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RESEARCH ARTICLE

Hepatitis B virus infection or reactivation and HBV-related liver dysfunction in patients with inflammatory bowel disease receiving infliximab: a nationwide real-world study

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Abstract Infliximab (IFX) for inflammatory bowel disease (IBD) treatment may increase the risk of hepatitis B virus (HBV) reactivation, particularly in areas with high HBV prevalence such as China. This study aimed to evaluate HBV reactivation/infection, liver dysfunction, vaccination efficacy and strategies in IBD patients undergoing IFX therapy. This retrospective, multicenter study included 4183 IBD patients from 15 hospitals across China, who were divided into six groups according to the HBV status. Demographic features, HBV vaccination status, reactivation/infection rates, and liver dysfunction outcomes were collected, with data collection performed from 2009 to 2022. We found that HBV reactivation rate was notably higher in HBsAg positive group than other groups ($P < 0.05$) despite antiviral treatment. Although only 29% of patients were immunized at IFX initiation and almost no patients got vaccinated against HBV during IFX treatment, no patients experienced HBV infection in the susceptible population group. The study underscores a critical need for rigorous HBV screening before IFX initiation. Despite antiviral prophylaxis, the importance of continuous monitoring of HBV DNA is necessary for HBsAg positive patients. HBsAg negative patients, including the susceptible population, had a very low risk of new HBV infection, thus reassuring patients and physicians of the safety of IFX in this cohort.

Keywords IBD; HBV; reactivation; vaccination

Introduction

The advent of biologics has revolutionized the clinical management of inflammatory bowel disease (IBD), which comprises Crohn's disease (CD) and ulcerative colitis (UC). Although novel biologics have emerged in recent

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years, anti-tumor necrosis factor (TNF) antibodies, including infliximab (IFX), remain the most widely utilized biologics in clinical practice [1]. IBD patients gain substantial benefits from IFX treatment, but the associated risk of opportunistic infections, including hepatitis B virus (HBV) reactivation, remains a concern. Reactivation of HBV potentially causes liver dysfunction, liver failure, liver cancer, or even death [2]. Hence, vigilant prevention and monitoring for HBV are crucial in IBD patients receiving IFX therapy.

Several studies have confirmed the increased HBV reactivation rate among HBV carriers after IFX treatment, because IFX blocks TNF and thus removes its suppressive effect on viral replication [2–5]. Limited literature is available about the HBV infection rate and prognosis in IBD patients susceptible to HBV who are receiving long-term IFX therapy. Since China is considered the nation with the highest number of HBV carriers [6,7], with the prevalence of HBV carriers is approximately 5.86% in the general Chinese population [8,9], there is an urgent need for additional studies to address the above research gap.

It is indispensable and effective for the general population to follow HBV prevention measures, mainly through vaccination [10–12]. Consequently, current guidelines recommend that IBD patients scheduled to receive IFX therapy should undergo HBV screening, followed by vaccination [13–15]. Despite the explicit clinical recommendation, the vaccination rate remains significantly low, with the reported coverage among adults in China of only 26.27% during 2011–2021 [16–19]. Moreover, the initial response rate to HBV vaccination is suboptimal (only 59%–76% of IBD patients achieve protective anti-HBs > 10 IU/mL vs. 100% in healthy controls), and protective titers decline more rapidly, with 15% of IBD patients losing seroprotection within 1 year—in sharp contrast to the 13%–25% decline observed over 5 years in the general population [20–22], especially those already receiving anti-TNF agents [23,24]. Owing to the low efficacy of HBV vaccination in IBD patients, the optimal dose, type, and schedule remain controversial [20,25,26].

