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Original article

Neurological manifestations of inflammatory multisystem syndrome

Mohamed Adel Abdel Tawab[1], Ahmed Samir Ali Abbas[1], Dalia Saber Morgan[1], Asmaa Fathelbab Ibrahim[2]

[1] *Department of Pediatrics, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt.*

[2] *Department of clinical and chemical pathology, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt.*

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Corresponding Author:

Ahmed Samir Ali Abbas

neomatrix201@gmail.com

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Abstract:

Background: Patients under the age of 21 who present with a high temperature, inflammatory markers in the lab, and a severe illness that necessitates hospitalization due to involvement of multiple systems (such as the cardiovascular, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological systems) and no other probable diagnoses; or who have recently been infected with SARS-CoV-2 (COVID-19) as confirmed by RT-PCR, serology, or antigen testing; or who have been exposed to COVID-19 without suspecting any other possible diagnosis. **Aim:** to analyze COVID-19 associated MIS-C by recognizing its signs, symptoms (particularly neurological manifestations), investigation, treatment, and prognosis. **Methods:** This study focuses on children with neurological symptoms to better understand MIS-C's etiology, symptoms, diagnosis, and prognosis in Beni-Suef university hospital Pediatrics ICU. 39 kids was included. **Results:** This study evaluated the signs,

Symptoms, investigation, therapy, and prognosis of MIS-C in COVID-19-infected children. 14 women (37.5%) and 25 males (62.5%) were included. Their ages ranged from 1.5 to 180 months, with a mean of 52.5 months. The average duration of stay was 9.1 days, ranging from 1 to 22 days. This study of (39) individuals showed that Misc patients commonly have problems in other organ systems. The neurological manifestation amonge studied patients showed that (30) case suffered from convulsion of different types, (6) cases suffered from headache, (20) case ssuffered from encephalopathy, (2) cases had acute flaccid paralysis and only one case suffred from acute cerebellar ataxia. 77% of patients have respiratory symptoms (cough, dysnea, cyanosis), 42% have gastrointestinal symptoms (vomiting, diarrhoea, abdominal pain), 30% have cardiac symptoms (shock and hypotension), and 17.5% have renal symptoms (hypertension, oedema, oligiurea). Conclusions: The neurological manifestation amonge MIS-C patients are very common including convulsions of different types , headache , encephalopathy, ataxia , acute flaccid paralysis and we notice that , patients with more sever neurological manifestations and had more than 2 organ system affections had poor prognosis (morbidity and mortality) while patients received early treatment IVIG and methyel prednsilone had better prognosis.

1. Introduction:

The COVID-19 pandemic has presented unprecedented challenges worldwide, not only due to the direct impact of the virus but also through its complex and varied complications. Among the pediatric population, a particularly concerning condition has emerged: the Multisystem Inflammatory Syndrome in Children (MIS-

C). MIS-C is a severe, hyperinflammatory syndrome that can develop after exposure to SARS-CoV-2, often resulting in significant morbidity and necessitating intensive care management [1]. Although the syndrome primarily involves the cardiovascular, gastrointestinal, and respiratory systems, emerging evidence highlights its significant neurological manifestations [2].

Neurological symptoms in MIS-C patients can range from headaches, altered mental status, and seizures to more severe outcomes like encephalopathy and stroke [3]. The pathophysiology behind these manifestations remains poorly understood, with hypotheses suggesting direct viral invasion, immune-mediated damage, or secondary effects of systemic inflammation [4]. These neurological complications not only complicate the clinical course but also pose additional challenges in management and prognosis of affected children [5].

The recognition and management of neurological symptoms in MIS-C are critical due to the potential for long-term neurodevelopmental sequelae. Pediatric intensive care units (PICUs) have seen an increasing number of MIS-C cases with neurological involvement, necessitating a multidisciplinary approach to care [6]. Despite the growing body of literature, substantial gaps in knowledge remain, particularly regarding the optimal strategies for diagnosis, treatment, and long-term follow-up of these neurological manifestations.

The aim of the present study was to evaluate COVID-19 associated Multisystem Inflammatory Syndrome in Children (MIS-C) especially neurological manifestation by detection its signs, symptoms, investigation and course of treatment and prognosis.

