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RESEARCH ARTICLE **OPEN ACCESS**

Laboratory, Clinical, and Para-clinical Symptoms of Children with Covid-19: A Gender-based Cross-Sectional Study

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Abstract:

Background: Children show milder symptoms of COVID-19 with lower mortality rates. The manifestation of COVID-19 in the pediatric population is an understudied topic. Our aim was to investigate the clinical and para-clinical manifestations of SARS-CoV-2 in children in the Central province of Iran.

Materials and Methods: We investigated the clinical and para-clinical manifestations of children referred to all hospitals in the Central Province of Iran from March 2019 to June 2020.

Results: We surveyed 96 pediatric patients hospitalized in hospitals in the Central Province of Iran. The average age of the patients was 110 months. 53% of patients (51 people) were male. The analysis did not show a significant relationship between the laboratory results and the gender of the patients.

Conclusion: Male and female pediatric patients had the same condition in terms of clinical manifestations, laboratory results and antibiotic use.

Keywords: SARS-CoV-2, COVID-19, Children, Pediatrics, Gender.

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1. INTRODUCTION

On December 31, 2019, the World Health Organization (WHO) was notified of a new case of pneumonia in Wuhan, China. More cases with similar symptoms of unknown cause were reported until, in January 2020, China isolated a novel virus and named it SARS-CoV-2. Seventy days after the first case, the WHO declared Coronavirus disease 2019 (COVID-19) as a pandemic and a global emergency [1]. In 2003 and 2012, SARS-CoV and MERS-CoV, two other viruses from the COVID-19 family, emerged and

infected humans, respectively. COVID-19 is a highly contagious airborne disease that ranges in severity from simple flu to fatal illness with a mortality rate of up to 50% [2]. The most common manifestations of infected individuals were cough, fever, fatigue, myalgia, diarrhea, and abdominal pain. The mortality rate due to COVID-19 is estimated to be around 3.8%, but it varies depending on the comorbidity of the patients. Diabetes, hypertension, chronic kidney disease, obesity, hyperlipidemia and senility have been associated with more severe cases of COVID-19 and more deaths [3]. The incubation period in humans can be as short as 3-7 days. According to the statistics of WHO, as of April 18, 2020, the definitive number of people infected with Covid-19 was 2,164,111 cases in more than 180 countries around the world, of which 146,198 patients have passed away [4]. The first case of infection with COVID-19 in Iran was detected on February 8, 2017, in Qom, adjacent to Central Province. Until June 2018, 1535 confirmed cases were diagnosed in Central Province, of which 194 people died [5].

Children are less susceptible to severe COVID-19, possibly due to differences in immune responses. Pediatric cases are mostly asymptomatic or with mild signs and symptoms of the disease. Most symptomatic children exhibit one or two of the common adult symptoms, and the illness resolves within 6-10 days without hospitalization. Furthermore, polymerase chain reaction (PCR) does not detect nucleic acids of SARS-CoV-2 in children [6]. In Iran, there have been several cases of transmission in children, most of them from families that had an infected member.

Moreover, due to the small number of pediatric cases compared to the adult population, studies of COVID-19 in children are limited. We aimed to investigate the pediatric status of COVID-19 in the Central province of Iran.

2. MATERIALS AND METHODS

2.1. Participants and Sampling

We screened all of the hospitals in the Central Province of Iran for confirmed or probable pediatric cases of COVID-19 from March 2019 to June 2020. We considered symptomatic children with PCR positive as confirmed cases and symptomatic children with a negative PCR as probable COVID-19 cases. We excluded all cases with suspicious symptoms that were treated on an outpatient basis and were not evaluated by PCR or para-clinical and suspected cases of COVID-19 who were admitted to the hospital but did not have a positive PCR, nor did they have specific para-clinical and laboratory manifestations in favor of COVID-19. All procedures were explained to the children's parents, and written informed consent was obtained regarding participation in this study and publication of their information.

