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Research Paper

Serological Findings of Children With COVID-19 and Clinical and Paraclinical Results

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ABSTRACT

Background and Aim: This research aims to examine the serological outcomes of pediatric patients with COVID-19 and their correlation with the clinical and paraclinical outcomes of children hospitalized at Hazrat Masoumeh Hospital in the mid-year of 2021.

Materials and Methods: The study collected data from a database of patients who were definitively diagnosed with COVID-19. The study also recorded the clinical outcomes of these patients (such as discharge, death, and length of hospitalization) for one month after their hospitalization, which was the last day of follow-up. Information on epidemiological, clinical, laboratory data, radiological indicators, treatment, and clinical consequences was extracted from the patient's electronic medical records using data collection forms. All the gathered information was then entered into SPSS software, version 22 and analyzed using statistical tests. The significance level for all tests was set at 0.05.

Results: No significant relationship was observed between the immunoglobulin (Ig) M response and any of the clinical symptoms ($P>0.05$). The IgG response was statistically significantly related only to diarrhea and abdominal pain among the clinical symptoms experienced by patients ($P<0.05$). Among laboratory symptoms, thrombocytopenia had a statistically significant relationship with IgM ($P=0.009$), and positive urine culture had a statistically significant relationship with IgG ($P=0.00$). Other laboratory symptoms had no statistically significant relationship with serological findings ($P>0.05$). Imaging results had a statistically significant relationship only with Ig G ($P=0.00$) and no significant statistical relationship with IgM ($P=0.23$).

Conclusion: The study results indicate that the serological results of these patients are also significant for diagnosing this disease.

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Introduction

On December 8, 2019, many cases of patients with pneumonia of an unknown cause appeared in Wuhan City, China [1, 2]. The ongoing outbreak of pneumonia is linked to a novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3]. After purifying and examining the genome sequence and gene sequences of this virus, it was found that it belongs to the coronavirus family and is closely related to the SARS and Middle East respiratory syndrome (MERS) viruses [4]. The disease is not common among 18-year-olds and young people, accounting for only 2.4% of all reported cases, but it is crucial to monitor the symptoms in children [4, 5]. The clinical manifestations of this disease in children may be different from adults, as studies have shown that children experience more gastrointestinal symptoms than adults. Additionally, most children with SARS-CoV have a fever [6]. Another point is that babies born to mothers with COVID-19 may suffer from problems, such as breathing difficulties, abnormal liver function, thrombocytopenia, and thermal instability [7] It is believed that children with this disease are either asymptomatic or may eventually show a mild form of symptoms [8]. Affected children may show symptoms, such as fever, and mild respiratory symptoms, such as a dry cough, distress, nasal discharge, sore throat, and fatigue [9]. In some cases, they may experience digestive symptoms [10]. Children with underlying diseases may experience acute respiratory symptoms due to the destruction of alveoli [11]. This disease may progress very quickly, leading to the progressive involvement of several organs in the body, such as shock, acute respiratory distress syndrome (ARDS), myocarditis, and acute kidney injury (AKI). It can even cause the death of patients very rapidly [5]. From the changes that occur in the laboratory, symptoms include leukopenia, lymphopenia, and thrombocytopenia, as well as increased prothrombin time (PT) and C-reactive protein (CRP) [5, 12]. To date, reverse transcription polymerase chain reaction (RT-PCR) on respiratory samples is the current gold standard method for diagnosing COVID-19 [13, 14]. Molecular tests are slow and need specialized operators, which limits their use in quick diagnosis. A serological test was used to differentiate COVID-positive patients from those with negative PCR tests [15]. Lab kits for COVID-19 testing have been made and used by the US Centers for disease control and prevention (CDC) and private companies. RT-PCR testing is the current standard diagnostic method, but these kits have limitations [16]. These tests have a long turnaround time and are complicated in practice. On average, they take more than 2-3 hours to get results [17]. The limitations of RT-PCR in detecting COVID-19 lead to many false negatives, making it unsuitable for quick and easy diagnosis and screening of patients. This hinders efforts to contain the outbreak. Therefore, a fast, accessible, sensitive, and precise test is needed to promptly identify SARS-CoV-2 infected patients, prevent virus spread, and ensure timely treatment [18, 19]. After a SARS infection, immunoglobulin (Ig) M antibodies can be detected in the patient's blood after 3 to 6 days, and IgG can be detected after the 8th day [19]. COVID-19 is similar to MERS and SARS viruses in terms of antibody production. Detecting IgG and IgM antibodies against SARS-CoV-2 indicates infection, IgM indicates recent infection and IgG indicates recent exposure. Detecting both antibodies can provide information on the time course of infection.

