Crohn's Disease Is Associated with Liver Fibrosis in Patients with Nonalcoholic Fatty Liver Disease

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Abstract

Background—Chronic inflammation in IBD is postulated to drive NAFLD progression from steatosis to fibrosis.

Aims—To study the histopathological spectrum of NAFLD in Crohn disease (CD) and Ulcerative colitis (UC).

Methods—Patients with biopsy proven NAFLD at a quaternary center from 2008 to 2018 were included in this retrospective analysis. Inflammatory bowel disease (IBD) diagnosed either clinically and/or endoscopically at the time of liver biopsy. Multivariable regression and propensity score (PS) weighted analysis were conducted. Statistical analysis were performed using SAS statistical software.

Results—Among 1009 patients with NAFLD a diagnosis of IBD was identified in 50 cases (34 CD and 16 UC). On multivariable analysis; CD was independently associated with significantly higher odds of advanced fibrosis (AF) on liver biopsy (adjusted OR = 4.09, 95% CI = 1.40–11.94) compared to NAFLD patients without IBD. Similar results were obtained with both the overlap PS

weighted model (OR = 3.17, 95% CI = 1.55–6.49) and the PS matched model (OR = 3.49, 95% CI = 1.50–8.13).

Conclusion—In a large cohort of patients with histologically well characterized NAFLD, AF was more common in CD patients than NAFLD patients without IBD. These findings must be confirmed in a larger cohort, but suggest CD patients with NAFLD could be at greater risk for liver fibrosis.

Keywords

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a clinico-pathological spectrum ranging from simple steatosis (SS) with a relatively benign course, to Non-alcoholic steatohepatitis (NASH), which can progress to cirrhosis. NASH is projected to be the leading indication for liver transplantation in the United States. The global prevalence of NAFLD is as high as 25% [1] however only a subset of these develop advanced liver disease characterized by hepatic fibrosis, cirrhosis or HCC. Chronic inflammation, oxidative stress and more recently alteration in the 'gut-liver' axis have been recognized as factors associated with progression from SS to NASH and cirrhosis [2]. Within NAFLD, the presence of advanced fibrosis (AF) is the most important parameter associated with outcomes such as decompensation of liver disease, mortality and need for liver transplantation [3]. Thus identification and treatment of AF is critical to improving outcomes in NAFLD. Despite advances in modalities to diagnose and follow disease activity non-invasively, a liver biopsy remains the gold standard to characterize and stage NAFLD [4].

Inflammatory bowel disease (IBD) is a group of chronic inflammatory diseases broadly divided into Crohn disease (CD) and ulcerative colitis (UC). IBD is characterized by an exaggerated systemic immune response to environmental factors based on a genetic predisposition resulting in chronic relapsing remitting inflammation of the gastrointestinal tract [5]. The inflammatory process is likely central to the pathophysiology of diseases associated with IBD, such as cardiovascular, neurological and gastrointestinal [4]. Even though NAFLD is known to have a higher prevalence in the IBD population [6, 7], it is unclear whether an increased prevalence is associated with higher rates of liver fibrosis which is the major risk factor for liver related outcomes. Most studies have used ultrasound as a surrogate marker of hepatic steatosis to define NAFLD in IBD but none has till now described the histopathological spectrum of NAFLD comparing patients with and without IBD.

Given a potential pathophysiological link between IBD and progression of NAFLD, we hypothesized that NAFLD patients with IBD to have a higher prevalence of advanced stages of NAFLD as well as histologically defined AF in comparison to NAFLD patients without IBD. In addition, we aimed to delineate risk factors related to AF in NAFLD patients with IBD and compare the performance of commonly used non-invasive tests (NITs) for liver fibrosis in NAFLD patients with and without IBD.

Methods

After IRB approval, records were reviewed for all patients aged over 18 with histologically diagnosed NAFLD at our institution from 2008 to 2019. In this retrospective analysis of data collected prospectively within the EMR, manual chart review was performed to identify patients with and without a diagnosis of IBD at the time of liver biopsy (Fig. 1). The presence of a diagnosis of IBD was confirmed based on clinical notes from an experienced gastroenterologist based on a combination of clinical, radiological and endoscopic features [8, 9].

NAFLD Grading and Assessment of Fibrosis

NAFLD was diagnosed based on established histological criteria and graded per the NASH-Clinical Research Network (NASH-CRN) criteria by experienced pathologists [10]. Other etiologies of liver disease such as hemochromatosis, documented history of significant alcohol consumption (> 21 drinks per week in men and > 14 weeks per week in women), chronic viral hepatitis, hemochromatosis, autoimmune hepatitis, Wilson's disease and or alpha-1 antitrypsin deficiency were excluded. Liver fibrosis was graded per the Kleiner staging system (grade I–IV) [10].

IBD Characteristics

Data regarding type of IBD (UC vs. CD); disease duration, location, phenotype and management was collected via manual chart review. We collected information regarding previous corticosteroid, immunomodulator (azathioprine, methotrexate) and biological agent use (antitumor necrosis factor-alpha [TNF-a], interleukin blockers, integrin inhibitors) prior to NAFLD diagnosis. History of previous intestinal surgery prior to NAFLD diagnosis was also collected and those with > 1 intestinal surgery were defined as having multiple surgeries.

