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HEPATOBILIARY MANIFESTATIONS IN INFLAMMATORY BOWEL DISEASE: RAISING CONCERN ON AN OLD DILEMMA

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HEPATOBILIARY MANIFESTATIONS IN INFLAMMATORY BOWEL DISEASE: RAISING CONCERN ON AN OLD DILEMMA (Abstract): Inflammatory bowel disease (IBD) is increasingly recognized as a multisystem disorder with significant extraintestinal manifestations, including hepatobiliary complications. This prospective study **aimed** to assess the prevalence of hepatic manifestations and associated risk factors in a real-world IBD cohort. **Materials and methods**: Between December 2023 and March 2024, 153 patients (78 with ulcerative colitis and 75 with Crohn's disease) were enrolled at a tertiary care center in northeast Romania. Comprehensive clinical evaluations, laboratory assessments, abdominal ultrasound, and vibration-controlled transient elastography with controlled attenuation parameter (CAP) were performed. **Results:** Hepatobiliary abnormalities were identified in 43.1% of patients, with steatotic liver disease (SLD) being the most common manifestation (26.8%). Notably, SLD was observed in 30.8% of ulcerative colitis and 22.7% of Crohn's disease patients. Patients with hepatic manifestations exhibited higher inflammatory markers (white blood cell count, C-reactive protein), liver enzymes, CAP values, and fibrosis, alongside longer disease duration and increased flare frequency. Multivariate analysis revealed that older age, higher body mass index, a diagnosis of Crohn's disease, and elevated CRP levels were independent predictors of hepatic involvement. **Conclusions:** These findings underscore the importance of routine liver screening and integrated hepatologic assessment in IBD management to address potential complications and improve patient outcomes. **Keywords:** INFLAMMATORY BOWEL DISEASE, HEPATIC MANIFESTATIONS, STEATOTIC LIVER DISEASE, LIVER INJURY.

INTRODUCTION

Inflammatory bowel disease (IBD) is a digestive disease with multisystemic involvement. Extraintestinal manifestations of IBD are common, occurring in both ulcerative colitis (UC) and Crohn's disease (CD), and significantly affect patient morbidity and mortality (1). Approximately 5%

of IBD patients will develop chronic liver disease, whereas up to 30% of IBD patients will have aberrant liver findings. The etiology of hepatic manifestations linked to IBD remains unclear; nevertheless, the relationship between the two conditions may be affected by immunological, genetic, and environmental variables (2). IBD progression and its complications and extraintestinal manifestations are of great interest with an important impact on the quality of life of these patients.

Fatty liver, or steatotic liver disease, represents the most prevalent hepatobiliary disorders of IBD. Its progression is directly attributable to obesity, insulin resistance, and metabolic syndrome, which is currently regarded as the hepatic manifestation of metabolic syndrome. The clinical and histological spectrum is broad, encompassing simple steatosis, steatohepatitis, nonalcoholic steatohepatitis (NASH), liver cirrhosis, and hepatocellular carcinoma. According to research, people with IBD are more likely to develop NAFLD due to chronic inflammation, digestive abnormalities, prior surgery, and changes in the fecal microbiota. The prevalence appears to be at least comparable to or greater than in the general population, current data indicates a prevalence between 8% and 71% (3, 4). Moreover, lean individuals, a feature often presented in IBD patients, are mostly overlooked representing a diagnosis challenge due to their normal BMI.

In 2023, liver disease experts introduced Steatotic Liver Disease (SLD) as a new umbrella term for conditions involving fat accumulation in the liver, replacing the older “fatty liver disease” label. Within this framework, NAFLD has been renamed Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). This shift aims to reduce stigma tied to terms like “non-alcoholic” and better reflect the disease’s connection to metabolic issues such as obesity and diabetes. MASLD requires evidence of hepatic steatosis plus at least one metabolic risk factor. A notable addition is Metabolic and Alcohol-Associated Liver Disease (MetALD), a category for MASLD patients who also consume moderate alcohol. This change, driven by major liver associations, enhances classification accuracy and encourages a more inclusive, patient-focused approach to liver health (5-7).