Materials and Methods

This study was conducted using a cross-sectional analytical approach. The same approach was used repeatedly throughout the study. The research sample included all children who were hospitalized with a diagnosis of COVID-19 in the first half of 2021 at Hazrat Masoumeh Hospital. Serology tests were administered to all of these patients. All these children were included in the study through a census.

Inclusion criteria

The inclusion criteria included children with positive PCR for COVID-19 to whom serology was sent.

Exclusion criteria

The exclusion criteria included patients with vascular collagen diseases, patients with negative serology, and immunocompromised patients.

The data for this study were extracted from the database of patients for whom the diagnosis of COVID-19 was confirmed. The clinical outcomes of these patients, such as discharge, death, and length of hospitalization, were also recorded in a checklist for one month after hospitalization, which marked the end of the patient's follow-up. Epidemiological, clinical, laboratory data, radiological indicators, treatment, and clinical consequences were extracted from the electronic medical records of these patients using data collection forms. Then, 5 mL of blood was taken from all these patients to measure blood antibodies and sent to a reference laboratory to determine the

Table 1. Examination of serology and imaging findings in children with COVID-19

Variables		No. (%)
IgM	Yes	4(6.2)
	No	61(93.8)
IgG	Yes	22(33.8)
	No	43(66.2)
Chest CT scan	Yes	49(75.4)
	No	16(24.6)

Ig: Immunoglobulin, CT: Computed tomography.

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antibody level. Finally, all the information was entered into SPSS software, version 26 and analyzed according to the chi-square statistical test and Fisher's exact test. The significant level for all tests was considered 0.05.

Results

A total of 34 boys (52.3%) and 31 girls (47.7%) were investigated. Concerning the age of the patients, 1 person (1.5%) was less than a month, 5 people (7.7%) were 1 month to a year, 33 people (50.8%) were 1 to 5 years and 26 people were 5 years and older (40%). Thirteen patients (20%) had an underlying disease and 23 patients (35.4%) had a history of previous antibiotic use.

In connection with the follow-up of the patients, it was observed that 2 patients died and the rest of the patients survived, while about 5% of all hospitalized cases were in the intensive care unit. Concerning the diagnosis of the disease, all children studied tested positive for COVID-19 and Table 1 presents other diagnostic findings.

The results in the Table 2 show that none of the clinical symptoms has a significant relationship with the IgM response (P>0.05). Among the clinical symptoms, only in diarrhea and abdominal pain in patients, a statistically significant correlation with IgG response was found (P<0.05).

A significant difference was observed between the laboratory results only concerning thrombocytopenia (P<0.05). The rest of the laboratory findings in the patients have no statistically significant relationship with the positive or negative result of IgM (P>0.05). Regarding IgG, a significant difference was observed between laboratory results only about urinary tract infection (UTI) (P<0.05). The remaining laboratory results in the patients have no statistically significant relationship with the positive or negative response of IgG (P>0.05) (Table 3).

Table 4 presents the correlation between positive imaging and serology results. A significant relationship is observed between IgG and imaging results (P=0.00). Out of the 22 cases with positive IgG, 21 individuals (32.3%) also had positive imaging results. However, no significant statistical correlation was found between IgM serology findings and imaging results (P=0.23).

Discussion

Due to the outbreak of the new coronavirus disease (COVID-19), although the PCR test has become a standard method to detect infection, this test has many limitations. Additionally, a high false negative rate has been reported. To quickly identify a large number of infected patients and asymptomatic carriers to prevent virus transmission and ensure timely treatment, an accurate and rapid test method is required. This study was conducted to determine the humoral responses of children with COVID-19

The aim was to clarify the potential pathophysiological effects of the virus. Serum samples from 65 children with SARS-CoV-2 were tested at Hazrat Masoumeh Children's Hospital in Qom. The results showed that 22 patients had positive IgG Ab and 4 patients had positive IgM Ab. In 3 patients, both IgM Ab and IgG Ab were positive simultaneously. The antibody test of 42 patients was negative.

