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ORIGINAL ARTICLE

A single-center observational study on clinical features and outcomes of 21 SARS-CoV-2-infected neonates from India

Ruchi Nanavati[1] · Dwayne Mascarenhas[1] · Medha Goyal[1] · Anitha Haribalakrishna[1] · Gita Nataraj[2]

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Abstract

Coronavirus disease-19 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an ongoing pandemic with significant morbidity and mortality. Neonates represent a vulnerable population, in which we have limited knowledge of its natural history, optimal management, and outcomes. In this retrospective observational study from a low-middle-income setting, clinical characteristics and outcomes of neonatal SARS-CoV-2 infection were evaluated. We report an incidence of 10.6% of SARS-CoV-2 infection (21 neonates), among a group of 198 neonates with suspected infection. Most of the SARS-CoV-2-infected neonates were term (80.9%) and none required any resuscitation. The infection was detected by a positive nasopharyngeal swab reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2. Neonatal COVID-19 manifestations developed in one-third (33.3%) of the infected neonates. Most of them demonstrated the involvement of respiratory (33.3%) and gastrointestinal systems (4.8%). Laboratory parameters suggested multi-systemic involvement, with elevated creatine kinase (CK) (76.2%), creatine kinase-myocardial band (CK-MB) (76.2%), and lactate dehydrogenase (LDH) (71.4%) levels. Supportive treatment was given to infected neonates with intensive care required in six neonates (28.6%). This included four preterm and two term neonates, of which two received non-invasive and one received invasive ventilation with intra-tracheal surfactant instillation. IgM antibodies against COVID-19 were detected in one neonate. All neonates with COVID-19 improved and were successfully discharged.

Conclusion: SARS-CoV-2 in neonates has a wide clinical spectrum. Further studies are needed which are adequately powered to completely understand the course of this infection in neonates, its implications not only in the neonatal period but also on long-term follow-up.

What is Known:
- *SARS-CoV-2 infection has a predilection for all age groups but with limited literature on clinical profile, outcomes, and long-term follow-up in neonates.*

What is New:
- *SARS-CoV-2 infection in neonates has a wide clinical spectrum and displays a significant overlap with common neonatal conditions.*
- *Most neonates with COVID-19 improved with supportive care, though a subset required intensive care, emphasizing the need for cautious monitoring and management.*

Keywords COVID-19 · Coronavirus · Newborn · RT-PCR · Antibodies · Low-middle income

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✉ Medha Goyal
medha_kv@yahoo.com

Ruchi Nanavati
drruchinanavati@gmail.com

Dwayne Mascarenhas
drdwaynem@gmail.com

Anitha Haribalakrishna
ani.gem81@gmail.com

Gita Nataraj
gitanataraj@kem.edu

[1] Department of Neonatology, Seth GS Medical College and King Edward Memorial Hospital, Parel, Mumbai 400 012, India

[2] Department of Microbiology, Seth GS Medical College KEM Hospital, Mumbai, India

Introduction

Coronavirus disease-19 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which started as an outbreak of atypical pneumonia in December 2019, has since become a global pandemic [1]. It has shown significant morbidity and mortality and over forty-one million cases and one million deaths have been reported globally (October 22, 2020) [2]. Neonates represent a vulnerable population, in which we have limited knowledge of the natural history, optimal management, and outcomes.

A recent meta-analysis of neonatal SARS-CoV-2 infections attributed 70% and 30% of infections to environmental and vertical transmission respectively. Symptoms were reported in 55% of infected neonates, mainly as fever (44%), respiratory (52%), gastrointestinal (36%), and neurological manifestations (18%). Furthermore, the report suggested the resemblance of clinical spectrum in neonates to adult population; however, the outcomes were more favorable [3]. Another review of 23 SARS-CoV-2-positive neonates found a male predominance and prematurity in one-third of cases [4].

Laboratory investigations in neonates with COVID-19 were often normal, though leucopenia or leukocytosis, lymphopenia, and raised lactate dehydrogenase (LDH) and creatine kinase (CK) have been reported [4, 5]. A large review on neonatal COVID-19 described lymphopenia (14.4%) and transaminitis (4.1%) and raised inflammatory markers (C-reactive protein) (15.5%) [3]. In SARS-CoV-2-infected neonates, pneumonia has been documented in few case reports [5, 6]. A recent review detected an interstitial-alveolar pattern in chest X-ray or lung ultrasound and ground-glass opacities in computed tomography scans [3].

An important knowledge gap in neonatal literature exists regarding the mode of transmission of SARS-CoV-2 infection in neonates. Many studies have suggested a horizontal mode, with frequent detection in the first 2 weeks of life [6–8]. However, substantial evidence is emerging on vertical transmission in neonates [9–11]. First, such a case report suggested transplacental passage of the virus from an infected mother in the third trimester as a proposed mechanism for detection of SARS-CoV-2 antigen by reverse transcriptase-polymerase chain reaction (RT-PCR) in maternal and neonatal tissues [11]. Current understanding on vertical transmission is based on detection of SARS-CoV-2 antigen in neonates and in products of conception such as placenta, amniotic fluid and fetal membranes [11, 12], interleukin-6 in cord blood and neonatal samples [13, 14], and IgG and IgM antibodies in neonates [13–15].

