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A multicenter retrospective study of clinical features, laboratory characteristics, and outcomes of 166 hospitalized children with coronavirus disease 2019 (COVID-19): A preliminary report from Iranian Network for Research in Viral Diseases (INRVD)

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Abbreviations: ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; CFR, case fatality rate; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FTT, failure to thrive; INRVD, Iranian Network for Research in Viral Diseases; LDH, lactate dehydrogenase; PT, prothrombin; PTT, partial thromboplastin time; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Abstract

Background: The objectives of this study were to analyze the clinical features and laboratory profiles and risk factors associated with critical illness of children with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Methods: One hundred and sixty-six coronavirus disease 2019 (COVID-19) Iranian pediatric patients were recruited through a collaborative research network between March and May 2020. Demographics, clinical, laboratory, and radiological results were obtained from patient files.

Results: Of 166 patients, 102 (61%) and 64 (39%) were males and females, respectively. Ninety-six (57.8%) and 70 (42.2%), had moderate and severe conditions, respectively. Thirty (18%) of patients died. The common symptoms were fever (73%), cough (54%), and shortness of breath, headache decrease in neutrophil and platelet counts; increase values in lactate dehydrogenase, decrease in the blood pH and HCO_3 were significantly associated with the disease severity. 54% and 56% of patients showed abnormal radiographic appearance in Chest X-ray and in chest computed tomography scan, respectively. Sixty-one (36.7%) of patients were referred to intensive care unit (ICU). The coexistence of comorbidity was the main factor associated with ICU admission, shock, arrhythmia, acute kidney injury, acute respiratory distress syndrome, acute cardiac injury, and death.

Conclusions: We describe a higher than previously recognized rate of COVID-19 mortality in Iranian pediatric patients. Epidemiological factors, such as the relatively high case fatality rate in the country and the presence of underlying diseases were the main factors for the high death rate.

KEYWORDS
children, COVID-19, severe acute respiratory syndrome coronavirus-2

1 | BACKGROUND

For reasons that are yet to be clarified, the course of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in children seems to be generally mild compared with that seen in adults.[1,2] Worldwide published reports have confirmed the small proportion of confirmed COVID-19 cases and lower mortality rate in children.[3–6]

Several hypotheses have been proposed so far for the mildness nature of COVID-19 disease in pediatrics, including: highly effectiveness of innate immune response in this age groups,[7] early childhood measles, mumps, and rubella (MMR) vaccination (due to molecular mimicry between amino acid residues),[8] memory to a cross-reactive antigen because of cross-reaction to related coronavirus strains from earlier infection (antibody-dependent enhancement due to original antigenic sin)[9] and protection of children against COVID-19 as a result of cross-immunity due to previous exposure to seasonal coronavirus.[10] Apart from the immunological point of view, the lower prevalence of cardiovascular diseases, diabetes types 2, and fair body max index (BMI) in children compared with adults might be the underlying reasons for such less disease prevalence and aggressiveness.

On the other hand, due to the aggressive nature of COVID-19, severe and fatal cases in children are expected to be continued and also to be increased due to its global spread along with the growing community transmission and overall current disease prevalence. Indeed, the proportions of severe and critical cases stratified by several age sub-categories obtained from a recent report from China on 2143 children with suspected COVID-19 were 10.6% for < 1 year, 7.3% for 1–5 years, 4.2% for 6–10 years, 4.1% for 11–15 years, and 3.0% for ≥16 years.[11] In the USA, children less than 18 years account for nearly 10%–13% of laboratory-confirmed cases reported to the Centers for Disease Control and Prevention (CDC).[12,13]

Other international data released so far indicated the same pattern. Of 137,047,945 population aged between 0 and 19 years old from seven countries, COVID-19 deaths as percentage of all-cause deaths reported to be only 0.48%.[14] Other investigation carried out on 585 pediatrics cases from 25 European countries showed 0.68% mortality rate.[15]

Since the COVID-19 pandemic, Iran has been among the list of the most affected countries in the world [16,17] and the estimated COVID-19 case fatality rate in Iran ranged from 1.85%[18] to 10.5%.[19] Nevertheless, information regarding COVID-19 among Iranian pediatrics is scarce. Those studies were single-center based and they were suffered from small sample sizes.

