

# Evaluation of Severity, Prevalence, and Complications of COVID-19 among Celiac Patients over the Age of 20 in Sistan Region, Iran

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## Abstract

**Introduction:** COVID-19 is an epidemic viral infection that has especially caused great concern for those with chronic diseases. Few studies have been conducted in Asian countries on the prevalence and severity of COVID-19 complications among celiac patients. This study aimed to determine the frequency, severity, and prevalence of COVID-19 complications among celiac patients in Sistan region.

**Methods:** In this descriptive cross-sectional study, a total of 200 patients including 40 celiac patients and 160 matched controls were studied from September to October 2021. All celiac patients in our registry were contacted and a detailed questionnaire was administered to collect required data. In addition, polymerase chain reaction (PCR) was performed on patients to detect COVID-19. Recorded variables were compared between celiac patients and controls using *t*-test and Chi-square test. Statistical analysis was carried out using Stata 14 software.

**Results:** Out of 200 patients, 25% of celiac patients and 18.13% of controls were infected with COVID-19. Additionally, 60% of COVID-19 infected celiac patients had severe gastrointestinal symptoms and none were hospitalized, while 31% of COVID-19 infected controls had gastrointestinal symptoms and 3.45% were hospitalized. The frequency of Marsh score above 2 was significantly lower among COVID-19 infected celiac patients compared with uninfected celiac patients.

**Conclusion:** The presence of celiac disease posed no additional risk for COVID-19 infection in terms of prevalence and frequency. However, in comparison to the general population, celiac patients experienced more severe gastrointestinal complications when infected with COVID-19.

**Keywords:** Celiac disease, COVID-19, Epidemiology, Gastrointestinal symptoms, Pandemic

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## Introduction

COVID-19, caused by SARS-CoV-2, has become a worldwide health problem.<sup>1</sup> This condition is known to be symptomatically similar to Middle East respiratory syndrome (MERS). Coronavirus is a spherical particle. This virus has a single-stranded positive RNA genome.<sup>2</sup> Respiratory distress symptoms are the most common symptoms of COVID-19. In addition to respiratory symptoms, various organs could get involved including the gastrointestinal tract, nervous system, skin, olfactory system, cardiovascular system, liver, kidneys, and eyes during COVID-19 infection. Extrapulmonary complications include common gastrointestinal symptoms such as diarrhea, nausea and vomiting, elevated liver enzyme levels, neurological complications, decreased

level of consciousness, and loss of sense of smell and taste.<sup>3</sup> It now appears that during COVID-19 infection, gastrointestinal symptoms are associated with increased respiratory complications. According to a study, about 20% of patients with COVID-19 infection can experience gastrointestinal symptoms, and preliminary studies show that gastrointestinal symptoms often appear during the early stages of COVID-19 infection; however, more research is required to confirm this finding.<sup>4</sup> According to the latest studies, 53% of patients who were hospitalized due to infection with COVID-19 experienced at least one type of gastrointestinal complication during their illness. There is growing evidence that people who experience gastrointestinal complications during COVID-19 infection or have a history of gastrointestinal disease are at



greater risk for a worse outcome in COVID-19 infection. Infection with COVID-19 may also damage the intestinal tissue or reduce bowel movements.

In fact, celiac disease is one of the most common diseases worldwide, whose prevalence is increasing. So far, the only accepted treatment for celiac disease seems to be the lifelong elimination of gluten from the diet which leads to complete clinical improvement in symptoms and related complications. The presence of HLA-DQ8 and HLA-DQ2 alleles is an important genetic factor in this disease and plays a vital role in its pathogenesis.<sup>5</sup> The *cxcl10* and *cxcl11* chemokines are the main determinants of innate immune responses in celiac patients.<sup>6</sup> Gastrointestinal side effects may also be the result of destruction or damage caused by COVID-19 infection. Some studies suggest that this infection can alter the gut microbiota. Because celiac patients suffer from intestinal complications, the most common gastrointestinal symptoms among them are diarrhea, nausea, vomiting, bloating, and heartburn. These symptoms may be more severe among celiac patients with COVID-19 infection. Researchers have also found that the presence of underlying diseases in patients can pose an additional risk for COVID-19 infection.<sup>7</sup> In particular, celiac patients are more likely to contract infectious diseases such as SARS and the flu; therefore, they may be at higher risk for COVID-19 than the general population.<sup>8</sup> Despite current treatments for COVID-19 infection, one of the best fundamental ways to prevent contracting the infection is to follow health protocols. Considering the availability of vaccines against this virus, vaccination is among the best prevention and control measures in the community. However, some patients with chronic diseases, such as celiac disease, have reservations about the safety and efficacy of available vaccines. They are concerned about potential side effects; therefore, they have uncertainties about getting vaccinated.<sup>9</sup> As a result, by obtaining information from these patients, we can determine the number of vaccinated patients and collect data on the complications they faced after receiving the COVID-19 vaccine.

