ORIGINAL ARTICLE

Prevalence and Predictors of Nonalcoholic Fatty Liver Disease (NAFLD) and Liver Fibrosis Among Patients with Inflammatory Bowel Disease – an Indian Tertiary Center Based Study

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ABSTRACT

Objective: Non-alcoholic fatty liver disease (NAFLD) is increasingly identified in patients with inflammatory bowel disease (IBD), but there are no studies in Indian literature.

Methods: We prospectively investigated prevalence and predictors of NAFLD diagnosed on ultrasound imaging and liver fibrosis assessed by NAFLD fibrosis score (NFS) and 2D Shear wave elastography and findings reconfirmed by Transient Elastography (TE). Significant liver fibrosis (≥ F2)) was defined as TE measurement ≥ 7.5 kPa. Predictors of NAFLD were determined by binary logistic regression analysis. Pearson correlation method was used to find out factors linked to liver fibrosis.

Results: A total of 109 patients [mean age 35.6 ± 12 years, males (54%), females (46%) with Ulcerative colitis (88%) and Crohn's disease (12%)] were included. Prevalence of NAFLD and significant liver fibrosis was 11% and 1.8%, respectively. Predictors of NAFLD were longer course of disease, presence of frequent relapses and presence of metabolic syndrome. After logistic regression analysis, only course of disease (frequent relapses) [p value = 0.001, adjusted odds ratio = 2.028] was the significant factor. Significant liver fibrosis was correlated with older age (r = 0.623, p = 0.031) and metabolic syndrome (r = 0.662, p = 0.019).

Conclusions: NAFLD prevalence and significant liver fibrosis in IBD population in our study cohort was low compared to western data however, this needs validation by larger studies in view of rising prevalence of both the diseases independently.

Key Words: Non-alcoholic fatty liver disease, Inflammatory bowel disease, Liver fibrosis, 2D Shear wave elastography, Transient elastography, NAFLD Fibrosis score.

Conflict of Interest- The authors have nothing to disclose.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a clinicopathological syndrome with a histologic spectrum ranging from benign steatosis to non-alcoholic steatohepatitis (NASH) along with subsequent development of cirrhosis and its complications in a proportion of these patients[1]. In fact, it has become the predominant cause of chronic liver disease in many parts of the world. Epidemiological studies have shown link between NAFLD and inflammatory bowel disease (IBD) with prevalence ranging between 6.2–40%[2-4]. With the global increase in prevalence of both IBD and NAFLD, the long-term morbidity and economic burden has become increasingly significant[5]. Diseases of the liver and the biliary tract are frequently observed in patients with inflammatory bowel disease (IBD). Abnormal liver biochemical tests can be identified in up to 30 percent of patients with IBD[6]. Traditionally, medication toxicity, primary sclerosing cholangitis and autoimmune hepatitis are some of the most frequently identified causes. Due to paradigm shift in treatment approach, the phenotype of patients with IBD has changed from one of underweight and malnourished to overweight and even obese, resulting in increase in the NAFLD prevalence. The pathogenesis of NAFLD in IBD is complex and related to disease specific risk factors, such as chronic inflammation,

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steroid exposure, drug induced hepatotoxicity, malnutrition and alteration of gut microbiota, which is emerging as a major factor in the pathogenesis of NAFLD[7]. This is in contrast to NAFLD in general population, where metabolic risk factors such as central abdominal obesity, insulin resistance, dyslipidaemia and hypertension play a major role[8]. Although most of the studies have been done on coexistence of NAFLD and IBD, there are very few studies which have evaluated the significant hepatic fibrosis in these patients. It is estimated that liver fibrosis occurs in 6.4 -10% of IBD patients with approximately 5% of adult patients developing clinically significant liver disease[9].