The objectives of this study were (i) to analyze the epidemiological characteristics, (ii) to describe the clinical features and laboratory profiles, and (iii) to investigate the risk factors associated with critical illness of 166 children with SARS-CoV-2 infection admitted to hospitals collaborative to the Iranian Network for Research in Viral Diseases (INRVD).

2 | METHODS

2.1 | Population and settings

The present study was a retrospective descriptive clinical study. Data were collected from a total of 166 cases through an extensive collaborative research network, including 15 general and pediatrics hospitals, coordinated by INRVD. We included all pediatric patients (aged 0–15 years) who were admitted to any of the recruiting centers between March 19 and May 31, 2020 and were diagnosed with COVID-19 (see below). Patients were screened for COVID-19 virus based on clinical manifestations at the initial presentation, or who underwent epidemiological investigation because of an exposure history to any epidemic region or close contact with known patients with confirmed COVID-19 within 14 days, especially within their family.

Nasal, oropharyngeal, or nasopharyngeal swab specimens were collected by trained personnel based on national guidelines issued by the Iranian Center for Disease Control (CDC) during the study period. All samples were referred to regional referral laboratories across the country using recommended real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assays.[20] All enrolled patients in this investigation were diagnosed for COVID-19 according to the criteria formulated by the Iranian CDC. Subsequently, the severity of COVID-19 between subjects was classified into an asymptomatic infection, as mild, moderate, severe, or critical in line with clinical features, laboratory testing, and chest scan imaging. All the laboratory-confirmed cases (166) were included in the analysis. For assessing the severity of disease, the following criteria were considered.

1. For asymptomatic cases, individuals infected by SARS-CoV-2 without any clinical symptoms and signs throughout the course of the infection with or without abnormal chest computed tomography (CT) imaging findings.
2. For mild cases, clinical symptoms of acute upper respiratory tract infection with or without fever, no radiographic findings of pneumonia. Some cases in this group might have had only digestive symptoms.
3. For moderate cases, the diagnostic criteria: either has clinical signs and symptoms or frequent fever and cough, but no obvious hypoxemia. However, chest computed tomography showed lung abnormalities presenting pneumonia, which were subclinical.
4. For severe cases, the diagnostic criteria: (i) respiratory distress, tachypnea ≥ 60/min in neonates, ≥50/min between 1 and 12

months, ≥40/min between 1 and 5 years old, and ≥30/min older than 5 years old; (ii) hypoxemia, with resting oxygen saturation ≦93%; and (iii) arterial partial oxygen pressure (PaO_2)/oxygen absorption concentration (FiO_2) ≦300 mmHg. The disease was usually progressed at about 1 week, and dyspnea occurred with central cyanosis.

5. Critical: for children who quickly progressed to acute respiratory distress syndrome or respiratory failure requiring mechanical ventilation and might also have shock, encephalopathy, myocardial injury or heart failure, coagulation dysfunction, complicated with other organ failure requiring intensive care unit (ICU) care.

Altogether, the presence of referral to ICU, shock, arrhythmia, acute kidney injury (AKI), acute respiratory distress syndrome (ARDS), and acute cardiac injury were considered as factors for the severity of the disease.

The project was approved by the ethics committee of Tehran University of Medical Sciences (No. 1399.378) and followed the Declaration of Helsinki. Written consent was obtained from the guardians of the patients.

2.2 | Procedures

2.2.1 | Laboratory indicators

Laboratory examinations included routine testing and measurement of biomarkers for monitoring lung, liver, and renal functions together with hematologic parameters, were carried out within general hospitals laboratories using CE-IVD assays.

