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Prevalence and outcomes of neonates with severe COVID-19: An observational study at Children's Hospital 1 in Ho Chi Minh City, Vietnam

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ABSTRACT

Objective: To evaluate the impact of the severe COVID-19 pandemic on neonates and develop strategies to improve their outcomes.

Methods: We conducted an observational cross-sectional study at Children's Hospital 1 (CH1) from July 25, 2021, to May 31, 2022. All neonates who had fever or respiratory symptoms or were born from mothers with COVID-19 and had a positive RT-PCR SARS-CoV-2 result would be included. We classified neonates with COVID-19 into 2 groups: mild/moderate and severe for analysis. Differences between groups were analyzed using Fisher's exact test/*Chi*-square test for categorical variables and Student's *t*-test/Wilcoxon Rank Sum test for continuous variables.

Results: This study included 88 newborns who had positive RT-PCR SARS-CoV-2 results. The severity COVID-19 rate among neonatal cases was found to be 13.6% (12/88), with a corresponding mortality rate of 1.1% (1/88). All severe cases showed lung abnormalities as evident on chest X-ray images. In addition to respiratory symptoms, a higher incidence of gastrointestinal manifestations, such as vomiting and diarrhea, was observed in the severe group, indicating a compelling association. The administration of anticoagulant and anti-inflammatory drugs in the study group resulted in a satisfactory outcome with no significant complications.

Conclusions: The COVID-19 pandemic has had a substantial impact on the well-being of neonates. The management of COVID-19 in this population presents significant challenges.

KEYWORDS: COVID-19; Neonate; Anti-inflammatory; Anticoagulant

1. Introduction

The COVID-19 pandemic has had a significant global impact on healthcare systems and economies, including Vietnam[1-3]. As of October 2023, the worldwide number of confirmed cases has exceeded 700 million, with 6 million deaths, and complex situations persist in many regions[4]. Vietnam has experienced multiple waves of COVID-19, with the most severe wave occurring from May to the

Significance

Existing knowledge on the impact of severe COVID-19 on neonates is limited, and there is a scarcity of clinical data and evidence regarding its incidence and treatment outcomes in this population. This study reveals that most neonatal COVID-19 cases in Vietnam experience mild to moderate symptoms. However, a small percentage still have severe symptoms that require more intensive interventions such as respiratory support, anticoagulants, and anti-inflammatory drugs. It provides valuable insights into the prevalence, outcomes, and management strategies of severe COVID-19 in neonates.

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end of 2021 in terms of infections and fatalities[5].

While severe cases of COVID-19 are mainly observed in adults, neonates and young children are also susceptible to serious consequences, including fatalities, associated with this infectious disease[6–8]. The symptoms of COVID-19 in children resemble those in adults, but their occurrence varies[9–11]. Additionally, the signs and symptoms of COVID-19 in children overlap with those of other infectious or non-infectious diseases, posing challenges for symptom-based screening[12–14]. Some children, especially those with underlying medical conditions, may develop severe illness requiring hospitalization, intensive care, or ventilatory support[15,16].

Although the impact of COVID-19 on neonates is crucial, information on the incidence and treatment outcomes in this vulnerable population is limited[6,17]. The scarcity of clinical data and evidence necessitates active research efforts to gain a comprehensive understanding of managing COVID-19 in infants[18]. Furthermore, variations in national epidemic strategies, treatment guidelines, and the availability of therapeutic drugs further influence the management of COVID-19 in children across different countries[11]. Therefore, this study aims to bridge this knowledge gap by collecting and analyzing data on the incidence of severe COVID-19 infections in neonates in Vietnam, while also evaluating treatment outcomes for these cases. Moreover, we also aim to provide valuable insights to the medical community, especially pediatric experts, and healthcare policymakers. The findings will enhance the ability to identify and treat COVID-19 in neonates, leading to improved strategies and outcomes for this vulnerable population. Through these efforts, we strive to contribute to the ongoing endeavors to mitigate the impact of COVID-19 on neonates and foster a brighter future for the younger generation amidst this global pandemic.

2. Subjects and methods

2.1. Study design

We performed an observational cross-sectional study at Children's Hospital 1 (CH1) at Ho Chi Minh city, Vietnam from July 25, 2021 to May 31, 2022.

