

Multisystemic Inflammatory Syndrome in Neonates: A Systematic Review

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Keywords

Neonate · Multisystem inflammatory · Severe acute respiratory syndrome coronavirus-2 · COVID-19 · Multisystem inflammatory syndrome

Abstract

Introduction: Multisystem inflammatory syndrome in neonates (MIS-N) related to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has increasingly been reported worldwide amid the spread of the SARS-CoV-2 pandemic.

Methods: We searched PubMed, EMBASE, and CINAHL and preprint servers (BioRxiv.org and MedRxiv.org) using a specified strategy integrating Medical Subject Headings terms and keywords until October 20, 2021. Our aim was to systematically review demographic profiles, clinical features, laboratory parameters, complications, treatments, and outcomes of neonates with MIS-N. Studies were selected when fulfilling the inclusion criteria. Articles were included if they fulfilled the World Health Organization (WHO), Centers for Disease Control (CDC) definitions of MIS-C, or our proposed def-

inition. **Results:** Sixteen reports of MIS-N including 47 neonates meeting MIS-N criteria were identified. Presentation included cardiovascular compromise (77%), respiratory involvement (55%), and fever in (36%). Eighty-three percent of patients received steroids, and 76% received immunoglobulin. Respiratory support was provided to 60% of patients and inotropes to 45% of patients. Five (11%) neonates died. **Conclusion:** The common presentation of MIS-N included cardiorespiratory compromise with the possibility of high mortality. Neonates with MIS-N related to SARS-CoV-2 may be at higher risk of adverse outcomes.

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Introduction

As the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic continues worldwide, increasing cases of severe disease are being reported, including multisystem inflammatory syndrome in children (MIS-C) [1]. Similar to macrophage activating syndrome

(MAS) and other inflammatory diseases in children, the presentation of MIS-C with SARS-CoV-2 infection is usually severe with a good prognosis [2]. Interestingly, MIS-C is reported more frequently in children of older age [3]. To date, there are more than 6,000 reported cases of MIS-C [1].

Recently, there have been reports of multisystem involvement following SARS-CoV-2 infection in neonates; however, the extent of involvement, assessment, and their management has varied. Of note, multisystem inflammatory syndrome in neonates (MIS-N) takes various forms with multiple cardiac presentations and complications, and the reported therapies include various immunological treatments [4–6]. MIS-N is postulated to develop because of immune-mediated multisystem injury either due to the transplacental transfer of maternal SARS-CoV-2 antibodies or due to late response to antibodies mounted by the newborn to SARS-CoV-2 infection [4, 5, 7, 8]. The SARS-CoV-2 virus was reported as one of the rare causes of foetal inflammatory response syndrome [4] and may also be associated with MIS-N, similar to a case reported in the paediatric population [9]. As these reports are surfacing, our objective was to conduct a systematic review and summarize the clinical and demographic profiles, management employed, and outcomes following MIS-N after SARS-CoV-2 exposure/infection.

Methods

Research Question

What are the demographic profile, clinical characteristics, management strategies, prognosis, and outcomes of MIS-N associated with SARS-CoV-2 infection?

Protocol and Registration

This systematic review was constructed in accordance with the framework of the PRISMA (see the PRISMA checklist in online suppl. material; see www.karger.com/doi/10.1159/000524202 for all online suppl. material). In addition, the protocol was registered under the International Prospective Register of Systematic Reviews (registration number CRD42021266065).

Data Sources and Searches

We searched MEDLINE, WHO COVID-19 database, LitCovid, Google Scholar, Science Direct, Web of Sciences, and preprints from medRxiv and bioRxiv using the search terms “COVID 19,” “SARS CoV2,” “Multisystem inflammatory syndrome in neonates,” “MIS-N,” “Fetal/Foetal multi-system inflammatory syndrome temporally associated with SARS-CoV-2,” and Project Management Information Systems Overviews – Transformation system “PMIS-TS” for all articles published up to October 20, 2021. Two independent reviewers performed the search using appropriately chosen relevant Medical Subject Headings terms and key-

words. A complete list of search terms is provided (online suppl. Table S1). A shadow search of the reference lists was performed manually by independent reviewers to avoid missing key articles and considering the ongoing pandemic. The search was restricted to articles in the English language.

Study Selection Based on Inclusion and Exclusion Criteria

The identified articles were reviewed critically based on title, date, place, authors, and type of study by two independent reviewers, L.S. and M, and differences were resolved by discussion with K.M. and P.S.S. All the included abstracts were screened and stratified based on their type and design. The following inclusion criteria were considered for quantitative data analysis: (1) case report or case series regardless of the sample size, (2) cohort studies and (3) retrospective observational studies, and (4) research letter or correspondence articles having detailed data on patient characteristics. We excluded narrative reviews, viewpoints, perspectives, correspondence articles lacking patient data, and articles focussing only on pathogenesis. Duplicate reports not providing additional information were excluded. The two reviewers independently analysed the included publications by full-text reading and screening (see online suppl. material). In cases of discrepancy, a unanimous decision was attained through Web-based conference discussions with all authors.

