggested that the syndrome results from an abnormal immune response to the virus, with some clinical similarities to Kawasaki disease (KD), macrophage activation syndrome (MAS), and cytokine release syndrome. However, based on the available studies, MIS-C appears to have an immunophenotype that is distinct from KD and MAS. The exact mechanisms by which SARS-CoV-2 triggers the abnormal immune response are unknown **[3].**

Cardiovascular involvement in MIS-C is prominently marked by acute myocardial injury (myocarditis) and the development of coronary artery aneurysms. Laboratory markers of inflammation are elevated uniformly. Most children require intensive care, and few need invasive ventilation **[4].**

MIF is considered an upstream regulator of inflammation and is released in the ischaemic heart, where it stimulates AMP-activated protein kinase (AMPK) activation through CD74, promotes glucose uptake and protects the heart during is chaemia-reper fusion injury **[5].**

Early-stage predictive biomarkers are needed to identify patients with a high risk of severe clinical courses and to stratify treatment strategies. Macrophage migration inhibitory factor (MIF) was previously described as a potential predictor for the outcome of critically ill patients and for acute respiratory distress syndrome (ARDS), a hallmark of severe COVID-19 disease **[6]**.

Aim of study:

This study aims at identifying the serum value of macrophage migration inhibitory factor and its role as an early predictor of cardiac affection severity in MIS-C patients.

Patients and Methods

This case-control study was conducted at the Pediatric Hospital of Ain Shams University on twenty-four children and adolescents diagnosed with MIS-C according to the Center for Disease Control and Prevention (CDC, 2021) and twenty-four age- and sex-matched apparently healthy controls with no clinical evidence of COVID-19 disease or any other diseases. The patients were recruited over a period of six months starting from June 2021 till December 2021. They were a total of 27 males and 21 females with age ranging from 2.1 to 13 years and with median (IQR) of 5.2 (3-7.8) years. Exclusion criteria included patients above 18 years of age, Kawasaki disease, Systemic lupus erythematosus, Toxic shock like syndrome, Vasculitis, and bacterial sepsis.

Ethical considerations:

All participants gave a written informed consent before participation and the study was carried out after approval of Ethical Committee and Institutional Reviewing Board, Faculty of Medicine, Ain Shams University FWA 000017585 FMASU MS 125/2022.

Methods:

All individuals participating in the study were subjected to full medical history and examination laying stress on history of contact to suspected or confirmed COVID-19 cases, Symptoms suggesting COVID-19 infection as fever, bony aches, loss of smell, cough, respiratory distress, History of acute illness: Suggesting incidence of MIS-C as skin rash, conjunctivitis, mucocutaneous lesions, fever, abdominal pain, vomiting and/or diarrhea. Medical history of any associated chronic comorbidities and Drug history. A comprehensive clinical assessment was done with emphasis on chest examination for signs of chest infection, Cardiac examination especially for heart sounds, murmurs, and gallop and abdominal examination for tender hepatomegaly. In addition, Radiological evaluation including chest X-ray and transthoracic echocardiography was done for all individuals in the study.

Laboratory investigations:

Ten milliliters of venous blood were collected from each participant under complete aseptic precautions divided into k3 EDTA vacutainers for complete blood count (CBC) (ADVIA, Siemens Healthineers, Germany), Citrate vacutainers for D-dimer (VIDAS, Biomerieus, France) and sterile plain vacutainer tubes. The blood samples in the plain tubes were allowed to clot for 30 minutes and then centrifuged at 3000 rpm for 10 minutes then sera were removed and stored at –20°C till time of analysisof C-reactive protein (CRP), Creatine kinase (Total, MB), Serum Creatinine, Blood urea nitrogen (BUN), Lactate dehydrogenase, serum albumin (COBAS C6000, Roche Diagnostic GmbH, Mannheim, Germany) Troponin and serum ferritin (COBAS e411, Roche Diagnostic GmbH, Mannheim, Germany).

Assessment of Serum Macrophage Migration Inhibitory factor (MIF) using commercially available ELISA kits supplied by Bioassay Technology laboratory co.catalog no. E0141Hu. (Shanghai, China) was done following the manufacturer's instructions. Absorbance of each well was measured at 450 nm by using a microtiter plate ELISA reader (BioTek, Winooski, VT, USA). The kit detection range was 0.1-40ng/ml.