2.2. Participants characteristics

All neonates with fever or respiratory symptoms or born from mothers with COVID-19 would be screened by antigen testing, if the child or caregiver is positive for COVID-19, the child was admitted to the COVID-19 ward. The antigen rapid test used at our hospital is the Panbio™ COVID-19 Ag Rapid Test Device from Abbott Diagnostics, Inc.. After then, SARS-CoV-2 infection condition would be confirmed by Realtime Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test within 24 hours after admission. Patients hospitalized for suspected COVID-19 but had negative RT-PCR results were excluded. All the neonates with COVID-19 confirmed by a positive RT-PCR SARS-CoV-2 result were included. Nasopharyngeal specimens were collected using Xpert FLOQSwabs® kit (COPAN Italia). The nasopharyngeal specimens were then fixed in the solution of Liofilchem s.r.l.. Nucleic acid extraction and RT-PCR were performed on CFX96 Touch Real-Time PCR Detection System (BIO-RAD) and Realtime PCR Rotor-Gene Q MDx (QIAGEN). The target genetic region for RT-PCR SARS-CoV-2 test in our hospital was *E* gene. RT-PCR was performed according to the procedures of the Microbiology Department, CH1 (validated and licensed by the Vietnam Ministry of Health).

Disease severity categorization was based on pediatric COVID-19 guidelines of the Ministry of Health of Vietnam (Supplementary Table 1). Results of laboratory investigations and chest radiography done at admission were collected. All patients were routinely tested including complete blood count, C-reactive protein, ferritin at the time of admission. Chest X-ray was taken when pneumonia was suspected. Moderate and severe cases would be further tested for liver function, kidney function and complete coagulation status. Biochemical tests were performed by BECKMAN COULTER AU-680 machine (Beckman Coulter, Inc.) at the Department of Biochemistry, CH1. The total blood count and coagulation test were performed by the Sysmex XN-2000TM (Sysmex America, Inc.) and STA R-Max machine (Stago Inc.), respectively, at the Department of Hematology Laboratory, CH1. Chest X-ray results were evaluated by radiologist of CH1.

2.3. Statistical analysis

Data were expressed as mean ± standard deviation (SD) for normally distributed continuous variables and as median with interquartile range (IQR) for abnormally distributed continuous variables. Categorical variables were presented as frequencies and percentages. Differences between the mild-moderate and severe/critical groups were analyzed using Fisher's exact test/*Chi*-square test for categorical variables, and Student's *t*-test/ Wilcoxon Rank Sum test for continuous variables. Statistical analysis was conducted through STATA 14, and a two-tailed $P<0.05$ was considered statistically significant.

2.4. Ethics consideration

This study was approved by the ethics committee of the CH1 with research code is CS/N1/21/65.

3. Results

3.1. Epidemiological characteristics

From July 25, 2021, to May 31, 2022, our center delivered comprehensive care and treatment to a group of children suspected or confirmed to have contracted SARS-CoV-2. Among the 103 patients included in our study, we employed PCR testing to confirm the presence of the virus and successfully identified 88 newborns who tested positive for this specific viral strain. It is worth noting that we observed two distinct peaks in diagnoses, which coincided with the waves of the pandemic in Vietnam occurring in August 2021 and March 2022 (Figure 1).

The median age of the newborns included in our study was 21 days, with the youngest being a mere two days old. Of the reported cases, 47 (53.4%) were male, while 41 (46.6%) were female, resulting in a male-to-female ratio of 1.12. However, no statistically significant sex-based differences were observed in relation to the severity of the disease. It is worth noting that a majority of the newborns (78.4%) (69/88) was born from mothers with COVID-19.

3.2. Clinical manifestations and disease severity

Regarding the severity distribution, the majority of cases (86.4%) (76/88) were classified as mild/moderate, while the remaining 13.7% (12/88) were categorized as severe/critical. This distribution aligns with previous studies, indicating that severe cases did not predominate among newborns. Clinical manifestations exhibited by the newborns encompassed a range of symptoms, with fever being the most prevalent, reported in 76.1% (67/88) of the cases. Additionally, a notable proportion experienced feeding difficulties (14.8%) (13/88) and jaundice (14.8%) (13/88). Underlying diseases were identified in 13 neonates (14.8%) (Table 1). These diseases included 5 unoperated and surgically corrected congenital heart disease cases, 4 congenital malformation cases, and 4 premature birth cases (the smallest gestational age was 32 weeks, and there were no cases of hyaline membrane disease). It is important to mention these underlying diseases, as we acknowledge the potential correlation between their presence and an increased likelihood of a severe disease course among the neonatal patients.

