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# The Mortality rate of pediatric with COVID-19 with and without multisystem inflammatory syndrome: Single-center study, Makkah Region, Saudi Arabia

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## ABSTRACT

**Background:** The medical presentations of COVID-19 in children vary. A newly emerged disorder identified as a multiple system inflammatory syndrome in children (MIS-C), mimics the symptoms of Kawasaki disease (KD) present in patients with an advanced form of COVID-19.

**Aim:** This study aimed to investigate the mortality risk for children's patients with corona virus with or without MIS-C

**Method**: An observational cohort study that performed at the Maternity and Children's Hospital, Makkah, Saudi Arabia, from April 1, 2020, till end of December 2022.

**Results:** A 95 patients met the inclusion criteria. Ten patients (10.5%) had MIS-C, and 50 (52.6%) were male. The mean age of the participants was 44.55 ± 4.31 months. Conjunctivitis, cutaneous rash, extended duration of fever, and elevation of inflammatory markers were significantly associated with the incidence of MIS-C. Amongst the 2 groups, there was no meaningful variation in admission to ICU, requirement for mechanical ventilation or vasopressors agents, duration of hospitalization, and incidence of mortality.

**Conclusion:** This study highlighted the magnitude of exploring MIS-C in children infected with COVID-19 who present complaining of conjunctivitis, cutaneous rash, and extended durations of fever. A large multi-center pediatric study is required to estimate the mortality rate of COVID-19 patients with MIS-C.

**Keywords:** MIS-C, Pediatrics, COVID-19, Mortality

## INTRODUCTION

Acute respiratory disorder coronavirus, recognized as COVID-19, was first registered in China. It has infected more than 426 million people worldwide and resulted in almost six million recorded deaths.[1,2] COVID-19 statistics for Saudi Arabia from February 2022 indicate that there have been almost one million patients of COVID-19, with a total death rate of 3.2%.[3,4]

Pediatric patients younger than 18 years represent a small ratio of COVID-19 cases. National statistics from various countries show that pediatric cases account for up to 13% of laboratory-established cases of COVID-19.[5,6] Pediatric hospitalization has increased in multiple states across the United States, with a cumulative rate of eight per 100,000 people. Almost 30% of these patients need to be transferred to an intensive care unit (ICU), and 6% require mechanical ventilation.[7]

The medical presentations of COVID-19 in children vary, ranging from benign, asymptomatic disease to life-threatening disorders.[8,9] The most frequently reported features are high temperature, cough, headache, abdominal pain, pharyngitis, muscle pain, shortness of breath, nausea, vomiting, and diarrhea.[10,11] Reductions in white blood cells, lymphopenia, and increased inflammation indicators, fibrinogen, and ferritin, are the most described laboratory manifestations in this group of patients.[12]

Chronic conditions among pediatric patients with coronavirus, and predominantly those in an immunosuppressive state, have been recognized in a small number of pediatric patient hospitalizations.[13,14] Recently, the clinical characteristics of a newly emerged disorder, called multisystem inflammatory syndrome in children (MIS-C) or pediatric inflammatory multisystem syndrome, have been found to mimic individuals of Kawasaki disease (KD), toxic shock syndrome, and pediatric hyper-inflammation disorder. This syndrome has been identified in numerous pediatric COVID-19 worldwide.[11,15,16] To our facts, this is the first study to estimate the COVID-19 mortality rate in Saudi pediatric patients with and without multi-inflammatory syndrome, including pediatric patients with previous persistent conditions.

This study was aimed to examine the mortality rate for pediatric COVID-19 patients with and without MIS-C. Factors such as admission to an ICU, need for mechanical ventilation, use of vasoactive agents, and length of hospital stay were considered. Additionally, the effects of treatments and risk factors, including chronic diseases and underlying conditions, in critical cases were examined.

