



# Prevalence and factors related to hepatitis B and C infection in inflammatory bowel disease patients in China: A retrospective study

Mei Lan Huang, Xi Tao Xu, Jun Shen, Yu Qi Qiao, Zhang Han Dai, Zhi Hua Ran\*

Department of Gastroenterology, Renji Hospital, Shanghai Jiao-Tong University School of Medicine, Shanghai Institute of Digestive Disease, Shanghai Inflammatory Bowel Disease Research Center, 160# Pu Jian Ave., 200127 Shanghai, China

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## KEYWORDS

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## Abstract

**Objectives:** The objectives of this retrospective study were to assess the prevalence of HBV and HCV infection in Chinese IBD patients, identify potential risk factors of the infection in this population, and discuss the prevalence of HBV and HCV in the general Chinese population.

**Methods:** A total of 714 IBD patients who had been investigated for HBV and/or HCV infection were consecutively enrolled in the study. Clinical and laboratory data on IBD and hepatitis infection were collected. A control group of 22,373 healthy individuals was also included in the study.

**Results:** Present and past HBV infection was found in 40.62% of IBD patients (ulcerative colitis: HBsAg +, 5.68%; anti-HBc +, 41.64%; Crohn's disease: HBsAg +, 5.29%; anti-HBc +, 39.80%;), and 27.58% of the non-IBD group (HBsAg +, 5.52%; anti-HBc +, 27.58% [P = 0.00]). HCV infection was found in 0.42% of IBD patients and 0.36% of the non-IBD group (P = 0.80). One hundred and fifty-four of the IBD patients (21.57%) had been effectively vaccinated for HBV. In a multivariate analysis, age, family history of hepatitis B, and IBD-related admission were significantly related to HBV infection in IBD patients. Potential risk factors for HCV were not analyzed due to the limited number of HCV-positive patients in the study.

**Conclusions:** Prevalence of HBV infection in IBD patients was higher than that in the non-IBD patients, whereas prevalence of HCV infection was similar to that of the non-IBD group. Effective vaccination for HBV was present in only a small proportion of IBD patients.

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\* Corresponding author. Tel.: +86 021 68383114.

E-mail address: [zhihuanan@vip.163.com](mailto:zhihuanan@vip.163.com) (Z.H. Ran).

## 1. Introduction

Patients with inflammatory bowel disease (IBD) are believed to be at an increased risk of HBV and HCV infection due to the elevated frequency of endoscopic, surgical, and transfusion procedures needed to effectively control the disease. The increased frequency of these procedures may put IBD patients at a greater risk of nosocomial transmission of HBV and HCV. Over the last decade, several studies have evaluated the prevalence of HBV and HCV in IBD patients from Europe and America.<sup>1-3</sup> In these studies, the prevalence rates of present or past HBV infection varied, ranging from 2.86% to 24.7%. The prevalence of HBV and HCV in patients with IBD has been reported to be higher than that in the general population.<sup>1,3</sup> However, more recently, some researchers have argued against this view, suggesting that IBD patients should no longer be considered to be at an increased risk of HBV and HCV infection.<sup>4-7</sup>

Viral reactivation is associated with significant morbidity and mortality in IBD patients receiving immunosuppressants.<sup>8</sup> Furthermore, reactivation of HBV related to infliximab administration has been reported in several cases,<sup>9-11</sup> and therefore, IBD patients should be considered as candidates for vaccination against primary HBV infection. However, the incidence of HCV reactivation was much lower than that of HBV reactivation in patients taking anti-tumor-necrosis factor drugs.<sup>12,13</sup>

To the best of our knowledge, only a few studies have been published on the prevalence of HBV and HCV infection and the risk factors for infection in Chinese patients with IBD. This study aimed to assess the prevalence of HBV and HCV infection in patients with IBD and investigate the epidemiological risk factors associated with infection. Furthermore, we aimed to investigate the HBV immunization status of patients with IBD, as well as the prevalence of HBV and HCV in the general Chinese population.