As the pandemic continues, there is a growing body of evidence on SARS-CoV-2 infection, but most data originates from the adult population. Current scientific literature in neonates comprises of scattered case reports, case series, and retrospective studies from across the globe [4–7], with a striking lack of evidence from the Indian subcontinent which has a considerable share of COVID-19 cases. In this study, the clinical characteristics, laboratory findings, management, and outcomes of SARS-CoV-2-infected neonates from high burden settings are described, which may contribute to the evolving literature in neonates.

Materials and methods

Study design and setting

This was a retrospective, single-center observational study conducted in a level III b neonatal intensive care unit (NICU) in one of the major public hospitals in Maharashtra, which serves as a referral center and caters to a large population especially belonging to underprivileged sections. All neonates with suspected SARS-CoV-2 infection admitted to the NICU from 15 April to 31 July 2020 were enrolled.

In our center, neonates are catered in postnatal wards and NICU. During the pandemic, a separate postnatal ward was allocated for mother-neonate dyads with suspected SARS-CoV-2 infection in mothers and a separate section in NICU (COVID-19 NICU) was designated for neonates. In NICU, separate sections were maintained for neonates with suspected and confirmed infection. All stable neonates were roomed-in and breastfed in the postnatal ward. Any neonate who became symptomatic or whose mothers tested positive postnatally was shifted to NICU for a brief duration for testing and monitoring. In case of antenatal diagnosis of infection in the mother, the neonate was shifted to NICU. Any neonate referred to our hospital was admitted to the NICU. For all neonates in COVID-19 NICU, expressed breast milk was arranged after explaining precautions to the mothers during milk expression. In case of non-availability of expressed breast milk, pasteurized donor breast milk was provided from a human milk bank.

Testing policy

The testing policy was as per national guidelines. Neonates born to mother diagnosed with SARS-CoV-2 infection antenatally were tested within 24 h of life. Those born to mothers diagnosed with SARS-CoV-2 infection postnatally were tested immediately following maternal diagnosis. Any neonate who developed symptoms was promptly evaluated with a nasopharyngeal swab which was processed using RT-PCR for detecting SARS-CoV-2 [16].

Case definition

A neonate was considered a SARS-CoV-2 suspect if (1) he/she was born to a mother with either COVID-19 infection diagnosed within 14 days prior to delivery, or suspected

infection (fever, sore throat, cough, myalgia, breathlessness), or living in a containment zone, or (2) he/she was directly exposed to close contacts (family members, caregivers, medical staff, and visitors), with COVID-19 infection, or (3) he/she presented with respiratory distress with or without fever and cough, onset beyond 48–72 h of age without any alternative explanation for the illness [16]. Additionally, a neonate was described as SARS-CoV-2 exposed, if born to a mother with confirmed COVID-19 infection. Any neonate with a positive nasopharyngeal swab for SARS-CoV-2 by RT-PCR was defined as SARS-CoV-2 infected. Neonatal COVID-19 refers to neonates with a positive swab with symptoms due to the infection. A positive nasopharyngeal swab for SARS-CoV-2 was required for the diagnostic confirmation.

Management and discharge criteria

Neonates who developed COVID-19 were given supportive care and discharged after resolution of symptoms and adequate monitoring. Antivirals, hydroxychloroquine, steroids, or therapies such as intravenous immunoglobulin or plasma exchange were not given [16]. Neonates who tested positive for SARS-CoV-2 and remained stable were roomed-in and discharged with their mother. Mother-neonate dyads in which the neonate tested negative, but whose mothers' were positive, were discharged home after counseling and explaining precautions. In case of maternal sickness, the neonates were discharged home by 48–72 h of life.

Data collection and analysis

The data was obtained from the neonatal case sheets of hospital records and entered in predesigned pro forma. Data related to maternal demographic characteristics, medical/obstetric complications, antenatal ultrasound, and presence of fetal distress was collected. History of symptoms of COVID-19 and of contact was collected. Maternal COVID-19 status (suspect/confirmed) based on RT-PCR results of throat swabs was documented.

Neonatal demographic characteristics such as birth weight, sex, gestational age, mode of delivery, and resuscitation details with Apgar scores were recorded. Key practices such as rooming-in, breastfeeding, and the presence of various symptoms in neonates were noted. The result of the nasopharyngeal swab and laboratory investigations such as complete blood counts, C-reactive protein, liver transaminases, LDH, CK, and CK-MB levels, including chest X-ray, was recorded. Treatment details of neonates such as the need for ventilation, surfactant and antibiotics, and outcome of discharge or death were noted.

Statistical analysis

Data was entered in MS Excel and analyzed using SPSS software version 23. Categorical variables were represented by percentages. Continuous variables were represented by mean with standard deviations and median with inter-quartile range. Independent *t*-test was used for continuous data and chi-square and Fisher's exact test were used for categorical data. A p value < 0.05 was taken as significant.