Given that HBV vaccination was implemented for newborns in China in 1992, a considerable proportion of IBD patients in this research exhibited insufficient protective antibodies against HBV. Besides, unlike the hierarchical diagnosis and treatment systems in Western countries, Chinese patients are more willing to perform convenient visits in tertiary hospitals directly. However, vaccinations in China are administered in community health centers, which presents a challenge to the effective implementation of HBV vaccination in IBD patients, particularly prior to IFX treatment. Importantly, seronegative patients with IBD are of considerable size, but studies assessing their susceptibility to HBV and the necessity of vaccination in this population are scarce. The aim of this study was to examine the vaccination rate, HBV reactivation/infection incidence, and liver dysfunction in a multicenter cohort of IBD patients receiving IFX therapy in China. Additionally, we aimed to assess the long-term safety of IFX in this population.

Materials and methods

Study design and inclusion criteria

This retrospective, multicenter study was conducted across 15 hospitals in China (1. Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang; 2. Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong; 3. The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu; 4. Zhongshan Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, Fujian; 5. The First Hospital of Jilin University, Changchun, Jilin; 6. The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu; 7. The Affiliated Wuxi People's Hospital of Nanjing Medical University, Wuxi, Jiangsu; 8. West China Hospital, Sichuan University, Chengdu, Sichuan; 9. Lishui People's Hospital, Lishui, Zhejiang; 10. Zhongnan Hospital of Wuhan University, Wuhan, Hubei; 11. The Affiliated Hospital of South-west Medical University, Chongqing; 12. Shengjing Hospital of China Medical University, Shenyang, Liaoning; 13. The Second Hospital of Jiaxing, Jiaxing, Zhejiang; 14. The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei; 15. Ningbo Medical Center Lihuili Hospital, Ningbo, Zhejiang). The enrolled IBD patients were aged over 18 years and fully met the criteria of the Chinese consensus on diagnosis and treatment of IBD [27], receiving IFX treatments at least three times. The patients were consecutively enrolled from January 2009 to August 2022 and followed up until six months after the last IFX infusion. This study was approved by the Ethics Committee of Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine (approval number 2022Y0356).

Data collection

Clinicodemographic characteristics were collected from medical records, including IBD type, Montreal classification, Crohn's Disease Activity Index (CDAI) or Mayo score prior to IFX infusion, duration of IFX treatment, liver function indexes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and bilirubin), concomitant medications (immunosuppressants, and steroids), HBV

DNA and hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), hepatitis B surface antibody (anti-HBs), and hepatitis B e antigen (HBeAg). Due to slightly different laboratory tests among the 15 hospitals, we differentiated between positive and negative antibodies, and did not record their exact titers. The cutoff values for different HBV serological markers were defined as follows: HBsAg negative was defined as HBsAg < 0.05 IU/mL; anti-HBs negative was defined as anti-HBs < 10.00 IU/L; anti-HBc negative was defined as anti-HBc < 1.00 S/CO (sample/cutoff); anti-HBe negative was defined as anti-HBe < 1.00 S/CO. Furthermore, HBV vaccination status, liver-related comorbidities, medications, and adverse events were recorded.

Follow-up and outcome definitions

Laboratory examinations were routinely performed to assess complete blood count, renal function, and liver functions before each IFX infusion. Serologic markers of HBV (HBsAg, anti-HBs, and anti-HBc) were assessed at the time of initial IFX treatment, annually thereafter, and six months after treatment discontinuation. Additionally, HBV DNA levels were measured annually in HBsAg positive patients and assessed in other patients whenever alterations in HBV antigens/antibodies were observed or at the discretion of the clinicians.

The primary endpoint was HBV reactivation, defined as a 10-fold elevation in HBV DNA load versus baseline, appearance of HBV DNA in serum, or reverse seroconversion of HBsAg from negativity to positivity [10]. The secondary endpoint was liver dysfunction, defined as ALT/AST levels at least twofold the respective limits of normal, and/or total bilirubin levels > 34.2 μmol/L. To differentiate liver dysfunction due to IBD medications from HBV reactivation, we reviewed details of IBD patients when transaminases were elevated. Medications used at the time of transaminase alterations and serologic markers of HBV were recorded. Liver dysfunction associated with HBV reactivation was considered probable when serology results of HBV were changed in the absence of other potential factors (including adjustment of medications).