## MATERIALS AND METHODS

An observational cohort study was performed at the Maternity and Children's Hospital, Makkah, Saudi Arabia, from April 1, 2020, to the end of end December 2022. During this period, 95 patients younger than 18 years old who had been exposed to confirmed COVID-19 cases or who had positive COVID-19 tests were studied. Before conducting the study, ethical approval was obtained (Number: H-02-K076-0621-519).

We used descriptive statistical methods to summarize the patients' sociodemographic characteristics, clinical manifestations, and underlying conditions. Data regarding age, gender, nationality, PCR test, clinical manifestations, and laboratory values were also studied. The following outcomes were examined and analyzed: length of hospital stay, admission to ICU, the need for mechanical ventilation, the use of vasoactive agents, and treatment.

Data analysis was executed using the Statistical Package for the Social Sciences (SPSS; Version 23). Frequencies and percentages were used to display the categorical variables. Means and standard deviations were used to present the continuous variables. Chi-squared and independent t-tests were used as appropriate. The level of significance was $< .05$.

MIS-C was described in the opinion of the Health Protocol of the Saudi Ministry for Patients with COVID-19: patients younger than twenty-one years old who had positive result of a recent SARS-CoV-2 infection via PCR test or who were exposed to COVID-19 within one month preceding the onset of their symptoms and who present with a fever lasting more than one day and have laboratory sign of inflammation, clinically advanced infection necessitating hospitalization, and multisystemic 2-or-more than 2- organs involvement with no rational alternative diagnoses.[17]

## RESULTS

A total of 95 patients met the study's inclusion criteria. Ten (10.5%) had MIS-C, 50 (52.6%) were male, and 45 (47.4%) were female. The majority were Saudi nationals (n = 64, 67.4%). The mean age of the participants was 44.55 ± 4.31 months. The youngest patient was one month old, and the eldest was 14 years old. Table 1 presents the patients' general characteristics. The patient's pre-infection medical history is displayed in Figure 1. Forty-three (45.3%) of the patients were healthy, 16 (16.8%) had a primary immunodeficiency, 11 (11.6%) had an autoimmune disease and/or were using immunosuppressants prior to COVID-19 infection, and four (4.2%) of the patients had chronic kidney disease.

**Table 1:** Socio-demographic profile of patients

| Demographical Characteristics | n | % |
|---|---|---|
| Gender | | |
| Male | 50 | 52.60 |
| Female | 45 | 47.40 |
| Nationality | | |
| Saudi | 64 | 67.40 |
| Non-Saudi | 31 | 32.60 |
| Age | | |
| Mean | 44.55 | |
| Standard Deviation | 4.31 | |