## 2. Methods

### 2.1. Study design and patient selection

This was a retrospective, single-center study conducted in China between January 2001 and August 2012. All included IBD patients were in-patients diagnosed with ulcerative colitis (UC) or Crohn's disease (CD) according to clinical, endoscopic, histological, and/or radiologic criteria. All patients in the IBD group were screened for HBV and HCV during patients selection. Furthermore, data on epidemiological factors associated with IBD and infection were collected. We also enrolled 22,373 age- and sex-matched healthy controls who had been tested for HBV and HCV markers in order to evaluate the prevalence in the general population. The control group comprised of individuals who had presented for routine health examination at the health center of the Shanghai Renji Hospital in 2011. More than one-third of the healthy controls were Shanghai natives, and the rest were from other parts of the country.

### 2.2. Viral infection markers

Markers for HBV and HCV include hepatitis B surface antigen (HBsAg), antibodies to hepatitis B surface antigen (anti-HBs),

antibodies to hepatitis B core protein (anti-HBc), hepatitis B e-antigen (HBeAg), antibodies to hepatitis B e-antigen (anti-HBe), and antibodies to hepatitis C virus (anti-HCV), which were detected using chemiluminescent immunoassays (Architect i2000 System; Abbott Laboratories, USA). HCV RNA and HBV DNA were assessed using Taqman reverse-transcription real time ([RT]-PCR) (ABI7700; Applied Biosystems; USA). Aminotransferase levels (ALT, AST), alkaline phosphatase (AKP),  $\gamma$ -glutamyltranspeptidase ( $\gamma$ -GT), and total bilirubin were also measured using routine laboratory methods.

### 2.3. Epidemiological information

Data on the different risk factors for hepatitis infection were recorded. The risk factors related to IBD were taken from the patient's medical records, including the type of diagnosis (CD or UC), number of admissions related to IBD, surgery related to IBD, endoscopic and surgical procedures, disease duration, and medical treatments (such as treatment with steroids, immunosuppressants, and biologics). Additionally, data on other risk factors that were related to IBD, including weight, age, alcohol consumption, type of residence (urban or rural), family history of hepatitis, surgical history, hospital admissions unrelated to IBD, and blood transfusion history, were recorded.

### 2.4. Definitions of HBV infection, HBV vaccination, and HCV infection

Some definitions such as present and past HBV infection were defined according to the terminology applied by the National Institutes of Health conferences on the Management of Hepatitis B.<sup>14</sup> Patients with positive HBV serological markers were classified as having either present HBV infection or past/resolved HBV infection. Present HBV infection included chronic hepatitis B and inactive HBsAg carrier state, and past HBV infection included resolved hepatitis B (presence of anti-HBc with or without anti-HBs). Effective vaccination was defined as an anti-HBs level  $\geq 10$  mIU/ml without the presence of anti-HBc.<sup>15</sup>

Patients who were anti-HCV-positive but HCV-RNA-negative were classified as having inactive HCV infection; patients who were HCV-RNA-positive were considered to have chronic HCV infection.

### 2.5. Statistical analysis

Results are expressed as mean  $\pm$  standard deviation (SD) and percentages. Univariate analysis, chi-squared test, and Fisher's exact test were used to compare proportions, and quantitative variables were compared using the Student's *t*-test. Furthermore, variables that showed a *P*-value  $< 0.10$  in the univariate analysis were entered into a logistic regression analysis.<sup>16</sup> The strength of each significant association is indicated by the odds ratio (OR) and its 95% confidence interval (CI). All statistical analyses were performed using an SPSS 15.0 software (SPSS, Chicago, USA).