3.3. Laboratory findings

Laboratory investigations revealed normal white blood cell counts in all 88 patients. Although the elevation of C-reactive protein (CRP) levels was not recorded, elevated ferritin levels were consistently observed. Notably, *D*-dimer levels were measured in 30 patients, with 66.7% (20/30) exhibiting concentrations five times higher than the normal range. However, no statistically significant difference was observed between the severe/critical and mild/moderate

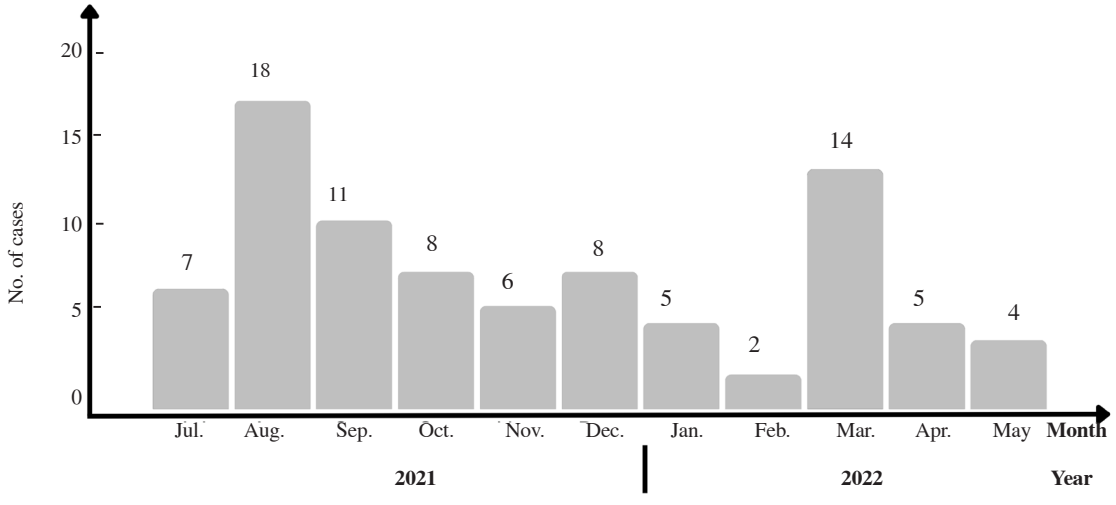

Figure 1. Number of confirmed COVID-19 neonates during the study period.

groups in terms of *D*-dimer levels. Instead, chest X-rays were performed, revealing distinct lung abnormalities that facilitated the differentiation of the two aforementioned groups. Among the severe cases, all exhibited lung lesions on their chest X-rays, with interstitial lesions being the predominant type (58.3%) (7/12). Consolidation and lung collapse were also observed in a subset of cases (Table 2). In terms of coagulation indices, a trend was observed towards normalization both before and after anticoagulant treatment in both moderate and severe/critical groups. When comparing coagulation indices between the moderate and severe/critical groups before and after anticoagulation treatment, we noted a statistically significant decrease in the *D*-dimer index after treatment in the moderate group. However, this difference in the severe/critical group did not reach statistical significance, indicating the need for further investigation (Table 3).

3.4. Treatment characteristics

Respiratory support was required in 25% (22/88) of the study population, with oxygen therapy *via* nasal cannula being the most commonly employed method (14.8%) (13/88). Mechanical ventilation and continuous positive airway pressure (NCPAP) were utilized in 3 and 2 patients, respectively. Notably, all cases requiring oxygen therapy *via* nasal cannula in the mild/moderate group had underlying conditions such as congenital heart disease, hematological disorders, or preterm birth. Among the severe cases, mechanical ventilation was required in two patients, unfortunately resulting in one fatality. Additionally, one case in the mild/moderate group necessitated mechanical ventilation following PDA stent placement.

Treatment interventions included corticosteroids, anticoagulant medication, antibiotics, and antiviral therapy. The indications for anti-inflammatory and anticoagulant treatments are presented in Supplementary Table 1. Corticosteroids were administered in 25% (22/88) of cases, with an average treatment duration of 7.2 days. Among the mild/moderate group, eleven patients received corticosteroid treatment. Anticoagulant medication was utilized in 21 cases, with an average treatment duration of 6.8 days. Antibiotics were prescribed to 83% (73/88) of the study population due to the severity of illness or the inability to rule out bacterial co-infection. Notably, differences were observed between the mild/moderate and severe/critical groups in terms of the choice of antibiotics. Carbapenems and vancomycin were more frequently administered in the severe /critical cases. Remdesivir, an antiviral medication, was employed in our study, consistent with its usage in Vietnam. However, due to the challenges associated with its availability and regulatory approval in the neonatal population, only a small subset of cases received remdesivir (Table 4).