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) for normally distributed data, and as median (interquartile range) for non-normally distributed data. One-way analysis of variance or the nonparametric Kruskal–Wallis test was utilized to compare multiple groups. *P* values were corrected by the Bonferroni method. Categorical variables were presented as absolute number or percentage and compared by the chi-square (χ^2) or Fisher's exact test as appropriate. The cumulative incidence rates of HBV reactivation/infection and liver dysfunction were calculated by the Kaplan–Meier method and compared by the log-rank test. To identify independent risk factors for HBV reactivation/infection, multivariable Cox proportional hazards regression models were employed. SPSS 22.0 was used for data analysis, with two-sided $P < 0.05$ considered statistically significant.

Results

Demographic and clinical characteristics of the IBD patients

A total of 4637 IBD patients (4318 CD and 319 UC cases) who met the eligibility criteria were recruited from 15 hospitals nationwide. Some patients received IFX treatment at 2 of the 15 hospitals; duplicate records were excluded, as well as patients administered fewer than three times and those with incomplete clinical data. Finally, 4183 IBD patients (3944 CD and 239 UC cases) were included (Fig. 1).

The clinical features of IBD patients according to the Montreal classification are shown in Table 1. Most CD patients were diagnosed between 17 and 40 years of age and had non-stricturing, nonpenetrating behavior and an ileocolic location. Most UC cases were extensive UC.

Hepatitis B serology results

The 4183 patients were divided into 6 groups according to HBV serologic markers (Table 2), including 187 with current HBV infection, 1209 susceptible to HBV infection, 1519 immunized after prior vaccination or natural infection, 159 with resolved infection, 34 only tested for anti-HBs levels at baseline, and 1075 with unknown HBV status at baseline. Nearly three-quarters of patients had baseline HBV serologic data, and the number of individuals receiving IFX was significantly increased in 2020 due to the inclusion of IFX in China's medical insurance list (Fig. 2). The median time on IFX was 468 days (IQR, 224–857), and the median follow-up duration was 624 days (IQR, 400–1007), the longest time on IFX and follow-up duration was over 10 years.

Anti-viral treatment

According to the current guidelines, antiviral treatment is recommended for IBD patients with chronic hepatitis B infection [28]. However, among the 187 patients with HBV infection, 29 did not receive antiviral treatment. Further investigation revealed that, although physicians recommended the medication, these patients—who typically had normal liver function—refused antiviral therapy due to concerns about inconvenience or potential

