Research Article **OJGH (2020) 3:40**

Open Journal of Gastroenterology and Hepatology
(ISSN:2637-4986)

Non-alcoholic Fatty Liver Disease among patients with Inflammatory Bowel Disease in Qatar: Prevalence and Risk Factors

Dr. Muneera Al-Mohannadi[1], Dr. Prem Chandra[2], Dr. Betsy Varughese[1], Dr. Abdulwahab Hamid[1], Dr. Ahmed Badi[1], Dr. Saad Al Kaabi[1], Dr. Rafie Yakoob[1], Dr. Khalid Al-Ejji[1], Dr. Khaleel Sultan[1], Dr. Adham A. H. Darweesh[3], Nevin Abunahia[1] and Dr. Moutaz Derbala[4]

[1]Gastroenterology & Hepatology, Hamad Medical Corporation, [2]Research Affairs, Hamad Medical Corporation, [3]Radiology, Hamad Medical Corporation, [4]Prof., Hamad Medical Corporation, Doha. Qatar.

ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) has been increasingly identified in patients with inflammatory bowel disease (IBD), though metabolic risk factors for NAFLD are less frequent in IBD patients. Qatar is among countries characterized by the high prevalence of fatty liver. We aimed to characterize NAFLD in IBD patients and to determine factors associated with its severity.

Methods: A retrospective observational study was conducted to estimate the prevalence of NAFLD in all IBD patients followed at Hamad hospital, Doha, Qatar between January 2008 to December 2017. The associations between two or more qualitative variables were assessed using $\chi 2$-test and quantitative data between two independent groups were analyzed using the unpaired t-test. Multivariate logistic regression analysis was applied to determine the predictive values of each predictor for NAFLD among IBD patients.

Results: Among 913 IBD patients with a mean age of 36.9±13.2 years and BMI 26.9±6.1; 550 were males (60.2%), 383(41.9%) with Crohn's disease and 530 (58.1%) with Ulcerative colitis. 24 (22.2%) patients had severe steatosis. The overall prevalence of NAFLD was 11.8% (95% CI 9.9, 14.1) and does not differ significantly between CD and UC patients (11.7% vs 11.9%; P=0.949). Patients who developed NAFLD were older at baseline (42.6±12.5 vs 36.2±13.1 years; P<0.001), had higher BMI (29.3±5.7 vs 26.6±6.1; P<0.001) and higher prevalence of diabetes (26% vs 10.3%; P<0.001) and hypertension (19% vs 10.3%; P=0.011).

***Correspondence to Author:**
Dr. Moutaz Derbala
Prof., Hamad Medical Corporation, Doha. Qatar.

How to cite this article:
Muneera Al- Mohannadi, Prem Chandra, Betsy Varughese, Abdulwahab Hamid, Ahmed Badi, Saad Al Kaabi, Rafie Yakoob, Khalid Al-Ejji, K-haleel Sultan, Adham AH Darweesh, Nevin Abunahia and Moutaz Derbala. Non- alcoholic Fatty Liver Disease among patients with Inflammatory Bowel Disease in Qatar: Prevalence and Risk Factors. Open Journal of Gastroenterology and Hepatology, 2020; 3:40.

eSciPub LLC, Houston, TX USA.
Website: https://escipub.com/

Multivariate analysis showed age >40 to 50 years (adjusted OR 2.98; 95% CI 1.62, 5.48; P=0.001), age >50 years (adjusted OR 2.03; 95% CI 1.03, 4.0; P=0.04), BMI > 30 kg/m^2 (adjusted OR 2.24; 95% CI 1.28, 3.91; P=0.01) and diabetes mellitus (adjusted OR 1.98; 95% CI 1.15, 3.4; P=0.02) significantly associated with an increased risk of NAFLD. Females were less likely having the risk of NAFLD (adjusted OR 0.58; 95% CI 0.36, 0.93; P = 0.02) in comparison to males. The treatment with biologic does not increase the risk of steatosis. The predicted cutoff NAFLD score ≥ -1.67 had good predictive ability for significant steatosis in IBD cases.

