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A Comparative Analysis of Clinical Characteristics and Laboratory Findings of COVID-19 between Intensive Care Unit and Non-Intensive Care Unit Pediatric Patients: A Multicenter, Retrospective, Observational Study from Iranian Network for Research in Viral Diseases (INRVD)

Alireza Fahimzad[1], Iraj Sedighi[2], Neda Pak[3], Mitra Khalili[4], Mohammad Farahmand[5], Mohammad Reza Shokrollahi[6], Hosein Heydari[6], Zahra Movahedi[6], Anahita Sanaei Dashti[7], Fatemeh Cheraghali[8], Ahmad Shamsizadeh[9], Mohammadreza Mirkarimi[9], Mohsen Alisamir[9], Houman Hashemian[10], Jafar Soltani[11], Ali Hosseininasab[12], Abdolkarim Hamedi[13], Mohammad Sadegh Rezai[14], Shirin Sayyahfar[15], Manijeh Kahbazi[16], Aliakbar Abedini[17], Afsaneh Akhondzadeh[18], Hamid Reza Sherkatolabbasieh[19], Ali Akbar Razlansari[19], Mina Alibeik[20], Soheil Omid Malayeri[21], Zohreh Shalchi[2], Ali Shahabinezhad[22], Parinaz Khalkhali Asl[23], Yousef Erfani[24], Mehdi Norouzi[5,25], Fatemeh Nafe Monfared[5], Shiva Maleki[26], Rezvan Kakavand[26], Babak Shahbaz[5,25], Vahdat Poortahmasebi[25,27], Sara Akhavan Rezayat[28], Mohammad Reza Karimi[29], Ali Jafarpour[5,25], Saber Soltani[5,25], Azam Ghaziasadi[5, 25], Razieh Dowran[5,25], Shohreh Azimi[25], Shima Sadeghipour Marvi[5,25], Foad Abazari[25], Milad Zandi[5, 25], Seyed Mohammad Jazayeri[5, 25]*, Ahmad Tavakoli[15, 30]**

1. Pediatric Infectious Diseases Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2. Department of Pediatric, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran.
3. Children Medical Centre of Excellence, Tehran University of Medical Sciences, Tehran, Iran.
4. Radiology Department, Mofid Children Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
5. Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.
6. Pediatric Medicine Research Center, Qom University of Medical Sciences, Qom, Iran.
7. Alborzi Clinical Microbiology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.
8. Department of Pediatric, Faculty of Medicine, Golestan University of Medical Sciences, Gorgan, Iran.
9. Aboozar Children Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
10. Pediatric Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran.
11. Department of Pediatrics, Faculty of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran.
12. Infectious and Tropical Research Center, Kerman University of Medical Sciences, Kerman, Iran.
13. Infection Control Hand & Hygiene Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
14. Pediatric Infectious Diseases Research Center, Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran.
15. Research Center of Pediatric Infectious Diseases, Institute of Immunology and Infectious Diseases, Iran University of Medical Sciences, Tehran, Iran.
16. Infectious Diseases Research Center, Arak University of Medical Sciences, Arak, Iran.
17. Department of Pediatrics, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
18. Infectious Disease Research Center (IDRC), Arak University of Medical Sciences, Arak, Iran.
19. Department of Pediatrics, School of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran.
20. Pediatric Infections Research Center, Mofid Children Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
21. Health Clinical Sciences Research Center, Zahedan Branch, Islamic Azad University, Zahedan, Iran.
22. Joint Reconstruction Research Center, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran.
23. Department of Microbiology, Faculty of Medicine, Golestsn University of Medical Sciences, Gorgan, Iran.
24. Department of Medical Laboratory Sciences, School of Allied Medical Sciences, Tehran University of Medical Sciences, Tehran, Iran.
25. Research Center for Clinical Virology, Tehran University of Medical Sciences, Tehran, Iran.
26. Department of Virology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran.
27. Department of Bacteriology and Virology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
28. Department of Health Care Management and Economics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.
29. Department of Laboratory Sciences, School of Allied Medical Sciences, Tehran University of Medical Sciences, Tehran, Iran.
30. Department of Medical Virology, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran.

***Primary corresponding author:** Seyed Mohammad Jazayeri; **Email:** jazayerism@tums.ac.ir
****Secondary corresponding author:** Ahmad Tavakoli; **Email:** tavakoli.a@iums.ac.ir

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Abstract

Introduction: To date, little is known about the clinical features of pediatric COVID-19 patients admitted to intensive care units (ICUs).

