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Original Article

Epidemiology and Clinical Features of COVID-19 among 4,015 Neonates in Iran: Results of the National Study from the Iranian Maternal and Neonatal Network

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Abstract

Objective The coronavirus disease 2019 (COVID-19) pandemic had a significant impact on pregnant women and neonates in Iran. This retrospective study describes the national experience among neonates having suspected and confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection following hospital admission to examine the epidemiology, demographic, and clinical features.

Study Design All nationwide cases of suspected and confirmed neonatal SARS-CoV-2 infection were drawn from the Iranian Maternal and Neonatal Network (IMaN) between February 2020 and February 2021. IMaN registers demographic, maternal, and neonatal health data throughout Iran. Statistical analysis of demographic, epidemiological, and clinical data were performed.

Results There were 4,015 liveborn neonates having suspected or confirmed SARS-CoV-2 infection that fulfilled the study inclusion criteria identified in the IMaN registry from 187 hospitals throughout Iran. There were 1,392 (34.6%) neonates that were preterm, including 304 (7.6%) less than 32 weeks' gestation. Among the 2,567 newborns admitted to the hospital immediately after birth, the most common clinical problems were respiratory distress (1,095 cases; 42.6%), sepsis-like syndrome (355; 13.8%), and cyanosis (300 cases; 11.6%). Of 683 neonates transferred from another hospital, the most frequent problems were respiratory distress (388; 56.8%), sepsis-like

Keywords
- COVID-19
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syndrome (152; 22.2%), and cyanosis (134; 19.6%). Among 765 neonates discharged home after birth and subsequently admitted to the hospital, sepsis-like syndrome (244 cases; 31.8%), fever (210; 27.4%), and respiratory distress (185; 24.1%) were most frequent. A total of 2,331 (58%) of neonates required respiratory care, with 2,044 surviving and 287 having a neonatal death. Approximately 55% of surviving neonates received respiratory support, compared with 97% of neonates who expired. Laboratory abnormalities included elevations of white blood cell count, creatine phosphokinase, liver enzymes, and C-reactive protein.

Conclusion This report adds the national experience of Iran to the list of reports from multiple countries describing their experience with COVID-19 in neonates, demonstrating that newborns are not exempt from COVID-19-morbidity and mortality.

Key Points

- Most common clinical problem was respiratory distress.
- Sepsis-like syndrome was also frequently present.
- A total of 58% of all neonates required respiratory care.

Iran became one of the most severely affected countries in the world after the start of the coronavirus disease 2019 (COVID-19) pandemic and following identification of the first case in Qom City on February 19, 2020.[1] In particular, there was widespread infection of pregnant women by the causative coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that rapidly resulted in excess morbidity and mortality including maternal death, pneumonia, and other complications.[2–4] Newborn babies were also affected, resulting in vertical transmission, preterm delivery, need for intensive care treatment, and other neonatal complications.[5–8] COVID-19 spread rapidly throughout both urban and rural areas of the country in 2020 and 2021, a period during which due to international sanctions there were limited resources available for surveillance and to reduce transmission of the virus. These deficiencies included medicines, personal protective equipment, ventilators, intensive care beds, and COVID-19 diagnostic testing kits.[9] Despite these challenges, Iran mobilized its health care community, and the Iranian government and Ministry of Health quickly implemented restrictions and guidelines based on the knowledge available at the time.

The COVID-19 pandemic has had a particular impact on pregnant woman and their newborns and is associated with maternal, fetal, and neonatal morbidity and mortality. Since the start of COVID-19 in Iran, neonatal surveillance for COVID-19 has been monitored through the Iranian Maternal and Neonatal Network (IMaN). This national network was begun in 2012, initially registering data from all hospitals and birth centers affiliated with Iranian medical universities. Beginning in 2014, IMaN registered out of hospital births occurring at maternity and childbirth facilities, homes, or other locations.[10] It is managed through the Iran Ministry of Health and since the start of the COVID-19 pandemic has been a valuable and unique source of real-time data for recording the effects of SARS-CoV-2 infection on pregnant women and their babies. In addition to hospital births, IMaN records almost all births, both liveborn and stillborn, selected demographics, and maternal and neonatal health information electronically from throughout the country[10–12]

To describe the Iranian national experience with COVID-19 among neonates, we conducted a retrospective analysis of the accumulated data in the IMaN for a 1-year period beginning at the start of the pandemic. This communication describes the epidemiological and clinical spectrum of COVID-19 from 4,015 neonates from throughout Iran who were suspected or confirmed as having SARS-CoV-2 infection following delivery to an infected mother and discusses current concepts of the pathophysiology of vertical infection.

