Clinical characteristics of neonates with coronavirus disease 2019 (COVID-19): a systematic review

Yuan Hu (547234283@qq.com)
Ministry of Education Key Laboratory of Child Development and Disorders
Jing Xiong
Ministry of Education Key Laboratory of Child Development and Disorders
Yuan Shi (shiyuan@hospital.cqmu.edu.cn)
Ministry of Education Key Laboratory of Child Development and Disorders

Systematic Review

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Abstract

This study aimed to summarize the existing literature on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in newborns to clarify the clinical features and outcomes of neonates with COVID-19. A systematic search was performed in PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Data, and VIP databases from January 1, 2019 to April 30, 2020. The references of relevant studies were also searched. A descriptive summary was organized by aspects of clinical presentations (symptoms, laboratory examinations, and imaging) and outcomes. We identified 14 studies reporting 18 newborns with COVID-19. The most common clinical manifestations were fever (62.5%), shortness of breath (50.0%), diarrhea/vomiting/feeding intolerance(43.8%), cough (37.5%), dyspnea (25.0%), and nasal congestion/runny nose/sneeze(25.0%). Atypical symptoms included jaundice and convulsion. Lymphocyte numbers decreased in 5 cases, and radiographic findings were likely to show pneumonia. All newborns recovered and discharged from the hospital, and there was no death.

Conclusion: Clinical symptoms of neonatal SARS-CoV-2 infection are atypical, most of them are mild. Up to now, the prognosis of newborns is good, and there is no death. Intrauterine vertical transmission is possible, but confirmed evidence is still lacking. The Long-term follow-up of potential influences of SARS-CoV-2 infection on neonates need further exploration.

Background

In December 2019, a cluster of patients with pneumonia of unknown etiology was identified in Wuhan, China. A previously unknown betacoronavirus was detected and was named SARS-CoV-2, which rapidly swept China and spread worldwide. The outbreak and rapid spread of SARS-CoV-2 infection have become a public health threat and emergency in the society. The neonatal intensive care unit (NICU) was not spared. However, at present, there are few reports on neonatal cases, the relevant data are not complete, and the understanding of the routes of transmission, clinical characteristics, treatment and prognosis of neonatal SARS-CoV-2 infection is not clear and unified. Therefore, it is necessary to systematically collect and evaluate the literature of neonatal COVID-19, and summarize the epidemiology, clinical characteristics and treatment measures of neonatal COVID-19, which is expected to be helpful for clinicians in the treatment of neonatal COVID-19.

Method

Search strategy

The study was registered in PROSPERO database with an ID of CRD42020178803. PubMed, Embase, Cochrane Library, CNKI, Wanfang Data, and VIP were searched for relevant studies published from January 1, 2019 to April 30, 2020. The search terms are given in Additional file 1. In addition, a hand search was performed to supplement the electronic search, and the references of relevant studies also were screened for any further material for inclusion.

Study selection

Screening and selection of literature were performed independently by two investigators, disagreements were settled by a third investigator. The inclusion and exclusion criteria were strictly followed in the process of literature screening. Inclusion criteria included: neonatal SARS-CoV-2 nucleic acid tests were positive and the language of qualified articles was confined to English or Chinese.

Exclusion criteria were as follows: First, the preliminary screening was performed by reading the title and abstract of the obtained literature, studies were excluded if they were conference papers, lectures, expert conversations, research-based on the virus and the mechanism of antiviral drugs, diagnostic reagents, molecular diagnosis, traditional reviews (excluding systematic review and meta-analysis), animals or cells as research objects, non-medical articles. Then studies lacking full-text articles were excluded, through reading the full text, the literature that can not be extracted neonatal data were excluded.

