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Liver Involvement in Children with COVID-19 and Multisystem Inflammatory Syndrome

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ABSTRACT

Background: At the beginning of the pandemic, the SARS-CoV-2 was perceived as a lower respiratory tract infection, affecting the lung parenchyma predominantly and potentially leading to acute respiratory distress syndrome (ARDS)

Objective: This study aimed to demonstrate the laboratory outcomes of liver involvement and clinical manifestation in multisystem inflammatory syndrome (MIS) and Covid-19 in children.

Subjects and methods: This cross-sectional case-control study was conducted at the Pediatric Department of Al Mabarra-Tanta Hospital, Health Insurance Authority Hospital. This study included 40 children who divided into two groups: Group I included 20 children affected with COVID-19 who met the Centers for Disease Control and Prevention (CDC) definition of MIS-C condition associated with COVID-19. Group II included 20 of sex- and age-matched children with alternative diseases of MIS due to causes other than COVID-19 (autoimmune disease and other types of infection).

Results: Alkaline phosphatase levels were significantly higher in group I compared to group II (325.6 ± 98.6 vs 271.9 ± 45.2 U/L). Total bilirubin and direct bilirubin levels were significantly higher in group I compared to group II. Albumin was significantly lower in group I ($p=0.01$). According to CT result, the percentage of positive findings was significantly higher in group I (100%) compared to group II (30%) ($p < 0.001$). Among the specific CO-RAD categories, there were significant differences in the distribution between the groups.

Conclusions: The findings emphasized the importance of early recognition of MIS-C by investigation and clinical manifestation. These insights could guide improved diagnosis, management, and treatment strategies for children affected by COVID-19-associated liver complications.

Keywords: Liver involvement, COVID-19, Multisystem inflammatory syndrome, Laboratory outcomes.

INTRODUCTION

At the beginning of the pandemic, the SARS-CoV-2 was perceived as a lower respiratory tract infection, affecting the lung parenchyma predominantly and potentially leading to acute respiratory distress syndrome (ARDS) [1]. However, with time, it became evident that COVID-19 can present with wide variability of symptoms, including gastrointestinal, neurologic, cardiovascular, and even multiorgan failure, as part of a severe inflammatory response syndrome (SIRS) [2].

Furthermore, research showed that the wide range of clinical manifestations is linked to the viral tropism to the angiotensin-converting enzyme 2 (ACE2) receptor found on many different cells, including liver and bile-duct epithelial cells [3]. The distribution of ACE2 receptors in the liver is unusual. The receptor is abundant in the endothelial layer of small blood vessels but not in sinusoidal endothelial cells. **Velikova *et al.*** [4] reported more robust surface expression of ACE2 in cholangiocytes (59.7%) than in hepatocytes (2.6%). The level of ACE2 expression in cholangiocytes was comparable to that of type 2 alveolar cells in the lungs, implying that the liver may be a possible target for SARS-CoV-2 as well. However, Kupffer cells, T and B lymphocytes tested negative for ACE2 on immunohistochemistry staining [5].

Reports to date indicate that SARS-CoV-2 infection precedes the onset of various autoimmune and inflammatory diseases, including pediatric inflammatory multisystem syndrome (PIMS), also classified as a multisystem inflammatory syndrome in children (MIS-C) [6]. This information further complicates the understanding of the course of COVID-19 infection in children and post-infectious immune transformation (alteration or readjustment) in children [7]. In children, the first reports of MIS-C changed the reputation of SARS-CoV-2 as an infection that mostly spares children with moderate or even asymptomatic presentation to a potentially fatal one with multiorgan involvement and uncertain outcome [8].

Lately, liver involvement has been included in assessing COVID-19 severity infection or MIS-C presentation and the possibility of using liver enzymes as a prognostic sign for the expected outcome [9]. There is a lack of reports and studies on COVID-19 infection in children with pre-existing chronic liver disease. However, in the non-pediatric population, infections are associated with decompensation of cirrhosis and the onset of acute or chronic liver failure. This by itself is a risk factor for a severe course of COVID-19 [10]. Among other organs involved in MIS-C, such as the heart, kidneys, lungs, gastrointestinal, skin, nervous system, and blood, the liver can also be damaged during COVID-19 infection and MIS-C particularly [11]. Therefore, we aimed to observe the clinical presentation and laboratory investigations in children with MIS-C

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and COVID-19 infection, focusing on liver involvement. Also, the study was to demonstrate the laboratory outcomes of liver involvement in MIS and Covid-19 in children.