Materials and Methods

Case Selection and Inclusion Criteria

Cases were drawn from the Iranian Maternal and Neonatal Network (IMaN) for the period between February 2020 and February 2021 inclusive. IMaN registers demographic, maternal, and neonatal health data electronically from almost all births throughout the 31 Provinces of Iran. These data consist of the demographic characteristics of the newborn's mother including gravidity and parity, medical history including previous miscarriage or abortion, risk factors, consanguinity of parents, gestational age and mode of delivery, date of birth, and pediatric data including baby's geographic location, gender, birth weight, presenting symptoms, diagnosis, neonatal complications, management, clinical outcome, and occurrence of perinatal death.[11,12] Greater than 97% of deliveries in Iran occur in hospitals, making the IMaN database a reliable sample of pregnancy and its complications throughout the country and an important source of epidemiological information for SARS-CoV-2 information in newborns.[11,12]

Study patients included liveborn neonates ≤ 28 days of age having suspected as well as confirmed SARS-CoV-2 infection that were admitted to the hospital following delivery. Inclusion criteria for suspected cases included having a clinical presentation consistent with neonatal COVID-19 or those neonates having a positive history of contact with SARS-CoV-2-infected persons who required hospital admission. Neonates were suspected to be infected with coronavirus if they had postpartum close contact to patients with SARS-COV-2, the mother was infected at the time of delivery, neonatal signs of sepsis, disseminated intravascular coagulation, respiratory distress, shock, gastrointestinal manifestations, poor feeding, fever, abnormal chest radiography or computed tomography imaging, and other signs or symptoms in association with suggestive clinical data (blood tests showing leukopenia or lymphocytopenia), following exclusion of other causes of respiratory infections and other diseases. Neonates with confirmed COVID-19 included newborns having positive testing for SARS-CoV-2 using polymerase chain reaction (PCR). PCR was performed from a nasopharyngeal, oropharyngeal, or endotracheal swab taken after 24 hours of age (according to the Iranian national guideline) to decrease contamination from maternal samples. The diagnostic criteria of COVID-19 were based on "Screening Protocols of Neonates in COVID-19 Virus Epidemic of Iran"[13].

During the study period between February 2020 and February 2021 there were three peaks of COVID-19 infections in Iran that occurred from March to April 2020, July to August 2020, and October to December 2020.[14] The first peak resulted from the ancestral strain of SARS-CoV-2, the second peak from B.1.36, and the third peak from B.1.1.413. Genomic surveillance and strain typing of SARS-CoV-2 was not routinely performed for persons testing positive for COVID-19 in Iran during the time frame of this study.

Statistical Analysis

Statistical data analysis was performed using IBM SPSS Statistics v24.0. Data were presented as mean ± standard deviation or percentage (%) where appropriate. A binominal logistic regression model was conducted to detect factors associated with neonatal death. In this analysis, neonatal death was measured as a binary variable taking the value of one or zero. Chi-squared analysis was used to compare categorical variables when appropriate. Adjusted odds ratios (aORs) were obtained. A p-value < 0.05 was considered statistically significant.

Results

There were 4,015 neonates that fulfilled the study inclusion criteria identified in the IMaN registry for the period between February 2020 and February 2021. Newborn infants were identified from 187 hospitals throughout Iran, and ►Table 1 lists the 31 provinces and the number of cases that were enrolled. As can be seen, most cases registered in the ImAN database were from Tehran Province (616), followed by Razavi Khorasan Province (382), Fars Province (290), Alborz Province (251), and Zanjan Province (229). Among the 4,015 neonates, there were 3,725 that underwent testing using PCR (92.8% of admitted neonates), and from these neonates 825 (20.5%) showed a positive PCR test for SARS-CoV-2. Most of the hospital admissions occurred in November (617 cases) and October (589 cases) 2020. ►Fig. 1 demonstrates the distribution of admitted cases from February 2020 to end of January 2021.

Table 1 Geographic distribution of the 4,015 neonatal study cases derived from the Iranian Maternal and Neonatal Network database by province

Province	Frequency	%
Alborz	251	6.3
Ardabil	11	0.3
Azerbaijan, East	161	4
Azerbaijan, West	102	2.5
Bushehr	91	2.3
Chaharmahal and Bakhtiari	100	2.5
Fars	290	7.2
Gilan	65	1.6
Golestan	114	2.8
Hamedan	108	2.7
Hormozgan	28	0.7
Ilam	17	0.4
Isfahan	190	4.7
Kerman	186	4.6
Kermanshah	145	3.6
Khorasan, North	89	2.2
Khorasan, Razavi	382	9.5
Khorasan, South	78	1.9
Khuzestan	161	4
Kohgiluyeh and Boyer-Ahmad	32	0.8
Kurdistan	72	1.8
Lorestan	47	1.2
Markazi	138	3.4
Mazandaran	175	4.4
Qazvin	6	0.1
Qom	34	0.8
Semnan	19	0.5
Sistan and Baluchestan	34	0.8
Tehran	616	15.3
Yazd	44	1.1
Zanjan	229	5.7
Total	4,015	100

