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***Original research article***

# MULTI-SYSTEM INFLAMMATORY SYNDROME IN PATIENTS ADMITTED AT NICU OF A TERTIARY CARE HOSPITAL

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**Abstract:** *Multi-inflammatory syndrome in neonates (MIS-N) associated with COVID-19 is an emerging concern in neonatal intensive care units (NICUs). Understanding its clinical spectrum and outcomes is crucial for developing management strategies and improving neonatal care.* ***Objective****: To explore the clinical spectrum, associated laboratory markers, and outcomes of neonates diagnosed with MIS-N and COVID-19 admitted to the NICU.* ***Methods:*** *This case series was conducted at the NICU of Shifa International Hospital, Islamabad, from January 2023 to June 2023. It included 47 infants diagnosed with COVID-19 who developed MIS-N. Data collected encompassed clinical presentations, laboratory markers, treatments administered in the ICU, and clinical outcomes. Descriptive statistics were used to analyze the data, focusing on symptoms, treatment efficacy, and complications.* ***Results:*** *The neonates had a mean age of 20.65 ± 16.60 days and a mean gestational age of 36.40 ± 2.62 weeks. Elevated inflammatory markers were noted, with D-Dimers elevated in 46.8%, serum ferritin in 66%, and C-reactive protein (CRP) in 48.9% of patients. The most common symptoms included respiratory distress (74.5%), poor feeding (38.3%), and fever (29.8%). Significant findings included pulmonary hypertension in 27.7% of the patients, patent ductus arteriosus in 23.4%, and other cardiovascular anomalies. Complications such as sepsis (70.2%), oxygen dependency (21.3%), and renal failure (29.8%) were prevalent. The mortality rate was 12.8%.* ***Conclusion:*** *MIS-N presents a severe threat to neonates with COVID-19, demonstrating high rates of serious complications and a notable mortality rate. Echocardiography is essential for early detection of cardiac dysfunctions. These findings underscore the urgent need for specific guidelines for the early recognition and management of MIS-N in neonates.*

**Keywords:** COVID-19, multisystem inflammatory syndrome, Mortality, Cardiac Involvement.

## Introduction

Coronavirus SARS-CoV-2 can infect people of any age group since it has a broad age range of host range. Children today appear to have a more favorable clinical course of the related illness COVID-19, according to observations conducted during the past two years of the pandemic. (1) These observations were made during the duration of the pandemic. Even currently, SARSCoV-2 infections in newborns appear to be less common. (2) The reason for this is most likely because term and preterm neonates express fewer SARS-CoV-2 entry receptors in their nasal epithelium than adults do. (3) even though Vivanti et al. demonstrated the remote possibility of a maternal-fetal transfer, the vast majority of neonatal occurrences are generally attributed to horizontal transmission due to the presence of familial clusters. (4)

A growing body of literature, however, describes SARS-CoV-2-infected infants who develop catastrophic illness as a result of the emergence of the multisystem inflammatory syndrome known as MIS-N. (5) There is still a lot of mystery around the actual etiology of MIS-C. It would suggest that post-infectious immunological dysregulation brought on by the virus is the primary contributor. (6) Because newborn immune systems are still developing, it is possible that they will not produce adequate SARS-CoV-2 antibodies. On the other hand, new findings from a large study cohort have shown that immunoglobulins (IG-G) antibodies can be effectively transferred from the mother to the fetus through the placenta. (7)

The clinical presentation of MIS-C is quite similar to that of Kawasaki illness (KD), and some of the affected children also present with characteristics of TSS. (8) In any child presenting with symptoms of MIS-C, both KD and TSS should be considered relevant differential diagnoses. These three conditions have been compared to one another in the past.4 The earliest definition of MIS-C provided by WHO includes clinical and laboratory characteristics, evidence of COVID-19, or potential interaction with a person who either now has or has had COVID-19 infection. (9) The majority of patients, ranging from 71% to 90%, came with involvement of at least four organ systems, and more than half of the patients required admission to an intensive care unit at some point during their time spent in the hospital. (10, 11)

In the present study, we determined the clinical spectrum and outcomes of MIS-C among neonates admitted to the NICU.

