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# Epidemiological Features of Neonates With COVID-19 Infection in Iran

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# Abstract

**Objective:** Although, the COVID-19 Pandemic has drawn the attention of physicians and researchers from all corners of the globe since it has been out broken in different countries, we have also started to invest more about the epidemiological features of neonates that had been affected by COVID-19 in Iran till now.

**Method:** This is a cross-sectional retrospective study including all neonates from a National Registry supported by Iranian Maternal and Neonatal Network (IMaN). Since February 2020 till February 2021, data of neonates under 28 days who were diagnosed with suspected or confirmed COVID-19 has been registered in this network were collected. General data including epidemiological, clinical outcomes and infection-related information were collected.

**Results:** In our retrospective study, data of 4015 neonates admitted to hospital all over the country and reported in IMAN is included. Totally 3725 PCR tests were performed (92.8% of admitted neonates) and from these neonates 825 (20.5%) showed positive PCR test. There were no differences between gender, weight and gestational age in neonates with positive and negative PCR test. Neonatal clinical findings were dependent to the type of admission. Respiratory distress was the most common sign in neonates, who were admitted immediately after birth (63.9%), and who were transferred from another hospital (17%); however in those who were admitted after one to several days after discharge (19.1%), the most common sign were sepsis like syndrome (31.8%) and fever (27.4%). Almost 50% of admitted neonate`s mothers had positive PCR test (25% during pregnancy and 24.3% after delivery). The most important factor of neonatal death was need for respiratory support (aOR=18.17, 95% CI; 9.24– 35.69). Gestational age of <32 weeks (aOR=2.35, 95% CI; 1.35-4.10) and birth weight of <1500 grams (aOR= 3.47, 95% CI; 1.96-6.17) were the other two factors that correlated to death.

**Conclusion:** This is the largest study of neonatal COVID-19 diseases in Iran published to date. The most common signs of COVID-19 diseases found in neonates are respiratory distress and sepsis-like syndrome.


# What Is Known

as covid-19 is a new disease all over the world, we do not know much about that, specially in children and neonates. There were not many articles evaluating their neonate s covid-19 signs and symptoms, specially with this volume in their articles (near 4000 neonates). We extracted all neonatal signs and symptoms with covid-19 in IRAN, their hospitalization and their death rates.

- Neonatal statistics of COVID_19 diseases in IRAN
- All neonatal epidemiological features, signs, symptoms, hospitalization, death rate.

# What Is New

neonatal statistics of covid_19 infection in one year for a country(IRAN), evaluating about 4000 neonates with covid_19,evaluating neonatal infection of covid_19 due to their gestational age, weight and their need to hospitalization and respiratory support and their death. They are all new epidemiological features and data proportional to their volume (about 4000 neonates with covid_19).

- evaluating 4000 neonates with COVID_19 diseases that never was done before
- evaluating all neonates with COVID_19 due to their gestational age, weight, day of admission, death rate and different comparison between them.

# Introduction

In December 2019, a new outbreak of novel coronavirus from Wuhan, China has been started [1]. Coronavirus disease 2019 (COVID-19) has spread across the world in a short time space. With increase in the number of infections, the number of neonates with COVID-19 has also rose. On Jan 30, COVID-19 infection was declared by WHO as a public health emergency of international concern [2]. Although the 2 types of human coronavirus cause severe and acute illnesses, the Middle East respiratory syndrome coronavirus (MERS-COV) causes Middle East respiratory syndrome (MERS) and SARS-COV causes severe acute respiratory syndrome (SARS), COVID-19 has its own clinical features and manifestations [1, 3]. COVID-19 manifestations in adults are different from pediatric patients, long incubation periods, high mortality rate in elderly and atypical clinical manifestations are common in adulthood [4, 5]. By knowing that SARS-COV-2 has been spread all over the world and become pandemic, and knowing that all ages are prone to the virus, even neonates, therefore COVID-19 will affect a long life period on people's health [1, 5, 6]. Comparing with adult studies, there are few studies on pediatrics and neonatal disease, especially for their epidemiological evaluations [7, 8]. Despite the worldwide spread, the epidemiological and clinical patterns of COVID-19 remain largely unclear yet, particularly among neonates. As a result, there remains much to learn about the spectrum of neonatal disease, best methods of diagnosis, long term consequences, the mechanism of transmissions and prevention of the disease [9]. SARS-COV-2 is known to cause different signs and symptoms such as respiratory distress, shock, early and late onset sepsis, cyanosis, fever, cough, gastrointestinal presentations, pneumonia, asphyxia, disseminated intravascular coagulation (DIC), and neonatal death [10–13]. The number of neonatal patients of COVID-19 has already been rising remarkably, and they are going to be diagnosed more from the first appearance of the disease [14]. Therefore it is important to define the epidemiological factors of neonates with COVID-19 disease to determine the early prevention, neonatal isolations in intensive care units, transmission of disease and limitation of the pandemic by controlling a small group of age spectrum [15]. In this study, we conducted a retrospective study, explored the epidemiological characteristics of 4015 neonatal patients with COVID-19 in Iran that could help for developing guidelines for the prevention and treatment of neonatal COVID-19 disease.

