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Original Article

Hepatic Steatosis but Not Fibrosis Is Independently Associated with Poor Outcomes in Patients with Inflammatory Bowel Disease

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Background/Aims: Increased prevalence of nonalcoholic fatty liver disease (NAFLD) and inflammatory bowel disease (IBD) has been reported. However, the effects of NAFLD on the outcome of IBD remains unclear. We investigated whether the presence of NAFLD could influence the outcomes of patients with IBD.

Methods: We recruited 3,356 eligible patients with IBD into our study between November 2005 and November 2020. Hepatic steatosis and fibrosis were diagnosed using hepatic steatosis index of ≥30 and fibrosis-4 of ≥1.45, respectively. The primary outcome was clinical relapse, defined based on the following: IBD-related admission, surgery, or first use of corticosteroids, immunomodulators, or biologic agents for IBD.

Results: The prevalence of NAFLD in patients with IBD was 16.7%. Patients with hepatic steatosis and advanced fibrosis were older, had a higher body mass index, and were more likely to have diabetes (all p<0.05).

Conclusions: Hepatic steatosis was independently associated with increased risks of clinical relapse in patients with ulcerative colitis and Crohn's disease, whereas fibrotic burden in the liver was not. Future studies should investigate whether assessment and therapeutic intervention for NAFLD will improve the clinical outcomes of patients with IBD. **(Gut Liver 2024;18:294-304)**

Key Words: Inflammatory bowel diseases; Non-alcoholic fatty liver disease; Hepatic steatosis; Liver fibrosis; Outcome

INTRODUCTION

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic, progressive, and a result of immune-mediated intestinal inflammation. IBD occurs due to defects in the intestinal mucosal barrier that leads to an increase in gut permeability. This in turn facilitates exposure of gut microorganisms and food antigens to the lamina propria, triggering an immunological response that consequently leads to intestinal inflammation.[1] An increase in both incidence and prevalence of IBD has social and public health implications and has, therefore, become an important issue requiring further attention in many countries.

Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of hepatic steatosis (5% or more) in the absence of secondary contributing factors, i.e., chronic viral hepatitis, certain drug treatments, autoimmune hepatitis, and excess alcohol consumption. The prevalence of NAFLD is rapidly increasing worldwide, and it is currently among the most common types of chronic liver disease.[2] Globally, the average prevalence of NAFLD is approximately 24.1%, but varies depending on the region, i.e., variations range from 13.5% to 31.8% by country.[3] The pathogenesis of NAFLD is related to a number of different factors, including lipotoxicity, immune system activation,

genetic susceptibilities, consumption of Western food, and dysbiosis.[4]

Gut dysbiosis is defined as disruption of the normal gut microbiota and results in an increase in intestinal permeability, intestinal inflammation, as well as hepatic inflammation and fibrosis.[5] Therefore, dysregulation of the gut microbiota and gut barrier impairment are associated with the pathogenesis and severity both of NAFLD and IBD.[6,7] The prevalence of NAFLD among IBD patients was shown to be significantly higher than that of the general population.[8] Various factors including chronic inflammation, a history of IBD surgery, drugs (i.e., steroids or azathioprine induced hepatotoxicity), malnutrition, and metabolic factors have been shown to be independently associated with NAFLD in patients with IBD.[9,10]

We aimed to investigate the outcome of IBD in patients with NAFLD. We evaluated two characteristics of NAFLD, hepatic steatosis and fibrosis, to determine if either were associated with clinical relapse.

MATERIALS AND METHODS

1. Study design and participants

We recruited a total of 4,114 eligible patients diagnosed with IBD between November 2005 and November 2020 for this retrospective cohort study (Fig. 1). The exclusion criteria were as follows: (1) age <18 years; (2) uncertain diagnosis of IBD; (3) insufficient clinical and laboratory information; (4) combined chronic viral hepatitis; (5) significant alcohol consumption (≥210 g in men and ≥140 g in women per week);[11] and (6) other chronic liver diseases such as autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, hemochromatosis, Wilson disease, or overlap syndrome (Fig. 1).

2. IBD diagnosis, assessment of disease activity and treatment

Diagnosis of IBD is through a combination of established tests and procedures, including clinical, serologic, endoscopic, histologic and/or radiologic examinations.[12,13] To assess disease severity, Mayo and Crohn's Disease Activity Index scores were used for patients with UC and CD, respectively. Clinical remission was defined as a Mayo score of ≤2 and a Crohn's Disease Activity Index score of <150.[14] According to the Montreal classification of IBD, patients with UC were classified into three subgroups: proctitis (E1), left-sided colitis (E2), and pancolitis (E3). Patients with CD were classified into four subgroups depending on disease location: ileal (L1), colonic (L2), ileocolonic (L3), and isolated upper gastrointestinal disease (L4). Furthermore, disease behavior was characterized as non-stricturing, non-penetrating (B1), stricturing (B2), and penetrating (B3) disease.[15]

The treatment agents used for IBD patients included 5-aminosalicylates (5-ASA; mesalazine, balsalazide, and sulfasalazine), corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate, and cyclosporine), biologic agents (infliximab, adalimumab, golimumab, vedolizumab, and ustekinumab), and small molecules (tofacitinib). Patients with IBD were treated according to the Korean IBD treatment guidelines.[16,17]