2. Patients and Methods:

Patients who presented with neurological symptoms consistent with Multisystem Inflammatory Syndrome in Children (MIS-C) were the subjects of this prospective observational research. In the Pediatric Department at Beni-Suef University Hospital, Faculty of Medicine, the purpose of the research was to catalog the symptoms, diagnoses, investigations, treatment plans, and outcomes for these patients. All participants and their parents were informed about the research methodology before the 39 pediatric patients were enrolled.

Inclusion Criteria

MIS-C was suspected in children presenting with:

1. Fever that is either based on personal opinion or supported by evidence (temperature of ≥38.0°C) for a minimum duration of 24 hours.

2. Indications indicate malfunction in one or many organs.
3. Anomalous testing results.
4. There are no other possible diagnoses that are likely (such as bacterial sepsis, staphylococcal or streptococcal shock syndromes, or infections related with myocarditis like enterovirus). However, waiting for these findings should not prevent you from obtaining professional guidance and developing a treatment strategy.
5. Presence of SARS-CoV-2 infection or exposure supported by RT-PCR, serology, or antigen test.

Clinical Evidence of Organ Dysfunction

- **Cardiac manifestations**: Hypotension, shock.
- **Gastrointestinal manifestations**: Abdominal pain, vomiting, and/or diarrhea.
- **Neurological manifestations**: Confusion, headache, convulsions, and/or localizing signs.
- **Respiratory manifestations**: Sore throat, cough, tachypnea, and shortness of breath.
- **Skin rash**: Polymorphous exanthem, erythroderma, erythematous macules, and/or papules, peeling.
- **Conjunctivitis**: Non-purulent.
- **Lymphadenopathy**: Cervical, unilateral, and ≥1.5 cm.
- **Mucous membrane changes**: Red and/or cracked lips, strawberry tongue.
- **Renal manifestations**: Acute kidney injury (AKI).
- **Extremities**: Swollen and/or erythematous hands and feet.

Laboratory Findings

- Increased concentrations of CRP, D-dimer, ferritin, LDH, fibrinogen, and/or neutrophils.
- Reduced concentrations of albumin, lymphocytes, and/or platelets. Additionally, one may also come across anemia, thrombocytosis, thrombocytopenia, neutropenia, and neutrophilia.

Exclusion Criteria

1. Children below 1 month of age or older than 21 years.
2. Patients with multisystem organ failure not due to COVID-19 infection.

Methods

All cases admitted to the PICU were subjected to the following procedures:

1. **Detailed History**
   - Recent COVID-19 infection in parents.
   - History of maternal COVID-19 infection during pregnancy.
   - Familial illness/condition/unexpected death.
   - Previous child infection with Kawasaki disease, bacterial sepsis, toxic shock

syndrome, appendicitis, other viral infections, systemic lupus erythematosus (SLE), or vasculitis.

2. **General Examination**

- Comprehensive physical examination including weight, head circumference, sex, temperature on admission.
- Thorough abdominal, cardiac, chest, and neurological examinations.

3. **Investigations**

All cases underwent (Covid 19)Viral RNA extraction according to manufacturer instruction . by (QIAamp viral RNA kits) and then detection of RT _PCR was done by (G=N_SIG) kits. step one instrument was used for RT PCR. And also all cases underwent test for serum antibody detection of covid 19 by (cobas e411) instrument .

- Laboratory findings as per case series [7,8]:

- Complete blood count (CBC): lymphocytopenia, neutrophilia, mild anemia, thrombocytopenia.
- Elevated inflammatory markers: CRP, ESR, D-dimer, ferritin.
- Cardiac markers: troponin.
- Hypoalbuminemia.
- Routine liver enzymes: AST, ALT, Pt, PTT, PC, and INR.
- Routine kidney function tests: serum urea, creatinine, Na, K.
- COVID-19 swab and detection of IgG antibodies and/or PCR for SARS-CoV-2.
- Imaging as needed: Chest X-ray, brain imaging (CT and MRI), abdominal imaging, echocardiography, ECG.

4. **Patient Treatment**

- Administration of antiviral drugs, solumedrol IV, intravenous immunoglobulins, and inotropes if indicated.