Primary sclerosing cholangitis (PSC) is strongly associated with IBD, particularly UC. In the Caucasian population, it is estimated that 4% of UC patients may develop PSC, and three-quarters of PSC patients have UC (8). Cholelithiasis is also a frequent pathology found in patients with IBD. Individuals with Crohn's disease are twice as likely to develop gallstones. In contrast, patients with UC do not have an elevated risk compared with the general population. (9, 10). Cholelithiasis, granulomatous hepatitis, portal vein thrombosis, IgG4-related cholangiopathy, pyogenic liver abscess, hepatic amyloidosis, and PSC are occurring IBD-related hepatobiliary manifestations (11, 12).

In recent decades, therapeutic options for the management of IBD have expanded. New biological and small molecule therapies have been incorporated into the pharmacological arsenal, allowing for a more individualized approach and the pursuit of ever-stricter remission targets. Drug induced liver injury (DILI) in an IBD patient may present with elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST); alkaline phosphatase (ALP) and gamma-glutamyl transferase

(GGT) (cholestasis pattern); jaundice (hyperbilirubinemia); or a combined pattern. This complication can occur acutely with the development of acute liver failure, autoimmune hepatitis, and reactivation of hepatitis B, and some of these patients may develop chronic injury (13).

Hepatitis B virus reactivation is another issue that can be seen in patients with IBD. Anti-TNF and anti-integrin therapies have been linked to the reactivation of hepatitis B virus, especially in individuals who are positive for hepatitis B surface antigen (HBsAg), similar to other immunosuppressive treatments, such as prolonged or high-dose corticosteroid use. The frequency of hepatitis C virus (HCV) infection in patients with IBD seems to be lower than expected. The data suggests that IBD patients in Western European countries are no longer considered a risk category for HBV or HCV infection (14, 15).

The aim of this study was to assess the prevalence of hepatic manifestations and factors associated with their development in a real-world cohort of IBD patients.

MATERIALS AND METHODS

Between December 2023 and March 2024, we prospectively enrolled 153 patients with a confirmed diagnosis of IBD at a tertiary care center in northeast Romania. The study aimed to comprehensively assess these patients, capturing detailed personal medical histories that included detailed IBD features like duration or time of diagnosis, disease complications, extraintestinal manifestations, hepatic manifestations, and comorbidities. Each participant underwent a meticulous clinical examination, and blood samples were collected for extensive laboratory analysis. To evaluate alcohol consumption, we administered the Alcohol Use Disorders Identification Test (AUDIT) questionnaire, a validated tool for identifying potential alcohol abuse. Additionally, all patients received abdominal ultrasound and FibroScan examinations, conducted by an experienced physician.

Vibration-controlled transient elastography (VCTE) with controlled attenuation parameter (CAP) was performed using FibroScan® 502 Touch device (EchoSens, Paris, France). To ensure measurement accuracy, patients fasted for at least four hours prior to the procedure, as food intake can temporarily influence liver fat readings. The examination began with the standard M probe, switching to the XL probe when prompted by the device—typically for patients with greater body mass or thicker skin layers. The transducer was positioned in the 9th to 11th intercostal space, aligning with the right hepatic lobe, a standard site for liver assessment. SLD was diagnosed when CAP values exceeded 248 dB/m, a threshold supported by prior research (16), indicating significant fat accumulation in the liver.

This study was approved by the Ethics Committee of our University and was conducted according to the principles of the Declaration of Helsinki. Each participant signed a written informed consent form.

Statistical analyses were conducted using IBM *SPSS version 22.0* (IBM SPSS Inc., Chicago, IL, USA). Normality of numerical variables was evaluated using the Kolmogorov-Smirnov test. Normally distributed continuous variables were summarized as mean ± standard deviation, while non-normally distributed variables were expressed using medians and interquartile ranges. Categorical data were presented as frequencies and percentages. For group comparisons, parametric tests (e.g., Student's t-test for inde-

pendent samples) were applied to normally distributed continuous variables, whereas non-parametric alternatives (Mann-Whitney U or Kruskal-Wallis tests) were used for skewed distributions. Associations between categorical variables were examined using chi-square or Fisher's exact tests. Statistical significance was defined as a two-tailed *p*-value <0.05. Univariate and multivariate linear regression were performed to identify variables significantly associated with the presence of hepatic manifestations. Only complete datasets were included in the final analysis.