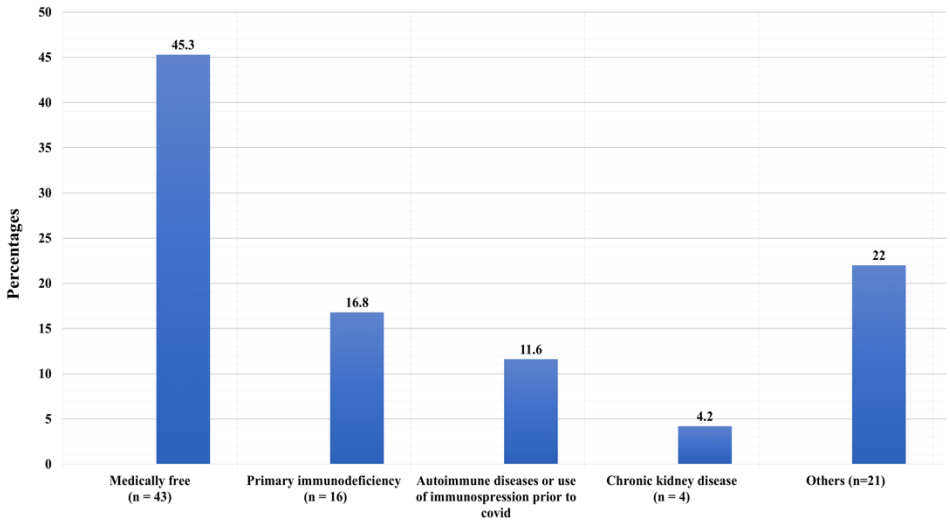


**Figure 1:** History of the Patients

The most detected symptoms were diarrhea, vomiting, and stomachache (n = 49, 51.9%), cough (n = 34. 35.8%), and dyspnea (n = 29, 30.5%). The least observed manifestations were headache (n = 3, 3.2%) and conjunctivitis (n = 5, 5.3%), and 11 (11.6%) of the patients were asymptomatic. The patients' clinical manifestations are displayed in Figure 2.

The incidence of MIS-C is shown in Figure 3. Ten patients had MIS-C (10.5%), while 89.5% did not.

Table 2 illustrates the patients' COVID-19 profiles. Only 75 (78.9%) reported exposure to COVID-19 within four weeks of the onset of their symptoms, and 82 (86.3%) had a PCR test confirming their infection with COVID-19. All patients were presented with fever, with a mean temperature of 38.34 ± 0.8,

and the duration of fever was 2.97 ± 0.8 days. The detailed lab results are presented in Table 2. Of the 17 (17.98%) patients who had their troponin measured, six (6.3%) had elevated troponin. Of the 10 (10.52%) patients who had their fibrinogen tested, five (5.3%) had elevated fibrinogen. Computed scan imaging revealed that 29 (30.5%) had a lung abnormality.

**Table 2:** COVID-19 Profile of Patients (n = 95)

| COVID-19 Profile | | |
|---|---|---|
| **Question** | **n** | **%** |
| COVID-19 exposure within the 4 weeks prior to the onset of symptoms | | |
| Yes | 75 | 78.9 |
| No | 20 | 21.1 |
| COVID-19 confirmed PCR | | |
| Yes | 82 | 86.3 |
| No | 13 | 13.7 |
| Temperature and Investigation Profile | | |
| **Item** | **Mean** | **Standard deviation** |
| Temperature | 38.34 | 0.80 |
| Duration of fever in days | 2.97 | 0.80 |
| Hemoglobin | 11.00 | 2.26 |
| White Blood Cells (WBC) | 11.96 | 6.79 |
| Platelet | 376.68 | 85.50 |
| C. Reactive Protein (mg/dl) | 4.37 | 7.80 |
| Ferritin (micro/l) | 516.28 | 41.57 |
| Erythrocyte Semination Rate (ESR) | 40.64 | 6.23 |
| D. Dimer | 6.42 | 3.20 |
| Albumin | 37.68 | 6.52 |
| LDH | 502.98 | 45.40 |
| AST | 53.77 | 9.15 |
| ALT | 24.56 | 5.15 |
| BUN | 4.52 | 6.54 |
| Serum Creatinine (Scr) | 63.41 | 15.25 |
| **Item** | **n** | **%** |
| Troponin (n =17) | | |
| Normal | 11 | 11.60 |
| High | 6 | 6.30 |
| Fibrinogen (n = 10) | | |
| Normal | 5 | 5.3 |
| High | 5 | 5.3 |
| Imaging Profile | | |
| **Question** | **n** | **%** |
| Lung abnormality | 29 | 30.5 |

The medications given to the patients are shown in Table 3. The most given medications were antibiotics (n = 88, 92.6%), systemic corticosteroids (n = 34, 35.8%), and oxygen therapy (n = 26, 27.4%). The least-

given medications were aspirin (n = 2, 2.1%), tocilizumab (n = 4, 4.2%), remdesivir (n = 1), and hydroxychloroquine (n = 4, 4.2%). The correlation between the incidence of MIS-C and other clinical factors is presented in Table 4. The patients' sociodemographic profiles and medical histories were not significantly associated with the incidence of MIS-C.