MIS-N Diagnosis

There is a clear definition of MIS-C in children as described by the World Health Organization (WHO) and Centers for Disease Control (CDC). In general, the MIS-C definition includes fever with multi-organ involvement (2 or more organs) and evidence of SARS-CoV-2 infection. The major difference between the CDC and WHO definitions is the duration of fever. Currently, there is no agreed definition of MIS-N for which we adapted criteria for diagnosis in this special group. We categorized neonates as having confirmed MIS-N when they fulfilled either the CDC or WHO criteria for MIS-C and had a confirmed infection or exposure to SARS-CoV-2 infection before 28 days of age after excluding other causes (Table 1) [12, 13]. The fulfilment of one of the criteria was sufficient to confirm the diagnosis of MIS-N. Neonates with confirmed infection or exposure to SARS-CoV-2 infection before 28 days of age and who presented without fever and had three-organ involvement were categorized as suspected MIS-N after excluding other possible causes, such as sepsis, birth asphyxia, and others.

We further categorized neonates into early and late presentation as follows:

1. *Early MIS-N* – hypothesized as presenting due to the transplacental transfer of maternal SARS-CoV-2 antibodies when a neonate is born to a mother who is SARS-CoV-2 positive, and the neonate is demonstrating clinical/laboratory features within 72 h after birth.
2. *Late MIS-N* – hypothesized as occurring due to antibodies produced secondarily to SARS-CoV-2 infection in the newborn when the neonate presents with clinical and laboratory features beyond the first 72 h of age [14].

Data Extraction and Quality Assessment

Data extraction was performed by two reviewers, independently, from the studies included. The extracted data were segregated into demographic parameters, which included the num-

Table 1. Diagnostic criteria for MIS-C as per the WHO and CDC [10, 11]

CDC case definition [10]	WHO case definition [11]
All 4 criteria must be met	All 6 criteria must be met
1. Age <21 years	1. Age 0–19 years
2. Clinical presentation consistent with MIS-C, including all of the following <ul style="list-style-type: none"> a – Fever: documented fever >38.0°C (100.4°F) for ≥24 h or report of subjective fever lasting ≥24 h b – Multisystem involvement: 2 or more organ systems involved <ul style="list-style-type: none"> Cardiovascular (e.g., shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia) Respiratory (e.g., pneumonia, ARDS, pulmonary embolism) Renal (e.g., AKI, kidney failure) Neurologic (e.g., seizure, stroke, aseptic meningitis) Haematologic (e.g., coagulopathy) Gastrointestinal (e.g., abdominal pain, vomiting, diarrhoea, elevated liver enzymes, ileus, gastrointestinal bleeding) Dermatologic (e.g., erythroderma, mucositis, other rash) c – Laboratory evidence of inflammation including, but not limited to, any of the following <ul style="list-style-type: none"> Elevated CRP Elevated ESR Elevated fibrinogen Elevated PCT Elevated D-dimer Elevated ferritin Elevated LDH Elevated IL-6 level Neutrophilia Lymphocytopenia Hypoalbuminemia d – Severe illness requiring hospitalization 	2. Fever for ≥3 days <ul style="list-style-type: none"> 3. Clinical signs of multisystem involvement (at least 2 of the following) <ul style="list-style-type: none"> Rash, bilateral non-purulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet) Hypotension or shock Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP) Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer) Acute gastrointestinal symptoms (diarrhoea, vomiting, or abdominal pain) 4. Elevated markers of inflammation (e.g., ESR, CRP, or PCT)
3. No alternative plausible diagnoses	5. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes
4. Recent or current SARS-CoV-2 infection or exposure <ul style="list-style-type: none"> Any of the following <ul style="list-style-type: none"> Positive SARS-CoV-2 RT-PCR Positive serology Positive antigen test COVID-19 exposure within the 4 weeks prior to the onset of symptoms 	6. Evidence of SARS-CoV-2 infection <ul style="list-style-type: none"> Any of the following <ul style="list-style-type: none"> Positive SARS-CoV-2 RT-PCR Positive serology Positive antigen test Contact with an individual with COVID-19
HAN, Health Alert Network; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase.	

ber of cases in each study, sex, and age; clinical parameters comprising gastrointestinal symptoms, neurological symptoms, pericardial disease, myocarditis, and left ventricular dysfunction. Also included are laboratory investigations comprising the requirement of vasopressor support or invasive ventilatory support and the incidence of coronary artery abnormalities and mortality. We also included management strategies, which included the use of intravenous immunoglobulin, corticosteroids,

and the need for second-line immunomodulators and COVID-19 status on RT-PCR testing as well as serological evidence (IgG, IgM, and IgA).

