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COVID-19 in Pediatric Patients with and Without Immunocompromised

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Abstract

Background: The effect of Coronavirus Disease 2019 (COVID-19) on pediatric patients with immunodeficiency is a major research priority. .. The objective of this investigation was to perform a comparative assessment of the symptomatology, clinical course, and endpoints of COVID-19 infection in children patients with and without immunocompromised conditions.

Methods: The current retrospective cohort study included children aged ≤18 years with confirmed COVID-19 infection, diagnosed via RT-PCR (Reverse Transcription Polymerase Chain Reaction) testing, who were admitted to Ali Asghar Children's Hospital in Tehran, Iran, from February 20, 2020, to February 20, 2023. A total of 200 patients were included, comprising 100 immunocompromised and 100 non-immunocompromised children, selected from hospital records. Categorical variables were compared using the chi-square or Fisher's exact test, and continuous variables were compared using the independent t-test or Mann-Whitney U test, based on their normality as determined by the Kolmogorov-Smirnov test. A P-value < 0.05 was considered statistically significant.

Results: The average age of patients with immunocompromised conditions was 76.48 ± 58.33 months, while those without such conditions had a mean age of 38.02 ± 44.47 months. Children with immunocompromised conditions had lower exposure to positive contacts (P = 0.010) and exhibited higher rates of cough (P < 0.001), respiratory distress (P = 0.001), vomiting (P = 0.024), diarrhea (P < 0.001), and lower oxygen saturation (P = 0.001). Additionally, they demonstrated significantly higher rates of mortality (P = 0.018), intubation (P = 0.018), and longer hospital stays (P < 0.001).

Conclusion: Pediatric patients with immunocompromised conditions who contracted COVID-19 experienced more severe symptoms than their non-immunocompromised counterparts. These patients had higher mortality and intubation rates, as well as longer hospital stays. This increased risk underscores the necessity for specialized management strategies tailored to this vulnerable population.

Keywords: COVID-19, Outcomes, Mortality, Pediatrics, Immunocompromised Host

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Introduction

The COVID-19 pandemic, triggered by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in early 2020 and rapidly escalated into a global crisis, resulting in widespread infections and significant

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↑What is "already known" in this topic:
Immunocompromised children face higher risks of severe COVID-19 outcomes than others, but most have mild illness and recover well. Risk varies by condition, with higher mortality in those with hematological cancers. Careful management is key, and vaccination is effective and recommended.

→What this article adds:
This study demonstrates that immunocompromised pediatric patients with COVID-19 experience significantly more severe symptoms compared to non-immunocompromised children. They face higher mortality rates, greater need for intubation, and longer hospital stays. These findings emphasize the necessity for specialized clinical management and close monitoring of immunocompromised children during COVID-19 infection.

mortality (1). To date, it has been observed that certain populations, particularly those with metabolic or cardiovascular conditions, are disproportionately affected (2). Additionally, individuals with compromised immune systems, such as those undergoing cancer treatment, are of particular concern (3). Patients with cancer. Cancer, hematopoietic cell transplants, and solid organ transplants represent a significant segment of immunocompromised individuals, characterized by diverse primary (inherited) and secondary (acquired) immune deficiencies (4). Over 180 immunodeficiency diseases have been identified, and immunocompromisation is defined as a weakened immune state in children, which increases their susceptibility to infections and severe illness. This impaired immune defense can result from medical conditions, genetic factors, or treatments (5).

Cancer is a leading cause of death and disease burden in children and adolescents, affecting over 400,000 individuals annually worldwide (6). The immunocompromised status in children with compromised immune systems, stemming from both their underlying conditions and treatments, may have altered responses to COVID-19 (7, 8). Patients with immunodeficiency are expected to be more susceptible to severe COVID-19 outcomes (9). Autoimmune diseases and medications such as corticosteroids, which modulate the immune system, may heighten the risk of severe infections in affected patients. COVID-19 can induce various changes in the immune system, likely influenced by existing immune-mediated diseases or prior use of immunomodulatory drugs (8).

The effect of the COVID-19 pandemic on immunodeficient individuals has been a subject of several investigations (10, 11). Individuals suffering from immunodeficiency, particularly those exhibiting deficiencies in antiviral innate immune signaling or those with combined immunodeficiency (CID), may experience an increased risk of severe cases of COVID-19 (12). The impairment in their immune system's ability to respond effectively to viral infections can lead to more serious manifestations of the disease.

