Research in Molecular Medicine

Evaluating COVID-19 Vaccine Side Effects in Patients With Inflammatory Bowel Disease: A Case-control Study in Iran

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Citation Tamizifar B, Kassaian N, Rahim khorasani M, Sabzali S, Shahzamani K, Adibi P. Evaluating COVID-19 Vaccine Side Effects in Patients With Inflammatory Bowel Disease: A Case-control Study in Iran. Research in Molecular Medicine. 2024; 12(1):39-48. https://doi.org/10.32598/rmm.11.4.1374.1

https://doi.org/10.32598/rmm.11.4.1374.1

Article Type:
Research Paper

Article info:
Received: 25 Sep 2023
Revised: 05 Oct 2023
Accepted: 26 Dec 2023

Keywords:
COVID-19, Vaccine, Inflammatory bowel disease (IBD), Ulcerative colitis (UC), Crohn's disease (CD)

ABSTRACT

Background: The COVID-19 pandemic has presented unique challenges for individuals with inflammatory bowel disease (IBD), a group already at increased risk due to altered immune function and immunosuppressive treatments. While vaccines remain the most effective tool for controlling the pandemic, concerns about their safety and potential to worsen IBD symptoms have led to hesitancy among patients. This study explored the side effects of COVID-19 vaccines in IBD patients compared to healthy individuals.

Materials and Methods: This case-control study was conducted in Isfahan, Iran, from September to December 2021. The study involved 86 IBD patients and 91 healthy participants who had received at least one dose of a COVID-19 vaccine. Information about vaccine-related side effects was gathered through interviews, and statistical methods were used to identify any significant differences between the two groups.

Results: The findings showed that vaccine side effects were mild and temporary in both groups, with no significant differences in overall frequency (70% in IBD patients vs 67% in healthy controls). Common side effects included localized pain, fatigue, headaches, and fever, all of which resolved quickly. Notably, no IBD patients reported a flare of their condition after vaccination. Despite this, fewer IBD patients opted for second or third doses, likely due to lingering concerns about adverse effects.

Conclusion: COVID-19 vaccination is safe for IBD patients, with side effects similar to or less frequent than those seen in the general population. Clear communication and targeted strategies are needed to alleviate vaccine hesitancy in this vulnerable group.

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Introduction

The new coronavirus, called SARS-CoV-2, which has created a global health emergency named COVID-19 since December 2019, has posed thought-provoking challenges to health systems and physicians [1, 2]. COVID-19 is a contagious disease that has caused numerous deaths worldwide and is known as a pandemic disease [3]. The risk of developing COVID-19 is particularly concerning in immunocompromised patients, such as those with inflammatory bowel disease (IBD) [4].

IBD, comprising Crohn's disease (CD) and ulcerative colitis (UC), is a state of altered immune function due to the underlying disease and the immune-modifying therapies. Thus, every infection may cause concern among gastroenterologists for patients who are affected by IBD, and patients with IBD may experience worse outcomes in the event of a COVID-19 infection [5]. Nowadays, vaccination against SARS-CoV-2 has been the key strategy for the control of global COVID-19 infection and its adverse outcomes, especially in high-risk individuals, such as those with pre-existing health conditions [6]. However, there is considerable concern about vaccination among patients and healthcare providers regarding immune-mediated inflammatory diseases, including IBD [7]. It has been found that the most common reasons that people do not get vaccines are a lack of understanding of the beneficial effects, concerns about side effects, the onset or flare-up of the disease, or even fear of pain and needles [8]. On the other hand, the efficacy and immunogenicity of vaccination may be altered in IBD patients due to the immune system deficiency or the use of immunosuppressive drugs prescribed to these patients, which may also affect booster doses [9].

There is infrequent and insufficient data about the effects and adverse effects of vaccination against COVID-19 in IBD patients [10]. Hence, this study was designed to investigate the frequency of adverse effects from receiving the COVID-19 vaccine in IBD patients in comparison with the healthy control group in Isfahan, Iran.

Materials and Methods

This is a case-control study among patients with IBD and healthy subjects who received any COVID-19 vaccine granted emergency use authorization in Iran. The IBD patients were recruited from the IBD registry of Isfahan Gastroenterology and Hepatology Research Center. The control group was healthy volunteers matched in age and sex with the case group, without any chronic diseases. The eligibility criteria were receiving one or more doses of any COVID-19 vaccine within the prior three months, the age of more than 18 years, and willingness to participate in the study.