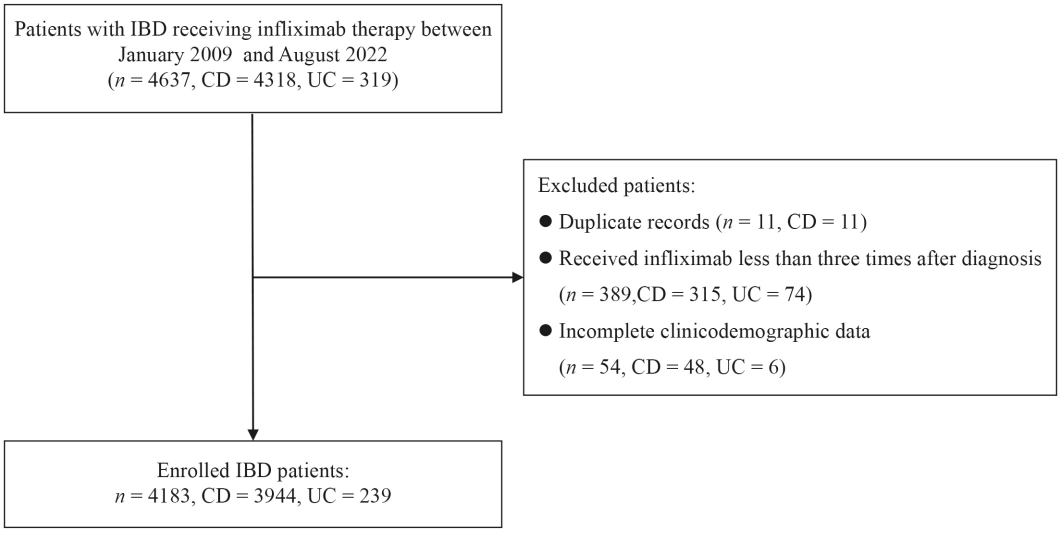

Fig. 1 Flowchart of selection and analysis for IBD. IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis.

side effects. Some refused the treatment from the beginning, while others discontinued the medication shortly after initiation because their liver function remained normal. A total of 158 patients received antivirals during IFX treatment. Of these, 137 (86.7%) patients were treated with entecavir, while other pharmacological therapies included tenofovir (8, 5.1%), lamivudine (5, 3.2%), adefovir dipivoxil (2, 1.3%), entecavir + tenofovir (5, 3.2%), and lamivudine + adefovir dipivoxil (1, 0.6%). None of the patients in the other groups underwent baseline HBV DNA testing, and none received prophylactic antiviral treatment.

Incidence of HBV reactivation or infection, liver function

HBV reactivation/infection occurred in 15 patients, with the exception of one from the undetermined group, of whom 7 of 187 (3.74%) in the HBsAg positive group, 3 of 1519 (0.20%) in the immunized group and 2 of 159 (1.26%) in the previous HBV infection group were detected with HBV reactivation and 2 of 34 (5.89%) in the only known HBsAg negative group developed new HBV infection. Detailed information for all 15 patients, including management following reactivation/infection, is provided in Table 3. Among the 15 patients with HBV reactivation/infection, antiviral therapy was initiated in 8 who had not been on prior prophylaxis. In one case, a patient previously on lamivudine plus adefovir dipivoxil was switched to Entecavir following reassessment of concurrent CD, along with a change in biologic therapy to ustekinumab (UST). The majority of reactivation cases, which presented with low viral load and unaffected liver function, were managed conservatively under close monitoring without additional intervention. The incidence of HBV reactivation was significantly higher in the HBsAg positive group compared to the other groups ($P < 0.05$). No significant differences were observed among the other four groups (Fig. 3A). A Cox proportional hazards regression model with Firth's penalized likelihood estimation was employed to identify independent predictors of HBV reactivation. The model included gender, vaccination history, and baseline HBV serostatus as covariates. After adjustment, baseline HBV serostatus emerged as a significant predictor. Using the infected group (HBsAg positive) as reference, both the susceptible group (aHR = 0.010, 95% CI 0.00–0.23, $P < 0.01$) and the immune group (aHR = 0.06, 95% CI 0.01–0.23, $P < 0.001$) showed significantly reduced hazards. Neither gender (male vs. female: aHR = 0.86, 95% CI 0.27–2.75, $P = 0.80$) nor vaccination history (aHR = 0.73, 95% CI 0.25–2.10, $P = 0.553$) demonstrated a statistically significant association with the outcome.

Patients with liver dysfunction before the initial IFX infusions were excluded; we then assessed the incidence rates of liver dysfunction. As shown in Fig. 3B, a total of 234 patients (5.78%) experienced liver dysfunction during IFX treatment, 70 of whom were from the undetermined group. No significant differences were detected among the different groups, and no cases of liver failure were observed. Although seven patients in the HBsAg positive group experienced HBV reactivation, none developed liver dysfunction.