Ethical approval

The study was conducted after approval by Institutional Ethics Committee (IEC)-II (14 September 2020, EC/OA-129/2020).

Results

A total of 198 neonates with suspected SARS-CoV-2 admitted to the NICU between 15 April and 31 July 2020 were enrolled in the study (Fig. 1). The study group included seven pairs of twins.

Of the 191 mothers with suspected SARS-CoV-2 infection, 122 (63.9%) tested positive, of which the majority were asymptomatic. Symptomatic mothers presented with fever (70.9%), cough (41.9%), and sore throat (9.7%). Pregnancy-induced hypertension was reported in 19 (61.3%) while preterm premature rupture of membranes was present in 11 (35.5%) and diabetes in two (6.5%). Doppler abnormalities such as absent end-diastolic flow and reversal of end-diastolic flow in umbilical vessels were noted in one (0.8%) case each. Our study included 125 neonates (SARS-CoV-2 exposed) born to these 122 COVID-19-positive mothers. The majority were born at term (81.6%), with 46 (36.8%) being low birth weight. Most had a favorable extra-uterine adaptation with the need for resuscitation only in six (4.8%) neonates. The characteristics of these neonates and their mothers are summarized in Table 1.

We detected SARS-CoV-2 infection in 21 (10.6%) neonates, among the group of 198 neonates with suspected SARS-CoV-2 infection. In the cohort of neonates with SARS-CoV-2, 18 were born to mothers with confirmed COVID-19. The remaining three were born to mothers who had tested negative. Among them, one neonate was referred at 36 h of life and had probably acquired infection postnatally. In the second case, the neonate's mother had clinical features and radiographic evidence of COVID-19 pneumonia but a negative throat swab. The third neonate tested positive on day 25 and possibly acquired infection by horizontal transmission. Within the SARS-CoV-2-infected neonates' cohort, 17 (80.9%) were term, nine (42.9%) were low birth weight, and none required any resuscitation. Twelve were roomed-in and exclusively breastfed (57.1%). The remaining nine neonates

were shifted to NICU in view of respiratory distress (five neonates), congenital heart disease (one neonate), and antenatal diagnosis of COVID-19 in mothers of three neonates. Detection of SARS-CoV-2 virus by nasopharyngeal swab RT-PCR was the diagnostic modality used in all our cases (100%). The samples were taken earliest at 16 h and latest by day 25. The clinical characteristics, laboratory, and management parameters of SARS-CoV-2-infected neonates are summarized in Table 2.

The SARS-CoV-2-infected neonates were mostly asymptomatic. Neonatal COVID-19 developed in seven of these neonates (33.3%), with respiratory and gastrointestinal involvement in 33.3% and 4.8% respectively. Respiratory distress was present in five neonates, of which three had respiratory distress syndrome and two had transient tachypnea of the newborn respectively. One neonate had multiple episodes of vomiting and another had central cyanosis due to tricuspid atresia. Laboratory evaluation also suggested a multisystemic involvement. A detailed description of all SARS-CoV-2-infected neonates is provided in Table 3.

Supportive treatment was given to all 21 neonates which included routine monitoring and feeds. Intensive care was required in four preterm and two term neonates. Three preterm neonates had respiratory distress syndrome, of which two required non-invasive ventilation and one required invasive ventilation with a single dose of intra-tracheal surfactant instillation. The term neonates had mild respiratory distress and required only supportive care. Antibiotics were given as per unit policy with the majority receiving first-line antibiotics (amoxicillin-clavulanate and amikacin) (33.3%) [7].

Neonates with COVID-19 had no statistically significant difference with asymptomatic SARS-CoV-2-infected neonates (Table 4). This could possibly be explained by the small number of SARS-CoV-2 infected and neonatal COVID-19 cases, making the study inadequately powered to detect a statistically significant difference.

Encouragingly, all 21 SARS-CoV-2-infected neonates, including those who developed neonatal COVID-19, improved, and were discharged. Neonates with SARS-CoV-2 infection were telephonically followed up at 2 months (6–8 weeks) following discharge, with a loss to follow-up for one neonate (Table 5).

Discussion

This study describes one of the largest cohort of SARS-CoV-2-infected neonates from a low-middle-income setting,