Patients were administered first-line induction therapy for the treatment of mild-to-moderate UC, which consisted of 5-ASA. If treatment with 5-ASA was ineffective or accompanied by systemic symptoms, corticosteroid treatment was provided. If corticosteroid treatment was not well tolerated, azathioprine or methotrexate was added according to the treatment guidelines.[16] Biologic or small-molecule therapy was recommended for patients with corticosteroid-dependent UC. If the patient did not respond to this treatment, a secondary biologic was considered.[18]

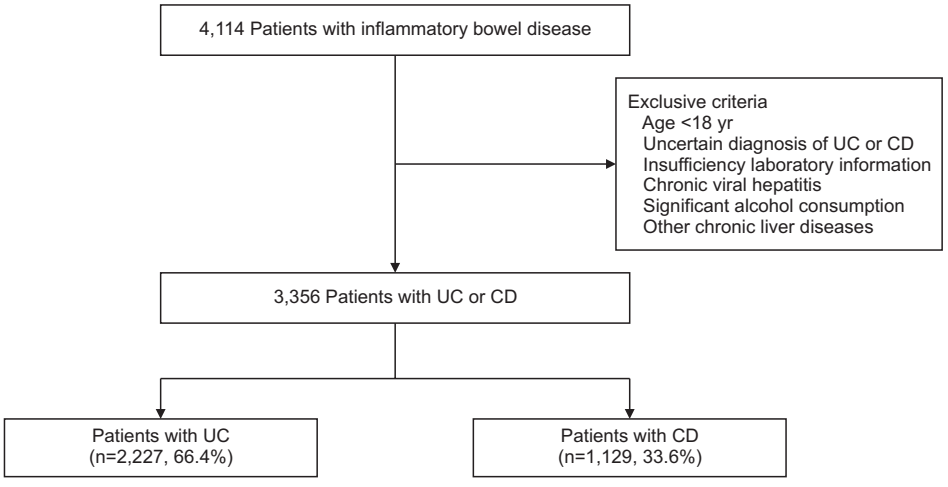

Fig. 1. Flowchart of the study population selection. A total of 4,114 patients were recruited into the study. After excluding 758 patients according our exclusion criteria, 3,356 patients were selected for statistical analysis (2,227 patients with UC and 1,129 patients with CD). UC, ulcerative colitis; CD, Crohn's disease.

First-line induction therapy for the treatment of moderate-to-severe CD consists of systemic corticosteroids. If the patient could not tolerate this treatment or did not respond to corticosteroids alone, azathioprine or methotrexate was added to the existing 5-ASA regimen. If the treatment failed, biologic therapy was indicated. If the patient experienced a primary non-response, a secondary loss of response, or the occurrence of side effects, dose escalation or drug switching was considered. After prior biologic therapy failure, second-line biologic drugs were recommended.[17] All patients were followed up regularly at 2- to 6-month intervals based on their individual needs.

3. Noninvasive models for NAFLD

Because liver biopsy is not always feasible, especially in asymptomatic and otherwise apparently healthy subjects, noninvasive assessments of liver steatosis and fibrosis have been widely used for patients with NAFLD.[19]

Liver steatosis is assessed noninvasively by several panels. These include the fatty liver index, NAFLD liver fat score, or hepatic steatosis index (HSI).[20] Of these, we opted to use the HSI for the assessment of steatosis burden because some of the clinical information required for the assessments was not available. For example, waist circumference and fasting insulin were required to calculate fatty liver index and NAFLD liver fat scores, respectively. Therefore, the use of these panels was limited in our study. The predictive accuracy of patients with fatty liver on the HSI range from 60.3% to 73.8%.[21] HSI was calculated using the following equation: 8 × (alanine aminotransferase [ALT]/aspartate aminotransferase [AST])+body mass index (BMI)+2 (if female) or +2 (if diabetes mellitus), with an area under the receiver operating characteristic curve of 0.812. Generally, the results are interpreted using two cutoff points: An HSI score of <30 indicates that NAFLD can be ruled out (sensitivity 93.1%). A score of ≥36 indicates a positive NAFLD diagnosis (specificity 92.4%).[21] In this study, we used an HSI cutoff of 30 to define NAFLD because most patients with CD or UC develop symptoms at a young age and often have a low BMI.[22,23] We did not use an HSI score of 36 as the cutoff value because the prevalence of fatty liver in our cohort using this cutoff value was significantly lower than the results of previous studies (16.7% vs 26.8%).[24,25]

Assessment of liver fibrosis is performed noninvasively using several panels such as NAFLD fibrosis score and fibrosis-4 (FIB-4) index.[20] Of these, we opted to use the FIB-4 index to assess fibrotic burden because insufficient information was available regarding diabetic status. This information was required to calculate the NAFLD fibrosis score and limited the use of this panel in our study. The FIB-4 index allowed accurate identification of patients with severe fibrosis with an area under the receiver operating characteristic curve of 0.85. The FIB-4 index was calculated as (age×AST)/(platelet count×$\sqrt{\text{ALT}}$). A score of <1.45 indicated that fibrosis may not be present (sensitivity 74.3% and negative predictive value 94.7%).[26]