HBV vaccination

According to the HBV markers in Table 2, only 36% of patients were immunized, including those who acquired immunity through HBV infection, which is lower than expected. Therefore, this study further investigated the

Table 1 Demographic and clinical characteristics of patients with IBD

Characteristic	CD (n = 3944), n (%)	UC (n = 239), n (%)
Male sex	2890 (73.3)	137 (57.3)
Age at diagnosis (A)		
A1 (≤ 16 years)	422 (10.7)	–
A2 (17–40 years)	3106 (78.8)	–
A3 (> 40 years)	416 (10.5)	–
Location (L)		
L1 (terminal ileum)	606 (15.4)	–
L2 (colon)	195 (4.9)	–
L3 (ileo-colon)	2618 (66.4)	–
L4 (upper GI)	15 (0.4)	–
Upper GI modifier (L4)		
L1 + L4	173 (4.4)	–
L2 + L4	6 (0.2)	–
L3 + L4	331 (8.4)	–
Behavior (B)		
B1 (non-stricturing, non-penetrating)	2277 (57.7)	–
B2 (stricturing)	984 (24.9)	–
B3 (penetrating)	683 (17.3)	–
Perianal disease modifier (p)	2249 (57.0)	–
Disease activity (CDAI)		
Remission	112 (2.8)	–
Mild	1695 (43.0)	–
Moderate	1225 (31.1)	–
Severe	448 (11.4)	–
Unknown	464 (11.8)	–
Extent (E)		
E1 (ulcerative proctitis)	–	16 (6.7)
E2 (left-sided UC)	–	57 (23.8)
E3 (extensive UC)	–	166 (69.5)
Disease activity (Mayo)		
Remission	–	3 (1.3)
Mild	–	16 (6.7)
Moderate	–	49 (20.5)
Severe	–	105 (43.9)
Unknown	–	66 (27.6)

HBV vaccination status of the patients. A total of 1326 patients were able to provide information on whether they had received the HBV vaccine (Table 4). Among them, 950 cases (72%) had been vaccinated before IFX treatment; however, by the time of IFX initiation, fewer than half of these patients (35%) were immunized. This indicates that more than half of the patients did not develop immunity at IFX initiation despite having received the hepatitis B vaccine previously. Additionally, few patients received the hepatitis B vaccine during IFX treatment. Therefore, hepatitis B screening before IFX use is crucial, even for patients with a history of vaccination.

Discussion

The management of IBD in patients with concurrent HBV infection constitutes a complex interplay between effective disease control and the prevention of viral reactivation [29]. The advent of biologics, particularly anti-TNF agents, has transformed the therapeutic landscape of IBD, providing substantial improvements in patient outcomes. However, this benefit is hampered by the potential risk of HBV reactivation, a concern amplified in regions with high HBV prevalence, e.g., China, which has the highest number of HBV carriers [6,7], due to its enormous population and a gradual decline of hepatitis B antibodies. To our knowledge, this is the first and largest study to assess HBV infection, reactivation, liver dysfunction rates, and HBV vaccination in IBD patients treated with IFX in China.

In this study, the incidence of HBV reactivation was significantly higher in the HBsAg positive group, although all these seven patients underwent antiviral treatment, corroborating previous studies [5]. Interestingly, there were no significant differences in HBV reactivation rates among the immunized, previous HBV infection, and susceptible groups, with no patients experienced *de novo* HBV infection in the susceptible group. However, three *de novo* infections were observed in the immunized group. Further analysis revealed that all three patients had low baseline anti-HBs titers (approximately 10–15 IU/mL), had been receiving IFX therapy for over 1000 days, and reported a household contact with chronic HBV infection. Since having household members with chronic HBV increases the risk of transmission [30,31], our findings suggest that a low anti-HBs titer, particularly in the context of ongoing household exposure, may be insufficient to confer protection against *de novo* HBV infection. This highlights the potential need for booster vaccination or enhanced monitoring in this subpopulation. Increasing evidence suggests that the risk of HBV reactivation after IFX treatment is very low. Fidan *et al.* reported that the rate of HBV reactivation following IFX treatment in patients with resolved infection (HBsAg negative/anti-HBc positive) is very low, approximately 0.4%. Other studies, including the study by Ditto and colleagues, also confirm that reactivation is rare under proper monitoring. A meta-analysis by El Jamaly *et al*. provides clear serological stratification: the reactivation rate was 40.5% in chronic HBV carriers (HBsAg positive), largely due to low uptake of prophylactic antiviral therapy, compared to