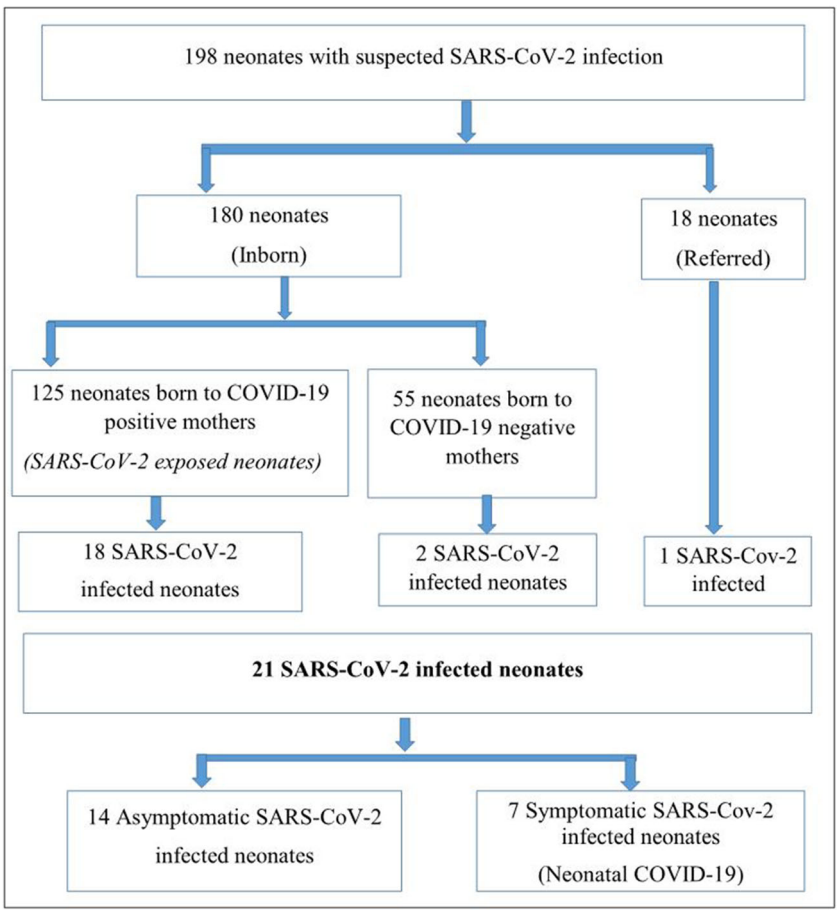

Fig. 1 Study profile

Table 1 Maternal and neonatal characteristics of SARS-CoV-2-exposed and -infected neonates

S. no	Characteristics	SARS-CoV-2-exposed neonates	SARS-CoV-2-infected neonates	Risk estimate (95% confidence interval)	*P* value
1.	Maternal characteristics	(*n* = 122)	(*n* = 21)		
	Age in years, mean (SD)	27.0 (4.9)	26.4 (5.6)		0.61
	Symptomatic, *n* (%)	30 (24.6%)	16 (76.2%)	9.8 (3.3–29)	< 0.0001
	Fetal distress, *n* (%)	18 (14.8%)	5 (23.8%)	1.8 (0.6–5.5)	0.33
	Meconium-stained liquor, *n* (%)	1 (0.8%)	1 (4.8%)	6.1 (0.36–100.7)	0.27
2.	Neonatal characteristics	(*n* = 125)	(*n* = 21)		
2.1	Birth weight in grams				
	Median (range)	2658 (988–4122)	2662 (996–3714)		
	< 1000 g	1 (0.8%)	1 (4.8%)		0.27
	1000–1500 g	5 (4%)	2 (9.5%)		0.26
	1500–2500 g	40 (32%)	6 (28.6%)		1.00
	> 2500 g	79 (63.2%)	12 (57.14%)		0.63
2.2	Gestation age in weeks				
	Median (range)	38 (30–41)	39 (30–41)		
	Term (> 37 weeks), *n* (%)	99 (79.2%)	17 (80.9%)	0.96 (0.29–3.11)	1.00
	Preterm (< 37 weeks), *n* (%)	23 (18.4%)	4 (19%)	1.04 (0.32–3.39)	1.00
	Late preterm (34 to 36 + 6)	13 (10.4%)	1 (4.8%)		
	Moderate preterm (32 to 33 + 6)	6 (4.8%)	1 (4.8%)		
	Early preterm (28 to 31 + 5)	4 (3.2%)	2 (9.5%)		
	Extreme preterm (< 28 weeks)	0	0		
2.3	Small for gestation age, *n* (%)	29 (23.2%)	7 (33.3%)	0.60 (0.22–1.64)	0.41
2.4	Male, *n* (%)	68 (54.4%)	11 (52.4%)	0.92 (0.36–2.32)	1.00
2.5	Mode of delivery				
	Vaginal, *n* (%)	54 (43.2%)	9 (42.9%)		1.00
	Assisted vaginal, *n* (%)	6 (4.8%)	1 (4.8%)		1.00
	Cesarean section, *n* (%)	65 (52%)	11 (52.4%)		1.00
2.6	Resuscitation, *n* (%)	6 (4.8%)	0 (0%)	0.85 (0.79–0.91)	0.59
2.7	APGAR at 1 min, median	9	9		
	APGAR at 5 min, median	9	9		
2.8	SpO_2 at admission				
	> 95%	110 (88%)	15 (71.42%)	0.63 (0.11–1.01)	0.08
	90–95%	13 (10.4%)	5 (23.8%)		0.14
	< 90%	2 (1.6%)	1 (4.8%)		0.37
2.9	Rooming-in & breastfeeding, *n* (%)	93 (74.4%)	12 (57.1%)	0.46 (0.17–1.19)	0.12
2.10	Clinical manifestations				
	Respiratory distress, *n* (%)	12 (9.6%)	5 (23.8%)	2.94 (0.91–9.45)	0.07
	Vomiting, *n* (%)	3 (2.4%)	1 (4.8%)	2.03 (0.20–20.52)	0.46
2.11	Management				
	Non-invasive ventilation, *n* (%)	5 (4%)	2 (9.5%)	2.53 (0.46–13.96)	0.26
	Invasive ventilation, *n* (%)	3 (2.4%)	1 (4.8%)	2.03 (0.20–20.53	0.47
	Surfactant administration, *n* (%)	2 (1.6%)	1 (4.8%)	3.07 (0.27–35.51)	0.37
	Antibiotics, *n* (%)	23 (18.4%)	9 (42.9%)	3.32 (1.25–8.82)	0.02
2.12	Outcomes				
	Death, *n* (%)	4 (3.2%)	0 (0%)		1.00
	Discharge, *n* (%)	121 (96.8%)	21 (100%)		1.00