Risk of Bias

Two reviewers assessed the risk of bias of each study by using the National Institute of Health quality assessment tool or the Joanna Briggs Institute's tool [15] for case series and observational

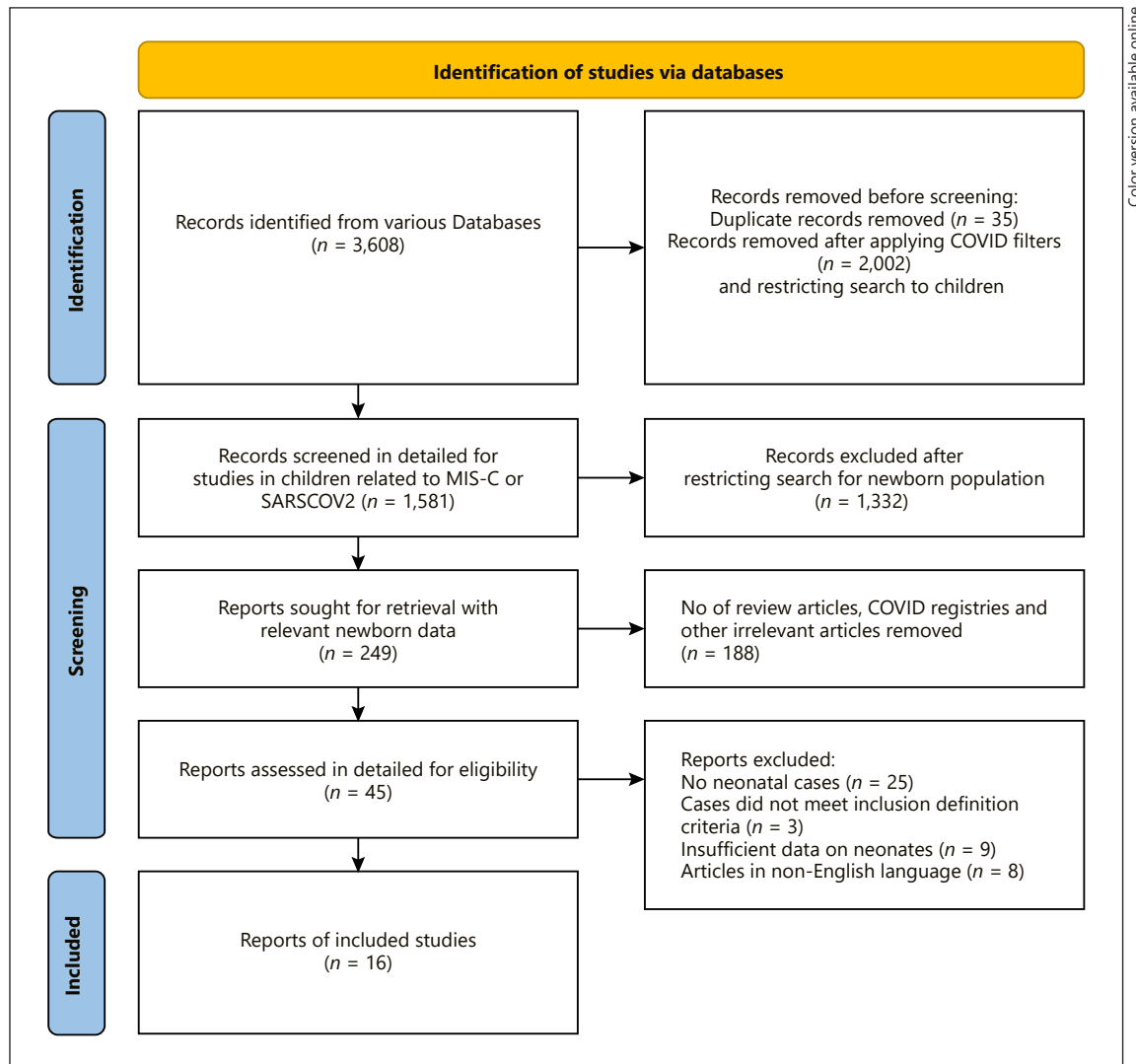


Fig. 1. PRISMA flow diagram for study selection.

cohort studies. Each study was evaluated for risk of bias in methodology, including patient selection, attrition, detection, confounding factors, and causality association. A third independent reviewer, K.M., sorted any discrepancies via group discussion between reviewers, which was further confirmed by an independent reviewer, P.S.S. The studies were assigned low risk of bias or high risk of bias. The studies with low risk of bias were then assigned “included,” and the studies with high risk of bias were then assigned “excluded” status based on the responses.

Data Synthesis and Statistics

The extracted data were tabulated in a predefined manner. Data were summarized from all included studies in a table format to provide the complete context of the available evidence. No statistical analysis was planned as we expected case reports or case series based on the low prevalence of the condition.