Adverse events of COVID-19 vaccination were gathered through making phone calls or in-person interviews by a trained person from September to December 2021. We employed a comprehensive approach for adverse event data collection, combining both self-reporting and clinical assessments to ensure thorough safety monitoring.

Self-reporting: Patients were provided with standardized questionnaires post-vaccination to capture both local and systemic reactions. These questionnaires documented local reactions (pain, redness, and swelling at the injection site) and systemic reactions (fatigue, headache, myalgia, arthralgia, chills, and fever). To further enhance reporting, patients had access to a dedicated reporting portal, allowing them to document any adverse events occurring between scheduled assessments. This allowed for the capture of patient-perceived adverse effects, including subjective symptoms not always apparent during clinical visits.

Clinical assessments: All participants underwent scheduled clinical evaluations at baseline (pre-vaccination) and at two and four-week follow-up appointments. These assessments included physical examinations and vital signs. For patients reporting moderate to severe adverse events, additional unscheduled clinical assessments were conducted to rigorously evaluate symptoms and determine potential correlation with vaccination. These clinical assessments were crucial for identifying and diagnosing adverse events that may not have been self-reported or that were clinically significant.

Extended monitoring timeline: Beyond the initial 28-day post-vaccination period, all participants were systematically followed for six months after their final vaccine dose. This extended surveillance allowed us to capture any delayed-onset adverse effects that might not manifest in the immediate post-vaccination period and to assess the longer-term trajectory of the immune response.

Clinical evaluation and IBD flare assessment: Participants underwent clinical assessments at each follow-up visit, which included physical examinations, IBD activity scoring (Crohn's disease activity index (CDAI)/mayo scores), and quality of life measures to assess any potential impact of vaccination on the disease course. Special attention was paid to documenting any IBD flares during the follow-up period, with careful analysis to determine potential temporal relationships to vaccination.

To ensure consistent and objective evaluation, all adverse events were graded according to the common terminology criteria for adverse events (CTCAE 5.0) and assessed for causality by an independent safety monitoring committee comprising gastroenterologists and immunologists not involved in the primary study. This multi-faceted approach allowed us to capture a holistic view of the adverse effects associated with vaccination in IBD patients, leveraging the strengths of both patient-reported outcomes and objective clinical findings.

Statistical analysis

Descriptive statistics were performed to characterize the study population, including age, gender, vaccine type, medication use, disease stage, and previous COVID-19 infection, and their correlations with adverse effects were analyzed. Chi-square, t-test, and logistic regression tests were used to compare variables between the case and control groups and to examine the relationship between disease-related characteristics and the onset of adverse effects. The SPSS software, version 20.0 (IBM, Chicago, IL, USA) was used for data analysis, and a $P<0.05$ was considered significant.

Results

In September-December 2021, 86 patients with IBD (44 females and 42 males, mean age: 42±3.5 years) and 91 healthy individuals without any chronic diseases (54 females and 37 males, mean age: 44.8±4.3 years) participated in the study (Table 1). The IBD patients included 69 patients with UC and 17 patients with CD. Additionally, 34% of the IBD patients were undergoing biological therapy (28%) or immunomodulatory therapy (6%), while 63 IBD patients (76%) were on 5-ASA and 6 patients (7%) were on steroid therapies. A history of flare, hospitalization, and surgery was reported in 63, 19, and 3 UC patients, and in 16, 6, and 2 CD patients, respectively.

The study population's past medical history revealed that 41 healthy individuals, 32 patients with UC, and eight patients with CD had previously been infected with the SARS-CoV-2 virus. Of all subjects, 177 cases (100%) had received their first dose of the COVID-19 vaccine, while 133 subjects (75%) had received both doses, and three subjects (1.7%) had received the third shot. The prevalence of receiving the second and third doses of vaccination was significantly higher in healthy participants than in IBD patients (P=0.01). The type of vaccines received by the three groups is shown in Table 2. Sinopharm was the most common vaccine in IBD patients (84%).

