

# Neonatal Multisystem Inflammatory Syndrome Consequent to Perinatal SARS-COVID-2- Infection: A Narrative Review Study

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## ABSTRACT

Several studies have described multisystem inflammatory syndrome (MIS) in children, but very few investigations presented this syndrome among neonates (MIS-N). The present study has reviewed the current knowledge about MIS-N, its etiology, symptoms, and outcomes to attract special attention with an eye on earlier diagnosis and treatment of newborns affected by perinatal SARS-CoV-2-infection. A narrative review study was conducted (Tehran, Iran, 2021). All types of full English articles (up to October 1 2021) were included. Detailed research on academic search engines was performed. The implemented Mesh-based keywords were "SARS-COVID-2" OR "COVID-19" OR "coronavirus" AND "Neonate" OR "Neonatal" OR "Newborn" AND "Multisystem Inflammatory Syndrome" OR "MIS-N" OR "inflammatory response syndrome" AND "Pregnancy" OR "Perinatal" OR "prenatal". Finally, 15 Full-text articles were included that met the eligibility criteria. Available data related to the disease, its etiology, presentations, and its outcome were collected and discussed. The cause of MIS-N is the transmission or production of SARS-CoV2 antibodies in response to SARS-CoV2 infection. By involving different organs, the clinical manifestations of MIS-N may mimic sepsis, toxic shock syndrome, RDS, Kawasaki disease, necrotizing enterocolitis, myocarditis, meningitis/encephalitis, aortic thrombosis, ETC. Besides the clinical presentations, detecting reactive anti-SARS-CoV-2 IgG antibodies could be a notable clue in MIS-N diagnosis. Supportive therapy, suppressing the autoimmune and inflammatory responses, anti-platelet agents, and anticoagulants were reported as the effective therapeutic agents to improve the outcome. The present study highlighted the possibility of MIS-N as an infrequent but severe syndrome consequent to perinatal COVID-19 infection. Although the diagnosis is still controversial, clinical suspicion, laboratory findings, and early treatment initiation could improve the outcome of this immunological disease.

**Keywords:** Multisystem Inflammatory Syndrome, Neonate, Perinatal, SARS-COVID-2



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## Introduction

Today, vertical transmission of SARS-CoV-2 is well identified (1, 2). Intrauterine transplacental transmission, Intrapartum secretions exposure, postnatal exposure to infected patients, and breastfeeding transmission are potential mechanisms for neonatal SARS CoV-2 infection (3). These perinatal transmissions are responsible for possible impairments of fetal health, resulting in severe neonatal morbidity and mortality (4, 5). Besides neonatal demise, respiratory, nervous, and immune

system complications are reported as the adverse effects related to neonatal SARS-CoV-2 infection (6).

Recently, few investigations showed that fetal inflammatory response syndrome secondary to maternal SARS-CoV-2 infection might be responsible for the immune system's overreaction and excessive production of pro/anti-inflammatory and immunoregulatory/modulatory cells. This overresponse of the immune system causes the release of a large amount of

interferon resulting in cytokine storm and neonatal multisystem inflammatory syndrome (MIS-N) (7-9).

MIS-N following perinatal SARS-CoV-2 infection as a new and rare condition has been reported by very few studies. In this life-threatening condition, different body organs (heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal) may become inflamed (10). The signs and symptoms associated with MIS-N include severe fever, cardiovascular and pulmonary complications, nausea, vomiting, diarrhea, inflammatory bowel disease, neck pain, bloodshot eyes, headache, and mucocutaneous symptoms (like Kawasaki disease) (3, 11). IgM and IgG antibodies against SARS-CoV-2 were also shown in more than 80% of cases with MIS (10, 11).

To prevent MIS-related adverse events, conducting further studies are worthy. Although several studies have described MIS in children, very few investigations presented this syndrome among neonates. Herein, this study reviewed the current knowledge about MIS-N, its etiology, signs, and symptoms to attract special attention with an eye on earlier diagnosis and treatment of newborns affected by perinatal SARS-CoV-2-infection.

