Research Paper

COVID-19 Infection in Pediatric Patients: An Epidemiological Study in Iran

Maryam Naseri[1], Gholamreza Khademi[2], Majid Khadem Rezaeian[3], Shahabaldin Sorouri[4], Majid Sezavar[5*]

1. Department of Pediatrics, Mashhad University of Medical Sciences, Mashhad, Iran.
2. Neonatal Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
3. Clinical Research Development Unit of Akbar Hospital, Mashhad University of Medical Sciences, Mashhad, Iran.
4. Internal Department, Mashhad University of Medical Sciences, Mashhad, Iran.
5. Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

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ABSTRACT

Background: COVID-19 is a highly infectious and contagious disease. Since the outbreak of COVID-19, most studies on children have focused on the incidence and prognosis of the disease, and few studies have investigated the epidemiological characteristics of the disease.

Objectives: This study aimed to investigate some epidemiological aspects of the disease in children with COVID-19.

Methods: We examined children with COVID-19 (under 18 years) hospitalized in the North East of Iran from the beginning of the outbreak until the end of September 2020. Study information was collected from patients' medical records and interviews with their parents. We recorded demographic data; history of diseases and taking medicine in children; educational, occupational, and smoking status of parents; patients' residence conditions; and any report of COVID-19 in patients' families and relatives.

Results: Of 107 children studied, 57% were male, and 52.3% had no underlying disease. The mean age of patients was 67 months. The Mean±SD weight of the children was 20.36±13.75 kg, and their Mean±SD length of hospital stay was 9±8 days. Multisystem inflammatory syndrome in children (MIS-C) was observed in 34.6% of patients, and its relationship with death was highly significant (P=0.001). The length of hospital stay was influenced by the history of medication consumption (P=0.013) and underlying disease (P=0.001), and its increase was associated with an increased risk of MIS-C (P=0.032) and death (P=0.047).

Conclusions: Male sex, length of hospital stay, and MIS-C were identified as risk factors associated with worsening the outcome of COVID-19 disease in children.

** Corresponding Author:*
Majid Sezavar, MD.
Address: *Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.*
E-mail: *Sezavardm@mums.ac.ir*

1. Introduction

A new coronavirus 2019-nCoV caused unusual cases of pneumonia in Wuhan, China, on December 29, 2019 (1). It was later named severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) (2, 3). The virus then rapidly spread to other parts of the world. The patient infects others mainly through droplet transmission (4), and the disease was named COVID-19 (2, 3). WHO then declared COVID-19 a public health emergency of international concern (5).

Coronaviruses are divided into four major types: alpha, beta, gamma, and delta. Beta viruses cause clinical manifestations in mammals, bats, rodents, cats, and humans (6). These manifestations vary in severity from mild to severe and even death. COVID-19, which has an incubation period of 2 to 14 days, presents with various symptoms such as fever, cough, shortness of breath, pneumonia, and other respiratory tract disorders (7).

Compared to adults, studies on children with COVID-19 disease are few (8). There are differences between children and adults in terms of clinical manifestations (7). According to studies, pulmonary involvement is the most important presentation of COVID-19 in adults, while the severity of pulmonary involvement in children is much less (9). Children with COVID-19 may be asymptomatic or have acute upper respiratory tract infection, gastrointestinal symptoms associated with shock, and in severe cases, coagulation dysfunction. Mild to moderate fever and cough are the most common complaints of children. The presence of comorbidities in children, like adults, increases the possibility to develop severe forms of COVID-19 (10). According to a study conducted in Turkey, the most common symptoms of sick children are fever followed by cough and sore throat (11). No particular drug has been indicated for COVID-19 in children, and antiviral agents must be used alone or combined with immunomodulators based on the severity of the disease and the patient's risk factors (9).

Contrary to initial reports regarding mild symptoms of children, some cases of children who were severely ill with hyper-inflammatory shock and multiorgan involvement were reported from England. This acute condition is known as a multisystem inflammatory syndrome in children (MIS-C) (12).

Despite the global spread, epidemiological patterns of COVID-19 are not well known among children (13). Therefore, studying the epidemiological characteristics of disease can be an urgent need and solution. This study aimed to investigate the epidemiology of children with COVID-19.

