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Original Article

Hepatitis B Viral Markers and Immune Status in Patients with Inflammatory Bowel Diseases: A Cross-Sectional Study Using Data Mining Approach

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ABSTRACT

Background:
Patients with inflammatory bowel diseases (IBDs) are at high risk of contracting hepatitis B virus (HBV) or its reactivation due to surgical procedures, blood transfusions, and immunosuppressive therapy. Little is known about the HBV immune status in patients with IBD.

Objective:
We aimed to evaluate the HBV serology of adult patients with IBD in Mashhad, northeastern Iran.
Materials and Methods:
A cross-sectional study was conducted among patients with IBD referred from Mashhad gastrointestinal clinics between June 2021 and August 2022. Demographic and other related data were collected. Hepatitis B surface antigen (HBS-Ag), hepatitis B surface antibody (anti-HBS Ab), and hepatitis B core protein antibody (anti-HBC Ab) were measured. Patients were classified into sub-groups of chronic HBV infection, past HBV infection, effective vaccination, and non-immune against HBV. A decision tree (DT) algorithm was applied to analyze data. Results also were performed using SPSS software version 23.0 at a significant level of 0.05.

Results:
90 patients (30 with Crohn's disease and 60 with ulcerative colitis) with an average age of 40.48±15.1 years were examined. 35.6% were men. The rate of past HBV infection and chronic HBV infection was 4.4% and 1.1%, respectively. Effective vaccination was 31.1%, and non-immunity against HBV was 63.4%. Use of biological agents was significantly higher among subjects with IBDs ≥10 years (P=0.032). The DT model showed that type of therapy, type of disease, and sex have the most effect on effective vaccination development and anti-HBS Ab level.

Conclusion:
We recommend fully vaccinating seronegative patients with IBD before the initiation of immunosuppressive therapy and routinely monitoring anti-HBS Ab levels, especially in patients under combined therapy.

Keywords: Hepatitis B virus, Inflammatory bowel diseases, Ulcerative colitis, Crohn's disease, Decision tree

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INTRODUCTION

Inflammatory bowel diseases (IBDs) are lifelong chronic gastrointestinal conditions of unknown origin, including ulcerative colitis (UC) and Crohn's disease (CD), which affect the gastrointestinal tract (1, 2). Although the exact cause of IBD is still unknown, genetic susceptibility, changes in intestinal microbiota, dysregulated immune system, and environmental factors are all associated with the disease (3). Medications including 5-aminosalicylates, corticosteroids, immunomodulators (including thiopurine, cyclosporine, and methotrexate), and biological agents (including anti-tumor necrosis factor (TNF) and anti-integrin agents) are the cornerstone of treatment of IBD (4). Because of the increase in the use of immunomodulatory and biological agents, especially over the past decade, concerns regarding the safety of these medications are growing globally. One of these issues is related to infectious diseases like hepatitis B virus (HBV) reactivation in patients with chronic HBV infection (5). HBV reactivation in patients receiving biological agents leads to an emerging cause of liver diseases (5). Moreover, patients with IBD are more at risk of contracting HBV due to blood transfusion, and invasive surgical and endoscopic procedures (6). HBV is a very common and important infection worldwide, especially in Asian countries, due to its almost moderate to high prevalence. Its reactivation in patients receiving immunosuppressive therapy, such as patients with IBD has been reported with significant morbidity (including fulminant liver failure) and mortality unless antiviral prophylaxis (6, 7). Patients with IBD with chronic HBV infection used immunosuppressive agents less frequently and had a worse prognosis compared with that of non-infected counterparts (7). Data showed that both hepatitis B vaccination coverage and seroprotection followed by immunization with standard doses of hepatitis B vaccine in patients with IBD are low (8). Many studies from Western countries have reported the prevalence of HBV infection in patients with IBD. However, the current data on this issue in Asia, especially in the Middle East, is limited (1, 9). Thus, the assessment of HBV serological markers is one of the most important quality issues regarding the management of patients with IBD (10). The present study aimed to elucidate the HBV serological markers in patients with IBD.