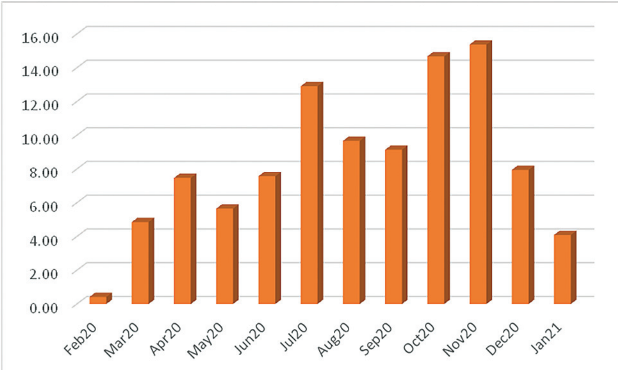

Fig. 1 Distribution of admitted cases from February 6, 2020, to January 31, 2021.

Demographics

There were no significant differences in sex, gestational age, and weight of those neonate admitted to the hospital with positive and negative PCR tests for SARS-CoV-2 (►Table 2).

Timing of Hospitalization and SARS-CoV-2 Testing

The mean age of neonates at the time of hospital admission was 3.48 ± 6.33 days. Most admissions (2,090 neonates; 52.1%) were between day of life 1 and 6 (►Table 2).

The timing of hospital admission fell into three major groups. The first group newborns were admitted to the hospital immediately after birth (2,567 cases; 63.9% of all study subjects). Of these neonates, 2,347 (91.40%) were tested for SARS-CoV-2 using either a nasopharyngeal, oropharyngeal, or endotracheal PCR test, with 419 (16.3%) having a positive result for the virus.

The second group included those neonates who were transferred from another hospital (either immediately after birth or later). This category contained 683 neonates (17% of this study group), of whom 643 (94.1%) neonates tested for SARS-CoV-2 and 171 (25%) had a positive PCR test. The third group consisted of neonates who had been discharged home after birth and subsequently admitted to the hospital after 1 or more days. This group included 765 neonates (19.1% of the total study group of 4,015 neonates), among whom 735 (96.0%) were tested for SARS-CoV-2, with 235 (30.7%) having a positive PCR result. Although there was a difference between these categories in regard to the prevalence of having a positive PCR test and day of admission, it was not significant ($p > 0.05$).

Contact History for COVID-19

Almost 50% of mothers tested had positive a PCR test. As a result of the difficulties in obtaining diagnostic reagents, testing for SARS-CoV-2 was performed using PCR obtained from a variety of different sources and manufacturers; however, all hospital laboratories performed PCR testing according to standard and approved methodology including the use of appropriate controls. A total of 1,005 mothers (25%) had a positive PCR test during pregnancy or childbirth. There were 974 mothers (24.3%) who had a positive PCR test following delivery and discharge from the hospital. Following

Table 2 Demographic characteristics of the 4,015 neonates in the study population

	Demographic characteristics (number and %)				
	Admitted to hospital	PCR tested	Positive PCR test	Required respiratory support	Died
Gender					
Male	2,264 (56.4%)	2,104 (56.5%)	454 (55.0%)	1,377 (59.1%)	160 (54.1%)
Female	1,751 (43.6%)	1,621 (43.5%)	371 (45%)	954 (40.9%)	136 (45.9%)
Total	4,015 (100%)	3,725 (100%)	825 (100%)	2,331 (100%)	296 (100%)
Gestational age (wk)					
< 32	304 (7.6%)	284 (7.6%)	66 (8%)	292 (12.5%)	103 (34.8%)
32–36	1,088 (27.1%)	1,021 (27.4%)	209 (20.2%)	758 (32.5%)	65 (22.0%)
≥37	2,623 (65.3%)	2,420 (65%)	550 (66.7%)	1,281 (55.0%)	128 (43.2%)
Birth weight (g)					
< 1,500	246 (6.1%)	231 (6.2%)	47 (4.7%)	234 (10.0%)	88 (29.7%)
1,500–2,499	888 (22.1%)	826 (22.2%)	180 (21.8%)	642 (27.5%)	75 (25.3%)
≥2,500	2,881 (71.8%)	2,668 (71.6%)	598 (72.5%)	1,455 (50.5%)	133 (44.9%)
Type of admission					
After birth in the same hospital	2,567 (63.9%)	2,347 (63.0%)	419 (50.8%)	1,441 (61.8%)	148 (50.0%)
Transfer from another hospital	683 (17.0%)	643 (17.3%)	171 (20.7%)	526 (22.6%)	98 (33.1%)
From home	765 (19.1%)	735 (19.7%)	235 (28.5%)	364 (15.6%)	50 (16.9%)
Total	4015 (100%)	3,725 (100%)	825 (100%)	2,331 (100%)	296 (100%)

Abbreviation: PCR, polymerase chain reaction.

discharge home, there was a positive history of close contact between a neonate with an infected family member who tested positive for SARS-CoV-2 in 419 (10.4%) of neonates.