Statistical Methods

The data analysis was performed using SPSS v.25, a statistical software package designed for social science research, using a Windows operating system. Quantitative variables are characterized by their mean and standard deviation (SD). Qualitative variables represented by numbers (No.) or percentages (%). The One-Way ANOVA statistical test was used to compare several groups in terms of continuous data, while the Chi-Square test was utilized for categorical data. A p-value greater than 0.05 is considered to be non-significant.

Ethical consideration:

All participants and their guardians provided informed permission after a comprehensive description of the study's objectives, methods, potential hazards, and

advantages. The research obtained permission from the Ethical Committee of Beni-Suef University, guaranteeing adherence to ethical norms. The personal and medical information was kept confidential and measures were taken to reduce any possible hazards or discomforts. Participants were notified of their entitlement to withdraw at any point without adverse repercussions, guaranteeing their voluntary involvement. The approval number is FMBSUREC/09012022/Abbas.

3. Results:

All cases were positive for covid 19 virus by RT PCR and serum antibody detection as shown in Figure 1.

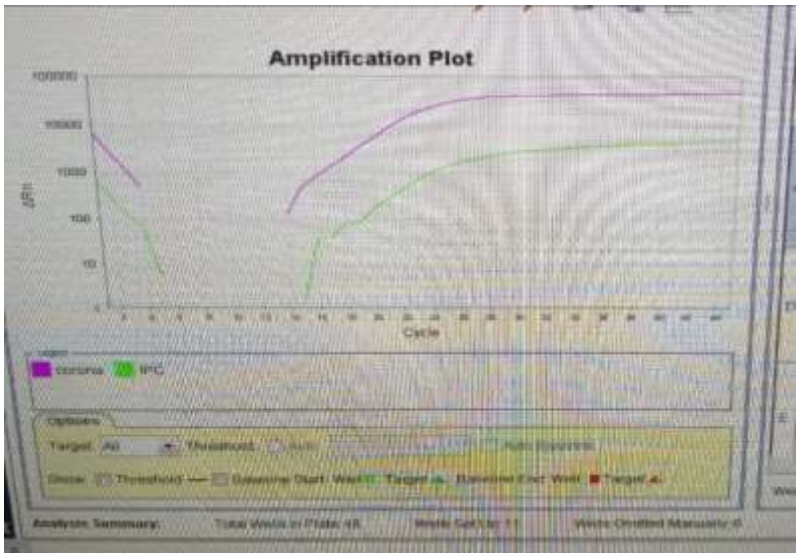

Figure (1) Application Plot for COVID 19 positive case

There were 25 (62.5%) males and 15 (37.5%) females. Their age was ranged from (1.5) to (180) with an average age of (52.5 ±54.9) months old. The duration of admission was ranged from (1) to (22) with an average duration of (9.1 ±5.1) days. The studied participants were 25 males (64.1%) and 14 females (35.9%).

Table (1) demonstrates distribution of the studied population by main complaint. DCL, Cough, Dyspnea and Cyanosis were the most frequent main complaints among the studied population, followed by fever, diarrhea and shock. While Encephalopathy and flaccid paralysis was among the least common main complaint among the studied population.

Table (1): demonstrate a distribution of the studied population according to their main complaint.

Main Complaint*		
	Frequency	**Percent**
Cough	9	22.5
Dyspnea	8	20.0
Vomiting	3	7.5
Diarrhea	5	12.5
Cyanosis	8	20.0
DCL	11	27.5
Convulsion	3	7.5
Fever	6	15.0
Shock	5	12.5
Tachypnea	3	7.5
Abnormal movement headache	1	2.5
Encephalopathy	1	2.5
Flaccid paralysis	1	2.5

*Most of patients presented with more than one complaint

Regarding the frequency of neurological manifestations among the studied population. Nine out of the studied 39 cases did not suffer from convulsions (23.1%), while the rest of the cases (30 cases) suffered from the presence of convulsions of different types, which were tonic clonic among 8 cases (26.7%), focal simple among 14 cases (46.7%), focal complex among 8 cases (26.7%). Flaccid Paralysis was detected among only two cases (5.1%), positive Encephalopathy GCs was among 20 cases (51.3%), Headache was reported by six cases (15.4%) while Cerebellar ataxia was detected only among one case of the studied population. Regarding the frequency of respiratory manifestations among the studied population. M.V was positive among 19 (48.7%) cases, cyanosis was among 14 (35.9%) cases, dyspnea was among 11 (28.2%) cases while cough was among 12 (30.8%) of the studied cases. Regarding the frequency of cardiac manifestation among the studied population. Hypotensive shock was positive among 12 (30.8%) cases, Tachycardia or bradycardia was detected among 5 (12.8%) cases of the studied population. Regarding the frequency of renal Manifestation among the studied population. Hypertension was positive among 6 (15.4%) cases, Oliguria was detected