Therefore, we based our study on celiac patients as celiac disease is a chronic autoimmune disorder that causes inflammation of the small intestine due to the activation of T cells in the immune system in genetically predisposed individuals because of hypersensitivity to gluten (a protein found in wheat and barley) and it damages the gastrointestinal villi during its course.<sup>5</sup> The purpose of this study was to better understand how to monitor, treat, and prevent COVID-19 infection in celiac patients as well as the side effects of the COVID-19 vaccines.

## Materials and Methods

In this cross-sectional descriptive study, 200 people including 40 patients with celiac disease and 160 control peers over 20 years of age were included. In other words,

for each celiac patient, 4 non-celiac patients of the same gender and age were selected. The control group in Sistan region was investigated by census method. The data collection was conducted as follows. In September 2021, all celiac patients in our registry were contacted. Required information for them was recorded using a detailed questionnaire and informed consent was obtained from all participants. All 40 celiac patients were diagnosed based on pathological and endoscopic examinations. These individuals underwent polymerase chain reaction (PCR) for COVID-19 diagnosis, except for those with obvious COVID-19 symptoms or positive diagnostic test results. For each celiac patient with or without COVID-19 infection in our study group, the information of at least four other similar patients in terms of age, sex, and area of residence (city or village) was randomly obtained from the University Health Department. These people were selected as controls and among celiac patients, individuals who reported having COVID-19 around the same date were selected as COVID-19 infected celiac patients. After collecting the required information, a comparison of quantitative and qualitative variables between celiac patients and the control group was performed using an independent *t* test and chi-square test. Statistical analysis was carried out using Stata 14 software. In this study, we used the following procedures.

First, we ran a comparison between celiac patients with and without COVID-19 infection to determine if COVID-19 infection could cause more severe celiac complications. Moreover, we investigated the characteristics of celiac disease which seemed to pose additional risk for COVID-19 infection (such as the degree of intestinal involvement in biopsy, comorbid disease, etc).

Second, we ran a comparison between COVID-19 infected patients with and without celiac disease in terms of the severity of COVID-19 symptoms and the frequency of gastrointestinal symptoms to determine if celiac disease could increase the severity and the frequency of COVID-19 symptoms.

Finally, we compared the prevalence of severe COVID-19 infection between celiac patients and the general population in Sistan region (population of areas from which COVID-19 patients were selected).

## Results

In this study, a total of 200 people including 40 celiac patients (35 women and 5 men) and 160 matched controls were studied. Besides, 20 patients (10%) were male and the rest were female. The mean ( $\pm$  SD) age of patients was  $36 \pm 11.9$  years. The youngest and oldest patients were 20 and 80 years old, respectively. The severity of celiac disease in patients is described in Table 1.

Dr. Michael Marsh introduced a classification system in 1992 to describe the stages of microscopic damage to the

small intestine, also known as histological changes, seen in people with celiac disease. The types of Marsh range from 0 to 4. Due to these diverse effects, Marsh's classification generally includes the stages through which a natural mucus (Marsh 0) is transformed into a more evolved level (Marsh I, II, III).<sup>10</sup> Duodenal biopsy is considered the gold standard for the diagnosis of celiac disease, which indicates the increase of intraepithelial T lymphocytes, crypt hyperplasia, and atrophy of celiac disease (Type 3 indicates celiac disease).<sup>11</sup> Table 2 presents the severity of celiac disease in the examined celiac patients based on Marsh's classification.

