Research Paper

Outcomes of Neonates Born to Mothers with Coronavirus Disease 2019 (COVID-19) – National Neonatology Forum (NNF) India COVID-19 Registry

NATIONAL NEONATOLOGY FORUM (NNF) COVID-19 REGISTRY GROUP*

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ABSTRACT

Background: Limited evidence exists on perinatal transmission and outcomes of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in neonates. **Objective:** To describe clinical outcomes and risk factors for transmission in neonates born to mothers with perinatal SARS-CoV-2 infection. **Design:** Prospective cohort of suspected and confirmed SARS-CoV-2 infected neonates entered in National Neonatology Forum (NNF) of India registry. **Subjects:** Neonates born to women with SARS-CoV-2 infection within two weeks before or two days after birth and neonates with SARS-CoV-2 infection. **Outcomes:** Incidence and risk factors of perinatal transmission. **Results:** Among 1713 neonates, SARS-CoV-2 infection status was available for 1330 intramural and 104 extramural neonates. SARS-CoV-2 positivity was reported in 144 intramural and 39 extramural neonates. Perinatal transmission occurred in 106 (8%) and horizontal transmission in 21 (1.5%) intramural neonates. Neonates roomed-in with mother had higher transmission risk (RR1.16, 95%CI 1.1 to 2.4; *P*=0.01). No association was noted with the mode of delivery or type of feeding. The majority of neonates positive for SARS-CoV2 were asymptomatic. Intramural SARS-CoV-2 positive neonates were more likely to be symptomatic (RR 5, 95%CI 3.3 to 7.7; *P*<0.0001) and need resuscitation (RR 2, 95%CI 1.0 to 3.9; *P*=0.05) compared to SARS-CoV-2 negative neonates. Amongst symptomatic neonates, most morbidities were related to prematurity and perinatal events. **Conclusion:** Data from a large cohort suggests perinatal transmission of SARS-CoV-2 infection and increased morbidity in infected infants.

Keywords: *Horizontal transmission*, *Outcome*, *Perinatal transmission, Risk*.

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has infected over 10 million individuals in India [1]. The SARS-CoV-2 infects both children and adults but has higher fatality in the elderly and individuals with co-morbidities [2]. SARS-CoV-2 infects pregnant women as much as other reproductive-age women [3]. The knowledge about the epidemiology, clinical characteristics, prevention, and treatment of SARS-CoV-2 infection is continually evolving. Currently available data on the consequences of SARS-CoV-2 infection in pregnancy, fetus, and the neonate is mostly from case reports, small case series, retrospective cohort or cross-sectional studies, compiled in a recent systematic review [4]. There is limited data on perinatal SARS-CoV-2 infection from the developing world. We report analysis from a large neonatal Coronavirus Disease 2019 (COVID-19) registry under the National Neonatology Forum (NNF) of India, on the incidence of perinatal transmission and the factors associated with it, and the clinical features of SARS-CoV-2 positive neonates.

METHODS

In this prospective cohort study, data were collected from various hospitals voluntarily enrolled in the NNF COVID registry, which was initiated in April, 2020. Neonates born to women with SARS-CoV-2 infection within two weeks prior to or two days after delivery and neonates with confirmed SARS-CoV-2 infection within 28 days of life were eligible for enrolment in the study. COVID status of mothers and neonates was assessed by nasopharyngeal RT-PCR in all participating hospitals.

(*i*) SARS-CoV-2 infected neonates were defined as those with a positive SARS-CoV-2 quantitative RT-PCR test in nasopharyngeal swab within 28 days of birth [5]. (*ii*) SARS-CoV-2 infected mothers were defined as those with a positive SARS-CoV-2 quantitative RT-PCR test in the nasopharyngeal sample during the peripartum period [5]. (*iii*) The perinatal transmission was defined as positive nasopharyngeal RT-PCR in a neonate in the first 72 hours after birth [6,7]. This included intrauterine and intrapartum transmission. Testing was avoided in the first 12 hours to minimize false positives due to superficial colonization. (*iv*) The horizontal transmission was considered in a neonate with negative RT-PCR within the first 72 hours who subsequently tested positive any time after 72 hours of birth irrespective of the mother's SARS-CoV-2 status [6,7].