among 7 (17.9%) cases, and Oedema also was detected among 7 (17.9%) cases of the studied population. Regarding the frequency of abdominal Manifestations among studied population. Vomiting was positive among 11 (27.5%) cases, Diarrhea was detected among 10 (25%) cases, and abdominal pain was detected among 4 (10%) cases of the studied population. Regarding the frequency of other manifestations among the studied population. Skin Rash was positive among 12 (30.8%) cases, non-purulent conjunctivitis was detected among 6 (15.4%) cases, and Mucous membrane manifestations was detected among 12 (30.8%) cases of the studied population.

Figure (1) demonstrates the distribution of the studied population according to their outcomes. Among the children in the current study, 15 (39.5%) died, while 14 (37.8%) were discharged from the hospital without complications, and nine other cases (23.7%) were discharged from the hospital with complications.

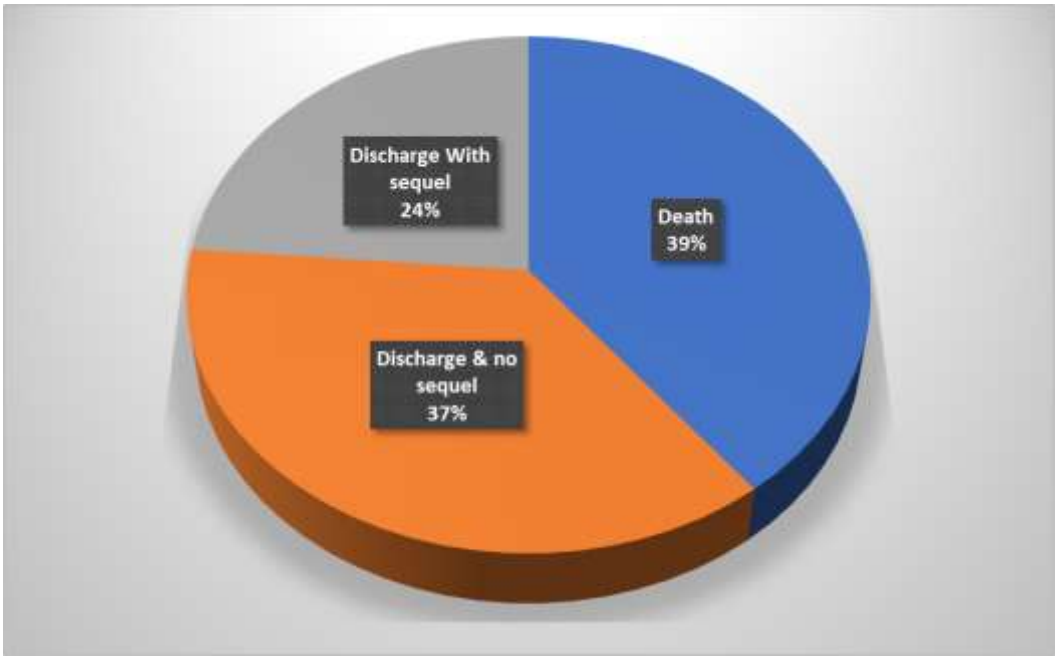

Figure (2): Distribution of the studied participants according to their outcomes.

Table (2) demonstrate a comparison of CBC between studied participants according to their outcomes, there was non-statistically significant associations between CBC and participants' outcomes, (p-values >0.05).

Table (2): comparison of CBC between studied participants according to their outcomes.

		N	Mean	SD	Minimum	Maximum	p-value
HB	Death	15	9.88	2.80	6	14	0.551
	Discharge & no sequel	14	10.51	3.4	6	15	
	Discharge With sequel	9	11.29	2.7	7	16	
Plt	Death	15	351.87	171.7	37	726	0.830
	Discharge & no sequel	14	316.71	159.6	45	551	
	Discharge With sequel	9	322.56	152.8	111	533	
TLC	Death	15	10.59	4.0	5	19	0.790
	Discharge & no sequel	14	11.84	6.0	4	27	
	Discharge With sequel	9	11.51	4.6	6	20	

Table (3) demonstrate a comparison of kidney function tests between studied participants according to their outcomes, there was non-statistically significant associations between kidney function tests and participants' outcomes, (p-values >0.05).