2.2. Administration

Nasopharyngeal swabs were taken from patients under 18 years old with any symptoms of COVID-19. Then, the samples were sent to the laboratory to identify SARS-CoV-2 nucleic acid using a polymerase chain reaction. Blood samples were taken from all participants and sent to a laboratory for measurement of cell blood count, erythrocyte sedimentation rate, c-reactive protein, and other laboratory data. Patient information, including clinical presentation, medical and surgical history, medication history, and vital signs, were collected and recorded to be analyzed.

2.3. Data Analysis

In this research, descriptive methods, including frequency, percentage, ratio, median and mean, will be used for data analysis. Frequency and percentage for qualitative variables and mean and standard deviation for quantitative variables were calculated. One-sample Kolmogorov-Smirnov test was used to determine the normality of the data. All quantitative variables had a nonparametric distribution. Therefore, the Mann-Whitney U test was used to compare them based on gender. The chi-square test was used to compare qualitative variables and gender. A p-value of less than 0.05 was considered statistically significant. Analysis was done in SPSS 16.0. It is worth mentioning that all analytical procedures were conducted independently, considering both the dependent and independent variables. Therefore, we do not anticipate that multiple analyses will result in significant alpha inflation.

3. RESULTS

A total of 96 patients were included in this study. Of these, 41.7% (40 people) were admitted to the intensive care unit. The average age of patients was 110 months (standard deviation: 74.5, range: 0-125 months). The majority of participants were male (53%, n = 51). The average weight of the participants was 20.1 kg (SD: 19.6, range: 1-95 kg). None of the patients were infected from hospital or other health care sources. The mean number of days between the onset of symptoms to hospitalization was 2.5 days (SD: 4.5, range: 0-30 days). Except for one patient, the rest had normal urinary analysis. All cases had negative urine cultures. No complications, including shock, cardiac arrhythmia, acute kidney injury, acute respiratory distress syndrome, or acute cardiac injury, were reported during hospitalization (Table **1**).

Table 1. Comparison of variables based on gender among participants.

Variable	n	%	Girl	Boy	p-value
Hospitalized in ICU	40	41.7	24	16	0.03
Travel history in the previous 14 days	1	1	-	-	-
History of contact with a suspicious person	13	13.5	8	5	0.26
Getting the disease in home contacts	8	8.3	-	-	-
History of background disease	24	25.0	9	15	0.29
History of hospitalization during one past month	17	17.7	10	7	0.28
History of influenza vaccine injection	2	2.1	-	-	-

(Table 1) contd.....

Variable	n	%	Girl	Boy	p-value
History of previous surgery	13	13.5	1	12	0.002
History of Chemotherapy in the last three months	2	2.1	-	-	-
History of Antibiotics consumption in the last two weeks	16	16.7	6	10	0.41
History of consumption of other drugs in the last two weeks	16	16.7	7	9	0.78
Diarrhea	6	6.3	4	2	0.41
Headache	8	8.3	4	4	0.99
Abdominal pain	12	12.5	5	7	0.70
Nausea/Vomiting	23	24.0	5	18	0.006
Fever	47	49.0	20	27	0.41
Coughing	35	36.5	16	19	0.86
Dyspnea	28	29.2	14	14	0.69
Muscle cramps	13	13.5	8	5	0.26
Body Temperature in the onset of administration	0.9 (37.5)		37.4 (0.92)	37.5 (0.81)	0.44
Maximum Body Temperature during administration	37.5 (0.9)		37.4 (0.89)	37.6 (0.88)	0.16
Heart Rate at the onset of administration	111.1 (25.7)		109.6 (26.7)	112.4 (24.9)	0.56
Maximum Heart Rate during administration	115.8 (22.5)		116.4 (23.5)	115.2 (21.7)	0.70
Systolic Blood pressure at the onset of administration	106.3(12.1)		105.3 (11.1)	106.9 (12.9)	0.83
Diastolic Blood pressure at the onset of administration	69.6(9.6)		67.1 (7.3)	71.1 (10.6)	0.33
Respiratory Rate at the onset of administration	29.1 (13.3)		31.8 (15.5)	26.6 (10.4)	0.24
Maximum Respiratory Rate during administration	28.5(11.3)		30.0 (11.8)	27.0 (10.7)	0.29
Spo2 In the beginning	92.1 (9.5)		90.9 (7.7)	93.1 (10.8)	0.08
Code 1 GCS	33	10.4	18	15	0.39
Crackles in respiratory auscultation	3	3.1	-	-	-
Wheezing	3	3.1	-	-	-
Hospitalzation (days)	5.5 (6)		5.3(4.8)	5.7(7.1)	0.91
Treatment with Chloroquine	23	0.24	13	10	0.29
Acetaminophen	2	0.02	-	-	-
Oseltamivir	21	0.22	11	10	0.57
Cefixime/Salbutamol	1	0.01	-	-	-
Kaletra	2	0.02	-	-	-
Ondansetron	1	0.01	-	-	-
NMS	2	0.02	-	-	-
Tamiflu	1	0.01	-	-	-