Gestational Age and Birth Weight

Among the 4,015 neonates admitted to the hospital there were 1,392 (34.6%) who were delivered preterm, including 304 (7.6%) less than 32 weeks' gestation and 1,088 (27.1%) between 32 and 36 weeks' gestation. There were 2,623 (65.3%) neonates who were full-term. These metrics corresponded closely with birth weights. There were 246 (6.1%) neonates with birth weights of less than 1,500 g; 888 (22.1%) neonates weighed between 1,500 and 2,499 g, and 2,881 (71.8%) weighed over 2,500 g. The probability of positive PCR testing results was directly proportional with gestational age and birth weight; the youngest (<32 wk) and smallest (<1,500 g) neonates having the lowest frequency of positive SARS-CoV-2 testing (8 and 4.7%, respectively) and the largest (≥2,500 g) and the oldest (≥37 wk) having the highest frequency (72.5 and 65.3%, respectively).

Clinical Features

Among the first group consisting of 2,567 newborns admitted to the hospital immediately after birth, the most common clinical problem was respiratory distress (1,095 cases; 42.6%), followed by sepsis-like syndrome (355; 13.8%) and cyanosis (300 cases; 11.6%). There were 1,441 neonates (56.2%) admitted after birth who required supplemental oxygen, noninvasive or invasive respiratory care.

In the second group of 683 neonates who had been transferred from another hospital, the most frequent problems were respiratory distress (388; 56.8%), sepsis-like syndrome (152; 22.2%), cyanosis (134; 19.6%), fever (51; 7.4%), and cough (30; 4.3%). In this group of neonates there were 526 (77%) that needed respiratory support.

The most frequent clinical problems in the third group containing 765 neonates were sepsis-like syndrome (244 cases; 31.8%), fever (210; 27.4%), and respiratory distress (185; 24.1%), with 364 (47.5%) newborns needing respiratory support.

There was a differing frequency of clinical signs and symptoms between the three groups according to the timing of hospital admission. However, there were no significant difference between the three groups according to their respiratory care requirements.

Respiratory Support

A total of 2,331 (58%) of neonates including in the study group required some form of respiratory care (ranging from oxygen therapy to noninvasive and invasive ventilation), with 2,044 surviving and 287 having a neonatal death. Approximately 55% of surviving neonates received respiratory support, compared with 97% of neonates who expired. Most of the neonates who admitted after birth or from another hospital (1,967/2,331; 60.5%) required respiratory support, but among those neonates admitted after discharge, respiratory care have been provided for 364 neonates (47.5%; ►Table 3).

Neonatal Mortality

Among all 4,015 study subjects there were 296 neonates who died following hospital admission, giving an overall neonatal mortality rate of 7.4% (296/4,015). Among the 825 neonates who had a positive PCR test, there were 85 (10.3%) deaths. Although the mortality rate was higher among those neonates testing positive by PCR for SARS-CoV-2 than among neonates with negative testing, the difference was insignificant using chi-square test. ►Table 4 summarizes demographic features of neonates with positive PCR who died with COVID-19 in the hospital. Among the 85 deaths occurring in newborns testing positive for SARS-CoV-2 infection, greater than 44% (38/85) occurred in full-term neonates; 28.2% occurred in neonates delivered between 32 and 36 weeks; and 27.1% occurred in neonates delivered prior to 32 weeks' gestation.

A binominal logistic regression model was conducted to detect factors associated with neonatal death with positive PCR. Gestational age, birth weight, need for respiratory support, age at admission, elevated C-reactive protein (CRP), and leukocytosis were associated predictors, and neonatal death was the dependent variable (►Table 5). The model explained 23.6% (Nagelkerke R^2) of the variance in neonatal death and classified 89.8% of cases correctly. The most important factor of neonatal death was need for respiratory support (aOR = 19.91; 95% confidence interval [CI] = 4.79–82.75). Birth weight of <1,500 g (aOR = 5.24; 95% CI = 1.61–17.02) was the other factor that correlated with neonatal death.

