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Clinical characteristics and outcomes of neonatal SARS-CoV-2 infection after the release of the epidemic situation of COVID-19

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Abstract

Background With the release of the coronavirus disease 2019 (COVID-19) pandemic in late 2022 in China, the number of people infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) roared, including neonatal cases. However, there were few studies on neonatal COVID-19, especially multi-center case reports. This study aimed to explore clinical characteristics and short-term outcomes of neonatal COVID-19 in China.

Methods We reviewed 187 cases of neonatal COVID-19 between December 11, 2022, and January 12, 2023. The diagnosis was assessed by symptoms, laboratory tests, X-ray manifestations, and diagnosis code. Clinical characteristics and outcomes were evaluated.

Results In 187 neonatal cases with COVID-19, 84 (44.9%) had severe SARS-CoV-2 infection. Most patients had confirmed exposure to SARS-CoV-2. Fever and respiratory symptoms were common (75.4% and 71.7%, respectively). Severe patients were more likely to have high alanine transaminase (ALT) (> 40U/L) (11.9% vs. 3.9%) and high N-terminal pro-brain natriuretic peptide (NT-proBNP) (> 2000pg/mL) (38.0% vs. 19.6%), compared with nonsevere ones ($P < 0.05$). None of the patients received COVID-19-specific medical interventions. A few severe patients received corticosteroids (1.1%), and immunoglobulin (0.5%), respectively. All patients were discharged home after the medical care with a median length of stay (LOS) of four days and none of them met the criteria of multisystem inflammatory syndrome in neonates (MIS-N).

Conclusions After the release of the epidemic situation of COVID-19 in late 2022 in China, more neonatal cases with severe COVID-19 had high ALT and NT-proBNP level. Few specific medical interventions were given, and the outcome was satisfying.

Keywords Coronavirus disease 2019, N-terminal pro-brain natriuretic peptide, Neonate, Severe acute respiratory syndrome coronavirus 2, Severe

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Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), was first reported in Wuhan, China, at the end of 2019, and the World Health Organization declared an international public health emergency in January 2020. During the three years of the COVID-19 pandemic, the variation of SARS-CoV-2 caused the infectivity to increase while virulence to decrease [1]. With the release of the epidemic situation of COVID-19 in late 2022 in China, case numbers roared, including neonatal cases. Among the patients infected with the Omicron variant, the elderly tended to develop severe illness, while most children were asymptomatic or only had mild symptoms [2, 3]. Likewise, although neonatal COVID-19 might cause severe presentation or death, most neonates had only developed mild illnesses [4]. However, there were few multi-center studies on the epidemiological and clinical characteristics of neonatal COVID-19 in China. Therefore, this study aimed to explore the clinical characteristics, treatment, and short-term outcomes of neonatal SARS-CoV-2 infection after the release of the epidemic situation of COVID-19.

Methods

Study design and patient selection

This was a multi-center cross-sectional study using retrospective data from four hospitals after the release of the COVID-19 pandemic. We extracted data from neonates diagnosed with SARS-CoV-2 infection between December 11, 2022, and January 12, 2023. Eligibility criteria required neonates to have a positive reverse transcription polymerase chain reaction (RT-PCR) or positive antigen test or positive serological tests. The exclusion criteria included patients with asphyxia, meconium aspiration, bacterial infection, which could have presentations similar to severe COVID-19. The cohort was divided into two groups according to the definition of COVID-19 severity in neonates [4, 5]. Severe COVID-19 was diagnosed if the case met at least two of the following three categories: (1) any of the clinical symptoms including hyperthermia (>37.5℃), apnea, cough, tachypnea, respiratory distress or failure, respiratory support, poor feeding or vomiting, or diarrhea; (2) laboratory examination including low white blood cell (WBC) count ($<5\times10^9$/L), low lymphocyte count ($<1\times10^9$/L), or raised C-reactive protein (CRP) concentration (>5 mg/L); (3) auxiliary examination including an abnormal chest X-ray or computed tomography (CT) or diagnosis of pneumonia [4, 5].

Data collection

Demographic, clinical, laboratory, radiological treatment and prognostic data of neonatal SARS-CoV-2 infection were obtained from the electronic medical records of the hospitals, including: (1) demographic characteristics: age, gestational age, sex, birth weight; (2) main clinical symptoms and vital signs at admission: fever, respiratory symptoms, gastro intestinal symptoms, neural symptoms; (3) main laboratory findings: WBC count, lymphocyte count, platelet count, CRP, ALT, aspertate aminotransferase (AST), N-terminal pro-brain natriuretic peptide (NT-proBNP); (4) treatment and prognostic data: use of supportive treatment and length of stay (LOS).