4. Discussion

Although the COVID-19 pandemic has subsided, its enduring repercussions continue to yield profound medical insights. While neonates generally exhibit milder symptoms compared to adults, studying pediatric cases offers invaluable insights into the pathogenesis, modes of transmission, and immune responses elicited by the virus[9,17]. Our research conducted at CH1, a prominent pediatric center in southern Vietnam, provides findings that resonate with the wider pediatric population in this region.

Table 1. Clinical characteristics of the study groups.

Characteristics	Total (*n*=88)	Mild-Moderate (*n*=76)	Severe/Critical (*n*=12)	*Z*/ χ^2	*P* value
Age, days, median (IQR)	21 (12.5-30.0)	21 (13.0-30.0)	21.5 (12.5-28.0)	0.17	0.88*
Male, *n* (%)	47 (53.4)	40 (52.6)	7 (58.3)	0.13	0.71***
Female, *n* (%)	41 (46.6)	36 (47.4)	5 (41.7)		
Born from mothers with COVID-19, *n* (%)	69 (78.4)	58 (76.3)	11 (91.7)	1.44	0.23**
Underlying disease, *n* (%)	13 (14.8)	8 (10.5)	5 (41.7)	7.98	<0.01***
Clinical symptom, *n* (%)					
Fever	67 (76.1)	58 (76.3)	9 (75.0)	0.01	0.92**
Cough	29 (33.0)	23 (30.3)	6 (50.0)	1.83	0.18***
Dyspnea/Tachypnea	15 (17.1)	7 (9.2)	8 (66.7)	24.19	<0.01**
Vomiting	16 (18.2)	11 (14.5)	5 (41.7)	5.15	0.02***
Runny nose	12 (13.6)	10 (13.2)	2 (16.7)	0.11	0.74**
Diarrhea	14 (15.9)	9 (11.8)	5 (41.7)	6.89	<0.01***
Poor latch	13 (14.8)	10 (13.2)	3 (25.0)	1.15	0.28**
Jaundice	13 (14.8)	11 (14.5)	2 (16.7)	0.04	0.84**

*: Wilcoxon Rank Sum test; **: Fisher's exact test; ***: *Chi*-squared test.

Table 2. Laboratory characteristics of the study groups.

Laboratory characteristics	Total (*n*=88)	Mild–Moderate (*n*=76)	Severe/Critical (*n*=12)	*P*–value	NR
WBC count, $\times10^9$/L, median (IQR)	9.6 (7.5–11.3)	9.7 (7.7–12.0)	7.6 (5.6–9.6)	0.04*	4.0–12.0, $\times10^9$/L
Neutrophil count, $\times10^9$/L, median (IQR)	2.7 (1.7–3.8)	2.7 (1.6–3.7)	2.8 (2.1–3.8)	0.81*	3.0–5.8, $\times10^9$/L
Lymphocyte count, $\times10^9$/L, median (IQR)	4.6 (3.4–5.6)	4.7 (3.7–5.7)	3.1 (1.7–4.1)	<0.01*	1.5–3.0, $\times10^9$/L
Platelet count, $\times10^9$/L, median (IQR)	306 (241–384)	311 (248–385)	260 (195–336)	0.11*	150–400, $\times10^9$/L
CRP, mg/L, median (IQR)	0.7 (0.3–1.3)	0.7 (0.3–1.3)	0.7 (0.5–4.0)	0.13*	< 5, mg/L
Ferritin, μg/L, median (IQR)	534 (377–777)	525 (377–756)	600 (533–842)	0.36*	6–60, μg/L
AST, U/L, median (IQR)	45.6 (36.0–58.3)	38.0 (35.1–45.0)	59.1 (45.2–65.5)	0.11*	15–60, U/L
ALT, U/L, median (IQR)	26.0 (19.0–31.4)	25.0 (22.7–32.0)	26.7 (18.7–31.4)	0.57*	13–45, U/L
E gene Ct value, median (IQR)	18.8 (16.7–23.1)	18.4 (16.6–22.5)	18.5 (17.0–23.1)	0.80*	
PT, s, median (IQR)	13.5 (12.4–14.6)	13.4 (12.8–14.1)	13.9 (12.4–16.5)	0.20*	13.1–16.3, s
APTT, s, median (IQR)	38.3 (34.5–43.4)	38.3 (34.5–42.7)	37.9 (34.4–50.3)	0.27*	28.6–35.8, s
Fibrinogen, g/L, median (IQR)	2.9 (2.2–3.4)	2.9 (2.1–3.2)	2.3 (2.2–3.4)	0.47*	2.03–3.77, g/L
D–Dimer, μg/mL, median (IQR)	0.81 (0.5–1.4)	0.8 (0.5–1.0)	0.7 (0.4–3.8)	0.24*	< 0.5, μg/mL
Chest X–ray, *n* (%)					
None	59 (67.1)	59 (77.6)	0 (0.0)	<0.01**	
Consolidation	12 (13.6)	6 (7.9)	6 (50.0)	<0.01***	
Interstitial pneumonia	14 (15.9)	7 (9.2)	7 (58.3)	<0.01***	
Atelectasis	4 (4.6)	3 (4.0)	1 (8.3)	0.50**	