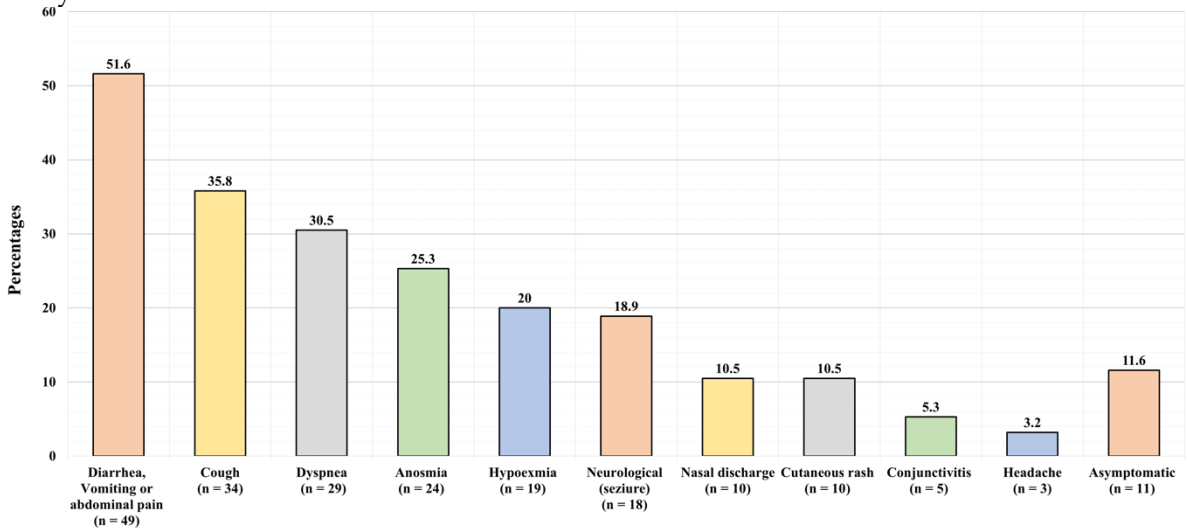


**Figure 2:** Clinical manifestation

However, having conjunctivitis was significantly associated with the incidence of MIS-C ($p < .001$), and patients with conjunctivitis had a greater rate of MIS-C compared to patients who did not (100% vs. 5.6%). Cutaneous rash was significantly associated with the incidence of MIS-C ($p < .001$), and those with a cutaneous rash had a higher rate of MIS-C compared to those who did not (70% vs. 3.5%). The following parameters were all significantly associated with the incidence of MIS-C: duration of fever (p = .007), C. reactive protein (CRP) (p = .046), ferritin (p = .007), and erythrocyte sedimentation rate (ESR) (p = 0.022). Also, significantly higher means for these parameters were detected in patients with MIS-C in comparison to those without it. There were no differences in ICU admission, need for mechanical ventilation or vasoactive agents, or incidence of death between the two groups.

**Table 3:** Management for the patients:

| **Medication** | **N** | **%** |
|---|---|---|
| Antibiotics | 88 | 92.6 |
| Systemic Steroid | 34 | 35.8 |
| Oxygen therapy | 26 | 27.4 |
| Favipiravir | 24 | 25.3 |
| Remdesivir | 1 | 1.1 |
| Anticoagulants | 21 | 22.1 |
| Intravenous immunoglobulin (IVIG) | 12 | 12.6 |
| Vasoactive agent | 8 | 8.4 |
| Hydroxychloroquine | 4 | 4.2 |
| Tocilizumab | 4 | 4.2 |
| Aspirin | 2 | 2.1 |