Table 3 Respiratory support in admitted neonates with suspected/confirmed COVID-19

Clinical neonatal outcome	Received any respiratory care	Oxygen therapy	Noninvasive respiratory care	Invasive respiratory care	Surfactant	Total ($n = 4,015$)
Discharged alive	2,044	1,556	643	437	95	3,719
Died	287	69	60	260	293	296
Gestational age (wk)						
< 32	292 (96.1%)	137 (44.6%)	140 (46.0%)	182 (59.8%)	152 (50.0%)	304 (100%)
32–36	758 (69.6%)	497 (45.6%)	301 (27.6%)	204 (18.7%)	141 (12.9%)	1,088 (100%)
≥37	1,281 (48.8%)	991 (37.7%)	262 (9.9%)	311 (11.8%)	95 (3.6)	2,623 (100%)

Abbreviation: COVID-19, coronavirus disease 2019.

Table 4 Demographic features of the 85 neonatal deaths with PCR-confirmed COVID-19

	Number	%
Sex		
Male	44	51.8
Female	41	48.2
Gestational age (wk)		
< 32	23	27.1
32–36	24	28.2
≥37	38	44.7
Birth weight (g)		
< 1,500	21	24.7
1,500–2,499	25	29.4
≥2,500	39	45.9
Type of admission		
Following delivery in same hospital	39	45.9
Transfer from another hospital	34	40
Transfer to hospital from home	12	14.1

Abbreviations: COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction.

Table 5 Factors associated with death among neonates having PCR-confirmed COVID-19

Variables	Adjusted OR	95% CI for OR		*p*-Value
		Lower	Upper	
Gestational age (wk)				
≥37 (reference value)	1.0			
< 32	0.99	0.33	2.99	0.998
32–36	0.68	0.32	1.43	0.311
Birth weight (g)				
≥2,500 (reference value)	1.0			
< 1,500	5.24	1.61	17.02	0.006
1,500–2,499	1.79	0.84	3.81	0.127
Sex (male)	1.08	0.660	1.77	0.752
Respiratory support	19.91	4.79	82.75	<0.001
Elevated CRP	1.14	0.691	1.14	0.608
Leukocytosis	1.20	0.488	2.99	0.684
Age at admission				
7–28 d (reference value)	1.0			
< 24 h	1.53	0.690	3.41	0.294
1–6 d	1.60	0.783	2.30	0.196
Multifetal pregnancy	1.85	0.860	3.98	0.115

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; OR, odds ratio; PCR, polymerase chain reaction.

Clinical Outcomes of SARS-CoV-2 PCR+ and PCR− Neonates

An analysis was also performed examining clinical outcomes and mortality between neonates who were PCR-positive for SARS-CoV-2 infection and those who tested negative for the virus (►Table 6). There were no statistically significant differences between these cohorts for the following outcomes evaluated in the IMaN registry: sex, gestational age, birth weight, leukocytosis, noninvasive respiratory care, invasive respiratory care, and surfactant administration. Oxygen therapy administration was of borderline significance ($p < 0.055$). Two variables demonstrated significant differences between the PCR+ and PCR− cohorts: both neonatal mortality ($p < 0.001$) and administration of any respiratory support ($p < 0.001$) were greater in the PCR+ cohort.

Discussion

Iran is ranked as a lower middle-income country, but despite this the government has been able to expand preventive services by creation of a nationwide primary health care network during the past 2 decades. This has resulted in a significant decrease in child and maternal mortality rates.[15]

The health care management of COVID-19 has been a tremendous challenge in Iran. In particular, the year of this study, 2020 to 2021, was a devastating one for children in Iran. The first year of the COVID-19 pandemic, taken together with other factors including the economic downturn and international sanctions, had a profound effect on the lives of 23 million children in Iran. By the close of 2021 and based on official data, there were greater than 131,000 deaths of all ages in Iran, making it the most severely affected country in the Middle East and Northern Africa region.[16] According to the United Nations International Children's Emergency Fund (UNICEF), more than 51,000 Iranian children have lost at least one parent to COVID-19.[16] In Iran during this time period, a cross-sectional study by Babaei et al found that 6.1% of neonates who were born to infected mothers or resided in the same household with relatives having COVID-19 had tested positive for SARS-CoV-2 after delivery.[17] Fortunately, a major turning point in the COVID-19 pandemic occurred in 2021 with the introduction of vaccines.