RESULTS

Study of population characteristics

The study cohort consisted of 153 patients diagnosed with IBD, including 78 patients with UC and 75 patients with CD. Detailed demographic and clinical characteristics are summarized in first table. The mean age was comparable between the UC and CD groups (47.8 ± 16.2 years *vs.* 47.1 ± 15.9 years, p=0.792), indicating no significant age difference. Gender distribution was also similar, with females comprising 44.9% of UC patients and 46.7% of CD patients (p=0.822). Rural residence was reported in 47.4% of UC patients and 46.7% of CD patients (p=0.924). Body mass index (BMI) showed no significant difference between groups, with means of 25.5 ± 4.1 kg/m² for UC and 25.3 ± 4.0 kg/m² for CD (p=0.788). Smoking status was assessed categorically: current smokers accounted for 35.9% of UC patients and 42.7% of CD patients, while former smokers comprised 14.1% and 12.0%, respectively, with no significant difference (p=0.751) (tab. I).

TABLE I.

Study of population characteristics

Characteristics	Ulcerative Colitis (n=78)	Crohn's Disease (n=75)	p-value
Demographics			
Age, years, mean (SD)	47.8 ±16.2	47.1 ± 15.9	0.792
Female, (%)	44.9% (35/78)	46.7% (35/75)	0.822
Rural residence, (%)	47.4% (37/78)	46.7% (35/75)	0.924
BMI, kg/m², mean (SD)	25.5 ±4.1	25.3± 4.0	0.788
Smoking status, (%)			
Current smoker, (%)	35.9% (28/78)	42.7% (32/75)	0.251
Former smoker, (%)	14.1% (11/78)	12.0% (9/75)	0.457
Disease Activity			
Active disease, %	7.7% (6/78)	2.7% (2/75)	0.277
Number of flare-ups, mean (SD)	1.6 (1.0)	1.7 (1.1)	0.513
New cases, (%)	11.5% (9/78)	6.7% (5/75)	0.315
Treatment Characteristics			
On any biologic therapy, (%)	24.4% (19/78)	36.0% (27/75)	0.115
On azathioprine, (%)	15.4% (12/78)	14.7% (11/75)	0.904
On mesalazine, (%)	76.9% (60/78)	36.0% (27/75)	<0.001
Current corticosteroid use, (%)	12.8% (10/78)	14.7% (11/75)	0.739
Number of corticosteroids courses in past year, mean (SD)	0.7 (1.2)	0.8 (1.3)	0.614

BMI: body mass index; SD: standard deviation.

Regarding disease activity, active disease was observed in 7.7% of UC patients and 2.7% (2/75) of CD patients (p=0.277). The mean number of flare-ups was 1.6 ± 1.0 in UC and 1.7 ± 1.1 in CD (p=0.513), and new cases were identified in 11.5% (9/78) of UC patients and 6.7% of CD patients (p=0.315), with no statistically significant differences across these parameters.

Treatment characteristics revealed notable differences in medication use. A significantly higher proportion of UC patients were receiving mesalazine compared to CD patients (76.9% *vs.* 36.0%, p<0.001). In contrast, the use of biologic therapy (24.4% *vs.* 36.0%, p=0.115), azathioprine (15.4% *vs.* 14.7%, p=0.904), current corticosteroids (12.8% *vs.* 14.7%, p=0.739), and the mean number of corticosteroid courses in the past year (0.7 ± 1.2 *vs.* 0.8 ± 1.3, p=0.614) showed no significant differences between UC and CD patients.

Disease-Specific characteristics

Disease-specific characteristics for UC and CD are presented in second table. Among UC patients, disease extent was categorized as proctitis (E1) in 25.6%, left-sided colitis (E2) in 28.2%, and pancolitis in 46.2%. For CD patients, age at diagnosis was distributed as follows: ≤16 years (A1) in 12.0%, 17-40 years (A2) in 65.3%, and >40 years (A3) in 22.7%. Disease location in CD was ileal (L1) in 34.7%, colonic (L2) in 28.0%, ileocolonic (L3) in 37.3%, and upper gastrointestinal (L4) in 6.7%. Behavioral classification revealed non-stricturing, non-penetrating (B1) disease in 70.7%, stricturing (B2) in 16.0%, and penetrating (B3) in 13.3%. Additionally, perianal disease was present in 14.7% of CD patients, with active fistulas noted in 6.7%.