However, limited evidence exists regarding the impact of COVID-19 on pediatric patients with immunocompromised conditions (8, 11). While the peak of the pandemic has passed, it remains essential to understand the effects of COVID-19 on pediatric patients with immunodeficiency. New variants of SARS-CoV-2 continue to emerge, potentially affecting vulnerable populations in various ways. Insights from this study may aid in developing strategies for managing future infectious disease pandemics. Thus, the present study aims to determine the COVID-19 outcomes in immunocompromised versus non-immunocompromised pediatric patients.

Methods

Study Design, Duration, and Setting

This retrospective cohort study (February 2020 - February 2023) included all pediatric patients admitted to Ali Asghar Hospital, Tehran, Iran, with RT-PCR-confirmed COVID-19. Enrollment was based solely on a positive RT-PCR, irrespective of clinical presentation.

Sampling Techniques and Procedures

All confirmed COVID-19 pediatric patients with immunocompromised conditions who were admitted to Ali Asghar Hospital during the study period were included in this study. Additionally, an equal number of pediatric patients without immunocompromised conditions, also diagnosed with COVID-19 and admitted to the same hospital during the same period, were randomly selected for comparison. The unexposed (control) group among pediatric patients with COVID-19 was randomly selected using Microsoft Excel. The RAND and RANDBETWEEN functions were utilized to generate random numbers, ensuring an unbiased and representative sampling process. Specifically, each eligible patient was assigned a random number, and the list was sorted based on these values. The required number of control subjects was subsequently selected from the top of the sorted list.

Inclusion Criteria

1. *Confirmed COVID-19 Diagnosis:* Subjects must have a positive RT-PCR test result for SARS-CoV-2.
2. *Complete Medical Records:* Subjects must have comprehensive and accessible medical and health records to facilitate data extraction.
3. *Age:* Subjects must be 18 years old or younger (≤ 18 years).

Exclusion Criteria

1. *Outpatients with Positive PCR Tests:* Patients who were managed as outpatients, despite having a positive RT-PCR test, were excluded from the study.

Baseline Information

The following variables were considered in the study: age (in months), sex (male, female), and various clinical symptoms. Data were extracted from medical records, including the following variables:

- *Age (months):* The exact age of the child at the time of COVID-19 diagnosis, recorded in completed months to provide precise pediatric age measurement (13, 14).
- *Sex:* Biological sex of the child, categorized as male or female (13).
- *Fever:* Presence of elevated body temperature as documented in medical records or reported by caregivers, indicating a common symptom of COVID-19 in children (13, 15).
- *Cough:* Presence of cough reported or observed during illness, a frequent respiratory symptom in pediatric COVID-19 (13, 15).
- *Myalgia:* Muscle pain or soreness reported by the child or caregiver, reflecting muscular involvement in COVID-19 (14, 15).
- *Distress:* Clinical signs of respiratory distress or difficulty breathing noted by healthcare providers, indicating severity of illness (13).
- *LOC (Low Level of Consciousness):* Any documented episode of reduced consciousness or altered mental status during illness (14).

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• *Anosmia:* Loss of smell reported by the child or caregiver, a recognized neurological symptom of COVID-19 (14, 15).

• *Ageusia:* Loss of taste reported by the child or caregiver, often accompanying anosmia in COVID-19 (14, 15).

• *Seizure:* Occurrence of any seizure episode during illness as recorded in medical records (14).

• *Cramp:* Presence of muscle cramps or spasms reported during illness (15).

• *Nausea:* Feeling of nausea as documented or reported (15).

• *Vomiting:* Episodes of vomiting during illness (13, 15).

• *Diarrhea:* Presence of loose or watery stools during illness, a gastrointestinal manifestation of COVID-19 (13, 15).

• *Loss of Appetite:* Reduced or absent appetite during illness, commonly reported in pediatric cases (15).

• *Headache:* Presence of headache reported by the child or caregiver, a neurological symptom associated with COVID-19 (14, 15).

• *Dizziness:* Sensation of dizziness or lightheadedness during illness (15).

• *Skin Involvement:* Any skin manifestations such as rash, discoloration, or lesions noted during illness (14, 15).

• *SpO_2 (Peripheral Capillary Oxygen Saturation):* Oxygen saturation level measured by pulse oximetry, expressed as a percentage, indicating blood oxygenation status (13).

• *Oxygen Therapy:* Whether supplemental oxygen was administered during hospitalization or treatment to manage hypoxia (13).