Outcome of Interest

The primary outcome of interest was advanced liver fibrosis, defined as liver fibrosis stage III–IV. Secondary outcomes were presence of NASH, defined as evidence of steatohepatitis with NAFLD activity score (NAS) > 3 and separately, presence of any stage of liver fibrosis.

Comparison of Non-invasive Fibrosis Tests (NITs) for Diagnosis of AF

We calculated individual patient scores for three commonly used NITs (fibrosis-4[FIB-4] index, NAFLD fibrosis score [NFS] and AST/Platelet index[APRI]) [11] in all patients with data available for calculation using previously described formulae for each score.

Statistical Analysis

Descriptive statistics characterizing patient demographics, laboratory and histopathological features according to IBD status and IBD subgroup were summarized as either percentage or median with interquartile range. *P* values for group comparisons were obtained from chi-square, Fisher's exact or Wilcoxon rank-sum tests as appropriate. Thirteen potential confounders were identified from the literature or expert opinion from the research team

(MA, RG, FR and BLC). Focusing on the primary outcome of AF, first multivariable logistic regression models were built utilizing: (1) all variables (full model); (2) forward selection; and (3) backward elimination. The two variable selection techniques resulted in the same seven variable model. Adjusted odds ratios and 95% confidence intervals are reported. Additionally, a propensity score (PS) for IBD was estimated from a multivariable logistic regression model containing age, sex, race, body mass index (BMI), presence of hypertension and diabetes. The overlap propensity score weighting method was then applied, in which each patient's weight is the probability of that patient belonging to the opposite IBD group. Logistic regression models adjusted for overlap PS weight investigated associations between IBD status and the probability of AF, NASH and liver fibrosis. Reported are weighted percentages, odds ratios and 95% confidence intervals. In a separate analysis, a PS matched cohort of CD and non-IBD subjects utilizing a caliper of ± 0.01 was created. Comparability of matched cohorts was assessed with absolute standardized differences (ASD), where a value greater than 0.20 indicates covariate imbalance. Simple logistic regressions were fit to the PS matched cohort assessing the association among CD status and AF, NASH and liver fibrosis. Reported are the odds ratios, 95% confidence intervals and P values. The diagnostic accuracy of NITs for AF was assessed by receiver operating characteristic (ROC) analysis. Areas under the ROC curves (AUROCs) were compared by the method of DeLong et al.[12] All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). P values were 2-sided with a significance threshold of 0.05.

Results

Demographics and Lab Values

A total of 1023 patients with histologically assessed NAFLD were identified and 14 were excluded due to incomplete data. Among a total of 1009 histologically proven NAFLD patients, 50 patients had IBD (34 CD and 16 UC). The mean age at diagnosis of patients with NAFLD was similar between patients with and without IBD (50.4 vs. 50.7 years), however NAFLD patients with IBD had lower BMI (32.5 vs. 40.2 kg/m^2, p < 0.0001). IBD patients were significantly less likely to have a history of hypertension (36% vs. 59%, p = 0.001) and a clinically notable but statistically non-significant lower frequency of history of T2DM (30% vs. 43%, p = 0.07). Their baseline demographic, clinical and laboratory features are depicted in Table 1.

Serum aminotransferase levels were not different but alkaline phosphatase (ALP) levels were higher in IBD patients (89 vs. 79 IU/L p = 0.004) compared to patients without IBD. Although IBD patients had a higher mean HDL (50 vs. 42 mg/dl, p = 0.03) and lower LDL levels (94 vs. 104 mg/dl, p = 0.03) supporting a favorable lipid profile, the mean triglyceride levels were significantly higher in IBD patients in comparison to patients without IBD (87 vs. 79 mg/dl, p = 0.01). IBD patients had a lower mean hemoglobin (13.5 vs. 14.0 gm/dl, p = 0.02) and the platelet count was similar between patients with and without IBD (245,000 vs. 254,000/mm^3, p = 0.92).

Comparison Between NAFLD Patients with CD and UC

Demographics including age, BMI and gender were similar between CD and UC patients. A history of T2DM was seen more frequently in patients with CD as compared with UC (32% vs. 25%, $p = 0.75$). Metformin use was similar (26% vs. 25%, $p = 0.99$). However, there was a clinically notable, but statistically non-significant, higher insulin use in CD when compared to UC (35% vs. 19%, $p = 0.33$). Laboratory parameters were similar between patients with CD and UC except for total bilirubin which was slightly higher in CD patients versus UC (0.6 vs. 0.4 mg/dl, $p = 0.04$). The demographic, clinical and laboratory features between CD and UC patients are presented in Table 1.