Data extraction

The following data were collected independently by two investigators: features of included studies (i.e. country, type of study, etc.), demographic data of patients (i.e. gender, gestation weeks, age, etc.), clinical symptoms (i.e. fever, diarrhea, vomiting, feeding intolerance, etc.), comorbidities (i.e. neonatal jaundice, neonatal respiratory distress syndrome, sepsis, etc.), laboratory findings (i.e. white blood cells, neutrophils, lymphocytes, platelets, hemoglobin, C-reactive protein, procalcitonin, aspartate aminotransferase, alanine aminotransferase, creatinine kinase, etc.), radiological images, treatment, and clinical outcomes.

Assessment of risk of bias of included studies

To date, most of the studies on the epidemiological and clinical characteristics of SARS-CoV-2-infected neonates are case reports and case series reports. There is no uniform bias risk assessment tool for the case report, and the bias risk assessment has not been carried out. The risk of bias of case series reports was evaluated by case series quality assessment tools.

Results

Research Selection

Based on the previous search strategy, 434 studies were searched from the online database. After deleting duplicate records, a total of 291 records were retained. 14[1-14]studies were eventually collated(see Fig. 1), comprising 9 case reports, 1 case series report, 4 cohort studies. Among them, 11 were English articles, and 3 were Chinese articles.

Assessment of risk of bias of included studies

Four studies[6,7,12,13] are cohort studies reporting on cases of infants born to SARS-CoV-2-infected mothers, in which 3 / 1 / 1 / 3 newborns were positive for SARS-CoV-2 real-time polymerase chain reaction (SARS-CoV-2-PCR), which are regarded as case reports. Article [9] is a case series report (4 cases). The case series study quality evaluation tool (IHE)[15] was used to evaluate the bias risk. IHE include 20 items, which are answered with "yes", "no" and "unclear", respectively. If the answer is "yes", the entry is judged to be "1" score, and items that meet more than 14 (70%) are acceptable bias risk. Table 1 shows that the literature [9] satisfies 14 (70%) items, which is an acceptable bias risk(Table S1).

Characteristics of included human studies and overview of findings

A total of 21 neonatal cases of COVID-19 have been reported in 14 studies. Repeated cases in these studies are as follows: the first repeated case is in the study [1] and study [9], the third repeated case is in the study [3] and study [9], the sixth repeated case is in the study [6] and study [12]. Finally, 18 cases of COVID-19 were included in this analysis.

The 18 newborns were from China (9 cases, 50%), Italy (4 cases, 22%), Spain (1), Iran (1), South Korea (1), Peru (1), and the United States (1). All newborns were positive for the SARS-CoV-2-PCR. As table 1 shows, the second newborn is the earliest infected patient who was diagnosed with SARS-CoV-2 infection on February 4, 2020. The youngest infant was the 14th newborn from Peru, who was diagnosed with SARS-CoV-2 infection only 16 hours after birth. Of these 18 cases, 6 had a clear history of contacting SARS-CoV-2 infected patients in their families, and 10 were isolated immediately after birth, because their mothers were diagnosed or suspected with COVID-19. As to the 10th and 18th cases, because their family members were not tested for SARS-CoV-2 nucleic acid, it was not possible to determine whether they had a history of contacting with SARS-CoV-2 infection(Table 1).

General information and clinical features of 18 newborns

Gestational age was described in 11 articles, patient 8 and 14 were premature infants, who underwent urgency cesarean because their mothers were confirmed with maternal COVID-19 pneumonia. The delivery of 15 newborns was reported, of whom 12 were born by cesarean and 3 by vaginal delivery. Three newborns were breastfed and more were fed with formula milk. There were 13 males (86.7%) and 2 females (13.3%), the gender of patient 14, 15, 16 were not described. The mothers of patient 4, 6, 7, 8, 11, 12, 14, 15, 16 and 17 were all suspected or diagnosed with COVID-19, so they were isolated immediately after birth.