Table (3) comparison of kidney function tests between studied participants according to their outcomes.

		N	Mean	SD	Minimum	Maximum	P-value
Urea	Death	15	48.73	52.4	15	222	0.677
	Discharge & no sequel	14	35.00	26.4	19	112	
	Discharge With sequel	9	37.00	51.2	11	173	
Creatin	Death	15	0.86	0.5	0.1	2	0.362
	Discharge & no sequel	14	0.76	0.5	0.1	2	
	Discharge With sequel	8	0.55	0.1	0.1	1	
Na	Death	15	145.33	9.8	134	166	0.535
	Discharge & no sequel	14	143.50	7.9	134	165	
	Discharge With sequel	9	141.22	7.6	131	158	
K	Death	15	4.13	1.3	1	6	0.936
	Discharge & no sequel	14	4.06	0.9	2	6	
	Discharge With sequel	9	3.97	0.8	2	5	

Table (4) demonstrate a comparison of ABG between studied participants according to their outcomes, there was non-statistically significant associations between ABG and participants' outcomes, (p-values >0.05).

Table (4) comparison of ABG between studied participants according to their outcomes.

		N	Mean	SD	Minimum	Maximum	p-value
Ph	Death	15	7.24	0.139	7	8	0.414
	Discharge & no sequel	14	7.18	0.127	7	7	
	Discharge With sequel	9	7.25	0.180	7	7	
PCo2	Death	15	45.93	17.148	20	76	0.700
	Discharge & no sequel	14	40.64	14.621	22	76	
	Discharge With sequel	9	40.78	14.298	26	65	
HCo3	Death	15	15.40	4.372	3	21	0.727
	Discharge & no sequel	14	15.54	4.472	9	23	
	Discharge With sequel	9	17.04	4.223	11	25	

Table (5) demonstrate a comparison of LFT between studied participants according to their outcomes, there was non-statistically significant associations between LFT and participants' outcomes, (p-values <0.05).

Table (5): comparison of LFT between studied participants according to their outcomes.

		Mean	SD	Minimum	Maximum	p-value
AST	Death	41.9	23.2	12.0	103.0	0.550
	Discharge & no sequel	34.5	17.0	12.0	66.0	
	Discharge With sequel	36.1	13.5	12.0	55.0	
ALT	Death	29.6	17.9	13.0	76.0	0.253
	Discharge & no sequel	38.3	19.1	17.0	87.0	
	Discharge With sequel	39.8	10.9	23.0	53.0	
INR	Death	1.34	0.20	1.00	1.90	0.692
	Discharge & no sequel	1.42	0.30	1.00	2.10	
	Discharge With sequel	1.36	0.30	1.00	1.80	
Albumin	Death	3.8	0.62	2.4	5.0	0.232
	Discharge & no sequel	3.7	0.94	2.0	5.0	
	Discharge With sequel	4.2	0.52	3.7	5.0	

Table (6) demonstrate a comparison of D-Dimer, CRP and Serum Ferritin between studied participants according to their outcomes, there was non-statistically significant associations between D-Dimer, CRP and Serum Ferritin and participants' outcomes, (p-values >0.05).

Table (6) comparison of D-Dimer, CRP and Serum Ferritin between studied participants according to their outcomes.

		N	Mean	SD	Minimum	Maximum	p-value
DD	Death	15	1.61	0.75	.75	3.30	0.814
	Discharge & no sequel	14	1.46	0.63	.45	2.60	
	Discharge With sequel	9	1.62	0.83	.50	2.70	
S. Ferritin	Death	15	455.6	216.2	127.00	800.00	0.801
	Discharge & no sequel	14	418.1	249.8	32.00	900.00	
	Discharge With sequel	9	391.6	260.1	77.00	840.00	
CRP	Death	15	22.87	23.2	6	96	0.091
	Discharge & no sequel	14	64.57	75.2	6	232	
	Discharge With sequel	9	30.56	38.4	6	113	

Table (7) demonstrates the number of systems affected in the current cohort, number of systems affected was ranged from no systematic affection in one patient, to a maximum of six systems affected among two patients, the median number of systems affected was three systems among 20 patients (50%).