Table 1. The demographic characteristics of patients with IBD and healthy controls

Variables	IBD Patients (n=86)	Healthy Controls (n=91)	P
Age (y) Mean±SD	42.1±3.5	44.8±4.3	0.20
Gender(female/male)	44/42	54/37	0.17

Table 2. The Frequency of vaccine types received by healthy participants and patients with IBD

Type of Vaccine	No. (%)	
	Healthy	IBD
Pfizer	2(2)	1(1.1)
Moderna	3(3.2)	0
Sputnik V	10(11)	2(2.3)
AstraZeneca	24(26.4)	7(8.1)
Barekat	9(9.8)	3(3.5)
Sinopharm	41(45)	72(84)
Bharat Biotech	1(1)	1(1.2)

Of the 177 participants, 122(69%) reported experiencing adverse effects after receiving their vaccine. There was no difference in the presence of side effects following the first, second, or third dose of the vaccine (73%, 67%, and 66%, respectively; P=0.8), nor was there a difference between patients and healthy subjects (70% vs 67%, respectively; P=0.62).

The reported adverse effects by the participants are demonstrated in Table 3. No one reported flares of the underlying IBD after vaccination, and there was no relationship between the medications used by the IBD patients and the adverse effects (P=0.9). To assess the relationship between immunosuppressive medications and reported adverse effects, we employed a comprehensive approach:

Detailed medication documentation and stratification: We collected detailed information on all immunosuppressive medications at baseline, including drug name, class, dosage, duration of therapy, and timing of the last dose relative to vaccination. This information was obtained through patient medical records, self-reported medication histories, and, where necessary, verification by treating physicians. Patients were then stratified into distinct categories based on their medication regimen: biologic monotherapy (anti-TNF, anti-integrin, and anti-IL12/23), immunomodulator monotherapy (thiopurines and methotrexate), combination therapy, corticosteroids, and no immunosuppression. This stratification allowed us to compare side effect profiles across different medication classes.

Temporal analysis: We implemented a time-dependent analysis approach, accounting for medication changes during the study period. This included documenting any dose modifications or treatment interruptions that occurred between vaccination doses or during the follow-up period. This allowed us to assess whether changes in medication status impacted the occurrence or severity of adverse events.

Correlation with side effects: The occurrence and severity of side effects were analyzed in relation to the use of immunosuppressive medications. Statistical models (e.g. logistic regression) were used to assess whether specific medications or medication classes were associated with an increase or decrease in the risk of certain adverse effects. Special attention was given to both systemic side effects (e.g. fever, fatigue) and local reactions (e.g. injection site pain), as these could potentially be influenced by the patient's immune status.

Table 3. The reported adverse effects in patients and healthy subjects

Adverse Effects	No. (%)			
	Healthy Controls (n=91)	IBD Patients		
		Total (n=86)	UC (n=69)	CD (n=17)
Injection site pain	47(51)	40(46)	31(45)	9(53)
Injection site itching	2(2.2)	2(2.3)	2(2.8)	0
Injection site swelling	7(7.7)	0*	0*	0*
Fast heartbeat	2(2.2)	3(3.5)	2(2.8)	1(5.8)
Dyspnea	2(2.2)	2(2.3)	1(1.4)	1(5.8)
Rash & urticaria	1(1.1)	2(2.3)	2(2.8)	0
Eye burning	5(5.5)	2(2.3)	2(2.8)	0
Body pain	27(29.7)	21(24.4)	19(27.5)	2(11.7)
Myalgia	18(19.8)	6(7)*	5(7.2)*	1(5.8)*
Bone pain	7(7.7)	5(5.8)	4(5.8)	1(5.8)
Arthralgia	8(8.8)	4(4.6)	2(2.8)	2(11.7)
Back pain	13(14)	10(11.6)	9(13)	1(5.8)

Adverse Effects	No. (%)			
	Healthy Controls (n=91)	IBD Patients		
		Total (n=86)	UC (n=69)	CD (n=17)
Flu-like symptoms	16(17.6)	5(5.8)*	4(5.8)*	1(5.8)*
Headache	36(39.5)	20(23)*	18(26)*	2(11.7)*
Fever	30(33)	15(17.4)*	12(17.4)*	3(17.6)*
Coryza	0	3(3.5)	2(2.8)	1(5.8)
Sore-throat	1(1.1)	5(5.8)	4(5.8)	1(5.8)
Pneumonia	0	1(1.2)	0	1(5.8)
Fatigue	36(39.5)	31(36)	27(39)	4(23.5)
Vertigo	10(11)	10(11.6)	8(11.6)	2(11.7)
Somnolence	22(24.2)	20(23)	18(26)	2(11.7)
Vomiting	7(7.7)	6(7)	4(5.8)	2(11.7)
Tenesmus	6(6.6)	0*	0*	0*
Diarrhea	6(6.6)	3(3.5)	3(4.3)	0
Anorexia	6(6.6)	4(4.6)	3(4.3)	1(5.8)
Hypertension	1(1.1)	2(2.3)	2(2.8)	0
Blurred vision	0	2(2.3)	2(2.8)	0
Urinary incontinence	0	1(1.2)	1(1.4)	0

*Data with significant difference

Propensity score matching: To minimize selection bias and address the non-random assignment of treatments in this observational study, we used propensity score matching when comparing adverse events between different medication groups. This technique allowed us to create more comparable groups, reducing the potential for confounding factors to influence our results.