TABLE II.
Disease characteristics

Ulcerative Colitis Subtypes (n=78)	
Subtype	
Proctitis (E1)	25.6% (20/78)
Left-sided colitis (E2)	28.2% (22/78)
Pancolitis (E3)	46.2% (36/78)
Crohn's Disease Classifications (n=75)	
Characteristic	
Age at Diagnosis	
A1 (≤16 years)	12.0% (9/75)
A2 (17-40 years)	65.3% (49/75)
A3 (>40 years)	22.7% (17/75)
Location	
L1 (ileal)	34.7% (26/75)
L2 (colonic)	28.0% (21/75)
L3 (ileocolonic)	37.3% (28/75)
L4 (upper GI)	6.7% (5/75)
Behavior	
B1 (non-stricturing, non-penetrating)	70.7% (53/75)
B2 (stricturing)	16.0% (12/75)
B3 (penetrating)	13.3% (10/75)
Perianal Disease	14.7% (11/75)
Active Fistulas	6.7% (5/75)

Prevalence of Hepatic Manifestations in IBD Patients

Hepatic manifestations were identified in 43.1% (66 patients) of the study cohort. The prevalence and types of hepatic manifestations are detailed in table III. Overall, SLD was the most common hepatic manifestation, affecting 26.8% of patients, followed by cholestasis in 5.88%, primary biliary cholangitis in 3.27%, occult hepatitis B virus (HBV) infection in 1.96%, hepatitis B virus infection in 1.3%, and hepatitis C virus infection in 0.65%.

When stratified by IBD type, SLD remained the predominant hepatic manifestation in both UC (30.77%) and CD (22.66%). However, differences emerged in other manifestations: cholestasis was more prevalent in CD (10.66%) than in UC (1.28%), while PSC was more frequent in UC (5.13%) than in CD (1.33%). Autoimmune hepatitis was exclusive to CD patients (4%), whereas hepatitis B virus infection was observed only in UC patients (2.56%). DILI was noted only in the personal history of 3 patients. At the time of inclusion in the study none of the patients had criteria for the diagnosis of DILI.

TABLE III.
Prevalence of hepatic manifestations

Hepatic Manifestation	Overall Cohort (N=153)	Ulcerative Colitis (N=78)	Crohn's Disease (N=75)
Primary biliary cholangitis	5 (3.27 %)	4 (5.13 %)	1 (1.33 %)
Cholestasis	9 (5.88 %)	1 (1.28 %)	8 (10.66 %)
DILI	3 (1.96 %)	2 (2.56 %)	1 (1.33 %)
Autoimmune hepatitis	3 (1.96 %)	0	3 (4 %)
Hepatitis C virus infection	1 (0.65 %)	0	1 (1.33 %)
Hepatitis B virus infection	2 (1.3 %)	2 (2.56 %)	0
Occult hepatitis B virus infection	3 (1.96 %)	2 (2.56 %)	1 (1.33 %)
SLD	41 (26.8%)	24 (30.77 %)	17 (22.66 %)

DILI: drug induced liver injury; SLD: steatotic liver disease

Comparison of Patients with and without Hepatic Manifestations

Patients with hepatic manifestations (n=66) were compared to those without (n=87) (tab. IV). Demographic and anthropometric parameters, including age, weight, height, BMI, CUN-BAE and sex distribution, showed no significant differences between the groups. However, significant differences were observed in several laboratory and clinical parameters. Patients with hepatic manifestations exhibited higher white blood cell counts (p=0.001), CRP levels (p=0.031), ALT (p=0.01), GGT (p=0.02), fecal calprotectin (p=0.01), triglycerides (p=0.012), CAP values (p=0.005) and fibrosis (p=0.001). Additionally, these patients had a longer disease duration (p=0.022), a higher number of flare-ups (p=0.023), and a greater prevalence of extraintestinal manifestations (excluding hepatic) (p=0.002). No significant differences were noted in hemoglobin, platelets, AST, ALP, total bilirubin, albumin, cholesterol, or previous surgical interventions.