4. Outcomes

The index date of our study population was either the date they first visited our institute, when IBD was first diagnosed at our institute or when IBD was previously diagnosed at another institute. The primary outcome of this study was clinical relapse. This was defined as any occurrence of IBD-related admission or surgery, as well as the first use of corticosteroids, immunomodulators, or biologics agents during follow-up.[27,28] IBD-related admission was defined as the first occurrence of hospitalization due to worsening of the disease. IBD-related surgery was defined as an IBD-related intestinal resection surgery.[29] Corticosteroid use was defined as an initial dose of ≥20 mg per day for 2 weeks after IBD was diagnosed.[30]

5. Statistical analysis

Continuous variables are reported as mean with standard deviation or as median with interquartile range depending on the normality of the underlying distribution using the Student t-test. Categorical variables are presented as percentage using the chi-square or Fisher exact tests. Cumulative clinical relapse rate of IBD were estimated by the Kaplan-Meier method. Multivariate analysis was conducted using the Cox proportional hazards model, and four models were created for patients with IBD. Model 1 was adjusted for age, sex, duration of IBD diagnosis, and BMI. Model 2 was adjusted for smoking, hypertension, and diabetes mellitus in addition to the variables used in model 1. Model 3 was adjusted for biochemical markers in addition to the variables used in model 2. For UC patients, model 4 was further adjusted for disease location. In CD patients, model 4 was further adjusted for Montreal location, behavior, and perianal disease modifier. In addition, model 5 was further adjusted for the use of steroid in addition to the variables used in model 4. All analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA) with significance set at a p-value of <0.05.

6. Ethics statement

This study was performed in agreement with the ethical guidelines of the Declaration of Helsinki. This study received the Institutional Review Board of Severance Hospital approval, and includes protocol number 4-2022-0530. Informed consent was not required due to the retrospective study design.

RESULTS

1. Baseline characteristics of the study population

After excluding 758 patients according to our exclusion criteria, a total of 3,356 patients were included in the statistical analysis (2,227 [66.4%] patients with UC, and 1,129 [33.6%] patients with CD) (Fig. 1). The baseline characteristics of the study population are summarized in Table 1.

Table 1. Baseline Characteristics of the Study Population

Variable	All (n=3,356)	Ulcerative colitis (n=2,227)	Crohn's disease (n=1,129)
Demographic variable			
Age, yr	44.1±15.8	47.4±16.0	37.7±13.1
Male sex	1,960 (58.4)	1,178 (52.9)	782 (69.3)
Body mass index, kg/m^2	25.2±4.0	25.9±3.6	24.0±4.3
Duration from IBD diagnosis, yr	7.6±5.6	7.4±5.7	8.0±5.3
Hypertension	180 (5.4)	160 (7.2)	20 (1.8)
Diabetes	108 (3.2)	81 (3.6)	27 (2.4)
Smoking status at diagnosis			
Never smoked	2,579 (76.8)	1,623 (72.9)	956 (84.7)
Ex-smoker	524 (15.6)	430 (19.3)	94 (8.3)
Current smoker	253 (7.5)	174 (7.8)	79 (7.0)
Ulcerative colitis disease location (n=2,227)	-		-
Proctitis (E1)		758 (34.0)	
Left sided (E2)		772 (34.7)	
Pancolitis (E3)		697 (31.3)	
Montreal location (n=1,129)	-	-	-
Ileal (L1)			412 (36.5)
Colonic (L2)			78 (6.9)
Ileocolonic (L3)			629 (55.7)
Isolated upper GI disease (L4)			10 (0.9)
Montreal disease behavior	-	-	
Non-stricturing, non-penetrating (B1)			698 (61.8)
Stricturing (B2)			201 (17.8)
Penetrating (B3)			230 (20.4)
Perianal disease modifier (p)			524 (46.4)
Disease activity index			
Mayo score	-		-
0–2		1,204 (54.1)	
3–5		783 (35.2)	
6–10		202 (9.1)	
11–12		38 (1.7)	
Crohn's Disease Activity Index	-	-	
<150			589 (52.2)
150 to <220			412 (36.5)
220 to <450			123 (10.9)
≥450			5 (0.4)
Laboratory variable			
White blood cell count, ×10^9/L	7.3±2.4	7.2±2.7	7.5±2.2
Hemoglobin, g/dL	13.4±2.1	13.4±2.0	13.4±2.4
Platelet count, 10^9/L	328.6±118.6	302.3±104.9	380.5±127.5
Erythrocyte sedimentation rate, mm/hr	28.0±27.1	24.3±25.0	35.2±29.3
Serum C-reactive protein, mg/dL	10.1±24.8	6.7±21.9	16.8±28.4
Serum albumin, g/dL	4.3±0.5	4.3±0.5	4.3±0.6
Total bilirubin, mg/dL	0.7±0.4	0.7±0.3	0.8±0.5
Aspartate aminotransferase, IU/L	20.3±14.1	19.5±11.4	21.9±18.3
Alanine aminotransferase, IU/L	18.3±18.0	18.4±18.5	18.2±17.2
Gamma-glutamyltransferase, IU/L	13.5±69.9	13.6±79.3	13.2±45.7
Noninvasive model			
HSI ≥30	560 (16.7)	427 (19.2)	133 (11.8)
FIB-4 ≥1.45	179 (5.3)	149 (6.7)	30 (2.7)

Data are presented as mean±SD or number (%).
IBD, inflammatory bowel disease; GI, gastrointestinal; HSI, hepatic steatosis index; FIB-4, fibrosis 4.