2. Patients and Methods

This descriptive-analytical study examined the epidemiological data of children with COVID-19 (the age range: 1 month to 18 years) admitted to hospitals in the North East of Iran in both retrospective and prospective forms for 8 months from the beginning of the COVID-19 outbreak. Most of the samples were referred to the Children's Reference Center in the study region. Since data collection began in April 2020, data on patients hospitalized from the onset of COVID-19 in the three months leading up to the study were retrospectively collected. The study then continued to collect data on new patients until late September 2020. A checklist was used to collect information. Demographic information was obtained from patients' medical records (both paper and health information system), and other information was gathered by conversation or phone contact with the children's parents. Accordingly, we recorded age, gender, weight, presence or absence of underlying disease or problems other than underlying disease, patient's residence (provincial center, cities, rural areas, orphanage), length of hospital stay, history of medication use by the patient, smoking and or drug use by the patient's parents, level of education of the patient's parents, occupational status of the patient's parents, multisystem inflammatory syndrome (MIS-C), number of cases of COVID-19 in the patient's family, COVID-19 infection in the patient's relative, death from COVID-19 in the patient's family and relative, house area, and the patient's final condition, including death or discharge. Relatives included grandparents, uncles, aunts, and their wives and children. Criteria for determining cases with COVID-19 included positive reverse transcription-polymerase chain reaction (RT-PCR) or clinical symptoms and computerized tomography (CT) scan. The diagnostic criteria of MIS-C in this study were as follows:

Age under 21, with fever, and laboratory evidence of inflammation and clinical evidence of severe disease that require hospitalization with involvement of at least 2 organs (heart, kidney, lung, blood, gastrointestinal system, skin, or nervous system):

When there is no other diagnosis for the disease,

When there is a positive test for previous or recent SARS-CoV-2 infection through RT-PCR on a nasopharyn-

geal specimen or contact with an infected person within 4 weeks of the onset of symptoms,

Fever of 38°C and above for at least 24 hours,

When there is at least one laboratory evidence of inflammation,

When manifestations similar to Kawasaki disease occur,

Any patient who dies with evidence of SARS-COV-2 must be considered a case of MIS-C.

SPSS software v. 26 was used to analyze the results of this study. Mean and standard deviation, median, and percentile were used to describe quantitative data. Frequency, percentage, and graph are used to show qualitative data. Microsoft Excel v.2016 was used to draw the bar graph. The Chi-square test was used to investigate the relationship between qualitative variables and outcome. The t test was used to analyze the relationship between quantitative variables and outcome. One-way analysis of variance was used to analyze other possible relationships between variables.

The research proposal of this study was approved by the Ethics Committee of Mashhad University of Medical Sciences (Code: IR.MUMS.REC.1399.154). The research was also confirmed by the Research Council of MUMS (Code: 990196).

3. Results

A total of 107 patients were studied. Of whom, 61 (57%) were male. The number of discharged patients was 88 (82.2%), and 19 patients died. Underlying diseases were observed in 56 cases (52.3%) that included 7 cases of neurologic problems, 5 cases of cerebral palsy, 3 cases of metabolic diseases, 3 cases with congenital cardiac problems, and 3 cases with biliary atresia. Cystic fibrosis, renal diseases, diabetes (DKA), growth impairment and developmental delays, asthma, repeated seizures, hematologic diseases, hepatitis, hydrocephalus, TORCH syndrome, neurovascular disease, rheumatism, pulmonary, Hirschsprung's disease, Down syndrome, and Addison disease were diseases that observed in less than 3 patients. Children whose parents had freelance and government-affiliated jobs were 86 (80.4%) and 10 (9.3%), respectively. The level of education in parents of 80 children (74.8%) was diploma or degrees. Places of residence in 50 (46.7%), 25 (23.4%), 31 (29%), and 1 (0.9) of children were provincial capital, cities, rural areas, and orphanages, respectively. Table 1 and Figure 1 show the status of quantitative variables. Table 2 compares discharged and deceased patients in terms of epidemiological characteristics.

Relationship between the main outcomes of the study (death or discharge) and other variables