Table (7): Number of system affection among studied population; (N= 40):

		Frequency	Percent
Number of system affection	No Systematic affection	1	2.5
	Two	12	30.0
	Three	20	50.0
	Four	2	5.0
	Five	3	7.5
	Six	2	5.0
	Total	40	100.0
	Minimum	0	
	Maximum	6	
	Median (IQR)	3 (1)	

IQR: Interquartile Range.

Table (8) demonstrate a comparison of IVIG usage between studied participants according to their outcomes, there was non-statistically significant associations between IVIG usage and participants' outcomes, (p-values >0.05). Regarding the comparison of Anti-Coagulant usage between studied participants according to their outcomes, there was non-statistically significant associations between Anti-Coagulant usage and participants' outcomes, (p-values >0.05).

Table (8) Association between prognosis and IVIG, use of anticoagulation

		Prognosis			Total	P-value
		Death	Discharge & no sequel	Discharge With sequel		
IVIG	No	3	4	3	10	0.690
		18.80%	28.60%	33.30%	25.60%	
	Yes	13	10	6	29	
		81.30%	71.40%	66.70%	74.40%	
Anti-Coagulant	No	4	8	4	16	0.197
		25.0%	57.1%	44.4%	41.0%	
	Yes	12	6	5	23	
		75.0%	42.9%	55.6%	59.0%	

4. Discussion:

The coronavirus disease 2019 (COVID-19) has garnered global prominence since its first identification in Wuhan, Hubei province, China, in December 2019. The World Health Organization (WHO) officially classified this ailment as a worldwide pandemic, which has since become a major public health crisis with severe repercussions on the global economy [9].

Approximately 9% to 12% of those diagnosed with COVID-19 infection are children. Typically, 90% of children who test positive for SARS-CoV-2 show no symptoms or have mild-to-moderate symptoms. Severe disease may manifest in children who are under the age of 1 and those who have other health disorders or underlying medical issues. The clinical manifestation and epidemiological features of SARS-CoV-2 remain rather uncertain [10].

This study was conducted at Beni-Suef University Hospital to evaluate the association between COVID-19 infection and Multisystem Inflammatory Syndrome in Children (MIS-C). The mean age of the studied patients 52.5 ±54.9 months and most of them were males (62.5%). The average duration of hospital admission was 9.1±5.1 days.

In their investigation on cardiovascular symptoms in children with multisystem

inflammatory syndrome linked with COVID-19 infection, Valverde et al. (2021) reported that the average age was 8.4 years (ranging from 1 month to 18 years), and the majority of the affected children were male (67.8%). [11].

Also, Tang *et al.*, (2020) reported similar age in their study about COVID-19 infection in children. They found that the mean age of the affected children was 6.9±0.7 years but most of them were females (65%) [12].

Shekerdemian *et al.*, (2020) in their study mentioned that the mean duration of hospital stay ranged from 4 – 13 days [13]. Also, the mean duration of hospital stay reported by the study of Feldstein *et al.*, (2020) was 7 days [1].

Most of patients presented with more than one complaint. The main presentations of the affected children were DCL (27.5%), cough (22.5%), dyspnea and cyanosis (20.0%). Only (15.0%) of cases presented with fever.

Mustafa and Selim (2020) conducted a meta-analysis and discovered that the predominant clinical symptoms were cough (49%), fever (47%), sore throat (36%), diarrhea and/or vomiting (17%), and runny nose (9%). [14].

The difference could be explained as the clinical manifestations of disease in adolescents differed from younger age groups: adolescents were more likely to suffer from dizziness, chills and myalgia, while these symptoms were rare in younger children [15].

As regards to the neurological manifestations among studied patients, our study showed that about 30 cases suffered from the presence of convulsions of different types, commonly focal simple seizures (46.7%). Tonic-clonic and focal complex seizures were detected in (26.7%) of cases for each type. Also, Encephalopathy was common seen in 20 cases (51.3%). Headache was reported by six cases (15.4%), flaccid Paralysis was detected among only two cases (5.1%), and cerebellar ataxia was detected only among one case of the studied population.