The mean age of the entire study population was 44.1±15.8 years, and the majority of the patients were male (n=1,960, 58.4%). Within the UC subgroup, the mean age was mean 47.4±16.0 years and most of the patients were male (52.9%). According to the UC Montreal classification, 758 (34.0%), 772 (34.7%), and 697 (31.3%) patients had proctitis, left-sided colitis, and pancolitis, respectively. Within the CD subgroup, the mean age was mean 37.7±13.1 years, and the majority of the patients were male (69.3%). According to the CD Montreal classification, 412 (36.5%), 78 (6.9%), 629 (55.7%), and 10 (0.9%) patients had ileal (L1), colonic (L2), ileocolonic (L3), and upper gastrointestinal tract involvement (L4), respectively. Moreover, 698 (61.8%), 201 (17.8%), and 230 (20.4%) patients had inflammatory (B1), stricturing (B2), and penetrating (B3) disease behaviors, respectively. Perianal involvement was observed in 524 (46.4%) patients.

In the entire study population, 560 patients had liver steatosis at baseline (427 [19.2%] patients with UC, and 133 [11.8%] patients with CD), and 179 (5.3%) patients had significant fibrosis at baseline (149 [6.7%] patients with UC, and 30 [2.7%] patients with CD).

2. Baseline comparison between patients with and without liver steatosis or fibrosis

The baseline characteristics of patients with and with-

Table 2. Comparison between Patients with and without Steatosis or Fibrosis

Variable	HSI ≥30 (n=560)	HSI <30 (n=2,796)	p-value	FIB-4 ≥1.45 (n=179)	FIB-4 <1.45 (n=3,177)	p-value
Demographic variable						
Age, yr	51.4±16.2	42.7±15.3	<0.001	68.4±13.7	42.7±14.8	<0.001
Male sex	246 (43.9)	1,714 (61.3)	<0.001	90 (50.3)	1,870 (58.9)	0.023
Body mass index, kg/m^2	31.2±2.9	24.0±2.9	<0.001	26.4±4.1	25.2±4.0	<0.001
Duration from IBD diagnosis, yr	7.9±5.7	7.5±5.5	0.120	8.4±5.6	7.6±5.6	0.037
Hypertension	42 (7.5)	138 (4.9)	0.014	13 (7.3)	167 (5.3)	0.246
Diabetes	60 (10.7)	48 (1.7)	<0.001	17 (9.5)	91 (2.9)	<0.001
Smoking status at diagnosis			0.631			0.001
Never smoked	430 (76.8)	2,149 (76.9)		125 (69.8)	2,454 (77.2)	
Ex-smoker	83 (14.8)	441 (15.8)		45 (25.2)	478 (15.1)	
Current smoker	47 (8.4)	206 (7.4)		9 (5.0)	244 (7.7)	
IBD			<0.001			<0.001
Ulcerative colitis	427 (76.3)	1,800 (64.4)		149 (83.2)	2,078 (65.4)	
Crohn's disease	133 (23.7)	996 (35.6)		30 (16.8)	1,099 (34.6)	
Ulcerative colitis disease location (n=2,227)			0.423			<0.001
Proctitis (E1)	154 (36.1)	604 (33.6)		68 (45.6)	690 (33.2)	
Left sided (E2)	150 (35.1)	622 (34.6)		57 (38.3)	715 (34.4)	
Pancolitis (E3)	123 (28.8)	574 (31.8)		24 (16.1)	673 (32.4)	
Montreal location (n=1,129)			0.003			0.563
Ileal (L1)	64 (48.1)	348 (34.9)		12 (40.0)	400 (36.4)	
Colonic (L2)	13 (9.8)	65 (6.5)		3 (10.0)	75 (6.8)	
Ileocolonic (L3)	56 (42.1)	573 (57.5)		15 (50.0)	614 (55.9)	
Isolated upper GI disease (L4)	0	10 (1.0)		0	10 (0.9)	
Montreal disease behavior (n=1,129)			0.167			0.245
Non-stricturing, non-penetrating (B1)	90 (67.7)	608 (61.0)		22 (73.3)	676 (61.5)	
Stricturing (B2)	24 (18.0)	177 (17.8)		2 (6.7)	199 (18.1)	
Penetrating (B3)	19 (14.3)	211 (21.2)		6 (20.0)	224 (20.4)	
Perianal disease modifier (p)	47 (8.4)	477 (17.1)	0.006	8 (26.7)	516 (47.0)	0.028
Laboratory variable						
White blood cell count, ×10^9/L	7.3±2.4	7.3±2.4	0.542	6.1±1.9	7.4±2.4	<0.001
Hemoglobin, g/dL	13.5±2.0	13.3±2.1	0.221	13.3±1.7	13.4±2.1	0.447
Platelet count, ×10^9/L	308.4±98.3	332.7±122.1	<0.001	210.5±60.7	335.3±117.8	<0.001
Erythrocyte sedimentation rate, mm/hr	28.1±25.5	27.9±27.3	0.888	22.4±21.4	28.3±27.3	0.001
Serum C-reactive protein, mg/dL	6.6±19.9	10.8±25.6	<0.001	6.3±16.3	10.3±25.2	0.003
Serum albumin, g/dL	4.3±0.5	4.3±0.5	0.153	4.3±0.5	4.3±0.5	0.698
Total bilirubin, mg/dL	0.7±0.3	0.7±0.4	0.065	0.8±0.5	0.7±0.4	0.008
Aspartate aminotransferase, IU/L	22.3±11.7	19.9±14.5	<0.001	36.2±43.2	19.4±9.6	<0.001
Alanine aminotransferase, IU/L	24.0±21.3	17.2±17.1	<0.001	26.3±43.2	17.9±15.4	0.010
Gamma-glutamyltransferase, IU/L	17.7±93.9	12.7±64.0	0.223	23.2±79.8	13.0±69.2	0.094