## Methodology

In this case series, we presented data from 47 infants diagnosed with COVID-19. We had MIS-N who were admitted to the NICU of Shifa International Hospital Islamabad from January 2023 to June 2023. Informed

consent was obtained from each infant's guardian. The following criteria were used for diagnosing MIS-N: fever for more than three days and who also have two of the following symptoms: a) A rash, signs of mucocutaneous inflammation, or bilateral non-purulent conjunctivitis, b) shock or Hypotension; c) Features of valvulitis, myocardial dysfunction, coronary abnormalities or pericarditis; and d) coagulopathy (raised PT, PTT, elevated d-Dimers). e) Acute gastrointestinal difficulties (such as diarrhea, abdominal discomfort, or vomiting), AND Elevated markers of inflammation such as an elevated ESR or C-reactive protein level. Infants who were positive for COVID-19 but were not fulfilling the criteria of MISC were excluded.

Data regarding clinical presentation, laboratory investigations, and in-hospital outcomes was collected. In patients, an echocardiogram was performed for cardiac evaluation the next day after admission to the NICU.

All the data was entered in SPSS v23. Frequency and percentages were used for qualitative variables, and mean and SD were used for the presentation of quantitative data.

**Results**

The mean age at presentation was 20.65±16.60 days. Mean gestational age was 36.40±2.62 weeks. There were 5 (10.6%) very preterm infants and 14 (29.8%) preterm infants. The mean birthweight was 2.46±0.71 Kg. The place of birth was the same hospital in 22 (46.8%) patients and the other hospital in 25 (53.2%) patients. D-Dimers were elevated in 22 (46.8%) patients, serum ferritin in 31 (66%) patients, and CRP was elevated in 23 (48.9%) patients (Table 1).

The most typical symptom at presentation was respiratory distress in 35 (74.5%) patients, poor feeding in 18 (38.3%) patients, fever in 14 (29.8%) patients, lethargy in 9 (19.1%) patients, Shock in 4 (8.5%), SVT in 1 (2.1%) and prune belly in 1 (2.1%) patients. On echocardiography, the most typical finding was pulmonary hypertension (PH) diagnosed in 13 (27.7%) patients, followed by patent ductus arteriosus (PDA) in 11 (23.4%) patients, patent foramen ovale (PFO) in 9 (19.1%) patients, ventricular septal defect (VSD) in 4 (8.5%) patients, tricuspid regurgitation (TR) in 3 (6.4%) and mitral regurgitation (MR) in 1 (2.1%) patients (Table 2).

Regarding the management plan, mechanical ventilation was provided to 21 (44.6%) patients, non-invasive O2 therapy was given to 13 (27.7%) patients, and the remaining 13 (27.7%) patients were managed on room air. Blood transfusion was given to 30 (63.8%) patients. Inotropes were needed in 7 patients (in 5 (10.6%) patients' single inotrope was given, and in 2 (4.2%) patients, double inotropes were given. Anti-coagulation was needed in 1 (2.1%) patient. Intravenous immunoglobulin (IVIG) was given to 4 (8.5%) patients. Out of 47, 6 (12.8%) patients died inside the hospital. At the same time, 41 (87.2%) were discharged from hospital (Table 3).

Regarding complications, sepsis occurred in 33 (70.2%) patients, O2 dependency in 10 (21.3%) patients, renal failure in 14 (29.8%) patients, respiratory failure in 7 (14.9%) patients, pneumonia in 8 (17%) patients, coagulopathy in 7 (14.9%) patients, anemia in 5 (10.6%) patients, pneumothorax in 4 (8.5%) patients, seizures in 3 (6.4%) patients, neonatal jaundice in 3 (6.4%) and SVT in 2 (4.2%) patients. At the same time, other complications such as AKI, UTI, pneumopericardium, ventilatory failure, and multi-organ failure occurred in one patient only (Table 4).

**Table 1. Baseline Characteristics.**

| Variable | Value |
|---|---|
| Age at admission (days) | 20.65±16.60 |
| Gestational Age (Weeks) | 36.40±2.62 |
| *Term Birth* | *28 (59.6%)* |
| *Preterm Birth* | *14 (29.8%)* |
| *Very Preterm Borth* | *5 (10.6%)* |
| Birthweight (Kg) | 2.46±0.71 |
| **Birth Place (%)** | |
| Same Hospital | 22 (46.8%) |
| Other Hospital | 25 (53.2%) |
| ***Laboratory Investigations*** | |
| Elevated D-Dimers | 22 (46.8%) |
| Elevated Serum Ferritin | 31 (66%) |
| Elevated CRP | 23 (48.9%) |