Outcome Variables

The outcome variables in this study included mortality, intubation, and the duration of hospitalization:

• *Mortality:* Defined as death occurring during the hospital stay attributable to COVID-19 or its complications. This includes any patient who died after testing positive by RT-PCR and during the course of treatment for COVID-19 in the hospital setting (16, 17).

• *Intubation:* Refers to the clinical intervention where a patient requires the insertion of an endotracheal tube to secure the airway and facilitate mechanical ventilation due to respiratory failure or severe respiratory distress caused by COVID-19 (16, 18)

• *Duration of Hospitalization:* The total length of time (measured in days) from the date of hospital admission for COVID-19 until discharge or death. This variable reflects the inpatient care period required for managing the disease (16).

Data Quality Control

Data collectors and supervisors underwent comprehensive training to ensure data integrity throughout the study. The data collection process was closely monitored daily by supervisors and principal investigators, who checked the collected data for completeness and consistency. The monitoring protocol involved designated clinical supervisors conducting daily rounds to ensure adherence to infection control practices, assess patient stability, and oversee compliance with study procedures. The specific protocols included:

• *Regular Patient Assessments:* Supervisors evaluated vital signs, oxygen saturation, and clinical symptoms at least twice daily.

• *Infection Control Adherence:* Supervision ensured the proper use of personal protective equipment (PPE), hand hygiene, and environmental disinfection procedures.

• *Data Accuracy and Completeness:* Supervisors verified data recording in medical records and ensured consistency across case documentation.

• *Protocol Adherence:* Daily oversight of treatment protocols and medication administration was conducted to ensure compliance.

• *Communication:* Supervisors coordinated daily with clinical staff to address any emerging concerns or complications.

Statistical Analyses

Categorical variables are presented as frequencies and percentages, and continuous variables as mean ± standard deviation (SD)or median and interquartile range, based on their distribution. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Group comparisons were performed using the chi-square or Fisher's exact test for categorical variables, and the independent t-test or Mann-Whitney U test for continuous variables, as appropriate. A p-value below 0.05 was considered statistically significant, and all analyses were conducted using IBM SPSS Statistics (Version 23.0).

Results

Demographic Characteristics of Study Participants

The current study included 200 pediatric patients with COVID-19, consisting of 100 with immunocompromisation and 100 without. The detailed demographic characteristics of the study cohort are presented in Table 1. The mean ± SD age of patients with immunocompromisation was 76.48±58.33 months, while the mean ± SD age of patients without immunocompromisation was 38.02±44.47 months (Table 1).

Clinical Characteristics of Study Participants

The clinical characteristics differed significantly between pediatric patients with and without immunocompromisation (Table 2).

Comorbidities in Pediatric Patients with Immunocompromisation

Among pediatric patients with immunocompromisation, neurologic involvement was the most prevalent comorbidity, observed in 17 patients (17%), followed by Acute Lymphocytic Leukemia (ALL) in 13 patients (13%). Congenital immunodeficiency was noted in 11 children

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Table 1. Demographic Characteristics of Study Participants

Variable	without immunocompromisation (n=100)	with immunocompromisation (n=100)	Total (n=200)	*P*-value
	N(%)	N(%)	N(%)	
Age, (Mean±Sd), (Month)	38.02±44.47	76.48±58.33	57.25±55.21	<0.001*
Gender				
Male	100 (100)	64 (64)	164 (82)	<0.001*
Female	0 (0)	36 (36)	36 (18)	

Table 2. Clinical Characteristics of Study Participants

Variable	without immunocompromisation (n=100)	with immunocompromisation (n=100)	Total (n=200)	*P*-value
	N(%)	N(%)	N(%)	
Exposure to a positive contact	52(52)	34(34)	86(43)	0.010
Fever	78(78)	80(80)	158(79)	0.728
Cough	17(17)	46(46)	63(31.5)	<0.001
Myalgia	7(7)	8(8)	15(7.5)	0.788
Respiratory distress	11(11)	29(29)	40(40)	0.001
Low level of consciousness	0(0)	2(2)	2(1)	0.497
Anosmia	1(1)	0(0)	1(0.5)	0.999
Seizure	1(0.5)	0(0)	1(0.5)	0.999
Cramp	6(6)	4(4)	10(10)	0.516
Nausea	11(11)	12(12)	23(11.5)	0.825
Vomiting	23(23)	11(11)	34(17)	0.024
Diarrhea	40(40)	14(14)	54(27)	<0.001
Loss of appetite	4(4)	3(3)	7(3.5)	0.999
Headache	5(5)	4(4)	14(7)	0.999
Dizziness	0(0)	2(2)	2(1)	0.497
Skin involvement	1(1)	1(1)	2(1)	0.999
Oxygen saturation, (Mean±Sd)	94.24 ±3.79	92.14±4.89	93.19±4.49	0.001
Oxygen therapy	31(31)	44(44)	75(37.5)	0.058

(11%). Figure 1 provides detailed information on the comorbidities in these pediatric patients.