Table 2 Demographic and clinical characteristics of patients with IBD

Group	Description	Number	IFX time, median (IQR), days	Follow-up time, median (IQR), days
Current HBV infection	HBsAg positive	187	503 (277–902)	719 (443–1064)
Susceptible individual	HBsAg, anti-HBs and anti-HBc negative	1209	540 (267–974)	682 (437–1155)
Immunized	Anti-HBs positive	1519	546 (262–945)	700 (433–1114)
Previous HBV infection	Anti-HBc and/or anti-HBe positive, HBsAg negative	159	493 (274–843)	622 (423–946)
Only HBsAg negative	HBsAg negative and other indicators not tested at baseline	34	502 (311–950)	649 (370–955)
Undetermined	Cannot determine at baseline	1075	315 (154–601)	491 (337–781)
Total	All patients	4183	468 (224–857)	624 (400–1007)

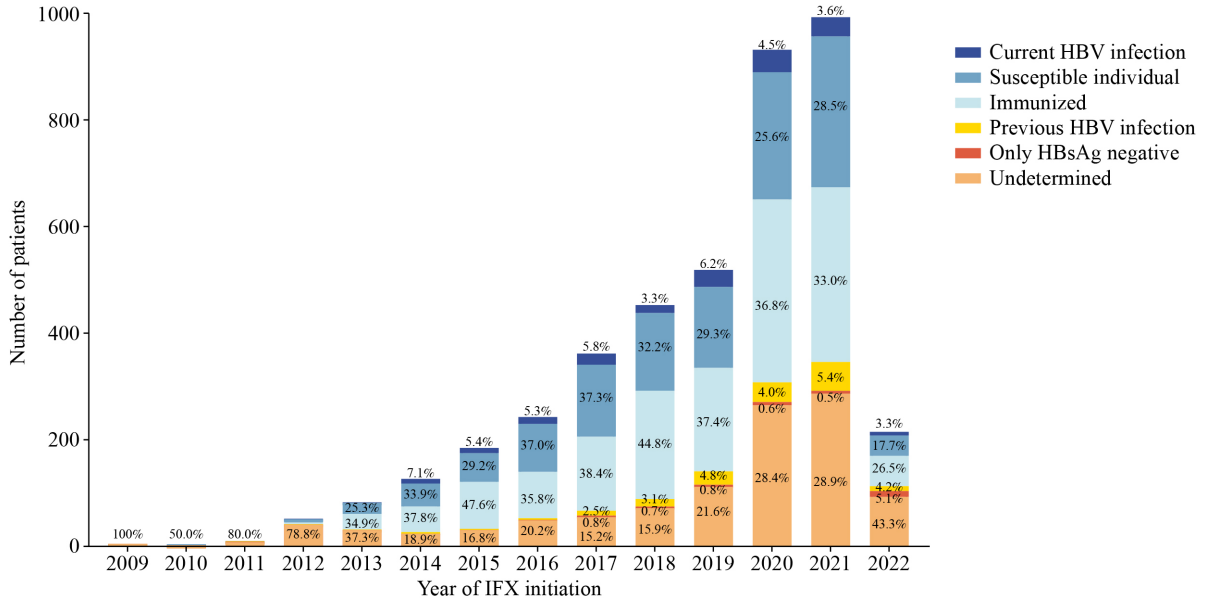

Fig. 2 Change in rates of different group over time.