Results

A total of 3,608 studies were retrieved from various databases with a broad search for “COVID 19,” “SARS CoV2,” and “Multisystem inflammatory syndrome”; however, only 1,581 were screened in detail after applying COVID-19 filters, removing duplicates and restricting the search to the child population. The details of the search terms and the results of the search strategies are contained in online supplementary Table 1. The PRISMA flow diagram for study selection is depicted in Figure 1. A total of 16 studies reporting on 47 neonates were included in the systematic review. The risk of bias among the included studies revealed that most reports met the

Joanna Briggs Institute criteria for the reporting of key characteristics; however, we could not exclude the possibility of publication bias (Table 2). The majority of all included studies' answers were reported as "yes," as shown in Table 2. These studies were from India (7), the USA (2), Saudi Arabia (2), Qatar (1), Israel (1), Iran (1), Netherlands (1), and Brazil (1). Fourteen studies were case reports, and two were case series. According to the CDC and WHO criteria for the diagnosis of MIS-C, 15 neonates had confirmed MIS-N, and 32 neonates had suspected MIS-N (Table 3) [6].

Clinical manifestation, laboratory evidence of inflammation, radiological investigation, and the associated diagnoses of 47 neonates are shown in Tables 3 and 4. At the time of MIS-N diagnosis, 34 neonates were ≤ 7 days of age, and 13 were > 7 days of age. Early neonatal MIS was identified in 28 neonates, while late MIS-N was identified in 19 neonates. Twenty-two neonates were born via vaginal route, 21 were born via caesarean section, and the mode of birth data were unavailable for 4 patients. Eighteen patients were delivered at full term, 27 were preterm, and data on gestation at birth were not available for 2 patients. Two neonates were reported to have a concomitant bacterial infection.

The clinical presentation of included neonates is summarized in Table 5. The most common presenting features were cardiovascular manifestations (77%). This included cardiac dysfunction in 14 neonates, arrhythmia in 11 neonates, dilated coronaries/aneurysm in five neonates, pericardial effusion in four neonates, and persistent pulmonary hypertension of the newborn in three as well as intracardiac thrombus in two neonates. Fever was present in 17 patients (36%).

Laboratory testing (Table 4) revealed that troponin was high in all neonates who were tested (8/8 neonates), 38/45 (84%) had elevated D-dimer, 4/6 neonates (67%) had an elevated erythrocyte sedimentation rate, 30/46 had elevated C-reactive protein (CRP) (65%), 5/8 (63%) had anaemia, 24/40 (60%) had high NT-beta-natriuretic peptide, 20/42 (48%) had high ferritin, 18/38 (47%) had high lactate dehydrogenase, 6/20 (30%) had lymphopenia, 11/38 (29%) had high procalcitonin (PCT), 13/46 (28%) had thrombocytopenia, and 9/43 (21%) had neutrophilia.

Eighteen neonates had a chest X-ray reported, of which 11 had opacities, four had cardiomegaly, three had pulmonary oedema, and three were normal (some had multiple abnormalities). A computed tomography scan of the chest was conducted in 4 cases and identified ground-glass opacities in 3 patients and atelectasis in 1 patient. Forty-six patients had echocardiograms (Table 4).

Table 2. Assessment of quality of studies [4, 5, 14, 16–28]

Author [ref]	Were patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or assessment methods and the results clearly described?	Were the interventions or treatment procedure clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?	Risk of bias
More et al. [14]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Pawar et al. [16]	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Low
Shaiba et al. [17]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Borkotoky et al. [5]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Diggikar et al. [18]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Divekar et al. [19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Diwakar et al. [20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Eghballian et al. [21]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Low
Kappanavi et al. [22]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Lima et al. [23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Magboul et al. [24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
McCarty et al. [4]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Orlanski-Meyer et al. [25]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Saha et al. [26]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Schoen-makers et al. [27]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Shaiba et al. [28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low

Table 3. Demographic, clinical presentation, length of the hospital stay, and outcome of neonates with MIS-N [4, 5, 14, 16–28]