Outcomes Among Study Participants

Outcomes, including mortality, intubation, and length of hospitalization, significantly differed between pediatric COVID-19 patients with and without immunocompromisation who were admitted to Ali Asghar Hospital from February 20, 2020, to February 20, 2023. The characteristics of these patients are summarized in Table 3. The outcomes showed significant differences ($P < 0.05$) between the two groups (Table 3).

Discussion

The current retrospective cohort research examines the impact of COVID-19 on pediatric patients with and without immunocompromisation. We found significant differences in outcomes: pediatric patients with immunocompromisation exhibited higher mortality rates, increased intubation rates, and longer hospital stays compared to their non-immunocompromised counterparts. Additionally, pediatric patients with immunocompromising conditions experienced more severe COVID-19 symptoms than those without such conditions.

Our results indicated a statistically significant difference in mortality rates between confirmed pediatric COVID-19 patients with and without immunocompromisation. The mortality rate was significantly higher in pediatric COVID-19 patients with immunocompromisation compared to those without. Children with specific immunocompromising conditions are at increased risk for severe COVID-19 outcomes, with mortality rates varying significantly based on the type of immune defect and existing comorbidities (10).

While most children with immunocompromisation experience mild to moderate cases, those with combined immunocompromisation (CID) or immune dysregulation face significantly higher mortality rates compared to both the general pediatric population and other immunodeficiency groups (10). Greenan-Barrett et al. demonstrated that immunocompromised children and young people experienced a significantly higher mortality rate from severe COVID-19 (6.5%) compared to their peers in the general population (0.2%) (19). Furthermore, cohort studies in adults involving 13,206 Spanish patients and 6,435 Korean patients revealed significantly higher inpatient mortality rates in immunocompromised individuals compared to their non-immunocompromised counterparts, at 31.3% versus 19.3% and 6.4% versus 2.0%, respectively (20, 21). These findings are consistent with the current research.

The current results demonstrated a statistically significant difference in intubation rates between pediatric COVID-19 patients with and without immunocompromisation, with the rate being notably higher in those with immunocompromisation. Belsky et al. conducted a systematic review indicating that COVID-19 outcomes in immunocompromised adults are more severe than in the general population, likely due to the presence of comorbidities in this group (22). These results are consistent with the findings of the current study, which align with previous research(19, 21, 22).

Additionally, our results indicated a significant difference in the duration of hospitalization between pediatric

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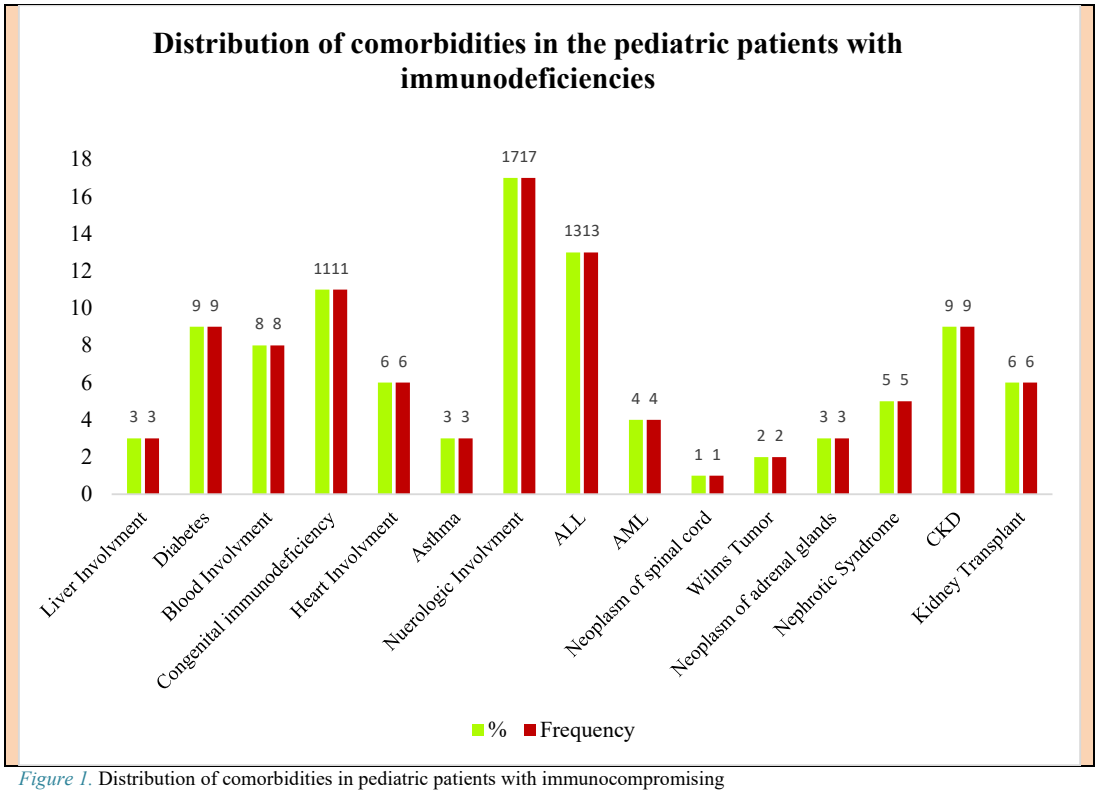