2.3 | Molecular assays

Screening for SARS-Cov-2 was performed for all pediatric cases admitted to the hospitals for the suspension of COVID-19 infection. According to Iranian CDC guidelines, SARS-Cov-2 infection was confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR) testing on throat specimens using flocked swabs, which were collected immediately upon admission. Collaborative clinical virology was obliged to apply two sets of primers for two target genes (E and RdP genes). The Iranian Pasture Institute provided these dual-target detection kits along with a protocol for all laboratories across the country. If respiratory samples obtained from patients were successfully tested positive by either or both genes, the specimens would have been considered positive, and the case was considered laboratory-confirmed.

2.4 | Radiological assessments

According to the guidelines issued by The Ministry of Health, all COVID-19 confirmed cases with any respiratory symptoms undergo a chest X-ray upon admission. A chest CT scan usually applies in the case of either the presence of any abnormality in their X-ray or for the patients who progress to the severe form of the disease.

2.5 | Data collection

Demographic data, exposure and medical history, clinical signs and symptoms at presentation, laboratory examinations, imaging data, and outcomes on all pediatric patients admitted to the hospital during the study period were placed in a predefined, standardized, field-tested electronic form provided by INRVD.

2.6 | Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) for Windows release 25.0 (SPSS Inc.). Descriptive statistics were generated for demographic and clinical characteristics. χ^2 or Fisher's exact tests were also used to compare categorical variables. To explore the risk factors associated with disease severity, multivariable logistic regression models were used. Regarding the total number of severe cases in this study (n = 166) and to avoid overfitting in the model, five variables were chosen for multivariate analysis based on previous findings and clinical constraints. p-values less than 0.05 were considered to indicate significance statistically.

3 | RESULTS

3.1 | Demographic and medical past history data

Of the total number of 166 pediatrics patients, 102 (61%) and 64 (39%) were males and females, respectively. The age of subjects ranged between 0 and 15 years old. The median age of the patients was 5.08 (interquartile range [IQR]: 1.5–12). There was no significant correlation between the distributions of cases in different age groups (p-value = 0.2). Logistic regression however showed a significant association between age groups with the severity of the disease (Table 1).

History of close contact with COVID-19 patients and/or travel to provinces with a high prevalence of COVID-19 was confirmed in 114 (69%) of patients (results not shown). Regarding the vaccine history of patients, 155 (93.3%) had received all routine childhood vaccines, and 9 (5.4%) received incomplete vaccination in fear of high-risk disease transmission in the healthcare centers. Only 22 (13%) received flu vaccination (results not shown). Previous medications (before the admission), including antibiotic therapy, corticosteroid therapy, and chemotherapy were reported in 54 (33%), 16 (9.6%), and 15 (9.0%) patients, respectively.

3.2 | Clinical characteristics

All 166 patients had at least one symptom before the admission. One hundred and twenty-two (73%) had a fever. The common respiratory symptoms were cough (54%), shortness of breath (36%), sore throat (4.2%), and rhinorrhea (1.8%). Gastrointestinal (GI) symptoms were seen in 136 (81.9% (of patients including nausea/vomiting (33%), anorexia (25%), diarrhea (18%), and abdominal pain (5.4%). Sixty (36.1% (of children had neurological symptoms including, fatigue (16%), drowsiness/loss of consciousness (5.4%), seizure (6.6%), headache (6%), and myalgia (1.8%). Six (3.6%) of patients experienced skin rash. Among the above symptoms, only shortness of breath and headache were significantly associated with the disease severity (p-values 0.04 and 0.005, respectively, results not shown). Ninety-six (57.8%) and 70 (42.2%), had moderate and severe conditions, respectively (see below).

Upon clinical examination, grunting (p-value 0.03), intercostal and subcostal retractions (p-value < 0.001), and nasal flaring (p-value < 0.001) were significantly associated with the disease severity (results not shown). Other signs including, wheezing, coarse respiratory crackles, and cyanosis, did not substantially correlate with disease severity.