Materials and Methods

Study Design

We prospectively enrolled patients with IBD aged 18 years or older with a diagnosis of UC or CD for at least 3 months confirmed by radiology, histology, and endoscopy who visited the gastrointestinal clinics of Mashhad from June 2021 to August 2022 who agreed to participate after obtaining written informed consent.

For the next step, a peripheral blood sample (5 cc) was collected from each participant for the evaluation of HBV infection serological markers. Three markers, including hepatitis B surface antigen (HBsAg), antibodies to HBsAg (anti-HBs Ab), and antibodies to hepatitis B core protein (anti-HBc Ab) were measured.

The methodology of our study consisted of two parts. First, we described the hepatitis B Viral markers among patients with IBD, according to standard classification; we grouped patients with IBD into four groups, including chronic HBV infection, history of HBV infection, effective vaccination, and non-immunity against HBV, which they were completely defined and described in the methodology section. Figure 1 shows the flowchart of this study.

Then, by a novel approach called the decision model, we investigated the factors affecting reaching effective vaccination (among subjects who received full vaccination according to national protocol) and factors affected by being non-immune against HBV (among total patients with IBD).

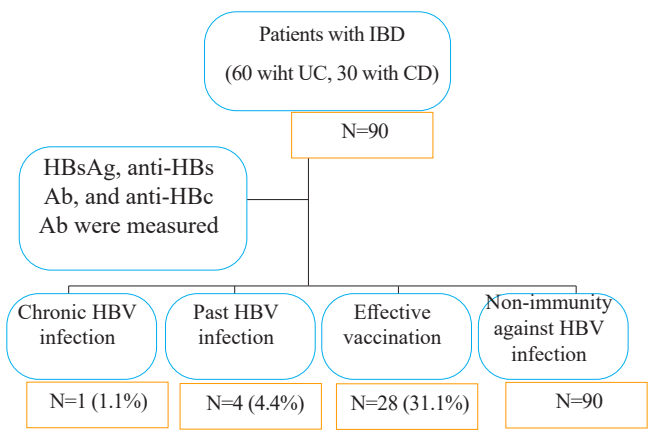

Figure1. Flowchart of the present study

Data collection

Demographic data including age, sex, type of IBD disease, disease duration, location of the disease, HBV vaccination history, related liver disorders, type of medications used (including monotherapy or combined therapy) and in patients who were under combined therapy, the presence or absence of a biological agent were recorded from the patient's medical records. The UC extension and CD location were classified based on the last version of the American College of Gastroenterology (ACG) clinical guideline of 2019 (11, 12).

Definitions

Present (chronic) and past (history of) HBV infections were defined based on what has been a consensus at the National Institutes of Health's conferences about HBV management (13). Chronic hepatitis B was defined as a positive HBsAg. Past HBV infection was defined as an positive anti-HBc with/without anti-HBs. Susceptible (non-immune) to HBV infection was defined as an anti-HBs level of <10 mIU/mL, negative anti-HBc, and negative HBsAg. Effective vaccination was defined as an anti-HBs level of ≥10 mIU/mL, negative HBsAg, and positive anti-HBc (14).

Statistical Analysis

Continuous variables were expressed as mean±standard deviation (SD), and categorical variables were expressed as numbers with percentages. The Chi-square test was used for comparisons between two groups of categorical variables, and the independent t-test was used for continuous variables. The data analysis was done using SPSS software version 23 (SPSS Inc., Chicago, IL, USA). P values <0.05 were considered significant. For decision tree (DT) models, the SAS JMP Pro 13 (SAS Institute Inc., Cary, NC) was used.

Decision Tree Model

This study used a predictive model based on machine learning classification algorithms: DT, a predictive model for data classification (15). A DT is a non-parametric supervised learning method used in various medical fields due to its simplicity of understanding and extraction (16, 17). DT aims to form a tree-like graph or model of decision in terms of predicting the value of a target variable by learning simple decision rules.