Table 3 compares the two groups of celiac and non-celiac patients in terms of clinical characteristics. As demonstrated, the two groups were not significantly different in terms of demographic variables, vaccination

**Table 1.** The Distribution of Celiac Disease by Gender

Participants	Number	Percent	Sex	Number	Percent
Controls	160	80.00	Male	20	10.00
Celiac patients	40	20.00	Female	180	90.00
Total	200	100.00	Total	200	100.00

**Table 2.** Severity of Celiac Disease in the Studied Patients (Based on Marsh's Classification)

Celiac stage/type	Number	Percent
I	8	20
II	17	42.5
IIIa	4	10
IIIb	5	12.5
IIIc	6	15

**Table 3.** Comparison of Study Groups in Terms of Demographic and Clinical Characteristics

Characteristics			Controls (n=160)	Celiac Patients (n=40)	P Value
Gender	Male	No	16	4	>0.99
		%	10	10	
	Female	No	144	36	
		%	90	90	
Location of residence	City	No	84	21	>0.99
		%	52.5	52.5	
	Village	No	76	19	
		%	47.5	47.5	
Vaccination history of two doses	No	No	75	13	0.089
		%	47.47	32.5	
	Yes	No	83	27	
		%	52.53	67.5	
Underlying disease	No	No	154	36	0.105
		%	96.25	90	
	Yes	No	6	4	
		%	3.75	10	
Age		Mean (SD)	36 (11.92)	36 (12.03)	>0.99

history, and underlying disease.

As Table 4 shows, PCR test results showed that 25% of the patients with celiac disease (10 patients) were infected with COVID-19. However, 18.13% of controls (29 people) had positive COVID-19 test results. The difference between the two groups was not statistically significant in terms of the incidence of COVID-19 ( $P=0.326$ ).

The evaluation of the severity of COVID-19 infection between the two groups of celiac patients and controls with COVID-19 infection showed that 60% of celiac patients had gastrointestinal complications, while the frequency of gastrointestinal symptoms among controls with COVID-19 infection was 31%. However, this difference was not statistically significant ( $P=0.104$ ).

The mean PO2 values in celiac and control patients were 92% and 94.1%, respectively, but this difference was not statistically significant ( $P=0.112$ ).

Regarding the hospitalization of patients following infection with COVID-19, 3.45% of controls were hospitalized after becoming infected with COVID-19, but none of the COVID-19 infected celiac patients were hospitalized. However, the difference between the two groups was not statistically significant ( $P=0.552$ ).

Finally, no COVID-19-related deaths were observed in either celiac patients or the control group.

The comparison of the characteristics between patients with and without COVID-19 infection demonstrated that the two groups were not different in terms of gender and place of residence (Table 5). However, the frequency of Marsh score above 2 among celiac patients with COVID-19 infection was significantly lower compared with uninfected celiac patients ( $P=0.006$ ).

**Table 4.** Comparison of Different Outcomes Between Celiac Patients and Controls

Characteristics		Controls (n=160)	Celiac Patients (n=40)	P Value
COVID-19 infection	Number	29	10	0.326
	%	18.13	25	
Gastrointestinal symptoms following COVID-19 infection	Number	9	6	0.104
	%	31.03	60	
Hospitalization due to COVID-19 infection	Number	1	0	0.552
	%	3.45	0	
COVID-19 fatalities	Number%	0	0	-
PO2 following COVID-19 infection	Mean (SD)	94.10 (3.70)	92 (3.68)	0.112

**Table 5.** Comparison of the Characteristics of Patients with and without COVID-19 Infection

Characteristics of Celiac Patients		Status of COVID-19 Among Celiac Patients		P Value
		Negative PCR Result	Positive PCR Result	
Marsh score	<3	15 (50)	10 (100)	0.006
	≥3	15 (50)	0	
Gender	Male	3 (10)	1 (10)	>0.99
	Female	27 (90)	9 (90)	
Place of residence	City	16 (53.33)	5 (50)	0.855
	Village	14 (46.67)	5 (50)	