# Methods

This was a national retrospective epidemiological study that included cases from a National Registry supported by the Iranian office of neonatal health.

Data collections: Iranian Maternal and Neonatal Network (IMAN) registers data about all birth (live and dead) in Iran [16]. Since February 2020 till February 2021, data of neonates under 28 days who were diagnosed with suspected or confirmed COVID-19 has been registered in this network.

Data about gender, age, birth weight, gestational age, geographic location, and discharge alive or dead was collected together with clinical features on presenting symptoms, diagnosis, management and outcome.

We defined the suspected cases as neonates who had suspected clinical presentations or had positive history of contact with confirmed patients of SARS-COV-2 and admitted in the hospital. Confirmed cases were infants with a positive PCR test. A nasopharyngeal, oropharyngeal or endotracheal swab was taken after 24 hours of age (according to the Iranian national guideline) to decrease contamination with maternal samples.

The patients were eligible to include the study if they met the following criteria: (1) from birth to the age of 28 days (2) who were suspected to be infected with coronavirus (if they had postpartum close contact to patients with SARS-COV-2, mother was infected meanwhile delivery, neonatal signs of sepsis, DIC, respiratory distress, shock, GI manifestations, poor feeding, fever or other signs or symptoms that were not related to other diseases or abnormal chest radiography or CT imaging), in association with suggestive clinical data (blood tests showing leucopenia or lymphocytopenia), and exclusion of other causes of respiratory infections.

The diagnostic criteria of COVID-19 were based on “screening protocols of neonates in COVID-19 virus epidemic of Iran” in January 2020.

# Statistical Analysis:

The statistical analysis of data was done using IBM SPSS v24.0. Data were presented as mean ± SD or number (%) where appropriate. A binominal logistic regression model was conducted to detect factors associated with neonate death. In our analysis, neonate 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.

# Ethical issue:

Anonymous data were obtained with permission from the Neonatal Health Office of Ministry of Health and Medical Education.

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.

# Results

In our retrospective study, data of 4015 neonates admitted to hospitals all over the country suspected of COVID-19 infection and being registered in Iranian neonatal network (IMAN) have been analyzed. Totally 3725 PCR tests were performed (92.8% of admitted neonates) and from these neonates 825 (20.5%) showed positive PCR test. Most of the admissions happened in November (617 cases) and October (589 cases) 2020. Figure 1 demonstrates the distribution of admitted cases from February 2020 to end of January 2021.

**Demographic factors:**

There is no difference in sex, gestational age and weight of admitted neonates with positive and negative PCR test (Table1).

Table 1
Demographic features of admitted neonates with suspected/confirmed COVID-19 (n=4015)