Objective: Herein, we aimed to describe the differences in demographic characteristics, laboratory findings, clinical presentations, and outcomes of Iranian pediatric COVID-19 patients admitted to ICU versus those in non-ICU settings.

Methods: This multicenter investigation involved 15 general and pediatrics hospitals and included cases with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection based on positive real-

time reverse transcription polymerase chain reaction (RT-PCR) admitted to these centers between March and May 2020, during the initial peak of the COVID-19 pandemic in Iran.

Results: Overall, 166 patients were included, 61 (36.7%) of whom required ICU admission. The highest number of admitted cases to ICU were in the age group of 1–5 years old. Malignancy and heart diseases were the most frequent underlying conditions. Dyspnea was the major symptom for ICU-admitted patients. There were significant decreases in PH, HCO3 and base excess, as well as increases in creatinine, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and potassium levels between ICU-admitted and non-ICU patients. Acute respiratory distress syndrome (ARDS), shock, and acute cardiac injury were the most common features among ICU-admitted patients. The mortality rate in the ICU-admitted patients was substantially higher than non-ICU cases (45.9% vs. 1.9%, respectively; p<0.001).

Conclusions: Underlying diseases were the major risk factors for the increased ICU admissions and mortality rates in pediatric COVID-19 patients. There were few paraclinical parameters that could differentiate between pediatrics in terms of prognosis and serious outcomes of COVID-19. Healthcare providers should consider children as a high-risk group, especially those with underlying medical conditions.

Key words: COVID-19; Intensive Care Units; Pediatric; Respiratory Tract Infections; SARS-CoV-2

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Introduction

The current Coronavirus Disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) generally causes mild to moderate respiratory tract infection in humans. Patients usually recover without any special treatment. However, older people and especially those with underlying medical conditions are at an increased risk of developing severe disease outcomes (1, 2).

Several studies on COVID-19 infection among pediatric patients have revealed differences in clinical signs and symptoms, prevalence rates, and mortality rates compared to adults (3, 4). Children are less affected by SARS-CoV-2 compared to older individuals in terms of the number of infected persons and the incidence of serious adverse outcomes (5, 6). Based on the results of previous epidemiological investigations, the prevalence of children affected by COVID-19 was 2.2% and 1.7% in China and the USA, respectively (4, 7). SARS-CoV-2 is transmitted among the pediatric population mainly through direct contact, contaminated droplets, and perhaps aerosols (8, 9).

Like adults, children can also experience a severe form of COVID-19 infection, leading to intensive care unit (ICU) admission. In previous studies, ICU admission rate among children with COVID-19 varied from 1.7% to 16% (7, 10-12). However, the rate was lower than that reported for adults (ranged from 5% to 32%) (13-17). To date, limited studies have been carried out to characterize the clinical, laboratory, and demographic features of pediatric COVID-19 patients in Iran (18-21). Among four studies reporting epidemiological and clinical data of pediatric patients with COVID-19 infection, the largest sample size was 35 cases in the survey conducted by Mahmoudi et al. (19).

Herein, we aimed to conduct a multicenter study to compare demographic characteristics, laboratory findings, clinical features, and outcomes between pediatric COVID-19 patients admitted to the ICU versus non-ICU cases.

Methods

Study design, setting, and participants

The current survey was a retrospective cross-sectional study carried out on pediatric patients diagnosed with COVID-19 who were admitted to 15 general and pediatrics hospitals in collaboration with the Iranian Network for Research in Viral Diseases (INRVD) between March 19th and May 31th 2020. Overall results have been submitted elsewhere (under revision) (22). A portion of this population, whose COVID-19 was confirmed via positive real-time reverse transcription polymerase chain reaction (RT-PCR) result for SARS-CoV-2 according to World Health Organization (WHO) interim guidance (15), was selected for further analysis (n= 166).

The major inclusion criteria were: patients who needed ventilation support either invasive mechanical ventilation or extra corporeal membrane oxygenation (ECMO) and/or organ dysfunction development who were transferred to the ICU.

All other patients were transferred to wards for

specialist care and were included as non-ICU cases. This study was approved by the Institutional Review Board of Tehran University of Medical Sciences (Ethics code number: 1399.378). Written informed consent was obtained from parents of pediatric patients.

Molecular detection of SARS-CoV-2

Throat and nasal samples were obtained using flocked swabs immediately after admission. Laboratory confirmation of the SARS-CoV-2 was made using the RT-PCR assay (15). RT-PCR was carried out using the diagnostic kits approved by the Iranian Pasteur Institute, targeting the E and RdP genes, in line with the protocol of all laboratories across the country. The samples were deemed positive if the cycle thresholds (Ct) value was ≤ 37 and negative if the Ct value was > 40. Samples with a Ct value between 37–40 were considered to have a borderline result and their tests were repeated.