Also, DT can manage missing data, a frequent occurrence in medical datasets (18). To form the tree, DT algorithms make splitting criteria at internal nodes. The DT algorithm is composed of two components: nodes and branches. The nodes are divided into three types.

First, a root node indicates the result of the subdivision of all records into two or more exclusive subsets. The internal nodes indicate a possible point in the tree graph that is connected to the root node from the top and to the leaf nodes from the bottom. The third node is the leaf node, which shows the tree results when dividing records into target groups. Branches in the tree represent the chance of placing records in target groups that emanate from the root node a. DT algorithm uses the Gini impurity index to select the best variable.

$$Gini(D)=1-\sum_{i=1}^{m}P_i^2$$

Where P_i is the probability that a record in D belongs to the class C_i and is estimated by $|C_i, D|/|D$.

Ethical issues

Our study was approved by the Ethics Committee, Faculty of Medicine, Islamic Azad University of Mashhad, with the ethics code of 013.1400.REC.MSHD.IAU.IR. In our study, the checklist data remained completely protected. Before carrying out the study, informed consent was obtained from all participants.

Also, no additional costs were imposed on the patients.

RESULTS

Description of patients with IBD population

A total of 90 patients with IBD were recruited from the gastrointestinal clinics of Mashhad between June 2021 and August 2022. Of these, 60 patients (66.6%) were diagnosed with UC (male, n=25; female, n=35; mean age, 39.48±15.09 years), and 30 patients (33.3%) were diagnosed with CD (male, n=7; female, n=23; mean age, 42.47±15.82 years).

The characteristics of patients are shown in Table 1.

There was no significant difference between patients with UC and CD in terms of sex and age. There was also no difference in the disease duration in patients with CD compared with those with UC (5.33±5.24 years vs 6.78±6.05 years; P=0.24).

Five patients had IBD-associated liver disease (named primary sclerosing cholangitis) in our study, and all of them had UC. Of 90 patients, 38 patients (42.2%) had full vaccination against HBV, and the rest (57.8%) had no history of vaccination. 13 patients (43.3%) of the CD group and 25 patients (41.7%) of the UC group had received full vaccination. In terms of the type of therapy, 34 (37.8%) patients were on monotherapy (including 5-aminosalicylates), and 56 (62.2%) patients were on combined therapy (including 5-aminosalicylates with immunomodulators or 5-aminosalicylates with biological agent).

Patients with UC significantly used both monotherapy and combined therapy more than patients with CD (P=0.037). We further categorized patients according to the use of biological agents and found that subjects with disease duration ≥10 years more significantly use biological agents than subjects with disease duration <10 years (45.80% vs 22.70%, P=0.032) (Table 2).

Table 1. Clinical and demographic characteristics of patients with IBD

		UC (n=60)	CD (n=30)	Overall (n=90)	P*
Sex	**Male**	25 (41.7%)	7 (23.3%)	32 (35.6%)	
	Female	39.48±15.09	42.47±15.82	40.48±15.31	0.396
Age (year)		39.48±15.09	42.47±15.82	40.48±15.31	0.396
Disease duration (year)		6.78±6.05	5.33±5.24	6.3±5.8	0.245
UC extent	E1 (proctitis)	9 (15%)			
	E2 (left-sided)	32 (53.3%)			
	E3 (extensive)	19 (31.7%)			
CD location	L1 (terminal ileum)		14 (46.7%)		
	L2 (colon)		4 (13.3%)		
	L3 (ileocolon)		11 (36.7%)		
	L4 (upper GI)		1 (3.3%)		
Full HBV vaccination (YES)		25 (41.7%)	13 (43.3%)	38 (42.2%)	0.528
		35 (58.3%)	17 (56.7%)	52 (57.8%)	
IBD-associated liver disorders		5 (100%)	0	5 (100%)	0.69
Type of medications	Monotherapy	27 (45%)	7 (23.3%)	34 (37.8%)	
	Combined-therapy	33 (55%)	23 (76.7%)	56 (62.2%)	0.037

IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease; HBV: hepatitis B virus.
*P-value is computed based on t tests for continuous data and the Chi-square test for categorical data.