PATIENTS AND METHODS

Study Design: This cross-sectional case-control study was performed at the Pediatric Department of Al Mabarra-Tanta Hospital, Health Insurance Authority Hospital during the period from the first of July 2020 to the first of July 2021 (retrospective), and from the first of July 2022 to the end of January 2023 (prospective).

Patients: This study included 40 subjects who were divided into two groups: Group I included 20 children affected with COVID-19 who met the CDC definition of MIS-C condition associated with COVID-19 in which different internal and external body parts become inflamed, including the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal tract. MIS-C case definition includes people who are younger than 21 years old. Group II included equal number of sex- and age-matched children with alternative diseases of MIS due to causes other than COVID-19 (Kawasaki 6 (30%), AIDS 2 (10%), Celiac disease 2 (10%), Encephalitis 2 (10%), Gillian Barrie syndrome 2 (10%), Infective endocarditis 2 (10%), Myocarditis 2 (10%), and SLE 2 (10%).

Inclusion criteria: Consecutive patients aged from one month to 18 years with fever (>38.0 °C for ≥24 hr or subjective fever lasting ≥24 h). Patients with laboratory-confirmed inflammation (laboratory confirmed by abnormal C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, D-dimer, ferritin, lactic acid dehydrogenase (LDH), low lymphocytes, and low albumin). Patients with clinically severe COVID-19 requiring hospitalization; presented with multisystem (more than two organs involved). Patients with SARS-CoV-2 recent (within 4 weeks before) or current affection proved by reverse transcription polymerase chain reaction (RT-PCR) antigen.

Exclusion criteria: Children with congenital liver diseases. Children with other causes of acute or chronic hepatitis e.g. HAV, HBV, and HCV. Patients with autoimmune or collagen disorders. Patients whose parents refused to participate in the study.

Methods:

All patients were subjected to full history taking (Personal history: name, age, gender, residence and telephone number). Medical history including any chronic disease such as diabetes mellitus, hypertension, medications, and drug allergy. History of contact with COVID-19 patient and the duration), clinical examination (General examination and abdominal examination), laboratory Investigation (RT-PCR for SARS-CoV-2, CBC, liver function tests and ESR), radiological examination (Computed tomography and abdominal ultrasound).

- **Abdominal examination:**

An abdominal examination was performed while the child lying flat on the bed, with the arms by the sides and legs uncrossed for the abdomen. This included inspection, palpation (including assessment of the liver and spleen measures), percussion, and auscultation.

Liver: Liver span is determined better by percussion than by palpation in children. Percussion was done along the midclavicular line to find the upper margin of the liver. The transition from resonance to dullness indicates the upper liver border. Palpation started from the lower right quadrant and work towards the costal margin, with the fingers directed inwards upon each inspiration to feel the liver edge. The span between the upper and lower border in the mid-clavicular line is measured and assessed in cm considering the reference measures. In addition to detection of edge, consistency, surface, tenderness and pulsation.

- **RT-PCR for SARS-CoV-2:** Following the recommendations of the US CDC, combined oropharyngeal and nasopharyngeal swabs were collected using sterile swabs with synthetic tips (Dacron/nylon) and plastic, flexible shafts. The swabs were rubbed against the posterior pharyngeal wall and tonsillar pillars, and then, the same swab was inserted into the patient's nostril while tilting the patient's head 70 degrees, and it passed slowly parallel to the palate until resistance was encountered. The swab was left in place for a few seconds to allow for secretion absorption and then was slowly removed while being twisted. Finally, the swab was immersed into a sterile tube containing 2 mL of viral transport media and was immediately transported to the laboratory at a temperature of 4 ± 1°C.

Blood sample: Ten milliliters of venous blood were drawn under aseptic conditions and distributed as follows: Two milliliter of whole blood was taken in an EDTA vacutainer (with violet cap) and mixed gently. This sample was used to measure complete blood count (CBC). Four milliliters of blood were taken in plain test tubes without anticoagulant (red cap) and left until coagulation. After coagulation, the samples were centrifuged at 1500 rpm for 15 min. The separated serum was used for the assay of liver function tests, hepatitis markers, CRP, ESR, Ferritin, procalcitonin, albumin, and LDH. 1.8 ml were added into light blue capped vacutainer tubes for coagulation studies (PT, PTT, INR, D-dimer, and fibrinogen). 1.6 ml were added into ESR tubes.

- **Liver function tests:** Liver function tests included transaminases (AST and ALT), alkaline phosphatase (ALP), total and direct bilirubin, and

serum albumin were done by Biosystem A1A-auto analyzer-Spain. Abnormal liver function was defined as any parameter (ALT, AST, ALP and total bilirubin) more than the upper limit of the normal (ULN) lab reference value. Liver injury was categorized as Mild: ALT and/or AST over the ULN, but less than 2× ULN, Moderate: 2–5× ULN. Severe: > 5 times ULN, ALP, and/or total Bilirubin over 2× ULN.