3.3 | Laboratory data

In the process of interpretation and analyzing the data, there was a high percentage of heterogeneity in the hematological and biochemistry results. Taken into consideration, to avoid any false data outputs, only those data which met the criteria have been included in the results. Therefore, the presented results have not included the whole study population.

Based on the results of the logistic regression, there was a significant association between the severity of the disease with decreased in neutrophil and platelet counts (OR = 0.01, 95% CI: 0.00–0.09; $p = 0.001$ and 12.2, 95% CI: 1.81–123; $p = 0.018$, respectively, Table 1). Among a list of biochemistry results, only increased levels of LDH was statistically associated with the severity of the disease (OR = 5.27, 95% CI: 1.28–28.4; $p = 0.034$).

3.4 | Blood saturation results

At the beginning of the pandemic and due to the shortage of facilities in some hospitals, blood saturation tests were carried only for 82 patients. A decrease in the blood pH and HCO_3 was associated with the illness severity (p values 0.002 and <0.001, respectively). Conversely, PO_2 and PCO_2 levels had no significant correlation with the disease outcome (results not shown).

3.5 | Radiological findings

Overall, of 137 patients who undertook chest X-ray, 54% showed abnormal radiographic appearance, whereas, in the chest CT scan from 111 subjects, 56% showed abnormal features. Statistics showed that chest X-ray abnormal results had a significant correlation with disease severity (p values < 0.001). Ground glass opacity (36.6%), lung consolidation (25.2%), peripheral airspace opacities (22.6%), patchy infiltration (15.5%), and pleural effusion (9.8%), were the common radiological findings (results not shown).

3.6 | Clinical outcome

Table 2 and Figure 1 show the correlation between different age groups and disease severity. Ninety-six (57.8%) and 70 (42.2%), had moderate and severe conditions, respectively. No significant correlation was found between different age groups of patients and death (p-value 0.12, Table 2). In total, 69 (41.5%) of patients had a history of at least one underlying disease. Malignancies (20, 12%), and heart disease (9, 5.4%) were amongst the most common comorbidities among the cases. Other morbidities were included: asthma (4, 2.4%), cystic fibrosis (1, 0.6%), chronic kidney diseases (4, 2.4%), diabetes (1, 0.6%), failure to thrive (4, 2.4%), and other medical conditions (24, 14%) (results not shown). Thirty (18%) of patients died.

TABLE 1 Logistic regression of characteristics

Characteristic	OR	95% CI	p-value
Age.cat			
0–1	–	–	
1–5	0.04	0.00–0.49	0.029
5–10	0.00	0.00–0.07	0.001
10–18	0.01	0.00–0.09	0.002
Neut			
Normal	–	–	
Decreased	0.01	0.00–0.09	0.001
Increased	0.73	0.11–5.09	0.7
Plt			
Normal	–	–	
Decreased	12.2	1.81–123	0.018
Increased	6.10	1.02–48.7	0.060
BUN			
Normal	–	–	
Increased	5.03	0.87–37.5	0.087
LDH			
Normal	–	–	
Decreased	37,679,265	0.00–NA	>0.9
Increased	5.27	1.22–28.4	0.034

Abbreviations: CI, confidence interval; BUN, blood urea nitrogen; LDH, lactic dehydrogenase; Neut, neutrophil; OR, odds ratio; Plt, platelet.

Due to patients' critical conditions, 61 (36.7%) cases were referred to ICU. The only factor which was correlated with ICU referrals was the presence of comorbidity (p-value < 0.001). A significant correlation was found between the age group and referral to ICU (p-value 0.048, Table 2). No other clinical symptoms, laboratory parameters, and radiological findings were associated with ICU admission (results not shown).