Statistical analysis

Data statistics and analysis were accomplished by SPSS 27. Normally distributed continuous variables, analyzed using student t-tests, were presented with means and standard deviations (SDs), whereas those with abnormal distributions, analyzed using Mann-Whitney U rank-sum tests, were presented using medians and interquartile ranges (IQRs). Categorical variables were described as counts and percentages and were analyzed by Chi-square and Fisher exact tests. A P value<0.05 was considered significant.

Results

Demographics

In this study, 190 neonates were diagnosed with COVID-19 between December 11, 2022, and January 12, 2023, in four hospitals in the Yangtze River Delta, East China. They all had a positive laboratory test (either a nucleic acid test or a COVID-19 antigen self-test kit) for SARS-CoV-2. Three patients were excluded from this study, one for diagnosis of bacterial pneumonia, one for early onset sepsis and one for suppurative meningtis. Totally, 187 infants were included in this study. Table 1 showed the demographics and medical history of them. 84 infants met the criteria for severe illness (44.9%) and 103 infants were in the nonsevere group. Most patients were full-term newborns; the median age at admission was 17 days. There was no significant difference in gestational age, birth weight, and mode of delivery between the two groups ($P>0.05$). Of these, 139 neonates (74.3%) had confirmed exposure to SARS-CoV-2, while 47 neonates had unknown epidemiological evidence. The most source of infection was their cohabitants.

Clinical presentations

We collected clinical symptoms of the neonates in Table 2. Regardless of severity, the most common symptom was fever (75.4%). Respiratory symptoms were presented in 71.7% of all infants. Tachypnea and cough were more common in the severe group than in the nonsevere group ($P<0.05$). Only one patient in the severe group had tachypnea, grunting, distinct retractions and cyanosis. Symptoms of the digestive system (36.9%) and the nervous system (13.9%) were relatively uncommon in all

Table 1 Demographics of the neonates with COVID-19

	Total (*n* = 187)	Severe group (*n* = 84)	Nonsevere group (*n* = 103)	*P*
Age at admission, d, median (IQR)	17(8–23)	18.5(11–24)	15 (6–23)	0.034*
Gestational Age, w, n (%)				0.259
32–36^{+6}	11(5.9)	3(3.6)	8(7.8)	
37–41^{+6}	174(93.0)	81(96.4)	93(90.3)	
≥ 42	1(0.5)	0	1(1.0)	
Unknown	1(0.5)	0	1(1.0)	
Sex, n (%)				0.067
Female	94(50.3)	36(42.9)	58(56.3)	
Male	93(49.7)	48(57.1)	45(43.7)	
Birth Weight, g, n (%)				0.274
< 2500	8(4.3)	2(2.4)	6(5.9)	
2500–3999	168(89.8)	79(94.0)	89(87.3)	
≥ 4000	10(5.3)	3(3.6)	7(6.9)	
Unknown	1(0.5)	0	1(1.0)	
Mode of delivery, n (%)				0.652
Cesarean	88(47.1)	38(45.2)	50(48.5)	
Vaginal	99(52.9)	46(54.8)	53(51.5)	
Source of infection, n (%)				0.099
Parents	116(62.0)	51(60.8)	65(63.1)	
Other cohabitants	24(12.8)	16(19.0)	8(7.8)	
Unknown	47(25.1)	17(20.2)	30(29.1)	

Table 2 Clinical symptoms and vital signs at admission of the neonates with COVID-19