Conclusion:

The prevalence of NAFLD is not uncommon among IBD patients in Qatar. Older age, high BMI and diabetes mellitus increase the risk of NAFLD in IBD patients. Patients with risk factors need to be monitored closely and considered for early interventions which can limit the use of more hepatotoxic drugs and can achieve early remission of the disease. Non-invasive screening of NAFLD using NAFLD Score in IBD patients with risk factors could help early diagnosis and treatment of the disease and can easily be implemented in any setting of IBD clinics.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a growing epidemic not only confined to residents of affluent industrialized western countries but also the general population worldwide [1]. It comprises a wide spectrum of disorders ranging from simple hepatic steatosis (NAFL) to non-alcoholic steatohepatitis (NASH) with or without fibrosis or cirrhosis [2]. It is associated with altered metabolism and metabolic syndrome (MetS) and increasingly found in patients with inflammatory bowel disease (IBD), though metabolic risk factors for NAFLD are less frequent in IBD patients [3]. Its prevalence is as high as 40% in patients with IBD, including Ulcerative colitis (UC) and Crohn's disease (CD) [4]. A recent meta-analysis reported that the overall prevalence of NAFLD is 25.24% globally, with the Middle East region being the highest (31.79%) followed by South America (30.45%), Asia (27.37%), North America (24.13%), Europe (23.71%), and Africa (13.48%) [5]. However, its incidence is ranging from 20 to 50 cases per 1,000 person-years in different countries, [6] making this disease a new epidemic in global chronic liver disease and creates a major clinical and economic burden worldwide [7].

The exact pathogenesis of NAFLD is still not clear. It may involve complex interactions among genetic susceptibility variants, environmental factors, insulin resistance, and changes in the gut microbiota [8]. The interaction between these factors may result in altered lipid metabolism and excessive lipid accumulation in hepatocytes, which may result in the development of NAFLD. It may be related to disease-specific risk factors in patients with IBD [9,10]. The changing lifestyles and dietary habits may have increased obesity and NAFLD in the Middle East region [11]. Qatar is one among the countries characterized by the high prevalence of fatty liver, however, there is no data available among the IBD patients. Thus, there is an urgent need to understand the prevalence and disease progression of NAFLD in IBD patients, which may enable to improve diagnostics, patient stratification, and identification of new therapeutic targets.

Since NAFLD is largely asymptomatic until end-stage complications occur, the analysis of the predictors of NAFLD could help the early

detection and interventions which can limit the use of more hepatotoxic drugs and can achieve early remission of the disease [12]. Hence, we aimed to characterize NAFLD in IBD patients comparing their clinical and metabolic characteristics. We also aimed to re-evaluate the screening of NAFLD in IBD patients using a non-invasive NAFLD score that can easily be implemented in any setting of IBD clinics.

Materials and Methods

A retrospective observational study was conducted on 913 IBD patients without any known liver disease, who were enrolled in the IBD program between January 2008 to December 2017 and followed at the IBD clinic, in Qatar. NAFLD was defined as Hepatic Steatosis Index (HSI) ≥36 and the absence of alcohol intake. The patients with viral hepatitis, autoimmune hepatitis, Wilson disease, hemochromatosis, any other known liver disease, history of alcohol consumption, hepatotoxic medication and secondary causes of fatty liver overload were excluded in the study. Data on demographics, body mass index, type of medication use, and metabolic risk factors were analyzed. The ultrasonographic presence and degree of steatosis were also assessed in this cohort. IBD patients with NAFLD by imaging were compared with those who had no evidence of NAFLD (control). NAFLD fibrosis score was calculated using an online calculator [13]. The study was exempted from the full ethical review board due to its retrospective nature and was approved with an expedite review (No.MRC-01-18-412).

Statistical analyses

Descriptive statistics were used to summarize demographics, anthropometry, medical history and all other clinical related characteristics of the IBD and NAFLD patients. The normally distributed data and results were reported with mean and standard deviation (SD); the remaining results were reported with median and interquartile range (IQR). Categorical data were summarized using frequencies and percentages. The prevalence of NAFLD among IBD patients was estimated and presented along with the 95% confidence interval (CI). Associations between two or more qualitative variables were assessed using $\chi 2$-test or Fisher's exact test as appropriate. Quantitative data between two independent groups were analyzed using unpaired t-test or Mann-Whitney U-test as appropriate depending on normality of the data distribution.

Univariate and multivariate logistic regression methods were used to determine and assess the predictive values of each predictor or probable risk factors for NAFLD among IBD patients. For multivariate logistic regression models, variables were considered if statistical $P < 0.10$ level in univariate analyses or if determined to be clinically important. The results of logistic regression analyses were presented as odds ratio (OR) with corresponding 95% CI. A two-sided P-value < 0.05 was considered statistically significant. All statistical analyses were performed using the IBM SPSS® Statistics for Windows, Version 22.0 (IBM Corp, Armonk, NY, USA) and Epi Info™ 2000 (Centers for Disease Control and Prevention, Atlanta, GA, USA).