Data are presented as mean±SD or number (%).
IBD, inflammatory bowel disease; GI, gastrointestinal; HSI, hepatic steatosis index; FIB-4, fibrosis 4.

out liver steatosis and/or fibrosis were compared and are depicted in Table 2. Patients with liver steatosis were significantly older (mean 51.4±16.2 years vs 42.7±15.3 years) and were more likely to be female (43.9% vs 61.3%). In addition, these patients had a significantly higher BMI (mean 31.2±2.9 kg/m^2 vs 24.0±2.9 kg/m^2), longer disease duration (mean 7.9±5.7 years vs 7.5±5.5 years), and were more likely to have diabetes mellitus (10.7% vs 1.7%) and UC (76.3% vs 64.4%) (all p<0.001). Patients with liver steatosis had a significantly higher prevalence of inflammation localized at the ileum (48.1% vs 34.9%, p=0.003), whereas the presence of perianal lesions was significantly less frequent (8.4% vs 17.1%, p=0.006). Regarding laboratory blood test results, patients with liver steatosis had significantly higher AST (mean 22.3±11.7 IU/L vs 19.9±14.5 IU/L) and ALT (mean 24.0±21.3 IU/L vs 17.2±17.1 IU/L) levels. In contrast, these patients had significantly lower platelet count (mean 308.4±98.3 ×10^9/L vs 332.7±122.1 ×10^9/L) and serum C-reactive protein (mean 6.6±19.9 mg/dL vs 10.8±25.6 mg/dL) level than those without steatosis (all p<0.05).

Patients with significant liver fibrosis were significantly older (mean 68.4±13.7 years vs 42.7±14.8 years), and majority were female (50.3% vs 58.9%). Furthermore, patients with liver fibrosis had significantly higher BMI (mean 26.4±4.1 kg/m^2 vs 25.2±4.0 kg/m^2), longer disease duration from IBD diagnosis (mean 8.4±5.6 years vs 7.6±5.6 years), and were more likely to have diabetes mellitus (9.5% vs 2.9%) and UC (83.2% vs 65.4%) (all p<0.001) than patients without liver fibrosis. The proportion of non-smokers was significantly lower in patients with liver fibrosis (69.8% vs 77.2%, p<0.001). Patients with significant liver fibrosis also had significantly higher prevalence of inflammation localized to the rectum (45.6% vs 33.2%, p<0.001), whereas the presence of perianal lesions was significantly less (26.7% vs 47.0%, p=0.028). Regarding laboratory test results, patients with liver fibrosis had significantly higher levels of total bilirubin (mean 0.8±0.5 mg/dL vs 0.7±0.4 mg/dL), AST (mean 36.2±43.2 IU/L vs 19.4±9.6 IU/L), and ALT (mean 26.3±43.2 IU/L vs 17.9±15.4 IU/L) (all p<0.05). They also had significantly lower white blood cell count (mean 6.1±1.9 ×10^9/L vs 7.4±2.4 ×10^9/L), platelet count (mean 210.5±60.7 ×10^9/L vs 335.3±117.8 ×10^9/L), erythrocyte sedimentation rate (mean 22.4±21.4 mm/hr vs 28.3±27.3 mm/hr), and C-reactive protein level (mean 6.3±16.3 mg/dL vs 10.3±25.2 mg/dL) than patients without significant liver fibrosis (all p<0.05).

3. Influence of liver steatosis or significant fibrosis on clinical relapse in UC patients

Multivariate Cox regression models were used to investigate the influence of liver steatosis and significant fibrosis on clinical relapse of UC (Table 3). In the minimally adjusted models (models 1 and 2), liver steatosis and significant fibrosis were significantly associated with a higher risk of clinical relapse (hazard ratio [HR], 1.510; 95% confidence