The Chi-square test was used to investigate the relationship between qualitative variables and patient outcomes, including death or recovery. Of 19 patients who died in the study, 11 patients (57.9%) were male. There was no significant relationship between patient sex and survival or death (P<0.999). Of all patients who died, 8 (42.1%) had an underlying disease. No significant relationship was reported between the presence of the underlying disease and the final status of the patients. Also, 5 of the dead (26.3%) and 19 of the surviving children (21.6%) had a history of medication use. Phenobarbital, insulin, salbutamol spray, CREON, clobazam, ursobil, lamotrigine, and l-carnitine were the drugs reported in more than one case. There was no significant relationship between the patient's final condition and history of medication use (P=0.762). Ten children (52.6%) were in the deceased group whose parents were smokers or drug users. The relationship between parental smoking and the patient's outcome was not significant (P=0.19). Parents of 17 children (89.5%) who eventually died and 69 children (78.4%) who survived had freelance jobs. The level of diploma education and less was reported in the parents of 17 children (89.5%) who eventually died and 63 children (71.6%) who survived. Regarding residence, 10 children (52.6%) of the deceased patients and 40 (45.5%) of the survivors were residents of the provincial capital. The presence of COVID-19 in the relatives of patients was reported in 4 (22.2%) of the deceased and 24 (27.3%) of survivors. No case of death from COVID-19 was reported in the family or relatives of the deceased children. The relationship between final status of patient was not significant with parents' job (P=0.139) and education level (P=0.149), location of residence (P=0.099), COVID-19 in relatives (P=0.775), and death caused by COVID-19 in relatives (P=0.988). Regarding MIS-C, 13 (68.4%) of the children who died experienced MIS-C, while 24 (27.3%) survivors also had MIS-C. The relationship between the patient's final condition with MIS-C was strong and significant (P=0.001).

The t test was used to evaluate the relationship between quantitative variables and patient outcomes, including death or recovery. Table 3 compares recovered and deceased patients in terms of quantitative variables. Accordingly, the relationship between the length

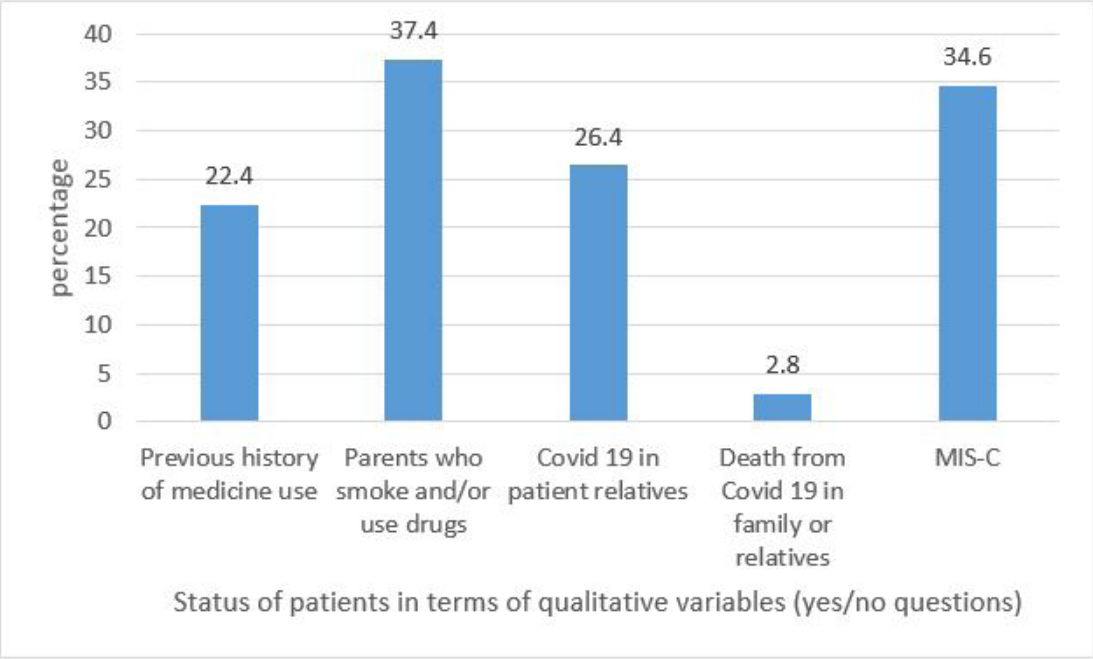

Figure 1. Qualitative variables in children with COVID-19

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of hospital stay and the final status of patients was significant (P=0.047).

Relationship between MIS-C and other variables

The Chi-square and t tests were used to investigate the possible relationship between MIS-C and other variables. Of 37 patients with MIS-C, 20 (54.1%) were male (P=0.685). Of children who experienced and did not experience MIS-C, 20 (54.1%) and 36 (51.4%), respectively, lacked any underlying disease (P=0.293). Previous use of medicines was reported in 5 patients (13.5%) with MIS-C and 19 (27.1%) of those without MIS-C (P=0.145). Sixteen children (43.2%) with MIS-C had parents who were smokers or drug users, and 24 children (34.3%) without MIS-C (24, 34.3%) had parents who were smokers or drug users (P=0.405). Parental occupation was not recognized as an effective parameter for the presence of MIS-C as 33 children (89.2%) with MIS-C, and 53 children (75.7%) had parents with freelance jobs. Similarly, the relationship between the education level of parents and the incidence of MIS-C was insignificant. Also, no significant relationship was observed between the variables of residence, COVID-19, and death from COVID-19 in the family and relatives of the patient with the presence or absence of MIS-C in children.