PT, PTT & INR: The prothrombin time (PT) activated partial prothrombin time (PTT), and international normalized ratio (INR) were analyzed using the HUMACLOT DUE PLUS® coagulation analyzer (Wiesbaden ®, Germany).

Serum ferritin analysis: The kit used a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) RayBio® Human Ferritin ELISA Kit, RayBiotech, Inc. The entire kit was stored at 20 °C.

C-reactive protein (CRP): This was performed using rapid latex agglutination test for the qualitative screening and semi-quantitative determination of serum CRP at 340 nm. It is an immunologic reaction between CRP as an antigen and the corresponding antibody coated on the surface of biologically inert latex particles. The expected normal CRP value: < 6.

Plasma fibrinogen: The test was performed by measuring the clotting time of the plasma. The sample was first diluted by reagent 1 (1:10) and then reagent 2 containing thrombin was added. Then, the clot formation time was measured using a stopwatch and according to the table existing in the kit, the fibrinogen level was determined based on the coagulation time. Normal levels were 150-400 mg/dL.

- **D-dimer level:** This was performed using latex agglutination by immune turbidimetry method at 570 nm. The normal values were < 500 ng/ml.

Erythrocyte sedimentation rate (ESR): The test was done using the Westergren's method, which measures the rate of gravitational settling in 1 h of anticoagulated RBCs from a fixed point in a calibrated tube of a defined length and diameter held in an upright position. The normal value of ESR was 0 - 20 mm/h.

C**omputed tomographic (CT) scan of the chest:** The examination was performed in the Radiology Department. No specific preparations were needed. The patients were scanned in a supine position with the arm above the head to avoid artefacts. Image acquisition was at 1.25 mm thickness, 0.625 mm interval using 512 × 512 matrix, tube speed 35 mm/rotation with 0.5 s rotation time. The kVp and mAs was used as low as possible controlled by the operator before scanning to get low radiation dose CT as possible. The images were transferred to the workstation for reviewing the axial slices along with multi-planar reformation. The images were interpreted by experienced radiologists blinded to the patients' PCR results and severity of the disease. Diagnosis of Covid-19 pneumonia was established considering the presence of ground glass opacities (GGO), crazy-paving, fibrosis, and consolidation. The radiological probability of COVID-19 infection was recorded according to Radiological Society of North America (RSNA) recommendation and scored according to the COVID-19 Reporting and Data System (CO-RADS). Scoring system was calculated per each of the 5 lobes considering the extent of anatomic involvement, as follows: No involvement = (0), < 5% involvement = (1), 5–25% involvement = (2), 26–50% involvement = (3), 51–75% involvement = (4) and > 75% involvement = (5). The resulting global CT score was the sum of each individual lobar score (0 to 25). The dominant pattern of affection was recorded including dominant GGO, dominant consolidation, mixed pattern, or dominant fibrotic. Any other associated radiological findings of importance were recorded.

Abdominal ultrasound: Ultrasound examinations were performed with the patient supine without any preparation. The examination was done using PHILIPS EPIQ5, PHILIPS IU Elite, with an abdominal 5 to 12 MHz probe transducer. Liver span was obtained in the midclavicular line. Both were obtained while the probe was oriented longitudinally. Measures were applied to the pediatric chart to assess the presence of hepatomegaly according to the child's age.

Ethical approval: Permission for the study was obtained from the parents who were fully informed about all study procedures and their consent was obtained prior to the children's enrollment in the study. This study was approved by The Ethical Committee of the Faculty of Medicine, Benha University Hospital (MS.8.7.2022). This work has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data underwent thorough processing using IBM SPSS Statistics version 28.0. (Armonk, NY: IBM Corp.). Normality of data distribution was assessed with the Shapiro-Wilk test. Descriptive statistics encompassed mean and standard deviation for numerical data and frequency/percentage for non-numerical data. Independent t-test was used for normally distributed quantitative variables, to compare between two studied groups. The Chi-Square test and Fisher's exact test examined qualitative variable relationships. Regression analysis was used to determine the predictors of MIS-C and liver affection in

children with COVID-19. Significance was established at $p \leq 0.05$ with a 95% confidence interval [12].