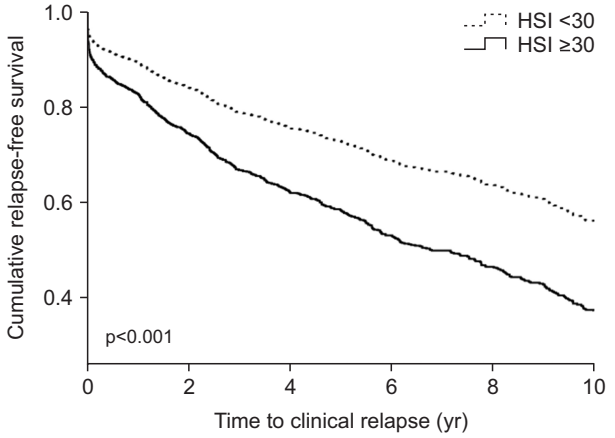

Fig. 2. Adjusted cumulative clinical relapse-free survival probability according to liver steatosis in ulcerative colitis patients. The adjusted cumulative incidence of clinical relapse was significantly higher in patients with (hepatic steatosis index [HSI] ≥30) than in patients without (HSI <30) liver steatosis (p<0.001).

Table 3. Adjusted HRs with 95% CIs of Steatosis and Significant Fibrosis to Predict Clinical Relapse in Ulcerative Colitis Patients

Adjustment	By HSI ≥30		By FIB-4 ≥1.45	
	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Model 1	1.510 (1.161–1.964)	0.002	0.705 (0.504–0.986)	0.041
Model 2	1.497 (1.144–1.959)	0.003	0.693 (0.496–0.969)	0.032
Model 3	1.687 (1.283–2.219)	<0.001	0.919 (0.642–1.315)	0.643
Model 4	1.697 (1.291–2.230)	<0.001	0.949 (0.663–1.359)	0.777
Model 5	1.557 (1.181–2.054)	0.002	0.786 (0.545–1.133)	0.197

HR, hazard ratio; CI, confidence interval; HSI, hepatic steatosis index; FIB-4, fibrosis 4.
Model 1: age, sex, duration of inflammatory bowel disease diagnosis, and body mass index; Model 2: model 1+smoking status, hypertension, and diabetes; Model 3: model 2+white blood cell count, hemoglobin, platelet count, erythrocyte sedimentation rate, serum C-reactive protein, total bilirubin, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, and serum albumin; Model 4: model 3+ulcerative colitis disease location; Model 5: model 4+use of corticosteroids.

interval [CI], 1.161 to 1.964; HR, 1.497; 95% CI, 1.144 to 1.959; all p<0.05 for steatosis and HR, 0.705; 95% CI, 0.504 to 0.986; HR, 0.693; 95% CI, 0.496 to 0.969; all p<0.05 for fibrosis). In further adjusted models (models 3 and 4), liver steatosis was associated with an increased risk of clinical relapse (HR, 1.687; 95% CI, 1.283 to 2.219; HR, 1.697; 95% CI, 1.291 to 2.230; all p<0.05), but significant liver fibrosis was not (all p>0.05). The cumulative incidence of clinical relapse was significantly higher in patients with liver steatosis than in those without liver steatosis (p<0.001) (Fig. 2). In model 5 which adjusted the use of steroid, liver steatosis was independently associated with an increased risk of clinical relapse (HR, 1.557; 95% CI, 1.181 to 2.054; p<0.05), but significant liver fibrosis was not (p>0.05). We also performed Cox regression based on the cutoff of HSI 36. In UC patients, the independent association between steatosis and outcomes was similarly maintained (adjusted HR, 2.672; 95% CI, 1.525 to 4.682; p=0.001 in model 5) (Supplementary Table 1).

4. Influence of liver steatosis and significant fibrosis on clinical relapse in CD patients

The adjusted multivariate Cox regression analysis (models 1 to 4) (Table 4) indicated that liver steatosis was significantly associated with an increased risk of clinical relapse in CD patients (HR, 1.596; 95% CI, 1.190 to 2.140; HR, 1.557; 95% CI, 1.155 to 2.098; HR, 1.516; 95% CI, 1.119 to 2.052; HR, 1.536; 95% CI, 1.130 to 2.087; all p<0.05 for steatosis). In contrast, significant liver fibrosis was not associated with an increased risk of clinical relapse (all p>0.05). The cumulative incidence of clinical relapse was significantly higher in patients with liver steatosis than in those without liver steatosis (p=0.006) (Fig. 3). In model 5 which adjusted the use of steroid, liver steatosis was associated with an increased risk of clinical relapse (HR, 1.459; 95% CI, 1.081 to 1.971; p=0.014), but significant liver fibrosis was not (p=0.541). We also performed Cox regression based on the cutoff of HSI 36. In CD patients, the independent association between steatosis and outcomes was similarly maintained (adjusted HR, 1.207; 95% CI, 0.661 to 2.204; p=0.540 in model 5) (Supplementary Table 2).