In examining the relationship between MIS-C and the quantitative variables presented in Table 4, the relationship between MIS-C and length of hospital stay was significant (P=0.032).

Relationship between length of hospital stay and other variables

One-way analysis of variance did not show a significant relationship between the length of hospital stay with the variables of parents' occupation, parents' level of education, and patients' residence. The relationship between the length of hospital stay and the underly-

Table 1. Quantitative epidemiological characteristics in children with COVID-19

	Statistics					
Variations	**Weight (kg)**	**Age (mo)**	**Duration of Hospital Stay (d)**	**Number of Members in Family**	**Number of Family Members With COVID-19**	**Home Area (m^2)**
Mean±SD	20.36±13.75	67.03±54.51	9.056±8.092	4.188±1.227	537±1.015	94.75±36.228
Minimum	2.50	0.00	1.00	0.00	0.00	40.00
Maximum	62.00	185.00	43.00	9.00	5.00	250.00

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Table 2. Comparison of epidemiological characteristics of discharged and deceased patients

Variations		Final Status of Patients (%)		Total%
		Discharge	Death	
Sex	Male	56.8	57.9	57.0
	Female	43.2	42.1	43.0
Underlying disease	Yes	44.3	63.2	47.7
	No	55.7	36.8	52.3
History of taking medicine	Yes	21.6	26.3	22.4
	No	78.4	73.7	77.6
Smoker or drug user parents	Yes	34.1	52.6	37.4
	No	65.9	47.4	62.6
Parents' job	Unemployed	3.4	0	2.8
	Government Employee	11.4	0	9.3
	Military	3.4	5.3	3.7
	Not Dependent	78.4	89.5	80.4
	Retired	3.4	0	2.8
	Unknown	0	5.3	0.9
The literacy level of parents	Illiterate	4.5	0	3.7
	Diploma and less	71.6	89.5	74.8
	Associate and bachelor	19.3	0	15.9
	Master of science and higher	3.4	5.3	3.7
	Unknown	1.1	5.3	1.9
Address	Capital of province	45.5	52.6	46.7
	Urban areas	22.7	26.3	23.4
	Rural areas	31.8	15.8	29
	Nursery	0	5.3	0.9
MIS-C	Yes	27.3	68.4	34.6
	No	72.7	31.6	65.4

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ing disease was significant. Accordingly, the Mean±SD of hospital stay for patients with the underlying disease was 12.5±9.2 days and for patients without underlying disease was 6.37±5.96 days (P=0.001).

Through the t test, a significant relationship was observed between the length of hospital stay and history of medication consumption (P=0.013). The Mean±SD hospitalization for patients with a history of taking medicine compared to those without medication were 12.6±8.7 and 8±7.6 days, respectively. Based on the t test, the relationship between patients' sex and length of hospital stay was not significant (P=0.712). Also, the t test did not show a significant relationship between the

Table 3. Comparison of patients' final status according to quantitative variables

Variables	Final Status	n	Mean±SD	P
Age (mo)	Discharge	88	63.50±50.69	0.246
	Death	19	83.36±68.80	
Weight (kg)	Discharge	87	20.09±13.20	0.667
	Death	19	21.60±16.37	
Duration of hospital stay (d)	Discharge	88	8.03±6.83	0.047
	Death	19	13.78±11.45	
Number of members in the family	Discharge	88	4.14±1.15	0.450
	Death	18	4.38±1.57	
Number of family members with COVID-19	Discharge	88	55±1.03	0.671
	Death	18	0.44±0.92	
Home area (m^2)	Discharge	88	95.27±36.23	0.739
	Death	17	92.05±37.20	

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length of hospital stay with parental smoking, COVID-19 in relatives, and death from COVID-19 in patients' families and relatives.

4. Discussion

The present research showed that the age group of children affected by COVID-19 disease was between 0 and 185 months, with a mean age of 67 months and a male to female ratio of 1.33:1. In a case series of 10 children with COVID-19 in China, the minimum, maximum and average age of children were 3, 131, and 74 months and the male to female ratio was 1: 1.5 (14). Differences in the values of demographic variables between different studies can be due to differences in sample size, duration of the study, and changes in virus behavior and power over time. In our study, 57% of the patients were

Table 4. Comparison of patients with and without MIS-C according to quantitative variables