Oxygen therapy was used for 61 (36.7%) of patients. 38 (22.8%) of patients experienced at least one clinical severe outcome as the followings: ARDS 19 (11.4%), shock 9 (5.4%), acute cardiac injury 4 (2.4%), arrhythmia 4 (2.4%), and AKI 2 (1.2%). Justification of these outcomes with the history of comorbidities showed that subjects who were had at least one underlying disease suffered from shock (p value, 0.035), arrhythmia (p value, 0.028), AKI (p value, 0.2), ARDS (p value, <0.001), and acute cardiac injury (p value, 0.3, Table 3).

Upon justifying with different age groups, only occurrence of ARDS and AKI showed a significant correlation (p values 0.032 and 0.024, Table 2). No other clinical outcomes or parameters were associated with the patients' age (Table 2).

4 | DISCUSSION

The data on medical course and clinical outcomes of COVID-19, as well as predisposing factors regarding the prognosis of the disease is obscure. In the present multicenter, country-wide investigation, we summarized the clinical, laboratory, and radiographically data of 166 pediatric patients with laboratory and/or clinically confirmed COVID-19 infection. We found a correlation between age and disease severity. However, the proportions of severe and critical cases stratified by several age sub-categories obtained from a recent report from China on 2143 children with suspected COVID-19 were 10.6% for < 1 year, 7.3% for 1–5 years, 4.2% for 6–10 years, 4.1% for 11–15 years, and 3.0% for ≥16 years.[21]

Our results showed that at the time of admission, fever (73%), cough (54%), shortness of breath (36%), nausea/vomiting (33%), and anorexia (25%) were the most common symptoms. Similarly, fever, cough, shortness of breath, and dyspnea have been reported as the most common symptoms among admitted children to the hospitals in the USA[22] and China,[23] respectively. Overall, in a systematic review published by Patel et al. of 633 patients from 10 studies, 296 (46.7%) had a fever.[24] Other publications emphasized the presence of fever as well as respiratory symptoms among children with different proportions, especially in severe cases.[22,23,25] GI symptoms were seen in 81.9% of Iranian pediatrics. Nevertheless, in other publications from China and the USA, GI manifestations were reported at 8%–29%.[1,25–27] Neurological manifestations were observed in 36.1% of Iranian COVID-19 infected children. On the other hand, some authors reported that children with COVID-19 had less often symptoms (especially fever).[28,29] Asymptomatic children have been observed in most of the published data so far ranged between 10% and 32%.[1,24,25,28–30] One of the reasons for the presence of such symptomatic cases in our study (99.38%) might be related to the fact that all collaborative hospitals in the present study were the referral centers for high-risk pediatrics admission.

The hematological assessment showed that decreases in neutrophils and platelet counts had substantial correlations with the disease's serious outcomes, a similar finding by Cao et al. from the USA.[22] Surprisingly, hemoglobin and WBC (including neutrophil and lymphocyte counts) were normal in 54%, 63%, 72%, and 56% of Iranian COVID-19 infected children, respectively. Unlike in adults, we did not find any correlation with severity of disease in our patients and CBC changes like lymphopenia or eosinophilopenia except thrombocytopenia. Other studies emphasized the correlation between these values and the disease severity with different values.[1,25,28,29,31]

Among a list of biochemistry results, only increased levels of LDH were statistically associated with the severity of the disease (Table 1). A long list of abnormal laboratory parameters has been reported in several publications from different countries with a variety of heterogeneity between studies. However, no absolute biochemistry indexes have been found to be associated with disease severity so far.

Blood saturation tests were accomplished only for 82 patients. A decrease in the blood pH and HCO_3 was associated with the disease severity. However, PO_2 and PCO_2 levels had no significant correlation with the disease outcome. Not many data are available in the database to compare blood saturation values and the disease severity between COVID-19 positive children.