### 3. Results

#### 3.1. Prevalence of viral markers in IBD patients

Overall, 714 IBD patients (415 men, 299 women; mean age,  $37.25 \pm 9.83$ ) were included in this study. Of these, 317 patients had UC and 397 had CD. Of the IBD patients, 21.99% had undergone IBD-related surgery, 22.97% had been treated with immunosuppressive therapy, and 8.54% had been treated with anti-TNF- $\alpha$  agents (infliximab). The clinical characteristics of IBD patients were also classified according to the Montreal classification (Table 1).<sup>17</sup>

Present HBV infection was found in 5.46% of the IBD group. Ten patients tested positive for HBV-DNA replication. Three patients tested positive for anti-HCV (0.46%) and none of them tested positive for HCV-RNA replication. Effective vaccination was detected in 21.57% of IBD patients (22.67% and 20.19% in CD and UC patients, respectively). The mean age of IBD patients with effective vaccination was lower than that of individuals with present or past HBV infection ( $31.79 \pm 1.38$  for those effectively vaccinated and  $42.75 \pm 1.93$  for those who were not vaccinated;  $P < 0.001$ ). Information on the different viral markers studied is detailed in Fig. 1. There was no significant difference between the prevalence of HBV, HBV-vaccination, and HCV between CD and UC patients (Table 2).

Of the ten HBV-DNA-positive patients, 2 had undergone surgery and 1 had previously had received blood transfusions. None of the 3 anti-HCV-positive patients had undergone

surgery or blood transfusions prior to hospitalization. Eight of the 39 HBsAg-positive patients had abnormal hepatological test results. Aminotransferase levels were elevated in 3 patients, alkaline phosphatase levels were increased in 3 cases, the  $\gamma$ -GT level was elevated in 2 patients, and bilirubin levels were high in 1 patient. One patient who had elevated aminotransferase levels also had HBV-DNA replication. The other two patients who had shown abnormal aminotransferase levels resumed normal liver function after regular treatment strategy, such as oral administration of polyene phosphatidylcholine and/or glycyrrhizic acid. All of the anti-HCV-positive patients had normal hepatological test results and none of them had HCV-RNA replication.

#### 3.2. Factors related to infection

The prevalence of HBV and HCV markers did not differ significantly between CD and UC patients (Table 2). Risk factors for present and past infection were investigated among the IBD group.

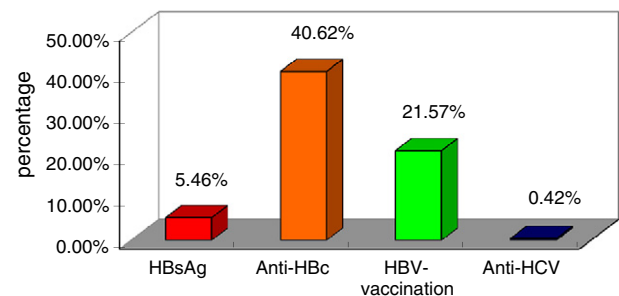
Factors related to infection according to the univariate analysis, and therefore included in the multivariate analysis, are shown in Table 3. Age, family history of hepatitis, and a previous IBD-related admission were found to be significant independent risk factors for HBV infection in the logistic regression analysis. Age (OR: 0.96; 95% CI: 0.95–0.97;  $P < 0.001$ ), family history of hepatitis B (OR: 2.35; 95% CI: 1.56–3.53;  $P < 0.001$ ), and previous IBD-related admissions (OR: 3.59; 95% CI: 2.07–6.23;  $P < 0.001$ ) were significantly associated with HBV infection in IBD. Use of immunosuppressants was also a risk factor for HBV infection in CD patients, according to the univariate analysis. The risk factors for HCV infection in IBD patients could not be analyzed due to the limited number of HCV-infected patients.

#### 3.3. Prevalence of HBV and HCV in the general population

Overall, there were 22,373 healthy controls (13,424 men, 8949 women; mean age,  $40.25 \pm 17.83$ ) enrolled in the survey. These people did not have obvious diseases or conditions. The prevalence of HBV and HCV in the control group is shown in Fig. 2, and Table 4 shows the difference in the prevalence of viral markers between the IBD group and healthy controls.