comprising 21 SARS-CoV-2-infected neonates, of which one-third developed COVID-19. The majority of the neonates with COVID-19 had respiratory and gastrointestinal symptoms and improved with supportive care.

We found an incidence of 10.6% (21 neonates) of SARS-CoV-2 infection, which was similar to another report from India, where 7 (10.7%) neonates were detected [17]. The Indian incidence was comparable to that described by Zeng et al. (9.1%) [6] but was in contrast to the report by Salvatore et al., who did not observe any positive neonate [18]. Another review reported a pooled proportion of 3.2% in an evaluation done immediately and within 48 h of birth [19]. A high incidence in our setting could probably be due to the lack of strict adherence to infection control measures and the non-availability of adequate isolation facilities for the infected mother-neonate dyad. Similarly, a higher prevalence of maternal SARS-CoV-2 infection was detected in our study, probably due to the critical cases being admitted and universal screening strategy for pregnant women in the public hospitals in Maharashtra. The prevalence of SARS-CoV-2 infection during pregnancy was reported to be between 0 and 40% in the state [20]. This was in contrast to the global literature, where a seroprevalence of 8% by SARS-CoV-2 IgG serology and 0.5% positivity by RT-PCR was described [21].

Currently, nasopharyngeal RT-PCR is recommended for the diagnosis of SARS-CoV-2 infection in neonates. In a

Table 2 Clinical and laboratory profile of SARS-CoV-2-infected neonates

Characteristics	Outcomes	
Clinical features (n = 21)		
Asymptomatic, n (%)	14 (66.7%)	
Symptomatic		
Respiratory distress, n (%)	5 (23.8%)	
Cough, n (%)	2 (9.5%)	
Vomiting, n (%)	1 (4.8%)	
Cyanosis, n (%)	1 (4.8%)	
Need for intensive care	6 (28.6%)	
Mechanical ventilation		
Invasive, n (%)	1 (4.8%)	
Non-invasive, n (%)	2 (9.5%)	
Surfactant, n (%)	1 (4.8%)	
Antibiotic use, n (%)	9 (42.9%)	
Laboratory investigations (n = 21)		
Total leucocyte count ($\times 10^3$ cells/mm^3), mean (SD)	10.8 (4535)	Leucopenia—2 (9.5%)
% lymphocyte, mean (SD)	39.6 (15.4)	Lymphopenia—8 (38.1%)
Platelet count, ($\times 10^3$ cells/mm^3), mean (SD)	180 (70)	Thrombocytopenia—7 (33.3%)
C-reactive protein (mg/L), median	1.1	↑ 5 (23.8%)
Aspartate aminotransferase (IU/L), median Alanine aminotransferase (IU/L), median	39 24	↑ 11 (52.4%)
Lactate dehydrogenase (LDH) (IU/L), median	1120	↑ 15 (71.4%)
Creatine kinase total (CK) (IU/L), median Creatine kinase-myocardial band (CK-MB) (IU/L), median	310 91	↑ 16 (76.2%)
Chest X-ray		
Normal, n (%)	19 (90.5%)	
Respiratory distress syndrome, n (%)	1 (4.8%)	
Pneumonia, n (%)	1 (4.8%)	
Positive RT-PCR for SARS-CoV-2, n (%)	21 (100%)	
< 24 h, n (%)	2 (9.5)	
24–48 h, n (%)	7 (33.3)	
48 h–7 days, n (%)	9 (42.9%)	
> 7 days, n (%)	2 (9.5)	
COVID-19 antibody (n = 14)	IgM	IgG
Positive, n (%)	1 (7.1 %)	1 (7.1 %)
Negative, n (%)	13 (92.9 %)	13 (92.9 %)