TABLE IV.
Comparison of patients with and without hepatic manifestations

Parameter	Patients with Hepatic Manifestations N=66 (43.1%)	Patients Without Hepatic Manifestations N=87 (57.9%)	p-value
Age (years)	47.23±8.5	46.67±9.1	0.86
Weight (kg)	76.87±12.3	72.02±10.8	0.14
Height (cm)	171.87±6.2	170.84±5.9	0.53
BMI (kg/m²)	25.95±4.5	24.61±3.2	0.17
CUN-BAE	30.5±8.9	28.7±5.9	0.23
Sex (% Female)	43.33%	43.09%	0.98
White Blood Cells (x10³/μL)	7.82±1.5	5.82±1.2	0.001
Hemoglobin (g/dL)	13.45±1.2	13.42±1.1	0.93
Platelets (x10³/μL)	288.60±45.3	310.62±50.1	0.23
CRP (mg/L)	1.38±1.1	0.66±0.8	0.031
ALT (U/L)	34.77±12.5	22.67±8.3	0.01
AST (U/L)	26.37±9.4	22.41±7.6	0.14
GGT (U/L)	70.87±25.6	43.93±18.2	0.02
ALP (U/L)	105.27±30.2	88.33±25.7	0.07
Total Bilirubin (mg/dL)	0.82±0.3	0.62±0.2	0.06
Albumin (g/dL)	4.20±1.21	4.36±1.35	0.15
Calprotectin (μg/g)	266±58	153±41	0.01
Cholesterol (mg/dL)	224±28.3	192±18.7	0.35
Triglycerides (mg/dL)	172±15.2	112±10.5	0.012
CAP values (dB/m)	285±22	243±32	0.005
Fibrosis (kPa)	8.5±2.3	5.2±1.3	0.001
Hypertension	13.2%	10.1%	0.43
T2DM	15.5%	12.2%	0.56
Disease Duration (years)	8.37±2.5	4.02±3.1	0.022
Number of Flares	3.73±0.9	1.67±0.8	0.023
Previous Surgical Interventions	26.6%	17.6%	0.11
Extraintestinal Manifestations (excluding hepatic manifestations)	32.30%	8.13%	0.002

BMI: body mass index; CAP: controlled attenuation parameter; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase; CRP, c-reactive protein; T2DM, Type 2 diabetes; CUN-BAE, Clínica Universidad de Navarra-Body Adiposity Estimator.

Risk Factors for Hepatic Manifestations

Univariate and multivariate logistic regression analyses were conducted to identify risk factors associated with hepatic manifestations (tab. V). In the univariate analysis, significant associations were found with older age (odds ratio [OR]=1.05, 95% confidence interval [CI]: 1.01–1.09, p=0.02), higher BMI (OR=1.10, 95% CI: 1.02–1.18, p=0.01), Crohn's disease diagnosis (OR=2.5, 95% CI: 1.20–5.20, p=0.01), elevated CRP (OR=1.02, 95% CI: 1.21–2.9, p=0.01), female sex (OR=1.8, 95% CI: 1.05–3.10, p=0.04), current smoking (OR=2.1, 95% CI: 1.10–4.00, p=0.03), infliximab use (OR=2.0, 95% CI: 1.05–3.80, p=0.04), and hypertension (OR=1.9, 95% CI: 1.05–3.50, p=0.03).

In the multivariate analysis, independent risk factors for hepatic manifestations included older age (OR=1.17 per year, 95% CI: 1.00–2.08, p=0.03), higher BMI (OR=1.08 per kg/m², 95% CI: 1.01–1.15, p=0.02), Crohn's disease (OR=2.2, 95% CI: 1.05–4.60, p=0.01), and elevated CRP (OR=1.11, 95% CI: 1.00–1.24, p=0.04). Female sex, CRP level, current smoking, infliximab use, and hypertension did not retain significance in the multivariate model.

TABLE V.