| Demographic features | Admitted in hospital (N & %) | PCR Tested (N & %) | Positive PCR Test (N & %) | Requiring respiratory support (N & %) | Died (N & %) |
|---|---|---|---|---|---|
| Gender | | | | | |
| Male | 2264 (56.4%) | 2104 (56.5%) | 454 (55.0%) | 1377 (59.1%) | 160 (54.1%) |
| Female | 1751 (43.6%) | 1621 (43.5%) | 371 (45.0%) | 954 (40.9%) | 136 (45.9%) |
| | 4015 (100%) | 3725 (100%) | 825 (100%) | 2331 (100%) | 296 (100%) |
| Gestational Age (weeks) | | | | | |
| < 32 | 304 (7.6%) | 284 (7.6%) | 66 (8%) | 292 (12.5%) | 103 (34.8%) |
| 32-36 | 1088 (27.1%) | 1021 (27.4%) | 209 (20.2%) | 758 (32.5%) | 65 (22.0%) |
| >/=37 | 2623(65.3%) | 2420 (65%) | 550 (66.7%) | 1281 (55.0%) | 128 (43.2%) |
| Birth Weight (grams) | | | | | |
| <1500 g | 246 (6.1%) | 231 (6.2%) | 47 (4.7%) | 234 (10.0%) | 88 (29.7%) |
| 1500-2499 g | 888 (22.1%) | 826 (22.2%) | 180 (21.8%) | 642 (27.5%) | 75 (25.3%) |
| >/=2500 g | 2881 (71.8%) | 2668 (71.6%) | 825 (72.5%) | 1455 (50.5%) | 133 (44.9%) |
| Type of Admission | | | | | |
| After birth in the same hospital | 2567 (63.9%) | 2347 (63.0%) | 419 (50.8%) | 1441 (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%) | 3725(100%) | 825 (100%) | 2331(100%) | 296 (100%) |

Table 2
Demographic features of neonates who died with suspected/confirmed COVID-19 (n=296)

| Demographic features | Admitted (N & %) | PCR Tested (N & %) | With Positive PCR Test (N & %) | Requiring respiratory support (N & %) |
|---|---|---|---|---|
| Male | 160 (54.1%) | 154 (55.8%) | 44 (51.8%) | 158 (55.1%) |
| Female | 136 (45.9%) | 122 (44.2%) | 41 (48.2%) | 129(44.9%) |
| Total | 296 (100%) | 276 (100%) | 85 (100%) | 287 (100%) |
| Gestational Age (weeks) | | | | |
| < 32 (w) | 103 (34.8%) | 94 (34.1%) | 23 (27.1%) | 101 (35.2%) |
| 32-36 (w) | 65 (22.0%) | 62 (22.5%) | 24 (28.2%) | 64 (22.3%) |
| >/=37 (w) | 128 (43.2%) | 120 (43.5%) | 38 (44.7%) | 122 (42.5%) |
| Total | 296 (100%) | 276 (100%) | 85 (100%) | 287 (100%) |
| Birth Weight (grams) | | | | |
| <1500 g | 88 (29.7%) | 83 (30.1%) | 21 (24.7%) | 87 (30.3%) |
| 1500-2499 g | 75 (25.3%) | 68 (24.6%) | 25 (29.4%) | 74 (25.8%) |
| >/=2500 g | 133 (44.9%) | 125 (45.3%) | 39 (45.9%) | 126 (43.9%) |
| Total | 296 (100%) | 276 (100%) | 85(100%) | 287 (100%) |
| Type of Admission | | | | |
| After birth in the same hospital | 148 (50.0%) | 139 (50.4%) | 39 (45.9%) | 145 (50.5%) |
| Transfer from another hospital | 98 (33.1%) | 90 (32.6%) | 34 (40.0%) | 96 (33.4%) |
| From home | 50 (16.9%) | 47 (17.0%) | 12 (14.1%) | 46 (16.0%) |
| Total | 296 (100%) | 276 (100%) | 85 (100%) | 287 (100%) |

Table 3
Characteristics of neonates with suspected/confirmed COVID-19 regarding age at admission time (n=4015)

| Age at admission (day) | Total | Male | Female | <32 weeks | 32-36 w | >=37 w |
|---|---|---|---|---|---|---|
| <24 h | 1282 (31.9%) | 692 (30.6. %) | 590 (33.7%) | 160 (52.6%) | 445 (40.9%) | 677 (25.8%) |
| 1-6 | 2090 (52.1%) | 1206(53.3%) | 884 (50.5%) | 118 (38.8%) | 550 (50.6%) | 1422 (54.2%) |
| 7-28 | 643 (16.0%) | 366 (16.2%) | 277 (15.8.3%) | 26 (8.6%) | 93 (14.5%) | 524 (20.0%) |
| Total | 4015 (100%) | 2264 (100%) | 1751 (100%) | 304 (100%) | 1088 (100%) | 2623(100%) |

Type of admission: Mean age of neonates at the time of admission was 3.48±6.33 days. Most admissions (2090 neonates; 52.1%) were between first and d 6th day of life (DOL) (Table-3).