RESULTS

Regarding demographic data, the age disparity between these two groups was statistically significant (p=0.04). The children with MIS-C were generally older than those in the control group. There were no significant differences in sex distribution and socioeconomic status between the two groups. Group I had a higher proportion of participants with no education compared to group II (p = 0.090). Moreover, the hospital stay duration was significantly shorter in group I compared to group II (p = 0.020). There were no significant differences between the two groups in terms of fever, lower limb edema, and conjunctivitis. However, pallor and lymphadenopathy were significantly more prevalent in group II compared to group I (p =0.006) and (p<0.001) respectively. Regarding skin manifestations, there were no significant differences between the groups in the occurrence of skin rash. However, lip cracks were significantly more common in group II compared to group I (p = 0.030). Group I had a significantly higher occurrence of distension, hepatomegaly, GIT bleeding, and ascites compared to group II (p < 0.001, p = 0.034, p < 0.001, p = 0.040 respectively). The occurrence of hepatosplenomegaly was not observed in group II. Hypotension and shock were significantly more prevalent in group II compared to group I (p = 0.006). There were no significant differences in the occurrence of hypertension (HTN) between the groups. Regarding respiratory manifestations, there were no significant differences between the groups in the occurrence of RD1, RD2, and RD3. However, RD4 was significantly more prevalent in group II compared to group I (p = 0.040) (Table 1).

Table (1): Comparison of study groups regarding demographic data, general, GIT, cardiorespiratory manifestations

Characteristics		Group I		Group II		p-value
		N=20		N=20		
Age (years)	M ± SD	6.85	5.23	3.78	3.9	0.040*
Sex, n (%)	Female	8	40.0%	8	40.0%	---
	Male	12	60.0%	12	60.0%	
Socioeconomic status, n (%)	Low	4	20.0%	6	30.0%	0.206
	Moderate	13	65.0%	14	70.0%	
	High	3	15.0%	0	0.0%	
Education, n (%)	No	17	85.0%	9	45.0%	0.090
	Preschool	0	0.0%	6	30.0%	
	Primary	3	15.0%	3	15.0%	
	Secondary	0	0.0%	2	10.0%	
Hospital stays (days)	M ± SD	9.9	9.27	18.4	12.46	0.020*
General manifestations	Fever	19	95	20	100	0.521
	Lymphadenopathy	2	10	7	35	0.006*
	Lower limb oedema	7	35	8	40	0.702
	Pallor	1	5	12	60	<0.001*
	Conjunctivitis	4	20	4	20	---
Skin manifestations	Skin rash	17	70	10	50	0.2
	Lip cracks	2	10	8	40	0.03*
GIT manifestations	Distension	12	60	3	15	<0.001*
	Hepatomegaly	5	25	2	10.0	0.034 *
	Hepatosplenomegaly	2	10	0	0.0	0.51
	GIT bleeding	10	50	4	20	<0.001*
	Ascites	6	30	1	5	0.040*
Cardiac manifestations	Hypotension and shock	2	10	10	50	0.006*
	HTN	1	5	2	10	0.5
Respiratory manifestations	RD1	9	55	10	50	0.801
	RD2	2	10	4	10	0.42
	RD3	3	10	5	0	0.41
	RD4	6	20	1	30	0.040*

*: Significant p value, SD: Standard Deviation, M: Mean

Group (I) had a longer prothrombin time (PT) with a mean of 16.47 seconds (SD = 4.24) compared to group II with a mean of 13.88 ± 1.34 seconds. Platelet count (PC) was lower in group II (76.15 ± 20.81 x 10^9/L) compared to Group II (89.2 ± 12.36 x 10^9/L). Fibrinogen levels and D-dimer levels were significantly higher in group I compared to group II. There was no significant difference in the erythrocyte sedimentation rate (ESR) between the groups. However, the mean ferritin level was significantly higher in group I (628.3 ± 329.58 ng/mL) compared to group II (258 ± 119.89 ng/mL). Hemoglobin (HB) levels were significantly lower in group I (9.29 ± 1.51 g/dL) compared to group II (11.17 ± 2.25 g/dL). Lymphocyte percentage and lactate dehydrogenase (LDH) levels were higher in group I compared to group II. Group I subject had a significant lower pH (7.23 ± 0.11) and significant higher CO_2 levels (47.1 ± 18.37 mmHg) compared to group II ($p < 0.05$). All subjects in group I had positive PCR for COVID and all subjects in group II had negative PCR (Table 2).