Table 3 Detailed description of 21 SARS-CoV-2-infected neonates

	Gestational age (week)	Birth weight (gram)	Sex	Mode of delivery	Rooming-in	Breastfeeding	Maternal COVID-19 detection	Maternal symptoms	Neonatal SARS-CoV-2 infection	Probable route of transmission	Clinical presentation	Laboratory parameters	Neonatal COVID-19 antibodies (IgM, IgG)	Management	Follow-up
1.	40	3142	M	LSCS	Yes	Yes	Postnatal	Fever, cough	Day 7	Horizontal	Multiple episodes of vomiting, dry cough	Raised CK/CK-MB, LDH	IgM positive, IgG negative	Supportive	Positive on day 21
2.	40	3714	M	LSCS	Yes	Yes	Postnatal	Fever	Day 9	Horizontal	Dry cough	Raised transaminases	Negative	Supportive	Positive on day 21
3.	40	3560	F	V	Yes	Yes	Postnatal	Fever	Day 2	Horizontal	Asymptomatic	Raised transaminases, CK/CK-MB, LDH	Not available	Supportive	Negative on day 14
4.	38	2370 (SGA)	M	V	No	No (EBM)	Antenatal	Nil	Day 2 (36 h)	Horizontal	Asymptomatic	Thrombocytopenia, lymphopenia, raised CK/CK-MB, LDH	Negative	Supportive	Negative on day 6
5.	40	2372 (SGA)	M	LSCS	No	No (EBM)	Postnatal	Nil	Day 3	Horizontal	Early-onset sepsis, respiratory distress	Raised CRP, lymphopenia, transaminases, CK	Negative	Supportive, antibiotics	Negative on day 9
6.	38	2662	F	V	Yes	Yes	Postnatal	Nil	Day 4	Horizontal	Asymptomatic	Thrombocytopenia, lymphopenia, raised CK/CK-MB, LDH	Negative	Supportive	Negative on day 7
7.	40	2832	M	LSCS	Yes	Yes	Postnatal	Nil	Day 3	Horizontal	Asymptomatic	Leucopenia, lymphopenia, raised transaminases, CK/CK-MB, LDH	Negative	Supportive	Negative on day 6
8.	37	2174	F	V	No	No (EBM)	Postnatal	Nil	Day 2 (40 h)	Horizontal	Transient tachypnea of the newborn	Lymphopenia, raised transaminases, LDH	Negative	Supportive, antibiotics	Negative on day 6
9.	39	2014 (SGA)	F	V	Yes	Yes	Postnatal	Nil	Day 5	Horizontal	Asymptomatic	Thrombocytopenia, raised LDH	Negative	Supportive	Negative on day 8
10.	39	2674	F	V	No	No (EBM)	Antenatal	Nil	Day 2 (30 h)	? Horizontal	Asymptomatic	Raised CK/CK-MB	Not available	Supportive	Negative on day 7
11.	40	3136	F	LSCS	Yes	Yes	Postnatal	Fever	Day 2 (40 h)	Horizontal	Asymptomatic	Raised CRP, CK, transaminases, LDH	Not available	Supportive, antibiotics	Negative on day 5
12.	41	3128	M	V	Yes	Yes	Postnatal	Nil	Day 5	Horizontal	Asymptomatic	Thrombocytopenia, raised transaminases, CK	Not available	Supportive	Not done
13.	38	3564	F	LSCS	No	No (EBM)	Postnatal	Nil	Day 2 (48 h)	Horizontal	Asymptomatic	Thrombocytopenia, raised CRP, transaminases	IgM negative, IgG positive	Supportive, antibiotics	Negative on day 4

Table 3 (continued)

	Gestational age (week)	Birth weight (gram)	Sex	Mode of delivery	Rooming-in	Breastfeeding	Maternal COVID-19 detection	Maternal symptoms	Neonatal SARS-CoV-2 infection	Probable route of transmission	Clinical presentation	Laboratory parameters	Neonatal COVID-19 antibodies (IgM, IgG)	Management	Follow-up
14.	38	2872	M	LSCS	Yes	Yes	Postnatal	Fever, cough	Day 2 (48 h)	Horizontal	Asymptomatic	Leucopenia, raised CK/CK-MB, LDH	Negative	Supportive, antibiotics	Not done
15.	30	1200	M	V	No	No (EBM)	Negative	Nil	Day 3	Horizontal	Respiratory distress syndrome, lethargy	Lymphopenia, thrombocytopenia, raised CRP, LDH, CK/CK-MB	Negative	Invasive mechanical ventilation, surfactant, antibiotics	Negative on day 4
16.	40	2592 (SGA)	F	LSCS	Yes	Yes	Postnatal	Nil	Day 3	Horizontal	Asymptomatic	Lymphopenia, thrombocytopenia, raised CK/CK-MB, LDH	Negative	Supportive, antibiotics	Not done
17.	40	2324 (SGA)	F	V	No	No (EBM)	Negative	Nil	Day 25	Horizontal	Central cyanosis	Raised LDH	Negative	Supportive, antibiotics	Not done
18.	31	996 (SGA)	F	LSCS	No	No (EBM)	Negative	Nil	Day 1 (18 h)	Horizontal	Respiratory distress syndrome	Raised transaminases, raised CK/CK-MB	Negative	Non-invasive mechanical ventilation, supportive	Negative on day 14
19.	39	3396	M	Forceps	Yes	Yes	Postnatal	Nil	Day 3	Horizontal	Nil	Raised CK/CK-MB, LDH	Not available	Supportive	Not done
20.	34	1360 (SGA)	M	LSCS	Yes	Yes	Postnatal	Nil	Day 3	Horizontal	Nil	Lymphopenia, raised transaminases, raised CK/CK-MB, LDH	Not available	Supportive	Negative on day 6
21.	33	1928	M	LSCS	No	No (EBM)	Antenatal	Nil	Day 1 (16 h)	? Horizontal	Respiratory distress syndrome	Raised CRP, raised transaminases, raised CK/CK-MB, LDH	Not available	Non-invasive mechanical ventilation, antibiotics, supportive	Negative on day 4