Adjustment for confounding factors: To further isolate the effect of immunosuppressive medications, our analyses adjusted for potential confounding factors, such as age, disease activity, comorbidities, and type of COVID-19 vaccine received.

Consideration of immunogenicity: While the primary focus of this study was on side effects, the potential impact of immunosuppressive medications on vaccine immunogenicity was also considered. For instance, patients on certain medications (e.g. anti-TNF agents) might exhibit a blunted immune response, which could indirectly influence the frequency or severity of side effects.

Local pain at the site of injection, fatigue, headache, and fever were the most common adverse effects in both IBD and healthy groups. The adverse effects were reported to be mild and lasted only a few days. Among the adverse effects of COVID-19 vaccination, the prevalence of injection site swelling, myalgia, flu-like symptoms, headache, fever, and tenesmus was significantly higher in the healthy group compared to patients with IBD. The most common side effects of the four common types of vaccines in healthy/patient groups are shown in Figure 1. The adverse effects were not associated with a previous history of COVID-19 infection, flare, hospitalization, and underlying diseases in our subjects (Table 4).

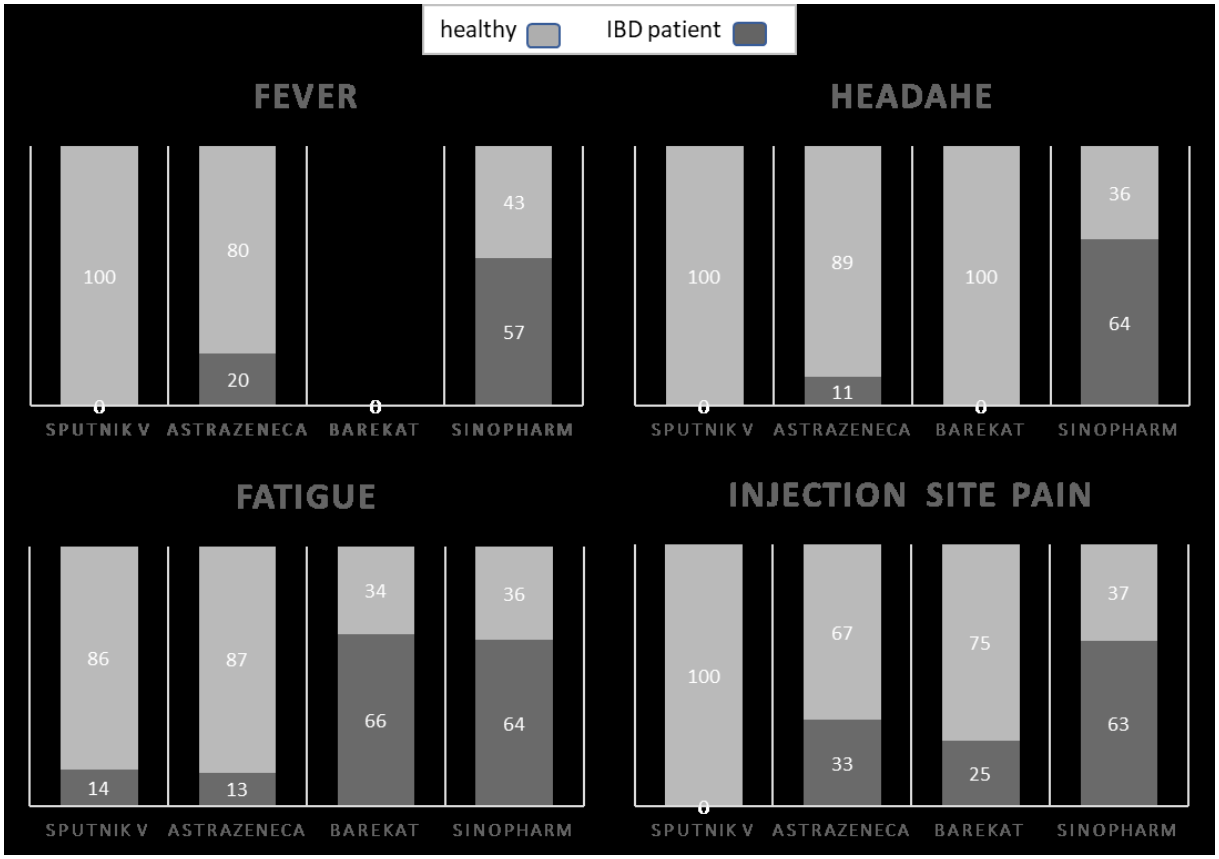

Figure 1. The cumulative percentage of the most common adverse effects based on four types of vaccines in patients with IBD and healthy subjects

*P<0.05: significant difference between patients with IBD and healthy controls derived from the Fisher's exact test was shown with *.

Discussion

There is initial concern regarding the potential for severe infections in IBD patients. Hence, vaccination against SARS-COV-2 has been authorized for emergency use in these patients. However, patients with IBD are hesitant to receive the vaccine due to insufficient data on efficacy or adverse effects. This case-control study was conducted to assess the side effects of vaccination against COVID-19 in IBD patients in comparison with healthy subjects.

In this study, the receipt of the second and third doses of COVID-19 vaccines was significantly lower in IBD patients than in healthy individuals, which may be attributed to concerns regarding adverse effects.

Table 4. The association between vaccine complications and history of flare, hospitalization, COVID-19, and underlying diseases

Factors	Vaccine Side Effects		OR*	95% CI*
	No	Yes		
Flare history	21	57	0.7	0.25-2.3
Hospitalization history	7	18	1.6	0.5-5.4
COVID-19 history	25	55	1.1	0.56-2.16
Underlying disease	9	25	0.7	0.3-1.7

*Derived from binary regression.