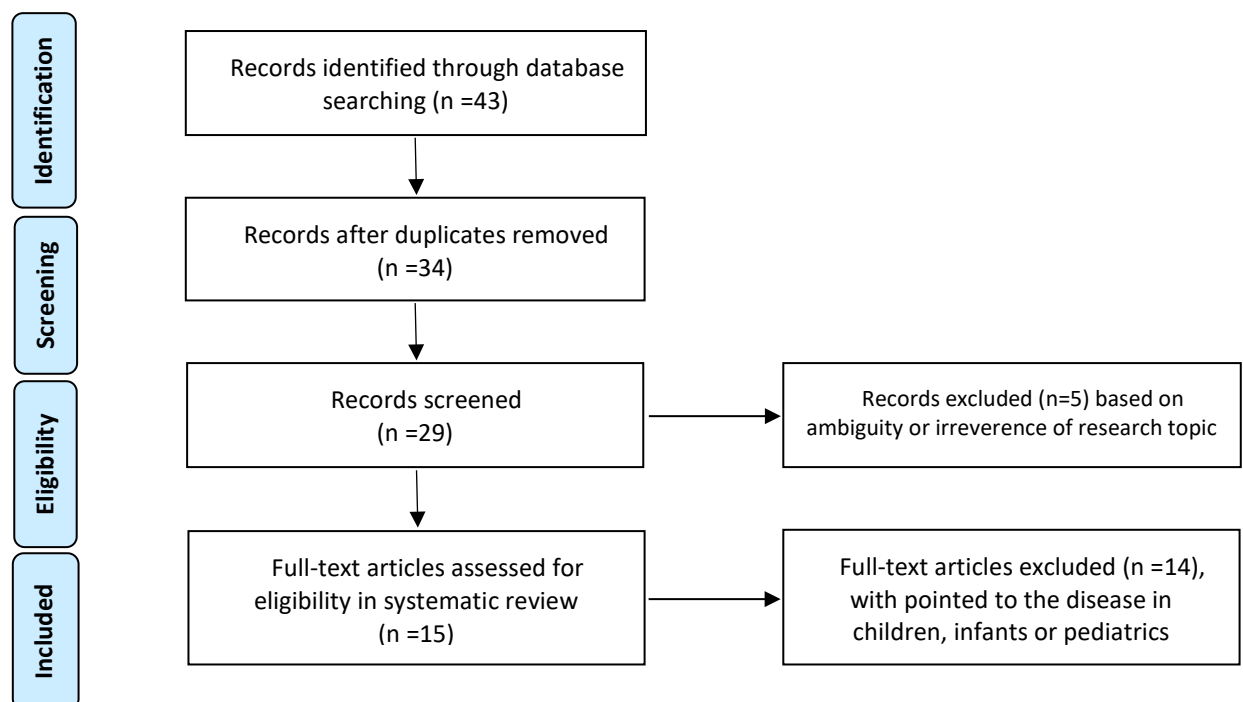
## Methodology

A narrative review study was conducted in the Maternal, Fetal, and Neonatal Research Center, affiliated with Tehran University of Medical Sciences, Tehran, Iran, in 2021.

All types of full English articles, including case reports, case series, pilot studies, letters to the editor, and original, systematic, and meta-analysis review studies (up to October 1, 2021) were included. Detailed research was performed on academic search engines (Cochrane Library, ISI of Web Science, Scopus, PubMed, and Google Scholar databases). The implemented Mesh-based keywords for the study were considered as "SARS-COVID-2" OR "COVID-19" OR "coronavirus" AND "Neonate" OR "Neonatal" OR "Newborn" AND "Multisystem Inflammatory Syndrome" OR "MIS-N" OR "inflammatory response syndrome" AND "Pregnancy" OR "Perinatal" OR "prenatal". Moreover, a few relevant studies were added through reviewing the reference lists. After reviewing the abstracts, irrelevant or duplicate research was excluded. All studies related to children or pediatric multisystem inflammatory syndrome (MIS-C) were also excluded. The primary outcome was gathering available data related to the disease, its etiology, presentations, and its outcome.

## Results and Discussion

Through a computerized search, 43 studies were yielded. After exclusion of duplicate references (9), irrelevant studies without pointing to the subject (2), studies related to Children, Pediatric, or Infant Multisystem Inflammatory Syndrome (12), and lack of information (3), finally, 15 Full-text articles were included that met the eligibility criteria (Figure 1).