Mao et al., (2020) said in their research concerning the neurological symptoms in hospitalized patients with COVID-19 infection that seizures, encephalopathy, agitation, diffuse upper motor neuron indications, anosmia, and Guillain-Barré syndrome have all been recorded [16].

Fewer number of cases was reported by the study of Abdel-Mannan *et al.*, (2020) who showed that 27 patients out of 50 had neurological symptoms included encephalopathy (n = 4), headache (n = 3), brainstem signs with

dysarthria or dysphagia (n = 2), meningism (n = 1), and cerebellar ataxia (n = 1) [4].

Encephalopathy (diffuse brain dysfunction) and encephalitis (acute, diffuse, inflammatory condition of the brain) are a major devastating presentation. Intense inflammatory response against the virus, triggers cytokine storm causing subsequent hypoxic and metabolic insults resulting in multiple organ failure including diffuse brain dysfunction [17].

Neurological symptoms in COVID-19 may occur when the virus crosses the blood-brain barrier and enters the brain through different pathways. This can happen by traveling through the olfactory mucosa and olfactory nerve, crossing the cribriform plate. Alternatively, the virus can enter the brain through the bloodstream, or as a result of sepsis-induced coagulopathy leading to cerebral infarction, or through an immune-mediated neurological syndrome. Another possible route is for the virus to travel in a retrograde manner through axonal transport from the gut or lungs to the brain. [18,19]

Furthermore, the presence of severe pneumonia may cause a condition known as systemic hypoxia, which can ultimately lead to brain damage. The contributing components consist of peripheral vasodilation, hypercarbia, hypoxia, and anaerobic metabolism resulting in the buildup of hazardous substances. These factors may lead to the enlargement of nerve cells and the accumulation of fluid in the brain, eventually causing harm to the nervous system. [20].

Regarding the respiratory manifestations, the most common manifestations were cough (30.8%), dyspnea (28.2%) and cyanosis (35.9%). Mechanical ventilation was needed for 19 cases (48.7%).

In agreement with our results was the study of Shekerdemian *et al.,* (2020) about the characteristics and outcomes of COVID-19 infected children. They found that 18 patients (38%) required endotracheal or tracheostomy ventilation [13].

Similar results were also reported by the study of Serrano *et al.,* (2020) who revealed that Fever was detected in (43.5 %), cough in (34.1 %), and difficulty respiratory in 15.9 % [21].

Our study also investigated the cardiac manifestation among studied population and revealed that hypotensive shock was the most common manifestation in 12 (30.8%) cases and hypertension was among 6 (15.4%) cases. Tachycardia or

bradycardia was detected among 5 (12.8%) cases of the studied population. In agreement with our results was the cohort study performed by Valverde *et al.,* (2021) who showed a very high incidence of myocardial involvement, shock was detected in (40%), and arrhythmia in (35%). They also revealed that the pathogenesis of the arrhythmias remains unclear and may be related to inflammation, electrolyte disturbances, or myocardial injury [11]. Also, the research by Samuel et al., (2020) concerning arrhythmias and electrocardiographic abnormalities in symptomatic pediatric patients with SARS-CoV-2 infection demonstrated that pediatric COVID-19 cases might display a rate of cardiac arrhythmia as high as 16%-20% [22].

The probable cause might be linked to myocarditis which is an inflammatory illness of the heart muscle with established histological and immunologic diagnostic criteria. Pathophysiology is connected to the combination of direct virus-mediated cardiac damage and host immune activation [23].

Direct myocardial damage seems to be a decisive cause for arrhythmia, even in youngsters. Hypoxemia and electrolyte imbalances are common occurrences during the acute phase of severe COVID-19 and may potentially induce cardiac arrhythmias. [24].

The study also found that GIT manifestations were frequent. Vomiting and diarrhea was the most common seen in 11 (27.5%) and 10 (25%) cases respectively. Abdominal pain was the complaint of 4 (10%) cases only. The effect of COVID-19 infection on kidney showed that 7 (17.9 %) cases had oliguria.