Table 2. Comparison of the use of biological agents and time of disease progression among patients with IBD

	Biological agent (NO)	Biological agent (YES)	P*
Time of disease progression			
<10 yrs	51 (77.30 %)	15 (22.70 %)	0.032
≥10 yrs	13 (54.20 %)	11 (45.80 %)	
Type of disease			
CD	18 (60.00 %)	12 (40.00 %)	0.082
UC	46 (76.70 %)	14 (23.30 %)	
Age			
<50 yrs	44 (67.70 %)	21 (32.30 %)	0.187
≥50 yrs	20 (80.00 %)	5 (20.00 %)	

IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease; HBV: hepatitis B virus.
*P-value is computed based on Fisher's exact test

HBV serological markers among patients with IBD

Table 3 depicts the HBV status in our study population. Only one patient (1.1%) had chronic HBV infection (HBsAg positive) who had UC. This patient was under antiviral therapy. History of HBV infection was seen in two patients of the CD group and in two patients of the UC group.

28 patients (31.1%) had effective vaccination (anti-HBs level of ≥10 mIU/mL), including eight patients of CD and 20 patients of UC. Non-immunity against HBV was seen in 57 patients (63.4%), including 20 patients of the CD group and 37 patients of the UC group.

Table 3. Prevalence of patients with IBD subgroups based on HBV serological markers

	UC	CD	Overall
Chronic HBV infection	1	0	1 (1.1%)
Past infection	2	2	4 (4.4%)
Effective vaccination	20	8	28 (31.1%)
Non-immunity	37	20	57 (63.4%)

IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease; HBV: hepatitis B virus.

DT model for patients with effective vaccination and susceptible to HBV

Figure 2 shows the DT algorithm results for factors including age, sex, disease (UC or CD), IBD-associated liver disorders, and type of medicine (monotherapy or combined therapy). In fact, we classified the patients with effective vaccination (anti-HBs level of ≥10 mIU/mL) by the mentioned factors. The DT training determines the various factors and categorizes them into three layers. In the DT model, the first variable (root) is of the highest importance for data classification, and the following variables have the next significance levels accordingly(19). Figure 2 shows that types of therapy, followed by type of disease and sex, have the greatest impact on patients for achieving effective vaccination. According to the DT model, the effective vaccination was 50% in participants under monotherapy with the female sex. Following other layers of the DT shows that 80% of patients had ineffective vaccination in the subgroup of patients who were under combined therapy with UC disease and male sex. Other rules can be obtained by following other DT branches, as shown in Table 4.

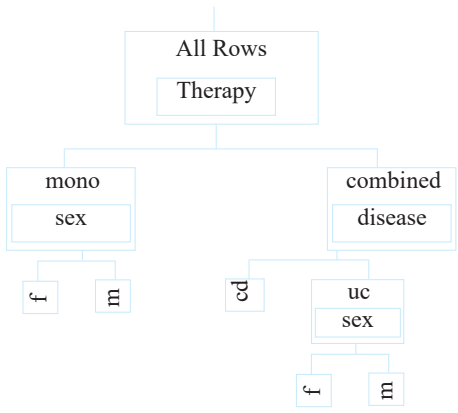

Figure2. Decision tree for effective vaccination

f: female; m: male; cd: crohn's disease; uc: ulcerative colitis

Table 4. Detailed rules based on DT for effective vaccination against HBV

Rules	Ineffective vaccination (%)	Effective vaccination (%)
Therapy (mono) & sex (f)	52.11	47.89
Therapy (mono) & sex (m)	60.79	39.21
Therapy (combined) & disease (CD)	66.63	33.37
Therapy (combined) & disease (2) & sex (f)	69.72	30.28
Therapy (combined) & disease (2) & sex (m)	77.82	22.18