This report adds the national experience of Iran to the list of reports from multiple countries describing their experience with COVID-19 in neonates.[18–25] Compared with other large studies of newborns delivered to mothers having COVID-19, our investigation was limited to neonates with either suspected or confirmed SARS-CoV-2 infection. This retrospective cross-sectional study of 4,015 newborns using data collected from IMaN represents one of the largest, if not the largest, cohorts of neonates with suspected or confirmed SARS-CoV-2 infection to be reported. The analysis of cases during the 1-year period from February 2020 to February 2021 includes the first cases of neonatal COVID-19 to occur in Iran, as the initial confirmed SARS-CoV-2 infection occurred in Qom on February 19, 2019.[26] The number of new

Table 6 Clinical outcomes in neonates having PCR+ and PCR− testing for SARS-CoV-2

PCR for SARS-CoV-2	Positive (*N* %)	Negative (*N* %)	*p*-Value
Sex			
Male	454 (55.0)	1,810 (56.7)	0.377
Female	371 (45.0)	1,380 (43.3)	
Gestational age (wk)			
< 32	66 (7.5)	238 (8.0)	0.421
32–36	209 (27.6)	879 (25.3)	
≥37	550 (65.0)	2,073 (66.7)	
Birth weight (g)			
< 1,500	47 (5.7)	199 (6.2)	0.806
1,500–2,499	180 (21.8)	708 (22.2)	
≥2,500	598 (72.5)	2,283 (71.6)	
Neonatal outcome			
Alive	740 (89.7)	2,979 (93.4)	<0.001
Dead	85 (10.3)	211 (6.6)	
Any respiratory support			
Yes	526 (63.8)	1,805 (56.6)	<0.001
No	299 (36.2)	1,385 (43.4)	
Leukocytosis			
Yes	49 (5.9)	154 (4.8)	0.194
No	776 (94.1)	3,036 (95.2)	
Oxygen therapy			
Yes	358 (43.4)	1,267 (39.7)	0.055
No	467 (56.6)	1,923 (60.0)	
Noninvasive respiratory care			
Yes	142 (17.2)	561 (17.6)	0.801
No	683 (82.8)	2,629 (82.4)	
Invasive respiratory care			
Yes	152 (18.4)	454 (17.1)	0.365
No	673 (81.6)	2,645 (82.9)	
Surfactant administration			
Yes	86 (10.4)	302 (9.5)	0.407
No	739 (89.6)	2,888 (90.5)	

Abbreviations: PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

cases in Iran increased dramatically until January 2021, with four peaks eventually developing that included the Nowruz peak (March 20 to April 4, 2020), After Nowruz (April 5 to May 2, 2020), Resurgence (May 3 to June 3, 2020), and the New Peaks (June 4, 2020 to the present). In this present study, the majority of our cases were admitted to the hospital during October and November 2020, all prior to the development of the COVID-19 vaccines.

The epidemiological features of COVID-19 in neonates has now been described from multiple reports.[20,24,27] A recent report of greater than one million neonatal clinical encounters derived from 109 health systems in the United States found that COVID-19 infection was diagnosed in 0.1% of newborns and that 7.7% of infected neonates developed serious disease.[27] A greater incidence of low birth weight (<2,500 g) or prematurity occurred among neonates with severe COVID-19 than among those with nonsevere infection ($p < 0.001$). The majority of infected neonates (63.5%) were asymptomatic, while among those with symptoms fever and tachypnea were the most common manifestations. The need for respiratory support was significantly higher among neonates with severe COVID-19 (50.7%) compared with those with nonsevere infection (5.2%).

The frequency of COVID-19 infections among neonates is lower than that in adults and children, which may be due to transplacental transfer of maternal antibodies and other protective factors. SARS-CoV-2 can be transmitted during the perinatal period by three mechanisms: intrauterine via maternal–fetal transplacental transmission,[28–30] during delivery, or postnatally from environmental exposure. Raschetti et al[31] performed a meta-analysis of neonatal SARS-CoV-2 infections that indicated that the majority (∼70%) were acquired following delivery from environmental exposure. Approximately 30% of neonatal infections were the result of either possible, probable, or confirmed vertical transmission, of which confirmed intrapartum and transplacental transmission occurred in 3.3 and 5.7% of cases, respectively. Transplacental transmission is associated with SARS-CoV-2 infection of the placenta,[28–30,32] and development of a characteristic inflammatory abnormality termed SARS-CoV-2 placentitis,[28–30,32,33] and in some cases, stillbirth and neonatal mortality.[34–36] In a recent study of 68 cases of stillbirth and early neonatal demise from 12 countries, Schwartz et al found the mechanism of death to be hypoxic ischemic injury from placental destruction and insufficiency resulting from SARS-CoV-2 placentitis.[36]

The diagnosis of SARS-CoV-2 infection in neonates can be suspected when there is a history of maternal COVID-19 illness, contact with a known case of infection (mostly mothers)[21,37] or other caregivers or family members, and from clinical, radiographic, and laboratory factors. The current gold standard to diagnose SARS-CoV-2 infection is based upon results of real-time PCR (RT-PCR) on respiratory specimens.[38] Although RT-PCR is a good test, it has potential faults in that it is subject to contamination resulting in false positives, there have been reports of variability in the timing and patterns of positive neonatal testing for the virus, and other potential issues such as low virus titers and inappropriate swabbing sites.[39,40] Diagnosis via serological testing in neonates is particularly challenging given the transplacental transmission of maternal IgG, and because IgM assays are prone to both false positives and false negatives they are not the gold standard for diagnosis of congenital infections.[41] In our study, 825 of 4,015 (20.5%) of all neonates suspected of having COVID-19 were found to test positive for SARS-CoV-2 using PCR. Based on the data available, it cannot be determined what the true neonatal infection rate was, or how many were the result of false negative PCR testing as has been previously reported.