Several studies agreed with our results and reported that the most common GIT manifestations were diarrhea, vomiting and abdominal pain. The difference in the percent could be explained as children usually present with variable symptoms. The symptoms of gastrointestinal tract (GIT) involvement consist of diarrhea (occurring in 2% to 50% of cases), anorexia (40% to 50%), vomiting (4% to 67%), nausea (1% to 30%), abdominal pain (2% to 6%), and gastrointestinal bleeding (4% to 14%).[25,26].

In their meta-analysis, Panahi et al. (2020) found that the predominant clinical symptoms seen in children with COVID-19 were fever (96%), dry cough (91%), and exhaustion (45%). The participants had stomach discomfort in 23% of cases, nausea and vomiting in 12% of cases, and diarrhea in 7% of cases. [27].

Also, the meta-analysis of De Souza *et al.,* (2020) showed that the most prevalent symptom was fever, reported in 47.5% of the cases, followed by cough (41.5%), nasal symptoms (11.2%), diarrhea (8.1%), nausea/vomiting (7.1%), fatigue (5.0%), and respiratory distress (3.5%) [28]. The most common symptoms in the study of Zheng *et al.,* (2020) were fever (52%), followed by dry cough (44%), diarrhea (12%), nasal congestion (8%), dyspnea (8%), abdominal pain (8%), and vomiting (8%) [29].

The GIT symptoms generated by SARS-CoV-2 does not appear to harm the colonic epithelium. Likewise, lymphocytic inflammatory infiltration may ultimately be observed in the esophagus, stomach, colon and liver of adult patients with COVID-19 [30].

Other manifestations observed in patients were skin rash 12 (30.8%), non-purulent conjunctivitis 6 (15.4%) cases, oedema 7 (17.9 %) cases and mucous membrane manifestations 12 (30.8%) cases of the studied population. Like our results the study of Kolivras *et al.,* (2020) found that cutaneous findings have been reported infrequently and are not well characterized; they include maculopapular, urticarial, and vesicular eruptions [31].

Whittaker *et al.,* (2020) mentioned in their study that manifestations of COVID-19 in children are variable and include rash (52%), conjunctivitis (45%), oral mucosal changes (27%), peripheral edema (9%), headache (29%), and altered mental status or confusion (9%) [32].

Among the children in the current study, 15 (39.5%) died, while 14 (37.8%) were discharged from the hospital without complications, and 9 other cases (23.7%) were discharged from the hospital with complications. There were non-statistically significant associations between CBC, KFTs, ABG, LFTs, CRP, D-dimer and serum ferritin and participants' outcomes (p-values <0.05).

Feldstein *et al.,* (2020) reported in their study about multisystem inflammatory syndrome in US children As of May 20, 2020, a total of 130 patients (70%) had been discharged alive [1].

Also, Dufort *et al.,* (2020) showed in their study about multisystem inflammatory syndrome in New York that a total of 76 patients (77%) had been discharged alive from the hospital [33].

In general, the mortality rate from COVID-19 infection in pediatrics is

low. The mortality rate increased in multisystem inflammatory syndrome and reached (67%) in the study performed by Pereira *et al.,* (2020) [34].

5. Conclusion:

The association between SARS-CoV-2 and multisystem inflammatory syndrome in children resulted in severe and potentially fatal sickness, leading to higher death rates in children who were previously in good condition.Neurological symptoms are frequently observed in patients with MIS-C, such as various types of seizures, headaches, encephalopathy, ataxia, and acute flaccid paralysis. It has been observed that patients with more severe neurological symptoms and involvement of more than two organ systems have a worse prognosis in terms of morbidity and mortality.

Recommendations:

Early diagnosis and treatment of pediatric COVID-19 patients, including the use of steroids, IVIG, anticoagulants, and inotropes if necessary, are crucial for a better prognosis. Prompt admission to a pediatric ICU and diligent monitoring of vital signs across all systems are recommended. A multidisciplinary team approach is essential for proper assessment, follow-up, and decision-making. Due to the high mortality rate associated with COVID-19 and multisystem inflammatory syndrome in hospitalized pediatric patients, heightened care and attention are necessary. Strict infection control measures are vital to minimize infection rates, particularly among children. Recommendations include avoiding large gatherings, maintaining a two-meter distance from others, wearing masks in enclosed public spaces, and practicing thorough hand hygiene with soap and 70% alcohol-based hand sanitizers. Additional studies involving a larger patient cohort are needed to validate these findings.

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