Increased risk of MAFLD and Liver Fibrosis in Inflammatory Bowel Disease Independent of Classic Metabolic Risk Factors

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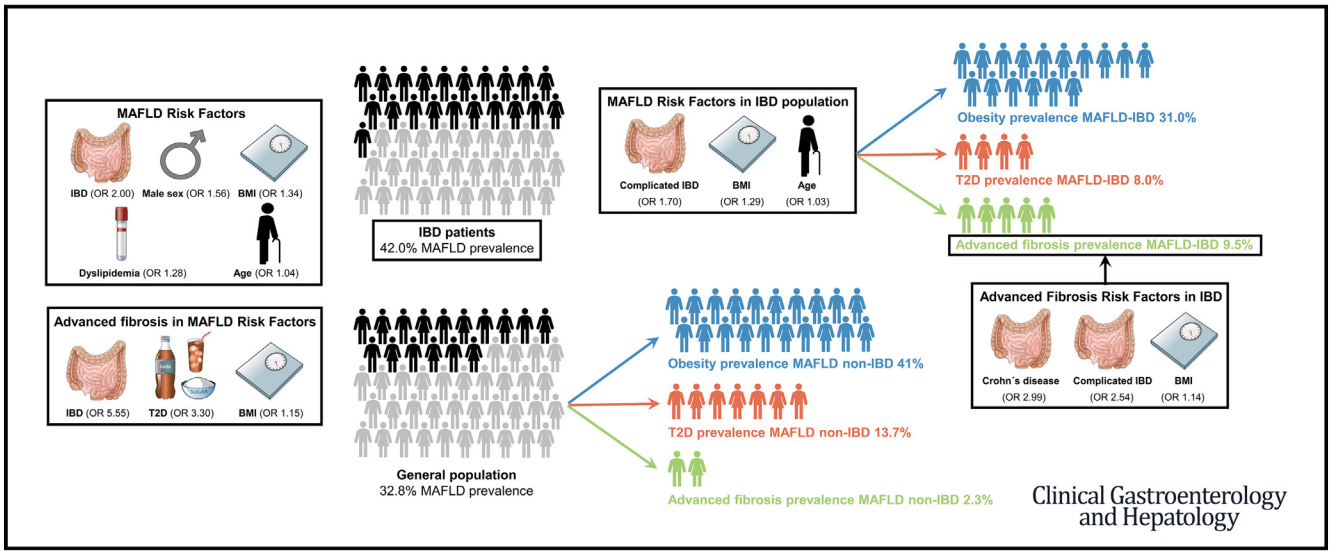

BACKGROUND & AIMS: There is conflicting evidence regarding the prevalence of and risk factors for metabolic-associated fatty liver disease (MAFLD) in patients with inflammatory bowel disease (IBD). We aimed to determine MAFLD prevalence and risk factors in IBD patients.

METHODS: Cross-sectional, case-control study included all consecutive IBD patients treated at 2 different university hospitals. Controls were subjects randomly selected from the general population and matched by age, sex, type 2 diabetes status, and body mass index in a 1:2 ratio. MAFLD was confirmed by controlled attenuation parameter. Liver biopsies were collected when MAFLD

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Abbreviations used in this paper: ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; CD, Crohn's disease; CI, confidence interval; FIB-4, Fibrosis-4 index; GFR, glomerular filtration rate; GGT, γ-glutamyl transpeptidase; HDL, high-density lipoprotein; HUMV, University Hospital Marques de Valdecilla; HUPH, University Hospital Puerta de Hierro; IBD, inflammatory bowel disease; IMID, immune-mediated inflammatory disease; LDL, low-density lipoprotein; LSM, liver stiffness measurement; MAFLD, metabolic-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OR, odds ratio; TD2, type 2 diabetes; TE, transient elastography.

Most current article

1542-3565
https://doi.org/10.1016/j.cgh.2022.01.039

with significant liver fibrosis was suspected. In addition, age- and fibrosis stage–paired non-IBD patients with biopsy-proven MAFLD served as a secondary control group.

RESULTS: **Eight hundred thirty-one IBD patients and 1718 controls were included. The prevalence of MAFLD and advanced liver fibrosis (transient elastography ≥9.7 kPa) was 42.00% and 9.50%, respectively, in IBD patients and 32.77% and 2.31%, respectively, in the general population ($P < .001$). A diagnosis of IBD was an independent predictor of MAFLD (adjusted odds ratio, 1.99; $P < .001$) and an independent risk factor for advanced liver fibrosis (adjusted odds ratio, 5.55; $P < .001$). Liver biopsies were obtained from 40 IBD patients; MAFLD was confirmed in all cases, and fibrosis of any degree was confirmed in 25 of 40 cases (62.5%). Body mass index and type 2 diabetes prevalence were significantly lower in IBD-MAFLD patients than in severity-paired patients with biopsy-proven MAFLD.**

CONCLUSIONS: **MAFLD and liver fibrosis are particularly prevalent in IBD patients, regardless of the influence of classic metabolic risk factors.**

Keywords: MAFLD; Inflammatory Bowel Disease; Liver Fibrosis; Metabolic Syndrome.

Liver disease is a common comorbidity in inflammatory bowel disease (IBD) patients,[1] and metabolic-associated fatty liver disease (MAFLD) is an emerging cause for concern in this population.[2] Several studies have addressed the mechanisms underlying the association between MAFLD and IBD. Whereas some of them indicate that a diagnosis of MAFLD in IBD patients is mainly due to the presence of well-established risk factors such as age, obesity, and type 2 diabetes (T2D),[3,4] other authors have drawn attention to the role of factors associated with IBD itself that may favor the development of MAFLD such as the degree of activity, the duration of the disease, and drug-mediated hepatotoxicity.[5–7]

Estimates of MAFLD prevalence in IBD patients vary widely from 8% to 88%.[6,8] This could be explained by the heterogeneity of the diagnostic methods and the selected study populations. The prevalence of liver fibrosis in IBD patients has been evaluated in only a few studies, resulting in a mixed range of estimates from 2.2% to 16%.[6,9] Again, this variability can be explained by the heterogeneous diagnostic methods and cutoffs used, with higher rates being noted when liver fibrosis is estimated from liver stiffness measurements (LSMs) obtained by transient elastography (TE)[9] than with noninvasive biomarkers such as the Fibrosis-4 index (FIB-4).[6] To our knowledge, no biopsy studies have been conducted to assess MAFLD disease activity and liver fibrosis in IBD patients. Finally, there is little available information about risk factors associated with the prevalence of advanced fibrosis in these patients. Only Magri et al[3] argued that the presence of metabolic syndrome is a risk factor specifically for advanced liver fibrosis in IBD-MAFLD patients.

The aim of the present study is therefore to analyze the prevalence of and risk factors for MAFLD diagnosis and liver fibrosis in a cohort of clinically characterized IBD patients and in a subset of patients with biopsy-proven IBD-MAFLD.