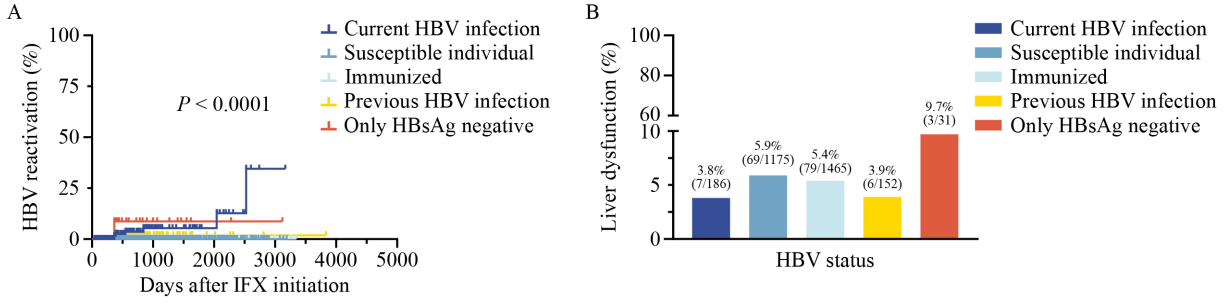

Fig. 3 (A) HBV reactivation rate. (B) Liver dysfuciton rate.

only 4.4% in those with occult infection (HBsAg negative/anti-HBc positive) [32–36]. The serology type thus plays a critical role, underscoring the importance of pre-treatment screening to guide prophylaxis and monitoring.

Admittedly, there were such biases in our study. First, the number of enrolled CD/UC patients was not comparable. Second, the non-mandatory management of antiviral therapy in HBsAg positive patients had caused bias in our study as a partial number of patients refused our medication recommendations due to various concerns in practice. Finally, among 15 patients with HBV reactivation, 10 of them received combination therapy with azathioprine, which was also associated with HBV

Table 3 Characteristics and management of the patients with HBV reactivation/infection

Patient	Group	Age (years)	Gender	HBsAg (IU/mL)	Anti-HBs (IU/L)	Anti-HBc (S/CO)	Anti-HBe (S/CO)	Peak HBV-DNA (IU/mL)	Time from IFX to reactivation/ infection (days)	ALT (U/L)	AST (U/L)	Total bilirubin (μmol/L)	Anti-viral treatment	Continue IFX	Outcome
1	1	39	Male	55.86	0.23	10.34	0.02	1200	843	9	10	10.1	Entecavir	Yes	Continue monitoring
2	1	43	Male	222.37	0.15	10.75	0.01	1300	1902	4	13	9.2	Entecavir	No	Change IFX to UST
3	1	31	Male	> 250	0.15	10.65	0.02	1.49×10^{8}	1844	33	16	20.5	Lamivudine + adefovir dipivoxil	No	Change anti-viral treatment to Entecavir, change IFX to UST
4	1	31	Male	60.36	0.38	10.86	0.01	1200	1340	14	15	19.4	Entecavir	Yes	Continue monitoring
5	1	39	Male	207.39	0	10.91	0.03	130	2347	49	37	12.0	Entecavir	Yes	Continue monitoring
6	1	61	Female	> 250	0.2	10.35	0.01	140	579	16	35	8.1	Entecavir	Yes	Continue monitoring
7	1	48	Male	158.23	0.92	10.69	0.02	220	625	34	33	15.6	Lamivudine	Yes	Continue monitoring
8	3	43	Female	0.02	11.31	0.15	1.14	< 30	1396	23	23	9.0	None	Yes	Add entecavir
9	3	28	Male	0.03	10.06	0.13	1.03	< 30	1422	11	14	6.8	None	Yes	Add entecavir
10	3	57	Male	0.02	11.01	0.15	1.21	< 30	1393	27	22	16.8	None	Yes	Add entecavir
11	4	56	Female	0.02	1.02	8.19	0.02	3400	389	12	13	10.2	None	Yes	Add entecavir
12	4	42	Male	0.01	0.38	9.37	1.10	400	1455	33	18	7.7	None	Yes	Add entecavir
13	5	40	Male	0.03	NA	NA	NA	< 30	256	12	16	8.5	None	Yes	Add entecavir
14	5	27	Female	0.02	NA	NA	NA	< 30	465	7	16	14.3	None	Yes	Add entecavir
15	6	35	Male	NA	NA	NA	NA	1.81×10^{4}	478	341	123	23.9	None	Yes	Add entecavir and hepatoprotective therapy

ALT, aminotransferase; AST, aspartate aminotransferase; IFX, infliximab; UST, ustekinumab.