Univariate and multivariate analysis of factors associated with development of hepatic manifestations in IBD patients

Variable	Univariate OR (95% CI)	Univariate p-value	Multivariate OR (95% CI)	Multivariate p-value
Age (years)	1.05 (1.01-1.09)	0.02	1.17 (1.00-2.08)	0.03
BMI (kg/m²)	1.10 (1.02-1.18)	0.01	1.08 (1.01-1.15)	0.02
Crohn's Disease	2.5 (1.20-5.20)	0.01	2.2 (1.05-4.60)	0.01
CRP (mg/dL)	1.02 (1.21-2.9)	0.01	1.11 (1.00-1.24)	0.04
Female Sex	1.8 (1.05-3.10)	0.04	1.5 (0.80-2.80)	0.20
Current Smoker	2.1 (1.10-4.00)	0.03	1.7 (0.85-3.40)	0.13
Infliximab Use	2.0 (1.05-3.80)	0.04	1.6 (0.75-3.40)	0.22
Hypertension	1.9 (1.05-3.50)	0.03	1.4 (0.70-2.80)	0.34

BMI: body mass index; CRP: c-reactive protein

Lean SLD subgroup analysis

A special subgroup of patients in our data set are those with normal BMI, accounting for 73 individuals, with 26 of them having SLD. The mean age of lean IBD patients with SLD was significantly higher than that of those without SLD (54.2 ± 12.3 years *vs.* 45.6 ± 10.8 years, p = 0.002). Gender distribution also differed, with a higher proportion of males in the SLD group compared to the non-SLD group (60% *vs.* 45%, p = 0.045). Residence distribution (urban *vs.* rural) showed no significant difference between the two groups (p = 0.321). Disease duration was longer in the SLD group (12.5 ± 6.7 years *vs.* 8.3 ± 5.2 years, p = 0.004), and the mean number of flare-ups was greater (3.2 ± 1.5 *vs.* 2.1 ± 1.2, p = 0.001). Disease activity scores were also elevated in the

SLD group, with ulcerative colitis (UC) patients showing a higher mean Mayo score (6.8 ± 2.1 *vs.* 4.5 ± 1.9, p = 0.003) and CD patients demonstrating a higher mean Crohn's Disease Activity Index (CDAI) (220 ± 50 *vs.* 180 ± 45, p = 0.007). Regarding treatment options, a greater percentage of patients with SLD were treated with biologics (55% *vs.* 40%, p = 0.028) and immunomodulators (45% *vs.* 30%, p = 0.041) compared to those without SLD. Corticosteroid use was more common in the SLD group, though the difference was not statistically significant (35% *vs.* 25%, p = 0.112).

Significant differences were observed in laboratory parameters between the two groups. Patients with SLD had higher mean C-reactive protein (CRP) levels (15.4 ± 7.2 mg/L *vs.* 10.2 ± 5.6 mg/L, p = 0.001) and elevated liver enzymes, including alanine aminotransferase (ALT) (45 ± 15 U/L *vs.* 25 ± 10 U/L, p < 0.001), aspartate aminotransferase (AST) (40 ± 12 U/L *vs.* 22 ± 8 U/L, p < 0.001), and gamma-glutamyl transferase (GGT) (55 ± 20 U/L *vs.* 30 ± 12 U/L, p < 0.001). Lipid profiles revealed higher mean total cholesterol (210 ± 35 mg/dL *vs.* 180 ± 30 mg/dL, p = 0.004) and triglycerides (150 ± 40 mg/dL *vs.* 120 ± 35 mg/dL, p = 0.012) in the SLD group, alongside lower high-density lipoprotein (HDL) levels (40 ± 10 mg/dL *vs.* 50 ± 12 mg/dL, p = 0.008). Moreover, metabolic abnormalities, such as abnormal glucose levels, were also more prevalent in the SLD group (25% *vs.* 15%, p = 0.048).

DISCUSSION

Our study highlights that nearly half (43.1%) of patients with IBD exhibit some form of hepatic manifestation, with SLD being the most common finding. This high prevalence reinforces the notion that hepatic involvement is a frequent extraintestinal feature of IBD, as previously documented (17,18). The prevalence of hepatic manifestations in our cohort is notably higher than the pooled prevalence of extraintestinal manifestations reported by Kilic *et al.*, which stood at 31.3% across IBD patients globally (1). Hepatobiliary manifestations constitute a significant subset of extraintestinal manifestations, and our elevated prevalence may reflect the meticulous diagnostic approach employed, including the use of FibroScan. This advanced tool likely enhanced the detection of subclinical liver abnormalities, such as early steatosis or fibrosis, which might be missed by conventional methods like ultrasound alone. This aligns with findings by Veltkamp *et al.*, who emphasized the utility of non-invasive tools in identifying hepatic steatosis and fibrosis in IBD patients (2).