Laboratory and imaging indicators

Laboratory examinations including routine blood tests, hematological and biochemical tests, and assessment of biomarkers for monitoring lung, liver, and renal functions along with blood saturation parameters were performed in hospitals' laboratories. In line with the guidelines issued by The Ministry of Health, all confirmed COVID-19 cases with any respiratory symptoms underwent a chest X-ray upon admission. A chest CT scan was usually performed in the case of either the presence of any abnormality in their X-ray or for patients who developed the severe form of the disease.

Data collection

The epidemiological and demographic data, comorbidities, clinical symptoms, and signs on admission of all laboratory-confirmed COVID-19 pediatric patients were retrospectively extracted from electronic medical records, using predefined standardized data collection forms provided by INRVD.

Statistical analysis

Statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria; http://cran.r-project.org/). Continuous variables were presented as mean ±standard deviation (SD), and categorical variables were expressed as counts (%). Fisher's exact test and chi-square test of independence were used to compare categorical variables, and student t test was used for continuous variables. For comparative analyses, a *P*-value less than 0.05 was considered statistically significant.

RESULTS

Demographic characteristics and associated comorbidities

A total of 325 cases were studied. Table 1 presents demographic characteristics and related comorbidities of pediatric patients with COVID-19 on hospital admission. Out of the 166 studied patients, 61 (36.7%) were admitted to ICU, and 105 (63.3%) were non-ICU cases. Based on the age group, the highest and the lowest numbers of admitted cases to ICU were in the age groups of 1–5 and 5-10 years, respectively (31.1% vs 14.7%, p=0.025). The mean age (±SD) of all patients was 79±64 months, and patients admitted to the ICU had a significantly lower age compared to non-ICU patients (63±63 vs. 88±64 months, respectively; p=0.004). Males were more affected in both ICU and non-ICU settings compared to the females (62.8% vs. 37.1% and 59.0% vs. 40.9%, respectively, p=0.704). Malignancies and heart diseases were the most common underlying conditions; each affecting 11.4% of ICU-admitted patients. 21.3% of ICU-admitted patients and 39.0% of non-ICU patients had history of antibiotic use (p=0.029). However, there were no significant differences in influenza vaccination history, corticosteroid therapy, and chemotherapy between the two groups.

Clinical characteristics

The most common respiratory symptoms were cough (n=89; 53.6%), dyspnea (n=59; 35.5%), sore throat (n=7; 4.2%), and rhinorrhea (n=3; 1.8%). Sixty (36.1%) children had neurological symptoms including fatigue (n=27; 16%), drowsiness/loss of consciousness (n=9; 5.4%), seizure (n=11; 6.6%), headache (n=10; 6.0%), and myalgia (n=3; 1.8%). Nausea/vomiting (n=55; 33.1%), anorexia (n=42; 25.3%), diarrhea (n=30; 18%), and abdominal pain (n=9; 5.4%) were the main gastrointestinal manifestations.

Fever and cough were the most frequent clinical symptoms among both groups. However, dyspnea was more prevalent among ICU patients compared to non-ICU cases (50.8% vs. 26.6%, respectively, p=0.003, Table 1). Signs such as grunting (11% vs. 1.9%) and nasal flaring (26% vs 2.9%) were more frequently seen in ICU cases versus non-ICU patients (p=0.013 and p<0.001, respectively, Table 2).

ARDS (n=19; 11.4%), nasal flaring (n=19; 11.4%), and wheezing (n=18; 10.8%) were the most common clinical signs among all patients. Among the list of complications, ARDS (28% vs 1.9%), shock (9.8% vs 2.9%) and acute cardiac injury (6.6% vs 0%) were the most important features

Table 1: Demographic characteristics and associated comorbidities of pediatric patients with COVID-19 in all subjects and intensive care unit (ICU) versus non-ICU cases