*: Wilcoxon Rank Sum test; **: Fisher's exact test; ***: *Chi*–squared test. NR: normal range. WBC: white blood cell, CRP: C–reactive protein, Ct: Cycle threshold. AST: aspartate aminotransferase; ALT: alanine aminotransferase; PT: prothrombin time; aPTT: activated partial thromboplastin time.

Table 3. Coagulation characteristics before and after anticoagulant treatment according to the severity of COVID–19.

Severity	Laboratory characteristics	Before	After	*P*–value
Moderate (*n*=11)	PT, s	13.3 (12.8–13.5)	12.2 (11.9–12.3)	0.02*
	APTT, s	38.3 (35.7–43.4)	34.0 (32.7–34.8)	0.047*
	Fibrinogen, g/L	2.7 (2.2–3.1)	3.0 (2.5–3.1)	0.54*
	D–Dimer, μg/mL	0.7 (0.4–0.9)	0.5 (0.3–0.7)	0.047*
Severe/Critical (*n*=10)	PT, s	13.7 (11.9–16.5)	12.8 (11.6–13.0)	0.04*
	APTT, s	38.7 (36.1–49.4)	34.2 (30.5–38.7)	0.08*
	Fibrinogen, g/L	2.5 (2.2–3.5)	2.4 (2.0–3.0)	0.51*
	D–Dimer, μg/mL	0.8 (0.4–1.9)	0.8 (0.5–1.7)	0.41*

Data were expressed as median (IQR); *: Wilcoxon Signed Rank test.

Table 4. Treatment characteristics of the study groups [*n* (%)].

Treatment	Total (*n*=88)	Mild–Moderate (*n*=76)	Severe/Critical (*n*=12)	*P* value
Antibiotic	73 (83)	61 (80.3)	12 (100)	0.09
Penicillin	20 (22.7)	18 (23.7)	2 (16.7)	0.59
Cephalosporin	45 (51.1)	37 (48.7)	8 (66.7)	0.25
Aminoglycoside	33 (37.5)	27 (35.5)	6 (50)	0.34**
Cabapenem	5 (5.7)	1 (1.3)	4 (33.3)	<0.01
Vancomycin	4 (4.6)	1 (1.3)	3 (25)	<0.01
Redesemvir	5 (5.8)	4 (5.3)	1 (8.3)	0.67
Anti–inflammatory	22 (25.0)	11 (14.5)	11 (91.7)	<0.01
Anticoagulant	20 (22.7)	11 (14.7)	10 (83.3)	<0.01
Respiratory support				
None	66 (75.0)	66 (86.8)	0 (0.0)	<0.01
Oxygene	13 (14.7)	5 (6.5)	8 (66.7)	<0.01
NCPAP	2 (2.3)	0 (0)	2 (16.7)	<0.01
Ventilator	3 (3.4)	1 (1.3)	2 (16.7)	<0.01

Fisher's exact test was used unless otherwise stated; **: *Chi*–squared test.

The monthly distribution of cases in our study mirrors the epidemiological trends observed nationwide during the same period, characterized by two distinct peaks corresponding to the Delta and Omicron variant outbreaks in Vietnam[5]. Vertical transmission, a matter of paramount concern in the context of COVID-19 in neonates, accounted for 78.4% of the cases, while the remaining cases were attributed to postnatal cross-infection or transmissions of unknown origin[19,20].

Notably, our study revealed a relatively higher incidence of severe COVID-19 cases compared to other investigations. This disparity can be attributed to our hospital's status as a tertiary center, attracting children with underlying comorbidities or a predisposition to severe disease progression. However, the mortality rate in our study aligns with established patterns, with a solitary fatality-a preterm neonate with lung disease and severe pulmonary hypertension-yielding a mortality rate of 1.1%[7,15,21].