DISCUSSION

As the prevalence of NAFLD in IBD patients has gradually increased,[8] appropriate management of NAFLD has emerged as an important health issue. Our single-center, retrospective cohort study showed relatively lower prevalence of hepatic steatosis in IBD patients (19.2% in UC and 11.8% in CD). The prevalence of significant liver fibrosis was also lower than that of the general population, but this was negligible (6.7% in UC and 2.7% in CD). Moreover, our study demonstrated that hepatic steatosis is associated with an increased risk of clinical relapse in both UC and CD patients. However, the association between fibrotic burden and the risk of clinical relapse was not statistically

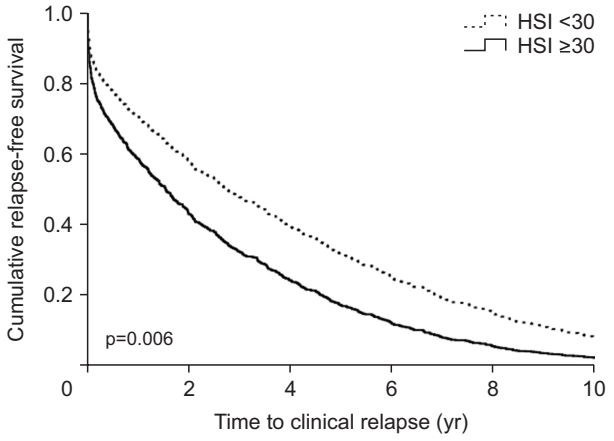

Fig. 3. Adjusted cumulative clinical relapse-free survival probability according to liver steatosis in Crohn's disease patients. The adjusted cumulative incidence of clinical relapse was significantly higher in patients with (hepatic steatosis index [HSI] ≥30) than in patients without (HSI <30) liver steatosis (p=0.006).

Table 4. Adjusted HRs with 95% CIs of Steatosis and Significant Fibrosis for Predicting Clinical Relapse in Crohn's Disease Patients

Adjustment	By HSI ≥30		By FIB-4 ≥1.45	
	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Model 1	1.596 (1.190–2.140)	0.002	0.738 (0.445–1.225)	0.240
Model 2	1.557 (1.155–2.098)	0.004	0.723 (0.435–1.201)	0.210
Model 3	1.516 (1.119–2.052)	0.007	0.777 (0.442–1.368)	0.382
Model 4	1.536 (1.130–2.087)	0.006	0.840 (0.476–1.480)	0.546
Model 5	1.459 (1.081–1.971)	0.014	0.839 (0.479–1.471)	0.541

HR, hazard ratio; CI, confidence interval; HSI, hepatic steatosis index; FIB-4, fibrosis 4.
Model 1: age, sex, duration of inflammatory bowel disease diagnosis, and body mass index; Model 2: model 1+smoking status, hypertension, and diabetes; Model 3: model 2+white blood cell count, hemoglobin, platelet count, erythrocyte sedimentation rate, serum C-reactive protein, total bilirubin, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, and serum albumin; Model 4: model 3+Montreal location, behavior, and perianal disease modifier; Model 5: model 4+use of corticosteroids.

significant.

Our study has several clinical implications. First, our study shows that hepatic steatosis can negatively affect the long-term outcomes of patients with IBD. The study design and results were based on a large patient cohort (n>4,000) to ensure optimal statistical power. Second, despite the fact that the study was conducted at a single, tertiary academic institution, the long follow-up period (median 10.0 years) provided sufficient time to obtain a high number of clinical relapse cases (33.9% in UC and 75.6% in CD). This allowed us to identify independent prognostic factors associated with disease outcome, such as hepatic steatosis. Third, we found that it is important to differentiate between hepatic steatosis and fibrosis to evaluate the impact of NAFLD on the prognosis of IBD. Our results suggest that early intervention to treat NAFLD may positively affect disease prognosis in patients with IBD.

In this study, the prevalence of hepatic steatosis in patients with IBD was 16.7%, which is lower than that reported in previous studies. Zou *et al.*[31] reported that prevalence of NAFLD of 27.5% in patients with IBD. Another single-center, cross-sectional study by Bargiggia *et al.*[32] revealed that the prevalence of moderate-to-severe hepatic steatosis was 39.5% in patients with CD and 35.5% in patients with UC. Although the exact reasons for this discrepant prevalence of NAFLD is not clear, we suspect that it may be due to differences in the study populations. For example, our patients were younger (mean 27.3 years vs 37.6 years) and therefore tended to have lower BMI (mean 24.0 kg/m^2 vs 25.9 kg/m^2) than patients in the study by Noorian *et al.*[28] NCD Risk Factor Collaboration included patients from Europe and North America. These countries have higher prevalence of obesity as well as NAFLD than Asia.[33] In addition, differences in disease prevalence may be related to the definitions that were used or the diagnostic tools to assess NAFLD between studies.

We found that the hepatic steatosis independently increased the risk of clinical relapse in both UC and CD patients. NAFLD is associated with pro-inflammatory status, insulin resistance, old age, and metabolic syndrome with overlap.[34-36] Although our study could not provide evidence for a potential causal relationship, the increase in cytokine secretion and tight junction disruption observed in NAFLD might support the possibility of clinical relapse in IBD patients in our study. Another possibility is that dysbiosis associated with NAFLD may negatively affect the prognosis of IBD. Obesity is also a strong risk factor for NAFLD and results in excessive accumulation of triglycerides in the liver, as well as an increase in the secretion of pro-inflammatory cytokines due to high caloric intake. This in turn would lead to simultaneous hepatic and intestinal inflammation as well as oxidative stress.[37] In addition to NAFLD-related obesity, NAFLD-related drugs (including statins and insulin sensitizers)[38] may have a response-lowering effect through interactions with IBD drugs.