Admission detail	Overall (n= 166)	Non-ICU (n=105)	ICU (n=61)	P-value
	N (%)			
Age group (Year)				
0-1	28 (16.8)	11 (10.4)	17 (27.8)	0.025*
1-5	53 (31.9)	34 (32.3)	19 (31.1)	
5-10	26 (15.6)	17 (16.3)	9 (14.7)	
10-15	56 (33.7)	41 (39.0)	15 (24.5)	
Gender				
Male	102 (61.4)	66 (62.8)	36 (59.0)	0.704
Female	64 (38.5)	39 (37.1)	25 (40.9)	
Associated comorbidities				
Asthma	4 (2.4)	3 (2.8)	1(1.6)	<0.001*
Cystic fibrosis	1 (0.6)	1 (0.9)	0 (0.0)	
Chronic kidney disease	4 (2.4)	1 (0.9)	3 (4.9)	
Diabetes	1 (0.6)	1 (0.9)	0 (0.0)	
Failure to thrive	4 (2.4)	2 (1.9)	2 (3.2)	
Heart diseases	9 (5.4)	2 (1.9)	7 (11.4)	
Immune suppression	2 (1.2)	0 (0.0)	2 (3.2)	
Malignancy	20 (12.0)	13 (12.3)	7 (11.4)	
Other	24 (14.4)	7 (6.6)	17 (27.8)	
No comorbidity	97 (58.4)	75 (71.4)	22 (36.0)	
Patient history				
Antibiotic use	54 (32.5)	41 (39.0)	13 (21.3)	0.029*
Flu vaccination	22 (13.2)	13 (12.3)	9 (14.7)	0.805
Corticosteroid therapy	16 (9.6)	9 (8.5)	7 (11.4)	0.706
Chemotherapy	15 (9.0)	9 (8.5)	6 (9.8)	0.999

Table 2: Clinical characteristics and outcomes of pediatric patients with COVID-19 in total population, intensive care unit (ICU)-admitted, and non-ICU cases

Admission details	Overall (n= 166)	Non-ICU (n=105)	ICU (n=61)	P-value
	N (%)			
Symptoms				
Fever	122 (73.4)	81 (77.1)	41 (67.2)	0.201
Fatigue	27 (16.2)	19 (18.0)	8 (13.1)	0.504
Cough	89 (53.6)	59 (56.1)	30 (49.1)	0.506
Anorexia	42 (25.3)	26 (24.7)	16 (26.2)	0.999
Dyspnea	59 (35.5)	28 (26.6)	31 (50.8)	0.003*
Sore throat	7 (4.2)	6 (5.7)	1 (1.6)	0.402
Diarrhea	30 (18.0)	18 (17.1)	12 (19.6)	0.805
Nausea/Vomiting	55 (33.1)	37 (35.2)	18 (29.5)	0.603
Headache	10 (6.0)	10 (9.5)	0 (0.0)	0.014*
Abdominal pain	9 (5.4)	7 (6.6)	2 (3.2)	0.501
Myalgia	3 (1.8)	3 (2.8)	0 (0.0)	0.306
Rhinorrhea	3 (1.8)	2 (1.9)	1 (1.6)	0.999
Drowsiness/Loss of consciousness	9 (5.4)	2 (1.9)	7 (11.4)	0.013*
Seizures	11 (6.6)	4 (3.8)	7 (11.4)	0.100
Skin rash	6 (3.6)	4 (3.8)	2 (3.2)	0.999
Clinical signs				
Cyanosis	7 (4.2)	2 (1.9)	5 (8.1)	0.100
Grunting	9 (5.4)	2 (1.9)	7 (11.4)	0.013*
Nasal flaring	19 (11.4)	3 (2.8)	16 (26.2)	<0.001*
Wheezing	18 (10.8)	9 (8.8)	9 (14.7)	0.301
Respiratory fine crackles	30 (18.0)	15 (14.2)	15 (24.5)	0.150
Respiratory Coarse Crackles	21 (12.6)	12 (11.4)	9 (14.7)	0.703
Shock	9 (5.4)	3 (2.8)	6 (9.8)	0.076
Arrhythmia	4 (2.4)	1 (0.9)	3 (4.9)	0.140
Acute kidney injury	2 (1.2)	0 (0.0)	2 (3.2)	0.130
Acute respiratory distress syndrome	19 (11.4)	2 (1.9)	17 (27.8)	<0.001*
Acute cardiac injury	4 (2.4)	0 (0.0)	4 (6.5)	0.017*
Clinical outcome				
Died	30 (18.1)	2 (1.9)	28 (45.9)	<0.001*
Recovered	136 (81.9)	103 (98.1)	33 (54.1)	

with statistically significant differences between the ICU-admitted patients and non-ICU patients (p<0.001, p=0.076 and p=0.017, respectively, Table 2). Two subjects experienced acute kidney injury; both were among the ICU group cases (Table 2). The mortality rate was significantly higher in the ICU than in non-ICU patients (45.9% vs. 1.9%, respectively; p<0.001, Table 2).