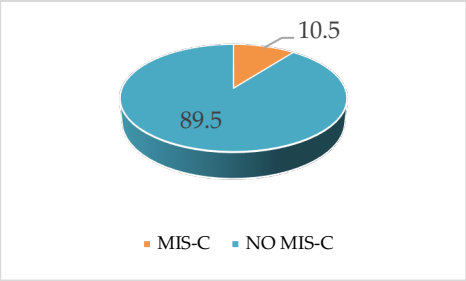


**Figure 3:** Incidence of multisystem inflammatory syndrome in children with COVID 1

**Table 4:** Relationship between the Prevalence of Multisystem Inflammatory Syndrome in Children (MIS-C) and other Clinical Factors

| Factor | Incidence of Multisystem Inflammatory Syndrome in Children (MIS-C) | | P-Value |
|---|---|---|---|
| | Yes | No | |
| **Sociodemographic Profile** | | | |
| Gender (n, %) | | | 0.245 |
| Male | 7 (14.3%) | 43 (86%) | |
| Female | 3 (6.7%) | 72 (93.3%) | |
| Nationality (n, %) | | | 0.851 |
| Saudi | 7 (10.9%) | 57 (89.1%) | |
| Non-Saudi | 3 (9.7%) | 28 (90.3%) | |
| Age (M + SD) | 5.78 + 3.75 | 3.51 + 3.64 | |
| **Medical History** | | | |
| Medically free (n, %) | | | 0.097 |
| Yes | 7 (16.3%) | 36 (93.7%) | |
| No | 3 (5.8%) | 49 (94.2%) | |
| Primary immunodeficiency (n, %) | | | 0.541 |
| Yes | 1 (6.3%) | 15 (93.8%) | |
| No | 9 (11.4%) | 70 (88.6%) | |
| Chronic Kidney Disease (n, %) | | | 0.483 |
| Yes | 0 (0%) | 4 (100%) | |
| No | 10 (11%) | 81 (89%) | |
| Autoimmune diseases or use of immunosuppressants prior to covid (n, %) | | | 0.869 |
| Yes | 1 (9.1%) | 10 (90.9%) | |
| No | 9 (10.7%) | 75 (89.3%) | |
| **Clinical Manifestations** | | | |
| Asymptomatic (n, %) | | | 0.226 |
| Yes | 0 (0%) | 11 (100%) | |
| No | 10 (11.9%) | 74 (88.1%) | |
| Nasal discharge (n, %) | | | 0.252 |
| Yes | 0 (0%) | 10 (100%) | |
| No | 10 (11.8%) | 75 (88.2%) | |
| Cough (n, %) | | | 0.072 |
| Yes | 1 (2.9%) | 33 (97.1%) | |
| No | 9 (14.8%) | 52 (85.2%) | |
| Dyspnea (n, %) | | | 0.492 |
| Yes | 4 (13.8%) | 25 (86.2%) | |
| No | 6 (9.1%) | 60 (90.9%) | |
| Diarrhea, Vomiting or abdominal pain (n, %) | | | 0.573 |
| Yes | 6 (12.2%) | 43 (87.8%) | |
| No | 4 (8.7%) | 42 (91.3%) | |
| Anosmia (n, %) | | | 0.716 |