Multiple studies have now confirmed that the large majority of neonates delivered to mothers having COVID-19 are uninfected with SARS-CoV-2. A metanalysis by Mirbeyk et al of 219 neonates delivered to mothers having confirmed COVID-19 infection demonstrated that 11 (5%) had positive nasopharyngeal swabs for SARS-CoV-2.[42] A review of neonates delivered to mothers with confirmed COVID-19 by Yoon et al[43] revealed that 4 of 167 (2.4%) of neonates tested for SARS-CoV-2 infection were positive. Trippella et al[44] reviewed 181 neonates delivered to mothers with COVID-19 infection and found that 28 (15%) tested positive for SARS-CoV-2 following a throat/nasopharyngeal/anal swab sample. In Iran, it has been estimated that 6.1% of neonates born to mothers with COVID-19 have positive PCR testing for SARS-CoV-2.[17] Although our study from the Iran birth registry only included newborns who were either suspected or confirmed to have infection, only 22.1% of neonates that underwent testing for SARS-CoV-2 had positive PCR results. This observation suggests that neonatal infection with SARS-CoV-2 may be underdiagnosed based on the PCR results of nasopharyngeal swabs after delivery. The special problems inherent in performing nasopharyngeal testing on neonates has been previously suggested by Schwartz and De Luca,[39] stating that classic swabs frequently do not penetrate to the newborn nasopharynx because of the small anatomic dimensions. In addition, neonatal swabs may retrieve biological fluids that are not representative of neonatal infection including inhaled amniotic fluid or vernix caseosa. Despite multiple studies of neonatal COVID-19 infection, there still remains scant information on the sensitivity of nasopharyngeal and oropharyngeal sampling for diagnosis of SARS-CoV-2 in neonates as well as the patterns of fetal and neonatal shedding of the virus into body secretions and fluids.

Our study of neonates throughout Iran has results consistent with those from other countries in having no significant differences between neonatal gender.[45–47] Among those neonates having a positive PCR test, most were full term and had normal weights (>2,500 g), with a minority having very low birth weight (<1,500 g). Our observations from this Iranian cohort are similar to those of Salvatore et al[47] in New York City in which 87% of neonates had birth weights ≥ 2,500 g, 12% were between 1,500 and 2,500 g, and 1% <1,000 g (26). In another study from Iran by Pirjani et al[48] there was no association between COVID-19 infection and neonatal and maternal outcomes including preterm birth and low birth weight; however, compared with uninfected mothers, the cesarean delivery rate and the need for intensive care support were higher in mothers with COVID-19.

In this study there were 3,372 (83%) neonates admitted to the hospital during the first week of life, with 16% admitted subsequently. Similar to some previous studies we also found a broad range of signs and symptoms ranging from asymptomatic virus carriage to critical neonatal illness, with the most frequently described symptoms demonstrating a significant correlation to the time of hospital admission. In our study, the most frequent symptoms were respiratory distress (1,668/4,015; 41.5%), sepsis-like syndrome (751/4,015; 18.7%), cyanosis (434/4,015; 10.8%), and fever (261/4,015; 6.5%). Approximately 58% of the hospitalized neonates in our study required respiratory support, with those newborns who died before discharge demonstrating the greatest need. These data were similar to other studies from Iran, including that by Mohagheghi et al[7] who found that respiratory distress was the most frequent presenting finding in hospitalized neonates with COVID-19. Our results are interesting in view of other neonatal studies, including that of Zimmerman et al[24] from Switzerland in which the most frequent presenting features of infected neonates were fever (71%), rhinorrhea or nasal congestion (44%), and respiratory distress (26%). The study by Devin et al[27] identified tachypnea as the most frequent presenting symptom of infection in both nonsevere and severely affected neonates, followed by fever and hypoglycemia. These observed differences in the relative frequency of clinical signs and symptoms of neonatal COVID-19 may result from numerous factors including the timing and extent of initial viral exposure, viral strain differences, host factors including genetic and immunological covariables, gestational age, and others.