DT: decision tree; HBV: hepatitis B virus; mono: patients under monotherapy; combined: patients under combined therapy; f: female; m: male; UC: ulcerative colitis; CD: Crohn's disease

Figure 3 shows the DT algorithm results for factors such as age, sex, type of disease (UC or CD), IBD-associated liver disorders, and type of medication (monotherapy or combined therapy). In fact, we classified patients with non-immunity against HBV (anti-HBs level of <10 mIU/mL) by the mentioned factors. The DT training determined the various factors and categorized them into four layers. Figure 3 shows that types of disease (UC or CD), followed by using biological agents and sex, have the greatest impact on being non-immune against HBV. According to the DT model, the non-immunity against HBV was 70% in participants with CD and male sex. Following other layers of the DT shows that 46% of patients were immune against HBV in the subgroup with UC, without biological agents, and female sex. Other rules can be obtained by following other branches of the DT, as shown in Table 5.

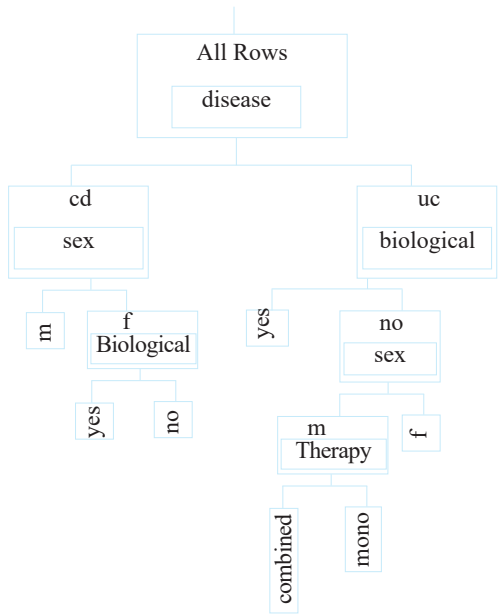

Figure3. Decision tree for non-immunity against HBV
cd: crohn's disease; uc: ulcerative colitis; f: female; m: male

Table 5. Detailed rules based on DT for non-immunity against HBV

Leaf label	Immunity against HBV (%)	Non-immunity against HBV (%)
Disease (CD) & sex (m)	29.54	70.46
Disease (CD) & sex (f) &Biological (yes)	29.52	70.48
Disease (CD) & sex (f) &Biological (no)	37.42	62.58
Disease (UC) & Biological (yes)	29.12	70.88
Disease (UC) & Biological (no) & sex (m) & Therapy (combined)	29.61	70.39
Disease (UC) & Biological (no) & sex (m) & Therapy (mono)	36.41	63.59
Disease (UC) & Biological (no) & sex (f)	46.11	53.89

DT: decision tree; HBV: hepatitis B virus; f: female; m: male; UC: ulcerative colitis; CD: Crohn's disease; no: patients not using biological agent; yes: patients using biological agent, mono: patients under monotherapy; combined: patients under combined thera

DISCUSSION

To the best of our knowledge, the present study is the first to assess the HBV serological markers and immune status against HBV in patients with IBD in Mashhad, northeast of Iran. In our study, 90 patients (30 with CD and 60 with UC) were examined. The results showed that the prevalence of history of (past) HBV infection and chronic HBV infection was 4.4% and 1.1%, respectively. Effective vaccination was reported in 31.1% of our patients, and non-immunity against HBV was 63.4%, which is considerable. The DT model showed that type of therapy, type of disease, and sex had the most effect on effective vaccination development and Anti-HBS Ab level.