Table (2): Comparison of study groups regarding Coagulation profile, inflammatory markers, sepsis work up and CBG

	Group I n (20)		Group II n (20)		p-value
	M	SD	M	SD	
PT (sec)	16.47	4.24	13.88	1.34	0.02*
PC (x10^9/L)	76.15	10.81	89.2	12.36	0.02*
PTT (sec)	50.64	8.3	45.3	10.61	0.08
INR	1.43	0.16	1.27	0.34	0.3
Fibrinogen (mg/dL)	413.7	62.46	314.2	79.04	<0.001*
D-dimer (mg/L)	1331.5	91.23	553	86.27	<0.001*
Inflammatory markers					
ESR 1mm/h	58.75	4.11	72.9	3.48	0.1
ESR 2mm/h	109.05	6.98	108	3.13	0.8
Ferritin ng/ml	628.3	29.58	258	19.89	<0.001*
sepsis work up					
HB (g/dL)	9.29	1.51	11.17	2.25	0.004*
PLT (x10^9/L)	228.95	13.36	350	29.76	0.1
Lymphocytes (%)	26.44	2.71	39.1	1.45	0.002*
WBCS (x109/L)	16.56	2.32	15.6	2.3	0.9
Positive CRP	20	10	16	80	0.1
Positive PCR for COVID	20	100	0	100	-
LDH (IU/L)	540.47	460.05	54.35	43.74	<0.001*
Procalcitonin (ng/ml)	16	80	20	100	0.053
Positive blood culture	15	75	14	70	0.7
CBG					
PH	7.23	0.11	7.31	0.12	0.03*
Co2 (mmHg)	47.1	18.37	36.55	13.92	0.04*
Hco3 (meq/l)	21.58	4.81	23.08	7.45	0.5

*: Significant p value, SD: Standard Deviation, M: Mean

Alkaline phosphatase levels were significantly higher in group I (325.6 ± 98.6 U/L) compared to group II (271.9 ± 45.2U/L). Total bilirubin and direct bilirubin levels were also significantly higher in Group I compared to Group II. ALT and AST showed no statistically significant difference between the studied groups. Albumin was significantly lower in group I (p=0.01) (Table 3).

Table (3): Comparison of study groups regarding Liver profile

	Group I n (20)		Group II n (20)		p-value
	M	SD	M	SD	
Alkaline phosphatase (U/L)	325.6	9.6	271.9	45.2	0.03*
T. Bilirubin (mg/dL)	2.7	0.9	1.1	0.3	<0.001*
D. Bilirubin (mg/dL)	0.5	0.14	0.2	0.05	<0.001*
ALT (U/L)	78.02	14.31	45.94	2.87	0.8
AST (U/L)	92.67	14.83	44.2	4.76	0.9
Albumin (gm/dL)	3.18	0.28	3.39	0.21	0.01*

*: Significant p value

According to CT result, the percentage of positive findings was significantly higher in group I (100%) compared to group II (30%) ($p < 0.001$). Among the specific CO-RAD categories, there were significant differences in the distribution between the groups. CO-RAD 3 had a significantly higher percentage in group I (50%) compared to group II (0%) ($p < 0.001$).

Similarly, CO-RAD 4 had a significantly higher percentage in group I (25%) compared to group II (0%) ($p = 0.01$). However, there were no significant differences in the percentage of CO-RAD 1, CO-RAD 2, CO-RAD 5, or pneumonia between the groups.

Overall, the CT chest findings indicated a higher prevalence of positive findings and specific CO-RAD categories in group I compared to group II. In terms of ultrasound results, the percentage of positive findings was higher in group I (65%) compared to group II (30%), although the difference was not statistically significant ($p = 0.06$). However, when examining specific findings, there were significant differences between the groups. Hepatomegaly had a higher percentage in group I (60%) compared to group II (20%) ($p = 0.05$).

On the other hand, there were no significant differences in the percentages of hepatosplenomegaly, ascites, or mesenteric lymphadenitis between the groups. These findings suggest a higher prevalence of hepatomegaly in group I compared to group II based on abdominal US. No isolated case with splenomegaly (Table 4**)**.

Table (4): Comparison of study groups regarding CT chest and Abdominal US

		Group I N (20)		Group I N (20)		p-value
		No.	%	No.	%	
Free		0	0	14	70	<0.001
Positive findings		20	100	6	30	<0.001*
Positive findings	CO-RADS1	2	10	0	0	0.11
	CO-RADS2	2	10	0	0	0.11
	CO-RADS3	10	50	0	0	<0.001
	CO-RADS4	5	25	0	0	0.01
	CO-RADS5	1	5	0	0	0.6
	Pneumonia	0	0	6	30	0.009*
Abdominal US						
Free		7	35	14	70	0.06*
Positive findings		13	65	6	30	0.03*
*Positive findings	Hepatomegaly	12	60	4	20	0.05*
	Hepato-splenomegaly	2	10	0	0	0.11
	Ascites	6	30	1	10	0.36
	Mesenteric lymphadenitis	0	0	2	10	0.52

*: Significant p value, CO-RAD: COVID-19 Reporting and Data System, CT: Computed Tomography, US: Ultrasound

DISCUSSION

The study's demographic analysis revealed that the mean age of children in the MIS-C group was 6.85±5.23 years, while in the control group, it was 3.78±3.90 years, which was significantly higher in group 1 ($p=0.04$) implying that the children with MIS-C were generally older than those in the control group. This study is in line with the systematic review conducted by **Rafferty *et al.*** [13], which included 14 studies encompassing 717 children described that the median age across the included studies varied from 7 to 10 years old.