Histopathological Features

IBD patients were more likely to have AF on liver biopsy (30% vs. 17%, $p = 0.02$) although the prevalence of fibrosis and NASH was similar. On subgroup analysis, CD patients were more likely to have hepatocyte ballooning compared with non IBD patients (85% vs. 64%, $p = 0.03$). CD patients were also significantly more likely to have AF (41% vs. 17%, $p = 0.0002$), NASH (76% vs. 56%, $p = 0.02$) and liver fibrosis (88% vs. 63%, $p = 0.003$). Conversely UC patients had significantly lower rates of lobular inflammation (62% vs. 85%, $p = 0.04$) and hepatocyte ballooning (31% vs. 64%, $p = 0.03$). UC patients had a lower rate of AF (6% vs. 17%), however this was not statistically significant ($p = 0.49$). UC patients also had lower rates of NASH (31% vs. 56%, $p = 0.04$) and liver fibrosis (31% vs. 63%, $p = 0.008$). A detailed description of histological features on the liver biopsy is depicted in Table 2.

Multivariable Regression and Propensity Score Analyses

On multivariable analysis controlling for demographic features and comorbidities (Table 3); CD was independently associated with higher odds of AF on liver biopsy (adjusted OR = 4.09, 95% CI = 1.40–11.94) compared to NAFLD patients without IBD. This increased risk was observed with the fully adjusted model as well as a reduced model that utilized either forward selection or backward elimination for variable selection. Similar results were obtained with both the overlap PS weighted model (Fig. 2; weighted OR = 3.17, 95% CI = 1.55–6.49) and the PS matched model (Supplementary Table 1 & 2; OR = 3.49, 95% CI = 1.50–8.13).

Both PS analyses were applied to the secondary outcomes with similar results. The risk of liver fibrosis was higher in CD patients (PS weighted OR = 3.30, 95% CI = 1.15–9.52; PS matched OR = 3.30, 95% CI = 1.09–10.02); however, the risk of NASH did not significantly differ among the CD patients and non-IBD controls (PS weighted OR = 1.69, 95% CI = 0.75–3.80; PS matched OR = 1.63, 95% CI = 0.68–3.92). UC patients, on the other hand, had odds of AF that did not significantly differ from those of NAFLD patients without IBD (OR = 0.29, 95% CI = 0.03–3.12).

Comparison Between CD Patients With and Without AF

On comparing characteristics of CD patients with and without AF (Table 4), CD patients with AF were older (median age 54y vs. 48y, $p = 0.03$) and were significantly more likely to have DM (57% vs. 15% $p = 0.02$). History of multiple (> 1) intestinal surgeries was the

only IBD related charac teristic associated with AF (57% vs. 20% $p = 0.04$). Presence of fistulizing disease ($p = 0.36$) perianal disease ($p = 0.72$) or extra-intestinal manifestations ($p = 0.25$) were similar between CD patients with and without AF. There were no differences in the rates of corticosteroid use ($p = 0.63$), azathioprine (0.38) or biological use (0.49) between the groups.

Comparison of Performance of NITs to Detect Advanced Fibrosis

On ROC analysis, NITs (FIB-4 and APRI) had similar performance in patients with and without IBD to detect AF except NAFLD fibrosis score [NFS] that had better performance in patients with IBD (AUROC = 0.87 vs. 0.65, $p = 0.0001$). Among patients with IBD, all three tests had similar performance to detect AF. The performance characteristics are depicted in supplementary table 3 and supplementary Fig. 1).

Discussion

This study described the association of IBD with histologic features of NAFLD in a large cohort of well phenotyped patients with IBD in a tertiary center. We found CD was associated with 4 times the odds of AF in comparison with NAFLD patients without IBD. UC was not associated with higher rates of AF. We compared the prevalence of liver fibrosis using the gold-standard histopathology in NAFLD patients with and without IBD and were able to control for several known risk factors for NAFLD progression. Based on our results, we suggest that CD patients with NAFLD may represent a higher risk subset for AF. Among patients with IBD and NAFLD, older age and history of DM were also associated with AF. Commonly used non-invasive test for diagnosis of AF (FIB-4, NFS and APRI) had similar performance in IBD patients suggesting that these tests can be used for stratification of NAFLD in patients with IBD.

Over the last decade, NAFLD has been shown to be more prevalent in patients with IBD with an overall prevalence ranging from 27.5 to 32% in different meta-analysis [6, 7]. Yet only a few studies have evaluated NASH or fibrosis in IBD patients and no study to date has compared the histological features between NAFLD patients with and without IBD. AF is the most important predictor of liver related morbidity and mortality in NAFLD [3] and thus it is critical to assess whether the higher prevalence of NAFLD in IBD patients is also associated with a higher prevalence of AF. In our study, NAFLD patients with CD had higher odds of AF in comparison with those without IBD. Recognizing that this study is observational, addressing potential confounding is important and we controlled for several factors known to be associated with NAFLD progression in our study [13]. CD patients had four times higher odds of having AF after controlling for age, gender and features of metabolic syndrome. IBD is characterized by chronic inflammation, oxidative stress and alteration of gut-liver axis, factors known to be associated with progression in NAFLD from steatosis to fibrosis [2]. Progression in NAFLD from liver steatosis to NASH and then liver fibrosis is complex and multifactorial [14]. In the initial stages of steatosis, lipid overload leads to lipotoxicity which contributes to inflammation and oxidative stress [15]. This ultimately leads to NASH and a milieu for progressive liver fibrosis. Chronic inflammation in NASH leads to hepatocyte death and a pro-fibrogenic response [16]. Multiple mediators