Liver biopsy has long been the gold standard to assess NAFLD and to stage liver fibrosis. However, this procedure is invasive, costly, impractical as a screening tool and prone to sampling error[10]. Non-invasive methods to diagnose fatty liver and liver fibrosis have been implemented in place of liver biopsy. Ultrasound is an accurate, reliable imaging technique for the detection of fatty liver, as compared with histology, with a sensitivity of 84.8% and a specificity of 93.6% for detecting ≥ 20–30% steatosis[11]. In five small comparative studies, ultrasound was as accurate as CT and MRI for detecting steatosis, with a sensitivity and specificity of 94% and 80%, respectively. Hepatic fibrosis can be assessed by various biomarkers in combination or by imaging [Shear Wave Elastography (SWE), Transient Elastography (TE), acoustic radiation forced impulse (ARFI) and magnetic resonance elastography (MRE)], but they are not easily available and costly. In liver elastography, various ultrasound based elastography measures the liver stiffness or elasticity by assessing at least 100 times the proportion of the liver that a biopsy does. A study evaluating clinically significant liver disease (F2 Fibrosis) using TE in patients with IBD found that the prevalence of potentially clinically significant liver disease is low (6.5%) and that any prevailing liver abnormality is most likely secondary to NAFLD[12]. TE has been validated in multiple studies but SWE may be preferred because unlike TE, which consists of a vibrator producing shear waves, the latter can perform a conventional ultrasound at the same time and is cheaper. The technique is integrated into an ultrasound system. The principle of SWE is that shear waves produced by a focused ultrasound beam are directly related to the stiffness of the liver from where they are generated[13]. SWE is also reportedly more accurate than TE in assessing significant fibrosis (≥ F2)[14]. The use of SWE in the diagnosis and staging of liver fibrosis has been increasing. SWE has many advantages being a non-invasive technique and repeatability in patients with chronic progressive liver diseases. Although there are some pitfalls as well like intra- and inter-observer variability, validated cut-offs have been demonstrated mainly in hepatitis C. Acute hepatitis can have false positives and patients with a high body mass index can have erroneous values. Non-invasive assessment of hepatic fibrosis can be done by NAFLD fibrosis score (NFS). NFS is found to independently identify NAFLD patients with and without advanced fibrosis at initial NAFLD diagnosis. A study validated the NFS and found it to have an acceptable sensitivity, specificity, positive and negative predictive values for advanced liver fibrosis of 100%, 83%, 63%, and 100%, respectively[15]. The prevalence of NAFLD in India is on rise in the general population, particularly in high risk groups (Diabetes and Obesity). In the general population, prevalence of NAFLD varies from 9% to 35% in India[16]. However, there are no studies on prevalence of NAFLD in IBD in India, hence this study was planned.

MATERIAL AND METHODS

Study Design and Population

A prospective cross-sectional study was performed involving adult IBD [Ulcerative colitis (UC) and Crohn's disease (CD)] patients followed at outpatient department in SMS Medical College, Jaipur between September 2016 and February 2019. The distribution of patients in the study group is shown in Figure 1. All patients provided informed consent for participation and study was approved from Ethical committee of the institute.