In the chest X-ray, 54% and in chest CT scan, 56% of patients showed normal radiographic appearance. Normal radiological results among pediatrics COVID-19 patients results were found in 20%,[29] 27%,[1] 37.9%,[25] and 42.9%–45% [24] of patients with confirmed COVID-19 disease. The present study showed that ground-glass opacity and lung consolidation showed significant correlations with disease severity. Similar findings were observed by others.[1,22,24,29] Two studies compared the radiological features between severe versus non-severe cases.[22,23] Both surveys found unilateral or bilateral opacities in CT scans of patients among two groups of patients. However, patchy consolidation was less frequently detected for nonsevere children.[23]

We did not find a significant correlation between different age groups and clinical outcomes, with the exception of ARDS and AKI (p-values 0.032 and 0.024, respectively). Even more, death was not related to a specific age group (p-values 0.12). Only admission to ICU was correlated to age group (p value, 0.048).

Death rates are relatively few cases among children. A systematic review across seven studies for which the information about mortality outcomes was available, there were a total of only five pediatric mortalities out of 2843 COVID-19 positive cases (0.0018%).[24] Among patients under 19 years old accounted for 2.2% of 44,672 confirmed cases, only one death was recorded (0.1%).[32] Basically, the crude mortality rate from COVID-19 in children is extremely low compared with that in current published data for adults (2.3% e 14.6%).[32–35] To our surprise, the present study showed that 30 (18%) of patients died. Reasons for such a high number of mortality might be due to several factors. First, the selection bias of patients for admission. It has to be remembered that all the

TABLE 2 Associations between age groups and clinical outcomes

Characteristic	N	0–1, *N* = 29[1]	1–5, *N* = 54[1]	5–10, *N* = 26[1]	10–15, *N* = 57[1]	*p*-value[2]
Shock	166					>0.9
Negative		27 (93%)	51 (94%)	25 (96%)	54 (95%)	
Positive		2 (6.9%)	3 (5.6%)	1 (3.8%)	3 (5.3%)	
Arrhythmia	166					>0.9
Negative		28 (97%)	53 (98%)	26 (100%)	55 (96%)	
Positive		1 (3.4%)	1 (1.9%)	0 (0%)	2 (3.5%)	
AKI	166					0.024
Negative		29 (100%)	54 (100%)	24 (92%)	57 (100%)	
Positive		0 (0%)	0 (0%)	2 (7.7%)	0 (0%)	
ARDS	166					0.032
Negative		22 (76%)	52 (96%)	24 (92%)	49 (86%)	
Positive		7 (24%)	2 (3.7%)	2 (7.7%)	8 (14%)	
Acute cardiac injury	166					0.8
Negative		28 (97%)	53 (98%)	25 (96%)	56 (98%)	
Positive		1 (3.4%)	1 (1.9%)	1 (3.8%)	1 (1.8%)	
ICU	166					0.048
Negative		12 (41%)	35 (65%)	17 (65%)	41 (72%)	
Positive		17 (59%)	19 (35%)	9 (35%)	16 (28%)	
Oxygen	166					0.4
Negative		17 (59%)	32 (59%)	15 (58%)	41 (72%)	
Positive		12 (41%)	22 (41%)	11 (42%)	16 (28%)	
Antibiotic	166					>0.9
Negative		5 (17%)	9 (17%)	4 (15%)	11 (19%)	
Positive		24 (83%)	45 (83%)	22 (85%)	46 (81%)	
Death	166					0.12
Negative		20 (69%)	48 (89%)	23 (88%)	45 (79%)	
Positive		9 (31%)	6 (11%)	3 (12%)	12 (21%)	

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

[1]*n* (%).