such as transforming growth factor beta (TGF-β), platelet derived growth factor (PDGF) are upregulated which induce liver fibrosis [17]. Recently the influence of gut and gut microbiota on liver and vice-e-versa, termed the gut-liver axis is increasingly recognized to play a role in pathogenesis of NAFLD [18]. Breakdown of the intestinal barrier, a hallmark in IBD, results in exposure of liver to gut bacteria, bacterial products and immune mediators which can result in hepatic inflammation [19, 20]. Gut is essential for regulating nutrient intake and metabolism via gut derived hormones such as GLP-1 which can be decreased in IBD and predispose patients to hepatic inflammation and fibrosis [21]. Thus, there are multiple pathogenic pathways linking IBD and liver fibrosis explaining the observed increase in liver fibrosis (Fig. 3). To our surprise in contrast to CD, patients with UC did not have higher odds of having fibrosis or AF in our study. Although they are both types of IBD, CD and UC are known to have different pathobiology. Prior studies have shown that CD poses a greater risk for NAFLD than UC however the exact mechanism remains unknown [7]. Decreased expression of ileal farnesoid X receptor (FXR) gene and lower levels of fibroblast growth factor 19 (FGF 19) are postulated mechanisms behind increased rates of NAFLD seen in CD [2]. Activation of FXR in the small intestine by bile acids is crucial for regulation of carbohydrate and lipid metabolism as well as decreasing the production of pro-inflammatory and fibrogenic mediators [22]. Consequently FXR agonism has emerged as a therapeutic option for treatment of NAFLD. FXR is predominantly found in the small intestine which may partly contribute to increased rates of fibrosis seen in CD as compared with UC. In addition, CD is associated with higher degree of gut microbiome alteration in comparison with UC which is linked to progression of NAFLD [23]. For instance, F. Prausnitzii, the most abundant bacterium in healthy human gut with immunosuppressive effects [24], was shown to be depleted in CD whereas upregulated in UC patients [25]. Such alterations in the gut microbiome may be associated with a pro-inflammatory liver milieu and contribute to inflammation in CD patients resulting in liver fibrosis.

Among CD patients, older age and history of DM were significantly associated with AF. No other IBD related factors such as disease duration, extent of involvement or treatment were associated with higher rates of AF in this study. Advancing age and DM are well established as risk factors for progression of NAFLD from SS to fibrosis [26]. As the survival of patients with CD continues to improve, the burden of AF and consequently NASH cirrhosis is likely to increase. Factors such as duration of IBD, history of bowel resection, exposure to corticosteroids, methotrexate and biological agents have been postulated to be related to a higher risk of developing NAFLD but data is conflicting [6, 7]. However no previous study till date has evaluated these factors in relation to liver fibrosis. Although we did not identify any IBD specific factors to be related to survival, this may have been due to a small sample size of IBD patients and lack of statistical power. Larger studies with IBD patients in future should evaluate the impact of disease activity and control on NAFLD progression in this sub-group of patients.

Non-invasive tests are routinely used to detect AF in patients with NAFLD however these have not been validated in patients with IBD. This study found that routinely used NITs (FIB-4, NFS, APRI) had similar (FIB-4 and APRI) or even better performance (NFS) to detect AF in IBD patients in comparison with non-IBD patients. Among IBD patients, the three tests had similar performance. Validation of NITs in IBD is key to stratify NAFLD

in patients with IBD which can help guide referral to hepatologists for specialized care and further investigation. NITs can also facilitate larger scale studies to accurately determine the prevalence of liver fibrosis in larger IBD populations without a need for liver biopsy and provide a marker to assess progression of disease. These results should be validated in further larger IBD populations.

Our study has the following key strengths. We focused on the most important predictor of clinically relevant outcomes in liver fibrosis, which was defined per the validated NASH-CRN system [10]. Further, liver biopsy is gold standard for assessment and grading of fibrosis. All biopsies were systematically evaluated using the NASH-CRN criteria by expert pathologists. This is in contrast to previous studies which used surrogate marker for fibrosis assessment not yet validated in patients with IBD. We also included detailed clinical data regarding both NAFLD and IBD related features, and adjust for several key variables that confound the association between both disease phenotypes. We used robust statistical methods including multivariable and propensity score weighted and matched analysis. However, we acknowledge limitations of our study. As we started from a cohort of patients who underwent liver biopsy, this selection bias would have excluded IBD patients who did not get a liver biopsy, which could have contributed to the relatively small subset of IBD patients. As this is a single center study conducted at a referral center, there is a possibility of referral bias selecting for patients with more complications. However, the rates of NASH and AF in our study were similar to prior epidemiological studies from other academic centers. We focused on fibrosis and did not evaluate the prevalence of NAFLD as assessed by other noninvasive modalities, which has already been described in patients with IBD [7]. Although we collected several characteristics of IBD phenotype and management in our cohort, we were not able to define IBD disease activity using standardized disease activity score and determine its correlation with NAFLD.