We investigated the time of admission of these infants and noticed three categories. The most prevalent admission type was in the first category who were admitted to the hospital immediately after birth (2567 cases; 63.9% of admissions) and 2347 (91.40%) of them were tested; only 419 (16.3%) cases had positive nasopharyngeal, oropharyngeal or endotracheal PCR test.

The second category was those who were transferred from another hospital (either after birth or later). There were 683 neonates (17% of admissions), and 643 (94.1%) of them were tested and 171 (25%) cases had positive PCR test.

The third category is those neonates who were discharged home after birth and admitted after one to several days after discharge. These were 765 cases (19.1% of total admissions) and 735 (96.0%) of them were tested and 235 (30.7%) cases had positive PCR test. There was a difference between these categories in regard to the positive PCR test and days of admission but the difference was not significant ($p>0.05$).

History of contact: Almost 50% of mothers had positive PCR test; 1005 (25%) of mothers had positive PCR test during pregnancy or childbirth and 974 (24.3%) of them had positive PCR test after delivery and discharge from the hospital. There was a positive history of close contact with positive family cases after discharge at home in 10.4% (419) of neonates.

Signs and symptoms: We found different signs and symptoms in three groups according to the time of admission. In the first category, the most common clinical problems were respiratory distress (1095 cases; 42.6%), sepsis like syndrome (355; 13.8%) and cyanosis (300 cases; 11.6%). Most of these

neonates needed some modes of respiratory care and our data showed 1441 (56.2%) neonates admitted after birth, needed oxygen or non-invasive or invasive respiratory care.

In the second category, the most common signs 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, 526 (77%) cases needed respiratory support.

In the third group, the most common signs were sepsis like syndrome (244 cases; 31.8%), fever (210; 27.4%), respiratory distress (185; 24.1%) and 364 (47.5%) cases needed respiratory support. There was not a significant difference between groups according to their respiratory care requirements.

Respiratory Support: Totally 2331 (58%) of admitted neonates needed some type of respiratory care (ranging from oxygen therapy to non-invasive and invasive ventilation). About 55% of live neonates received respiratory support, compared with 97% of neonates who died. Most of the neonates who admitted after birth or from another hospital (1967; 60.5%) required respiratory support but in those neonates admitted after discharge, respiratory care have been provided for 364 neonates (47.5%) (Table 1). Table 4 displays distribution of respiratory support in admitted neonates with suspected/confirmed COVID-19.

Table 4
Respiratory support in admitted neonates with suspected/confirmed COVID-19

| | **Receiving respiratory care** | **Oxygen therapy** | **Non-Invasive respiratory care** | **Invasive respiratory care** | **Surfactant administration** | **Total** |
|---|---|---|---|---|---|---|
| Discharged alive | 2044 (55%) | 1556 (41.8%) | 643 (17.2%) | 437 (11.7%) | 95 (2.5%) | 3719 (100%) |
| Dead | 287 (97%) | 69 (23.3%) | 60 (2.3%) | 260 (87.8%) | 293 (98.9%) | 296 (100%) |
| Gestational Age (weeks) | | | | | | |
| <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%) | 1088 (100%) |
| >=37 | 1281 (48.8%) | 991 (37.7%) | 262 (9.9%) | 311 (11.8%) | 95 (3.6) | 2623 (100%) |

Surfactant Therapy: In 388 neonates (16.6%) surfactant was administrated at some time after mechanical ventilation.

Laboratory tests: Elevated CRP (681; 17%) and leukocytosis (203; 5.1%) were the most common findings.

Chest CT Scanning was performed in 174 (4.3%) cases and in 84 (2.1%) of them some abnormalities were reported.

Death rate: Of all admitted neonates, 296 (7.4%) died, and between 825 neonates with positive PCR test, 85 (10.3%) neonates died. Based on chi-squared test, in PCR test positive neonates, death rate was higher than negative one; but the difference was insignificant. Table 2 showed demographic features of neonates who died with COVID-19 diagnosis in hospital.