Variables	MIS-C	n	Mean±SD	P
Weight (kg)	Yes	37	22.87±14.30	0.170
	No	69	19.02±13.35	
Duration of hospital stay (d)	Yes	37	11.35±7.33	0.027
	No	70	7.84±8.25	
Number of members in the family	Yes	37	4.10±1.48	0.623
	No	69	4.23±1.07	
Number of family members with COVID-19	Yes	37	0.70±1.22	0.270
	No	69	0.44±0.88	
Home area (m^2)	Yes	37	97.97±45.66	0.504
	No	68	93.00±30.13	

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male. In the study conducted at Wuhan Children's Hospital, 65% of the patients were male, and the age range was 0 to 168 months, with a median age of 24 months (15). The median age of children with COVID-19 in the present study was 55 months, and in a case series of COVID-19 was 84 months. Also, 56.6% of the case series were boys (16), which is very close to 57% of the male population in the present study. Overall, epidemiological findings indicate that male children are slightly more likely to develop COVID-19 disease than female children. Nevertheless, in different studies, the age range of children with COVID-19 is different, and it can be said that the age range of affected children is very wide.

Our results showed that 47.7% of the hospitalized children due to COVID-19 had an underlying disease. Similarly, 8 of the 20 (40%) patients studied in Wuhan, China, had a history of surgery, congenital or acquired diseases, which led researchers to report that children with underlying diseases were more susceptible to COVID-19 disease (15).

This study also showed that 19 patients (17.8%) of all studied children died. Based on an analysis of the hospitalization data of children with COVID-19 from 14 states in the US, children are at risk for severe COVID-19. Although the cumulative rate of COVID-19–associated hospitalization was low among children compared with that in adults, one in three hospitalized children was admitted to an intensive care unit (17). In the present study, 37 children (34.6%) experienced MIS-C. Also, 13 out of 19 deaths (68.4%) were related to children with MIS-C. According to a study performed in three tertiary care centers in India, among 21 children with COVID-19 who developed MIS-C, the mortality rate was 9% (18). In a multicenter retrospective cohort study, the incidence of thrombosis was compared between children with COVID-19 and MIS-C. Patients with MIS-C had the highest incidence of thrombosis (6.5%). The mortality rate was 28% in patients with thrombotic events and 2.3% in other cases of COVID-19 (19).

The results showed that the relationship between the incidence of MIS-C and the final status of the patients was highly significant. In our study, the Mean±SD length of hospital stay was 9.05±8.09 days, with a median of 7 days. In a systematic review that examined 662 patients, 11 deaths (1.7%) were reported, and the Mean±SD duration of hospitalization was 7.9±0.6 days (12). According to a case series of children in England who met the criteria for MIS-C, 34% of the 58 identified cases were girls, and 45 (78%) had evidence of current or previous infection with COVID-19 disease (20). After the start of the COVID-19 outbreak, 78 cases (67% male) of MIS-C were admitted to pediatric intensive care units in the UK. This study showed that the rate of admissions to the pediatric intensive care units for MIS-C compared to similar inflammatory conditions was at least 11-fold higher than historical trends (21).

According to a study performed in the north of Iran on 10 children with COVID-19 infection with characteristics of MIS-C, there was only one (10%) death (22). While in the present study, 13 of the 37 children with MIS-C (35.13%) died. This difference can be due to the remarkable difference in terms of the sample size between the present study and the mentioned study. Based on a systematic review conducted on 68 records of COVID-19 related MIS-C, most patients (73.3%) were admitted to the intensive care unit, and 3.8% needed extracorporeal membrane oxygenation. Despite the severe conditions caused by the disease, the mortality rate was 1.9% (23).

This study showed no association between the number of COVID-19 patients in the family and the child with COVID-19. This finding is in contrast to all other studies that show that majority of children with COVID-19 disease are part of a family cluster outbreak (24-26). This difference could be due to secrecy and inaccurate transfer of information by the parents or the latent illness at the time of the interview.

5. Conclusion

In this study, the death or survival of children with COVID-19 was not affected by gender or age. Epidemiological parameters related to home and family did not show a significant relationship with the outcome of COVID-19 disease in children. About 35% of children with COVID-19 showed simultaneous MIS-C, and according to the results, children were more likely to die if MIS-C was associated with COVID-19 compared with the presence of COVID-19 disease alone.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this research. The parents were informed about the purpose of the research and were also assured of the confidentiality of their information.

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Authors' contributions

Conceptualization and Supervision: Naseri, Sezavar, and Khademi; Data Analysis: Khadem Rezaeiyan; Writing – original draft: Sorouri, Naseri; Writing – review & editing: Khademi, Sezavar; Statistical analysis: Khadem Rezaeiyan.

Conflicts of interest

The authors declared no conflict of interest.

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