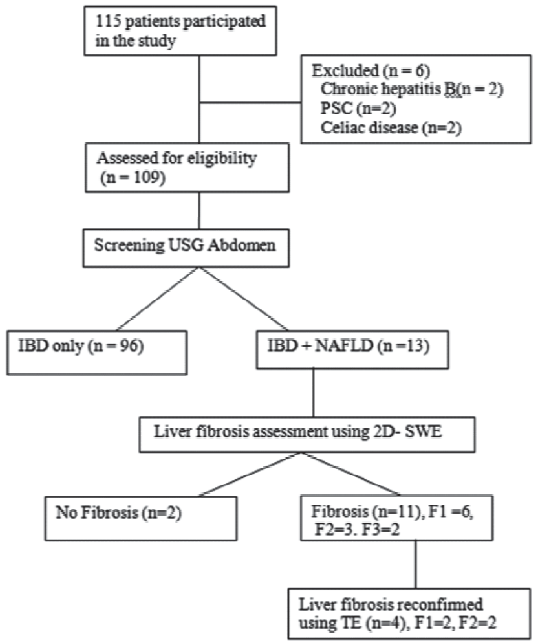

Figure 1. Consort diagram showing distribution of patients

Data Collection

Data on demographics, IBD subtype, duration of IBD, type of medication received was collected and analysed. Medications included use of any biologic (anti–tumor necrosis factor), immunomodulator (azathioprine and methotrexate), or corticosteroid (budesonide and prednisone). Data was collected on body mass index (BMI), lipid profile, hypertension, obesity and diabetes and patients were categorised as having metabolic syndrome based on Adult Treatment Panel III criteria for metabolic syndrome[8]. Overweight (BMI ≥ 23 kg/m^2) and obesity (BMI ≥ 25 kg/m^2) were defined considered as per revised guidelines for Asian Indians[17]. Data was collected on proportion of patients with NAFLD and liver fibrosis, which was assessed by imaging of liver using USG abdomen and 2D shear wave elastography (2DSWE) done in all patients by expert senior radiologist. However, during study period, it was observed that there was overestimation of fibrosis by 2DSWE when it was performed routinely in all patients and this finding was also confirmed in normal non IBD subjects (n=25). So, to reconfirm the findings, all the patients with any amount of fibrosis on 2DSWE underwent TE, which is also a validated modality in fibrosis assessment shown in prior studies[18]. All the patients underwent imaging for NAFLD and fibrosis while in clinical and endoscopic remission.

Diagnostic criteria

For IBD: based on a combined assessment of symptomatology, endoscopy, histology and abdominal imaging as per ECCO consensus[19].

For NAFLD: A diagnosis of NAFLD was based on imaging of the liver. Typical radiographic findings indicative of NAFLD include a heterogeneous appearance of the liver, echogenicity exceeding that of the renal cortex or spleen by ultrasound, greater attenuation than in the spleen and blood[20].

Fibrosis assessment was done using

- **NAFLD Fibrosis Score (NFS):** This is a composite score of age, body mass index, hyperglycemia, platelet count, albumin, and aspartate aminotransferase and alanine aminotransferase (AST/ALT) ratio.
- **NFS score: (**-1.675 + 0.037 x age [years]) + (0.094 x BMI [kg/m^2]) + (1.13 x impaired fasting glucose or diabetes [yes = 1; no = 0]) + (0.99 x AST/ALT ratio) – (0.013 x platelet [10^9/L]) – (0.66 x albumin [g/dl])
- NFS score is used to classify the probability of fibrosis as < -1.5, > -1.5 to < 0.67 and > 0.67 for low, intermediate and high probability respectively[15].
- **2D Shear wave elastography:** was done using Toshiba Aplio 500 Ultrasound Machine using a convex array probe at a frequency of 4 MHz. In 2DSWE, shear waves are created by US generated pulses of an acoustic radiation force. The velocity of the shear wave is then estimated by a Doppler-like effect over a region of interest (ROI) and is related to the stiffness or elasticity of the medium. This shear wave velocity can be used to calculate the tissue stiffness by the formula $E = \rho c^2$, where E is tissue elasticity (Young's modulus, kPa), ρ is tissue density (kg/m^3), and c is shear wave velocity (m/s)

Interpretation of liver fibrosis by shear wave elastography in kPa (Automatic median value) was done as: <4.6 - no fibrosis (F0), 4.6 – 5.6 - mild fibrosis (F1), 5.7–7.0 - severe fibrosis (F2), 7.1–12 - significant fibrosis (F3), >12 - cirrhosis (F4)[13,14].

- **Transient Elastography:** TE examination was performed by fibroscan mini 430 (Echosens™ Paris, France) machine on a 3-hour fasting patient by an experienced operator. The standard M probe was used in all patients. At least 10 validated measures and an interquartile range <30% of the median were required for the exam to be considered valid. The median value, expressed in kPa, was recorded as representative of the liver stiffness. Cut-off used for fibrosis assessment was F1 = 6-7, F2 =7.5-10, F3=10= 14, F4 = >14 as per manufacturer recommendations[21].
- **Exclusion criteria included:** 1) positive for hepatitis C virus antibody or hepatitis B surface antigen 2) other concomitant liver disease (3) significant alcohol consumption, as per American Association for the Study of Liver Diseases (AASLD) guidelines on NAFLD: "ongoing or recent alcohol consumption >21 drinks on average per week in men and >14 drinks on average per week in women"[22].

Outcome Measures

The primary outcomes of the study were: (a) prevalence and predictors of NAFLD and b) assessment of significant liver fibrosis, assessed by NFS (score > 0.67) and ≥F2 fibrosis on 2DSWE and TE.

Statistical Analysis

Continuous variables were expressed as mean ± SD and categorical variables were presented as numbers and percentage (%). We compared characteristics of participants by outcome status using student's t test for continuous variables and Pearson's $\chi 2$ or Fisher's exact test for categorical variables. Binary logistics regression analysis was done to find out the significant parameters between two groups. Pearson's correlation test was used to find the factors predicting liver fibrosis. All tests were 2-tailed and with a significance level of <0.05. All calculations were performed using SPSS version 17

(Statistical Packages for the Social Sciences, Chicago, IL).