Sixteen newborns' clinical manifestations were reported. The most common clinical manifestations were fever (62.5%), shortness of breath (50.0%), diarrhea/vomiting/feeding intolerance(43.8%), cough (37.5%), dyspnea (25.0%), and nasal congestion/runny nose/sneeze(25.0%). Atypical symptoms included jaundice and convulsion. Patient 2 had vomiting and milk refusal as the first symptom, patient 5 was admitted to hospital with fever and convulsion as the first manifestation. Patient 6 and 9 did not have any obvious clinical symptoms, but the nucleic acid tests were positive. Among the 16 newborns, there were 6 severe cases (37.5%), and three of them had complications. Patient 3 showed atrial septal defect (6.9mm) by echocardiography and was complicated with cardiac insufficiency. Patient 8 underwent neonatal resuscitation at birth with neonatal respiratory distress syndrome(NRDS) and neonatal early-onset septicemia, and patient 18 was complicated with pneumothorax(Table 2).

Laboratory examination and imaging findings of 18 newborns

Table 3 shows that blood routine were described in 11 cases, including case 1, 2, 3, 6, 7, 8, 10, 13, 18, with white blood cell(WBC) fluctuating between 4.51~20.4(×10^9/L), lymphocyte(L) number decreased in case 4, 7, 8, 10, 18. Patient 3 was reported with anemia with a hemoglobin of 85(g/L). Thrombocytopenia had been reported in patient 2 and 8. Fortunately, all of these cases were normal when reexaminating during hospitalization. C-reactive protein(CRP) and procalcitonin(PCT) increased significantly in the 18th case. The liver function was abnormal in the 4th case, which showed slight increase of transaminase and serum total bilirubin, and no renal function impairment was found in all reports. The laboratory examinations of patient 3, 4, 5, 7 showed myocardial function damage, patient 3 showed an increase in N-Terminal pro-brain natriuretic peptide(NT-proBNP) , patient 4 showed an increase in creatine kinase(CK), patient 5 showed an increase in serum creatine kinase and lactate dehydrogenase(LDH), and patient 7 showed an increase in the level of creatine kinase isoenzymes (CK-MB) .

Nasopharyngeal swabs were positive for SARS-CoV-2 in all newborns, and anal swabs was performed in 8 newborns, of which 7 were positive.

Imaging examinations were mentioned in 10 cases. Chest X-ray of Patient 1, 2, 3, 4, 6, 7, 8, 18 showed pneumonia, and other abnormal chest radiograph appearances including neonatal respiratory distress syndrome in case 8 and unilateral lesions and pneumothorax in case 18. Six newborns had computed tomography(CT) examination, 3 cases had positive appearances. Patient 1 showed small strip blurred shadow scattered in both lung fields, patient 3 showed patchy high-density and adjacent pleural thickening, and patient 4 showed high-density nodular shadow under the pleura of the posterior segment of the upper lobe of the right lung(Table 3).

Treatment and clinical outcomes of 18 newborns

Table 4 shows that 6 cases were treated with antibiotics (6/12), 3 studies mentioned antiviral therapy, including interferon, ribavirin, lopinavir / ritonavir, and oseltamivir. 4 infants needed oxygen therapy, patient 2 needed non-invasive ventilation, and patient 14 received invasive ventilation and non-invasive ventilation for respiratory support. Seven newborns were mentioned of time that the nucleic acid test turned negative, the longest time was 21 days. The longest hospital duration was in the case 3, who was in hospital for 30 days. All newborns recovered and discharged from hospital, and there was no death.

Discussion

By May 21, 2020, COVID-19 has been confirmed in 216 countries with 4,904,413 cases and 323,412 deaths worldwide, with a mortality rate of 6.59%[17]. People of all ages are susceptible to the disease, but people with complications or the elderly are more likely to develop severe infections. Although most of the children showed mild manifestation[16], the potential harm of this disease to newborns, especially premature infants, is still unknown. To date, the largest published pediatric infection population[18], which included 2143 patients, reported that more than 90% showed asymptomatic or moderate manifestation. However, the proportion of severe and critical cases under 1-year-old is 10.6%, in contrast the proportion of 1-5 years old, 6-10 years old, 11-15 years old and over 15 years old is 7.3%, 4.2%, 4.1% and 3.0%, respectively, indicating that the risk of infants develop to severe respiratory failure may be higher than initially thought. In our study, we identified all infected newborns that had been reported by April 30, and we described the epidemiological characteristics, clinical features, treatment, and outcomes to provide help for clinical and epidemic prevention and control of the disease. To our best knowledge, this review is the largest to date describing clinical features of SARS-CoV-2 infection in neonates.