SGA, small for gestational age; *M*, male; *F*, female; *LSCS*, lower section cesarean section; *V*, vaginal delivery; *CK*, creatine kinase; *CK-MB*, creatine kinase-myocardial band; *LDH*, lactate dehydrogenase; *CRP*, C-reactive protein; *EBM,* Expressed breast milk

Table 4 Comparison of SARS-COV-2-infected asymptomatic and symptomatic neonates

S. no	Parameter	Symptomatic SARS-CoV-2-infected neonates neonatal COVID-19 (n = 7)	Asymptomatic SARS-CoV-2-infected neonates (n = 14)	Risk estimate	P value
1.	Male (%)	4 (57.1%)	7 (50%)	1.33 (0.21–8.28)	1.00
2.	Preterm (%)	3 (42.8%)	1 (7.1%)	9.75 (0.78–121.84)	0.88
3.	Small for gestational age (%)	3 (42.8%)	4 (28.6%)	1.85 (0.28–12.45)	0.64
4.	Breastfeeding and rooming-in (%)	3 (42.8%)	9 (64.3%)	0.41 (0.06–2.66)	0.39
5.	SpO_2 < 90 % (%)	3 (42.8%)	3 (21.4%)	2.75 (0.38–19.66)	0.35
6.	Raised C-reactive protein (%)	3 (42.8%)	2 (14.3%)	4.50 (0.54–37.28)	0.28
7.	Raised transaminases (%)	4 (57.1%)	7 (50%)	1.33 (0.21–8.29)	1.00
8.	Raised CK-MB (%)	4 (57.1%)	12 (85.7%)	0.22 (0.03–1.85)	0.28
9.	Raised LDH (%)	5 (71.4%)	10 (71.4%)	1.00 (0.13–7.45)	1.00

recent meta-analysis of 176 cases, 98.8% were detected with RT-PCR [3]. The role of antibodies in diagnosis is uncertain, as most infections occur late in pregnancy with inadequate time for antibody generation. Recently, a classification system was proposed by Shah et al. based on maternal testing, clinical status of the neonate, and neonatal testing. However, this requires recognition of the virus in placental tissue, umbilical cord blood, and amniotic fluid apart from nasopharyngeal and rectal swabs [22]. Using this classification, in this study, 12 SARS-CoV-2-infected neonates could be categorized as a probable neonatal infection acquired postpartum (57.14%) and there is a possibility that few cases were missed due to the paucity of testing of various specimens.

Studies have demonstrated a male predominance in SARS-CoV-2-infected neonates [4, 15], though we found equal predilection for both sexes. Preterm comprised 19.1% of infected neonates and 42.9% were low birth weight. A review by Sheth et al. reported a 30% prematurity rate in infected neonates [4]. Karabay et al. in their systematic review found no significant relationship between birth weight and frequency of infection [23]. A lower mean birth weight with one-third being small for gestational age was probably due to a study being conducted in a public hospital catering to the low-middle class population with poor health-seeking behavior. SARS-CoV-2-infected neonates did not show an increased need for resuscitation consistent with other studies [3, 4, 15].

Two-thirds of the SARS-CoV-2-infected neonates was asymptomatic, while the remaining developed respiratory and gastrointestinal manifestations. None of the neonates had acute respiratory distress syndrome as per Montreux's definition [24]. This clinical presentation is concordant with findings of a recent meta-analysis that showed 55% of infected neonates developed symptoms, commonly with gastrointestinal (36%) and respiratory manifestations (52%) [3]. Interestingly, fever was detected in 44% of cases in the meta-analysis, unlike our cohort of neonatal COVID-19, which could represent a variation in immunological response in population subsets.

Intensive care admission was indicated in six neonates for prematurity, low birth weight, and respiratory distress. This