Laboratory data

There were no substantial differences between the two groups in terms of white blood cell counts, serum inflammatory indices (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)), and other hematological parameters (Table 3). Exceptionally, 19 (32%) patients admitted to the ICU had normal platelet counts compared to 46 (51%) of non-ICU patients (p=0.081, Table 3). Regarding biochemistry parameters, significant increases in creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) levels were observed in ICU patients compared to non-ICU cases (65% and 78% vs. 27% and 57%, p=0.010 and 0.060, respectively, Table 3). An elevated level of potassium was seen in 25% and 6.9% of ICU and non-ICU admitted patients, respectively; while it was decreased in 7.0% and 2.3% of ICU-admitted and non-ICU patients, respectively (p=0.002, Table 3).

Blood saturation indices

In terms of blood saturation values, PH was decreased in 26 (68%) of ICU patients and 15 (34%) of non-ICU cases (p=0.002, Table 3). Moreover, HCo3 was decreased in the former group compared with the latter group (76% and

Table 3: Laboratory findings of pediatric patients with COVID-19 between intensive care unit (ICU)-admitted and non-ICU patients

Parameters	Overall (n= 166)	Non-ICU (n=105)	ICU (n=61)	P-value
		N (%)		
White blood cell				
Decreased	36 (22%)	27 (27%)	9 (15%)	0.102
Increased	23 (14%)	11 (11%)	12 (20%)	
Normal	102 (63%)	63 (62%)	39 (65%)	
Neutrophil				
Decreased	19 (12%)	15 (16%)	4 (7.1%)	0.150
Increased	24 (16%)	12 (12%)	12 (21%)	
Normal	109 (72%)	69 (72%)	40 (71%)	
Lymphocyte				
Decreased	52 (34%)	38 (39%)	14 (25%)	0.106
Increased	15 (9.7%)	11 (11%)	4 (7.1%)	
Normal	87 (56%)	49 (50%)	38 (68%)	
Hemoglobin				
Decreased	68 (44%)	37 (39%)	31 (53%)	0.205
Increased	3 (1.9%)	2 (2.1%)	1 (1.7%)	
Normal	83 (54%)	57 (59%)	26 (45%)	
Platelet				
Decreased	27 (18%)	15 (16%)	12 (20%)	0.081
Increased	58 (39%)	30 (33%)	28 (47%)	
Normal	65 (43%)	46 (51%)	19 (32%)	
C-reactive protein				
Increased	34 (72%)	22 (69%)	12 (80%)	0.504
Normal	13 (28%)	10 (31%)	3 (20%)	
Erythrocyte sedimentation rate				
Increased	52 (37%)	36 (40%)	16 (31%)	0.307
Normal	89 (63%)	54 (60%)	35 (69%)	
Blood urea nitrogen				
Increased	35 (23%)	18 (20%)	17 (28%)	0.208
Normal	117 (77%)	74 (80%)	43 (72%)	
Creatinine				
Increased	70 (46%)	48 (52%)	22 (37%)	0.061
Normal	82 (54%)	44 (48%)	38 (63%)	
Sodium				
Decreased	13 (9.0%)	6 (6.9%)	7 (12%)	0.106
Increased	2 (1.4%)	0 (0%)	2 (3.4%)	
Normal	130 (90%)	81 (93%)	49 (84%)	
Potassium				
Decreased	6 (4.2%)	2 (2.3%)	4 (7.0%)	0.002*
Increased	20 (14%)	6 (6.9%)	14 (25%)	
Normal	118 (82%)	79 (91%)	39 (68%)	

Table 3 (in continue): Laboratory findings of pediatric patients with COVID-19 between intensive care unit (ICU)-admitted and non-ICU patients