Materials and Methods

Study Design and Participants

We performed a cross-sectional, case-control study (Immunomediated Non-alcoholic SteaTohepatitis; Prevalence and Characterization INSTInCT Study; ClinicalTrials.gov Identifier: NCT03760172). The study included a cohort of consecutive IBD patients aged 18+ years who attended the IBD outpatient clinic at the University Hospital Marques de Valdecilla (HUMV) in Santander and University Hospital Puerta de Hierro (HUPH) in Madrid between December 2018 and December 2019. Patients who had clinical evidence of malignancy or another secondary cause of chronic liver disease were excluded. Patients with excessive alcohol intake (>20 g/day for women, >30 g/day for men) without concomitant overweight or obesity, T2D, or evidence of metabolic dysregulation were excluded from the study.[10]

A random sample from the general population from the Spanish Hepatitis C Prevalence Study (ETHON cohort; ClinicalTrials.gov Identifier: NCT02749864)[11] was included as a control group. Patients and controls were matched by age, sex, T2D status, and body mass index (BMI) in 1:2 ratio. A more detailed description of the study design is available in the online version.

A secondary control group was formed from samples from a real-world cohort of patients with biopsy-proven MAFLD who attended the monographic MAFLD outpatient clinics at HUMV and HUPH. Both hospitals are referral centers for liver diseases, and the MAFLD liver biopsies comprised samples obtained during clinical practice mainly when the presence of metabolic syndrome or the results of TE led to suspicion of nonalcoholic steatohepatitis (NASH) and/or advanced liver fibrosis.[12] Patients with a known diagnosis of immune-mediated inflammatory disease (IMID) were excluded from the analysis to allow comparison of the clinical and

histologic characteristics of patients with classic MAFLD with those of patients with MAFLD in the context of IMID, as in the IBD cohort. Patients with biopsy-proven MAFLD and IBD were paired with patients with biopsy-proven MAFLD by age and grade of liver fibrosis in 1:2 ratio.

Written informed consent was obtained from all patients and controls, and the study was conducted in accordance with the ethical guidelines of the Helsinki Declaration and with the approval of local ethics committees (CEIC-Cantabria, code: 2018.139). All authors had access to the study data and reviewed and approved the final manuscript.

Clinical Evaluation and Laboratory Collection

Anthropometric data were collected from all participants at inclusion to calculate their BMI and waist circumference. Information about smoking status, self-reported alcohol consumption, concomitant presence of classic cardiovascular risk factors, and the use of potential hepatotoxic medications was collected during clinical interviews.

Information about disease phenotype, disease duration, disease activity, complications, and past and current treatments was prospectively and systematically collected from IBD patients. Fasting venous blood samples were collected at inclusion.

Diagnosis of MAFLD

A diagnosis of MAFLD was established according to recently proposed criteria.[13] For the purpose of the study, controlled attenuation parameter (CAP) (CAP; Echosens, Paris, France) measured by TE was used to diagnose and quantify the degree of hepatic steatosis. The cutoff used to determine the presence of steatosis was 248 dB/m for >S0.[14] CAP performance might be altered by the concomitant presence of T2D or obesity, so the results were adjusted when needed, as previously described.[14]

Thus, a diagnosis of MAFLD was made on the basis of the presence of hepatic steatosis in patients with BMI $\geq$25 kg/m^2, T2D, or evidence of metabolic dysregulation.[10]

Liver Fibrosis and Histologic Assessment

The extent of liver fibrosis in all patients was estimated by TE (FibroScan; Echosens). The same experienced hepatologists performed all FibroScan examinations following the manufacturer's recommendations. Significant liver fibrosis was concluded in patients with values $\geq$7.2 kPa, whereas patients with a value $\geq$9.7 kPa were considered to have advanced liver fibrosis.[15]

What You Need to Know

Background

People with various autoimmune disorders appear to be at higher risk of developing fatty liver disease.

Findings

Patients with inflammatory bowel disease are at higher risk of developing fatty liver, regardless of their weight or the presence of hypertension, diabetes, or high cholesterol.

Implications for patient care

Fatty liver disease should be ruled out in patients with inflammatory bowel disease; in fact, in some of them these liver disorders can be advanced and require further studies.

Liver biopsies were obtained from patients with suspected significant liver fibrosis according to LSM percutaneously with a Tru-Cut biopsy needle following a standard procedure. All tissue samples were digitalized, centralized at HUMV, and reviewed by a single expert pathologist blinded to the clinical findings. Four histologic features (steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis) were evaluated according to the activity score and staging system devised by the Pathology Committee of the NASH Clinical Research Network.

Statistical Analysis

Statistical analyses were performed using SPSS v22.0 (IBM, Armonk, NY). Differences in normally distributed values between groups were analyzed by Student *t* test or one-way analysis of variance, whereas differences in non-normally distributed variables were assessed by the Mann-Whitney *U* test. Categorical comparisons were performed by using χ^2 or Fisher exact test as appropriate. Initial univariate analyses were performed to determine the differences between IBD patients and the control group, between MAFLD and non-MAFLD patients, and between patients with and without advanced liver fibrosis. A detailed description of the stepwise multivariate conditional logistic regression analysis is available in the online version. Receiver operating characteristic curves were constructed for the levels of noninvasive serum biomarkers of advanced fibrosis and TE data in the subset of patients with biopsy-proven IBD and MAFLD. Two-sided *P* values <.05 were considered statistically significant.

Results

Baseline Participant Characteristics

As depicted in the study flow chart (Figure 1), of the 1651 consecutive IBD patients treated at both hospitals,

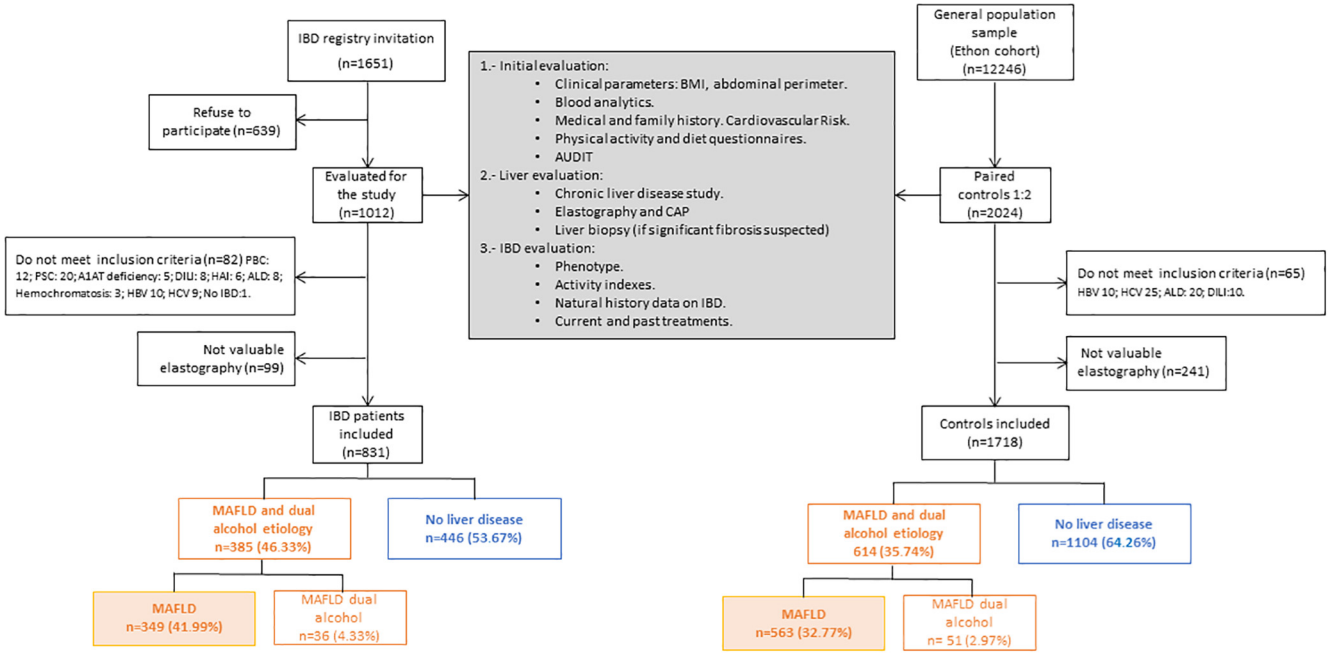

Figure 1. Study flowchart.