There is still no powerful conclusion on the intrauterine transmission of SARS-CoV-2 and the possibility of breastfeeding. There were 3 cases of early-onset SARS-CoV-2 infection in literature [6]. Because strict infection control and prevention procedures were implemented during delivery, and newborns were isolated immediately after delivery, the way of these three newborns infection was probably maternal, but unfortunately there was no virus test for amniotic fluid, placenta or umbilical cord blood. In literature [4], author described delivery process in detail, the mother had been wearing an N95 mask throughout the operation, and the baby had no contact with the mother after birth, they performed nucleic acid tests for SARS-CoV-2 on cord blood and placenta specimens, but the results were negative, and the mother's breast milk sample was negative for SARS-CoV-2 as well. Chen[19] et al tested 9 maternal amniotic fluid, umbilical cord blood and neonatal throat swab samples, all of which were negative for SARS-CoV-2, indicating that there was no intrauterine fetal infection caused by COVID-19 infection in the third trimester of pregnancy. However, in literature [7], it was mentioned that the placenta and umbilical cord blood of 1 pregnant woman were positive for SARS-CoV-2-RT-PCR, and 3 samples of breast milk collected within 5 days after birth were positive, but the baby had still no SARS-CoV-2 infection after 18 days of follow-up. Therefore, the possibility of mother-to-child vertical transmission can not be ruled out. Therefore, it is very important to screen pregnant women, implement strict infection control measures, isolate infected mothers, and closely monitor newborns who are at risk of being infected with coronavirus.

The clinical characteristics of newborns infected with SARS-CoV-2, especially premature infants, may be non-specific[20]. In our study, there were 10 cases (62.5%) of asymptomatic infection, upper respiratory tract infection and mild infection, presenting low-grade and moderate-grade fever, accompanied with shortness of breath and digestive tract symptoms. In some cases, convulsion and jaundice were the first symptoms. It should be pointed out that among the 6 newborns with severe infection, one was due to preterm delivery, asphyxia and septicemia, and the other one was due to preterm delivery, and neither of these two cases were mainly caused by respiratory failure caused by SARS-CoV-2 infection[6], so the proportion of severe cases caused by SARS-CoV-2 infection should be lower than that of our result. In addition, 2 cases had complications, including cardiac insufficiency and pneumothorax, so it can be considered that newborns with complications are more likely to develop severe infection.

In laboratory tests, the most common manifestation is lymphocytopenia, while CRP and PCT are usually within normal values. Other findings may include mild thrombocytopenia and elevated transaminase, creatine kinase, lactate dehydrogenase, creatine kinase isoenzymes. Chest CT scans show lung lesions more clearly than X-rays, and common manifestations in chest CT imagings include ground-glass opacities, multiple bilateral lobules and segmental consolidation, especially in the peripheral lungs[21]. In this study, 3 cases of chest CT showed small strip blurred shadow, flaky hyperdense shadow, and subpleural high-density nodular shadow, respectively. In order to avoid inappropriate use of resources, it is not practical to detect SARS-CoV-2 nucleic test in all hospitalized infants with respiratory symptoms, because neonatal respiratory failure may be caused by a variety of causes[22]. So all admitted babies should be evaluated the risk of COVID-19 according to their exposure history, and only high-risk patients shall undergo SARS-CoV-2 nucleic acid tests[23].