	Total (*n* = 187)	Severe group (*n* = 84)	Nonsevere group (*n* = 103)	*P*
Clinical Symptoms				
Fever, n (%)	141(75.4)	62(73.8)	79(76.7)	0.648
Highest temperature, mean ± SD	38.2 ± 0.5	38.2 ± 0.5	38 ± 0.4	0.083
Respiratory symptoms, n (%)	134(71.7)	72(85.7)	62(60.2)	0.000*
Tachypnea, n (%)	16(8.6)	13(15.5)	3(2.9)	0.002*
Cough, n (%)	97(51.9)	56(66.7)	41(39.8)	0.000*
Nasal congestion, n (%)	81(43.3)	40(47.6)	41(39.8)	0.283
Nasal discharge, n (%)	26(13.9)	13(15.5)	13(12.6)	0.575
Gastro-intestinal symptoms, n (%)	69(36.9)	30(35.7)	39(37.9)	0.762
Vomiting, n (%)	6(3.20)	2(2.4)	4(3.9)	0.557
Diarrhea, n (%)	9(4.8)	4(4.8)	5(4.9)	0.977
Anorexia, n (%)	57(30.5)	25(29.8)	32(31.1)	0.847
Neural symptoms, n (%)	26(13.9)	12(14.3)	14(13.6)	0.892
Lethargy, n (%)	25(13.4)	12(14.3)	13(12.6)	0.739
Seizure, n (%)	2(1.1)	0	2(1.9)	0.121
Vital signs at admission				
Heart rate, bpm, mean ± SD	141 ± 12	143 ± 12	143 ± 13	0.881
Respiratory rate, bpm, mean ± SD	44 ± 7	44 ± 7	45 ± 7	0.366
Systolic blood pressure, mmHg, mean ± SD	75 ± 8	76 ± 8	75 ± 8	0.112
Diastolic blood pressure, mmHg, median (IQR)	40(35–45)	42(35–46)	39(35–43)	0.127
SpO2, %, mean ± SD	97 ± 7	96 ± 12	98 ± 1	0.155
Temperature, ℃, mean ± SD	37.2 ± 0.6	37.3 ± 0.6	37.3 ± 0.6	0.998

infants. None of the patients had symptoms indicating heart failure. Vital signs at admission of most patients were within normal limits, and there was no statistical difference between two groups ($P > 0.05$).

Laboratory findings

The laboratory data were presented in Table 3. The patients in the severe group had lower WBC count than those in the nonsevere group ($P < 0.05$) and

Table 3 Laboratory findings, Treatment and Outcome of the neonates with COVID-19

	Total (*n* = 187)	Severe group (*n* = 84)	Nonsevere group (*n* = 103)	*P*
Laboratory Findings				
CRP > 5 mg/L, n (%)	15(8.0)	13(15.5)	2(1.9)	0.001*
WBC count, /L, median (IQR)	7.87(5.91–10.15)	7.01(5.77–9.99)	7.97(6.60–9.69)	0.010*
WBC count < 5×10^9/L, n (%)	22(11.8)	21(25)	1(1.0)	0.000*
Lymphocyte count, /L, mean ± SD	3.38 ± 1.79	3.30 ± 1.93	3.45 ± 1.69	0.164
Lymphocyte count < 1×10^9/L, n (%)	13(7.0)	11(13.1)	2(1.9)	0.009*
NLR, mean ± SD	1.32 ± 1.32	1.27 ± 1.18	1.36 ± 1.43	0.546
PLT, 10^{12}/L, mean ± SD	268 ± 86	253 ± 87	281 ± 83	0.794
PLR, mean ± SD	104.61 ± 69.46	106.06 ± 69.33	103.42 ± 69.89	0.201
SII, median (IQR)	231.92(141.36-414.11)	160.89(107.26-261.36)	182.75(107.58-298.67)	0.285
Hb, g/dl, mean ± SD	150 ± 26	149 ± 25	150 ± 27	0.882
Na < 135mmol/L, n (%)	49(26.2)	28(33.3)	21(20.4)	0.080
ALT, U/L, mean ± SD	22.04 ± 11.77 (*n* = 186)	24.71 ± 12.76 (*n* = 84)	19.84 ± 10.46 (*n* = 102)	0.073
ALT > 40U/L, n (%)	14(7.5) (*n* = 186)	10(11.9) (*n* = 84)	4(3.9) (*n* = 102)	0.037*
AST, U/L, mean ± SD	50.29 ± 29.36 (*n* = 186)	50.86 ± 19.85 (*n* = 84)	49.82 ± 35.42 (*n* = 102)	0.237
AST > 40U/L, n (%)	111(59.4) (*n* = 186)	56(66.7) (*n* = 84)	55(53.9) (*n* = 102)	0.078
TnI, ng/mL, median (IQR)	0.050(0.040–0.070) (*n* = 103)	0.053(0.040–0.070) (*n* = 55)	0.052(0.041–0.076) (*n* = 48)	0.738
NT-proBNP, pg/mL, median (IQR)	1372(681–2135) (*n* = 96)	1708(701–2641) (*n* = 56)	1144(558–1834) (*n* = 40)	0.056
NT-proBNP > 2000 pg/mL, n (%)	28(29.2) (*n* = 96)	19(38.0) (*n* = 56)	9(19.6) (*n* = 40)	0.035*
Treatment				
Physical cooling, n (%)	31(16.7)	15(17.9)	16(15.7)	0.693
Oxygen therapy, n (%)	5(2.7)	3(3.6)	2(1.9)	0.817
Non-invasive ventilation, n (%)	1(0.5)	1(1.2)	0	0.449
Ambroxol, n (%)	25(13.4)	22(26.2)	3(2.9)	0.000*
Budesonide nebulization, n (%)	44(23.5)	31(36.9)	13(12.6)	0.000*
Nasal drops, n (%)	34(20.5)	22(28.9)	12(13.3)	0.013*
Antibiotics, n (%)	79(42.2)	49(58.3)	30(29.1)	0.000*
Corticosteroids, n (%)	2(1.1)	2(2.4)	0	0.200
IVIG, n (%)	1(0.5)	1(1.2)	0	0.449
Dopamine, n (%)	1(0.5)	1(1.2)	0	0.449
Outcome				
LOS, d, median (IQR)	4(3–6)	5(4–8)	5(4–6)	0.013*