[2]Fisher's exact test; Pearson's χ^2 test

above-mentioned medical centers were the referral hospitals for very sick children across the country. Second, unawareness of medical staff for the nature of some patients' disease and mismanagement at the beginning of epidemics in Iran could have been the other reason. Because of the absence of insights into the clinical outcome of COVID-19, especially multiorgan dysfunction, we did not assess the criteria for this observation due to the unknown features of the disease at the beginning of the epidemics. A majority of those cases were suspected of Kawasaki disease. Even more, Iranian pediatricians were surprised about the acquisition of Kawasaki among a higher age group (>5 years old) children. Undeniably, late presentation of patients by children's parents to the hospitals due to unawareness of the disease nature of the society could have been worsened this scenario. Third, at the beginning of pandemics, limitation in health resources including access to oxygen saturation tests and ICU-associated equipment might have contributed to the high mortality rate, especially among ICU patients (18%). Fourth, at the time of the preparation of this article, Iran still has been located in the list of countries with a proportional high raw case fatality rate (CFR) in the world.[17] Although the true CFR ratio might not have been known for some time, the estimated CFR among medically attended Iranian patients has been reported to be approximately 2%.[36] It should be acknowledged that, by contrast with other low mortality rate surveys, this investigation includes

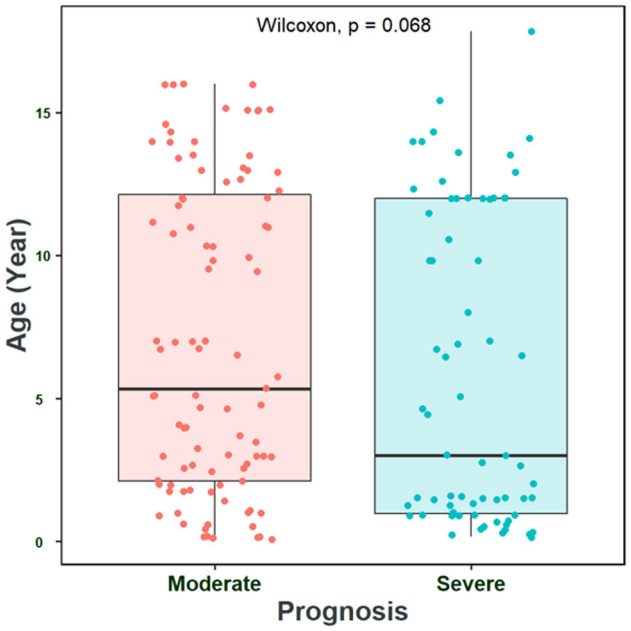

FIGURE 1 Correlation between different age groups and illness severity [Color figure can be viewed at wileyonlinelibrary.com]

the patients from some provinces which initially had a very high net reproductive number, which subsequently decreased after the passage of COVID-19 epidemic days. Lastly, one of the critical criteria for COVID-19 adverse clinical outcomes and death in both childhood and adulthood patients includes the coexistence of underlying disease.[3,37] The presence of comorbidities has been the second cause (after age) of increased mortality and morbidity between adults with COVID-19 patients. There is not enough international data on the relation between specific morbidities and COVID-19 clinical outcomes and the definite pathogenesis is unknown. In the current survey, this was the main critical factor that showed a strong association with ICU admission, arrhythmia, ARDS, acute cardiac injury, and death. Conversely, Chang et al. observed that of 444 pediatric patients, 349 were reported to have no comorbidities (78.6%).[1] On the other hand, many others recent reports emphasized the negative influence of the previous history of congenital or acquired diseases on the outcome of COVID 19 among children.[23,29,38–40] It is tempting to speculate that unlike the adults, underlying diseases are rare in children (such as diabetes mellitus, cardiovascular disease, or chronic kidney diseases). These underlying diseases may persuade patients to severe medical conditions during COVID-19. Nevertheless, the causes of death yet to be determined globally.

5 | CONCLUSIONS

In conclusion, the present study clearly showed that Iranian pediatric COVID-19 patients showed a remarkably high mortality rate. Epidemiological factors (such as relatively high case fatality rate, carelessness about infection control measures, etc.) and the presence of underlying diseases were the main factors for the high death rate