Author/(ref) country/N	Type of study	Sex	Age presented	Mode of birth	Gestational age	Clinical manifestation	ICU length of stay	Outcome	Diagnosis
More et al. [14] (India) N = 12	Case series	F:M = 8:4	1–7 days: 6/12 7–28 days: 6/12	V/CS: 5/7	Term = 9 Late preterm (32–37 wk) = 3	Fever 6/12, respiratory–6/12, CVS 6/20, GI manifestations–8/12, haematological 3/12, neurological 1/12	5 days to 11 week	Death-2 Survived-10	Confirmed MIS-N in 7 Suspected MIS-N in 5
Pawar et al. [16] (India) N = 20	Case series	F:M = 10:10	1–5 days	V/CS: 13/7	Term = 3, late preterm (34–37 wk) = 13, less than 33 wk = 4	Fever 2/20, respiratory 11/20, CVS 18/20, GIT 6/20, renal 1/20, haematological 2/20, neurological 2/20, cutaneous 1/20	7–36 days	Death-2 Survived-18	Confirmed MIS-N in 2 (duration of fever is not mentioned, appearance on day 1 of life) Suspected MIS-N in 18
Shaiba et al. [17] (KSA) N = 1	Case series	F	30 days	NA	NA	Fever, respiratory, CVS, GIT, renal, haematological	15 days	Death	Confirmed MIS-N
Borkotoky et al. [5] (India) N = 1	Case report	M	4 h	CS	38 3/7	Fever, respiratory, CVS, GIT, haematological, cutaneous	34 days	Survived	Confirmed MIS-N
Diggikar et al. [18] (India) N = 1	Case report	NA	7 days	NA	Term	Fever, CVS, neurological	NA	Survived	Confirmed MIS-N
Divekar et al. [19] (USA) N = 1	Case report	F	1 day	CS	30 wk	Respiratory, CVS, liver, renal, haematological	2 months (mostly due to prematurity)	Survived	Suspected MIS-N
Diwakar et al. [20] (India) N = 1	Case report	M	19 days	CS	39 wk	Fever, GIT, haematological, cutaneous	6 days	Survived	Confirmed MIS-N
Eghbalian et al. [21] (Iran) N = 1	Case report	M	9 days	CS	39 wk	Fever, respiratory, GIT: Yes, haematological	4 days	Survived	Suspected MIS-N (did not specify the duration of fever)
Kappanavil et al. [22] (India) N = 1	Case report	F	24 days	V	Term	Respiratory, CVS Liver, renal, cutaneous	20 days	Survived	Suspected MIS-N
Lima et al. [23] (Brazil) N = 1	Case report	F	1 day	CS	33 wk	Respiratory, CVS, liver	22 days	Survived	Suspected MIS-N
Magboul et al. [24] (Qatar) N = 1	Case report	F	14 days	V	36+6 wk	Fever, liver, haematological	14 days	Survived	Suspected MIS-N (duration fever 11 h)
McCarty et al. [4] USA N = 1	Case report	M	1 day	V	34+6 wk	Fever, respiratory CVS, haematological	22 days	Survived	Suspected MIS-N (the neonate became febrile at 12 h of age, and duration is not mentioned)
Orlanski-Meyer et al. [25] (Israel) N = 1	Case report	F	8 wk	NA	NA	Fever, CVS, GIT, liver, haematological	NA	Survived	Confirmed MIS-N

Table 3 (continued)

Author/[ref] country/N	Type of study	Sex	Age presented	Mode of birth	Gestational age	Clinical manifestation	ICU length of stay	Outcome	Diagnosis
Saha et al. [26] (India) N = 1	Case report	F	25 days	NA	Term	Fever, respiratory CVS, GIT, liver, renal, haematological, neurological, cutaneous	25 days	Survived	Confirmed MIS-N
Schoenmakers et al. [27] (Netherlands) N = 1	Case report	F	1 day	CS	31+4 wk GA	Respiratory, CVS, liver, renal, haematological	NA	Survived	Suspected MIS-N (absence of fever)
Shaiba et al. [28] (Saudi Arabia) N = 2	Case report	F	1 day	V/CS: 1/1	36 wk, 32 wk	Respiratory yes in both, CVS yes both Liver yes in 1 case, haematological yes in both	Case 1: 12 days Case 2: 30 days	Both survived	Suspected MIS-N (both)

F, female; M, male; V, vaginal delivery; CS, caesarean section; CVS, cardiovascular system; GIT, gastrointestinal system; ICU, intensive care unit.

Maternal SARS-CoV-2 swab was positive for 13/23 (37%) mothers, and serology was positive in 20/23 (87%) mothers. Among neonates, 7/26 (27%) had a positive RT-PCR test for SARS-CoV-2, 19/26 had a negative RT-PCR (21 had no RT-PCR done), and 34/40 (85%) neonates had positive serology; 32 neonates had positive IgG and two had nonspecific positive serology; 7 neonates had no serology reported (Table 4).

Most neonates received immunoglobulins as part of treatment for suspected/confirmed MIS-N (36/47, 77%). The dose of immunoglobulin ranged between 1g/kg/dose for one or two doses or 1–2g/kg/dose once. Specific treatments targeted for anti-inflammatory/anti-infective agents and supportive managements are reported in Table 6. Most neonates received steroids (83%) as part of the management of MIS-N. Anakinra was only given in 4 patients. Respiratory support was needed in 60% of patients. Many neonates required inotropic support (45%), and 40% of neonates received heparin. A total of 42 infants (89%) survived till discharge, and five neonates died (5/47, 11%). Two neonates died due to multi-organ dysfunction, two neonates died due to shock with left ventricular dysfunction, and one neonate died due to necrotizing enterocolitis. The length of hospital stay ranged between 6 days to 11 weeks; however, many stayed in the hospital for their underlying reasons for admission, which mainly was preterm birth (Table 3).