Mothers were either tested at admission or referred for admission because of the SARS-CoV-2 positive reports. Testing and management were as per the Indian Council for Medical Research (ICMR) and NNF guidelines, and local standard operating procedures [8,9]. SARS-CoV-2 status of the neonate was tested as per NNF guidelines and local institutional protocols, which in most centres was done within the first 72 hours after birth or when the neonate was symptomatic and admitted to the neonatal unit [8]. All neonates were monitored for clinical symptoms for the first seven days after birth and for as long as the mother was admitted to the hospital. Data on mothers and neonates was available till disposition from the hospital.

Data collection: Data was prospectively submitted to the registry by the participating hospitals in a web-based secure platform (https://innc.org/covid). All the registered hospitals received a short message alert every week on the number of enrolled cases and data completeness. Twenty percent of the enrolled cases from each participating centre were randomly cross-checked for data quality. A closed group of clinical leads from participating hospitals was formalized for secure, encrypted communication. This group managed the updates to the database, day-to-day problems in data management, the progress of the registry, and sharing of education and communication. Any inconsistency in data was highlighted to the respective hospital lead for verification.

The data included baseline characteristics of the mothers, mode of delivery, type of feeding, rooming-in with mother or isolation from mother, clinical features, diagnosis, and neonatal outcomes.

The clinical status of patients was classified as per guidelines from the Ministry of Health and Family Welfare, Government of India [10].

The primary outcomes of the study were: (*i*) The incidence of perinatal transmission; (*ii*) the rates of SARS-CoV-2 virus positivity in the neonates in association with risk factors of transmission such as mode of delivery, type of feeding and care practices, and (*iii*) comparisons between intramural and extramural, SARS-CoV-2 positive and SARS-CoV-2 negative neonates born to SARS-CoV-2 positive mothers. The secondary outcomes were respiratory morbidities, the need for respiratory support, and mortality in these infants.

Statistical analyses: Descriptive statistics were used, and comparisons were made using the chi-square test for categorical variables and the Student t-test or Mann-Whitney U test as appropriate for continuous variables. A *P*-value of <0.05 was considered significant.

RESULTS

The web-based COVID-19 registry received a total of 1733 entries for mothers and their neonates. Almost all (1730/1733) of the enrolled mother-infant dyads were from tertiary care hospitals, 1649 (95%) from public sector hospitals, and 82 (5%) from private hospitals. We excluded 22 entries where both mothers and neonates were negative but were referred because of suspicion of SARS-CoV-2 infection, and 1711 mother-infant dyads were enrolled in this study. Most of the mothers (94.5%) were asymptomatic, and only 1% were critically ill. Cesarean section was the mode of delivery in 68%.

Of the 1711 enrolled neonates, 1589 were intramural, while 122 were extramural births. The extramural infants were referred to the participating hospitals for either symptomatic status or for SARS-CoV-2 positive status of the mother. Figure 1 gives a study flow for intramural neonates enrolled in the registry. Out of 1589 intramural infants, SARS-CoV-2 testing was either not done or not reported in 259, so we excluded them from the analysis. Amongst 1330 tested neonates, 143(10.8%) were SARS-CoV-2 positive. Of these, 68(5.1%) tested positive on day one (**Fig. 1 and 2**). Amongst the intramural newborn infants, 106 (8%) were positive for SARS-CoV-2 within 72 hours (perinatal transmission) and 21 (1.5%) beyond 72 hours (horizontal transmission) of birth. The risk of transmission was not associated with the mode of delivery or type of feeding. The risk of transmission of SARS-CoV-2 from mother to neonate was marginally higher if the baby was roomed-in with the mother (RR 1.16, 95% CI 1.1-2.4; *P*=0.01). **Tables I and II** compare the SARS-CoV-2 positive and negative infants born to SARS-CoV-2 positive mothers. The demographic parameters in both the groups were not different except for the prematurity rate, which was higher in SARS-CoV-2 positive group. SARS-CoV-2 positive neonates were five times more likely to be symptomatic and twice more likely to need resuscitation. They had significantly higher probability of having sepsis and septic shock. SARS-CoV-2 positive neonates were more likely to have abnormal radiological findings and need respiratory support. They were also more likely to have received

surfactant, steroids and inotropes. The risk of mortality was however not significantly different between the two groups. No significant association was noted between mother's symptomatic status and baby's SARS-CoV-2 positivity, need for resuscitation, and symptoms.