The sequence of seroconversion in this disease may also be different. The use of IgG Ab during the early stages of the disease can be used for diagnosis, or the IgM Ab titer can be detected during the disease. Additionally, all patients with positive IgM Ab had thrombo-

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Table 2. Examination and comparison of the frequency of clinical symptoms of patients according to the serological response to COVID-19

Variables		No. (%) IgM		P	No. (%) IgG		P
		Positive	Negative		Positive	Negative	
Fever	Yes	3(75)	1(25)	0.316*	12(54.5)	10(45.5)	0.249
	No	26(42.6)	35(57.4)		17(39.5)	26(60.5)	
Sore throat	Yes	1(25)	3(75)	0.796*	5(22.7)	17(77.3)	0.694
	No	12(19.7)	49(80.3)		8(18.6)	35(81.4)	
Chili	Yes	2(50)	2(50)	0.093	5(22.7)	17(77.3)	0.737
	No	10 (16.4)	51 (83.6)		7(16.3)	36(83.7)	
Rhinorrhea	Yes	2(50)	2(50)	0.187	7(31.8)	15(68.2)	0.232
	No	13(21.3)	48(76.9)		8(18.6)	35(81.4)	
Headache	Yes	1(25)	3(75)	0.796*	3(13.6)	19(86.4)	0.359
	No	12(19.7)	49(80.3)		10(23.3)	33(76.7)	
Coryza	Yes	1(25)	3(75)	0.425*	3(13.6)	19(86.4)	0.816
	No	7(11.5)	54(88.5)		5(11.6)	38(88.4)	
Fatigue	Yes	1(25)	3(75)	0.582*	6(27.3)	16(72.7)	0.057
	No	9(14.8)	52(85.2)		4(9.3)	39(90.7)	
Sweating	Yes	1(25)	3 (75)	0.582*	2(9.1)	20(90.9)	0.978
	No	9(14.8)	52(85.2)		4(9.3)	39(90.7)	
Seizure	Yes	1(25)	3(75)	0.261*	1(25)	3(75)	0.261*
	No	5(8.2)	56(91.8)		5(8.2)	56(91.8)	
Disorders of consciousness	Yes	1(25)	3(75)	0.105	1(4.5)	21(95.5)	0/712*
	No	3(4.9)	58(95.1)		3(7)	40(93)	
Diarrhea	Yes	0	4(100)	0.439*	6(27.3)	16(72.7)	0.001
	No	8(13.1)	53(86.9)		2(4.7)	41(95.3)	
Constipation	Yes	1(25)	3(75)	0.105*	3(13.6)	19(86.4)	0.073*
	No	3(4.9)	58(95.1)		1(2.3)	42(97.7)	
Abdominal pain	Yes	1(25)	3(75)	0.180*	4(18.2)	18(81.8)	0.023*
	No	4(6.6)	57(93.4)		1(2.3)	42(97.7)	
Nausea and vomiting	Yes	1(25)	3(75)	0.657*	5(22.7)	17(77.3)	0.372
	No	10(16.4)	51(83.6)		6(14)	37(86)	

Ig: Immunoglobulin.

*Fisher's exact test.

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Table 3. Review and comparison of the frequency of clinical laboratory symptoms of patients according to the serological response of COVID-19

Variables		No. (%) IgM		P	No. (%) IgG		P
		Positive	Negative		Positive	Negative	
Leukopenia	Yes	0	4(100)	0.154*	6(27.3)	16(72.7)	0.535
	No	21(34.4)	40(65.6)		15(34.5)	28(65.1)	
Leukocytosis	Yes	2(50)	2(50)	0.576	5(22.7)	17(77.3)	0.947
	No	22(36.1)	39(63.9)		16(37.2)	27(62.8)	
Thrombocytopenia	Yes	4(100)	0	0.009*	12(54.5)	10(45.5)	0.057
	No	21(34.4)	40(65.6)		13(30.2)	30(69.8)	
Na	Yes	1(25)	3(75)	0.796	3(13.6)	19(86.4)	0.264
	No	12(19.7)	49(80.3)		10(23.3)	33(76.7)	
K	Yes	0	4(100)	0.510*	3(13.6)	19(86.4)	0.978
	No	6(9.8)	55(90.2)		4(9.3)	39(90.7)	
CRP	Yes	2(50)	2(50)	0.773	13(59.1)	9(40.9)	0.062
	No	26(42.6)	35(57.4)		15(34.9)	28(65.1)	
LDH	Yes	2(50)	2(50)	0.303	7(31.8)	15(68.2)	0.595
	No	16(26.2)	45(73.8)		11(25.6)	32(74.7)	
ALT	Yes	0	4(100)	0.379*	4(18.2)	18(81.8)	0.655
	No	10(16.4)	51(83.6)		6(14)	37(86)	
ALP	Yes	0	4(100)	0.302*	1(25)	3(75)	0.693*
	No	13(21.3)	48(78.8)		5(8.2)	56(91.8)	
AST	Yes	0	4(100)	0.379*	4(18.2)	18(81.8)	0.655
	No	10(16.4)	51(83.6)		6(14)	37(86)	
UTI	Yes	2(50)	2(50)	0.061	8(36.4)	14(63.6)	0.001
	No	9(14.8)	52(85.2)		3(7)	40(93)	