Radiological assessment:

Chest X-ray: The patient was positioned at standing, sitting or in supine position according to clinical condition. Transthoracic echocardiography: All patients underwent standard echocardiography with Doppler studies, using a vivid E95 machine. All subjects were examined in the left lateral decubitus position according to the recommendations of the American Society of Echocardiography **[7]**.

Statistical analysis:

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when parametric and median, inter-quartile range (IQR) when data found non-parametric.

Also, qualitative variables were presented as number and percentages. The comparison between groups with qualitative data was done by using Chi-square test. The comparison between two independent groups with quantitative data and parametric distribution were done by using Independent *t*-test

while with non-parametric distribution was done using Mann-Whitney test.

Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group.

Receiver operating characteristic curve (ROC) was used to assess the best cut off point with its sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under curve (AUC).

Results

Table (1) showed that there was statistically significant increase in the TLC, neutrophil, CRP, serum ferritin, LDH, D-dimer, CK-MB and troponin levels in patients' group than control group. Also, the table showed that there was statistically significant decrease in the levels of lymphocytes, hemoglobin, platelets, MCV and MCH levels in patients' group than control group while no statistically significant difference found between both groups regarding BUN and creatinine levels.

There were 11 patients (45.8%) had leukocytosis, also there were 23 patients (95.8%) had increase in CRP, also 23 patients (95.8%) had increased serum ferritin, also 22 patients (91.7%) had increased LDH, also 20 patients (83.3%) had increased D-dimer level, also 19 patients (75%) had increased CK-MB also 9 patients (37.5%) had increased in troponin.

There were 18 patients (75%) had lymphopenia, also there were 11 patients (45.8%) had decrease in Hb level.

Table (1) showed there was statistically significant increase in the levels of AST, ALT and ESR in patients' group than control group; also, statistically significant decrease in the level of albumin in patients' group than control group; while there was no statistically significant difference found between both groups regarding serum Na and K levels.

Table (1): Comparison between control group and patients group regarding laboratory investigations.

	Patients group No.=24	Control group No.=24	Test-value	p-value	Sig.
TLC (U/L):					
Median (IQR)	14.3 (11.35 – 22.65)	8.1 (6.4 – 12.25)	-3.351$	0.001	HS
Range	3.2 – 32.5	5.2 – 28.2			
Low	1 (4.2%)	5 (20.8%)	7.810*	0.020	S
Normal	12 (50.0%)	16 (66.7%)			
High	11 (45.8%)	3 (12.5%)			
NEUT (cells/µL):					
Median (IQR)	11.65 (7.15 – 18.2)	3.61 (3.01 – 5.52)	-4.310$	0.000	HS
Range	0.5 – 46.4	2.32 – 10.2			
Lymphocytes(cells/µL):					
Median (IQR)	2.05 (1.32 – 3.25)	4.09 (3.7 – 5.92)	-4.053$	0.000	HS
Range	0.02 – 7.27	3.02 – 15.7			
Low	18 (75.0%)	0 (0.0%)	29.143*	0.000	HS
Normal	6 (25.0%)	22 (91.7%)			
High	0 (0.0%)	2 (8.3%)			
Hb (g/dl):					
Mean ± SD	9.99±1.74	11.55±0.86	3.946•	0.000	HS
Range	4 – 12.8	9.7 – 13.5			
Low	11 (45.8%)	1 (4.2%)	11.111*	0.001	HS
Normal	13 (54.2%)	23 (95.8%)			
Platelets (cells/µL):					
Median (IQR)	267 (188 – 337)	330 (282 – 391)	-2.083$	0.037	S
Range	62 – 775	140 – 620			
MCV (femtoliters ((fl):					
Mean ± SD	71.3±6.16	81.06±10.74	3.858•	0.000	HS
Range	58 – 82	56.3 – 94.29			
MCH (picogram):					
Mean ± SD	23.73±2.88	25.69±2.39	2.568•	0.014	S
Range	18.4 – 28.7	20.1 – 29.6			

p-value >0.05: Non-significant. p-value <0.05: Significant. p-value <0.01: Highly significant.
*: Chi-square test. •: Independent t-test. $: Mann Whitney test.

Table (1): Comparison between control group and patients group regarding laboratory investigations (Cont...).