In this study, 6 cases used antibiotics due to bacterial infection, and 3 cases received antiviral therapy, including interferon, ribavirin, lopinavir / ritonavir, and oseltamivir. According to the perinatal and neonatal prevention and control guidelines put forward by Chinese experts[20], improper use of antibiotics, especially broad-spectrum antibiotics, should be avoided unless there are signs of secondary bacterial infection. There is no evidence to support the effectiveness of interferon or hormone therapy. The newborns infected with SARS-CoV-2 recovered well after treatment and there was no death.

In conclusion, symptoms of neonatal SARS-CoV-2 infection are generally mild as compared to adult patients. A meta-analysis showed[24], the main clinical symptoms of COVID-19 adult patients were fever (88.5%), cough (68.6%), myalgia or fatigue (35.8%), expectoration (28.2%), and dyspnea (21.9%). Minor symptoms included headache or dizziness (12.1%), diarrhea (4.8%), nausea and vomiting (3.9%). In addition, laboratory examinations and chest imagings may be non-specific, no severe clinical complications or deaths were reported in neonate, as compared to fatality rates in adults.

The limitations of this study are as follows: 1) 13 articles included in the systematic review are case reports without appropriate bias risk assessment tools, at the same time, the case report itself is of very low-quality evidence. 2) Existing reports are incomplete because they included small sample sizes and limited data. 3) There is a lack of long-term follow-up studies on newborns with SARS-CoV-2 infection, and so far, we do not know the long-term effects of SARS-CoV-2 infection on neonated. There are options proposed[7], these children need long-time follow-up, including 15 days after birth and 1, 3, 6, 9 and 12 months of life, during each visit, these children should be done clinical evaluation and nasopharyngeal / rectal swabs, and cranial ultrasounds need to be performed at 1 to 6 months, visual and hearing tests be performed at 6 to 12 months.

Conclusion

Our findings highlight that clinical symptoms of neonatal SARS-CoV-2 infection are atypical, most of cases are with mild infection. Newborns with complications are more likely to develop into severe infection. Up to now, the prognosis of newborns is good, and there is no death. Whether there is intrauterine transmission and the long-term follow-up of potential influences of SARS-CoV-2 infection on neonates need further exploration.

Declarations

Additional file

Additional file 1: Search terms of electronic databases in the systematic review. (DOCX 24 kb)

Additional file 2: Table S1. Risk assessment of case report bias according to IHE criteria. (DOCX 28 kb)

Authors' contributions

YS developed the idea; YH wrote the first draft, participated in data extraction, and drafted the final manuscript. JX provided editorial advice, and edited all versions of manuscript. All authors read and approved the final manuscript.

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Conflict of interests

The authors declare that they have no competing interests.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Tables

Table 1 Characteristics of included human studies and overview of findings

Patient[1)]	Study	Region, country	Case number	Time of tests positive[2)]	Diagnostic time[3)]	Contact with COVID-19 infected patients
1	Zeng[1], Zhang[9]	Wuhan, China	1	2020.02.07	9d	yes
2	Wang[2]	Wuhan, China	1	2020.02.04	7d	yes
3	Yu[3], Zhang[9]	Zhengzhou, China	1	2020.02.07	2d	yes
4	Wang[4]	Wuhan, China	1	2020.02.05	36h	no
5	Isabel[5]	Spain	1	\	\	yes
6	Zeng[6], Hu[12]	Wuhan, China	1/3	2020.02.05	2d	no
7	Zeng[6]	Wuhan, China	2/3	2020.02.07	2d	no
8	Zeng[6]	Wuhan, China	3/3	2020.02.10	2d	no
9	Danilo[7]	Italy	1	2020.03.13	\	yes
10	Aghdam[8]	Iran	1	\	\	Not clear
11	Zhang[9]	Wuhan, China	1/4	\	30h	no
12	Zhang[9]	Wuhan, China	4/4	\	5d	no
13	Han[10]	Seoul, South Korea	1	2020.03.08	\	yes
14	Alzamora[11]	Lima, Peru	1	2020.03.30	16h	no
15	Enrico[13]	Italy	1/3	\	1d	no
16	Enrico[13]	Italy	2/3	\	3d	no
17	Enrico[13]	Italy	3/3	\	3d	no
18	Alvaro[14]	America	1	\	7d	Not clear