TABLE 3 Association between the presence of comorbidities and clinical outcomes

Characteristic	N	Negative, N = 97[1]	Positive, N = 69[1]	p-value[2]
Shock	166			0.035
Negative		95 (98%)	62 (90%)	
Positive		2 (2.1%)	7 (10%)	
Arrhythmia	166			0.028
Negative		97 (100%)	65 (94%)	
Positive		0 (0%)	4 (5.8%)	
AKI	166			0.2
Negative		97 (100%)	67 (97%)	
Positive		0 (0%)	2 (2.9%)	
ARDS	166			<0.001
Negative		93 (96%)	54 (78%)	
Positive		4 (4.1%)	15 (22%)	
Acute cardiac injury	166			0.3
Negative		96 (99%)	66 (96%)	
Positive		1 (1.0%)	3 (4.3%)	
ICU	166			<0.001
Negative		75 (77%)	30 (43%)	
Positive		22 (23%)	39 (57%)	
Oxygen	166			0.13
Negative		66 (68%)	39 (57%)	
Positive		31 (32%)	30 (43%)	
Antibiotic	166			0.4
Negative		19 (20%)	10 (14%)	
Positive		78 (80%)	59 (86%)	
Death	166			<0.001
Negative		89 (92%)	47 (68%)	
Positive		8 (8.2%)	22 (32%)	

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

[1]*n* (%).

[2]Fisher's exact test; Pearson's χ^2 test.

may be more common in severe/fatal cases of COVID-19 between pediatrics. In contrast, hematological and biochemistry biomarkers in children are nonspecific and milder than that in adults. This information will pave the way for future studies on the pathogenesis of COVID-19 in pediatrics.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT AND INFORMED CONSENT

The project was approved by the ethics committee of Tehran University of Medical Sciences (No. 1399.378) and followed the Declaration of Helsinki. Written consent was obtained from the guardians of the patients.

AUTHOR CONTRIBUTIONS

Iraj Sedighi: methodology (equal); supervision (equal). **Alireza Fahimzad**: data curation (equal); methodology (equal). **Neda Pak**: data curation (equal). **Mitra Khalili**: data curation (equal). **Mohammad Reza Shokrollahi**: data curation (equal). **Hosein Heydari**: data curation (equal). **Zahra Movahedi**: data curation (equal). **Anahita Sanaei Dashti**: data curation (equal). **Fatemeh Cheraghali**: data curation (equal). **Ahmad Shamsizadeh**: data curation (equal). **Mohsen Alisamir**: data curation (equal). **Houman Hashemian**: data curation (equal). **Jafar Soltani**: data curation (equal). **Ali Hosseininasab**: data curation (equal). **Abdolkarim Hamedi**: data curation (equal). **Shirin Sayyahfar**: data curation (equal). **Manijeh Kahbazi**: data curation (equal). **Aliakbar Abedini**: data curation (equal). **Afsaneh Akhondzadeh**: data curation (equal). **Hamid Reza Sherkatolabbasieh**: data curation (equal). **Ali Akbar Razlansari**: data curation (equal). **Mina Alibeik**: data curation (equal). **Soheil Omid Malayeri**: data curation (equal). **Zohreh Shalchi**: data curation (equal). **Ali Shahabinezhad**: data curation (equal). **Parinaz Khalkhali Asl**: validation (equal). **Fatemeh Nafe Monfared**: validation (equal). **Shiva Maleki**: validation (equal). **Rezvan Kakavand**: validation (equal). **Mohammad Farahmand**: formal analysis (lead). **Babak Shahbaz**: data curation (equal). **Ahmad Tavakoli**: writing review & editing (equal). **Sara Akhavan Rezayat**: data curation (equal). **Mohammad Reza Karimi**: data curation (equal). **Yousef Erfani**: data curation (equal). **Ali Jafarpour**: data curation (equal). **Saber Soltani**: data curation (equal). **Azam Ghaziasadi**: data curation (equal). **Razieh Dowran**: data curation (equal). **Shohreh Azimi**: data curation (equal). **Shima Sadeghipour Marvi**: data curation (equal). **Mohammad Foad Abazari**: data curation (equal). **Iman Rezaee Azhar**: data curation (equal). **Seyed Mohammad Jazayeri**: funding acquisition (lead); supervision (lead); writing original draft (lead); writing review & editing (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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