However, this study demonstrated that patients with IBD develop COVID-19 vaccination adverse effects at even lower rates than the healthy population. This result is comparable to other studies. The data of more than 40,000 individuals demonstrated that mild local injection site reactions and systemic features were common following SARS-CoV-2 vaccination, with serious adverse events being rare [11]. In Edelman-Klapper et al.'s study, no severe adverse events were reported in IBD patients after mRNA COVID-19 vaccines, and the side effects, which were mainly local pain and headache mostly observed after dose 2 [12].

In Botwin et al.'s study, 39% of IBD patients had side effects after dose one, and 62% after dose two of mRNA vaccines. The most common symptoms were fever/chills, fatigue/malaise, and headache. The symptoms (except for injection site reactions) were resolved in less than two days, and the frequency of side effects was similar to the general population. In this study, the frequency of side effects was associated with the medication used, history of COVID-19, and age [13].

Garrido et al. reported mild and transitory side effects in 56.8% of IBD patients after the first dose and 74.1% after the second dose of vaccination, which were lower than those observed in the general population during the first week after vaccination. The vaccines received included Pfizer-BioNTech (59.0%), Moderna (20.5%), Janssen (14.2%), and AstraZeneca (6.3%) in Portugal. The side effects were not found to be associated with gender, biological medication, vaccine type, or disease [14].

However, Classen et al. found that IBD patients experienced significantly more side effects (muscle pain, pain at the injection site, and fatigue) after the first dose compared to the control group [15].

According to existing studies, the overall risk of exacerbation was reported as 29% in vaccinated IBD patients and 26% in unvaccinated patients; however, the difference was not statistically significant [5]. There is concern that the use of different medications during various stages of the disease in IBD patients may affect their response to and reaction to vaccination against COVID-19. Since there are few studies on this subject, it is not possible to determine whether vaccination affects the severity of IBD activity [16]. However, it is believed that the use of immunosuppressants and disease activity are both implicated in causing lower rates of seroconversion in IBD patients [7]. Therefore, ideally, patients with IBD are recommended to be in a remission phase and, if possible, to have their corticosteroid dosage minimized before vaccination. For those with severe IBD flares or who require hospitalization, it is preferable to consider a short delay until recovery to prevent confusion arising from complications of acute illness that may be mistaken for vaccine-related adverse effects.

Side effects of SARS-CoV-2 vaccines may reflect the transient production of type I interferons, which is an immune reaction to contact with pathogens [18].