Note \: no related results; 1): 18 newborns were numbered and indicated by 1-18; 2): SARS-CoV-2 nucleic acid tests; 3): the diagnostic time was from the onset of symptoms to the positive result of nucleic acid test, if infants were isolated immediately after birth, the time of diagnosis shall prevail from birth to positive nucleic acid test.

Table 2 General information and clinical features of 18 newborns

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Article	[1,9]	[2]	[3,9]	[4]	[5]	[6,12]	[6]	[6]	[7]	[8]	[9]	[9]	[10]	[11]	[13]	[13]
Gestational age	39	38^{+6}	38^{+5}	40^{+1}	\	40	40^{+4}	31^{+2}	38^{+3}	full term	40	40^{+1}	38^{+6}	33	\	\
Birth weight(g)	\	3030	\	3205	\	3250	3360	1580	3390	3460	\	\	3730	2970	\	\
Cesarean	\	no	yes	yes	\	yes	yes	yes	yes	yes	yes	yes	no	yes	yes	yes
Apgar 1	\	\	\	8	\	\	\	3	9	\	\	\	\	6	\	\
Apgar 5	\	\	\	9	\	\	\	4	10	\	\	\	\	8	\	\
Breastfeeding	no	\	no	no	yes	no	no	no	yes	\	no	no	yes	no	\	\
Male	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	no	\	\	\
Admission age	17d	19d	5d	0	26d	0	0	0	\	15d	0	0	27d	0	0	0
Fever	yes	yes	yes	no	yes	yes	yes	yes	no	yes	no	no	yes	no	no	no
Cough	no	yes	yes	no	no	no	no	no	no	yes	no	no	yes	yes	\	\
Shortness of breath	no	no	yes	no	no	no	no	yes	no	yes	yes	no	yes	yes	\	\
Dyspnea	no	no	no	no	no	no	no	yes	no	yes	no	no	no	yes	\	\
Nasal congestion/runny nose/sneeze	yes	no	no	no	yes	no	no	no	no	no	no	no	yes	no	\	\
Diarrhea/vomiting/feeding intolerance	yes	yes	no	no	yes	no	yes	yes	no	no	no	no	yes	no	\	\
Jaundice	no	no	no	no	no	no	no	no	no	no	no	no	yes	no	\	\
Drowsiness	no	no	no	no	no	no	no	no	no	yes	no	no	no	no	\	\
Provoke	no	no	no	no	yes	no	no	no	no	no	no	no	no	no	\	\
Convulsion	no	no	no	no	yes	no	no	no	no	no	no	no	no	no	\	\
No symptoms	no	no	no	no	no	yes	no	no	yes	no	no	no	no	no	\	\
Complication	no	no	yes	no	no	no	no	yes	no	no	no	no	no	no	\	\
Classification[1)]	□	□	□	□	□	□	□	□	□	□	□	□	□	□	\	\

Note \:no related results; 1): according to 'Diagnosis and Treatment Recommendations for Pediatric Respiratory Infection Caused by the 2019 Novel Coronavirus[16]', clinical classification is divided into: □asymptomatic infection (recessive infection), □acute upper respiratory tract infection, □mild pneumonia, □severe pneumonia, □critical illness.