| | | | |
|---|---|---|---|
| Yes | 3 (12.5%) | 21 (87.5%) | |
| No | 7 (9.9%) | 64 (90.1%) | |
| Headache (n, %) | | | 0.191 |
| Yes | 1 (33.3%) | 2 (66.7%) | |
| No | 9 (9.8%) | 83 (90.2%) | |
| Conjunctivitis (n, %) | | | < 0.001* |
| Yes | 5 (100%) | 0 (0%) | |
| No | 5 (5.6%) | 85 (94.4%) | |
| Cutaneous rash (n, %) | | | < 0.001* |
| Yes | 7 (70%) | 3 (30%) | |
| No | 3 (3.5%) | 82 (96.5%) | |
| Neurological (seizure) (n, %) | | | 0.928 |
| Yes | 2 (11.1%) | 16 (88.9%) | |
| No | 8 (10.4%) | 69 (89.6%) | |
| Hypoxemia (n, %) | | | 0.403 |
| Yes | 3 (15.8%) | 16 (84.2%) | |
| No | 7 (9.2%) | 69 (90.8%) | |
| Temperature and Investigations | Mean + Standard deviation | | |
| Temperature | 38.78 + 0.37 | 38.29 + 0.83 | 0.068 |
| Duration of fever in days | 5.2 + 3.46 | 2.71 + 0.61 | 0.007* |
| Hemoglobin | 11.13 + 2 | 10.99 + 2.3 | 0.850 |
| White blood cells (WBC) | 13.42 + 6.93 | 11.79 + 6.68 | 0.475 |
| Platelet | 352 + 29.93 | 379.65 + 13.54 | 0.659 |
| C-Reactive Protein (CRP) (mg/dl) | 9.26 + 4.71 | 3.76 + 7.24 | 0.046* |
| Ferritin (mico/l) | 2302.1 + 824 | 269.97 + 79.55 | 0.007* |
| Erythocyte sedimentation rate (ESR) | 66.33 + 23.15 | 36.96 + 13.96 | 0.022* |
| D.Dimer | 3.03 + 2.45 | 6.91 + 35.5 | 0.776 |
| Albumin | 39.88 + 6 | 37.42 + 6.56 | 0.285 |
| Lactate Dehydrogenase (LDH) | 676.17 + 19.67 | 476.33 + 55.42 | 0.190 |
| Aspartate transaminase (AST) | 45.7 + 5.57 | 54.76 + 5.18 | 0.766 |
| Alanine transaminase (ALT) | 29.3 + 2.79 | 23.97 + 5.49 | 0.531 |
| Blood urea nitrogen (BUN) | 3.14 + 1.57 | 4.7 + 6.91 | 0.481 |
| Serum creatinine (Scr) | 42.46 + 1.05 | 65.96 + 1.87 | 0.546 |
| Troponin (n, %) | | | 0.057 |
| Normal | 1 (9.1%) | 10 (90.9%) | |
| High | 3 (50%) | 3 (50%) | |
| Fibrinogen (n, %) | | | 0.058 |
| Normal | 1 (20%) | 4 (80%) | |
| High | 4 (80%) | 1 (20%) | |
| Lung abnormality (n, %) | | | 0.970 |
| Present | 3 (30%) | 26 (30.6%) | |
| Not present | 7 (70%) | 59 (69.4%) | |
| Outcome | | | |
| ICU admission (n, %) | | | 0.218 |
| Yes | 4 (40%) | 19 (22.4%) | |
| No | 6 (60%) | 66 (77.6%) | |
| Need for mechanical ventilation (n, %) | | | 0.080 |
| Yes | 3 (30%) | 9 (10.6%) | |
| No | 7 (70%) | 76 (89.4%) | |
| Need of vasoactive agent (n, %) | | | 0.229 |
| Yes | 2 (20%) | 7 (8.2%) | |
| No | 8 (80%) | 78 (91.8%) | |
| Death (n, %) | | | 0.431 |

| | | | |
|---|---|---|---|
| Yes | 0 (0%) | 5 (5.9%) | |
| No | 10 (100%) | 80 (94.1%) | |
| Duration of hospitalization (days) (M + SD) | 16.16 + 17.1 | 11.67 + 12.71 | 0.267 |
| Medications | | | |
| Vasoactive agent (n, %) | | | 0.229 |
| Yes | 2 (80%) | 7 (92.9%) | |
| No | 8 (20%) | 78 (4.7%) | |
| hydroxychloroquine (n, %) | | | 0.335 |
| Yes | 1 (10%) | 3 (3.5%) | |
| No | 9 (90%) | 82 (96.5%) | |
| Oxygen therapy (n, %) | | | 0.844 |
| Yes | 3 (30%) | 23 (27.1%) | |
| No | 7 (70%) | 62 (72.9%) | |
| Antibiotics (n, %) | | | 0.346 |
| Yes | 10 (100%) | 78 (91.8%) | |
| No | 0 (0%) | 7 (8.2%) | |
| Favipiravir (n, %) | | | 0.716 |
| Yes | 3 (30%) | 21 (24.7%) | |
| No | 7 (70%) | 64 (75.3%) | |
| Remdesivir (n, %) | | | 0.730 |
| Yes | 0 (0%) | 1 (1.2%) | |
| No | 10 (100%) | 84 (98.8%) | |
| Intravenous immunoglobulin (IVIG) (n, %) | | | < 0.001* |
| Yes | 9 (90%) | 3 (3.5%) | |
| No | 1 (100%) | 81 (96.5%) | |
| Anticoagulants (n, %) | | | 0.025* |
| Yes | 5 (50%) | 16 (18.8%) | |
| No | 5 (50%) | 69 (81.2%) | |
| Aspirin (n, %) | | | < 0.001* |
| Yes | 2 (20%) | 0 (0%) | |
| No | 8 (80%) | 85 (100%) | |
| Systemic glucocorticoid (n, %) | | | 0.002* |
| Yes | 8 (80%) | 26 (30.6%) | |
| No | 2 (20%) | 59 (69.4%) | |
| Tocilizumab (n, %) | | | < 0.001* |
| Yes | 3 (30%) | 1 (1.2%) | |
| No | 7 (70%) | 84 (98.8%) | |