Discussion

MIS-N is emerging as a new disease in the newborn population, similar to MIS-C in children, and this is the first systematic review summarizing the available literature on the clinical course and outcome of MIS-N. The perinatal vertical transmission of SARS-CoV-2 is fortunately infrequent, with a reported incidence varying from 1 to 10% in different registries [29, 30]. However, newborns may still present soon after birth due to immune-mediated systemic effect secondary to the transplacental transfer of maternal antibodies along with other chemical mediators, leading to MIS-N [10, 11, 31]. Some newborns acquiring the SARS-CoV-2 infection during the perinatal or postnatal period may remain asymptomatic for the infection yet can produce antibodies against SARS-CoV-2, which may manifest as MIS-N, similar to the process of MIS-C in children [8]. The latent period for antibody production may range from 2 to 4 weeks, and thus, it may be difficult to predict the onset of MIS-N. Understanding the immune mechanisms of MIS-N is critical for advising

Table 4. Serologies of mothers and their neonates presenting with MIS-N and laboratory/radiological investigation [4, 5, 14, 16–28]

Author [ref]	Maternal SARS-CoV-2 NPA RT-PCR	Maternal SARS-CoV-2 serology	Neonatal SARS-CoV-2 NPA RT-PCR	Neonatal SARS-CoV-2 serology	Laboratory evidence of inflammation	Radiological investigation	Echocardiogram
More et al. [14]	Positive in 5/12 History of COVID-19 positive in 9/12	IgG-positive in all	Negative in all	IgG-positive in all	↑CRP: 4/12 ↑PCT: 3/12 ↑D-dimer: 7/12 ↑Ferritin: 5/12 ↑LDH: 4/12 ↑NT-proBNP: 7/12	CXR: pneumonia like change 2/12, RDS 4/12	Cardiac dysfunction 6/12 Dilated coronaries 1/12
Pawar et al. [16]	NA	4 IgG positive 3 IgG below cut-off limit	NA	IgG positive: 17 IgG below cut-off limit: 2 IgG negative: 1	↑CRP: high 15/20 ↑PCT: 4/20 ↑D-dimer: 19/20 ↑Ferritin: 4/20 ↑LDH: 8/20 ↑NT-proBNP: high 9/20	CXR: cardiomegaly 1/20	Arrhythmia – 11 Dilated coronaries – 2 intracardiac thrombus – 2 shock/cardiac dysfunction – 5
Shaiba et al. [17]	NA	NA	Positive	NA	↑CRP ↑PCT ↑D-dimer ↑Ferritin ↑LDH ↑NT-proBNP ↑Troponin	CXR: bilateral opacities/ pulmonary oedema/ atelectasis	Small pericardial effusion, EF 80.5%
Borkotoky et al. [5]	Negative	IgG positive IgM negative	Negative	IgG positive IgM negative	↑CRP ↑PCT ↑D-dimer ↑Ferritin ↑LDH ↑NT-proBNP ↑Troponin	Chest CT: diffuse bilateral ground-glass opacities	Severe PHT
Diggikar et al. [18]	Positive	NA	Positive	Negative	↑CRP ↑D-dimer ↑Ferritin	CXR: normal	a small coronary artery aneurysm and good biventricular function
Divekar et al. [19]	Positive	NA	Negative	NA	↑D-dimer ↑NT-proBNP ↑Troponin	CXR: cardiomegaly/ pulmonary oedema	Small pericardial effusion
Diwakara et al. [20]	Positive	NA	Negative	NA	↑CRP ↑D-dimer	CXR NA	Normal
Eghballian et al. [21]	Negative	NA	Positive	NA	↑CRP ↑ESR	CT chest: bilateral peripheral ground-glass infiltration and opacity	NA
Kappanavil et al. [22]	Positive	Positive IgG	Negative	Positive IgG	↑CRP ↑D-dimer ↑Ferritin ↑LDH ↑NT-proBNP ↑Troponin	CXR: cardiomegaly	Severe biventricular dysfunction LVEF of 10% and global hypokinesia. Coronary arteries appeared prominent and hypercholeic

Table 4 (continued)

Author [ref]	Maternal SARS-CoV-2 NPA RT-PCR	Maternal SARS-CoV-2 serology	Neonatal SARS-CoV-2 NPA RT-PCR	Neonatal IgG positive IgM negative	Laboratory evidence of inflammation	Radiological investigation	Echocardiogram
Lima et al. [23]	Swab: NA	Positive	Positive	IgG positive IgM negative	↑D-dimer ↑Ferritin ↑LDH ↑Troponin	CXR: normal Chest CT: ground-glass opacities	Pericardial effusion
Magboul et al. [24]	Negative	NA	Positive	NA	↑CRP ↑ESR ↑PCT ↑D-dimer ↑Ferritin ↑NT-proBNP ↑Troponin	CXR: bilateral opacities	Normal
McCarty et al. [4]	Positive	NA	Negative	NA	↑CRP: high	CXR: bilateral granular opacities	Severe PHT
Orlanski-Meyer et al. [25]	NA	NA	NA	Positive	↑CRP ↑ESR ↑D-dimer ↑Ferritin	CXR NA	Mild-moderate mitral regurgitation
Saha et al. [26]	NA	NA	Positive	NA	↑CRP: high ↑D-dimer ↑Ferritin ↑NT-proBNP	CXR: pulmonary oedema/ cardiomegaly Chest CT: atelectasis of both lower lobes of lung	Systolic dysfunction (EF ~ 40%)/mild pericardial effusion
Schoenmakers et al. [27]	Positive	Positive	Negative	Negative	↑D-dimer ↑Ferritin	CXR: bilateral opacities	PPHN/significantly enlarged LMCA
Shaiba et al. [28]	Positive for both mothers	NA	Case 1: negative Case 2: positive	Case 1 positive Case 2 negative	↑CRP: 1/2 ↑ESR: 1/2 ↑PCT: 1/2 ↑D-dimer: 1/2 ↑Ferritin: 2/2 ↑LDH: 2/2 ↑NT-proBNP: 2/2 ↑Troponin: 2/2	CXR Case 1: normal Case 2: bilateral ground- glass appearance	Case 1: moderately dilated LV with poor systolic function myocarditis/PDA with a bidirectional shunt Case 2: normal