Parameters	Overall (n= 166)	Non-ICU (n=105)	ICU (n=61)	P-value
		N (%)		
Prothrombin time				
Decreased	0 (0%)	0 (0%)	0 (0%)	0.070
Increased	17 (35%)	4 (19%)	13 (46%)	
Normal	32 (65%)	17 (81%)	15 (54%)	
Partial thromboplastin time				
Decreased	21 (43%)	8 (38%)	13 (46%)	0.506
Increased	12 (24%)	7 (33%)	5 (18%)	
Normal	16 (33%)	6 (29%)	10 (36%)	
International normalized ratio				
Decreased	0 (0%)	0 (0%)	0 (0%)	0.082
Increased	11 (24%)	2 (10%)	9 (35%)	
Normal	35 (76%)	18 (90%)	17 (65%)	
Lactate dehydrogenase				
Decreased	2 (2.3%)	1 (1.8%)	1 (3.1%)	0.060
Increased	57 (65%)	32 (57%)	25 (78%)	
Normal	29 (33%)	23 (41%)	6 (19%)	
Creatine phosphokinase				
Decreased	0 (0%)	0 (0%)	0 (0%)	0.010*
Increased	22 (42%)	9 (27%)	13 (65%)	
Normal	31 (58%)	24 (73%)	7 (35%)	
Aspartate aminotransferase				
Decreased	0 (0%)	0 (0%)	0 (0%)	0.801
Increased	34 (40%)	19 (38%)	15 (42%)	
Normal	52 (60%)	31 (62%)	21 (58%)	
Alanine aminotransferase				
Decreased	4 (4.7%)	2 (4.1%)	2 (5.6%)	0.406
Increased	21 (25%)	15 (31%)	6 (17%)	
Normal	60 (71%)	32 (65%)	28 (78%)	
Alkaline phosphatase				
Decreased	4 (44%)	3 (43%)	1 (50%)	0.999
Increased	2 (22%)	2 (29%)	0 (0%)	
Normal	3 (33%)	2 (29%)	1 (50%)	
D-dimer				
Increased	6 (38%)	3 (38%)	3 (38%)	0.999
Normal	10 (62%)	5 (62%)	5 (62%)	
Total Bilirubin				
Increased	4 (27%)	3 (38%)	1 (14%)	0.604
Normal	11 (73%)	5 (62%)	6 (86%)	
Calcium				
Decreased	26 (47%)	14 (54%)	12 (41%)	0.306
Increased	1 (1.8%)	1 (3.8%)	0 (0%)	
Normal	28 (51%)	11 (42%)	17 (59%)	
Phosphorus				
Decreased	2 (67%)	2 (67%)	0 (NA%)	0.900
Increased	1 (33%)	1 (33%)	0 (NA%)	
Normal	0 (0%)	0 (0%)	0 (NA%)	
pH				
Decreased	41 (50%)	15 (34%)	26 (68%)	0.002*
Increased	5 (6.1%)	5 (11%)	0 (0%)	
Normal	36 (44%)	24 (55%)	12 (32%)	
PCo2				
Decreased	35 (43%)	17 (39%)	18 (49%)	0.603
Increased	30 (37%)	18 (41%)	12 (32%)	
Normal	16 (20%)	9 (20%)	7 (19%)	
HCo3				
Decreased	44 (54%)	16 (36%)	28 (76%)	<0.001*
Increased	7 (8.6%)	2 (4.5%)	5 (14%)	
Normal	30 (37%)	26 (59%)	4 (11%)	
Po2				
Decreased	48 (62%)	26 (60%)	22 (63%)	0.501
Increased	6 (7.7%)	2 (4.7%)	4 (11%)	
Normal	24 (31%)	15 (35%)	9 (26%)	
Base excess				
Decreased	46 (73%)	23 (64%)	23 (85%)	0.093
Increased	8 (13%)	5 (14%)	3 (11%)	
Normal	9 (14%)	8 (22%)	1 (3.7%)	