**Table 2. Clinical Presentation.**

| **Fever** | **14 (29.8%)** |
|---|---|
| Poor Feeding | 18 (38.3%) |
| Respiratory Distress | 35 (74.5%) |
| Respiratory Failure | 1 (2.1%) |
| Cardiovascular manifestations | 26 (55.3%) |
| Loose Stool | 3 (6.4%) |
| Vomiting | 3 (6.4%) |
| Lethargy | 9 (19.1%) |
| Prune Belly | 1 (2.1%) |
| Shock | 4 (8.5%) |
| SVT | 1 (2.1%) |

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| | |
|---|---|
| Echocardiography Findings | |
| Patent Ductus Arteriosus (PDA) | 11 (23.4%) |
| Pulmonary Hypertension (PH) | 13 (27.7%) |
| Patent foramen ovale (PFO) | 9 (19.1%) |
| Ventricular Septal Defect (VSD) | 4 (8.5%) |
| Tricuspid Regurgitation (TR) | 3 (6.4%) |
| Mitral Regurgitation (MR) | 1 (2.1%) |

**Table 3. Treatment Given**

| **Need for Oxygen therapy.** | |
|---|---|
| Mechanical Ventilation | 21 (44.6%) |
| Non-invasive $O_2$ therapy | 13 (27.7%) |
| Room Air | 13 (27.7%) |
| **Blood Transfusion** | |
| Given | 30 (63.8%) |
| Not Given | 17 (36.2%) |
| **Inotropes** | |
| Single | 5 (10.6%) |
| Double | 2 (4.2%) |
| Not Given | 40 (85.1%) |
| **Need for Anticoagulation** | |
| Yes | 1 (2.1%) |
| No | 46 (97.9%) |
| **Intravenous Immunoglobulin (IVIG)** | |
| Given | 4 (8.5%) |
| Not Given | 43 (91.5%) |
| **In-hospital Outcome** | |
| Discharged | 41 (87.2%) |
| Expired | 6 (12.8%) |

**Table 4. Complications of MISC**

| **Complication** | **Frequency** |
|---|---|
| Sepsis | 33 (70.2%) |
| $O_2$ Dependency | 10 (21.3%) |
| Renal Failure | 14 (29.8%) |
| Respiratory Failure | 7 (14.9%) |
| Pneumonia | 8 (17%) |
| Coagulopathy | 7 (14.9%) |
| Anemia | 5 (10.6%) |
| Pneumothorax | 4 (8.5%) |
| Seizures | 3 (6.4%) |
| Neonatal Jaundice | 3 (6.4%) |
| SVT | 2 (4.2%) |
| AKI | 1 (2.1%) |
| Pneumopericardium | 1 (2.1%) |
| UTI | 1 (2.1%) |
| Encephalopathy | 1 (2.1%) |
| Bronchiolitis | 1 (2.1%) |
| NEC | 1 (2.1%) |
| Hypoglycemia | 1 (2.1%) |
| Cholestasis | 1 (2.1%) |
| Inborn Error of Metabolism (IEM) | 1 (2.1%) |
| Pulmonary Hypertension | 1 (2.1%) |
| Pulmonary Hemorrhage | 1 (2.1%) |
| Methemoglobinemia | 1 (2.1%) |
| Pulmonary Hypertension | 1 (2.1%) |
| Ventilatory Failure | 1 (2.1%) |
| Multiorgan Failure | 1 (2.1%) |
| Massive Pulmonary Edema | 1 (2.1%) |

| | |
|---|---|
| Pseudo-hypoaldosteronism | 1 (2.1%) |
| Complicated meconium ileus | 1 (2.1%) |

## Discussion

With few instances reported globally, MIS-C in the pediatric population poses a new problem in the COVID-19 pandemic. (12) It is assumed that MIS-C is produced by abnormal cellular or humoral adaptive immune responses that create inflammation or mediate organ damage because it typically manifests after a lag period following SARS-CoV-2 infection and correlates with the timing of acquiring anti-spike antibodies (IgG). (13) SARS-CoV-2 infections in infants can manifest as early-onset infections that are probably the result of vertical or intrapartum transmission or late-onset infections that appear more than 72 hours after birth and may be contracted through close contacts. (4) Due to trophoblasts' lack of expression of the two central host membrane receptors for SARS-CoV-2 entry, angiotensin-converting enzyme (ACE) 2 and transmembrane protease serine (TMPRSS2), transplacental transmission of SARS-CoV-2 is less common in term babies; however, this raises concerns in preterm infants. (14) Along with secretory IG-A that are released in breast milk, maternal SARS-CoV2 infection leads to the production of protective anti-spike IgG antibodies that cross the placenta and may protect babies. (15) However, it is hypothesized that in some neonates who are genetically predisposed, these antibodies may bind to neutrophil and macrophage receptors, activating cytokines and resulting in a variety of MIS-C symptoms.