CRP C-reactive protein; WBC white blood cell; NLR neutrophil to lymphocyte ratio; PLT platelet; PLR platelet to lymphocyte ratio; SII systemic immune-inflammation index; Hb hemoglobin; ALT alanine transaminase; AST aspertate aminotransferase; TnI troponin I; NT-proBNP N-terminal pro-brain natriuretic peptide; IVIG intravenous immunoglobulin; LOS length of stay

the percentage of the patients with low WBC count (<5×109/L) was also higher in the severe group than that in the nonsevere group. More patients had raised CRP (>5 mg/L) in the severe group than those in the nonsevere group (15.5% vs. 1.9%) ($P<0.05$). More patients had low lymphocyte count (<1×109/L) in the severe group than in the nonsevere group (13.1% vs. 1.9%) ($P<0.05$). However, there was no statistical difference in neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and systemic immune-inflammation index (SII) between the two groups ($P<0.05$). There was also no statistical difference in hyponatremia between the two groups ($P>0.05$). In addition, more patients in the severe group had high ALT level (>40U/L) and high NT-proBNP (>2000pg/mL) than those in the nonsevere group ($P<0.05$).

Treatment and outcomes

None of the patients met the criteria of MIS-N. The treatment and outcomes of the neonates with COVID-19 were also shown in Table 3. The supportive treatment included physical cooling, expectorant (Ambroxol),

budesonide nebulization, nasal drops, etc. Only five neonates received oxygen therapy or non-invasive ventilation. There was a significantly higher rate of expectorant, budesonide nebulization, and nasal drops use in the severe group than in the nonsevere group ($P<0.05$). There were more cases who received antibiotics in the severe group than in the nonsevere group ($P<0.05$). Two cases with wheezing received corticosteroids, and one case with thrombocytopenia received intravenous immunoglobulin (IVIG). None of the infants received specific antiviral agents. All neonates were discharged home, and the LOS was higher in the severe group than in the nonsevere group ($P<0.05$).

Discussion

This multi-center retrospective study found that more neonatal cases with severe COVID-19 had higher liver enzymes (ALT>40U/L) and NT-proBNP (>500 pg/mL), and the outcome was satisfying after the release of the epidemic situation of COVID-19 in China. There was no evidence of vertical transmission in neonates born to mothers with COVID-19 [6, 7]. However, immaturity of both innate and adaptive immune systems makes neonates highly vulnerable to infection [8, 9]. Devin J et al. showed that 71 (7.7%) of 918 neonates had severe COVID-19 in the United States [4]. However, in our study, nearly half of the patients met the criteria for severe COVID-19, which might be explained by the fact that some nonsevere neonates were observed and treated at home because of the limited beds in the hospitals at that time. Fortunately, none of the neonates developed severe complications like MIS-N or died in our cohort. It was reported that neonates with critical illness usually had a higher incidence of comorbidities [4]. However, neonates with severe diseases in neonatal intensive care unit were not infected with COVID-19 due to strict protective measures during this study period.