In summary, this is the first study to provide detailed clinical and histopathological characteristics of NAFLD in IBD patients and compare it with NAFLD patients without IBD. We recommend that further prospective data be collected in CD patients with NAFLD to ascertain their true risk for liver fibrosis. Results of such studies can help in prognosticating CD patients with NAFLD, and support screening and prevention strategies in the same. Future studies should evaluate effects of aggressive control of IBD disease activity and treatment of metabolic risk factors on liver fibrosis in patients with CD and NAFLD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflict of interest

Abbreviations

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AF	Advanced fibrosis
CD	Crohn Disease
IBD	Inflammatory bowel disease
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
PS	Propensity score
TNF	Tumor necrosis factor
UC	Ulcerative colitis

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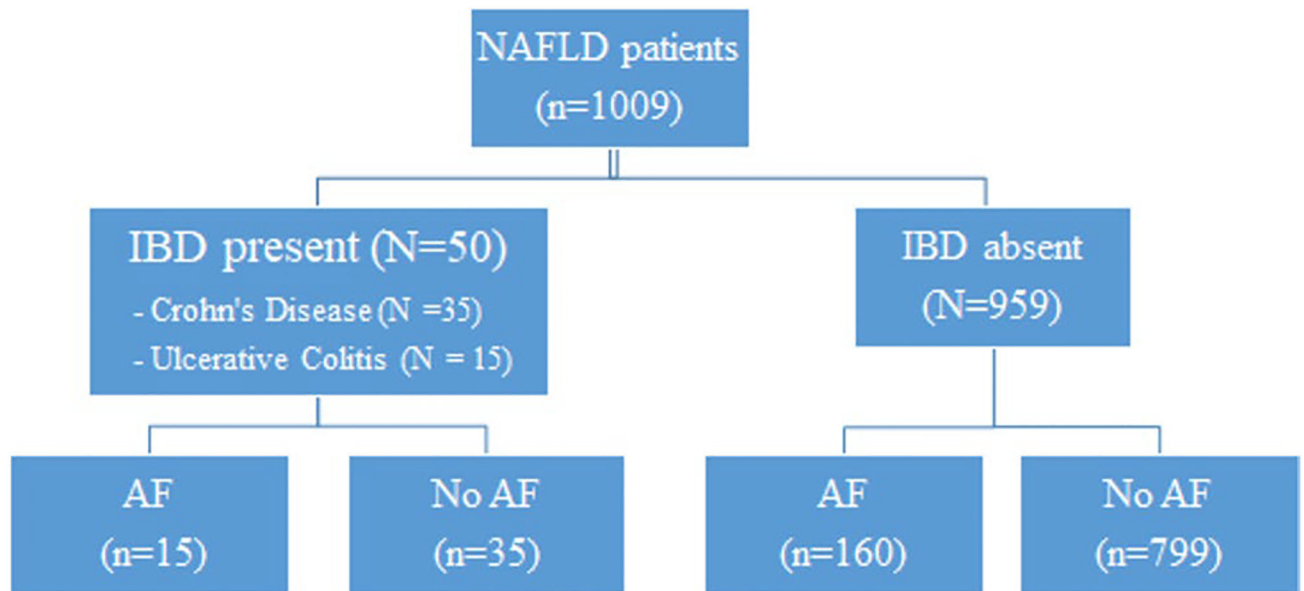
Fig. 1.
Flowchart of patients included in the study AF, Advanced fibrosis; IBD, Inflammatory bowel disease; NAFLD, Non-alcoholic fatty liver disease Advanced Fibrosis: Defined as Fibrosis stage 3–4
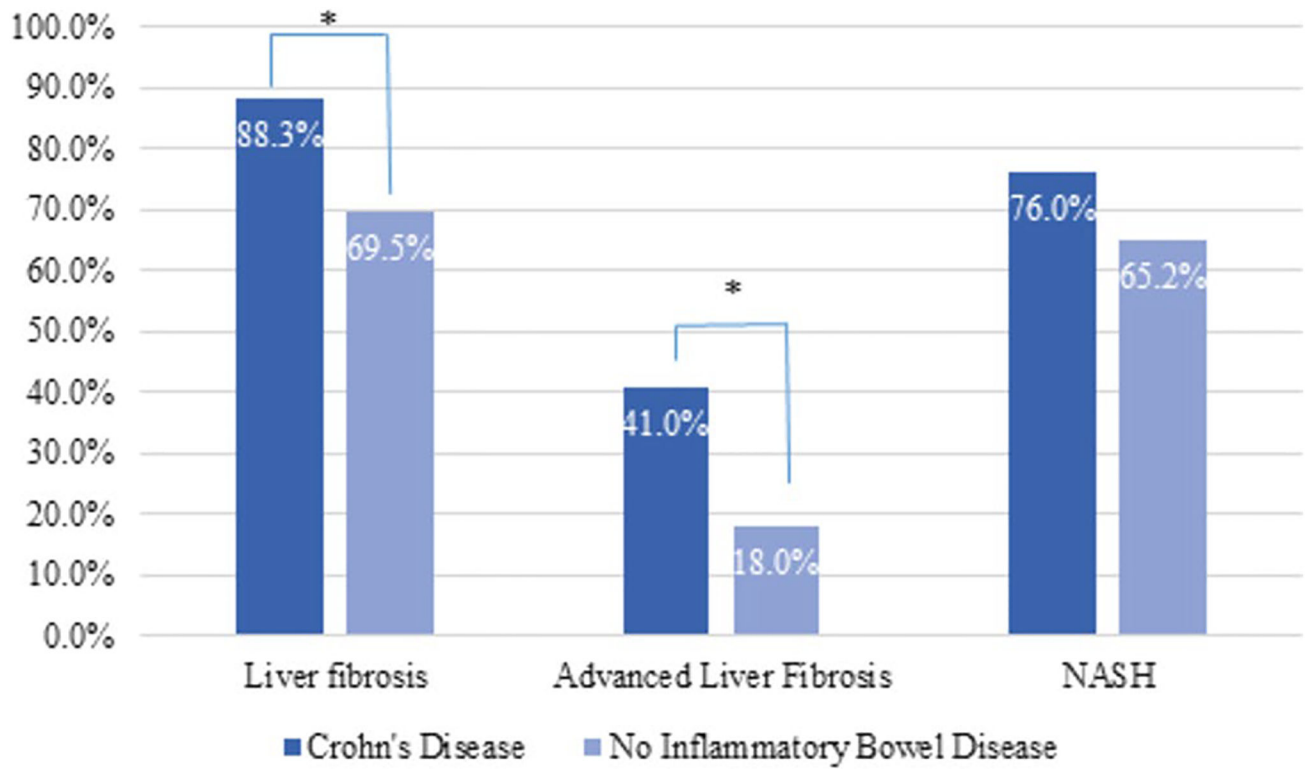
Fig. 2.
Rates of non-alcoholic fatty liver disease (NAFLD) histopathological features between
NAFLD patients with Crohn's disease (CD) and without inflammatory bowel disease (IBD)
after overlap propensity score weighting
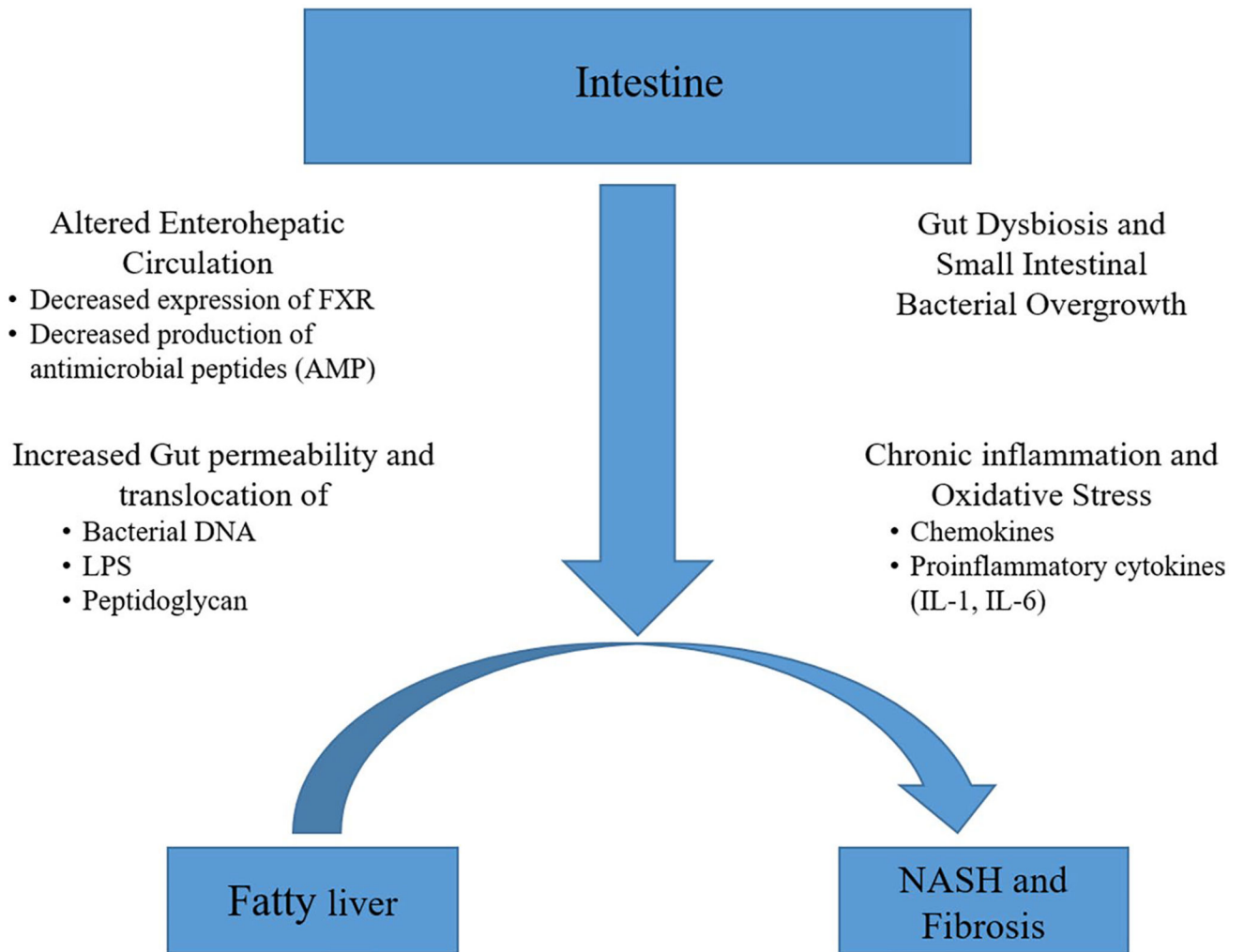
Fig. 3.
Proposed pathogenesis of non-alcoholic fatty liver disease progression in patients with inflammatory bowel disease