In this case series, there were 47 cases of neonatal multisystem inflammatory syndrome, which contributed to premature labor, respiratory distress, and involvement of many organ systems. This adds to the growing body of information that suggests that neonatal outcomes could have potentially severe consequences. Those neonates who were affected by MIS-N would have varied degrees of involvement in many organ systems (gastrointestinal, cardiovascular, respiratory, hematological, hepatic, and dermatological), as well as substantial morbidity. (16)

To rule out the possibility of myocardial dysfunction and damage to the coronary arteries, which have been observed in neonates with MIS-N and in neonates/infants with MIS-C (17-19), echocardiography should be performed on all infants with a suspected inflammatory disease. Functional echocardiography can directly evaluate cardiovascular anomalies and hemodynamics even while the patient is still lying in the hospital bed. (20) We propose performing echocardiography in neonates with MIS-N after 24–48 h of life (or earlier in the case of symptoms), taking into consideration the changes in hemodynamics that occur physiologically during the transition from fetal to neonatal life. This would be done after considering the changes in hemodynamics that occur physiologically during the transition from fetal to neonatal life. On the other hand, echocardiography ought to be done as soon as possible after admission in newborns diagnosed with MIS-C. In addition, neonates diagnosed with MIS-N were more likely to require inotropic care (54.5%), whereas newborns diagnosed with MIS-C required inotropic support just 15.6% of the time. As an extra benefit, the added advantage of longitudinally monitoring neonates and their response to therapeutic intervention is provided by targeted echocardiography. The current study has made it possible to identify microvascular dysfunction in pediatric patients diagnosed with SARS-CoV-2 pneumonia. (21) This finding was made possible due to current research.

Yasuhara et al. reported that fever is among the most common symptoms in children with MIS-C. In our research, only 29.8 percent of newborns diagnosed with MIS-N had a fever. However, temperature changes are not always present at the beginning of infectious or even inflammatory febrile diseases in preterm or term neonates. (22) Therefore, this fever frequency gap could be explained by variations in the ages of MIS-N newborns and MIS-C infants. We were able to show that cardiovascular dysfunction and respiratory distress are the predominant findings in newborns with MIS-N. This is in contrast to older children who had MIS-C, where gastrointestinal symptoms were the most common manifestation (87.3%). (23) In neonates with MIS-N, we found these were the predominant findings.

In our study, the outcomes of MIS-N were favorable, with a mortality rate of 12.8%. De Rose et al., in their cases series, reported a mortality rate of 9.2%. (24) Pawar et al., in a similar study, reported a mortality rate of 10% in MIS-N. (25)

Some factors limit the present study. First, the case series was why we could not compare the study results. However, we included 47 patients, while many other studies have included only minimal (<10) patients in their case series. However, the treatment given was not constant in all patients. Therefore, more studies still need to be conducted to determine the spectrum of clinical presentation and outcomes of MIS-N.

## Conclusion

MIS-N is a fatal disease in neonates. Echocardiography should be performed in these neonates to rule out cardiac dysfunction. Moreover, these neonates also have a high percentage of inflammatory markers. There is a need to make guidelines for early recognition and management of these infants presenting with MIS-N.

## Declarations

**Data Availability statement**

All data generated or analyzed during the study are included in the manuscript.

**Ethics approval and consent to participate.**

It is approved by the department concerned. (IRBEC-TCHIS-03/22)

**Consent for publication**

Approved

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## Conflict of interest

The authors declared an absence of conflict of interest.

## Authors Contribution

***MIDHAT ZAHRA (Resident Pediatrics )***
*Final Approval of version & Data Analysis*
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*Drafting*
***SHEHLA CHOUDHRY (Consultant Pediatrician)& EJAZ A. KHAN (Consultant /Chief of Pediatrics)***
*Revisiting Critically, Drafting, Concept & Design of Study*

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