Regarding gender distribution, the study found that the MIS-C group consisted of and 12 males (60.0%) and 8 females (40.0%). This was the same distribution in the control group since their participants were selected to be sex-matching to the MIS-C group. These data are consistent with the previous reports by **Dufort *et al.*** [14] and **Levy *et al.*** [15] that MIS-C occurs predominantly in males with a male to female ratio of about 3:2. The higher male percentage in patients with MIS-C could be attributed to the well-documented differences between the immune systems of males and females that result from the hormonal differences. These differences can impact how the immune system responds to infections and inflammatory conditions. It's possible that the immune response to the virus that causes MIS-C could be different in males and females, leading to varying susceptibility and severity of the condition.

The clinical findings in the MIS-C patients in this study were fever (95%), respiratory distress (95%), skin rash (70%), abdominal pain (35%), vomiting and diarrhea (35%), ascites (30%), edema (35%), lymphadenopathy (10%), pallor (5%), conjunctivitis (20%), lip cracks (10%), cardiac affection (30%), hypotension and shock (10%), hypertension (5%), renal affection (5%), and neurological manifestations (convulsion: 15%, encephalitis: 5%, and DCL: 10%). These features generally reflect the systemic inflammatory response as well as the multiple organs affection. It is worth noting that the occurrence of lymphadenopathy, pallor, lip cracks, and hypotension and shock were significantly lower in the MIS-C group (10%, 5%, 10%, and 10% compared to 50%, 60%, 40%, and 50% in the control group respectively). On the other hand, ascites and respiratory distress grade 4 (RD4) were significantly higher in the MIS-C group (30% and 20% compared to 5% in the control group, respectively). In consistency with our study, **Butters *et al.*** [16] performed a study to identify distinguishing features of MIS-C to other paediatric febrile diseases in the acute setting and reported that the presence of hypotension was less indicating to MIS-C.

In this study, the laboratory assessment included the coagulation profile, which showed that there was evident higher prothrombin time, fibrinogen levels, and d-dimer, and lower prothrombin concentration in the MIS-C group. In accordance with these finding, the study of **Tong *et al.*** [17] reported that MIS-C patients had more elevated D-dimer, and fibrinogen, than other

inflammatory disorders such as Kawasaki disease. D-dimer reflects the increased production of thrombin and dissolution of fibrin, and fibrinogen is an important substrate for thrombosis. A high level of D-dimer and fibrinogen correlates with increase of the risk for venous and arterial thrombosis. Both arterial and venous thrombosis are theoretically at risk in patients with MIS-C because of endothelial injury and abnormal platelet activation and coagulation [18]. Probably, endothelial damage in MIS-C differs from other inflammatory diseases due to the unique characteristics of the pathogen SARS-CoV-2 and its affinity to the endothelium. The vascular wall damage due to COVID is primarily caused by the virus penetration into the cells of the vascular endothelium through the ACE2 receptor, and then after a certain period of time immuno-mediated endothelial damage develops.

The present study demonstrated that inflammatory markers such as ferritin, LDH and procalcitonin were significantly higher in the MIS-C group. Similarly, **Tong *et al.*** [17] reported that ferritin, and other inflammatory markers were more elevated in MIS-C patients. The specific viral components or antigens associated with SARS-CoV-2 could potentially stimulate a more robust and sustained immune reaction, leading to higher levels of inflammatory markers.

Moreover, our study is supported by the recent study of **Khafaja *et al.*** [19], which compared patients with MIS-C to patients with Near MIS-C (with criteria similar to MIS-C but not fulfilling typical features for the diagnosis) and to those with alternative diagnosis (proved to be other inflammatory disorder). They found higher fibrinogen, ferritin and D-dimer [19]. Similarly, **Butters *et al.*** [16] found that serum ferritin was higher in MIS-C subjects than those with other febrile pediatric conditions.

This study showed that HB levels and lymphocytes count were significantly lower in the MIS-C group. In congruence with our study, **Butters *et al.*** [16] found that MIS-C was associated with low lymphocytic count compared to other febrile diseases of the children. Also, the study of **Consiglio *et al.*** [20] observed that, compared to other inflammatory disorders, MIS-C was associated with lymphopenia.