In our study, only 38 patients received HBV vaccination. It has been reported that the HBV vaccination rate among patients with IBD is low. An American study reported that among 75 patients with IBD and HBV-related risk factors, only 23 received adequate immunization (20). Moreover, in terms of the vaccination response rate, a low response rate of 31.1% was found in our study, which was much lower than studies by Cunha et al. (72%) and Sempere et al. (47.6%) (21, 22), almost similar to a study by Vida et al. (34.1%) (23), but higher than a study by Loras et al. (12%) (24). The anti-HBs Ab cut-off point was ≥10 mIU/mL in all mentioned studies. Chronic diseases and immunodeficiency are factors associated with a decreased response to HBV vaccine (25). In Iran, a retrospective cohort study conducted in 2021 in Shiraz reported that the estimated vaccine effectiveness against HBV, according to the national program, was 29% (95% CI: 6%–46%) for those who received the vaccine three times at birth, 2 and 6 months of age (26). Although that study indicated that Iran had successfully integrated the HBV vaccine into routine immunization programs and had achieved a significant effect on decreasing the rate of HBs-Ag carrier, the results enforce the importance of checking HBV serological markers, especially among patients under immunosuppressive medications and if necessary, revaccinating them. The effectiveness of increased-dose combined vaccination was reported by Nyström and coworkers (27).

Cunha et al. reported that the use of immunosuppressive medications and the type of disease appear to influence the vaccine response, so patients with CD and under immunosuppressive drugs had negative responses to vaccination (21). Conformingly, DT analysis in our study showed that 80% of those who did not reach an effective vaccination rate were under combined therapy (5-aminosalicylates with immunomodulators or 5-aminosalicylates with biological agents) but with UC and male sex. Similar to our finding, Yang et al. reported that the male sex was a risk factor for a poor immune response to the HBV vaccine in the general adult population (28). It has been reported that patients with UC were significantly more responsive to develop effective vaccination than patients with CD (21, 25). However, a study reported that there was no significant difference in the rate of vaccination response among patients with CD and UC (29). Gisbert et al. found that the only factor associated with a higher risk of loss of anti-HBs in patients with IBD was treatment with anti-TNFs (30).

We found that 57 patients (63.4%) were susceptible to (non-immune) HBV infection. While Yeo et al reported that non-immunity against HBV infection (negative HBsAg, negative anti-HBc with anti-HBs level less than 10 mL/mIU) was observed in only 32.4% of patients

compared with 19.5% of the control group in South Korea (14). Among DT analysis, the susceptibility to HBV was 70% in male participants with CD using biological agents. Immunomodulatory and biological medications make far-reaching changes in the IBD prognosis, diminishing inflammation and flares and the need for surgical interventions and also increasing the quality of life of such patients. However, they can potentially increase the risk of infections (23). Thus, checking the vaccination history to diminish the risk of preventable infections such as tetanus, influenza, and hepatitis B is recommended (31), as well as the administration of a higher dose or further doses of the standard vaccine according to the regional or national guidelines to achieve anti-HBs IgG >10 IU/L (32).

In our study, among 90 patients, four (4.4%) had a history of HBV infection (positive anti-HBc). The risk of occult HBV infection has been reported to be high in anti-HBc positivity, which is an HBV reactivation indicator, especially in patients under chemotherapy or immunosuppressant (33). The prevalence of a history of HBV infection in the general population of Iran was reported as 13.59% (34), which is higher than what we have found among patients with IBD. It has been reported that the prevalence of a history of HBV infection is significantly greater in patients with IBD than in healthy individuals in China (35). Patients with IBD who are positive only for anti-HBc should be evaluated for viremia (HBV DNA) every 2–3 months, with antiviral drugs being given if HBV-DNA is detected (8). For patients who are HBsAg negative but anti-HBc positive and anti-HBs positive, as well as patients with isolated anti-HBc positive, periodic monitoring of aspartate transaminase (AST) and alanine transaminase (ALT), as well as for changes in HBV serology is also recommended (36).