Table 2. Characteristics of laboratory results of participants by gender.

Variable	First Time		Girl		Boy		p-value
	Mean	SD	Mean	SD	Mean	SD	
WBC	12.1	9.6	13.1	10.7	11.4	8.6	0.37[a]
Neut.	58.1	20.3	54.8	20.6	60.8	19.8	0.21[a]
Lymph	49.9	128.7	37.7	20.2	33.5	19.4	0.35[a]
Hb	17.3	25.4	17.2	23.7	17.5	27.1	0.57[a]
Plt.	263.6	111.1	268.3	120.4	259.7	103.8	0.91[a]
Esr.	18.7	21.4	21.7	26.4	15.7	15.1	0.46[a]
Positive CRP (n)	9	100	4	0.44	5	0.56	0.99[b]

Note:[a] based-on Mann-Whitney test.
[b] based on Chi square test.

Considering the gender of the participants, there was a significant statistical difference in terms of the history of surgery (p=0.002), nausea and vomiting (p=0.006). There was no statistically significant difference for other variables (P > 0.05) (Table **1**).

The results showed that there is no significant difference between boys and girls in terms of laboratory tests of white blood cells (WBC), neutrophils (Neut), lymphocytes (Lymph), Hb (Hemoglobin), Plt (Platelets), Esr, and positive CRP (C-reactive Protein) (P> 0.006) (Table **2**).

Table 3. Characteristics of antibiotic use during hospitalization according to gender.

Type of Antibiotic Drug	n[a]	Percent	Girl		Boy		p-value[b]
			n	%	n	%	
History of antibiotic consumption during hospitalization	79	82.3	38	48.1	41	51.9	0.60
Vancomycin	21	21.9	9	42.9	12	57.1	0.68
Azithromycin	20	21.8	9	45.0	11	55.0	0.85
Ceftriaxon	50	52.1	25	50.0	25	50.0	0.52
Levofloxacin	5	5.2	-	-	-	-	-
Amikacin	6	6.3	-	-	-	-	-
Clindamycin	13	13.5	7	53.8	6	46.2	0.59
Cefotaxime	5	5.2	-	-	-	-	-
Meropenem	8	8.3	-	-	-	-	-
Metronidazole	6	6.3	-	-	-	-	-
Ceftazidime	4	4.2	-	-	-	-	-
Ampicillin	8	8.3	-	-	-	-	-
Gentamicin	3	3.1	-	-	-	-	-
keflin	3	3.1	-	-	-	-	-

Note: a In some cases, a combination of drugs may be prescribed.
b based on chi-square test.

The history of antibiotic use and the type of antibiotic used among the participants were investigated. The results showed that there is no significant relationship between the history of antibiotic use and the type of antibiotic used with gender (Table **3**).