Table 3 Laboratory examination and imaging findings of 18 newborns

Num	Article	WBC ×10^9/L[1)]	L ×10^9/L	Hb g/L	PLT ×10^9/L	CRP mg/L	PCT ug/L	Liver function[2)]	Nenal function[3)]	Myocardial markers[4)]	Nasopharyngeal swabs positive	anal swabs positive	chest X-ray positi
1	[1,9]	7.7	5.6	132	399	0.75	0.08	N	N	\	yes	yes	yes
2	[2]	4.5	5.4	138	94	N	N	N	N	\	yes	yes	yes
3	[3,9]	13.1	3.2	85	394	N	N	N	N	A	yes	yes	yes
4	[4]	N	2.4	N	N	\	\	A	\	A	yes	no	yes
5	[5]	N	N	N	N	N	\	N	N	A	yes	\	\
6	[6,12]	8.6	3.1	\	245	N	A	N	\	N	yes	yes	yes
7	[6]	19.2	2.6	\	265	\	\	N	\	A	yes	yes	yes
8	[6]	20.4	0.8	\	11	\	\	N	\	N	yes	yes	yes
9	[7]	\	\	\	\	\	\	\	\	\	yes	\	\
10	[8]	6.7	2.4	144	351	1.00	\	\	N	\	yes	\	no
11	[9]	\	\	\	\	\	\	\	\	\	yes	\	\
12	[9]	\	\	\	\	\	\	\	\	\	yes	\	\
13	[10]	7.3	4.5	\	\	0.21	N	N	N	\	yes	yes	no
14	[11]	\	\	\	\	\	\	\	\	\	yes	\	\
15	[13]	\	\	\	\	\	\	\	\	\	yes	\	\
16	[13]	\	\	\	\	\	\	\	\	\	yes	\	\
17	[13]	\	\			\	\	\	\	\	yes	\	\
18	[14]	10.4	1.1	113	193	6.53	172	N	N	\	yes	\	yes

Note all indicators are based on the most abnormal indicators detected during hospitalization; \: indicates that there is no related result; N: indicates that the result is within the normal range; A: indicates that the result is abnormal; 1): the author defines that the normal range of WBC is (5-15)×10^9/L, lymphocyte(L) is (3-8)×10^9/L, platelet(PLT) is (100-300)×10^9/L, and hemoglobin(Hb) should be not less than 110(g/L); 2): any abnormality of aspartate aminotransferase(AST) or alanine aminotransferase(ALT) is regarded as abnormal liver function; 3): any abnormality of creatinine(Cr) or urea nitrogen(Bun) is regarded as abnormal renal function; 4) : any abnormality of NT-proBNP, CK-MB, CK or LDH is regarded as abnormal myocardial marker.

Table 4 Treatment and discharge outcome of 18 newborns

Num	Article	Antibiotics	Antiviral therapy[1)]	Oxygen therapy	Other treatment	Time of RT-PCR turn negtive[2)]	Duration of hospital stay	Death
1	[1,9]	no	no	no	Montmorillonite powder	\	23d	no
2	[2]	no	A	no	\	4d	14d	no
3	[3,9]	yes	ABC	yes	IVIG[2)], albumin, intravenous nutrition, dopamine, furosemide, blood transfusion	21d	30d	no
4	[4]	yes	\	no	VitK	12d	17d	no
5	[5]	yes	no	no	\	\	6d	no
6	[6,12]	no	\	\	\	4d	\	no
7	[6]	no	\	\	\	4d	\	no
8	[6]	yes	\	yes	Caffeine	5d	\	no
9	[7]	\	\	\	\	\	\	no
10	[8]	yes	D	yes	\	\	6d	no
11	[9]	\	\	\	\	\	\	no
12	[9]	\	\	\	\	\	16d	no
13	[10]	no	no	no	\	17d	18d	no
14	[11]	no	no	yes	\	\	\	no
15	[13]	\	\	\	\	\	\	no
16	[13]	\	\	\	\	\	\	no
17	[13]	\	\	\	\	\	\	no
18	[14]	yes	\	yes	\	\	9d	no

Note \: no related results; 1) :antiviral drugs include: A interferon; B ribavirin; C Lopinavir / ritonavir; D oseltamivir; 2) IVIG:intravenous immunoglobulin.