We found that only one person (1.1%) was HBsAg positive and had chronic HBV infection in our study. She was one of the patients with UC and was using antiviral therapy. Earlier studies have compared the prevalence of HBV between patients with IBD and the general population. In a recent paper from China, the HBV prevalence in patients with IBD was similar to that of the general population (37). In a study from India, the prevalence of HBV in the general population of India and among 908 patients with IBD was reported at 3.7% and 2.4%, respectively, which was not statistically significant. Huang et al. reported that the HBV prevalence among patients with IBD was higher than among non-IBD patients in China. These may be attributed to the increased need for transfusion and surgery intervention in patients with IBD (38). In Iran, the prevalence of HBV infection is geographically heterogeneous among different provinces. Highly endemic areas include the Golestan and Sistan and Baluchistan provinces (39-41). In addition, according to the latest study in 2017, the prevalence of HBsAg in the general population of Iran is 1.79%, which is equivalent to 1,347,000 individuals with chronic HBV infection (34), which is near to our finding (1.79% vs. 1.1%). Fortunately, it has been reported that the prevalence of HBV infection among blood donors and the general population has declined (42). According to the last study conducted in Mashhad city in 2011, the prevalence of HBV in the general population of Mashhad city was reported as 1.39% (43), almost near its prevalence in patients with IBD in our study. This could prove that the prevalence of HBV infection in patients with IBD is similar to the general population. Nevertheless, because of the high risk of HBV flare after immunosuppressive therapy, routine screening for patients with IBD for viral markers is warranted. We suggest testing HBV serological markers (HBsAg, anti-HBc, and anti-HBs) among patients with IBD at the time of disease diagnosis and before starting immunosuppressive treatments. In case of non-immunity against HBV, complete vaccination according to the national protocol and then, re-examination of anti-HBs at regular intervals in terms of achieving adequate immunity against HBV is recommended. According to latest study conducted in Mashhad city in 2011, the prevalence of HBV in the general population was reported as 1.39% (43), which is almost near to its prevalence among patients with IBD in our study. This could prove that the prevalence of HBV infection in patients with IBD is similar to the general population. Nevertheless, because of the high risk of HBV flare after immunosuppressive therapy, routine screening for patients with IBD for viral markers is warranted (44).

Our study has several limitations. First is the small sample study population. Second, we did not include participants as the control group to compare with patients with IBD. This issue was due to the fact that, as the sample collection was during the COVID-19 pandemic, a large number of the patients did not cooperate properly with us. Thus, we were finally able to include 90 samples in our study for final analysis. Third, HBV DNA levels were not checked in patients with positive anti-HBc and negative HBsAg, and last, we did not examine factors that may affect HBV contracting, including occupation, history of addiction, cupping, etc. However, the preliminary findings may shed light on the IBD population and their management process. Since the risk of flare if HBV goes undetected is high, primary care physicians and gastroenterologists should be cognizant of treating patients with IBD for HBV and routine screening of HBV serological markers, preferably before receiving immunosuppressive therapy in addition to managing IBD itself. Moreover, patients need to be informed about the importance of vaccination, as well as

the need to verify if the vaccine was performed properly.

CONCLUSION

In conclusion, this study is the first to assess the HBV serological markers and immune status against HBV in patients with IBD in Mashhad. We found that the frequency of non-immunity against HBV was high, and response to vaccination was low. Types of medication, disease, and sex have considerable effects on anti-HBs levels. Screening HBV serology in patients with IBD at the time of disease diagnosis and before starting immunosuppressive treatments and in case of non-immunity, complete vaccination according to the national protocol and then re-examination of anti-HBs at regular intervals in terms of achieving adequate immunity against HBV is recommended.

Declarations and Statements

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CONFLICT OF INTEREST:

The authors declare no conflict of interest related to this work.

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AVAILABILITY OF DATA:

The datasets used during the present study are available from the corresponding author upon reasonable request.

ETHICAL CONSIDERATION:

Our study was approved by the ethics committee, faculty of medicine, Islamic Azad University of Mashhad, with the ethics code of 013.1400.REC.MSHD.IAU.IR.

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