1012 agreed to participate in the study. A total of 831 of these patients met the inclusion criteria and were considered for analysis. A sample of 2024 controls was drawn from the 12,246 subjects in the ETHON cohort. Patients and controls were initially paired at a ratio of 1:2 and evaluated for inclusion in the study. Ultimately, 1718 met the inclusion criteria and were enrolled in the study. Because of the study design, patients and controls did not differ in terms of age, sex, BMI, or T2D diagnosis. Despite this, IBD patients tended to have a greater abdominal circumference and a higher prevalence of dyslipidemia than controls. The main clinical, anthropometric, and laboratory characteristics of the participants are summarized in Table 1 and Supplementary Table 1.

Higher Prevalence of MAFLD and Advanced Fibrosis in IBD Patients

MAFLD was significantly more prevalent in the IBD population than in the general population (349/831, 42.00% vs 563/1718, 32.77%; $P < .001$). In a comparative analysis (Supplementary Table 2), we observed that MAFLD patients with and without IBD were comparable in terms of age and sex. However, the prevalence of metabolic comorbidities such as overweight or obesity, T2D, and hypertension was significantly lower in IBD patients with MAFLD than in controls with MAFLD. This was also reflected in the main differences observed between the 2 populations, ie, that IBD patients had significantly better glycemic and lipidic profiles. Despite this, IBD patients with MAFLD had higher mean LSM values than controls, and the proportion of patients suspected to have advanced fibrosis (LSM $\geq$9.7 kPa) was also higher in the IBD group (33/349, 9.45% vs 13/563, 2.31%; $P < .001$). Conversely, mean CAP values were significantly lower among IBD patients.

IBD Is an Independent Risk Factor for MAFLD and Advanced Liver Fibrosis

By stratifying patients according to MAFLD diagnosis, we observed that IBD was associated with MAFLD along with other well-known risk factors for the disease, such as male sex, high BMI, older age, and the concomitant presence of T2D, hypertension, or dyslipidemia. These factors were included in a conditional multivariate analysis, and after adjusting for classic metabolic risk factors, the presence of IBD, together with high BMI, older age, male sex, and the presence of dyslipidemia (Figure 2*A*), remained a significant and independent risk factor associated with the diagnosis of MAFLD (odds ratio [OR], 1.999; 95% confidence interval [CI], 1.592–2.511; $P < .001$).

Similarly, when analyzing patients according to the presence of advanced fibrosis, well-established metabolic risk factors such as BMI, T2D, and hypertension, together with a concomitant diagnosis of IBD, were identified as risk factors associated with the presence of advanced fibrosis in MAFLD. These factors were included in a multivariate conditional analysis alongside other known risk factors for liver fibrosis such as age and sex. The logistic regression confirmed that the presence of IBD was a significant and independent risk factor associated with the presence of advanced fibrosis in MAFLD (OR, 5.550; 95% CI, 2.687–11.465; $P < .001$), in addition to high BMI and T2D (Figure 2*B*).

In light of these results, we analyzed patients with suspected advanced fibrosis according to the absence of

Table 1. Baseline Clinical and Laboratory Characteristics

	IBD (n = 831)	Controls (n = 1718)	*P* value
Clinical characteristics			
Age (*y*), median (range)	52 (19–76)	51 (20–79)	.965
Male sex, n (%)	401 (48.3)	832 (48.4)	.935
BMI (kg/m^2), mean (SD)	26.2 ± 4.9	26.3 ± 4.8	.565
Abdominal perimeter (*cm*)	93.1 ± 12.8	89.4 ± 13.5	.003
T2D, n (%)	51 (6.1)	124 (7.2)	.31
Hypertension, n (%)	197 (23.7)	350 (20.4)	.073
Dyslipidemia, n (%)	317 (38.2)	429 (25.0)	.046
Active smoker, n (%)	193 (23.2)	458 (26.7)	<.001
Moderate alcohol intake,[a] n (%)	411 (49.5)	770 (44.8)	.028
Excessive alcohol intake,[b] n (%)	47 (5.7)	81 (4.7)	.308
MAFLD, n (%)	349 (42.0)	563 (32.8)	<.001
Elastography (*kPa*), median (range)	5.0 (2.0–24.6)	4.5 (2.5–52.4)	<.001
Laboratory characteristics, mean (SD)			
Plasma glucose level (*mg/dL*)	81.3 ± 16.6	85.1 ± 19.1	.001
Plasma triglyceride level (*mg/dL*)	117.0 ± 92.2	145.5 ± 100.8	<.001
Total cholesterol level (*mg/dL*)	191.3 ± 36.6	198.8 ± 36.0	.638
HDL cholesterol level (*mg/dL*)	57.5 ± 15.3	57.2 ± 15.6	.278
LDL cholesterol level (*mg/dL*)	112.4 ± 30.1	113.4 ± 32.3	.21
ALT level (*U/L*)	24.7 ± 17.7	24.1 ± 18.4	.071
Bilirubin level (*mg/dL*)	0.6 ± 0.3	0.6 ± 0.3	.109
Albumin level (*mg/dL*)	4.5 ± 0.3	4.5 ± 0.2	.001
GFR ($mL/min/1.73\ m^2$)	88.1 ± 7.4	86.5 ± 8.7	<.001
Hemoglobin level (*g/dL*)	13.9 ± 1.4	14.0 ± 1.3	.052
MCV fL	90.0 ± 6.2	90.3 ± 4.8	<.001
Leukocyte number ($10^3/\mu L$)	7.2 ± 2.1	7.5 ± 1.9	<.001
Platelet number ($10^3/\mu L$)	241.8 ± 64.8	227.9 ± 56.8	<.001
Neutrophil/lymphocyte index	2.6 ± 1.7	2.2 ± 1.8	<.001

NOTE. Quantitative data are presented as means and standard deviations (SD).
ALT, alanine aminotransferase; BMI, body mass index; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MCV, mean corpuscular volume; T2D, type 2 diabetes.
[a]Moderate alcohol intake: ≤20 g/day for women and ≤30 g/day for men.
[b]Excessive alcohol consumption: >20 g/day in women and >30 g/day in men.

obesity or T2D as the main drivers of MAFLD pathogenesis. We observed that whereas advanced fibrosis was 3 times as prevalent in MAFLD-IBD patients than in control subjects with MAFLD, the differences were increased in patients without obesity, who showed 4 times greater prevalence. In patients without T2D, the prevalence of advanced fibrosis was almost 5 times that in the IBD population, and in patients without obesity and T2D, the difference was almost 7 times as large, as shown in Figure 3.