Table 4 Vaccination status of patients

Group	Vaccinated	Without vaccination	HBV infection/ reactivation
HBsAg positive	24	19	2
Susceptible individual	328	163	0
Immunized	428	87	1
Previous HBV infection	56	11	2
Only known HBsAg negative	1	0	0
Undetermined	29	12	0

reactivation. Due to the minior number of HBV reactivation, we did not further explore potential factors as mentioned. Considering constraints such as no response to hepatitis B vaccination, inconvenience and costs, IBD cases have a lower response rate to HBV vaccination compared with controls [22,24,37]. Therefore, each patient should consider whether to receive the vaccine based on individual circumstances after understanding the infection risk during IFX treatment.

In this study, 5.78% of patients had liver dysfunction during treatment, and no liver failure was detected. IFX did not increase the risk of liver dysfunction in the HBsAg positive group compared with the immunized group. Surprisingly, liver dysfunction was not significantly associated with HBV reactivation in this study, suggesting that IFX-induced HBV reactivation does not invariably lead to liver dysfunction, which may be due to the small number of reactivation cases. Therefore, larger samples with prolonged observation time are warranted. In HBsAg positive patients, it is essential to strictly monitor not only liver function but also HBV DNA.

Nearly one-third of patients in this study made up the susceptible population. Given that HBV vaccination for newborns was implemented in China in 1992, and considering that IBD (especially CD) cases are generally young, this proportion seems high. Therefore, we assessed the vaccination status. As shown above, in all groups, even in the HBsAg positive group, the majority of cases were administered the vaccine, but protective anti-HBs antibodies declined over time [38]. Since even after previous vaccination, patients may still test positive for HBsAg, showing a higher risk of HBV reactivation than other groups, hepatitis B screening before IFX injection is crucial.

In summary, the present study highlights the critical importance of rigorous HBV screening before IFX initiation. Despite antiviral prophylaxis, the risk of HBV reactivation in HBsAg positive patients still exists, underlining the need for continuous monitoring of HBV DNA and comprehensive management strategies to effectively mitigate this risk. On the other hand, individuals with HBsAg negativity, including the susceptible population, have a low risk of HBV reactivation, thus reassuring patients and physicians of the safety of IFX in this cohort. By highlighting these critical issues, we hope to pave the way for improved management approaches that may increase the safety of IFX therapy.

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Compliance with ethics guidelines

Conflicts of interest Rongbei Liu, Tingting Wu, Jian Tang, Hongjie Zhang, Yanyun Fan, Haibo Sun, Chen Xie, Qunyan Zhou, Hongzhen Xu, Yabi Zhu, Mei Ye, Xiaomin Shi, Feng Tian, Haiyan Shen, Dan Xu, Ying Zhou, and Qian Cao declare that there is no conflict of interests in this study.

This study was approved by the Ethics Committee of Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine (approval number 2022Y0356), and the study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Due to the retrospective nature of this study and the anonymity of its participants, the ethics committee waived the requirement for written informed consent.

Data availability and compliance statement

The authors declare that the acquisition and subsequent use of all data presented in this manuscript comply fully with all relevant local, national, and international laws, regulations, ethical guidelines (including Ethics Committee of Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine approval number 2022Y0356), and the terms of use associated with the original data sources.

The authors bear full legal responsibility for ensuring the legality of data acquisition and all subsequent uses.

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