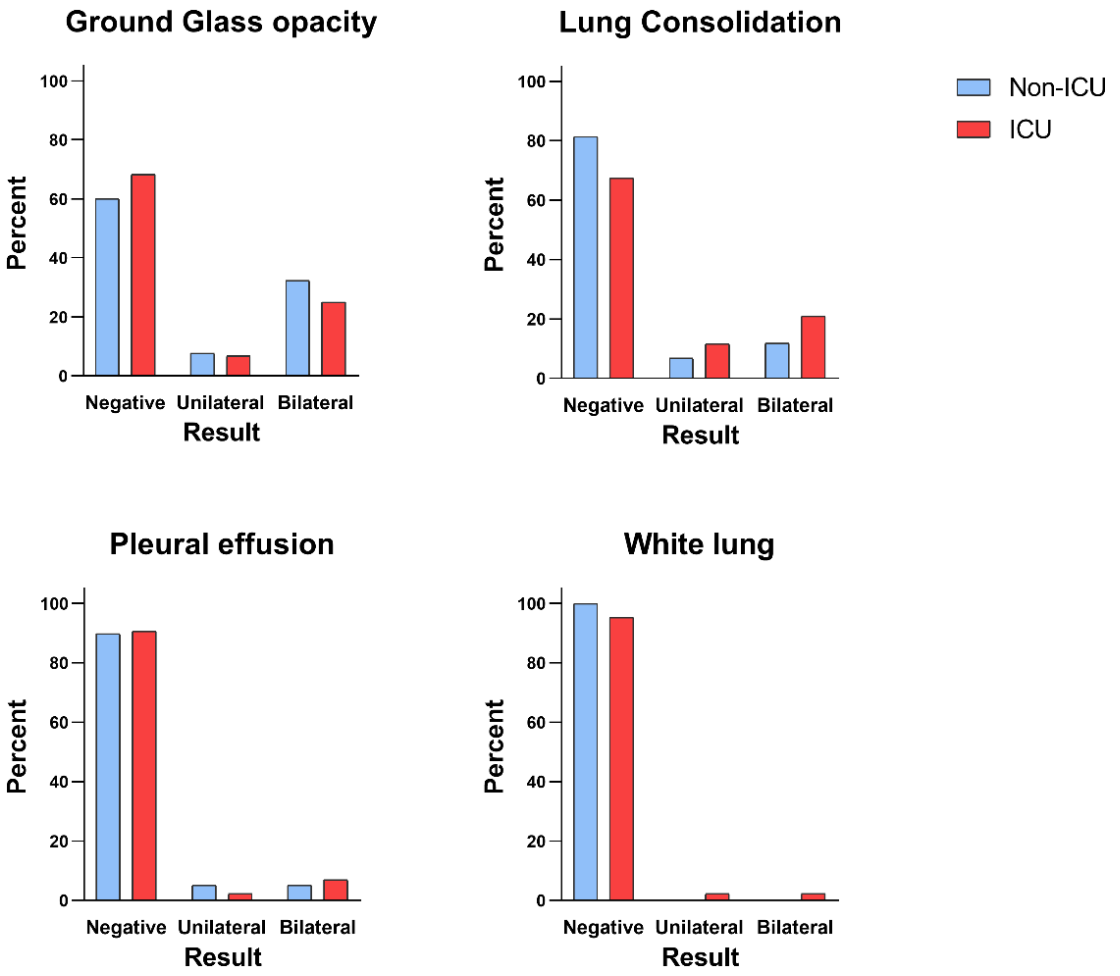

Figure 1: Comparisons of major radiological findings between intensive care unit (ICU)-admitted and non-ICU admitted patients

36%, respectively, Table 3). Lastly, Base Excess decrease was more commonly observed in ICU compared to non-ICU cases (85% vs. 64%, p=0.093, Table 3).

Radiological features

Overall, out of the 111 patients who underwent chest CT scan, 62 cases (55.8%) showed abnormal radiographic appearance. Ground glass opacity (n=40; 36.0%), lung consolidation (n=26; 23.4%), and pleural effusion (n=10; 9.0%) were the main radiological findings (Figure-1). The results of CT scans performed on admission showed bilateral and unilateral ground glass opacity in 32% and 7.7% of non-ICU-admitted patients, respectively, and 25% and 6.8% of ICU admitted patients, respectively (p=0.708). Bilateral and unilateral lung consolidation were also observed in 12% and 6.7% of non-ICU-admitted patients, respectively, and 21% and 12% of ICU-admitted patients, respectively (p=0.305). Pleural effusion (bilateral or unilateral) was found in 5.1% of non-ICU admitted patients, and 7% and 2.3% of ICU admitted patients, respectively (p=0.804). In ICU admitted cases, white lung (unilateral or bilateral) were seen in 2.3% of cases and these findings were not observed in non-ICU cases (p=0.201) (Figure 1).

Discussion

Iran is considered one of the most affected countries by COVID-19 globally, with high incidence and mortality rates. To date, several studies have reported clinical parameters associated with COVID-19 infection in children; however, data on pediatric patients in Iran are still scarce. On the other hand, there are minimal

published data on pediatric patients requiring ICU worldwide. This descriptive cross-sectional country-wide investigation compared the epidemiologic and clinical features of ICU-admitted and non-ICU-admitted pediatric patients with confirmed COVID-19 in Iran.

The present survey showed that malignancies and cardiac disorders were the most common underlying diseases among ICU-admitted pediatric COVID-19 patients. Similar results were found in the surveys conducted by Shekerdemian et al. (23) and Alfraij et al. (24), where malignancy was the most frequent underlying disease among children with COVID-19 admitted to ICU. Prata-Barbosa et al. and Alfraij et al. also reported that heart disease was amongst the most frequent comorbidities among COVID-19 pediatric patients admitted to ICU (24, 25). According to these results, cancers and heart diseases in children were associated with increased risk of severe complications of COVID-19.