Fig. 2 depicts the study flow for extramural neonates. Extramural SARS-CoV-2 infected neonates were more likely to present with pneumonia, seizures, and septic shock, and were more likely to present after the first 72 hours of birth (**Tables III and IV**). This cohort of neonates was generally symptomatic. Like intramural neonates, extramural SARS-CoV-2 infected neonates tended to have more respiratory symptoms, radiological abnormalities, and needed more respiratory support.

There were 17 neonates in the registry, who were positive for SARS-CoV-2, but their mothers were reported negative. Five of these neonates were positive within 72 hours of life, and the remaining tested positive beyond 72 hours of birth. In this sub-group, 3 (17.6%) needed resuscitation at birth, 3 (17.6%) had pneumonia, 5 (29%) had respiratory distress, and 4 (23.5%) had sepsis. One (5.9%) infant had encephalopathy, and 3 (17.6%) had seizures.

DISCUSSION

In this large registry of neonates born to SARS-CoV-2 positive mothers, we report the incidence of neonatal infection, type of symptoms, and neonatal outcomes. Neonates acquired infection most commonly in the first 72 h after birth. The 5.1% neonates who tested positive on day one may have acquired the infection intrauterine or intrapartum. Those neonates who tested positive on days two or three may also have been due to intrauterine transmission but could have acquired the infection postnatally from mother, other family members, or healthcare providers. In the absence of serial testing and testing of various body fluids from mother, it is not possible to pinpoint the timing of acquisition. It is also to be noted that many neonates were tested for the first time on day three as per the local protocols, and the absence of testing soon after birth could have led to misclassification of the type of infection. We found a significantly higher incidence of perinatal transmissions than that reported in a recent review [10].

This study highlights that SARS-CoV-2 positive neonates are more likely to be symptomatic, more likely to have respiratory symptoms, and other neonatal morbidities. However, the mortality is not increased significantly. Neonatal SARS-CoV-2 infection has been reported in a large number of publications which were mainly case reports or case series . In a systematic review by Raschetti et al., the median age at diagnosis was five days, and 55% of neonates were symptomatic [4]. Common symptoms reported include respiratory distress, fever, and those related to gastrointestinal illness. Most of the infected neonates were not reported to need any respiratory support and had a good outcome after a median duration of hospitalization of 10 days. In our study cohort, 21% (30/143) of SARS-CoV-2 positive intramural neonates were symptomatic, and the most common symptoms included respiratory

distress and sepsis-like features. However, fever and gastrointestinal symptoms were not commonly reported. The prematurity rate of 20.7% in our cohort was significant and similar to what was reported by the UK registry [11]. This raises concerns about the possibility of increased risk of premature labour in SARS-CoV-2 positive pregnant women. The incidence of symptomatic infection reported by us is lower than that reported in the previous reviews [4,12-13] and an Indian case series, [14] but similar to that reported by Anand et al. [15]. This can be explained by possible selection bias inherent in the type of studies - case reports and case series- included in the systematic reviews.

Another important finding in our cohort is that SARS-CoV-2 infected neonates were significantly more likely to need resuscitation, be symptomatic, need NICU admission, have abnormal chest X-rays, and need respiratory support. Previous studies have reported a high incidence of NICU admissions in SARS-CoV-2 positive neonates or neonates born to SARS-CoV-2 infected mothers [4]. Some of the variations in NICU admission rates may be due to local protocols for admission and isolation rather than due to the illness per se. Prematurity is an obvious confounder for higher respiratory and other morbidities in the SARS-CoV-2 positive group, and we did not adjust for prematurity rates. However, the difference in prematurity rates is unlikely to explain the magnitude of differences in morbidities.