Crohn's disease (n = 397)			
Age at diagnosis (years)		%	
A1( $\leq 16$ )		16.12	
A2(17 - 40)		63.72	
A3(>40)		20.15	
Location	%	Upper GI modifier (L4)	%
L1 (Terminal ileum)	31.74	L1 + L4	1.26
L2 (Colon)	26.45	L2 + L4	0.00
L3 (Ileocolon)	38.29	L3 + L4	1.26
L4 (Upper GI)	1.01		
Behavior	%	Perianal disease modifier (p)	
B1 (Nonstricturing, nonpenetrating)	43.58	B1p	12.09
B2 (Stricturing)	24.69	B2p	2.52
B3 (Penetrating)	10.83	B3p	6.30
Ulcerative colitis (n = 317)			
		%	
E1 (Ulcerative proctitis)		14.20	
E2 (Left-sided UC)		38.17	
E3 (Extensive UC)		47.63	

Prevalence of HBV, HBV vaccination and HCV in IBD patients



**Figure 1** The prevalence of HBV, HBV vaccination, and HCV in IBD patients.

**Table 2** Prevalence of HBV and HCV markers in CD and UC.

	Crohn's disease (n = 397)	Ulcerative colitis (n = 317)	P value
HBsAg n/N	21/397	18/317	0.82
Anti-HBc# n/N	158/397	132/317	0.62
HBeAg n/N	3/397	2/317	1.00
Anti-HBe n/N	18/397	16/317	0.75
Anti-HBs* n/N	90/397	64/317	0.42
Total negative serology for HBV n/N	149/397	121/317	0.86
Anti-HCV n/N	2/397	1/317	1.00

Anti-HBc#: including present and past HBV infection.

\* Effective vaccination without anti-HBc.

#### 4. Discussion

At present, researchers are not unanimous in their opinions on the rate of hepatitis infection among IBD patients. It has previously been suggested that IBD patients are a high-risk group for viral hepatitis infection. We assessed the prevalence of HBV and HCV infection in both Chinese IBD patients and the general population of China. In this study, the prevalence of past HBV infection in IBD patients was significantly higher than that reported previously in some cohorts of IBD patients from Europe and America, with positivity for HBsAg ranging from 0.68% to 2.1% and positivity for anti-HBc ranging from 7.5% to 10.9%.<sup>1,16</sup> In an Italian cohort of IBD patients, a higher prevalence of HBV markers was also found in CD patients than in UC patients<sup>1</sup>; however, our study did not find any difference between the 2 groups. A Spanish study of hepatitis B infection in IBD patients conducted by Loras et al.<sup>16</sup> found no difference between hepatitis infection rates in UC and CD patients. With regard to HCV infection prevalence, the values obtained from this study (0.50% in CD and 0.32% in UC) are lower than those from previously reported studies in IBD patients from Europe and America.<sup>1,3,16</sup> No HCV-RNA-positive patients were found, and therefore, HCV genotype was not assessed.

The results of an epidemiological study performed in the general population of China by Wang et al. showed that the percentages of present and past hepatitis B infection were 6.1% and 13.6%, respectively.<sup>18</sup> A national epidemiological survey performed by Liang et al. showed that the weighted prevalence of HBsAg and anti-HBcAb was 7.2% and 34.1%, respectively.<sup>19</sup> A sero-epidemiological study performed by Chen et al. showed that the anti-HCV prevalence rate was 0.43% in the general population of China.<sup>20</sup> The prevalence of HBV and HCV in healthy persons was also analyzed in our study and showed that the rates of present HBV infection, past HBV infection, HBV-vaccination, and HCV infection were 5.52%, 22.06%, 35.47%, and 0.36%, respectively. Thus, the prevalence of present HBV infection in Chinese IBD patients in this study was similar to that in the general population. However, the prevalence of past HBV infection in IBD patients in our study was much higher than that in the general population. These results support the hypothesis that IBD patients are at an increased risk of contracting HBV infection in China. In studies by Biancone et al.<sup>1</sup> and Tolentino et al.,<sup>21</sup> the