**Figure 1.** Flow chart of the included studies

After reviewing included studies, a data extraction list was designed to gather information regarding the author's name, country, publication date, study design, as well as neonate's age, sex, disease manifestations,

laboratory findings, medical treatments, and neonatal outcomes. [Table 1](#) summarizes the information of included studies. Based on the findings extracted from studies, the results are categorized as follows:

**Table 1. List of information (author's name, country, publication date, study design, neonate's age, sex, disease manifestations, laboratory findings, medical treatments, and neonatal outcomes) related to included articles**

Authors' name, country, publication date, study design	n (male/female, age at Presentation (day), preterm/term)	Maternal COVID- 19 RT PCR & antibody statuses	Clinical presentations	Serology, laboratory & Echo findings	Treatment	Outcome; Deat/ Discharge
Amulya <i>et al.</i> , (22), 2021 Sep 27, Letter to the Editor	1(male),10days, term	-ve* RT PCR + ve** IgG	Fever, tachycardia, tachypnea, moderate subcostal and intercostal retraction, rhonchi	+ve IgG -ve RT PCR Normal Blood count, septic screen, metabolites, and renal function, elevated LDH, CKMB, troponin T, and CPK Echo: Coronary artery dilatation of LAD and RCA  + ve IgG + veRT PCR	Antibiotics, anticonvulsant, immunoglobulin, methylprednisolone, aspirin	
Thakur <i>et al.</i> , (20), India, September 24, 2021, Case Report	1(male), 1 day, preterm:34 weeks)	+ve RT PCR	Afebrile, respiratory distress, feed intolerance, abdominal distention, dehydrated, tachypneic, shock, lethargic, bilious discharge, dilated bowel loops, bowel wall edema, Stage 111A necrotizing enterocolitis	metabolic acidosis, hyponatremia, neutropenia, thrombocytopenia, elevated BUN, CRP, procalcitonin, deranged Prothrombin time international normalized ratio, positive Stool occult blood, protein urea	Oxygen therapy, antibiotics, IV immunoglobulin	discharged
More <i>et al.</i> , (13) India, September 7, 2021, Case series	20 (16/4), 1-30 days, 4/16	+ve IgG =9 cases +ve IgM=4 cases +ve RT PCR=9 cases	Respiratory Distress, Shock, Encephalopathy, refusal of feeds, Lethargy, Fever, Seizure, Hypoglycaemia, Vomiting, Cardiac murmur, Tachycardia, Ascites, Excessive crying, Right sided submandibular swelling	+ve IgG =19 +ve IgM=1 +ve RT PCR=0 Leukocytopenia, Leucocytosis, Elevated D-dimer, Troponin T, PROBNP, LDH, CRP, Procalcitonin, Ferritin, Thrombocytopenia, Thrombocytosis, Deranged coagulation profile  Echo : LV Dysfunction, Biventricular Dysfunction, pericardial Effusion, Prominent RCA	Oxygen therapy, ventilation and respiratory support, Cardiac support, Antibiotics, Steroids, IVIG, Aspirin, Surfactant	2/18
Amonkar <i>et al.</i> , (23) India, 2021 September 5, case report	1,(N/A), 6 days, term	+ve IgG +ve IgM -ve RT-PCR	Blackish discoloration of the toes of feet	+ve IgG +ve IgM -ve RT-PCR Elevated CRP, ESR, ITL6, procalcitonin, ferritin, LDH, N-terminal pro-brain natriuretic peptide, D-dimer	Corticosteroids, heparin, recombinant tissue plasminogen activator, surgical embolectomy followed by right limb amputation	Right limb amputation, discharged
Diggikar <i>et al.</i> , (24), India, 2021 August 13, Case Report	1(N/A), 7-day-old, term	N/A	Poor feeding, reduced activity, reduced tone, sluggish reflexes, seizures, fever	+ve RT-PCR Elevated D-dimer, ferritin, CRP, Echo: small coronary artery Aneurysm,	Antibiotics, Ventilation and respiratory support, remdesivir, Levetiracetam, phenobarbitone, Dexamethasone, methylprednisolone, immunoglobulin, enoxaparin,	Discharged
Pawar <i>et al.</i> , (11), India, July 2 2021, Case Series	20(10/10), 1 to day 5, 27-38 weeks	+ve IgG =4 +ve RT PCR=2	Cardiac, Hematologic, Respiratory, Gastrointestinal, Neurological, Cutaneous, Renal complications, Fever/temperature instability	+ve IgG =17 +ve IgM=0 Thrombocytopenia, leucocytosis, Elevated CRP, PCT, Ferritin, D Dimer, LDH, BUN, Creatinine, NT Pro BNP, IL-6 Echo: Arrhythmia, Dilated coronaries, Intracardiac thrombus, Shock/ cardiac dysfunction	Supportive therapy, mechanical ventilation, IVIG, LMWH, Inotropes, Steroids	2/18