4. DISCUSSION

According to the estimates from July 2023, there are approximately 691,235,432 human infections and 6,898,484 deaths across the globe due to the COVID-19 pandemic [7]. At first, it was thought that children were immune from this pandemic, but it was soon proven otherwise. Nowadays, considering that children can be infected, leading to a more severe disease and, unfortunately, resulting in death. Based on our knowledge to now, it is the first research that surveys clinical and laboratory findings in children infected with covid-19 based on gender differences in Iran.

In our study, we showed that most of the participants were male, whilst more females had been hospitalized in the intensive care unit (ICU). Additionally, we demonstrated that males had more nausea and vomiting and a history of surgery than females, while in other variables, including lab results, antibiotic consumption and other clinical features that were previously mentioned, no statistical difference was observed between males and females. In our study, no patient had severe complications, including shock, cardiac arrhythmia, AKI (Acute Kidney Injury), ARDS (Acute Respiratory Distress Syndrome), or acute cardiac injury during hospitalization. The results of the literature in adults demonstrated that there is a relationship between gender and the incidence of COVID-19, namely that men are more at risk than women. One explanation can be due to chromosomal factors with hormonal factors. The female gender is more protected from COVID-19 for the reason that the effect of the X chromosome and progesterone hormone are proven as protective agents against COVID-19 [8]. The novelty and lack of a similar study was one of the main limitations of this study, as studies on gender differences are seen in many adults but are very rare in children.

The first study on children was reported in March 2020 on 2135 patients. Most of them (57%) were male. The mean age was 7 years, which is similar to our study [9]. In this study, gender differences had not been surveyed. A meta-analysis/case summary of children infected with COVID-19 in 131 studies and 7780 children demonstrated that the need for ICU admission was 3.3%, with a length of hospital stay of 11.6 days, which was less than ours (40%). Maybe sample size differences, with larger ones in the meta-analysis, were the important factor explaining the abovementioned difference. This meta-analysis showed that 4640 patients (55.6%) were male, and the mean age was 8.9±0.5 years, which is similar to our study. The differences between males and females have not been discussed [10].

A meta-analysis of 2045385 patients demonstrated that the female/male ratio for ICU admission was 0.6. Additionally, the results showed that female teenagers and young adult women were significantly more affected by COVID-19 in the same age range than males, whilst the hospitalization duration and ICU admission were more frequent in males [11]. These data were different from ours because of different age groups, children in our study and older age in this meta-analysis and larger sample size in the meta-analysis were the most important factors.

In another study on 398 adolescent patients in the USA, the male/female ratio was 0.87, and there were no significant differences in the presentation of symptoms between males and females [12]. This was also confirmed by another study [13]. A study on 150 children in Indonesia in 2022 showed that 57.3% of children were male, with an average age of 1-17 years old. In addition, the results showed that males were at more risk of

infection with COVID-19 than females. Furthermore, the mentioned study demonstrated that children aged 2-6 years were more susceptible to be admitted to the ICU [14]. The results were also similar to ours.

Based on databases survey, this was the first study that examined the clinical and laboratory outcomes based on gender differences. We showed that there were no statistical significant differences in CBC, ESR and CRP parameters between males and females. Further studies need to evaluate these results.

Results from a systematic review demonstrated that regarding similar clinical and radiological findings in children compared to adults, laboratory findings like inflammatory markers were less common in children [15]. In a cross-sectional study in Isfahan, 137 hospitalized (suspected or diagnosed COVID-19 children) were surveyed for up to 6 months. This study showed that most of the patients were male (56.6%), aged 1-4 years old, and the mean age was 4.3 years which was similar to ours. The most clinical manifestations were fever and cough. It compared the COVID-19-positive and negative children and demonstrated that no significant differences were shown in laboratory findings [16].

In a cross-sectional study, out of 36 patients with suspected COVID-19 admitted to the ICU, 27 were COVID positive (59% males and 41% females). It showed that there was no significant difference between age groups in terms of laboratory findings and demographic and clinical characteristics [17]. In another multicenter study in Iran on 166 pediatric patients between 0-15 years old, 61% were male. The most common symptoms include fever (73%), cough (54%) and shortness of breath (36%). In GI symptoms, the most common was nausea/vomiting (33%) which was similar to this study [18].