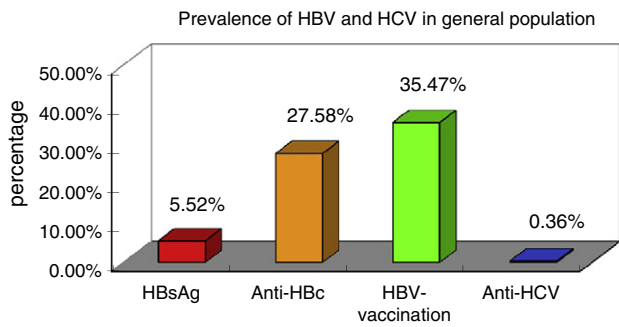
prevalence of anti-HBc positivity was also higher in IBD patients than in the general population. However, we found no differences in the prevalence of HCV infection between IBD patients and the general population. The prevalence of HCV in

**Table 3** Factors related to present and past HBV infection in IBD patients.

		Positive viral markers	Negative viral markers	P value
Age (years)	UC	45.47 ± 15.83	39.33 ± 15.81	0.00*
	CD	37.77 ± 12.96	30.32 ± 12.03	0.00*
Alcohol consumption (%)	UC	15.15	15.13	0.68
	CD	11.34	9.62	0.57
Habitat (rural) (%)	UC	51.52	56.76	0.36
	CD	55.70	57.74	0.69
Family history of hepatitis B (%)	UC	11.36	0.04	0.02*
	CD	13.92	0.07	0.03*
General surgeries (%)	UC	10.61	8.65	0.56
	CD	13.92	8.79	0.25
General admissions (%)	UC	9.09	6.49	0.39
	CD	11.39	7.53	0.19
IBD-related surgeries (%)	UC	24.24	20.25	0.21
	CD	25.32	20.08	0.22
IBD-related admissions (%)	UC	49.24	37.29	0.03*
	CD	43.67	33.42	0.04*
Antibiotics therapy (%)	UC	86.36	86.49	0.98
	CD	94.30	92.05	0.25
Steroid (%)	UC	46.97	45.41	0.78
	CD	55.70	54.39	0.80
Immunosuppressants (%)	UC	15.91	16.21	0.94
	CD	35.44	24.69	0.02*
History of blood transfusion (%)	UC	5.30	5.40	0.97
	CD	8.86	8.37	0.88
Hemoglobin level (g/L)	UC	118.78 ± 23.21	117.18 ± 21.99	0.59
	CD	112.80 ± 24.45	111.47 ± 21.66	0.58
Hematocrit level	UC	0.35 ± 0.16	0.35 ± 0.03	1.00
	CD	0.35 ± 0.72	0.35 ± 0.51	0.51
C-reactive protein (mg/l)	UC	19.05 ± 25.87	22.6 ± 28.16	0.51
	CD	34.86 ± 42.59	39.30 ± 34.65	0.42
Erythrocyte sedimentation rate (mm/h)	UC	31.66 ± 24.02	37.06 ± 28.81	0.18
	CD	32.03 ± 24.04	38.22 ± 25.25	0.11
Weight (kg)	UC	56.98 ± 10.88	58.26 ± 11.03	0.57
	CD	53.31 ± 11.84	53.43 ± 10.99	0.69

UC:ulcerative colitis;CD:Crohn's disease.

\* Indicating a significant difference; positive viral markers indicating HBsAg and/or HBcAb positive.



**Figure 2** The prevalence of HBV and HCV in the general population.

IBD patients was low in our study, which was similar to that in the general population. Only 3 patients were positive for anti-HCV without HCV-RNA replication. Therefore, the risk factors related to HCV could not be analyzed in these patients.