Table 1. Baseline Demographic Parameters of Study Group (n=109)

PARAMETER	Mean (± SD)
MEAN AGE AT DIAGNOSIS (Years)	35.6 ± 12
MALE: FEMALE	59:50
ULCERATIVE COLITIS	96 (88%)
LOCATION	
• PANCOLITIS	38 (40%)
• LEFT SIDED COLITIS	51 (53 %)
• PROCTITIS	7 (7.2%)
CROHN'S	13 (11.9%)
• ILEAL	-
• COLONIC	-
• ILEOCOLONIC	11 (85%)
• PERIANAL FISTULISING	2 (15.3%)
MEAN DURATION OF DISEASE (years)	3.8 ± 4.1
More than 1 relapse/year	36 (33%)
SURGERY	1 (0.91%)
ONGOING MEDICATIONS	
• 5 ASA	32 (29%)
• AZA +5 ASA	34 (31%)
• AZA+ CCS+ 5ASA	40 (36%)
Anti TNF	4 (3.6%)
BMI (kg/m^2)	21± 2.8
TG (mg/dl)	121± 37
HDL (mg/dl)	38 ± 9.6
FASTING BLOOD GLUCOSE (mg/dl)	85 ± 18
WC (cm) Males	80 ± 14
Females	70 ± 9
METABOLIC SYNDROME	5 (4.5%)
DIABETES	1 (0.91%)
HTN	1 (0.91%)
HEMOGLOBIN (g/dl)	10.4 ± 2.3
ESR (mm in Ist hour)	31± 16
CRP (mg/dl)	2.2 ±1.65
PLATELET COUNT (x10^3/cumm)	3.2 ±1.15
SGOT (IU/L)	27.3 ±13
SGPT (IU/L)	23 ± 14
ALBUMIN (g/dl)	3.7± 0.8

Comparison of different parameters in IBD with and without NAFLD

Table2. Shows that out of the various parameters studied, longer duration of disease, presence of frequent relapses and presence of metabolic syndrome were associated with NAFLD with statistically significant P value. On binary logistic regression analysis, the variable with highest significant difference between two groups was course of disease (frequent relapses) [p value = 0.001, adjusted odds ratio = 2.028].

Table 2. Comparison of Parameters Between IBD with and Without NAFLD[#]

PARAMETERS		IBD only (n=97)	IBD +NAFLD (n=12)	P- value
AGE (years)		35.0 ± 11.5	41 +11.2	0.972
MALE (%)		52 (88)	7 (12)	0.757
UC	PANCOLITIS	33 (29.4)	5 (4.6)	0.876
	LEFT SIDED COLITIS	47 (43)	4 (3.7)	0.673
	PROCTITS	6 (5.5)	1 (0.9)	
CROHN'S	ILEAL (L1)	-		
	COLONIC (L2)	-		
	ILEOCOLONIC(L3)	9	2	0.673[‡]
	PERIANAL (p)	2	-	
MEAN DURATION OF DISEASE (years)		3.47 ± 4.0	6.6 ± 4.35	**0.049***
ONGOING MEDICATIONS				
AZA+ CCS+ 5ASA		34 (35%)	6 (50%)	0.585
AZA +5 ASA		30 (31%)	4 (33%)	0.584[‡]
5 ASA		30 (31%)	2 (17%)	
ANTI TNF		4 (4.1%)	0 (0%)	
RELAPSE	(>1/year)	29 (30%)	7 (58%)	**0.048***
	(<1/year)	68 (70%)	5 (42%)	
SURGERY		1 (1.03%)	0 (0%)	1.000[‡]
BMI (kg/m^2)		20.5± 2.7	22.9 ± 3.1	0.470
TG (mg/dl)		119± 30	122 ± 39	0.506
HDL (mg/dl)		37± 9.3	47±8.2	0.248
FASTING BLOOD GLUCOSE (mg/dl)		80± 18	96 ±18	0.90
WC (cm)	M	73.6± 8.8	82.5±10.2	0.978[§]
	F	69±4	70±5	
METABOLIC SYNDROME		1 (1.03%)	4 (33.3%)	**0.000*[‡]**
DIABETES		0 (0%)	1 (8.3%)	0.110[‡]
HTN		0 (0%)	1 (8.3%)	0.110[‡]
HEMOGLOBIN (g/dl)		10.3 ±2.1	11.7±1.8	0.716
TLC (x 10^3/ml)		8.3±7.7	8.5± 2.8	0.626
PLATELET COUNT(lac/ml)		3.3 ± 1.16	2.3 ±0.53	0.009
ESR (mmHg in Ist hour)		31±16	33±9.2	0.457
CRP (mg/dl)		2.3±1.7	2.25±0.77	0.662
SGOT (IU/L)		25.8 ±12	35.9±15	0.142
SGPT (IU/L)		22.2 ± 12	26±9.2	0.993
ALP (U/L)		82.8±25	76±9	0.075
ALBUMIN (g/dl)		3.7± 0.8	4.08±0.8	0.248
NAFLD fibrosis score		–	- 0.847 ±1.48	–