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Abbreviations: Ig: Immunoglobulin; Na: Sodium; K: Potassium; CRP: C-reactive protein; LDH: Lactate dehydrogenase; ALT: Alanine transaminase; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; UTI: Urinary tract infection.

*Fisher's exact test.

cytopenia, indicating a relationship between acute viral disease and thrombocytopenia. Also, a significant correlation was found with IgG Ab, confirming the secondary bacterial infection caused by the suppression of the patient's immune system following SARS-COV-2 disease.

In examining the symptoms of the studied patients, a significant relationship was found between diarrhea and abdominal pain with IgG antibodies, confirming the relationship between digestive system involvement and SARS-COV-2 disease. During the study, two patients

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Table 4. Examining the relationship between serology findings and imaging findings in patients with COVID-19

Variables		No. (%)		P*
		Imaging		
		Positive	Negative	
IgM	Positive	4(6.2)	0	0.23
	Negative	45(69.2)	16(24.6)	
IgG	Positive	21(32.3)	1(1.5)	0.006
	Negative	28(43.1)	15(23.1)	

Ig: Immunoglobulin.

*Fisher's exact test.

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with complications of COVID-19 died, while four patients with MISC involvement due to severe complications of SARS-COV-2 were admitted to the intensive care unit. In all of them except for one, IgG antibodies were reported positive. Furthermore, IgM antibody-positive patients were reported, indicating the relationship of severe disease and multi-organ involvement in SARS-COV-2 with IgG antibodies. Additionally, the study showed that a high percentage of seronegative patients have lymphopenia, which can be a factor in reducing antibody production. In summary, PCR-negative patients may present with a severe inflammatory syndrome, the cause of which can only be determined by an antibody test.

The significance of this case is that serology was not effective for diagnosis in the past and was only utilized in epidemiology. This issue is crucial as it highlights the need for improved diagnostic measures. The value of serology has now increased in identifying and comprehending infections caused by SARS-CoV-2. The full results were not provided and another attempt is being made. In connection with the studies conducted in this field, the study conducted by Perez-Toledo et al. [20] aimed to determine the serology of SARS-CoV-2 infection in PCR-negative children presenting with the pediatric multisystem inflammatory syndrome. The study confirmed that strong IgG antibody responses can be detected in these patients. It was also observed that the low rate of IgM detection in these patients is consistent with an infection that occurred weeks earlier, and the onset of the syndrome occurs well after the SARS-CoV-2 viral load has been controlled.

Conclusion

The results showed that the serological findings of these patients can facilitate the diagnosis of COVID-19 in children. Considering that early diagnosis of SARS-CoV-2 disease is vital to prevent the spread of the disease and its complications, the PCR test has a high number of false negative cases, and in some cases, it may be able to detect carriers and early stages of the disease. In comparison, serology tests are cost-effective and provide the possibility of diagnostic results in less time. Additionally, considering the importance of serology tests in evaluating disease prevalence and cumulative incidence, research statistics, and epidemiology, they are recommended to diagnose and evaluate patients.

Ethical Considerations

Compliance with ethical guidelines

This study has been approved by the Ethics Committee of the Qom University of Medical Sciences (Code: IR.MUQ.REC.1399.146).

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Authors' contributions

All authors participated equally in the design, execution, and writing of all parts of this research.

Conflict of interest

The authors declared no conflict of interest.

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