Authors' name, country, publication date, study design	n (male/female, age at Presentation (day), preterm/term	Maternal COVID- 19 RT PCR & antibody statuses	Clinical presentations	Serology, laboratory & Echo findings	Treatment	Outcome; Deat/ Discharge
<b>Skafi et al., (25), Lebanon 2021.06.06, Case Report</b>	1 (female), 21 days, term	-ve RT-PCR	Tonic, mildly hypoactive, dehydration, vomiting, fever, jaundice, tachycardia, oliguria, abdominal tenderness, shock, ileal necrosis and ischemia, generalized edema, maculopapular rash, gastrointestinal complications, cardiopulmonary arrest	+ve IgM -ve RT-PCR elevated CRP, BUN , creatinine, troponin, ferritin  Normal Echo	Hydration, inotropes, packed red blood cells, fresh frozen plasma & platelets transfusion, antibiotic, furosemide, steroids	Death
<b>Schoenmakers et al., (16) The Netherlands, 2021 May, Case Report</b>	1 (female), at birth, Pre term (31 <sup>+</sup> 4 weeks)	+ve RT-PCR +ve IgG	Mucocutaneous signs, rash, hepatosplenomegaly, respiratory distress syndrome, bilateral intraventricular hemorrhage	-ve IgG -ve IgM -ve RT-PCR Thrombopenia, leucopenia, elevated creatinine, ferritin, D-dimers, cardiac enzymes Echo: persistent pulmonary hypertension of the neonate, flattened interventricular septum, tricuspid regurgitation, patent ductus arteriosus , right-to-left shunt, enlarged left main coronary artery (LMCA)	Mechanically ventilation, surfactant, antibiotics, nitric oxide (iNO), inotropic agents, hydrocortisone	Discharged
<b>Shaiba et al., (8), Saudi Arabia., 2021 May 13; Case Report</b>	1 (female), 15min old, Pre term (36 weeks)	+ve RT-PCR	Mild cyanosis, progressive respiratory distress, myocarditis, pulmonary hypertension	+ve IgG -ve RT-PCR  Lymphopenia, Thrombocytopenia, anemia, prolonged INR, elevated procalcitonin, CRP, liver & Cardiac enzymes, metabolic acidosis, Echo: duct-dependent cardiac lesion, dilated left ventricle, poor systolic function, widely patent ductus arteriosus, bidirectional shunt	Continuous positive airway pressure, mechanical ventilation, prostaglandin E1, dobutamine, NitricOxide, Antibiotics, fresh frozen plasma, IVIG, hydrocortisone	Discharged
	1 (female), at birth, Pre term (32 <sup>weeks</sup> )	+ve RT-PCR	Grunting, respiratory Distress,	-ve IgG -ve IgM +ve RT-PCR Leukocytopenia, lymphocytopenia, elevated ferritin, troponin, procalcitonin, liver enzymes, D-dimer  Normal Echo	Nasal CPAP, NIMV, Antibiotics, IVIG, hydrocortisone	Discharged
<b>McCarty et al., (7), USA, 2021 April 1; Case Report</b>	1 (male), 4-hour-old, Pre term (34 <sup>+67</sup> )	+ve RT PCR	Fever, hypotonic , poor respiratory effort	-ve RT PCR  Elevated CRP, Leukocytosis, metabolic acidosis, positive herpes simplex Virus, elevated interleukin 6, TNF Echo: severe pulmonary hypertension, +ve IgG -ve RT-PCR	Positive pressure ventilation, intubation and mechanical ventilation, ampicillin, cefepime, nitric oxide, surfactant, Acyclovir	Discharged
<b>Kappanayil et al., (21), India, 2021 April 1, Case Report</b>	1 (female) 24-day-old, term	+ve RT-PCR +ve IgG	Tachypnoea, Drowsy, hypotension, Erythema, tachypnoea, chest retractions, cool peripheries, delayed capillary refill, Hepatomegaly, cardiomegaly, heart failure, systemic hypoperfusion cardiogenic shock Echo: biventricular dysfunction	Metabolic acidosis, leucocytosis, elevated CRP, BUN, creatinine , ferritin, D-dimer , cardiac enzymes N-terminal-pro-B-type natriuretic peptide, troponin T	Supportive care, mechanical ventilation, inotropic support, milrinone , diuretic antibiotics, IVIG, methylprednisolone , heparin, Calcium, vitamin C, vitamin D, fluid and electrolyte management	Discharged
<b>Borkotoky et al., (14), United Kingdom ,2021 April 1, Case Report</b>	1 (male), 4-hour-old, term	-ve RT PCR +ve IgG	Respiratory distress, cyanosis, feed intolerance, large aspirates prefeed, increasing abdominal girth and vomiting; vasculitic rash, Persistent Pulmonary Hypertension, early necrotizing enterocolitis	+ve IgG -ve IgM -ve RT-PCR  Bilateral ground glass opacities considered, Echo: consistent with moderate PPHN	Mechanical ventilation with 100% oxygen, Sildenafil, Dexamethasone, Dopamine, Furosemide, Tazobactam/Piperacillin, intravenous fluids, Meropenem	Discharged
<b>Charlesworth et al., (12) 2021, United Kingdom, Case Report</b>	1 (female), 14 days, term	+ve IgG -ve RT PCR	Fever, jittery movements	+ve IgG -ve RT PCR  Normal full blood count, CSF WBC= 347/mL with 65% neutrophils, RBC 105/mL,	Antibiotic	Discharged