[#]Continuous variables are expressed as mean ± SD and categorical variables as number (%). For continuous variables student t test and for categorical variables Chi square ($\chi 2$) and Fisher exact ([‡]) test (for cells with expected count <5) was used to compare between patients with and without NAFLD. *P < 0.05 was considered significant.

Predictors of NAFLD related liver fibrosis in the IBD with NAFLD group

To study the NAFLD fibrosis, calculation of NAFLD fibrosis score (NFS) and liver elastography (2DSWE followed by TE as described previously) was done. Mean NFS of the group was – 0.847±1.48 and only 4 (3.66%) patients were found to have fibrosis grade F1 (2) and F2 (2) respectively. On Pearson correlation

analysis, (Table 3) out of the various parameters studied, age (r = 0.623, p = 0.031) and metabolic syndrome (r = 0.662, p = 0.019) were found to be significantly correlated with NFS and liver fibrosis.

Table 3: Correlation of Factors Associated with NAFLD with Liver Fibrosis

Parameter	Pearson correlation coefficient (r value)	P value
Age	**0.623**	**0.031***
Duration of disease	0.519	0.084
BMI	0.308	0.331
Waist Circumference	0.120	0.709
Metabolic Syndrome	**0.662**	**0.019***
TG	- 0.366	0.242
HDL	0.440	0.152
Hemoglobin	0.137	0.672
TLC	- 0.126	0.696
APC	0.509	0.091
ESR	- 0.275	0.387
CRP	- 0.359	0.252
SGOT	0.558	0.059
SGPT	0.213	0.505
ALP	0.203	0.513
Albumin	- 0.451	0.141

Liver biopsy

We also performed liver biopsy in two patients who were having persistent unexplained rise in transaminases for more than 6 months. One patient was having grade I steatohepatitis (Brunt grading)[23] whereas second patient showed mild portal based inflammation without any steatohepatitis. There was no evidence of fibrosis in any patient.

RESULTS

The demographic and clinical characteristics of the study population are summarized in Table 1. There were 59 males (54%) and mean age was 35.6 ± 12 years. Ulcerative colitis affected 96 (88.1%) patients. Extent of disease in UC was pancolitis in 38 (39.5%), left sided colitis in 51 (53%), proctitis in 7 (7.3%), whereas 13 (11.9%) patients of crohn's disease had ileo-colonic [L3=11(10%] and peri-anal [p=2, (1.8%)] location of disease. 33% patients were frequent relapsers (>1 relapse/year). Current medications were azathioprine, oral steroids and 5-ASA combination in 40 (36%), Azathioprine and 5-ASA in 34 (31%), 5-ASA only in 32 (29%) and biological (Adalimumab) in 4 (3.6 %) patients respectively. The mean BMI was 21± 2.8 kg/ m2 and only 5 patients (4.5%) fulfilled the criteria of metabolic syndrome at baseline. Mean duration of IBD at baseline was 3.8 ± 4.1 years. Mean SGOT and SGPT at baseline were 27.3 ±13 IU/ml and 23 ± 14 IU/ml respectively. Mean albumin level was 3.7± 0.8 g/dl. Mean hemoglobin, platelets, ESR and CRP were 10.4 ±2.3 g/dl, 3.2 ±1.15 x 10^5 lac/mm^3, 31± 16 mm in Ist hour and 2.2 ±1.65 mg/dl respectively.