PPHN, pulmonary hypertension of the newborn; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; PHT, pulmonary hypertension; LMCA, left main coronary artery; LV, left ventricle.

Table 5. Summary of clinical presentation

Clinical manifestations	Numbers (N = 47), N (%)
Cardiovascular	36 (76.6)
Shock/cardiac dysfunction	14/36
Arrhythmia	11/36
Dilated coronaries/aneurysm	6/36
Tachycardia	4/36
PPHN	4/36
Pericardial effusion	3/36
Intracardiac thrombus	2/36
Mitral regurgitation	1/36
Respiratory	27 (55.3)
Respiratory distress	27/27
Pulmonary oedema	3/27
Respiratory failure	1/27
Gastrointestinal	20 (42.6)
Feeding intolerance	13/20
Loose stool/diarrhoea	4/20
Vomiting	2/20
Enterocolitis	2/20
GI bleeding	2/20
Fever	17 (36.2)
Haematological	17 (36.2)
Thrombocytopaenia	14/17
Leukopenia	6/17
Anaemia	5/17
Neutropenia	5/17
Lymphopenia	2/17
Hepatic	8 (17.0)
Liver dysfunction	5/8
Hepatomegaly	3/8
Renal	6 (12.8)
Acute kidney injury	6/6
Cutaneous	5 (10.6)
Rash	5/5
Neurological	5 (10.6)
Seizure	5/5
Decreased reflexes	1/5

PPHN, pulmonary hypertension of the newborn.

on management strategies and potential preventive measures [7, 8]. MIS-N is a multifactorial disease with an unknown pathophysiology. Three mechanisms have been postulated, as mentioned above: either secondary to in utero exposure to maternal antibodies or via transplacental infection acquired from maternal infection and the endogenous production of antibodies in the foetus/child or via a postinfectious immune response to SARS-CoV-2 infection in a neonate. These antibodies can initiate a cascade of inflammatory response and result in multi-organ involvement [8]. Most of the neonates (60%) included in this systematic review were categorized as early MIS-N, signifying possible in utero exposure to maternal anti-

Table 6. Summary of management of neonates with MIS-N

Management	N = 47, N (%)
Anti-inflammatory/anti-infective agents	
Steroid	39 (82.9)
Immunoglobulin	36 (76.6)
Antibiotics	25 (53.2)
Anakinra	4 (8.5)
Antiviral (remdesivir)	1 (2.1)
Supportive therapies	
Respiratory support	28 (59.6)
Inotrope	21 (44.7)
Heparin	19 (40.4)
iNO	3 (6.4)
Antihypertensive	2 (4.3)
Aspirin	2 (4.3)

iNO, inhaled nitric oxide.

bodies or via transplacental acquired immune response. The remainder of the neonates (40%) presented as late MIS-N and are possibly postinfectious immune response to SARS-CoV-2 infection in a neonate.

In this review, we summarized data from 16 studies reporting on 47 newborns, and most of these studies were from India. Of note, none of the included neonates had a pre-existing comorbidity other than preterm birth, which was present in more than half of the included cases. Interestingly, although fever is a major criterion for diagnosing MIS-C, it was only present in approximately one-third of the neonates. Most neonates had cardiovascular involvement, and most received steroids and immunoglobulin for management. The presence of cardiovascular manifestations in MIS-N is similar to features seen in typical Kawasaki disease or systemic haemophagocytic lymphohistiocytosis/MAS. Both these conditions occur as a result of delayed hyperimmune response, and it is thought that a similar situation occurs with exposure to SARS-CoV-2 infection. The majority of patients included in this review exhibited changes in inflammatory markers, such as elevated CRP, ferritin, and PCT, as well as lymphopenia, similar to children reported as having MIS-C [19, 20]. However, there were differences in the presentation features of MIS-N. The differences in MIS-C and MIS-N could be due to the differential activation of the immune system as it is developmentally immature in neonates. A systematic review on MIS-C reported that most children presented with fever [2] (compared to 36% of the neonates had fever in our review) or gastrointestinal symptoms (70%)

[32] (compared to 40% in neonates). However, cardiovascular manifestations were comparable (60–70% in MIS-C and 77% in MIS-N) [2, 32].