Figure 1. Distribution of comorbidities in pediatric patients with immunocompromising

Table 3. Outcomes in COVID-19 Patients with and without Immunocompromisation

Variable	without immunocompromisation (n=100)	with immunocompromisation (n=100)	Total (n=200)	*P*-value
	N(%)	N(%)	N(%)	
Mortality in COVID-19 Patients	1(1)	9(9)	10(5)	0.018
Intubation	2(2)	11(11)	13(6.5)	0.018
Duration of hospitalization by day (Mean±Sd)	6.51±4.75	10.96±11.17	8.74±8.85	<0.001

COVID-19 patients with immunodeficiency, who experienced a notably longer hospital stay, and those without. A systematic review of 68 studies involving 459 patients with primary immunodeficiency (PI) reported a 9% case fatality rate, a 49% hospitalization rate, and a 29% oxygen requirement rate (23). These findings further support the conclusions of the current research.

It is noteworthy that various factors can affect the outcomes of COVID-19 in pediatric patients with and without immunocompromisation, including the impact of vaccination in children and the presence of comorbidities.

Strengths and Limitations of the Study

One notable strength of this study is its rigorous inclusion criteria and meticulous participant selection, which enhance the internal validity of the results. However, this study has several limitations that should be considered. The single-center design introduces potential biases and limits the generalizability of the results to broader populations. Additionally, the sample size was relatively small, and a gender imbalance was observed, which may affect the applicability of the findings across different demographic groups. These constraints were largely unavoidable, as all confirmed pediatric COVID-19 cases with immunocompromised status during the study period were included.

We recommend that future research be conducted over extended periods and involve larger, more diverse cohorts to improve the robustness and external validity of the results. Lastly, our analysis did not account for potential confounding variables, primarily due to the limitations of the regression method used and the limited information available in medical records regarding these factors. Addressing these issues in future studies would provide a clearer understanding of the influences on outcomes.

Conclusion

The present study underscores the critical need for optimized clinical management of COVID-19 in immunocompromised children. The findings indicate that symptoms and outcomes of COVID-19 are significantly more severe in this population compared to their non-immunocompromised counterparts. Specifically, pediatric patients with immunocompromisation exhibited higher rates of mortality, intubation, and longer hospital stays due to COVID-19. To mitigate adverse consequences in

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low- and middle-income countries (LMICs), such as Iran, prioritizing the care of pediatric patients with immunocompromisation is essential. Prospective longitudinal studies with sufficient power are needed to definitively establish causality between COVID-19 and adverse consequences in this vulnerable population.

Authors' Contributions

M.S.: Data collection, data analysis, manuscript writing, and editing; A.E.: Project development and data analysis; A.N.: Project development and data analysis; M.A.: Manuscript writing and editing; R.Kh.: Manuscript writing and data analysis; R.H.: Manuscript writing and editing; S.Kh.: Data collection; and N.Gh.: Data collection and manuscript writing.

Ethical Considerations

This study received approval from the Research Ethical Review Board of Iran University of Medical Sciences (approval number: IR.IUMS.FMD.REC.1401.243). The ethics committee waived the requirement for informed consent due to the retrospective nature of the study. All methods were carried out in accordance with relevant guidelines and regulations.

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Conflict of Interests

The authors declare that they have no competing interests.

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