According to the type of admission, in the first category, 148 (5.7%) neonates died before discharge. In the second category, 98 (14.3%) died and in the third category, 50 (6.6%) neonates died. Although those infants who were transferred between hospitals died more frequently, but the cause of death was mostly related to their difficult transfer and delayed respiratory care that was not available in their first hospital. A binominal logistic regression model was conducted to detect factors associated with neonatal death. Gestational age, birth weight, need for respiratory support, age at admission, elevated CRP, and leukocytosis were the predictors and neonate's death were the dependent variable. There was no difference between sex, type of admission, lab tests and mortality (Table5). 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=18.17, 95% CI; 9.24– 35.69). Gestational age of <32 weeks (AOR=2.35, 95% CI; 1.35-4.10) and birth weight of <1500 grams (AOR= 3.47, 95% CI; 1.96-6.17) were two other factors that correlated to death.

Table 5
Associated factors for neonate death among neonates with suspected/confirmed COVID-19

| Variables | Adjusted OR | 95% C.I. for OR | | p-value |
|---|---|---|---|---|
| | | lower | Upper | |
| Gestational age | | | | |
| >/=37 (w) (Reference) | 1.0 | | | |
| < 32 (w) | 2.35 | 1.35 | 4.10 | 0.002 |
| 32-36 (w) | 0.750 | 0.49 | 1.12 | 0.169 |
| Birth Weight (grams) | | | | |
| >/=2500 g (Reference) | 1.0 | | | |
| <1500 g | 3.47 | 1.96 | 6.17 | <0.001 |
| 1500-2499 g | 1.45 | 0.96 | 2.19 | 0.076 |
| Respiratory support | 18.17 | 9.24 | 35.69 | <0.001 |
| Elevated CRP | 1.24 | 0.925 | 1.64 | 0.147 |
| Leukocytosis | 1.56 | 0.989 | 2.47 | 0.056 |
| Age at admission (day) | | | | |
| <24 h (Reference) | 1.0 | | | |
| 1-6 | 1.32 | 0.841 | 1.52 | 0.414 |
| 7-28 | 1.81 | 1.23 | 2.66 | 0.002 |
| Positive PCR Test | 1.33 | 0.981 | 1.70 | 0.751 |

Gestational age, birth weight and mortality: Between 85 infants with positive PCR test who died, 23 cases (27.1%) were born at less than 32 weeks of pregnancy, 24 cases (28.2%) were between 32-36+6 weeks of gestation and 38 cases (44.7%) were term infants (Table 2). Death rate in infants who were born < 32 weeks was 34% compared to 6% in infants 32-36+6 weeks and 5% in term infants. This higher death rate is supposed to be mostly due to prematurity and its complications and the national death rate due to prematurity < 32 weeks is about 29% (IMAN network) that is not different from premature infants with or without COVID-19 infection. Between the group of infants who died, 21 cases (24%) which were less than 1500 grams, 25 cases (29.4%) were 1500-2499 grams and 39 cases (45.9%) were equal or more than

2500 grams (Table 2). Death rate in infants with birth weight of <1500 grams who were diagnosed with COVID-19 infection was 36% compared to 8% in infants 1500-2499 grams and 55 in infants who was born 2500 grams and more (Table5). This higher rate is mostly due to very low birth weight and the national death rate in this group is about 33% in 2019.

Respiratory support: Totally 287 (96.9%) of the dead neonates needed some types of respiratory care like oxygen therapy (23.3%), non-invasive respiratory cares (2.3%), invasive respiratory cares (87.8%) and surfactant administration (98.9%).

# Discussion

In this retrospective cross-sectional study using data collected from IMaN network, we have included 4015 neonates with suspected/confirmed SARS-CoV-2 infection in one year from Feb 2020 to Feb 2021 and it is one of the largest reported studies in neonates. As the infection is still spreading worldwide, this study can provide physicians and policy makers with useful information about different aspects of SARS-CoV-2 infection in neonates.