MIS-N seems to be more severe in presentation compared to MIS-C as the 11% mortality rate in our review far exceeds the 1.9% reported in MIS-C [3]. The mortality was high in neonates presenting with MIS-N and is reported at 11% among the cases included in this report, which is concerning for clinicians. A recent multicentre study from Latin America has reported high mortality in children with MIS, where the mortality rate was 2.1% of the whole cohort [33]. Of interest, in the same study, two out of 36 neonates died for reason other than MIS [33]. Since it is not clearly reported to be the cause of death, it is difficult for us to tease out the reasons as it could be secondary to issues related to preterm birth. Three of the babies who died in our review were born at preterm gestation, one each at 27, 32, and 36 weeks' gestation, and one was at full-term gestation. One of the neonates who died had no gestational age reported. Moreover, our review included only 47 neonates, whereas MIS-C is reported in over 6,000 cases [1]. There might be under-recognition of MIS-N, leading to less reported cases, and, thus, publication bias could not be ruled out.

The management employed by various clinicians when faced with suspected or confirmed MIS-N varied, especially due to this being uncharted territory for neonatologists. Many clinicians adopted treatments employed in children or adults, which also was in a phase of evolution during this pandemic. The most employed modes were to provide some form of anti-inflammatory/anti-infective therapies and supportive management, including respiratory support, cardiovascular support, and the prevention of thrombosis. Intravenous immunoglobulin and corticosteroids were the mainstays; however, the mechanism of action for these therapies in MIS-C is unknown [34]. Most of the included neonates recovered with evidence of reduced inflammatory markers and cardiovascular recovery within 48–72 h of the initiation of therapy. It will be difficult to determine whether this was secondary to therapies or the natural course of illness. Sixty per cent of neonates received some form of respiratory support compared to 24%, 33%, and 6% of children having received non-invasive ventilation, mechanical ventilation, and extracorporeal membrane oxygenation, respectively, in MIS-C [3]. Although more neonates presented with cardiac compromise, only 45% of them required inotropic support, and 6.4% required inhaled nitric oxide compared to 77% of children requiring inotropic support in MIS-C [32].

Currently, there is no evidence that maternal vaccination can be protective against developing MIS-N, as seen in protecting children against MIS-C [35], and it is not demonstrated that these transmitted vaccine-related antibodies can lead to the development of MIS-N. However, the presence of these transmitted antibodies and its effect on neonates in the evolution of MIS-N is unknown. Thus, in such situations, the typing of antibodies to differentiate anti-spike versus anti-nucleoprotein antibodies may be helpful to differentiate the two.

Our systematic review has strengths. We conducted a comprehensive search, meticulously collected data from the included studies, and assessed the studies for risk of bias. However, we must acknowledge its limitations. Most reports are case reports and thus the possibility of publication bias cannot be ruled out. Moreover, the reported laboratory investigations and management principles are not evidence informed and may reflect local/clinicians' practices and may or may not help in the development of clinical practice guidelines. One of the limitations of the review is that there is no consistent report of SARS-CoV-2 serologies in the included neonates and their mothers. Considering the scope of the review as well as the type of studies included in the review, we can only recommend physicians have a low threshold of suspicion of MIS-N managing neonates presenting with SARS-CoV-2 infection. However, strong research implications can be generated with regard to the development of a registry for such cases and the standardization of investigations needed to confirm diagnosis as well as the management and possibility of evaluating various modalities in proper experimental settings.

MIS-N may manifest with varied presentations and varying severity in neonates. The diagnosis of MIS-N can be challenging and requires a high index of suspicion whenever encountering an unusual presentation of an infant exposed in utero or postnatally to SARS-CoV-2. It is advisable that attending teams perform specific investigations to evaluate the inflammatory state and perform a cardiac evaluation as well as provide supportive measures as appropriate. Neonatologists should perform specific investigations when managing neonates presenting with SARS-CoV-2 infection including but not limited to; SARS-CoV-2 antigens and antibodies, CRP, PCT, ferritin, interleukin-6 levels, and D-dimers, especially when the neonate is presenting with at least two systems involvement after excluding other causes. Also, in newborns with suspected or confirmed MIS-N, the measurement of proBNP, lactate dehydrogenase, and troponin should be considered, and early ECHO screening should

be performed to assess for myocardial dysfunction. Vigilance is warranted in a situation where MIS-N is suspected as, according to these estimates, the mortality rate is of concern. Further larger observational studies are needed to characterize this evolving condition to guide clinicians in its management.

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Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Lana A. Shaiba, Kiran More, and Prakesh Shah conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript, and reviewed and revised the final manuscript. Adnan Hadid and Rana Almaghrabi were involved in design of the study; contributed, coordinated, and supervised data collection; formatted Tables; and reviewed/approved initial and final manuscript. Muneera Almarry and Mahdi Alnamnakani were involved in design of the study; they contributed and coordinated data collection and carried out the initial analyses and critically reviewed the manuscript and approved final manuscript. All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data Availability Statement

The research data obtained from the included articles are available and can be requested from the corresponding author and will be made available when requested.

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