Table 1

Baseline characteristics of included patients

Characteristic	Inflammatory bowel disease (IBD)	No inflammatory bowel disease	P value [a]	Crohn's Disease (CD)	Ulcerative Colitis (UC)	P value [b]
Count	50	959		34	16	
Age, years	50.4 [39.7–56.8]	50.7 [39.9–58.7]	0.81	50.4 [37.0–56.7]	51.6 [43.0–59.8]	0.76
Female	62%	62%	0.97	59%	69%	0.50
Caucasian race	90%	84%	0.26	94%	81%	0.31
BMI, Kg/m2	32.5 [27.6–39.7]	40.2 [33.3–47.4]	<.0001	32.9 [27.7–37.1]	30.8 [27.1–42.5]	0.99
Hypertension	36%	59%	0.001	35%	38%	0.88
Statin use	32%	48%	0.02	29%	38%	0.57
Diabetes Mellitus	30%	43%	0.07	32%	25%	0.75
Insulin use	30%	24%	0.37	35%	19%	0.33
Metformin use	26%	41%	0.04	26%	25%	0.99
Albumin, gm/dl	4.2 [3.5–4.6]	4.3 [4.0–4.5]	0.52	4.2 [3.5–4.6]	4.3 [3.7–4.7]	0.95
Alkaline phosphatase, IU L^{-1}	89 [71–123]	79 [64–95]	0.004	92 [71–123]	88 [71–118]	0.72
Alanine transaminase, IU L^{-1}	47 [26–77]	46 [27–82]	0.82	46 [27–81]	52 [23–75]	0.76
Aspartate aminotransferase, IU L^{-1}	45 [28–56]	36 [23–60]	0.07	46 [28–68]	44 [28–49]	0.26
Total Bilirubin, mg/dl	0.5 [0.4–0.7]	0.4 [0.3–0.6]	0.002	0.6 [0.4–0.8]	0.4 [0.3–0.6]	0.04
High-density lipoproteins, mg dl^{-1}	50 [37–57]	42 [36–51]	0.03	47 [37–55]	53 [35–61]	0.49
Iron,	81 [49–100]	76 [59–95]	0.79	88 [58–107]	70 [40–92]	0.35
Low-density lipoproteins, mg dl^{-1}	94 [65–114]	104 [83–129]	0.03	81 [62–103]	104 [85–124]	0.14
Total cholesterol, mg dl^{-1}	176 [145–201]	180 [157–209]	0.37	167 [140–196]	179 [168–224]	0.26
Triglycerides, mg dl^{-1}	87 [71–117]	79 [64–95]	0.01	86 [71–117]	88 [71–118]	0.94
Hematocrit, %	40.6 [36.8–43.6]	42.2 [39.3–44.6]	0.009	40.4 [36.8–44.0]	41.6 [37.2–42.8]	0.98
Hemoglobin, gm dl^{-1}	13.5 [11.8–14.8]	14.0 [12.9–15.0]	0.02	13.6 [11.9–15.0]	13.5 [11.6–14.3]	0.51
Mean platelet volume	10.6 [10.1–11.2]	10.6 [10.0–11.3]	0.81	10.6 [9.8–11.2]	10.6 [10.3–11.2]	0.74
Platelet count, k ul^{-1}	254 [194–302]	245 [203–289]	0.92	238 [159–286]	287 [202–334]	0.15
White blood cells count	7.2 [5.5–8.3]	7.4 [6.1–9.0]	0.13	7.5 [5.9–9.1]	6.7 [5.3–7.4]	0.11

P values are obtained from chi-square/Fisher's exact or Wilcoxon rank-sum tests

[a] p values represent comparison between IBD and No IBD

[b] p values represent comparison between CD and UC

Table 2

Histopathological features on liver biopsy among patients with and without inflammatory bowel disease (IBD) and stratified by Crohn disease (CD) and ulcerative colitis (UC)