Crohn's Disease and History of IBD Complications Promote the Development of Advanced Liver Fibrosis

The main characteristics of the IBD study group when stratified according to a concomitant diagnosis of MAFLD are provided in Supplementary Table 3. Compared with IBD patients without MAFLD, IBD patients with MAFLD were significantly older, more likely to be male, more likely to be obese, had a greater abdominal circumference, and had a higher prevalence of T2D, hypertension, and dyslipidemia. In terms of IBD characteristics, MAFLD-IBD patients had significantly later onset of disease, longer duration of disease, and higher prevalence of previous severe complications. The differences were particularly striking in the case of toxic megacolon, because 100% of patients presenting this complication had MAFLD. Importantly, we found no significant differences in terms of disease phenotype or concomitant and current treatments. We found no differences in MAFLD prevalence between patients with active and inactive IBD, but we observed a significantly higher prevalence of MAFLD in active IBD patients than in controls (Supplementary Table 4).

Next, we performed a conditional multivariate analysis to examine the specific factors associated with IBD that had a putative role in MAFLD diagnosis. Once we adjusted for previously described independent risk factors for MAFLD, history of IBD-related complications, together with older age and high BMI, remained an independent and significant risk factor for a diagnosis of MAFLD (Figure 4*A*).

Finally, we addressed the risk factors associated with advanced fibrosis in MAFLD-IBD patients. In the univariate analysis, Crohn's disease (CD), hypertension, and

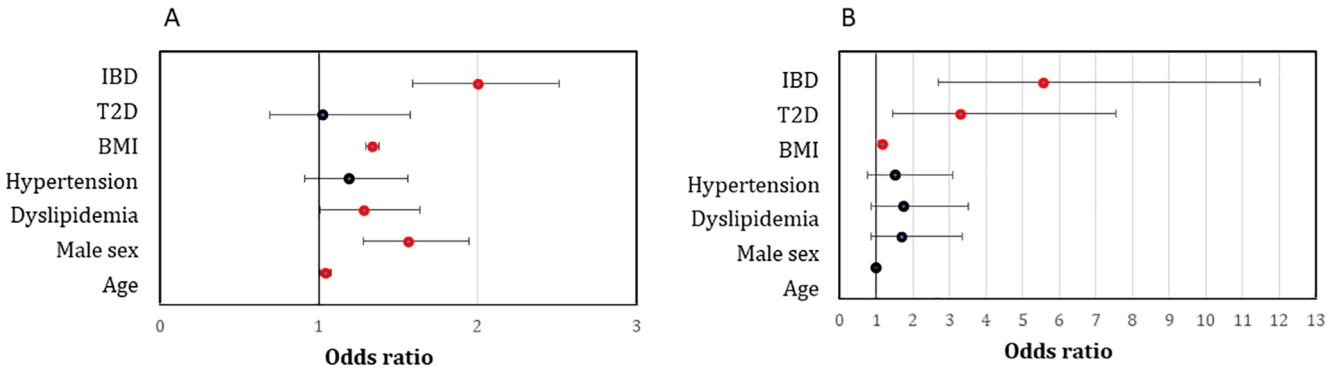

Figure 2. (*A*) Logistic regression analysis of MAFLD risk factors. Data are presented as adjusted ORs and 95% CIs. Statistically significant variables are indicated in *red*. IBD: OR, 1.999; 1.592–2.511; $P < .001$); BMI: OR, 1.337; 1.295–1.381; $P < .001$; dyslipidemia: OR, 1.284; 1.008–1.636; $P = .043$; male sex: OR, 1.561; 1.248–1.951; $P < .001$); and age: OR, 1.037; 1.026–1.048; $P < .001$. (*B*) Logistic regression analysis of MAFLD with advanced fibrosis risk factors. Data are presented as adjusted ORs with 95% CIs. Statistically significant variables are indicated in *red*. IBD: OR, 5.550; 2.687–11.465; $P < .001$; T2D: OR, 3.301; 1.444–7.550; $P = .005$; and BMI: OR, 1.145; 1.069–1.204; $P < .001$.

obesity were identified as risk factors associated with the presence of suspected advanced fibrosis. Regarding the specific factors associated with the natural history and treatment of IBD, we observed a significant association between history of complicated IBD and LSM value ≥9.7 kPa. In the multivariate analysis, diagnosis of CD and history of IBD-related complications, along with high BMI, remained independent and significant risk factors for advanced fibrosis in MAFLD-IBD (Figure 4*B*).

Comparative Analysis of Biopsy-Proven MAFLD in IBD and Non-IBD Patients

According to the LSM results, 86 of the 349 IBD patients with MAFLD (23.5%) were suspected of having significant liver fibrosis (LSM ≥7.2 kPa). Following the study protocol, we offered a liver biopsy, and this option was accepted by 40 of the 86 patients. MAFLD was confirmed histologically in all cases, and fibrosis of any degree (F1–F4) was confirmed in 25 of 40 cases (62.5%). Advanced fibrosis (F3-F4) was found in 6 of 40 cases (15%). We then compared the clinical and histologic characteristics of this subset of patients with biopsy-proven IBD-MAFLD with those of a control group comprising age- and liver fibrosis stage–paired patients with biopsy-proven MAFLD from the monographic outpatient clinic (Supplementary Figure 1) in which a concomitant IMID diagnosis was excluded.

Although the biopsies were paired with respect to the severity of liver fibrosis, we found that the prevalence of metabolic comorbidities such as T2D and mean BMI were significantly lower in the IBD group than in the controls (Table 2). When we assessed the histologic characteristics of both groups, we found a significantly lower degree of steatosis in the IBD group than in the controls.

Diagnostic Accuracy of TE and Serum Biomarkers

We tested the diagnostic performances of 4 non-patented serum biomarkers for fibrosis staging (FIB-4, aspartate aminotransferase to platelet ratio index [APRI] score, nonalcoholic fatty liver disease [NAFLD] fibrosis score, and HEPAMet fibrosis score) in the detection of

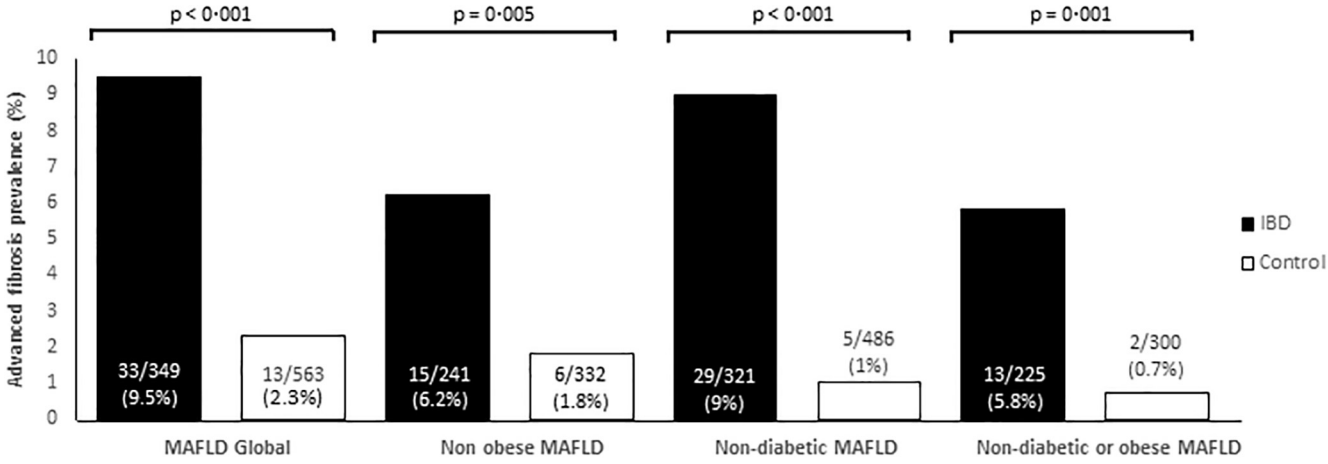

Figure 3. Advanced fibrosis prevalence stratified according to absence of T2D or obesity in IBD patients and controls.