Table 5 Follow-up of SARS-CoV-2-infected neonates

S. no	Follow-up variables	Number (percentage)
1.	Number of neonates	21
	On follow-up	20 (95.2%)
	Loss to follow-up	1 (4.8%)
2.	Neonates on exclusive breastfeeding	20 (95.2%)
3.	Neonates completed immunization	20 (95.2%)
4.	Neonate reporting appearance of symptoms/requiring repeat hospitalization	0 (0%)
5.	Precautions followed by caregivers while handling neonate	
	Wearing mask	19 (90%)
	Handwashing	7 (33.3%)
	Alcohol-based hand rubs	15 (71.4%)
6.	Any family member handling neonate reporting symptoms or testing positive for SARS-CoV-2	0 (0%)

suggests that infected neonates mostly required supportive care and strict monitoring in mildly symptomatic cases. Bernardo et al. also emphasized in their study that the routine events in the neonatal period were seldom altered by the COVID-19 infection [15]. Utilization of intensive care facilities for all infected neonates without clinical consideration will cause unnecessary maternal-neonate separation and burden on health care facilities, especially with resource limitation. Gale et al. proposed that SARS-CoV-2 infection within the first 7 days was generally mild or asymptomatic [25], based on criteria described by Dong and colleagues [26]. We did not observe such correlation and rather, a majority of neonates who received intensive care were diagnosed in the first 7 days of life. Larger studies will be required to define the temporal relationship between acquisition on infection and its clinical severity.

We found leucopenia, lymphopenia, and thrombocytopenia in few infected neonates, a pattern consistent with neonatal viral infections. However, raised inflammatory markers detected in more than two-thirds of cases suggest a systemic inflammatory response in SARS-CoV-2-infected neonates similar to adults [27]. These findings corroborate with a recent meta-analysis, where 14.4% and 4.1% of neonates demonstrated lymphopenia and raised liver enzymes [3]. The majority of our neonates showed normal chest X-rays (90%), which was significantly low in comparison to a recent report, possibly due to lack of additional assessment with ultrasound and computed tomography [3].

In this study, a majority of neonates were roomed-in and exclusively breastfed till the time of maternal diagnosis, making horizontal transmission more likely. One neonate developed IgM antibodies on day 12 of life but was negative for IgG. IgM usually does not have transplacental passage owing to its structure, though in SARS-CoV-2-infected placentas, a possibility has been suggested in reports by Ng et al. or could be due to endogenous production of IgM in the neonate after postnatal infection [28]. In a recent large review, the authors attributed 70% of infections to horizontal transmission [3].

Recommendations on rooming-in and breastfeeding in SARS-CoV-2 are evolving with emerging evidence. Raschetti et al. suggested that neonates not transiently separated from their mothers had a higher incidence of SARS-CoV-2 infection after the first 72 h of life [3]. Under the light of such evidence, the decision of rooming-in should be cautious with emphasis on hygiene precautions. The safety of breastfeeding has been debated and concerns arise from the detection of viral RNA in breast milk [29–31]. Costa et al. analyzed breast milk in two lactating mothers and detected viral RNA in multiple samples [31]. The benefits of breastfeeding outweigh the potential risk of viral transmission, especially in developing countries where artificial feedings have been associated with significant morbidity and mortality [32].

All neonates with COVID-19 improved with supportive care. Currently, the use of anti-viral drugs is not recommended and is limited to select cases after risk-benefit assessment [33]. Ventilation should be guided by principles of lung protective strategies. The outcomes of COVID-19-positive neonates were favorable with no mortality, a finding noted in other reviews [3, 4, 6]. The protective role of fetal hemoglobin and immaturity of angiotensin-converting enzyme-2 which interferes with the entry of the virus into the cells have been postulated as probable protective theories [34].

The study describes the clinical characteristics, hematological, and biochemical parameters along with antibody status of SARS-CoV-2-infected neonates including their outcomes and a short follow-up. This adds to the emerging data from low-middle-income settings with underresourced health systems where economic and cultural diversity impacts neonatal care. Current literature from such settings is heterogeneous with reports of mild and self-limiting infection in neonates, to that requiring ventilatory support with mortality [35–37]. Diagnostic constraints arise due to limited testing capacity for repeat samples. Management constraints such as lack of negative pressure area, inadequate space for maintaining recommended distance of six feet as recommended by national guidelines [16], sub-optimal compliance to hand, and respiratory hygiene practices emphasize the need of tailoring the management as per the local resources. This study however is limited by its retrospective design and paucity of amniotic fluid, placental membranes, and breast milk testing.

In conclusion, most SARS-CoV-2-infected neonates showed a milder clinical profile, though a subset required intensive care. In resource-limited settings, it is mandatory to ensure the allocation of resources to care for these infected neonates within the existing infrastructure. Further studies which are well powered are needed to address challenges with rooming-in, breastfeeding, repeat testing of these neonates, and analyze the impact of SARS-CoV-2 infection on the long-term follow-up.

Abbreviations COVID-19, Coronavirus disease-19; CK, Creatine kinase; CK-MB, Creatine kinase-myocardial band; LDH, Lactate dehydrogenase; NICU, Neonatal intensive care unit; RT-PCR, Reverse transcriptase-polymerase chain reaction; SARS-CoV-2, Severe acute respiratory syndrome coronavirus-2

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Authors' contributions Dr. Ruchi conceptualized and designed the study, coordinated and supervised data collection, critically reviewed and revised the manuscript for important intellectual content, and finalized the manuscript.

Drs. Dwayne and Medha conceptualized and designed the study, conducted a literature search, collected data, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. Anitha supervised data collection and critically reviewed and revised the manuscript.

Dr. Gita coordinated and supervised data collection and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Declarations

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