Iran has reported its first confirmed cases of infections in Qom on 19 February 2019 [17]. The number of new cases exceeded suddenly and since the beginning of SARS-COV-2 until Jan 2021 there have been 4 peaks; Nowruz peak (March-April), after Nowruz (April- May), Resurgence (May- June), and the new peak (June – July).

According to the Figure 1, we have a coordination between neonatal covid-19 peaks in comparison to peaks in the whole country and most of our cases have been admitted in Oct and Nov 2020.

The diagnosis of SARS-CoV-2 infection in neonates depends on history of contact with a known case of infection (mostly mothers) [18, 19] or other care- givers and laboratory and clinical findings. The current gold standard to diagnose SARS-CoV-2 infection is RT-PCR on respiratory specimens [20]. Diagnosis via serological testing in neonates is particularly challenging given the transplacental transmission of maternal IgG, and that IgM assays are prone to false-positives and false-negatives, they are not the gold standard for diagnosis of congenital infections [21].

Twenty and a half percent of neonates had positive PCR test in our study which is lower than reported in another case study from Iran with 56% positive swab test [19], but higher than a Chinese study that reported 8.1% positive test in 1391 children younger than 16 years of age [22]. In a literature review, Trippella, et al. showed 92% of tests in neonates were negative [8], however, among the negative neonates, some authors reported clinical symptoms [8, 23]. Multiple causes have been found for a negative swab test such as low virus titers, inappropriate swabbing sites, or variability on laboratory test performance [22].

There was no significant difference between genders of neonates in our study as was shown in other reports [14, 24, 25]. In those neonates with positive PCR, most of them were born at term gestation which

is in line with other studies [25, 26, 27] and in Trippella`s study with 72% term infants [8].

Most of the neonates with PCR positive tests had normal weight (> 2500 g) and a minority of neonates had very low birth weight (< 1500 grams) as was seen in the study by Christine M Salvatore, et al., with 87% of neonates with weight ≥ 2500 gram, 12% between 1500 to 2500 grams and 1%< 1000 gram [25]. In another study from Iran, no significant relation between COVID-19 infection and neonatal and maternal outcomes including preterm birth and low birth weight was reported but cesarean delivery and the need for ICU were higher in mothers with Covid-19 [27].

Different signs and symptoms were reported in neonatal period ranging from asymptomatic carriage to critical illness, and in this study the most frequently described symptoms showed a significant correlation to the time of admission. In our study, the most frequent symptoms were respiratory distress, sepsis like syndrome, cyanosis, sepsis like syndrome and fever. In other reports among symptomatic neonates, the most common clinical presentation was respiratory distress (40%), with fever (32%) and feeding intolerance (24%) [23]. In an Iranian review article the most common symptoms were shortness of breath, tachypnea, cough, apnea, temperature instability and tachycardia [19]. Respiratory changes are therefore the most common finding in studies in infected neonates.

The laboratory findings in our study, in order of prevalence, were as follows: elevated white blood cell count, elevated creatine phosphokinase (CPK), abnormal liver enzymes, and elevated C-reactive protein and/or procalcitonin. In an Iranian review article leukopenia, lymphopenia, thrombocytopenia in, elevated CPK, elevated CRP in, elevated procalcitonin and abnormality in liver test was seen in infected infants, in order of prevalence [19]. In the published article by Al-Matary A, et al. most neonates had normal laboratory results and the most abnormal result was hyperbilirubinemia seen in 40% of neonates [28].

Different types of respiratory support were needed in neonates with COVID-19 diseases. About 58% of our admitted neonates needed some kinds of respiratory support and it was more prevalent in those infants who died before discharge that showed a significant difference between dead and alive infants. There is a difference between our study and a study by Belén Fernández Colomer, et al. from Spain in needing some kind of respiratory support [24]. As in their study most of the neonates showed community-acquired infection, in 85.7% of admitted neonates there was no need for any respiratory support and in another article with Al-Matary A, et al., although 43% of neonates born to infected mothers were admitted to NICU, only 7% needed respiratory support [28].

However, the need for respiratory support might have been related to other conditions, such as prematurity, rather than SARS-CoV-2 infection. Among all types of respiratory support; invasive ventilation was the most prevalent way of support in preterm infants ≤ 32 weeks (59.8%) vs 11.8% in those ≥ 37 weeks (p value<0.01) and oxygen therapy was the most prevalent way of support in infants ≥ 37 gestational weeks (Table 4).