It was reported that vaccination with two doses of mRNA vaccine in pregnant women could effectively prevent infants (under six months) from hospitalization and critical illness due to SARS-CoV-2 infection [10]. In our study, most neonates were infected with SARS-CoV-2 by contact infection, and most of their mothers did not receive SARS-CoV-2 vaccine during pregnancy. All patients in our study were infected with the Omicron variant. The severity caused by the Omicron variant dominated in this pandemic was significantly less than that caused by previous variants, with lower incidence of comorbidities than the Alpha or Delta waves [11]. In 676 pediatric cases hospitalized in Shanghai Children's Medical Center, the most common symptom was fever, cough and rhinorrhea [11]. Shen N et al. revealed that children with high viral load tended to have low WBC counts, neutrophil counts and platelet counts [11]. As for neonates, the clinical symptoms were nonspecific [7]. Fever was not as common as in older patients, and they were inclined to have more obvious respiratory symptoms, more abnormal laboratory findings, more clinical intervention, and longer lengths of stay [12, 13]. In this study we found that most of the patients had respiratory symptoms, including cough, nasal discharge, tachypnea. Some patients had low WBC counts and low lymphocyte counts. It was reported that NLR and SII increased in neonates born to COVID-19 mothers [14]. In adult COVID-19, NLR was effective in prognosticating patient outcomes, including but not limited to severe disease, hospitalization, intensive care unit admission, intubation, and death, while SII outperformed it in predicting outcomes [15, 16]. Furthermore, Cai J et al. found that NLR determined the clinical efficacy of corticosteroids [17]. PLR also had certain prognostic value in determining severe cases together with NLR and SII [18]. However, there was no statistical difference in NLR, PLR and SII between severe and nonsevere neonatal cases in this study. Hao J et al. found that pediatric patients with moderate COVID-19 had higher cardiac troponin I (TnI) level than those with mild COVID-19 [13]. In this study, TnI level was similar in two groups, however, more neonates with severe infection had high NT-proBNP level than nonsevere cases. We also found more patients with severe infection had high ALT level than those with nonsevere infection, which was rarely mentioned in previous studies. A few children developed life-threatening complications like multisystem inflammatory syndrome (MIS-C), and the mortality of MIS-N was significantly higher than in older children because the symptoms of MIS-N were less typical, and it was more likely to be misdiagnosed as sepsis at the early stage of the disease [12, 19].

Most neonatal patients only received supportive treatment for COVID-19 [19]. There were few studies on the effect of antiviral drugs like Paxlovid in children under twelve, and Liu GB et al. showed that it did not reduce the vial shedding time in three severely illed children [20]. It was reported that corticosteroids, IVIG, and Remdesivir were used for critical illness under some circumstances [21]. None of the patients met the criteria of MIS-N and received specific antiviral agents in this study.

There were several limitations for this study. First, the study population was limited to neonatal inpatients recorded in the electronic medical record system rather than all SARS-CoV-2-positive neonates. Incidence and mortality of COVID-19 were not available in our study. Second, some SARS-CoV-2-positive neonates were not hospitalized, so this cohort might need to be more representative. Furthermore, this study was a retrospective study, so there could be some missing data and possible ascertainment bias.

In conclusion, our study presented a comprehensive characteristic of neonatal COVID-19 in late 2022 in China. The neonatal cases with severe COVID-19 had higher liver enzymes and NT-proBNP levels. Few specific medical interventions were given, and the prognosis was satisfying. Our findings provide clinical information that could inform further research and policy decisions for the subsequent waves of the pandemic that might happen in the future.

Abbreviations

COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
ALT	Alanine transaminase
NT-proBNP	N-terminal pro-brain natriuretic peptide
LOS	Length of stay
MIS-N	Multisystem inflammatory syndrome in neonates
RT-PCR	Reverse transcription polymerase chain reaction
WBC	White blood cell
CRP	C-reactive protein
CT	Computed tomography
AST	Aspertate aminotransferase
SD	Standard deviation
IQR	Interquartile range
NLR	Neutrophil to lymphocyte ratio
PLR	Platelet to lymphocyte ratio
SII	Systemic immune-inflammation index
Hb	Hemoglobin
TnI	Troponin I
IVIG	Intravenous immunoglobulin
MIS-C	Multisystem inflammatory syndrome

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None.

Author contributions
SYX, FB and CC analyzed the data and drafted the manuscripts. LQX, XHG and JJW collected and interpreted the data. YJZ supervised the study. HFH, HPX conceived and designed the study. All authors read and approved the final version of this manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was reviewed and approved by Ethics Committee of Xinhua Hospital (Approval No. XHEC-D-2023-156). The need for informed consent was waived by the Ethics Committee of Xinhua Hospital because of the retrospective nature of the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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