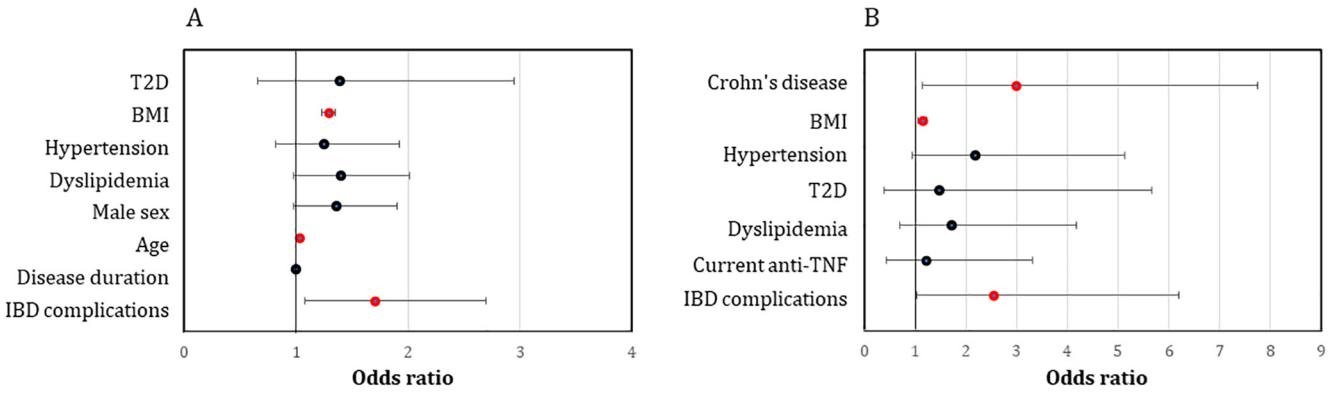

Figure 4. (*A*) Logistic regression analysis of MAFLD risk factors in IBD population. Data are presented as adjusted ORs with 95% CIs. Statistically significant variables are indicated in *red*. BMI: OR, 1.286; 1.226–1.348; $P < .001$; age: OR, 1.032; 1.016–1.048; $P < .001$; and complicated IBD: OR, 1.703; 1.077–2.691; $P = .043$. (*B*) Logistic regression analysis of MAFLD with advanced fibrosis risk factors in the IBD population. Data are presented as adjusted ORs with 95% CIs. Statistically significant variables are indicated in *red*. CD: OR, 2.989; 1.152–7.754; $P = .024$; BMI: OR, 1.144; 1.064–1.229; $P = .001$; and complicated IBD: OR, 2.541; 1.042–6.200; $P = .040$.

advanced liver fibrosis in the subset of patients with biopsy-proven MAFLD-IBD (see data on Supplementary Table 5), as well as one serum biomarker that has been validated for steatosis detection but has yielded previous positive results in the detection of fibrosis in the general population (FLI).[16] Of the 5 biomarkers analyzed, FIB-4,

Table 2. Comparative Analysis of Biopsy-Proven MAFLD in IBD and Non-IBD Patients

	MAFLD-IBD (n = 40)	MAFLD non-IBD (n = 81)	*P* value
Age (*y*), median (range)	57 (32–68)	57 (35–74)	.326
Male sex, n (%)	20 (50.0)	47 (58.0)	.404
Hypertension, n (%)	24 (60.0)	60 (74.1)	.114
T2D, n (%)	9 (22.5)	38 (46.9)	.011
Dyslipidemia, n (%)	19 (47.5)	45 (55.6)	.404
BMI, n (%)	32.8 ± 6.8	37.4 ± 8.4	.003
Smoker, n (%)	4 (10.0)	6 (7.4)	.153
Steatosis, n (%)			.001
S0	0 (0.0)	0 (0.0)	
S1	25 (62.5)	24 (29.6)	
S2	11 (27.5)	26 (32.1)	
S3	4 (10.0)	31 (38.3)	
Lobular inflammation, n (%)			.308
0	9 (22.5)	11 (13.6)	
1	20 (50.0)	36 (44.4)	
2	10 (25.0)	27 (33.3)	
3	1 (2.5)	7 (8.7)	
Ballooning, n (%)			.425
0	6 (15.0)	8 (9.9)	
1	16 (40.0)	28 (34.6)	
2	17 (42.5)	45 (55.6)	
Fibrosis, n (%)			.991
0	15 (37.5)	28 (34.6)	
1	15 (37.5)	30 (37.0)	
2	4 (10.0)	8 (9.9)	
3	3 (7.5)	8 (9.9)	
4	3 (7.5)	7 (8.7)	

NOTE. Data are presented as absolute frequencies and percentages (in parentheses) for qualitative data and means and standard deviations for continuous data.
BMI, body mass index.

APRI score, NAFLD fibrosis score, and FLI were the most accurate, producing highly negative predictive values (>90%), which allowed us to rule out advanced fibrosis with thresholds of 1.30, 0.70, −1.455, and 60, respectively. We also analyzed the performance of TE in the detection of advanced liver fibrosis in our subset of patients with biopsy-proven MAFLD-IBD. We obtained an area under the receiver operating characteristic curve of 0.931, the highest of all the noninvasive biomarkers evaluated. The highest sensitivity (100%) and negative predictive value (100%) were obtained with a threshold of 9.5 kPa.

Discussion

In this article, we report the results of one of the largest studies using liver biopsies to analyze the prevalence of and risk factors for MAFLD in a multicentric cohort of consecutive patients with IBD. Although previous studies have addressed this topic, we believe that the debate about whether IBD patients are at a higher risk of MAFLD remains unsettled because the variety of previously used approaches makes it difficult to reach a consensus. The variation in findings is largely due to differences in the diagnostic performances of imaging techniques. CAP, which was used to diagnose steatosis in our study, has emerged as a useful and standardized tool for steatosis detection that correlates well with histologic liver fat content. The accuracy of CAP for the estimation of steatosis quantification is good and better than that of liver ultrasound, serum markers, and clinical variables.[17] Although magnetic resonance techniques are considered the most sensitive methods, they are expensive and time consuming and therefore not routinely used.[18] In contrast, CAP has a point-of-care nature that makes it ideal for population-based studies.