According to the time of admission after birth, 3372 (83%) of cases were admitted in the first week of life and 16% were admitted after the first week. In a study by Ronchi A., et al., from 62 infants born to 61

mothers with confirmed COVID-19 infection, only 1 infant (1.6%) was diagnosed as having SARS-CoV-2 infection at 7 days of life [29]. A cohort study done by Pierce-Williams R., et al, indicates that about 63.6% of neonates born to infected mothers were transferred to the NICU [30].

About 4015 suspected COVID-19 neonates were admitted to the hospital, among which 7 percent died with a positive PCR in third of them. About half of positive PCR departed neonates were term and about one third of them were less than 32 weeks. Gestational age less than 32 weeks was related with newborn death as the 34% of them died in comparison to 6% death among neonates between 32 to 36 weeks and 5% death among neonates >=37 week (95% CI= 1.35-4.10 and *p value <0.01).* Death rate was not different in preterm infants with or without positive PCR test.

Also a birth weight of <1500 grams was connected with neonatal death. As 36% of newborns with birth weight of <1500 grams died while this ratio was 8% in neonates between 1500 to 2499 grams and 5% in neonates >= 2000 grams. (aOR=1.96; 95% CI=1.96-6.17) (*p value <0.01)*, (Table 5).

Laboratory factors such as a positive PCR test, elevated CRP and leukocytosis were not significantly associated with neonatal death. (Table 5).

Among all neonates who were admitted to the hospital and required respiratory support (2331 from 4015; 58%), there is a significant association between death and respiratory support with OR= 18.17 and 95% CI 9.24-35.69 and p *value<0.01*. This difference could partially be due to more severe respiratory problem from the time of admission in those neonates who required respiratory care and died and as respiratory failure was the most common cause of death, but it could be related to other lung pathologies such as respiratory distress syndrome and pneumonia at the time of admission (Table 5).

About 58% of all neonates who were admitted to the hospital, required respiratory support which was a predictive factor for neonatal death (OR= 18.17 and 95% CI 9.24-35.69 and p *value<0.01).* Among those neonates who required respiratory care and died, the severity of respiratory problem at the admission was determinative. Respiratory failure was the most common cause of death along with other possible etiologies such as respiratory distress syndrome and pneumonia at the time of admission (Table 5).

There were several limitations in our study; although we had a large number of neonates with COVID-19 diseases, we were unable to screen the virus in amniotic fluid, umbilical cord or vagina to study vertical transmission. We did not have required facilities in our country to detect the virus in urine, stool or blood samples to confirm the disease in suspected cases with negative PCR test. Furthermore, we used PCR test to diagnose COVID 19 which has a notable false negative rate, as only 22% of our cases showed positive test and 77% of suspected cases had negative PCR.

# Conclusion

Our study was the largest study and analysis of neonatal COVID-19 diseases in Iran based on IMAN registry system. The most common signs and symptoms in neonates were respiratory distress and sepsis

like syndrome. Despite the world pandemic situation, this article demonstrates that neonates are not an exception population from COVID-19 diseases and our data provides an additional guidance to enhance pre and postnatal counselling in mothers with COVID-19 diseases whilst they are pregnant and even after their delivery.

# Abbreviations

IMaN: Iranian Maternal and Neonatal Network (IMAN)

PCR: Polymerase Chain Reaction

COVID-19: Coronavirus Disease of 2019

MERS-COV: Middle East Respiratory Syndrome-related Coronavirus

SARS-COV: Severe Acute Respiratory Syndrome- related Coronavirus

AOR: Odds Ratio

SARS: Sever Acute Respiratory Syndrome

MERS: Middle East Respiratory Syndrome

DIC: Disseminated Intravascular Coagulation

DOL: Day of Life

# Declarations

**Acknowledgement:**

NA

**Ethic approval and consent to participants:**

the study received approval form the institutional review board of IUMS and the ethical committee code is: IR.IUMS.REC.1399.1365.

**Consent of publication:**

No applicable

**Availability of data and material:**

databases of Pubmed, Embase and web of science were searched systematically up to 2021.