Biopsy outcomes	Inflammatory bowel disease	No inflammatory bowel disease	P value	Crohn's Disease	P value [a] (CD vs. No IBD)	Ulcerative Colitis	P value [b] (UC vs. No IBD)
Count	50	959		34		16	
Steatosis			0.80		0.31		0.39
<5%	2%	2%		0%		6%	
5–33%	42%	48%		35%		56%	
34–66%	40%	33%		47%		25%	
>66%	16%	17%		18%		13%	
Lobular Inflammation			0.41		0.91		0.04
No foci	20%	13%		12%		38%	
<2 foci per 200×field	48%	50%		47%		50%	
2–4 foci per 200×field	32%	35%		41%		13%	
>4 foci per 200×field	0%	2%		0%		0%	
Hepatocyte Ballooning			0.68		0.03		0.03
None	32%	36%		15%		69%	
Few Balloon Cells	46%	46%		59%		19%	
Many Cells/Prominent Ballooning	22%	18%		26%		12%	
Fibrosis Stage			0.06		0.001		0.09
0	30%	37%		12%		69%	
1	24%	30%		29%		12%	
2	16%	16%		18%		12%	
3	16%	12%		23%		0%	
4	14%	5%		18%		6%	
Advanced Fibrosis	30%	17%	0.02	41%	0.0002	6%	0.49
NASH	62%	56%	0.40	76%	0.02	31%	0.048
Fibrosis	70%	63%	0.34	88%	0.003	31%	0.008

Descriptive statistics are reported as either percentage or median [Q1–Q3]

P values are obtained from chi-square, Fisher's exact or Wilcoxon rank-sum tests

[a] Tests comparing Crohn's Disease versus no Inflammatory Bowel Disease groups

[b] Tests comparing Ulcerative Colitis versus no Inflammatory Bowel Disease groups

Advanced Fibrosis: Fibrosis stage 3–4

Fibrosis: Presence of any stage fibrosis

NASH: Nonalcoholic steatohepatitis (NASH) activity score > 3 and evidence of steatohepatitis

Table 3

Associations among Patient Characteristics and Advanced Fibrosis in non-alcoholic fatty liver disease (NAFLD) using Multivariable Logistic Regression

Characteristic	Full model			Forward selection & backward elimination		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
IBD Status (reference=non-IBD)			0.02			0.005
Crohn Disease	4.09	1.40–11.94		3.23	1.47–7.12	
Ulcerative Colitis	0.29	0.03–3.12		0.21	0.02–1.86	
Age	1.03	1.01–1.05	0.003	1.04	1.02–1.05	<.0001
Female	0.87	0.55–1.35	0.53			
White race	1.88	1.01–3.51	0.048	1.74	0.99–3.04	0.05
BMI	0.98	0.95–0.99	0.03	0.98	0.96–1.00	0.09
Hypertension	1.03	0.63–1.69	0.89	0.90	0.61–1.34	0.60
Statin	1.00	0.64–1.56	0.99			
Diabetes Mellitus	1.30	0.68–2.50	0.43			
Insulin	1.31	0.81–2.11	0.28			
Metformin	2.05	1.12–3.77	0.02	2.49	1.72–3.60	<.0001
High-density lipoproteins (HDL)	0.99	0.98–1.01	0.49			
Low-density lipoproteins (LDL)	0.99	0.99–1.01	0.86			
Total cholesterol	0.99	0.99–1.01	0.89			
Triglycerides (=10 units)	1.10	1.04–1.16	0.0008	1.08	1.04–1.14	0.0004

Table 4

Comparison of Clinical features between Crohn diseases (CD) patients with and without advanced liver fibrosis

Characteristic	Advanced fibrosis	No advanced fibrosis	P value
Count	20	14	
Age at NAFLD diagnosis, years	54 [49–62]	48 [31–55]	0.03
Duration of Crohn's Disease (months)	264 [48–357]	161 [68–248]	0.31
Female gender	43%	70%	0.11
White race	100%	90%	0.50
Body Mass Index (BMI), Kg/m2	32 [29–35]	34 [27–41]	0.41
Hypertension	36%	35%	0.99
Statin use	43%	20%	0.25
Diabetes Mellitus	57%	15%	0.02
Crohn's disease characteristics			0.16
Crohn's Disease Location			
L1: Ileal	14%	20%	
L2: Colonic	14%	40%	
L3: Ileocolonic	71%	40%	
Fistulizing disease	7%	25%	0.36
Perianal disease	29%	40%	0.72
Extraintestinal Manifestations	0%	15%	0.25
Prior Intestinal Surgery	71%	55%	0.33
Multiple Prior Surgeries (> 1)	57%	20%	0.04
Aminosalicylic Acid (ASA)	86%	65%	0.25
Corticosteroid use	79%	90%	0.63
Azathioprine use	50%	65%	0.38
Methotrexate use	0%	5%	0.99
Biological use	43%	55%	0.49

Descriptive statistics are reported as column percentages

NAFLD, Non-alcoholic fatty liver disease

P values are obtained from chi-square or Fisher's exact tests