Authors' name, country, publication date, study design	n (male/female, age at Presentation (day), preterm/term)	Maternal COVID-19 RT PCR & antibody statuses	Clinical presentations	Serology, laboratory & Echo findings	Treatment	Outcome; Deat/ Discharge
Magboul <i>et al.</i> , (26), Qatar, August 24, 2020, Case Report	1 (female), 14days, term	-ve RT PCR	Fever, tachycardia, bilateral pneumonitis, hepatosplenomegaly	positive leukocyte, nitrite, glucose, E. coli and Enterococcus in urine  +ve RT PCR  Lymphocytic leukocytosis, normocytic normochromic anemia, thrombocytopenia, Elevated CRP, hypoalbuminemia, hyponatremia, AST, , LDH, ALT, ferritin, Troponin, Natriuretic peptide test  normal coronary arteries and contractility	Antibiotics, IVIG infusion, Aspirin, Dexamethasone, Methylprednisolone, immunomodulatory therapy (Anakinra)	Discharged

\* Negative

\*\* Positive

## Etiology

The cause of MIS-N is the transmission or production of SARS-CoV2 antibodies in response to SARS-CoV2 infection. MIS-N may present following Early or Late-onset infections (13);

- Early-onset infection: SARS-CoV2 antibodies can vertically transmit from the infected mother to the neonate, or the antibodies could be potentially produced by the neonate in response to maternal viral infection. It has been shown seropositive neonates who were born to mothers with negative or positive COVID-19 tests (14). Morek *et al.* indicated more neonates with positive IgG antibodies compared to their mothers (19 vs. 9 neonates) (13). Charlesworth *et al.* demonstrated an active uteroplacental transport of IgG from an asymptomatic COVID-19 infected mother to her neonates (3.5-fold; 1.84 vs. 0.53 AU/mL) (12). The other study demonstrated that of 83 seropositive mothers associated with SARS-CoV-2, IgG antibody was detected in 72 neonates (15). Postnatal SARS-CoV-2 transmission may also occur through intrapartum exposure to the maternal birth canal and respiratory secretions or body fluids (13). An investigation showed positive SARS-CoV-2 RT-PCR tests in different collected samples of a mother (during delivery), including the oropharynx, blood, vagina, urine, maternal and fetal sides of the placenta; however, the results related to collecting samples of her symptomatic neonate were negative (16).
- Late-onset SARS-CoV-2 infection: The late-onset neonatal COVID-19 defines as a diagnosis of illness beyond 5-7 days after birth. Close contacts with mothers and health staff were responsible for 26% and 52% of late-onset SARS-CoV-2 infections in newborns, respectively (3). Moreover, there are conflicting results regarding the possible transmission of SARS-CoV-2 through breastfeeding. A systematic review study reported a positive SARS-CoV-2 RNA in the breast milk of 9 infected breastfeeding mothers (17). The other study indicated negative SARS-CoV-2 and IgG,