*Significant at level 0.05

## DISCUSSION

COVID-19 data[18] suggest that the medical manifestation of COVID-19 disease in pediatrics is more critical than in adults. Of the 95 patients in the current study, we found that pediatric patients with laboratory-confirmed COVID-19 or recent exposure to COVID-19 within four weeks with MIS-C had a

critical clinical spectrum, including elevated inflammatory markers, CRP, ferritin, and ESR, but no statistically significant mortality rate was found.

Gastrointestinal symptoms and hypoxemia have been reported as the most common features associated with severe hyperinflammatory disorders.[11] Our study confirmed that diarrhea, vomiting, and abdominal pain were the most reported symptoms; however, they were not statistically significantly associated with children with or without MIS-C. However, conjunctivitis, cutaneous rash, and duration of fever were significantly elevated in patients with MIS-C. Patients with MIS-C had more critical disease courses: 40% were admitted to the ICU, 30% required mechanical ventilation, and 20% necessitated vasoactive agents. Their mean hospitalization duration was also the longest.

There was an overlap between KD and MIS-C, with both having cardiovascular involvement.[15] Troponin was elevated by 50% across all patients, and some studies have suggested that patients with MIS-C usually present with immunoglobulin G antibodies.[19] A previous study reported that the incidence of thrombosis in MIS-C patients reached 6.5% and that the d-dimer was an independent predictor for thrombosis.[20] Understanding the pathophysiology of MIS-C should be mandatory for making clinical judgments regarding its management. In our study, most patients in the MIS-C group were treated with intravenous immunoglobulin (IVIG), aspirin, anticoagulants, steroids, and tocilizumab.

Previous studies have found a relationship between ethnicity and the incidence of MIS-C: MIS-C is more common among Hispanic and non-Hispanic Black children and less frequent among White and Asian children.[21] For Middle Eastern patients, the reported incidence ranged from 5% to 12%.[22] In our study, although MIS-C occurred more in Saudi children than in non-Saudi children, the difference was not statistically significant.

This study has some limitations. As a retrospective study, it rationalized the mortality outcome and other outcomes of interest. Also, it was a single-center study, which may limit its generalizability. This emphasizes the need for a large-scale multi-center study on pediatric patients with COVID-19 infections to improve their management and outcomes.

## CONCLUSION

The COVID-19 data suggest that children exhibit more severe clinical manifestations of the disease than adults. COVID-19 with MIS-C has a critical clinical disease course, with high ICU admission, a need for mechanical ventilation and vasoactive agents, and a mortality rate comparable to that of the non-MIS-C group. Our study highlighted the magnitude of examining MIS-C in pediatric COVID-19 patients who present with conjunctivitis, cutaneous rash, and extended durations of fever. A large, multi-center pediatric study is required to estimate the mortality rate of MIS-C patients with COVID-19.

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Nil

**Conflict of Interest**

The authors declare that there is no conflict of interest relevant to this article.

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