The associations found between previous IBD-related admissions and HBV infection in the univariate and multivariate analyses suggest that preventive measures may sometimes be insufficient in some cases, which can result in nosocomial HBV infections. The results of a Spanish study showed that drug abuse and risky sexual behavior were risk factors for viral hepatitis infection (both HBV and HCV) in IBD patients.<sup>16</sup> These results could not be replicated in this study, as Chinese IBD patients may be inclined to conceal such behaviors. In addition, anti-HCV screening in blood banks and hepatitis B vaccination for newborns have been mandatory in China since 1994 and 2002, respectively. It is also validated by a major proportion of HBV-effective vaccination in the younger IBD patients in this study.

The frequency of an effective HBV vaccination in IBD patients was 21.57%, which was higher than that reported previously in IBD populations,<sup>22</sup> but lower than that in the general Chinese population. In study by Papa et al.,<sup>4</sup> the prevalence of HBV vaccination in IBD patients was 23.9%, which was similar to that found in an IBD group in this study. The frequency of total HBV-negative serology was 37.82% in IBD patients. In our study, 3 patients treated with infliximab plus azathioprine underwent serological transformation from totally negative viral markers to isolated anti-HBc-positive markers after a long-term treatment. In 1 patient, isolated anti-HBc-positive serology transformed to inactive chronic hepatitis B infection after 1 yr of infliximab plus azathioprine therapy. Fortunately, the patient did not develop acute icteric hepatitis due to timely detection by the physician. Importantly, several severe and fatal reactivations of HBV related to immunosuppressants and biologics have been reported in recent years.<sup>10,23–27</sup> HBV infection or reactivation can be a life-threatening problem for disease management in IBD patients undergoing immunosuppressive treatment. Therefore, HBV vaccination status should be assessed at the time of IBD diagnosis. In China, the universal HBV vaccination of preadolescents in schools has been introduced gradually since 1992 partly reflected by the large proportion of effective vaccination among the younger IBD patients in this study. In the future, these interventions may be able to minimize HBV-infection risk in IBD patients.

Reactivation of occult HBV infection has been observed in some studies, especially in patients with hematological malignancies treated with chemotherapy.<sup>27,28</sup> Reactivation of occult HBV has also been reported in CD patients treated with biologics.<sup>29,30</sup> However, the true frequency of the reactivation of occult HBV infection still remains unknown. Consequently, physicians need to be aware that anti-HBc-positive IBD patients are potential occult HBV carriers.<sup>30–32</sup> Prophylactic antiviral therapy should also be administered to IBD patients with anti-HBc-positive serology who need immunosuppressive or biological therapies according to the Chinese inflammatory bowel disease-treatment guidelines. Furthermore, HBV DNA levels and liver function tests need to be periodically performed for patients undergoing immunosuppressive and/or biological therapies.

In conclusion, the prevalence of HBV infection in IBD patients in China was higher than that seen in Europe and America. Additionally, the prevalence of past HBV infection in Chinese IBD patients was higher than that in the general population. The prevalence of HCV infection in IBD patients was similar to that of the general population, which was much lower than that seen in the IBD population of Europe and America. Chinese physicians should pay more attention to the HBV status of IBD patients during immunosuppressive therapy, particularly during biological therapy. HBV vaccination should be performed as soon as possible in patients with negative serology for HBV. In addition, a nationwide, multi-center study is needed to improve our understanding of the risk factors related to HCV infection in Chinese IBD patients.

## Conflict of Interest

The authors declare that there is no conflict of interest.

## Acknowledgments

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**Table 4** Comparison of the prevalence of viral markers between IBD and general population.

	IBD (n = 714)	General population (n = 22373)	P value
HBsAg n/N	39/714	1235/22373	0.95
Anti-HBc# n/N	290/714	6170/22373	0.00
HBeAg n/N	5/714	142/22373	0.81
Anti-HBe n/N	34/714	1093/22373	0.88
Anti-HBs* n/N	154/714	7936/22373	0.00
Total negative serology for HBV n/N	270/714	7032/22373	0.00
Anti-HCV n/N	3/714	81/22373	0.80

Anti-HBc#: including present and past HBV infection.

\* Effective vaccination without anti-HBc.

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