Arterial blood gasses assessment in this work showed significantly lower pH levels and higher CO_2 levels in the MIS-C group. The lower pH levels and higher CO_2 levels observed in the arterial blood gas assessment of the MIS-C group can be indicative of certain physiological and metabolic changes associated with this condition. The lower pH and higher CO_2 levels suggest the presence of respiratory acidosis. This occurs when the lungs are unable to remove enough CO_2 from the body, leading to an accumulation of CO_2 in the blood. In the context of MIS-C, it's possible that some children may experience respiratory distress or lung involvement, which could contribute to respiratory acidosis. In addition, the hyperinflammatory state and organ involvement in MIS-C can lead to metabolic acidosis. Inflammatory processes can generate lactic acid and other metabolites that contribute to a decrease in pH. Respiratory compensation may also occur, where the body tries to increase ventilation to eliminate excess CO_2 and correct the pH imbalance. Given that higher grades of respiratory distress and levels of inflammatory markers were evident in MIS-C, this could explain the higher rate of such metabolic changes.

Firstly, the mean ALT and AST levels were 78.02 ± 114.31 and 92.67 ± 194.83, respectively, in the MIS-C group, while they were 45.94 ± 22.87 and 44.20 ± 24.76, respectively, in the control group. Despite higher mean values in the MIS-C group, the difference did not reach the level of significance ($p>0.05$). Our study partially agrees with the study of **Lazova *et al.*** [21] and **Grama *et al.*** [22] that reported higher levels of liver enzymes in children with MIS-C compared to other inflammatory disease.

Concerning albumin levels, we found a more intriguing result, with a mean albumin level of 3.18 ± 0.28 in the MIS-C group, and a mean of 3.39 ± 0.21 in the control group. The difference was clinically significant ($p=0.01$). Our findings are congruent to the studies of **Lazova *et al.*** [21], **Grama *et al.*** [22], and **Buda *et al.*** [23] where children with MIS-C had significantly lower albumin levels compared to children without MIS-C.

Regarding alkaline phosphatase, the data revealed that in MIS-C group, the mean alkaline phosphatase level was 325.6 and the control group displayed a mean alkaline phosphatase level of 271.9. The difference was statistically significant ($p= 0.03$). Contradictory to our results, the study of **Lazova *et al.*** [21] did not find significant higher alkaline phosphatase levels in children with MIS-C.

Shifting the focus to total bilirubin and direct bilirubin, the MIS-C patients displayed mean level of 2.7 and 0.5, respectively. In stark contrast, the control group demonstrated a substantially lower mean levels of 1.1 and 0.2, respectively, with a p-value below 0.001, indicating an exceedingly significant difference between the two groups. Similarly, **Lazova *et al.*** [21] reported significantly higher bilirubin levels in children with MIS-C.

Finally, concerning the patients' outcome, significantly worse outcome was observed in the MIS-C patients (a mortality rate of 65% compared to 10% in the control group). This result is consistent with the data highlighted by **Sharma *et al.*** [24], who proposed that in contrast to other inflammatory diseases such as Kawasaki disease, patients with MIS-C tend to have a worse acute clinical course and multisystem involvement, as illustrated by an increased requirement for intensive care management. Unlike the relatively low ICU admission rate of 2.4% observed among patients with Kawasaki disease [25], a substantially higher proportion of 68% of patients with MIS-C required intensive care unit (ICU) admission [13]. Although, the reason for a more critical illness in the acute phase of

MIS-C than in other inflammatory disorders is unclear, it is thought to be linked to the cytokine storm in MIS-C [26]. Similar data was reported by **Khafaja *et al.*** [19], who found that patients with MIS-C had worse outcome with higher ICU admission and mortality rates than patients with Near MIS-C and those with alternative diagnosis.

CONCLUSION

The global impact of COVID-19 has been substantial, with multisystem involvement observed in both adults and children. MIS-C, a complication linked to SARS-CoV-2 infection, had sparked interest in understanding hepatic damage in pediatric patients. The findings emphasized the importance of early recognition of MIS-C and offered insights into the intricate mechanisms contributing to liver injury. These insights could improve diagnosis, management, and treatment strategies for children affected by COVID-19-associated liver complications.

LIMITATIONS

This was a single center study with a relatively small sample size of 20 infants, which may limit the generalizability of our findings to a broader population.