We found a marginally higher incidence of infection in neonates who were roomed-in with mother. However, we did not find any association with breastfeeding. Similar findings have been reported by Raschetti et al., wherein lack of mother–neonate separation from birth was associated with late SARS-CoV-2 infections, while breastfeeding was not associated with increased risk [4]. Recent systematic reviews have found a very low rate of detection of SARS-CoV-2 RNA in breastmilk, with a much higher prevalence of antibodies to the virus in the breastmilk [16,17]. The World Health Organization recommends that neonates should be roomed-in with mother and exclusively breastfed while following precautions to limit the spread of SARS-CoV-2 infection to neonates [18]. A higher incidence of neonatal infection in infants roomed-in with mothers is likely due to incomplete adherence to the suggested precautions. Salvatore, et al. found no perinatal transmission in a cohort of 116 SARS-CoV-2 positive pregnant women from 3 New York hospitals with rooming-in and breastfeeding, if correct hygiene precautions, maternal masking and parental education were undertaken [19]. Similarly Anand, et al., report a low risk of transmission of infection from mother to baby with rooming-in and breastfeeding [15]. This is important information for families to be aware of, along with the finding that infection is asymptomatic in the majority of neonates, and the outcome is largely favorable. Meanwhile, more research is needed to evaluate measures to prevent postnatal transmission to neonates and improve adherence to currently prescribed precautions.

We also report on extramural neonates referred to tertiary care hospitals following contact with an infected adult in the family or for other morbidities. SARS-CoV-2 positivity was more likely if these

neonates were symptomatic at admission. The repertoire of symptoms was similar to symptomatic intramural neonates. The high incidence of infection in neonates who are symptomatic at presentation underscores the need for universal testing guidelines for this category of neonates [20].

This large registry was created for the new COVID-19 disease within a short span of time after the WHO's announcement of the pandemic and data was contributed by 20 hospitals on a voluntary basis across the country. The most important limitation, as highlighted above, was non-uniformity in age at testing of neonates born to SARS-CoV-2 positive mothers. As this was a registry-based study, testing of other biological sources like amniotic fluid, placenta, blood, or breastmilk was not pursued. We also did not test for the presence of specific antibodies in the neonatal blood to look for intrauterine infection as suggested by a recent guideline to classify the type of neonatal infection [7]. We did not capture data for neonates with the possibility of multi-System Inflammatory Syndrome in Children (MIS-C) following SARS-CoV-2 Infection, which is recently being reported [21].

In conclusion, our study provides important data on neonatal infection, clinical features, and outcomes in neonates born to SARS-CoV-2 positive women. This information can be used to make informed decisions and policies on neonatal SARS-CoV-2 testing, healthcare organization for neonates born to SARS-CoV-2 positive women, and counseling of families regarding various management options.

Contributors: KM: initiated and wrote the proposal for the registry and created a data collection form, analyzed the data, and finalized the first draft of the manuscript; BT, SM and PK: facilitated the creation of the data registry on web-portal hosted by the Indian Neonatal Collaborative (INCC), India; BT: coordinated data collection and helped to extract relevant data from the portal; Murki: wrote the introduction and methods sections, helped in biostatistics and approved the final draft of the manuscript; DC: reviewed the analysis, results section and wrote an interpretation of data and discussion; AD: approved the proposal, encouraged and coordinated hospitals' participation through National Neonatology Forum, India and reviewed the final draft of the manuscript; PK: approved the proposal, created a registry on the portal, encouraged hospitals' participation and approved the final draft of the manuscript. All the remaining Collaborators contributed significantly towards data collection and sharing from their respective institutes, and also reviewed and approved the final draft of the manuscript.

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WHAT IS KNOWN?

- Limited evidence exists on the perinatal transmission and the management of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among newborns, especially from the developing world.

WHAT THIS STUDY ADDS?

- Our data confirms perinatal transmission of SARS-CoV-2 and suggests increased morbidity in infected infants. Breastfeeding and rooming-in seem to be safe but require compliance with additional precautions.