	Patients group No.=24	Control group No.=24	Test-value	p-value	Sig.
CRP (mg/dl):					
Median (IQR)	101.95 (50.75 – 143.75)	4.45 (4 – 5)	-5.584#	0.000	HS
Range	4 – 339.2	3.5 – 5			
Normal	1 (4.2%)	24 (100.0%)	44.160*	0.000	HS
High	23 (95.8%)	0 (0.0%)			
ESR (mm/hr):					
Median (IQR)	142.5 (10 – 110)	6.5 (4 – 9.5)	-5.949#	0.000	HS
Range	65 – 110	3 – 10			
Normal	0 (0.0%)	24 (100.0%)	48.000*	0.000	HS
High	24 (100.0%)	0 (0.0%)			
Serum ferritin (ng/ml):					
Median (IQR)	711.5 (449 – 1176)	88.5 (63.5 – 105)	-5.897$	0.000	HS
Range	119.9 – 8922	47.3 – 130			
Normal	1 (4.2%)	24 (100.0%)	44.160*	0.000	HS
High	23 (95.8%)	0 (0.0%)			
LDH (U/L):					
Mean ± SD	630.46±247.17	99.5±19.55	10.491•	0.000	HS
Range	294 – 1435	79 – 153			
Low	0 (0.0%)	0 (0.0%)	40.615*	0.000	HS
Normal	2 (8.3%)	24 (100.0%)			
High	22 (91.7%)	0 (0.0%)			
D-dimer (ug/ml):					
Mean ± SD	4.05±1.59	1.54±0.59	-7.280•	0.000	HS
Range	1.46 – 7.88	0.46 – 2.56			
Normal	4 (16.7%)	24 (100.0%)	34.286*	0.000	HS
High	20 (83.3%)	0 (0.0%)			

p-value >0.05: Non-significant. p-value <0.05: Significant. p-value <0.01: Highly significant.
*: Chi-square test. •: Independent t-test. $: Mann Whitney test.

Table (1): Comparison between control group and patients group regarding laboratory investigations (Cont...).

	Patients group No.=24	Control group No.=24	Test-value	p-value	Sig.
CK-Total (IU/L):					
Median (IQR)	66.5 (48 – 125.5)	31 (19.5 – 43.5)	-4.312#	0.000	HS
Range	9 – 1152	9 – 48			
Normal	6 (25.0%)	24 (100.0%)	28.800*	0.000	HS
High	18 (75.0%)	0 (0.0%)			
CK-MB (IU/L):					
Median (IQR)	31 (24 – 56.5)	6 (5 – 7)	-5.945$	0.000	HS
Range	15 – 110	5 – 16			
Normal	5 (20.8%)	24 (100.0%)	31.448*	0.000	HS
High	19 (79.2%)	0 (0.0%)			
TROPNIN (mg/dl):					
Median (IQR)	0.006 (0.002 – 0.102)	0.002 (0.001 – 0.007)	-2.438#	0.015	S
Range	0 – 0.921	0 – 0.028			
Normal	15 (62.5%)	24 (100.0%)	11.077*	0.001	HS
High	9 (37.5%)	0 (0.0%)			
BUN (mg/dl):					
Median (IQR)	14 (7.5 – 22.5)	14 (7.9 – 16.5)	-0.568#	0.570	NS
Range	0.8 – 75	6 – 24			
Low	1 (4.2%)	0 (0.0%)	11.077*	0.004	HS
Normal	15 (62.5%)	24 (100.0%)			
High	8 (33.3%)	0 (0.0%)			
Creat (mg/dl):					
Median (IQR)	0.6 (0.4 – 1.05)	0.6 (0.5 – 0.85)	-0.166#	0.868	NS
Range	0.2 – 2.9	0.3 – 1.2			
Low	1 (4.2%)	0 (0.0%)	6.857*	0.032	S
Normal	18 (75.0%)	24 (100.0%)			
High	5 (20.8%)	0 (0.0%)			

p-value >0.05: Non-significant. p-value <0.05: Significant. p-value <0.01: Highly significant.
*: Chi-square test. •: Independent t-test. $: Mann Whitney test.

Table (1): Comparison between control group and patients group regarding laboratory investigations (Cont...).