**Competing interests:**

on behalf of all authors, the corresponding author states that there is no conflict of interests

**Funding:**

there is no funding in this article

**Consent of participate:**

there is not any individual s data or image in this article and we have a consent form in the neonatal file when admitting.

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# Figures

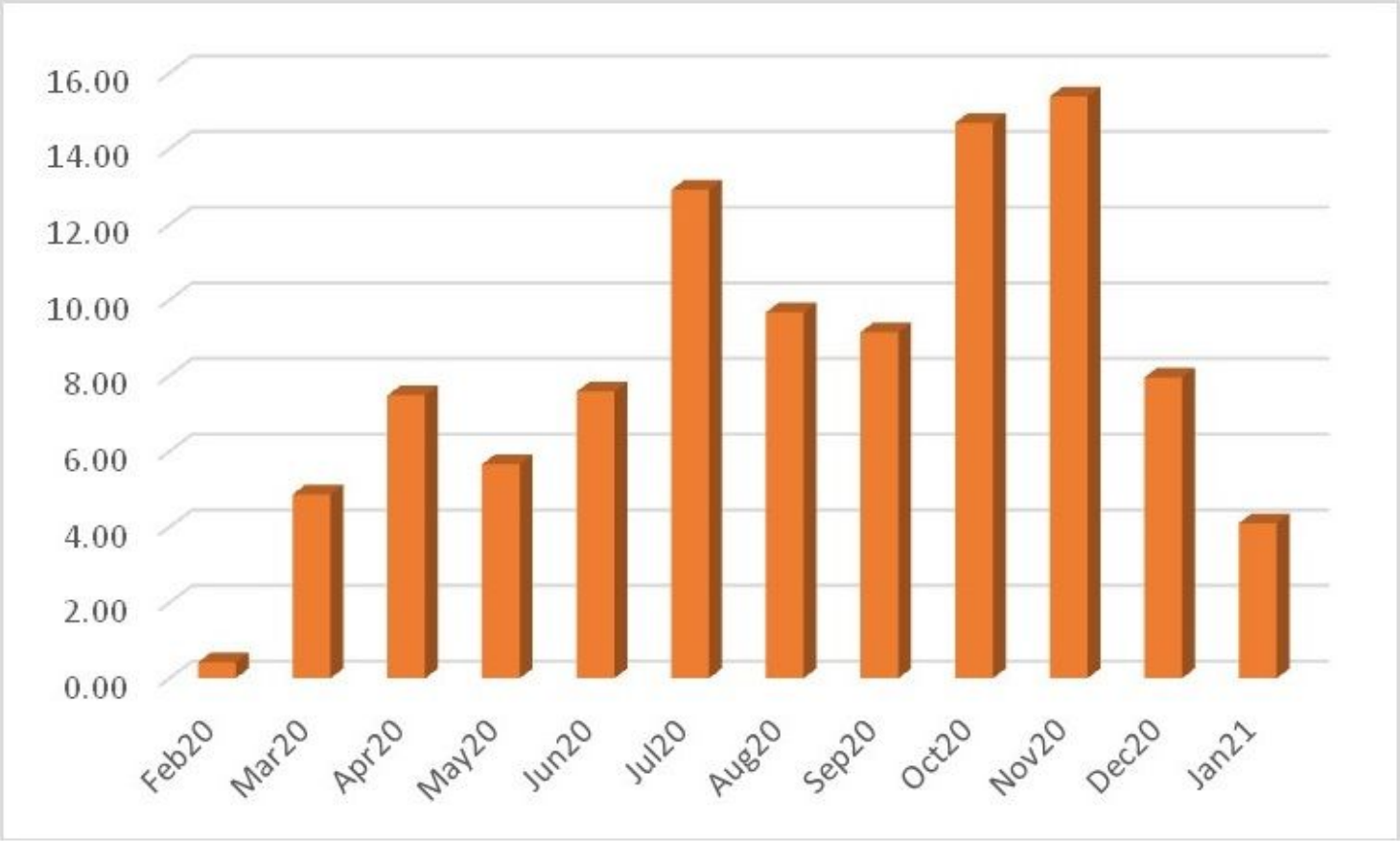


**Figure 1**

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