Our data clearly show that MAFLD is more prevalent in IBD patients than in the general population and that IBD is a significant independent risk factor for MAFLD once the classic metabolic risk factors have been adjusted for. Moreover, we observed that the prevalence of advanced fibrosis MAFLD was also significantly higher among the IBD population and that IBD was an independent factor explaining the severity of the disease. To analyze the prevalence of MAFLD and advanced fibrosis MAFLD, we used a control group that has several strengths from our point of view. First, it is a random sample from the general population; thus, use of this sample avoids the problem of selection bias, and the distribution of MAFLD in the general population is accurately reflected in the sample. Second, by matching not only by sex and age but also by BMI and T2D status, we closely paired the controls so that they were similar in terms of metabolic profile. We believe this is of great importance because IBD patients have a distinct metabolic and cardiovascular risk profile from the general population.[19] Furthermore, when comparing patients with biopsy-proven MAFLD in the IBD group with those in the general population, we were able to confirm that IBD patients with MAFLD have lower prevalence of T2D, lower mean BMI, and lower degree of steatosis than non-IBD patients with MAFLD and an equivalent stage of fibrosis, which was also verified on the basis of CAP levels in MAFLD-IBD patients and controls. Thus, we believe that the ability to identify a significant proportion of MAFLD patients with IBD without relying on classic metabolic risk factors is of outstanding importance and should increase awareness of the concomitant presence of MAFLD by clinicians responsible for managing IBD patients. We have proven in a subset of patients with biopsy-proven IBD-MAFLD that current commonly used noninvasive techniques for fibrosis detection, such as TE and serum biomarkers, can be useful tools to identify IBD patients at risk of advanced fibrosis.

Finally, we would like to emphasize that our results are consistent with those of previous studies on the prevalence of and risk factors for MAFLD under different IMID settings, some of which were carried out by our study group.[20,21] Thus, our data support the hypothesis that MAFLD has a disproportionately high tendency to develop in IMID populations, which may be explained, at least in part, by the distinctive chronic inflammatory burden of these conditions. MAFLD pathogenesis is driven by a combination of metabolic disturbances and proinflammatory events that take place commonly in the setting of obesity and insulin resistance. Nonetheless, our data suggest that in a subset of patients such as IBD patients, there might be a metabolism-independent mechanism driving MAFLD development and progression. In seeking evidence to support this hypothesis, we observed that IBD patients with disease that follows a more aggressive course are at a higher risk not only of a MAFLD diagnosis but also of advanced disease. This is of special relevance to CD patients, who are at the greatest risk of advanced MAFLD, as well as patients with previous disease complications as surrogate markers of severe and persistent disease.

However, the design of the study does not allow us to draw any conclusions about the effect of current IBD therapies on the course and severity of MAFLD. More studies are needed to answer these questions.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.01.039.

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Reprint requests

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Acknowledgements

The authors report funding support from the Spanish Instituto de Salud Carlos III-FEDER Grant (FIS - PI18/01304) related to this manuscript. The authors are indebted to patients and volunteers that disinterestedly agreed to participate in this study.

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Conflicts of interest

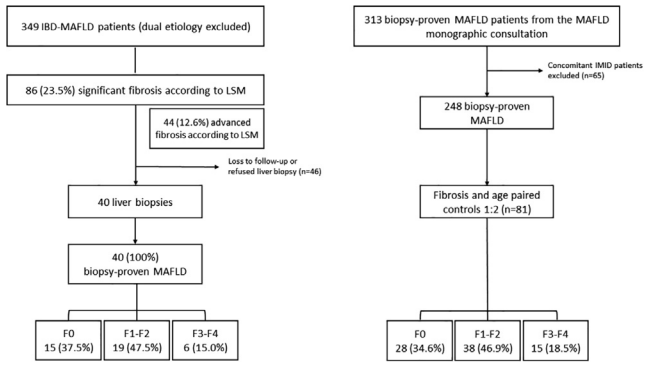
These authors disclose the following: JL Calleja is a consultant for Intercept and Gilead Sciences. J Crespo reports grants and research support from Gilead Sciences, Echosens, AbbVie, MSD, Shionogi, and Intercept Pharmaceuticals (none of them related to the submitted work) and is a speaker for Gilead Sciences and AbbVie. The remaining authors disclose no conflicts.

Funding

Supported by Spanish Instituto de Salud Carlos III grant (FIS - PI18/01304), "Immunomediated Non-alcoholic SteaTohepatitis; Prevalence and Characterization. INSTInCT Study".

Supplementary Information Regarding Univariate and Multivariate Analysis

Raw (unadjusted) and adjusted ORs with 95% CIs were estimated by stepwise multivariate conditional logistic regression, incorporating variables found to be significant in the univariate analyses, as well as biologically relevant covariates associated with the diagnosis and severity of MAFLD and IBD (age, sex, coexisting T2D, arterial hypertension, obesity, and dyslipidemia), to test the risk factors for MAFLD diagnosis and significant liver fibrosis in our study population.



Supplementary Figure 1. Flow chart of comparative biopsy-proven analysis of MAFLD-IBD patients and controls.

Univariate and Multivariate Analysis of MAFLD Risk Factors

	Univariate		Multivariate	
	MAFLD		MAFLD	
	Raw OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
IBD	1.534 (1.291–1.824)	<.001	1.999 (1.592–2.511)	<.001
T2D	3.399 (2.435–4.745)	<.001	1.027 (0.669–1.577)	.902
BMI	1.392 (1.351–1.431)	<.001	1.337 (1.295–1.381)	<.001
Hypertension	3.466 (2.809–4.275)	<.001	1.192 (0.911–1.561)	.201
Dyslipidemia	2.242 (1.857–2.707)	<.001	1.284 (1.008–1.636)	.043
Male sex	1.912 (1.618–2.254)	<.001	1.561 (1.248–1.951)	<.001
Age	1.048 (1.040–1.055)	<.001	1.037 (1.026–1.048)	<.001

Univariate and Multivariate Analyses of Advanced Fibrosis Prevalence in MAFLD Patients With and Without IBD

	Univariate		Multivariate	
	Advanced fibrosis in MAFLD		Advanced fibrosis in MAFLD	
	Raw OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
IBD	3.549 (2.087–6.031)	<.001	4.629 (2.524–8.488)	<.001
T2D	2.722 (1.487–4.981)	.001	3.029 (1.469–6.244)	.003
BMI	1.134 (1.084–1.187)	<.001	1.122 (1.066–1.182)	<.001
Hypertension	2.014 (1.204–3.369)	.009	1.718 (0.934–3.161)	.082
Dyslipidemia	1.164 (0.694–1.952)	.566	1.663 (0.913–3.032)	.097
Male sex	1.075 (0.646–1.789)	.790	1.338 (0.752–2.381)	.322
Age	0.997 (0.974–1.021)	.821	0.992 (0.962–1.019)	.509

Supplementary Table 1. Baseline Characteristics of IBD Patients

		IBD (n = 831)
IBD phenotype, n (%)		
	UC	420/831 (50.5)
	CD	389/831 (46.8)
	Indeterminate colitis	22/831 (2.7)
CD behavior, n (%)		
	Inflammatory	210/389 (54.0)
	Stenosing	90/389 (23.1)
	Fistulizing	35/389 (9.0)
	Stenosing + fistulizing	54/389 (13.9)
Extent of CD, n (%)		
	Terminal ileum	243/389 (62.5)
	Colon	42/389 (10.8)
	Ileocolon	103/389 (26.5)
	Upper gastrointestinal tract	1/389 (0.3)
	Perianal	49/389 (12.6)
Extent of UC, n (%)		
	Proctitis	166/420 (39.5)
	Left-sided colitis	134/420 (31.9)
	Extensive colitis	120/420 (28.6)
Extraintestinal manifestations,[a] n (%)		143/831 (17.2)
	Skin	39/831 (4.7)
	Axial arthropathy	50/831 (6.0)
	Peripheral arthropath	52/831 (6.3)
	Ocular	23/831 (2.8)
IBD duration (*y*), mean (SD)		13.0 ± 9.6
Age at onset (*y*), mean (SD)		38.0 ± 13.5
IBD severity, n (%)		
	Partial Mayo score:	
	Remission	365/420 (86.9)
	Mild	48/420 (11.4)
	Moderate	7/420 (1.7)
	Severe	0/420 (0.0)
	Harvey-Bradshaw index:	
	Remission	356/389 (91.5)
	Mild	23/389 (5.9)
	Moderate	11/389 (2.8)
	Severe	0/389 (0.0)
	Complications	131/831 (15.8)
	Clinical flares in the last 5 years	139/831 (16.7)
	Hospitalizations in the last 5 years	10/831 (1.2)