Investigators observed that COVID-19 patients with cancer had higher ICU admission rates, severe complications, invasive mechanical ventilation, and mortality rate compared with COVID-19 patients without cancer. The higher susceptibility of cancer patients to severe COVID-19 infection might be explained in part by their systemic immunocompromised status induced by the underlying malignancy and anticancer therapy. Furthermore, most childhood malignancies have aggressive behavior and require prolonged periods of intensive therapy, which are potentially associated with long-term side-effects such as severe impairment of innate and adaptive immunity (26-28). On the other hand, some other studies suggested that children with cancer are not more susceptible to severe COVID-19 infection than other normal children (12, 28-31). This controversy stems, at least in part, from the fact that different kinds of cancers have distinct clinical features such as different growth rates, different responses to treatment, and different prognoses. Unfortunately, we were not able to find data about the type of tumors in our patients due to the retrospective design of our study and so, further conclusions cannot be drawn at this stage.

A portion of ICU-admitted patients were children less than five years old. Similar findings were reported in two studies conducted by Dong et al. (3, 10), in which infants and younger children were more likely to develop severe clinical manifestations of COVID-19 compared with older children. A potential explanation for this phenomenon might be the immaturity of the immune system. The immune system of neonates and young children is underdeveloped and subdued, which might render them more susceptible to most infections, including SARS-CoV-2.

Among different clinical symptoms, dyspnea was significantly more frequent in pediatric patients admitted to ICU than the non-ICU patients. This finding was consistent with the result of a survey conducted in New York City (32). As reported, dyspnea was the only clinical symptom, which was significantly more frequent in pediatric patients admitted to the ICU than those admitted to the medical wards (92.3% vs. 30.3%, respectively). Similar results were obtained in the study conducted by Bhumbra et al. (33), where 71% and 58% of pediatric COVID-19 patients admitted to the ICU and general ward presented dyspnea, respectively. Thus, it seems that in most cases, the severe form of COVID-19 in children might be associated with lung involvement. This interpretation is supported by another finding: ARDS rate was substantially higher in patients admitted to the ICU (27.8%) than those who were not admitted to the ICU (1.9%). Moreover, Chao et al. reported that the rate of ARDS was higher in patients admitted to the ICU (76.9%) compared with patients admitted to the medical unit (0%) (32). The present survey showed that acute cardiac injury and acute kidney injury cases were only seen among ICU-admitted patients. In parallel, Stewart et al. reported that most acute kidney injury cases (93%) were found in those admitted to the pediatric ICU (34). Chao et al. also showed a significantly higher rate of acute kidney injury among pediatric patients admitted to the ICU than non-ICU patients (38.5% vs. 0%, respectively) (32). It has been reported that heart failure and acute cardiac injury are significantly associated with in-hospital death (35). Alfraij et al. also reported that circulatory failure was significantly associated with pediatric death in their cohort study (24). Taken together, these findings indicate that acute cardiac injury and acute kidney injury are associated with severe COVID-19 among children.

The present investigation showed that with the exception of few blood test parameters, abnormalities, and also some atypical blood saturation indices, the differences in the rest of laboratory test results were not significant between the ICU and non-ICU individuals. These findings shed important light on the nature of the disease in this population. Unlike in the adults, it seems that no significant laboratory parameters could be characterized for the prognosis of COVID-

19 clinical outcomes in pediatrics.

Limitations

This study was limited to a small number of patients. In fact, the preliminary number of study population was shrunk from 325 to 166 due to the unavailability of molecular test results at the beginning of the epidemic in the country. Therefore, we only analyzed the data of patients who were positive for SARS-Cov-2 on RT-PCR. Second, all the laboratory assays were performed as routine tests. Hence, we were not able to assess other medical conditions based on the specific laboratory tests.

Conclusions

In conclusion, this multicenter study demonstrates that underlying diseases were the major contributing factors to increased ICU admissions and mortality rates in pediatric COVID-19 patients. There are few paraclinical parameters for differentiating pediatrics in terms of prognosis and serious outcomes of COVID-19. Our findings emphasize that healthcare providers should consider children as a high-risk group, especially those with younger age and underlying medical conditions, and define strategies to control and prevent COVID-19 transmission in this population.

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Authors' contribution

Study inception and design: S.M.J, A.F, I.S; Data collation: A.F, N.P, M.K, M.R.S, H. H, Z.M, A.S.D, F.C, A.S, M.M, M.A, H.H, J.S, A.H, A.H, M.S.R, S.S, M.K, A.A, A.A, H.R.S, A.A.R, M.A, S.O.M, Z.S, A.S, V.P, D,Y, M.N, Y.E; Statistical analysis: M.F; Drafting of the manuscript: A.T; Sorting data: P.K.A, F.N.M, S.M, R.K; Interpretation of data: B.S, A.T, S.A.R, M.R.K, A.J, S.S, A.G, R.D, S.A, S.S.M, F.A; Supervision: S.M.J, A.F, A.T; All authors have read and approved the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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