Alongside respiratory symptoms, it is noteworthy that our study unearthed an intriguing association between the severe group and a higher prevalence of gastrointestinal manifestations such as emesis and diarrhea. This novel finding, sparsely reported to date, adds an additional layer to our understanding of the disease's clinical presentation[10,21]. Furthermore, our analysis demonstrated a significant decrease in lymphocyte counts among individuals in the severe group, consistent with previous investigations involving both pediatric and adult populations affected by COVID-19. However, no significant differences were observed in the remaining clinical and laboratory parameters between the mild/moderate and severe groups. Consequently, constructing a predictive model to assess disease severity based on these variables presented challenges[21,22].

The treatment landscape for COVID-19 in neonates and children encountered formidable challenges during the nascent stages of the pandemic in Vietnam. The absence of standardized treatment guidelines necessitated decisions influenced by drug availability and evolving therapeutic indications[23]. Consequently, treatment rates with various pharmaceutical agents exhibited inconsistencies within our study[11,24].

Approximately equivalent proportions of cases received anti-inflammatory and anticoagulant therapies within our study. However, the empirical evidence supporting the utilization of these interventions in COVID-19-infected neonates remains limited[25]. Despite the absence of statistically significant disparities in D-dimer levels between the pre- and post-anticoagulant treatment cohorts in the severe/critical group, the relatively modest sample size of cases receiving anticoagulant therapy might have impeded the demonstration of conclusive differences. Nonetheless, clinical observations evinced discernible enhancements in inflammatory response, respiratory distress, lung injury severity, and D-dimer levels among those subjected to anti-inflammatory and anticoagulant treatment. Encouragingly, no severe adverse effects associated with these therapeutic modalities were documented in our study[25,26].

Although this observational study does not yield strong treatment recommendations for neonatal COVID-19, it provides a valuable dataset of 88 cases that experts can consult. The management of neonatal COVID-19 requires a comprehensive approach, encompassing a thorough and accurate evaluation of the disease's various aspects and characteristics. Special attention should be given to gastrointestinal symptoms such as vomiting and diarrhea beside respiratory symptoms, as well as laboratory markers like decreased lymphocyte count, which correlate with disease severity. The administration of medication in neonatal COVID-19 management poses challenges, as there is no standardized guideline available. However, drawing on the insights from this study, appropriate pharmacological interventions, including antibiotics, anti-inflammatory agents, and anticoagulants, have shown promise in improving outcomes without significant adverse effects. It is important to emphasize that caution and further research are necessary to establish robust treatment protocols for neonatal COVID-19.

The limitations of our study lie in the restricted scope of data collection, which was limited to a single healthcare center in the southern region (CH1). However, CH1 receives and treats children in Ho Chi Minh City, five adjacent provinces in the Southeast region, and 13 provinces in the Mekong Delta. Therefore, with a diverse population and large locality, CH 1 can represent the population of the southern region. Moreover, the lack of standardized treatment plans and guidelines presents challenges in decision-making, resulting in the reliance on individualized approaches. Furthermore, it is essential to recognize that symptoms involving organs beyond the respiratory system should be considered as potential sources of interference in future studies. Differentiating between symptoms related to COVID-19 and those associated with other conditions in neonates can be challenging, and this should be acknowledged to avoid potential bias. It is crucial to acknowledge that these aforementioned limitations may have implications for the generalizability and comprehensiveness of our findings. To address these limitations, future research endeavors should strive to include a more diverse and representative sample, incorporate standardized treatment protocols, and conduct long-term follow-up studies. By doing so, we can enhance the robustness and applicability of our research in the field of COVID-19 management in children.

In summary, the COVID-19 pandemic transcends being a mere historical event, serving as a profound source of valuable insights

for the field of medical science, especially in the realm of infectious diseases. With this research, we aspire to contribute to the broadening of knowledge concerning COVID-19 in children, with a particular emphasis on the vulnerable population of neonates. By delving into unexplored avenues, we aim to uncover essential understandings that can further inform medical practices and interventions in the face of this pandemic.

Conflict of interest statement

The authors declare no conflicts of interest.

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Authors' contributions

All authors played significant roles in drafting, revising, and providing final approval for the article to be submitted. PNTN, TTT, NTH, and NNQM contributed to the study's design. The data analysis and interpretation were conducted by PNTN, TTT, and NHD. DQD, TMN, TNAN, and DNCT were involved in data acquisition.

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