ANNEXURE

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Table I Demographics and Risk Factors in SARS-CoV-2 Positive and Negative Intramural Neonates

Parameters	*SARS-CoV-2*		*RR (95% CI)*
	Positive (n=143)	*negative (n=1187)*	
Male gender	81 (57)	581(49.2)	1.1(0.9 -1.3)
Weight,[a] g	2746 (618)	3024 (170)	
Gestation, [a] wk	37.5 (2.1)	37.7 (1.5)	
Prematurity	Reported in 130 (90.9)	Reported in 1142 (96.2)	
34-36 wk	21 (16.1)	106 (8.9)	1.6(1-2.5) [c]
<34 wk	6 (4.6)	15 (1.3)	3.3(1.3-8.4)[b]
<37 wk	27 (20.7)	121(10.2)	1.8(1.2-2.7)[b]
Caesarean delivery	88 (61.5)	821 (69.7)	0.8(0.7-1)[e]
Mother positive[d]	135 (94.4)	1167(98.3)	0.1 (0.08-0.12)[b]
Roomed-in with mother	111 (77.6)	800 (67.4)	1.16 (1.1-2.4)[c]
Breastfeeding	119 (83.2)	998 (84.1)	0.97 (0.6-1.5)[e]

Values in no. (%) or [a]mean (SD);[b]P<0.01; [c]P=0.01; [d]RT-PCR for SARS-CoV-2; e- Not significant

Table II Clinical Features and Management of SARS-CoV-2 Infection in Intramural Neonates at Birth

Parameters	*SARS-CoV-2*		*RR (95% CI)*
	Positive (n=143)	*Negative (n=1187)*	
Resuscitation [d]	15 (10.4)	26 (2.1)	4.4 (2.4 - 8.2)[a]
Symptomatic	30 (21)	49(4.1)	5 (3.3 - 7.7) [a]
RDS	13 (9)	12 (1.1)	7.5(3.4 -16.8) [a]
Pneumonia	10 (7)	1 (0.08)	83 (10.7- 643) [a]
Sepsis	5 (3.5)	1 (0.08)	41.5 (4.8-352) [a]
Seizures	5 (3.5)	6 (0.5)	6.9 (2.1-22.3) [b]
Septic Shock	6 (4.2)	6 (0.5)	8.3 (2.7-25.3) [a]
DIC	4 (2.8)	4 (0.3)	8.3 (2 -32)[c]
Encephalopathy	3 (2.1)	7 (0.6)	3.5 (0.93-13.6)
Jaundice	6 (4.2)	6 (0.5)	8.3 (2.7-25.4) [a]
Other morbidities	28 (19)	43 (4.5)	5.4 (3.4-8.4) [a]
Abnormal CXR	16 (11.2)	7 (0.6)	18.9(7.9-45.3)[a]
Oxygen therapy	11 (7.7)	27 (2.3)	3.3(1.7-6.6)[a]
CPAP	7 (4.9)	13 (1)	4.5(1.8-11)[a]
Ventilation	8 (5.6)	14 (1.2)	4.7 (2- 11.1)[a]
Surfactant	5 (3.5)	7 (0.6)	5.9 (1.9-18.4)[c]
Inotropes	8 (5.6)	10 (0.8)	6.6 (2.6-16.5)[a]
Corticosteroids	4 (2.8)	2 (0.2)	16.6(3-89.8)[b]
IVIG	0	1(0.08)	-
Oseltamivir	2 (1.4)	0	-
Mortality	2 (1.4)	4 (0.3)	4.1(0.76-22.4)[e]

[a]P<0.001; [b]P=0.001; [c]P<0.05; [d]at birth. CXR-chest X-ray; IVIG – intravenous immunoglobulin, CPAP- continuous positive airway pressure; e- Not significant

Table III Demographics and Risk Factors in SARS-CoV-2 Positive and Negative Extramural Neonates

Parameters	*SARS-CoV-2*	
	Positive(n=39)	*Negative(n=65)*
Male gender	22 (57)	32 (49.2)
Weight[c] (g)	2572 (600)	2822 (582)
Gestation [c] (wk)	36.9 (2.2)	37.3 (1.7)
Prematurity	27	35
34-36 weeks	4 (14.8)	2(5.7)
<34 weeks	3 (4.6)	4 (1.3)
Total < 37 wk	7 (19.4)	6 (7%)
Caesarean delivery	17 (43.6)	43 (66.1)
Mother positive[b,d]	26 (76.5)	62 (95.4)
Roomed-in	17 (43.6)	23 (35.9)
Breastfeeding[c]	18 (48.6)	45 (70.3)

Values in no. (%) or [a]mean (SD). [b]RR (95%CI) = 0.7(0.6-0.9), P<0.001; [c] RR (95%CI) = 0.7 (0.4-0.9), P=0.05; [d]RT-PCR for SARS-CoV-2.