	Patients group No.=24	Control group No.=24	Test-value	*p*-value	Sig.
Na (Mmol/L):					
Mean ± SD	134.67±6.57	136.17±3.00	1.017•	0.314	NS
Range	124 – 159	131 – 142			
Low	13 (54.2%)	7 (29.2%)	4.615*	0.100	NS
Normal	10 (41.7%)	17 (70.8%)			
High	1 (4.2%)	0 (0.0%)			
K (Mmol/L):					
Mean ± SD	4.32±0.77	4.52±0.44	1.129•	0.265	NS
Range	3.1 – 6.7	3.8 – 5.3			
Low	3 (12.5%)	0 (0.0%)	3.714*	0.156	NS
Normal	19 (79.2%)	23 (95.8%)			
High	2 (8.3%)	1 (4.2%)			
A*ST (U/L):*					
Median(IQR)	39 (26.5 – 78)	23 (17.5 – 29.5)	-3.487$	0.000	HS
Range	12 – 151	12 – 42			
Normal	13 (54.2%)	23 (95.8%)	11.111*	0.001	HS
High	11 (45.8%)	1 (4.2%)			
ALT (U/L):					
Median (IQR)	35 (17.5 – 81)	18.5 (11 – 27)	-2.683$	0.007	HS
Range	8 – 288	8 – 39			
Low	1 (4.2%)	2 (8.3%)	12.648*	0.002	HS
Normal	13 (54.2%)	22 (91.7%)			
High	10 (41.7%)	0 (0.0%)			
Alb (g/dl) :					
Mean ± SD	3.05±0.5	4.21±0.54	7.667•	0.000	HS
Range	2.1 – 4.1	3.4 – 5.2			
Low	17 (70.8%)	0 (0.0%)	26.323*	0.000	HS
Normal	7 (29.2%)	24 (100.0%)			

p-value >0.05: Non-significant. *p*-value <0.05: Significant. *p*-value <0.01: Highly significant.
*: Chi-square test. •: Independent *t*-test. $: Mann Whitney test.

As regard serum Na, 54.13% of patients (13 patients) had hyponatremia while 4.2% of patients (1 patient) had hyper natremia. Also 12.5% of patients (3 patients) had hypokalemia while 8.3% of patients (2 patients) had hyperkalemia, also 70.8% of patients had hypoalbuminemia (17 patients).

As regards liver function 45.8% of patients (11 patients) had an increase in AST also there were 41.7% of patients (10 patients) had increase in ALT.

Table (2) showed that there was statistically significant increase in the level of macrophage migration inhibitory factor on admission in patients group (27.85±10.82) than control group (3.11±1.16).

Table (4) shows that there was statistically significant negative correlation found between macrophage migration inhibitory factor on admission and age of the studied patients, lymphocytic count, hemoglobin level and EF% and also positive correlation between macrophage migration inhibitory factor on admission and serum ferritin, LDH, D-dimer, CK total, CK-MB, troponin level, Z-score of RCA, and Z-score of LCA while no statistically significant correlation found with the other studied parameters.

Table (2): Comparison between control group and patients group regarding the level of macrophage migration inhibitory factor on admission.

	Patients group No.=24	Control group No.=24	Test-value	*p*-value	Sig.
Macrophage Migration Inhibitory factor on admission(ng/ml):					
Median (IQR)	27.85±10.82	3.11±1.16	–11.130•	0.000	HS
Range	7.73 – 48	1.09 – 5.89			

p-value >0.05: Non-significant. *p*-value <0.05: Significant. *p*-value <0.01: Highly significant. •: Independent *t*-test.

Table (3): Comparison between control group and patients group regarding the echocardiographic parameters.