Figures

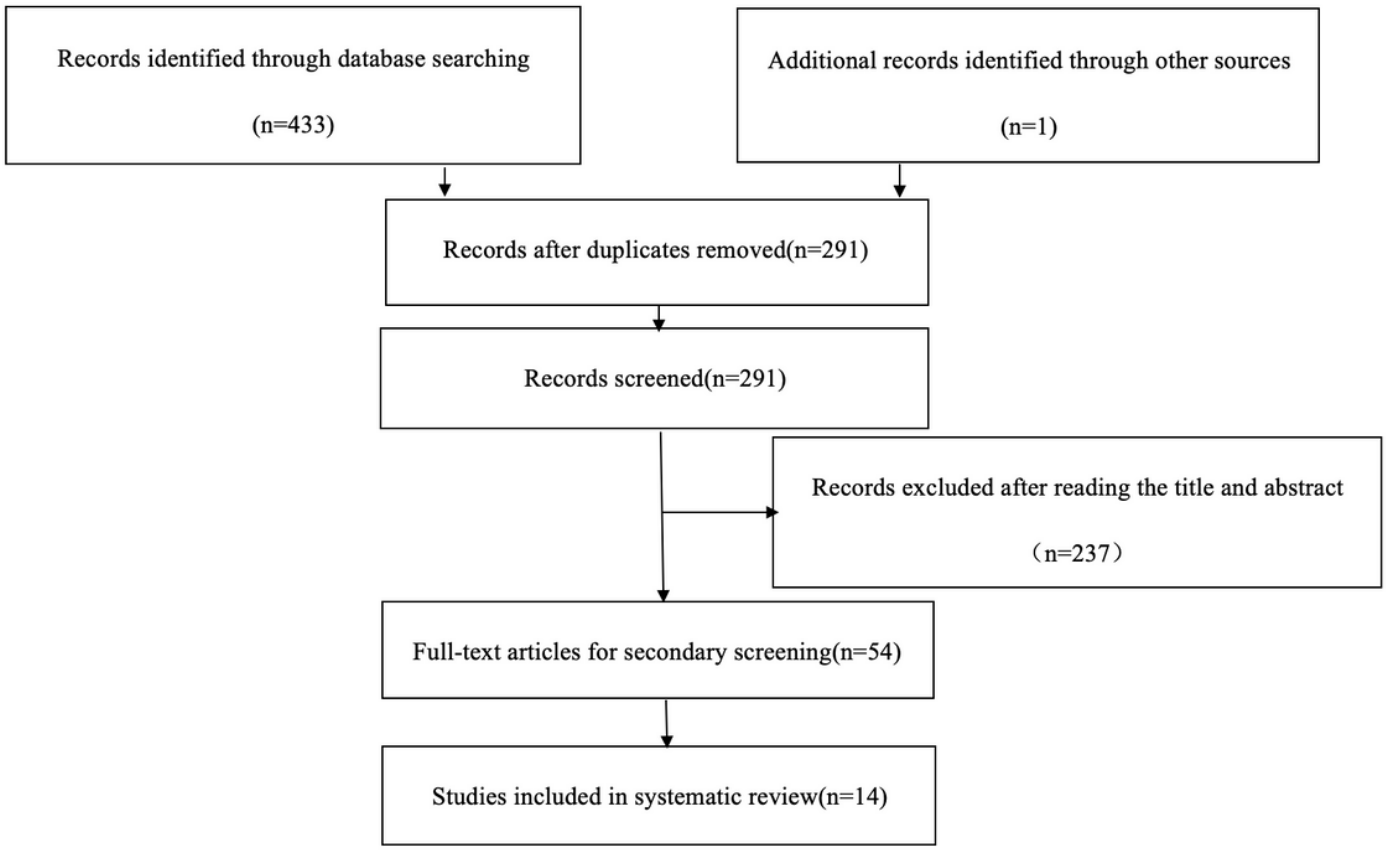

Figure 1

PRISMA flow diagram for study selection

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