Table IV Clinical Features and Management of SARS-CoV-2 Infection in Extramural Neonates

Parameters	*SARS-CoV-2*		*RR (95% CI)*
	Positive(n=39)	*Negative(n=65)*	
Symptomatic	13/27 (48)	6/36 (16.6)	2.9(1.2-6.6)[d]
RDS	13 (33.3)	8 (12.2)	2.7(1.2-5.9)[c]
Pneumonia	6 (15.4)	1 (1.5)	10.1(1.2- 81)[c]
Seizures	4(10.2)	1 (1.5)	6.6(0.7-57)[d]
Septic Shock	6 (15.4)	1 (1.5)	10(1.2-80)[d]
DIC	3 (7.7)	0	12.1(0.6-229)[e]
Encephalopathy	1 (2.6)	1 (1.5)	1.6(0.1-25.8)[e]
Diarrhoea	2 (5.1)	2 (3.1)	1.6(0.2-11.3)[e]
Other morbidities	11 (28)	2 (3.1)	9.1(2.1-39)[b]
Abnormal CXR	16 (11.2)	7 (0.6)	18.9 (7.9- 45.3)[a]
Oxygen therapy	10 (25.6)	4 (6.1)	4.1(1.4-12.3)[c]
CPAP	3(7.7)	3 (4.6)	1.7(0.3-8.2)[e]
Ventilation	7 (17.9)	1 (1.5)	11.6 (1.5-91)[c]
Inotropes	5 (12.8)	1 (1.5)	7.7 (0.9-64)[e]
Corticosteroids	2 (5.1)	0	8.2(0.4-167)[e]
IVIG	2 (5.1)	0	8.2(0.4-167)[e]
Mortality	1 (2.6)	1 (1.5)	1.6(0.1-25.8)[e]

CXR-chest X-ray, IVIG – Intravenous immunoglobulin, CPAP- Continuous positive airway pressure, RDS-respiratory distress syndrome. [a]*P<0.001;* [b]*P=0.001;* [c]*P<0.01;* [d]*P<0.05; e- Not significant*