	Patients group No.=24	Control group No.=24	Test-value	*p*-value	Sig.
EF (%):					
Mean ± SD	57.5±13.14	73±6.85	5.126•	0.000	HS
Range	26 – 81	61 – 85			
Normal (≥ 55)	14 (58.3%)	24 (100.0%)	12.632*	0.002	HS
Mild (41-54)	9 (37.5%)	0 (0.0%)			
Moderate (31 – 40)	0 (0.0%)	0 (0.0%)			
Severe (≤ 30)	1 (4.2%)	0 (0.0%)			
LVESD:					
Mean ± SD	2.35±0.39	2.14±0.29	-2.129•	0.039	S
Range	1.7 – 3	1.6 – 3			
LVEDD:					
Mean ± SD	4.07±0.62	3.48±0.53	-3.496	0.001	HS
Range	3.1 – 6	2.5 – 4.6			
Z-Score RCA:					
Normal <2	21 (87.5%)	24 (100.0%)	3.200*	0.202	NS
Dilatation (2 – 2.5)	2 (8.3%)	0 (0.0%)			
Aneurism (>2.5)	1 (4.2%)	0 (0.0%)			
Z-Score LCA:					
Normal <2	20 (83.3%)	24 (100.0%)	4.364*	0.113	NS
Dilatation (2 – 2.5)	1 (4.2%)	0 (0.0%)			
Aneurism (>2.5)	3 (12.5%)	0 (0.0%)			
PE:					
No	21 (87.5%)	21 (87.5%)	0.000*	1.000	NS
Mild	3 (12.5%)	3 (12.5%)			
MR:					
No	0 (0.0%)	24 (100.0%)	48.000*	0.000	HS
Mild	12 (50.0%)	0 (0.0%)			
Moderate	4 (16.7%)	0 (0.0%)			
Sever	1 (4.2%)	0 (0.0%)			
Trival	7 (29.2%)	0 (0.0%)			
TR:					
No	0 (0.0%)	20 (83.3%)	36.571*	0.000	HS
Mild	10 (41.7%)	4 (16.7%)			
Moderate	4 (16.7%)	0 (0.0%)			
Sever	3 (12.5%)	0 (0.0%)			
Trival	7 (29.2%)	0 (0.0%)			

p-value >0.05: Non-significant. *: Chi-square test.
p-value <0.05: Significant. •: Independent *t*-test.
p-value <0.01: Highly significant. ‡: Mann Whitney test.

Table (4): Correlation between macrophage migration inhibitory factor on admission and the other studied parameters among patients' group.

	Macrophage Migration Inhibitory factor on admission	
	r	p-value
Age (years)	-0.455*	0.025
Weight	-0.375	0.071
Height	-0.400	0.053
Heart rate	-0.086	0.690
TLC	0.121	0.574
NEUT	0.094	0.662
Lymphocytes	-0.516**	0.000
Hb	-0.417*	0.043
Platelets	0.031	0.884
MCV	-0.160	0.454
MCH	-0.087	0.687
CRP	-0.085	0.694
Serum ferritin (ng/ml)	0.519**	0.009
LDH (U/L)	0.800**	0.000
D-dimer	0.607**	0.002
BUN	-0.236	0.268
create	-0.049	0.821
Na	-0.180	0.401
K	0.185	0.386
AST	-0.175	0.413
ALT	-0.190	0.374
Alb	-0.081	0.708
ESR	-0.143	0.504
CK-Total	0.640**	0.001
CK-MB	0.685**	0.000
TROPNIN	0.558**	0.000
Z-Score RCA	0.608**	0.002
Z-Score LCA	0.430*	0.036
EF (%)	-0.786**	0.000
LVESD (cm)	0.948**	<0.001
LVEDD (cm)	0.892**	<0.001

Discussion

Immune dysregulation of MIS-C in children has been suggested that the syndrome results from an abnormal immune response to COVID-19 virus, with some clinical similarities to Kawasaki disease (KD), macrophage activation syndrome (MAS), and cytokine release syndrome. However, based on the available studies, MIS-C appears to have an immunophenotype that is distinct from KD and MAS. The exact mechanisms by which SARS-CoV-2 triggers the abnormal immune response are unknown *[8]*.

Cardiovascular involvement in MIS-C is prominently marked by acute myocardial injury (myocarditis) Laboratory markers of inflammation are elevated uniformly *[4]*.

In most cases diagnosed with MIS-C, left ventricular systolic dysfunction has been reported *[9]*.

MIF was previously described as a potential predictor for the outcome of critically ill patients and for acute respiratory distress syndrome (ARDS), a hallmark of severe COVID-19 disease *[6]*.

In this study, median total leucocytic count (8.1 vs. 14.3; p=0.001) and neutrophil count (3.6 vs. 11.65; p<0.001) were higher while lymphocyte count (3.33 vs. 2.05; p<0.001) was lower among MIS-C group than control group with statistically significant differences. In agreement with the present study, in a meta-analysis by Esposito & Principi [10] included 8 studies on MIS-C patients, leukocytosis and neutrophilia were the commonest laboratory findings among MIS-C patients. Farzad et al. [11] demonstrated in his study on 60 MIS-C patients and 30 controls that MIS-C patients had significantly higher leucocytic count (12.3±7.2; p=0.006) and neutrophil count (11.4±2.09 vs. 4.07± 0.5; p=0.001) and significantly lower lymphocytic count (1.4±0.12 vs. 3.1±0.5; p=0.002). Also, Aksakal et al. *[12]* found that MIS-C patients had significantly higher total leucocytic count and neutrophils and lower lymphocytic count the healthy controls.