but positive IgM tests in the breast milk samples of 8 confirmed COVID-19 mothers (18). A narrative review study also presented that of 13 included studies, one article demonstrated RNA of virus, and the other detected IgG antibody in the breast milk samples (19).

Maternal or neonatal SARS CoV-2 infection results in the secretion of the IgG antibodies against virus protein. An excessive level of IgG antibodies was detected in MIS-N cases as a genetically susceptible group. IgG antibodies in these cases can bind to macrophages and neutrophil receptors, causing hypersecretion of pro-inflammatory agents and Multi Inflammatory syndrome in neonates (11).

## MIS-N Signs and Symptoms

It has been reported that COVID-19 infected neonates present mild symptoms with a fast recovery because of passive transfer of antibodies, fetal hemoglobin properties, immature immune system, and low expression of Angiotensin-Converting Enzyme-2 (3). While, a few studies indicated devastating complications following COVID-19 infection among neonates (3, 13). By evolving new mutant strains (like  $\beta$  and  $\delta$ ), newborns are now presenting more severe symptoms (20). Recent studies reported MIS-N as a severe complication with various organ involvement. The clinical manifestations of MIS-N may mimic sepsis, prematurity, toxic shock syndrome, RDS, Kawasaki disease, necrotizing enterocolitis (NEC), myocarditis, meningitis/encephalitis, aortic thrombosis, ETC (Table 1). Persistent pulmonary hypertension and bilateral ground-glass opacities were reported in a neonate with MIS diagnosis by Sankaran *et al.* (3). Skafi *et al.* reported a poor outcome case with severe hemodynamic instability and gastrointestinal problems due to cardiogenic shock, coagulopathy, and necrosis of the ileum (25). Pawar also reported cardiovascular disorders including shock, ventricular dysfunction, prolonged QTc, Atrioventricular thrombosis, hypotension, elevated cardiac enzymes, and coronary artery abnormalities to be the most frequent (90%) presentation among 20 subjects with MIS-N (11). Thakur *et al.* reported an MIS neonate

with dilated bowel loops, bowel wall edema, and NEC diagnosis (20). The MIS-N cases with meningitis/encephalitis-similar manifestations (fever, cough, convulsion, and jittery movements) were also presented by 2 case-report studies (12, 22). Neonatal multi-organ failures with severe myocardial problems, skin lesions, and erythema accompanied by hyperinflammatory responses were reported in a case by Kappanayil (21). A COVID-19 infected neonate was reported as an MIS case with lower limb gangrene due to spontaneous aortic thrombosis (23).

## Diagnosis

Diagnosis of MIS-N is challenging because of diverse signs and symptoms. In addition, as very limited evidence is existent, the diagnosis is still controversial and may be postponed in the MIS-N cases. Biochemical parameters were also confusing in the disease with multi-organ involvement and inflammatory responses that may cause misdiagnosis.

The results of included studies have delineated that besides the clinical presentations, detection of reactive anti-SARS-CoV-2 IgG antibodies could be a notable clue in MIS-N diagnosis (16, 21). Of 14 included studies, 10 case-report studies have shown high IgG titers in their cases (8, 12-14, 20-23). Pawar *et al.* have also indicated a positive IgG test (cut-off-index  $\geq 1$ ) in 17 out of 20 MIS-N cases (11). On the other hand, several studies have shown that this diagnostic criterion was not observed in their reported cases (24).

As data are shown in [Table 1](#), a history of perinatal COVID-19 infection/exposure or detection of maternal, placental, amniotic fluid, and neonatal positive SARS-CoV-2 RT-PCR tests could be also beneficial for MIS-N diagnosis (21).