HSI and FIB-4 are the noninvasive surrogates for the assessment of hepatic steatosis and fibrosis, respectively. These assessments are easy-to-use in clinical practice and are based on several clinical variables such as age, sex, and laboratory tests, which might explain the reason for their frequent use in large-scale studies. A recent study showed that HSI has a high predictive accuracy and can been used as a simple and efficient NAFLD screening tool to select individuals for liver ultrasonography.[25] Furthermore, another study showed that FIB-4 had a significantly higher diagnostic accuracy than other noninvasive panels for liver fibrosis. It was found that the accuracy was similar to that of MR elastography in patients with biopsy-proven NAFLD.[39] Indeed, it might not be clinically feasible to perform liver specific imaging such as ultrasonography, transient elastography, magnetic resonance elastography, or magnetic resonance imaging-based proton density fat fraction without eminent evidence of underlying liver disease, especially in asymptomatic IBD patients. Thus, the routine use of noninvasive surrogates, especially HSI for the assessment of hepatic steatosis, is appropriate. For these reasons, HSI as a prognostic tool in our study was clinically relevant. Cutoffs for both HSI 30 and 36 were calculated, but the sample size was significantly reduced when using the cutoff HSI 36 (n=133 [11.8%] and n=22 [1.9%]).

Lastly, although fibrotic burden is one of the most important prognostic factors in fatty liver disease,[40] it was not associated with an increased risk of clinical relapse in our study. The prevalence of patients with advanced fibrosis (FIB-4 ≥3.25) was only 0.36% (12/3,356), probably due to the young age of our study population. Immune-related diseases are more apparent at a young age and are associated with an activated inflammatory state.[41] Active liver inflammation induces intestinal inflammation through increased secretion of pro-inflammatory cytokines, acute phase proteins, and disruption of tight junctions.[42] NAFLD is a spectrum of chronic liver disease ranging from simple steatosis to nonalcoholic steatohepatitis, which can progress to fibrosis, cirrhosis, liver failure, and cancer.[43] Because steatosis occurs earlier than fibrosis, early control of NAFLD may be indirectly beneficial in the treatment of IBD. If fibrosis has already progressed, the inflammatory burden is lower than that of steatosis, and it may have a reduced effect on the intestines.

We acknowledge several limitations in this study. First, patient identification and data were collected retrospectively. This can potentially be a confounding variable, and

result in selection bias. Second, the effect of medications to treat IBD on the outcomes could not be adjusted as variable factors. IBD medications were included in the primary outcome and could not be used as a variable due to statistical error. In particular, unlike CD, the use of steroids in UC might have influenced our results, although we found consistent results even after adjusting for its potential influence. Third, we did not include fecal calprotectin and endoscopic analysis. Therefore, unevaluated or severe disease activity may have caused elevation of liver enzymes, which may have resulted in biased estimation of steatosis or fibrosis. Fourth, because we used noninvasive surrogates such as HSI and FIB-4, which might be incomplete screening tool for defining fatty liver or fibrosis, the detailed histological assessment of the presence and degree of hepatic steatosis and fibrosis was not available. Fifth, we could not investigate whether the dynamic change in hepatic steatosis, based on serial assessment of HSI, is associated with the increased risk of clinical relapse. Lastly, the cutoff values of HSI and FIB-4 did not provide sufficient statistical power. The statistical power values of HSI 30 and FIB-4 1.45 were 2.54% and 4.38%, respectively, in patients with UC and 4.04% and 3.25%, respectively, in those with CD, probably due to the extremely small proportion of patients with fatty liver and significant fibrosis. Further studies with large sample sizes are needed to validate our findings.

In conclusion, hepatic steatosis was independently associated with an increased risk of clinical relapse in patients with UC and CD. Fibrosis burden in liver was not associated with clinical relapse. Further studies are warranted to investigate whether the assessment and therapeutic intervention of NAFLD improve clinical outcomes in patients with IBD.

CONFLICTS OF INTEREST

S.U.K. has served as an advisory committee member of Gilead Sciences, Bayer, Eisai, and Novo Nordisk. He is a speaker for Gilead Sciences, GSK, Bayer, Eisai, Abbvie, EchoSens, MSD, Eisai, Otsuka, and Bristol-Myers Squibb. He has also received a research grant from Abbvie and Bristol-Myers Squibb. S.J.P., S.U.K., and J.H.C. are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

Study concept and design: H.K.H., H.W.L., S.U.K., J.H.C. Data acquisition: H.K.H., H.W.L., J.H.P., J.J.P., T.I.K., J.S.L, B.K.K., J.Y.P., D.Y.K., S.H.A., S.U.K., J.H.C. Data analysis and interpretation: H.K.H., H.W.L., S.U.K., J.H.C. Drafting of the manuscript: H.K.H., S.U.K., J.H.C. Critical revision of the manuscript for important intellectual content: H.K.H., S.U.K., J.H.C. Statistical analysis: H.K.H., S.U.K., J.H.C. Administrative, technical, or material support; H.K.H., H.W.L., J.H.P., J.J.P., T.I.K., J.S.L., B.K.K., J.Y.P., D.Y.K., S.H.A., S.U.K., J.H.C. Study supervision: S.U.K., J.H.C. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl220409.

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