The present study showed that MIS-C patients had significantly lower mean values for hemoglobin (11.55±0.86 vs. 9.99±1.74; p<0.001) and median platelets count (330 vs. 267; p=0.037). MCV and MCH showed significantly lower mean values among MIS-C patients than control group. In agreement with the present study, Ahmed et al. *[13]* showed that hemoglobin levels were significantly lower among MIS-C patients than control group. Radia et al. *[14]* similarly found that MIS-C patients had lower mean values for hemoglobin.

In the present study, inflammatory markers included C- reactive protein, ESR, serum ferritin and LDH were significantly higher among MIS-C group than control group. In concordance with the present results, Farzad et al. *[11]* demonstrated that inflammatory markers as CRP and LDH were significantly higher among MIS-C group and correlated positively to disease severity. Esposito & Principi *[10]* and Ahmed et al. *[13]* in their 2 meta-analyses included MIS-C showed that inflammatory markers as ESR, CRP and LDH were significantly higher in MIS-C than healthy controls.

Cardiac biomarkers as D-Dimer, troponin and CK- MB had higher mean and median values among MIS-C patients than control group with statistically significant differences. In concordance with the present study, Aksakal et al. *[12]* showed that D-Dimer

was elevated significantly among COVID-19 MIS-C patients however troponin I was comparable between mild, severe and control groups. Esposito & Principi *[10]* and Ahmed et al. *[13]* also demonstrated that in MIS-C patients, biomarkers for heart damage including troponin, D-Dimer and pro BNP increased significantly. Similarly, Syrimi et al. *[15]* demonstrated that myocardial dysfunction markers (troponin I and CK-MB) were higher significantly among MIS-C than controls.

In this study, there were no statistically significant differences between MIS-C and control groups as regard BUN and s. creatinine. In agreement with the present study, Aksakal et al. *[12]* did not show presence of significant differences between COVID-19 with MIS-C and control groups as regard S. creatinine.

According to the present study, ALT and AST had higher median values among MIS-C group (ALT: 35; AST: 39) than control group (ALT: 18.5; AST: 23) with statistically significant differences (p=0.007; <0.001). In concordance with the present study, Ahmed et al. *[13]* found that MIS-C had significantly higher mean values for ALT and AST than healthy children.

Serum albumin as a negative phase reactant had lower mean values among MIS-C patients (3.05±0.5) than control group (4.21±0.54) with statistically significant difference (p<0.001). In concordance with the present study, Ahmed et al. *[15]* found that serum albumin was 2.8±0.2 among MIS-C patients which was significantly lower than control group (4±1.2). Son et al. *[16]* also showed that MIS-C patients had significantly lower serum albumin levels than control group (2.1±1.3 vs. 3.9±0.3; P<0.001).

Echocardiographic parameters were compared between MIS-C group and control group. Coronary arteries dilatation wasn't proven by presence of significant differences between MIS-C group and control group as regard Z-score for LCA and RCA, according to Z-score of LCA there was 1 patient (4.2%) with dilation and 3 patients (12.5%) with aneurysm. according to Z-score of RCA there was 2 patient (8.3%) with dilation and 1 patient (4.2%) with aneurysm. In agreement with the present study, Blondiaux et al. *[17]* did not find statistically significant differences in coronary arteries diameter between MIS-C and control groups. Also, Yakut et al. *[18]* reported that coronary dilatation occurred to only 1 patient out of 57 MIS-C patients.

According to the present results, Ejection fraction was lower among MIS-C group than control group with statistically significant difference (73±6.85 vs. 57.5±13.14; P<0.001) and left ventricle was significantly dilated in MIS-C group than control group showing higher mean values of LVEDV and LVESV among MIS-C group (P=0.039; 0.001). These findings came in agreement with El- Saied et al. *[9]* who reported that impaired LV function was present in 58% of MIS- C patients. Vukomanovic et al. *[19]* showed that mean EF of 19 MIS children was 49.9±7.8% which was significantly lower than normal ranges for age. Yakut et al. *[18]* found that 21% of 57 MIS-C patients had reduced ejection fraction and increased LVEDV and LVESV in comparison to control group with statistically significant differences.