DISCUSSION

NAFLD is a frequent comorbidity, with a proportion of patients developing significant liver fibrosis and associated morbidity on long term. Overall prevalence of NAFLD in this study was 11.0 % which lies between estimated prevalence ranging between 6.2 and 40%[2-4]. An important observation in the studies from west with higher prevalence of NAFLD in IBD is the presence of more than half number of patients with crohn's disease. This is in contrast to our IBD database where predominant form of IBD is UC although there is a recent surge in crohn's disease occurrence in the last decade[24]. It needs to be investigated whether this epidemiological difference is linked to more NAFLD in western population.

In this study, the main predictors of NAFLD were longer course of disease, presence of frequent relapses and presence of metabolic syndrome thereby explaining the fact that more degree of inflammation for a longer period is implicated in NAFLD development. Secondly, the presence of metabolic syndrome which is established risk factor in general population for NAFLD is also implicated as important factor even in the IBD population. This is supported by the data from most of the cross-sectional studies from western population, which have suggested age, obesity, insulin resistance and other metabolic conditions as well as dominant role of inflammatory bowel disease related factors such as disease activity, duration, steroid use and prior surgical intervention in the development of NAFLD. This also highlights the potentially more complex pathogenesis and relationship between the two diseases which may be contributed by factors including altered intestinal permeability, gut dysbiosis and chronic inflammatory response. A recent study comparing NAFLD with and without IBD population showed that NAFLD with IBD patients were younger, less likely to have altered liver enzymes, had lower mean body weight, smaller waist circumference and lower body mass index (BMI) and less proportion of metabolic syndrome and concluded that NAFLD in IBD patients is different from that in patient's without IBD, who seem to develop different NAFLD phenotypes according to intestinal disease. The study also

showed that independent risk factors for severe steatosis in IBD patients were more than one relapse per year, surgery for IBD and more extensive intestinal involvement[25]. In our study also the proportion of patients with raised transaminases (4.6%) on at least two occasions were similar in both groups and were not related to the development of NAFLD. In addition, although the mean BMI was higher in NAFLD group, overall mean BMI in both groups was low suggesting that IBD patients can develop NAFLD at normal or low BMI as well compared to general population. This is also linked to the presence of malnutrition and higher inflammatory burden in our patient's due to nonadherence to drug therapy which is quite common[26]. Only two patients with persistent unexplained transaminases were subjected to liver biopsy, who showed Grade I NASH (as per Brunt[23] classification) in one patient and nonspecific portal inflammation in the other.

The data on steroids, methotrexate use and anti-TNF agents in NAFLD in IBD is conflicting with few studies showing positive correlation of steroid and methotrexate use with development of NAFLD and biological therapy either showing no correlation or protective role[6,7]. However, a recent systematic analysis revealed that steroid therapy, anti-TNF drugs and methotrexate were not associated with increased risk of NAFLD in IBD patients whereas IBD-related surgical treatment was associated with elevated risk for NAFLD[27]. In our study we could not find any statistically significant difference for use of medications (ASA, AZA, CCS) in NAFLD development. In our study, no patient was given methotrexate and biologicals were used in only 4 patients, which is too low to have any conclusion.

In our study, although age was higher in NAFLD group, it was not found to be statistically significant predictor of NAFLD. This could be explained by the fact that mean age of our study population with IBD with NAFLD was lower compared to western studies and also second peak observed in onset of IBD is not seen in Indian IBD population which could account for this variation[28]. However, when predicting liver fibrosis in NAFLD with IBD group using NFS and TE, we found significant correlation of age and metabolic syndrome with liver fibrosis. The prevalence of fibrosis was 3.7 % with significant fibrosis (F2) being 1.8%. This is low in comparison of previous studies with prevalence ranging from 6.4-12%[9,10,29,30].

Limitations: This is a cross sectional study with small sample size. Histological assessment was not done in all patients. The validity of modalities of fibrosis assessment in NAFLD in IBD are not defined well and there are limited studies to show the same, so we need more number of studies with large sample size to validate these results.

CONCLUSION

This study highlights that prevalence of NAFLD in IBD and significant liver fibrosis in our study cohort is low compared to west. However, with rising prevalence of IBD particularly crohn's disease in recent years, westernization of diet and treat to target strategy leading to better care and control of inflammation in IBD may lead to increased incidence of obesity and NAFLD and its delayed sequelae.

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