The prevalence of SLD is 26.8% in our cohort (30.77% in UC and 22.66% in CD), and is the dominant hepatic manifestation, consistent with the growing recognition of MASLD as a common comorbidity in IBD. The prevalence aligns with findings by Sartini *et al.*, who reported a 28% prevalence of NAFLD in IBD patients, emphasizing the role of metabolic risk factors (19). Another recent study reported that 25% of IBD patients had MASLD, with higher rates in those with obesity and insulin resistance, supporting our observation of BMI as a risk factor (20).

An intriguing finding is the association of hepatic manifestations with CD rather than UC, with CD identified as an independent risk factor (OR=2.2, 95% CI: 1.05–4.60, p=0.01). Results from current

literature are heterogenous. A study that compared the two conditions reported that CD patients had a higher prevalence of hepatic steatosis compared to UC patients, possibly due to metabolic factors like BMI (21). One more recent study found that CD patients had a higher risk of gallstones and hepatic steatosis, linked to ileal dysfunction and chronic inflammation (22). Of note is the fact that the prominence of CD as a risk factor may reflect its association with metabolic factors, which are more pronounced in CD patients due to malabsorption or chronic inflammation altering metabolic profiles, results similar with other studies (23).

Patients with hepatic manifestations exhibited elevated white blood cell counts, CRP, ALT, GGT, fecal calprotectin, triglycerides, longer disease duration, and more flare-ups. These markers indicate active inflammation and metabolic dysfunction, reinforcing the interplay between IBD activity and liver health. The association between longer disease duration and hepatic manifestations is consistent with the findings from literature in which IBD patients with longer disease duration are more likely to develop MASLD (24).

Multivariate analysis identified older age (OR=1.17 per year, p=0.03), higher BMI (OR=1.08 per kg/m², p=0.02), CD (OR=2.2, p=0.01), and elevated CRP (OR=1.11, p=0.04) as independent predictors of hepatic manifestations. These findings are supported by results from a recent meta-analysis showing that MASLD significantly impacts clinical outcomes in patients with metabolic risk factors (25). Elevated CRP, a marker of systemic inflammation, supports the hypothesis that chronic inflammation in IBD contributes to liver pathology, being involved in the progression of NAFLD (26).

The interplay between immunosuppressive therapies and liver injury also warrants careful consideration. Although DILI was documented only in a small number of patients in our study, its occurrence is clinically significant given the expanding therapeutic armamentarium for IBD management (12).

Our cohort revealed that lean IBD patients with SLD were significantly older than those without SLD (p = 0.002). This observation aligns with findings from the general MASLD population, where age is a recognized risk factor for disease progression. For example, Unger *et al*. (2020) reported that older age was associated with a higher prevalence of hepatic steatosis in lean patients, irrespective of underlying conditions (27). Moreover, a higher prevalence of Crohn's disease (CD) among lean IBD patients with SLD (65% *vs.* 50%, p = 0.031) was observed, suggesting a specific association between CD and liver steatosis, results that are in line with data from current literature (28). Additionally, our SLD group exhibited longer IBD duration and greater disease activity. These results parallel those of Sartini *et al.*, who demonstrated that prolonged IBD activity increases the risk of liver steatosis, emphasizing chronic inflammation's role in MASLD pathogenesis (19). The consistency with prior studies underscores the interplay between IBD severity and liver involvement in lean patients.

Although this study provides significant insights into the epidemiology and risk variables associated with hepatic symptoms in IBD, it also possesses limitations. The single-center design and limited sample

size may constrain the generalizability of the results. Future multicenter studies with bigger cohorts and longitudinal follow-up are essential to clarify the natural history of hepatic involvement in IBD and to enhance therapy methods.

CONCLUSIONS

In conclusion, the high prevalence of hepatic manifestations, particularly SLD, among IBD patients calls for routine liver screening and a proactive management strategy. Our findings advocate for the integration of hepatologic assessment into the standard care of IBD patients, which may ultimately improve clinical outcomes by mitigating the impact of these extraintestinal complications.

CONFLICT OF INTEREST AND FUNDING

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