In the current study, incidence of mitral and tricuspid regurgitation with variable grades was higher among MIS- C group than control groups with statistically significant differences (P<0.001). In agreement with the present study, Valverde et al. *[20]* in his study on 286 MIS-C patients showed that 10% of patients had variable degrees of MR and TR. Yakut et al. *[18]* reported that 29% of MIS-C patients had MR and TR in his study on 57 patients. On contrary, El-Saied et al. *[9]*.

Could not report presence of significant association between MIS-C patients and incidence of MR or TR.

The present study showed that Macrophage migration inhibitory factor (MIF) on admission had significantly higher mean values among MIS-C group (27.85±10.82) than control group (3.11±1.6) with statistically significant difference (P<0.001). In consistency with the present results, Farzad et al. *[11]* showed that mean values of MIF in control group was 20.63±6.1 which was significantly lower than that in mild MIS disease group (40.45±6.6) and severe MIS disease group (65.31±6.2) with statistically significant differences (P<0.001).Another study by Aksakal et al. *[12]* was performed on 110 patients diagnosed with COVID-19 and 40 healthy volunteers. Significantly, higher MIF levels were reported in the patients than in the controls. Furthermore, there was a higher level of MIF in severe patients than in moderate cases. Dheir et al. *[20]* studied 87 COVID-19 patients, including 47 ICU-admitted and 40 ward-admitted patients. Regarding MIF levels, a significant difference was observed between the ICU and ward patients (P<0.024).

At cutoff equal to 5.89, Macrophage migration inhibitory factor (MIF) had 100% sensitivity and specificity in differentiation between patients with and without MIS-C. In agreement with the present study, MIF had 86.7% sensitivity and 97.7% speci-

ficity in diagnosis of MIS at cutoff value equal to 5.07 in a study by Farzad et al. [11]. Aksakal et al. [12] considered MIF equal to 4.55 as a cut-off value for differentiation between mild and severe disease with 83% sensitivity and 62% specificity. Dheir et al. [20] found that at cut-off value 4.7, MIF could differentiate between patients with mild and severe diseases with high sensitivity and specificity.

We tried to assess the correlations between macrophage migration inhibitory factor (MIF) and other parameters. There was statistically significant negative correlation between MIF and patients' age (r: –0.455; p=0.025). However, there were no statistically significant correlations between MIF and sex, weight, or height. Similarly, Aksakal et al. [12] demonstrated presence of significant inverse correlation between MIF and age (r: –0.19; p=0.04). On the other hand, Luedike et al. [21] did not find statistically significant correlation between MIF and age in patients with cardiac affection.

There were no statistically significant correlations between MIF and leucocytic count or neutrophils. However, there was statistically inverse correlation between MIF and lymphocytic count (r: –0.66; p<0.001). In agreement with the present study, Bleilevens et al. [6] and Luedike et al. [21] did not find statistically significant correlation between white blood cell count and MIF. Farzad et al. [11] and Aksakal et al. [12] confirmed the presence of significant inverse correlation between MIF and lymphocytic count in MIS group.

In the presents study, there were statistically significant positive correlations between MIF and inflammatory markers as ferritin (r: 0.52; p=0.009), LDH (r: 0.8; p<0.001) and D-dimer (r: 0.607; p=0.002). However, there were no statistically significant correlation between MIF and CRP or ESR. In agreement with the present study, Aksakal et al. [12] demonstrated presence of statistically significant correlation between LDH, ferritin and D-dimer. Bleilevens et al. [6] reported absence of significant correlation between MIF and CRP among MIS-C patients. Also, Luedike et al. [21] did not find statistically significant correlation between CRP and MIF.

The current study showed presence of significant positive correlations between MIF and cardiac biomarkers as total CK (r: 0.64; p=0.001), CK-MB (r: 0.685; p<0.001) and troponin I (r: 0.558; p<0.001). In concordance with the present study, Luedike et al. [22] showed presence of statistically significant correlations between cardiac biomarkers as pro-BNP, troponin, CK-MB and MIF levels. Zhao et al. [23] obtained similar results and demonstrated presence of significant correlation between MIF and circulating CK-MB or troponin among acute coronary syndrome patients.

According to the present study, there was statistically significant positive correlation between COVID-19 IgM and MIF (p=0.032) but not with COVID-IgG.