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REFERENCES

1. **Mehta O, Bhandari P, Raut A, Kacimi S, Huy N (2020):** Coronavirus Disease (COVID-19): Comprehensive Review of Clinical Presentation. Front Public Health., 8: 582932.
2. **Sarkesh A, Daei Sorkhabi A, Sheykhsaran E *et al.* (2020):** Extrapulmonary Clinical Manifestations in COVID-19 Patients. Am J Trop Med Hyg., 103: 1783-96.
3. **Fierro N (2020):** COVID-19 and the liver: What do we know after six months of the pandemic? Ann Hepatol., 19: 590-1.
4. **Velikova T, Kotsev S, Georgiev D, Batselova H (2020):** Immunological aspects of COVID-19: What do we know? World J Biol Chem., 11: 14-29.
5. **Jothimani D, Venugopal R, Abedin M, Kaliamoorthy I, Rela M (2020):** COVID-19 and the liver. J Hepatol., 73: 1231-40.
6. **Rubens J, Akindele N, Tschudy M, Sick-Samuels A (2021):** Acute covid-19 and multisystem inflammatory syndrome in children. BMJ., 372: n385.
7. **Merad M, Martin J (2020):** Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol., 20: 355-62.
8. **Rowley A (2018):** Is Kawasaki disease an infectious disorder? Int J Rheum Dis., 21: 20-5.
9. **Rowley A (2020):** Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. Nat Rev Immunol., 20: 453-4.
10. **Di Giorgio A, Hartleif S, Warner S, Kelly D (2021):** COVID-19 in Children With Liver Disease. Front Pediatr., 9: 616381.
11. **Strnad P, Tacke F, Koch A, Trautwein C (2017):** Liver - guardian, modifier and target of sepsis. Nat Rev Gastroenterol Hepatol., 14: 55-66.
12. **Flechner L, Tseng T (2011):** Understanding results: P-values, confidence intervals, and number need to treat. Indian J Urol., 27: 532-5.
13. **Rafferty M, Burrows H, Joseph J *et al.* (2021):** Multisystem inflammatory syndrome in children (MIS-C) and the coronavirus pandemic: Current knowledge and implications for public health. J Infect Public Health, 14: 484-94.
14. **Dufort E, Koumans E, Chow E *et al.* (2020):** Multisystem Inflammatory Syndrome in Children in New York State. N Engl J Med., 383: 347-58.
15. **Levy M, Recher M, Hubert H *et al.* (2022):** Multisystem Inflammatory Syndrome in Children by COVID-19 Vaccination Status of Adolescents in France. JAMA., 327: 281-3.
16. **Butters C, Spracklen T, Stander R *et al.* (2022):** 72 Distinguishing features of MIS-C to other paediatric febrile diseases in the acute setting. Rheumatology (Oxford), 61: 496.
17. **Tong T, Yao X, Lin Z *et al.* (2022):** Similarities and differences between MIS-C and KD: a systematic review and meta-analysis. Pediatr Rheumatol Online J., 20: 112.
18. **Conway E, Pryzdial E (2020):** Is the COVID-19 thrombotic catastrophe complement-connected? J Thromb Haemost., 18: 2812-22.
19. **Khafaja S, Youssef N, El Zein Z *et al.* (2022):** Multisystem inflammatory syndrome in children (MIS-C) and "Near MIS-C": A continuum? Front Pediatr., 10: 988706.
20. **Consiglio C, Cotugno N, Sardh F *et al.* (2020):** The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. Cell,183: 968-81.
21. **Lazova S, Alexandrova T, Gorelyova-Stefanova N *et al.* (2021):** Liver Involvement in Children with COVID-19 and Multisystem Inflammatory Syndrome: A Single-Center Bulgarian Observational Study. Microorganisms, 9: 1958.
22. **Grama A, Căinap S, Mititelu A *et al.* (2022):** Multisystemic Inflammatory Syndrome in Children, A Disease with Too Many Faces: A Single-Center Experience. J Clin Med., 11: 5256.
23. **Buda P, Strauss E, Januszkiewicz-Lewandowska D *et al.* (2022):** Clinical characteristics of children with MIS-C fulfilling classification criteria for macrophage activation syndrome. Front Pediatr., 10: 981711.
24. **Sharma C, Ganigara M, Galeotti C *et al.* (2021):** Multisystem inflammatory syndrome in children and Kawasaki disease: a critical comparison. Nat Rev Rheumatol., 17: 731-48.
25. **Kuo C, Lee Y, Lin M *et al.* (2018):** Characteristics of children with Kawasaki disease requiring intensive care: 10 years' experience at a tertiary pediatric hospital. Journal of Microbiology, Immunology and Infection, 51: 184-90.
26. **Gurlevik S, Ozsurekci Y, Sağ E *et al.* (2022)**: The difference of the inflammatory milieu in MIS-C and severe COVID-19. Pediatr Res., 92: 1805-14.