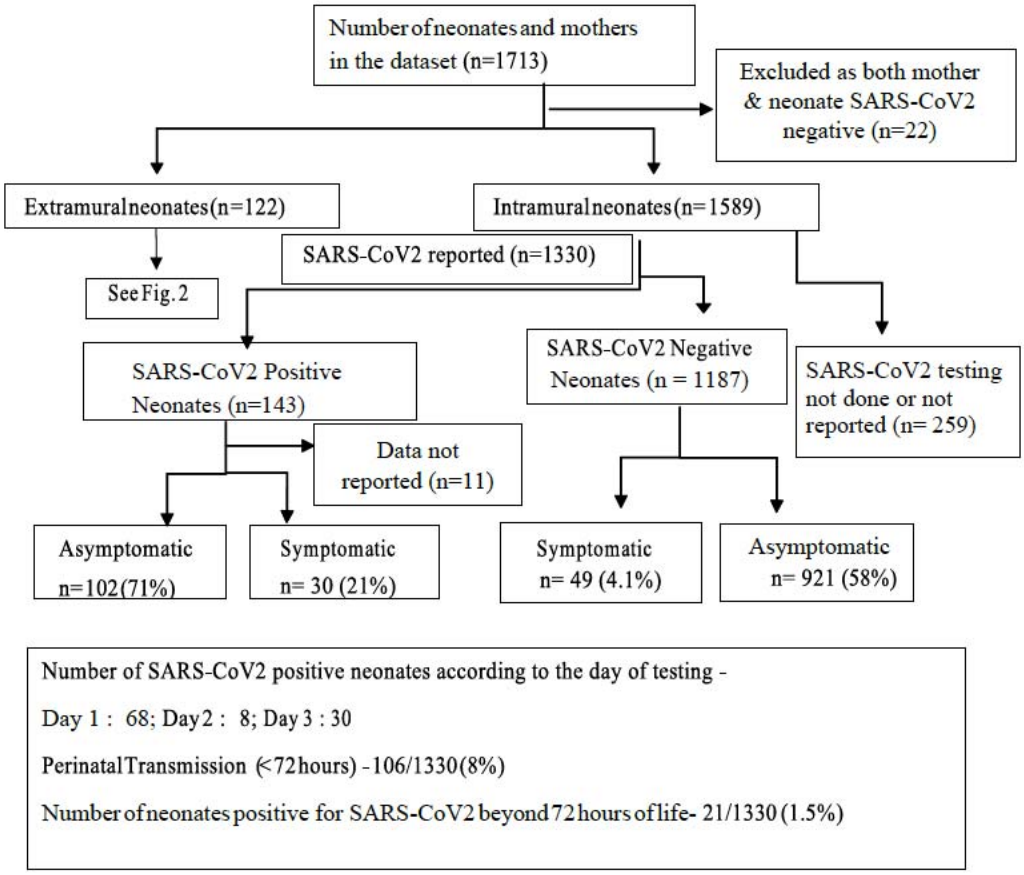

Fig. 1 Study population flow for intramural neonates.

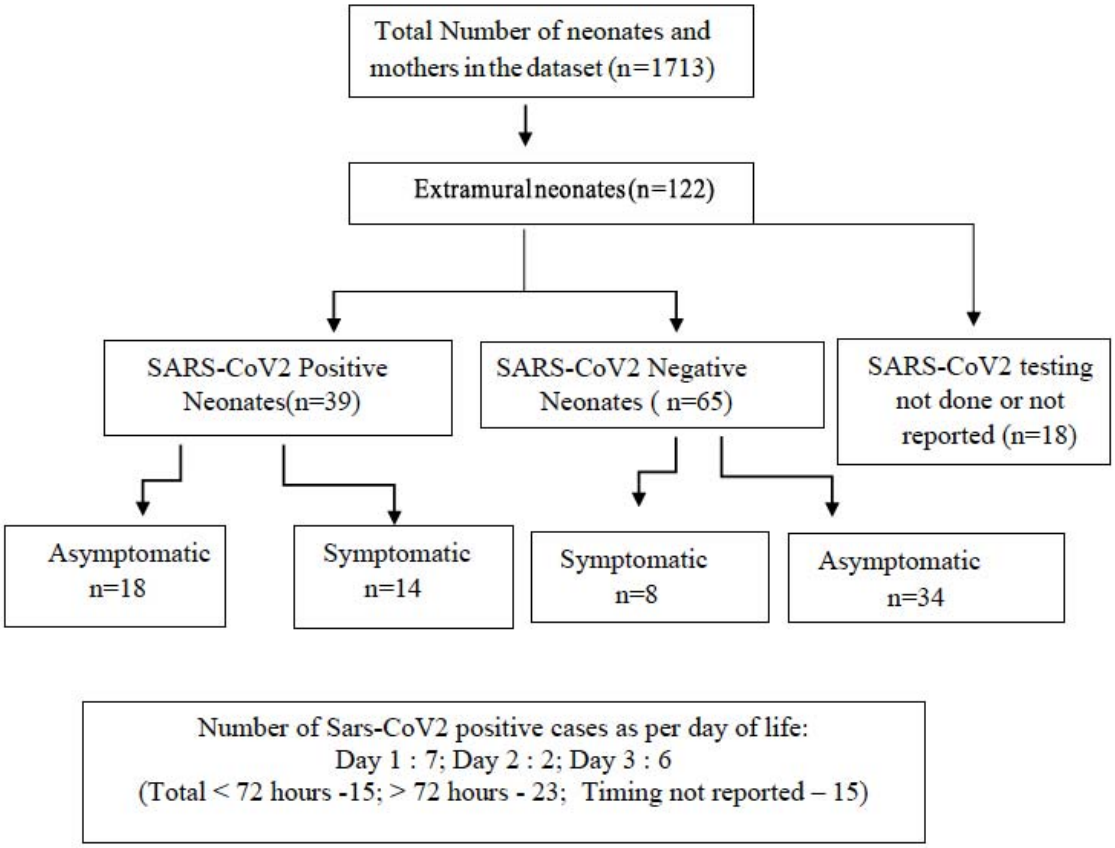

Fig. 2 Study population flow for extramural neonates.