It has been found that by producing a neutralizing antibody, vaccine efficacy will be reduced, and side effects will occur. There are limited studies on the efficacy of COVID-19 vaccination in IBD patients focused on the immediate immune response, neutralization activities, and T cell responses. However, IBD patients taking immunosuppressive drugs have a weaker antibody response to SARS-COV-2 infection than IBD patients taking biological drugs [19]. The results of this study may be partly explained by the fact that our subjects with IBD received the most biologic medication.

Although spike protein antibody levels will be higher following mRNA vaccinations [20], Sinopharm, Barekat, AstraZeneca, and Sputnik-V have been mostly used in Iran to control SARS-CoV-2. Sinopharm, an inactivated vaccine, has been the most commonly chosen option among IBD patients in our study. Evidence has shown that the use of inactivated vaccines is generally safe for IBD patients and is not associated with disease flares [9].

In some studies, the various side effects of SARS-CoV-2 vaccination have been reported in associated with the type of vaccine, the frequency of its injection, age, sex, and the presence of underlying diseases [21]. However, these associations were not observed in our study. This may be due to our small sample size.

Despite guidelines recommending a third dose for patients with IBD, fewer IBD patients opted for the third dose compared to controls in this study. According to the Isfahan Irritable Bowel Disease Registry, only 74% of IBD patients have received each COVID-19 vaccine to date. These data are somewhat similar to findings from other studies worldwide.

In a study conducted at the Nancy University Hospital, France, the data from 104 patients with UC or CD were evaluated to identify their intention to receive a COVID-19 vaccine. In this study, although the risk of long-term adverse reaction to the COVID-19 vaccine for IBD patients was not reported, only 50% of patients intended to receive the vaccine [22]. Costantino et al.

reported on COVID-19 vaccine hesitancy and willingness among Italian IBD patients, finding that 20% of IBD patients were hesitant or currently refused vaccination. They noted that the lack of data on long-term safety may contribute to reduced vaccine acceptance [23].

There appears to be a gap between global healthcare providers and patients. Urgent action is needed to provide specific recommendations to address the significant confusion faced by patients with chronic diseases like IBD. Also, to manage IBD patients effectively, it is essential to update gastroenterologists on the efficacy and safety of the SARS-CoV-2 vaccine, enabling them to reduce skepticism [24].

Although other studies have used smaller or approximately the same sample size, we acknowledge that the relatively small sample size of our study (n=100 in each group) may be a limitation that could affect the statistical power of our findings, especially when comparing adverse events between IBD patients and healthy subjects. To address this limitation, we took several steps: we were careful not to overstate our conclusions; we have transparently reported confidence intervals alongside point estimates to reflect the uncertainty in our findings; we acknowledged the limitations of our sample size in the discussion section of the manuscript; and we emphasized the need for larger, multi-center studies to confirm our preliminary findings and to explore potential differences in adverse event profiles across IBD subgroups. Furthermore, in interpreting the results, we focused on effect sizes and clinical significance rather than relying solely on P.

Conclusions

Although diverse effects of COVID-19 vaccination are common, they are generally mild and transient in IBD patients. The side effects of the COVID-19 vaccine in IBD patients are even lower than in the general population. Therefore, patients with IBD, including both UC and CD, should be vaccinated against COVID-19 with minimal concern. Given the additional risk of infections in IBD patients, it is highly recommended to implement strategies that promote an appropriate vaccination schedule for these individuals.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of Isfahan University of Medical Sciences, Isfahan, Iran (Code: IR.MUI.MED.REC.1400.380). Participation in this study was voluntary. Informed consent was obtained by adhering to all ethical guidelines for research studies, including providing complete information, ensuring voluntary participation, and facilitating easy access to researchers for the subjects. Additionally, the collected data were kept confidential.

Funding

The research chancellor of Isfahan University of Medical Sciences supported this project.

Authors contribution's

Study design: Babak Tamizifar, Nazila Kassaian and Peyman Adibi; Writing the original draft: Babak Tamizifar, Nazila Kassaian, Marzieh Rahim khorasani, Somaieh Sabzali and Kiana Shahzamani; Review and editing: Kiana Shahzamani and Peyman Adibi.

Conflict of interest

The authors declared no conflicts of interests.

Acknowledgements

The authors would like to thank the staff of Isfahan Gastroenterology and Hepatology Research Center for supporting this research.

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