Supplementary Table 1. Continued

		IBD (n = 831)
IBD family history, n (%)		161/831 (19.4)
IBD treatment, n (%)	Current corticosteroid use	25/831 (3.0)
	Previous corticosteroid use	567/831 (68.2)
	Current biological treatment	144/831 (17.3)
	Previous biological agent use	207/831 (24.9)
	Current azathioprine use	147/831 (17.7)
	Previous azathioprine use	348/831 (41.9)
	Current methotrexate use	1/831 (0.1)
	Previous methotrexate us	19/831 (2.3)
	Previous surgery	178/831 (21.4)

NOTE. Qualitative data are presented as total number and percentage (in parentheses).
CD, Crohn's disease; UC, ulcerative colitis.
[a]Patients with hepatobiliary extraintestinal manifestations, such as primary sclerosing cholangitis, autoimmune chronic hepatitis, or granulomatous disease, were not included in the study.

Supplementary Table 2. Comparative Characteristics of MAFLD in IBD and Non-IBD Patients

	MAFLD-IBD (n = 349)	MAFLD non-IBD (n = 563)	*P* value
Age (*y*), median (range)	55 (23–76)	56 (28–78)	.057
Male sex, n (%)	188 (53.9)	336 (59.7)	.084
BMI (kg/m^2), mean (SD)	28.6 ± 4.8	29.9 ± 4.4	<.001
Overweight (BMI >25), n (%)	283 (81.1)	541 (96.1)	<.001
Obesity (BMI >30), n (%)	108 (31.0)	231 (41.0)	.002
Abdominal perimeter (*cm*), mean (SD)	99.3 ± 10.0	99.4 ± 10.8	.868
T2D, n (%)	28 (8.0)	77 (13.7)	.009
Hypertension, n (%)	122 (35.0)	188/449 (41.9)	.047
Dyslipidemia, n (%)	161 (46.1)	198/438 (45.2)	.795
Active smoker, n (%)	80 (22.9)	120 (21.3)	.235
LSM (*kPa*), median (range)	5.4 (2.4–21.8)	4.6 (2.5-52.4)	<.001
CAP (db/m), median (range)	284. 0 (204–400)	296.0 (249–400)	<.001
Advanced fibrosis,[a] n (%)	33 (9.5)	13 (2.3)	<.001
Fasting glucose level (*mg/dL*), mean (SD)	83.8 ± 20.7	90.4 ± 24.2	<.001
Triglyceride level (*mg/dL*), mean (SD)	147.8 ± 122.3	181.8 ± 124.0	<.001
Total cholesterol level (*mg/dL*), mean (SD)	195.8 ± 38.6	203.1 ± 37.7	.006
HDL cholesterol level (*mg/dL*), mean (SD)	53.9 ± 14.1	51.8 ± 14.0	.034
LDL cholesterol level (*mg/dL*), mean (SD)	116.0 ± 31.3	117.0 ± 34.7	.685
ALT level (*U/L*), mean (SD)	29.7 ±22.1	28.0 ± 15.4	.185
AST level (*U/L*), mean (SD)	28.1 ± 18.8	25.0 ± 8.2	.001
GGT level (*U/L*), mean (SD)	45.4 ± 37.2	34.7 ± 33.9	.161
Bilirubin level (*mg/dL*), mean (SD)	0.6 ± 0.3	0.5 ± 0.3	<.001
Albumin level (*mg/dL*), mean (SD)	4.5 ± 0.3	4.5 ± 0.2	.052
GFR ($mL/min/1.73\ m^2$), mean (SD)	87.3 ± 8.2	85.4 ± 10.2	.003
INR, mean (SD)	1.1± 0.2	1.1 ± 0.2	.086
Platelet number ($10^3/\mu L$), mean (SD)	241.4 ± 66.8	228.3 ± 58.8	.002

NOTE. Qualitative data are presented as frequencies and percentages (in parentheses). Quantitative data are presented as means and standard deviations (in parentheses).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; GFR, glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; HDL, high-density lipoprotein; INR, international normalized ratio; LDL, low-density lipoprotein; LSM, liver stiffness measurement; SD, standard deviation; T2D, type 2 diabetes

[a]Advanced fibrosis is considered when LSM ≥9.7 kPa.

Supplementary Table 3. Comparative Characteristics of IBD Patients According to MAFLD Status