## Discussion

This is the first study that has been conducted on celiac patients infected with COVID-19 in Sistan region. Considering the severity, prevalence, and complications of COVID-19 infection, a comparison was made between the data of the general population and celiac patients. In this case, we found that the prevalence of COVID-19 infection was not higher among celiac patients than among the general population. In addition, we examined the frequency of various outcomes of COVID-19 infection (hospitalization, length of hospital stay, death, intensive care, and intubation) among patients with celiac disease and found that none of them were hospitalized. Their condition had improved with medicine, care, and home quarantine. In this regard, Rathore et al reached similar results. They said that SARS-CoV-2 infection in patients with celiac disease is not associated with an increased risk of hospitalization or mortality.<sup>12</sup> Additionally, the frequencies of symptoms and outcomes of COVID-19 infection were compared between patients with and without celiac disease. Frailty was more common in COVID-19 infected celiac patients, perhaps due to anorexia and nutritional restrictions. COVID-19 infection affects the gastrointestinal tract of celiac patients more than the general population. Abdominal bloating, diarrhea, vomiting, and nausea were more common in celiac patients than in the normal population. However, symptoms including fever, cough, sore throat, shortness

of breath, respiratory complications, blood oxygen levels, and body pain were almost identical between patients with and without CD. Gokden et al also found in their study that the risk of COVID-19 in patients with CD was not higher compared to other people who were on a gluten-free diet, and both groups with COVID-19 had a similar clinical course.<sup>13</sup>

In a similar study conducted in Sweden by Lebwohl et al, the severity of complications of COVID-19 among celiac patients was assessed during the first 6 months of the COVID-19 pandemic in 2019. Based on the results, the prevalence of COVID-19 infection was low and the severity of its subsequent complications was not increased in COVID-19 infected celiac patients.<sup>14</sup> In 2021, Lionetti et al investigated the prevalence and severity of COVID-19 infection among children (<16 years) with celiac disease in Italy and concluded that no children with celiac disease were infected with COVID-19. In fact, the prevalence of COVID-19 infection was not significantly higher among these individuals.<sup>15</sup> In another study conducted by Zhen et al in 2020, celiac patients from several different countries were electronically enrolled in the study, and the prevalence of COVID-19 infection among these patients was investigated. It was concluded that celiac patients performed less diagnostic tests for COVID-19 infection. Therefore, they were less symptomatic mainly because they were less exposed to COVID-19 infection due to preventive care and precautions.<sup>16</sup> Moreover, in our study,



we examined the number of patients who were vaccinated against COVID-19 infection, the type of vaccines they received, and the complications they had after vaccination. Finally, we compared these complications between celiac patients and the control group. According to our findings, by the end of our study, more than 88 subjects in the control group had received their first dose of vaccine. Among the control group, 28 people had previously been infected with COVID-19, and of these patients, 20 people had received COVID-19 vaccine after being infected with COVID-19. Furthermore, celiac patients seem to have responded well to COVID-19 vaccines. Out of 40 patients, about 27 celiac patients had received 2 doses of vaccination. Most of them, about 22 patients, had received the Sinopharm vaccine, while 1 patient received AstraZeneca, 2 patients received Sputnik vaccine, and 1 patient received COVIran Barekat vaccine. Of the 160 subjects in the control group, 83 had received 2 doses of the vaccine, and of the 8 COVID-19 infected celiac patients, 1 patient had received the first dose of the vaccine prior to infection. In the case of the control group, 3 people with COVID-19 were infected after receiving their first dose of the vaccine. Some people did not experience any significant side effects after receiving the vaccine. However, in some cases, fever, body pain, weakness, sore throat, cough, and diarrhea have been reported. These complications do not seem to be more severe in celiac patients compared to the control group. A total of 14 patients had refused to be vaccinated against COVID-19 infection due to their severe general condition, fear of disease exacerbation, fear of the vaccine itself, and risk of contracting COVID-19 at the time of vaccination. In a study conducted in Italy in 2021, Costantino et al investigated the reasons for skepticism about vaccination against COVID-19 infection in celiac patients and sent anonymous questionnaires to patients. They concluded that special campaigns should be launched to resolve patients' doubts and concerns about vaccination.<sup>17</sup>

## Conclusion

According to our findings, the prevalence and severity of COVID-19 infection among celiac patients were not higher in comparison to COVID-19 infected patients without celiac disease of the same age and gender. This could be explained by the fact that patients followed health protocols and refused to be in the community due to their underlying diseases and fear of COVID-19 infection and its complications. However, patients must be informed that the most efficient way to control the COVID-19 outbreak is through vaccination.

## Authors' Contribution

**Conceptualization:** Iraj Shahramian, Mahdie Arefi.

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**Formal analysis:** Mahdie Arefi, Masoud Tahani.

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## Competing Interests

None.

## Ethical Approval

This study was approved by the Ethics Committee of Zabol University of Medical Sciences (IR.ZBMU.REC.1400.107).

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