Correlation analysis of MIS-C with echocardiographic findings proved presence of significant association between MIF and myocardial dysfunction incidence among MIS-C patients. The current study showed presence of significant association between MIF and incidence of dilated cardiomyopathy as there were positive correlations between MIF and left ventricular end diastolic (r: 0.94; p<0.001) and systolic (r: 0.89; p<0.001) diameters. Such association reflected presence of significant inverse correlation between MIF and LV function as represented by EF (r: –0786; p<0.001). In agreement with the present study, Bleilevens et al. [6] proposed that MIF is correlated significantly to organ failure among COVID-19 infection patients.

The current study also evaluated the differences in MIF levels between MIS-C patients with variable clinical manifestations and there were no statistically significant association between variable systems affection and MIF levels. Also, there were no statistically significant sex differences in MIF levels among MIS-C patients.

The study had some advantages. To the best of our knowledge, this is the first study to assess macrophage migration inhibitory factor in MIS-C patients with cardiac affection particularly in children. Also, we evaluated the correlation of MIF levels in comparison to variable demographics, clinical and laboratory data. In the present study, we included detailed assessment of echo findings in patient with MIS and correlated these findings with MIF levels.

The study had some limitations as lack of randomization as we did not evaluate the response to certain treatment plans, and we did not evaluate the value of this biomarker in prediction of response to treatment also the effect of treatment lines on MIF concentrations.

Conclusion:

Patients with multiple systems inflammatory syndrome after COVID-19 infection usually presented with fever, skin, mucocutaneous manifestations and gastrointestinal manifestations. Patients with multiple systems inflammatory syndrome usually had leucocytosis, neutrophilia and lymphocytopenia with positive inflammatory markers.

Cardiac affection in patients with multiple systems inflammatory syndrome is common and manifested by impaired ejection fraction, left ventricular dilatation and to less extent by mitral or tricuspid regurge. Macrophage migration inhibitory factors increased significantly in patients with multiple systems inflammatory syndrome and correlated to patients age and inflammatory markers.

Macrophage migration inhibitory factors could predict cardiac affection in patients with multiple systems inflammatory syndrome and correlated significantly to cardiac injury markers and echocardiographic parameters.

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تقييم دورالعامل المثبط لهجرة الماكروفاج فى التنبؤ بالآثار القلبية لدى الاطفال المصابين بمتلازمة التهاب الأجهزة المتعددة الناشئة عن الاصابة بمرض فيروس كورونا عند الأطفال

المرضى الذين يعانون من متلازمة التهاب الأجهزة المتعددة الناشئة عن الاصابة بمرض فيروس كورونا عند الأطفال ١٩عادة ما يعانون من الحمى وآثار على الجلد وآثار جلدية مخاطية ومظاهر معدية معوية.

المرضى الذين يعانون من متلازمة التهاب الأجهزة المتعددة الناشئة عن الاصابة بمرض فيروس كورونا عند الأطفال عادة ما يعانون من زيادة عدد الكريات البيضاء وخلايا العدلات وقلة الخلايا الليمفاوية مع وجود علامات التهابية إيجابية.

إصابة الكبد شائعة عند المرضى الذين يعانون من متلازمة التهاب الأجهزة المتعددة الناشئة عن الاصابة بمرض فيروس كورونا عند الأطفال.

اعتلال القلب لدى المرضى الذين يعانون من متلازمة التهاب الأجهزة المتعددة الناشئة عن الاصابة بمرض فيروس كورونا عند الأطفال شائع ويتجلى فى ضعف الكسر القذفى، وتوسع البطين الأيسر، وبدرجة أقل فى ارتجاع الصمام التاجى أو ثلاثى الشرفات.

زادت العوامل المثبطة لهجرة الماكروفاج بشكل ملحوظ فى المرضى الذين يعانون من متلازمة التهاب الأجهزة المتعددة الناشئة عن الاصابة بمرض فيروس كورونا عند الأطفال وترتبط بعمر المرضى وعلامات الالتهاب.

يمكن للعوامل المثبطة لهجرة الماكروفاج التنبؤ بتأثيرات القلب لدى المرضى الذين يعانون من متلازمة التهاب الأجهزة المتعددة الناشئة عن الاصابة بمرض فيروس كورونا عند الأطفال وترتبط بشكل كبير بعلامات الإصابة القلبية ومعلمات تخطيط صدى القلب.