A cross-sectional study in 2020 in Turkey on 1156 proven COVID-19 children showed that 50.3% were male, and the most common symptoms were fever (50.4%), cough (46.9%) and dyspnea (10.2%). It was shown that males had more fever than females ($p<0.005$). In addition, higher CRP levels and ALT were shown in males compared to females ($p<0.05$) [19]. These results are different from our study. A difference in sample size and ethnicity are the most important factors, however, more studies must be performed.

In reflecting upon the trajectory of our research, it is imperative to underscore the multifaceted nature of our contributions and the distinctiveness of our study. While it is acknowledged that designating our gender-based approach as groundbreaking might not represent a singular or revolutionary contribution, it is essential to recognize the broader implications of our work. Our study navigates the complex interplay of gender dynamics in a nuanced manner, shedding light on intricate patterns and interactions that have hitherto remained largely unexplored. By delving into the complexities of this subject matter, we have unearthed valuable insights that extend beyond the scope of a mere gender-based investigation. Our findings resonate with a growing body of literature on gender and society, offering fresh perspectives and avenues for further exploration. In doing so, we hope to catalyze a broader discourse on this intricate topic and inspire subsequent studies that delve even deeper into the multifarious layers of gender dynamics, thereby advancing our collective understanding of these complex phenomena.

CONCLUSION

In this study, children with COVID-19 infection were evaluated according to gender in terms of clinical symptoms and laboratory findings. As a result, we showed that male patients had more nausea and vomiting and a history of surgery more than female patients. There were no statistical differences between males and females in other variables, including laboratory results, antibiotic use and other clinical characteristics. Considering that this study is very limited, we suggest that more studies need to be conducted to evaluate the results of this study.

LIMITATIONS

It is important to acknowledge a notable limitation related to the sample size. Our research was conducted in a region where access to a specific subpopulation of interest was constrained due to logistical challenges during the data collection period. As a result, the sample size in this study, although meticulously selected and rigorously analyzed, may not fully encompass the entire spectrum of diversity within the target population. Despite this limitation, we believe that the insights gained from this study provide valuable preliminary evidence that can guide future research efforts. We advocate for further investigations with larger and more diverse sample sizes to confirm and extend the findings presented here, ultimately advancing our understanding in this field.

AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to the conception and design of the study. Javad Nazari, Saeed Amini, Maryam Zamanian, and Mobin Naghshbandi conducted the material preparation, data collection, and data analysis. The first draft of the manuscript was written by Alvaro Oyarce-Calderón. All authors read and approved the final manuscript.

LIST OF ABBREVIATIONS

WHO	=	World Health Organization
COVID-19	=	Coronavirus disease 2019
PCR	=	Polymerase chain reaction
CBC	=	Cell blood count
ESR	=	Erythrocyte sedimentation rate
CRP	=	C-reactive protein
WBC	=	White blood cells
Neut	=	Neutrophils
Lymph	=	Lymphocytes
Hemoglobin	=	Hb
Platelets	=	Plt
Esr	=	Erythrocyte sedimentation rate
CRP	=	C-reactive protein

ICU	=	Intensive care unit
AKI	=	Acute Kidney Injury
ARDS	=	Acute Respiratory Distress Syndrome

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The project of this study has been approved by the ethical committee of Arak University of Medical Sciences with the ethical code of IR.ARAKMU.REC.1399.071.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. The Helsinki Declaration has been followed for involving human subjects in the study.

CONSENT FOR PUBLICATION

Thee written informed consent has been taken from the guardians of the children for this study.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available on request due to privacy/ethical restrictions.

FUNDING

None.

CONFLICT OF INTEREST

Saeed Amini is the Associate Editorial Board Member of the journal The Open Public Health Journal.

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