	IBD-MAFLD (n = 349)	IBD non-MAFLD (n = 446)	*P* value
Clinical characteristics			
Age (*y*), median (range)	55 (23–76)	47 (19–76)	<.001
Male sex, n (%)	188 (53.9)	185 (41.5)	.001
BMI (kg/m^2), mean (SD)	28.6 ± 4.8	24.0 ± 3.8	<.001
Overweight (BMI >25), n (%)	283 (81.1)	143 (32.1)	<.001
Obesity (BMI >30), n (%)	108 (31.0)	31 (7.0)	<.001
Abdominal circumference (*cm*), mean (SD)	99.3 ± 10.9	87.2 ± 11.1	<.001
T2D, n (%)	28 (8.0)	16 (3.6)	.007
Hypertension, n (%)	122 (35.0)	59 (13.2)	<.001
Dyslipidemia, n (%)	161 (46.1)	130 (29.2)	<.001
Ischemic heart disease, n (%)	9 (2.6)	7 (1.6)	.315
Peripheral arterial disease, n (%)	4 (1.2)	3 (0.7)	.478
Active smoker, n (%)	80 (22.9)	106 (23.8)	.926
OSAHS, n (%)	23 (6.6)	10 (2.2)	.001
Menopause, n (%)	116/161 (72.1)	113/261 (43.3)	<.001
Thyroid abnormalities, n (%)	39 (11.2)	44 (9.9)	.549
Polycystic ovary syndrome, n (%)	9/161 (5.6)	12/261 (4.6)	.649
Family history of obesity, n (%)	26 (7.5)	10 (2.2)	<.001
Other associated IMIDs[f], n (%)	50 (14.3)	49 (11.0)	.157
LSM (*kPa*), median (range)	6.1 (3.1–24.6)	4.8 (2.0–22.3)	<.001
Laboratory characteristics			
Fasting glucose level (*mg/dL*), mean (SD)	83.8 ± 20.7	78.7 ± 11.6	<.001
Insulin level (*mg/dL*), mean (SD)	10.6 ± 13.3	5.2 ± 4.0	<.001
HOMA index, mean (SD)	2.5 ± 4.0	1.1 ± 1.1	<.001
Hemoglobin A1c, %, mean (SD)	5.6 ± 0.7	5.3 ± 0.4	<.001
Triglyceride level (*mg/dL*), mean (SD)	147.8 ± 122.3	91.0 ± 44.7	<.001
Total cholesterol level (*mg/dL*), mean (SD)	195.8 ± 38.6	187.5 ± 35.0	.002
HDL cholesterol level (*mg/dL*), mean (SD)	53.9 ± 14.1	60.6 ± 15.7	<.001
LDL cholesterol level (*mg/dL*), mean (SD)	116.0 ± 31.3	109.8 ± 28.9	<.001
ALT level (*U/L*), mean (SD)	29.7 ± 22.1	20.0 ± 11.6	<.001
AST level (*U/L*), mean (SD)	28.1 ± 18.8	23.3 ± 8.9	<.001
GGT level (*U/L*), mean (SD)	45.4 ± 17.2	20.0 ± 15.3	.002
INR, mean (SD)	1.1 ± 0.2	1.1 ± 0.2	.349
Bilirubin level (*mg/dL*), mean (SD)	0.6 ± 0.4	0.6 ± 0.3	.679
Albumin level (*mg/dL*), mean (SD)	4.5 ± 0.3	4.4 ± 0.3	.002
GFR ($mL/min/1.73\ m^2$), mean (SD)	87.3 ± 8.2	88.6 ± 7.0	.018
Leukocyte number ($10^3/\mu L$), mean (SD)	7.5 ± 2.0	7.3 ± 1.9	.164
Lymphocyte number ($10^3/\mu L$), mean (SD)	2.3 ± 1.4	2.2 ± 0.7	.124
Neutrophil number ($10^3/\mu L$), mean (SD)	4.5 ± 2.2	4.5 ± 2.9	.688
Neutrophil/lymphocyte index, mean (SD)	2.3 ± 1.5	2.3 ± 1.9	.162
ESR, *mm/h*, mean (SD)	15.3 ± 14.1	12.2 ± 11.6	.125
CRP level (*mg/dL*), mean (SD)	0.6 ± 0.6	0.5 ± 0.9	.807
Ferritin level (*ng/mL*), mean (SD)	135.2 ± 4.8	94.7 ± 2.7	<.001
Platelet number ($10^3/\mu L$), mean (SD)	233.4 ± 62.3	232.7 ± 58.6	.179
IBD characteristics			
IBD phenotype, n (%)			
Ulcerative colitis	174 (50.0)	224 (50.2)	.332
Crohn's disease	166 (47.6)	211 (47.3)	.249
Indeterminate colitis	9 (2.6)	11 (2.5)	.189
Duration of IBD (*y*), mean (SD)	13.9 ± 9.8	12.4 ± 9.4	.031
Age at onset (*y*), mean (SD)	40.4 ± 13.5	35.4 ±13.0	<.001
IBD treatment, n (%)			
Current corticosteroid use	9 (2.6)	16 (3.6)	.419
Previous corticosteroid use	222 (63.6)	291 (65.2)	.234
Current azathioprine use	74 (21.2)	73 (16.4)	.081
Previous azathioprine use	149 (42.7)	199 (44.6)	.587
Current biological agent use[a]	55 (15.8)	85 (19.1)	.226
Previous biological agent use	87 (24.9)	113 (25.4)	.475
No. of biological agents used,[b] median (range)	1.4 (1–3)	1.4 (1–4)	.246
Previous surgery	85 (24.4)	88 (19.7)	.117
IBD severity, n (%)			
Partial Mayo active disease[c]	18/174 (10.3)	36/224 (16.1)	.094

Supplementary Table 3. Continued

	IBD-MAFLD (n = 349)	IBD non-MAFLD (n = 446)	*P* value
Harvey-Bradshaw active disease[d]	20/166 (12.1)	14/211 (6.6)	.069
Extraintestinal manifestations	59 (15.0)	78 (17.5)	.828
Complications[e]	68 (19.5)	61 (13.7)	.028
Toxic megacolon	6/174 (3.5)	0/224 (0.0)	.01

NOTE. Qualitative data are presented as frequencies and percentages (in parentheses). Quantitative data are presented as means and standard deviations (in parentheses).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GFR: glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; HDL, high-density lipoprotein; IMIDs, immune-mediated inflammatory diseases; INR, international normalized ratio; LDL, low-density lipoprotein; OSAHS, obstructive sleep apnea-hypopnea syndrome; SD, standard deviation.
[a]Biological agents include infliximab, adalimumab, golimumab, vedolizumab, and ustekinumab.
[b]No. of biological agents prescribed in the previous 5 years.
[c]Partial Mayo score ≥2 points.
[d]Harvey-Bradshaw index ≥5 points.
[e]Complications include hemorrhage, abscess, perforation and toxic megacolon.
[f]IMIDs: immune-mediated inflammatory diseases include psoriasis, psoriatic arthritis, rheumatoid arthritis, non-infectious uveitis, hidradenitis suppurativa, ankylosing spondylitis, sarcoidosis, and systemic lupus erythematosus

Supplementary Table 4. Comparative Characteristics of Active IBD, Inactive IBD, and Non-IBD Patients

	Active IBD (n = 89) A	Inactive IBD (n = 742) B	Controls (n = 1719) C	*P* value A vs B	*P* value A vs C
Male sex, n (%)	50 (56.2)	352 (48.8)	886 (51.6)	.376	.396
Hypertension, n (%)	19 (19.1)	180 (24.3)	350 (27.2)	.280	.095
T2D, n (%)	5 (5.6)	46 (6.2)	124 (7.2)	.629	.564
Dyslipidemia, n (%)	23 (25.8)	294 (39.6)	429 (33.9)	.011	.120
Age (*y*), mean (SD)	49.8 ± 11.5	51.2 ± 12.7	51.0 ± 12.6	.316	.359
BMI (kg/m^2), mean (SD)	26.6 ± 5.0	26.14 ± 4.9	26.3 ± 4.8	.382	.541
MAFLD, n (%)	39 (43.8)	346 (46.6)	614 (35.7)	.615	.040
CAP (*db/m*), median (range)	245.0 ± 63.1	245.6 ± 59.5	247.6 ± 64.5	.622	.919
LSM (*kPa*), median (range)	5.7 ± 2.9	5.6 ± 2.5	4.9 ± 2.7	.700	.089
Advanced fibrosis,[a] n (%)	6 (14.0)	41 (12.6)	13 (2.3)	.799	<.001

NOTE. Qualitative data are presented as frequencies and percentages (in parentheses). Quantitative data are presented as means and standard deviations (in parentheses).
[a]Advanced fibrosis is considered when LSM ≥9.7 kPa.

Supplementary Table 5. Diagnostic Performance of Noninvasive Biomarkers and Transient Elastography in Advanced Fibrosis Detection

	Advanced fibrosis detection (F3-F4)					
	Cutoff	AUROC (95% CI)	NPV (%)	PPV (%)	Se (%)	Sp (%)
FIB-4	1.30 2.67 3.25	0.853 (0.67–1.00)	95 89 87	28 67 50	83 33 17	62 97 97
APRI score	0.7 1.0 1.5	0.828 (0.63–1.00)	94 87 100	57 50 —	67 17 —	91 97 85
NAFLD FS	–1.455 0.676	0.797 (0.62–0.97)	95 87	26 100	83 17	59 100
HEPAMet FS	0.12 0.47	0.583 (0.30–0.86)	88 87	33 100	33 17	88 100
FLI	60	0.792 (0.619–0.963)	100	19	100	24
LSM (*kPa*)	9.5 10.5 12.5	0.931 (0.85–1.00)	100 100 94	27 50 57	100 100 67	53 82 91

AUROC, area under the receiver operating characteristic curve; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.