Abnormal clinical biomarkers including sepsis-like and inflammatory markers (lymphocytic leukocytosis, metabolic acidosis, elevated C-reactive protein: CRP, ESR, Ferritin, D-dimers, Procalcitonin, thrombocytopenia subsequent to thrombocytosis, neutropenia, neutrophilia, anemia, elevated interleukin-6, and interferon type 1) with negative blood, urine and CSF cultures, or markers showing coagulopathy (elevated prothrombin, activated partial thromboplastin time, international normalized ratio), pulmonary complications (low oxygen saturation: SpO<sub>2</sub>, and acidosis), liver dysfunction (elevated transaminases, aspartate aminotransferase: AST and alanine aminotransferase), cardiac dysfunction (Troponin T, aminotransferase, CKMB, CPK, lactate dehydrogenase, N-terminal pro-brain natriuretic peptide: ProBNP), renal failure (hypoalbuminemia, hyponatremia, severe anemia, increased blood urea concentration, hyper creatinine with abnormal urine analysis by elevated WBC and protein in urine) and abnormal stool exam (occult blood) were the other significant findings that have been shown by the included studies ([Table 1](#)).

Echocardiogram findings in the reported cases were prolonged QTc, dilated coronary arteries with prominent

and hyperechoic appearance due to viral myocarditis, left ventricle dilatation, global hypokinesia, aneurysm, and severe myocardial dysfunction (11, 16, 21, 24). Ground glass opacities have also been observed in a neonate reported by (14). Almost all included studies have demonstrated that the diagnosis of MIS-N could be confirmed with clinical improvement to treatment with steroids and immunoglobulin (11, 24).

## Treatment and Outcome

The results of included studies have shown that of the total of 53 reported subjects in the present study, 4 neonates had poor prognoses and died. The other subjects were successfully managed, and the neonates completely recovered. All included case-report studies have demonstrated that besides supportive therapy (hydration, electrolyte balance, inotropic support, oxygen therapy, and mechanical ventilation), suppressing the autoimmune and inflammatory responses by immunoglobulin-IVIG and steroids (methylprednisolone, prednisolone, or dexamethasone), anti-platelet agents (aspirin), and anticoagulants (heparin, Enoxaparin, recombinant tissue plasminogen activator) were effective in the alleviation of MIS-N symptoms. Along with these medications, Remdesivir was given to a SARS-CoV-2-positive neonate with neurological manifestations and possible MIS-N (24). Symptomatic treatments like administration of antibiotic regimen, Sildenafil, Furosemide, packed red blood cells, and fresh frozen plasma were reported by the studies (14, 20, 25). A study by Magboul *et al.* has also indicated the effectiveness of Anakinraas, the second agent and interleukin-1 inhibitor besides IVIG and steroid for a neonate with hyper-inflammatory syndrome (26) ([Table 1](#)).

So far, clinical guidelines have been implemented based on the decisions of experts and multidisciplinary teams. In contrast, it seems that the management of MIS-N needs a large number of clinical trials, including neonates and pregnant women, to assess the benefits and risks of treatment modalities. In addition, vaccination of pregnant women would be another effective effort to prevent such an adverse outcome in neonates with the transmission of antibodies from their infected mothers.

## Conclusion

The present study aimed to highlight the possibility of MIS-N as an infrequent but severe syndrome consequent of perinatal COVID-19 infection. The diagnosis is still controversial, but clinical suspicion and awareness regarding this immunological disease is of importance for early diagnosis. Varied and severe neonatal presentations along with detection of maternal or neonatal reactive anti-SARS-CoV-2 IgG antibodies, could be substantial clues in MIS-N diagnosis. A positive perinatal COVID-19 infection or exposure history can also help with the diagnosis. Besides supportive therapy and symptomatic treatments associated with affected organs, immunoglobulin-IVIG,

steroids, anti-platelet agents, and anticoagulants were reported as effective therapies. On the other hand, the management of MIS-N needs a large number of clinical trials, including the neonates, to assess appropriate treatment modalities with benefits and risks.

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### Conflict of Interest

The authors declared no conflict of interest.

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