The most frequent laboratory abnormality identified in our study of neonates with COVID-19 was elevation of the white blood cell count, followed by elevated creatine phosphokinase (CPK), abnormal liver enzymes, and elevated CRP and/or procalcitonin. A review by Saeedi et al[37] identified (in order of prevalence) leukopenia, lymphopenia, thrombocytopenia, elevations of CPK, CRP, and procalcitonin, and liver enzyme abnormalities in infected infants.

There were two significant differences in our study between the neonatal cohorts based upon the results of PCR testing for SARS-CoV-2 infection. Neonatal mortality was greater, and administration of any respiratory support was more frequent, among those neonates having positive testing for SARS-CoV-2. However, when evaluating several specific modalities of respiratory care, including need for oxygen therapy, noninvasive and invasive respiratory support, and surfactant administration, PCR+ and PCR− cohorts showed no significant differences. It would have been useful to examine neonatal outcome differences between mothers who were PCR+ and PCR− for SARS-CoV-2, but these data were not available from the IMaN registry. Likewise, analysis of differences of clinical outcomes based upon the neonatal age of onset of testing and symptomatology would have been interesting, especially among mothers testing positive for SARS-CoV-2, but these data were also not specified in the IMaN registry.

In a multinational cohort study of 2,130 pregnant women from 18 countries by Villar et al,[49] mothers having COVID-19 had a higher severe neonatal morbidity and perinatal morbidity and mortality index compared with newborns born from mothers without a COVID diagnosis. Liu et al reported that in southwest China the neonatal mortality rate increased by 8.7% during the COVID-impacted period compared with the pre-COVID period.[50] In November 2021, the U.S. Centers for Disease Control and Prevention confirmed the association of SARS-CoV-2 infection with stillbirth in a population-based study of 1,249,634 delivery hospitalizations,[51] with magnitude being greatest during the surge of the SARS-CoV-2 Delta (B.1.617.2) variant. Following that, a multi-institutional study from 12 countries by Schwartz et al[36] found that among 68 cases of stillbirth and early neonatal demise the cause of death was placental insufficiency. Placental destruction that averaged 77.7% had resulted in fetal hypoxic–ischemic injury, with no evidence that direct infection of the fetus was a major contributing factor.[34–36] Although our present study did not include stillborns, there were 296 neonates who died after hospital admission, giving an overall neonatal mortality rate of 7.4% (296/4,015). The neonatal mortality rate was highest in the cohort of 825 neonates who had a positive PCR test, where 85 (10.3%) deaths occurred.

In recent studies maternal COVID-19 has been associated with an increased risk for preterm birth compared with uninfected mothers.[49,52,53] However, the underlying cause (s) of this association, and the relative role of maternal, fetal, placental, inflammatory, and viral factors is not fully understood. In our study 34.6% of deliveries occurred preterm; these neonates had the lowest rate of PCR positivity for SARS-CoV-2 and the greatest need for respiratory support.

There are multiple limitations inherent in our investigation, some of which are inherent in a large, retrospective investigation based upon data from a national registry. These include variation in the accuracy of observing and reporting data, differences in the clinical assessment and diagnoses of neonates, and variations in laboratory testing and reporting. As a result of infrastructure and economic situations that were nationwide in Iran during this period as well as the large number of neonates, we were unable to routinely screen for SARS-CoV-2 in amniotic fluid, umbilical cord, or vagina or to analyze placental pathology to study vertical transmission. We did not have required facilities in our country to detect the virus in urine, stool, umbilical cord, or peripheral blood samples to confirm the disease in those 79.5% of neonates suspected of being infected but having negative PCR test results.

This study, which is based on the national IMaN registry system, represents the largest investigation of neonatal COVID-19 in Iran. The resulting data demonstrate both similarities as well as differences from other reports of neonates with COVID-19. It should be noted that this study examined neonatal data before the COVID-19 vaccine was available, and thus, all mothers were unvaccinated. With the increasing global distribution and acceptance of COVID-19 vaccines to pregnant women it may be that the epidemiological and clinical characteristics of neonatal SARS-CoV-2 infection will change. It has recently been suggested maternal COVID-19 vaccination may not only save the life of the mother but may also inhibit the development of SARS-CoV-2 placentitis and potentially save the life of the fetus.[35] However, despite the shifting world pandemic situation, this article demonstrates that neonates are not exempt from COVID-19-related morbidity and mortality, and it is hoped that our data provide additional guidance to enhance our knowledge about SARS-CoV-2 infection in neonates.

Ethical Concent

Anonymous patient data were obtained with permission from the Neonatal Health Office of the Iran Ministry of Health and Medical Education in Tehran. The ethical issues of this study were approved in the Vice Chancellor for Research Affairs of Faculty of Medicine, Iran University of Medical Science. The ethics committee code is IR.IUMS.REC.1399.1365. This study was performed in accordance with the principles stated in the Declaration of Helsinki.

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Conflict of Interest

None declared.

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