A receiver operating characteristic (ROC) curve was calculated using significant predictors to derive the best suitable cut-off values and to assess model discrimination and predictive accuracy. ROC curves provide a comprehensive and visually attractive way to summarize the accuracy of predictions. The ROC curve shows the trade-off between sensitivity and specificity and is a better method to detect the performance of a developed test, which classifies patients into two categories such as mild to moderate and significant steatosis.

Results

Patients' Characteristics

During the study period from January 2008 to December 2017, a total of 913 patients with IBD (383 patients with CD and 530 with UC) and active follow-up were included. The main demographic, anthropometric and clinical characteristics of the study population are summarized in Table 1.

Table 1: Demographic & Clinical characteristics of the study population (N=913)

Variables	Categories	N (%)
Age	Age <= 30 years	330 (36.1)
	Age > 30 to 40 years	243 (26.6)
	Age > 40 to 50 years	182 (19.9)
	Age >50 years	158 (17.3)
Sex	Male	550 (60.2)
	Female	363 (39.8)
Nationality	Qatari	338 (37)
	Non-Qatari	575 (62.9)
Diagnosis	UC	530 (58.1)
	CD	383 (41.9)
Level of UC	E1	121 (22.9)
	E2	254 (48.1)
	E3	153 (29)
Location of CD	L1	156 (43.0)
	L2	49 (13.5)
	L3	145 (39.9)
	L4	13 (3.6)
Severity of IBD	Mild	28 (38.9)
	Moderate	28 (38.9)
	Severe	16 (22.2)
BMI	BMI <=25	364 (40.9)
	BMI >25 to 30	294 (33.0)
	BMI >30	232 (26.1)
Fatty liver	Yes	108 (11.8)
Fatty liver grading	Mild steatosis	47 (43.5)
	Moderate steatosis	37 (34.3)
	Severe Steatosis	24 (22.2)
NAFLD Score Category	No fibrosis	758 (86.3)
	Fibrosis	19 (2.2)
	Intermediate	101 (11.5)
Medication	Biologicals	279 (30.6)
	Non-Biologicals	634 (69.4)
Surgery	Yes	166 (18.2)
Comorbidities	Hypertension	103 (11.3)
	Diabetes Mellitus	111 (12.2)
	Coronary artery disease (CAD)	23 (2.5)
	Chronic kidney disease (CKD)	5 (0.5)
Smoker	Yes	152 (16.6)

The data of some of the variables like Level of UC, Location of CD, Severity of IBD, BMI, NAFLD scores were not available in all patients during retrospective data/chart review.

All respective percentages (%) were computed based on non-missing values.

There were 550 males (60.2%) and the mean age was 36.9±13.2 (median 35; IQR, 27-47) years. Crohn's disease affected 42% of the patients. The mean BMI was 26.9±6.1 (median 26.2; IQR, 23-30.3) kg/m^2 and 232 patients (26.1%) had BMI>30 were obese at baseline. 375 (71%) patients had limited ulcerative colitis (E1 or E2) whereas 153 (29%) patients had extensive colitis at diagnosis. Among the Chron's patients, 156 (43.0%) were seen with the L1 disease, 49 (13.5%) patients with L2 disease, 145 (39.9%) with L3 disease, and 13 (3.6%) with L4 disease. Over the study period, 16 (22.2%) had severe IBD and 37 (34.3%) and 24 (22.2%) had moderate and severe steatosis, respectively. Approximately, 30% of IBD patients had received biological medications (Figure 2).

Prevalence of NAFLD among IBD cases

The prevalence of NAFLD in patients with IBD categorized according to demographic and clinical characteristics. Table 2 depicts comparative baseline characteristics and relative univariate logistic regression analysis of patients who developed and who did not develop NAFLD during the follow-up period.

Table 2: Univariate analysis of factors associated with NAFLD

Variables	Categories	NAFLD N (%) 108 (11.8)	Non-NAFLD N (%) 805 (88.2)	Unadjusted Odds ratio (95% CI)	P-Value
Age	Age <= 30 years	20 (6.1)	310 (93.9)	1.00 (Reference)	
	Age > 30 to 40 years	22 (9.1)	221(90.9)	1.54 (0.82 - 2.90)	0.18
	Age > 40 to 50 years	38 (20.9)	144 (79.1)	4.09 (2.30 -7.28)	0.001
	Age >50 years	28 (17.7)	130 (82.3)	3.34 (1.82 – 6.14)	0.001
Sex	Male	75 (13.6)	475 (86.4)	1.00 (Reference)	
	Female	33 (9.1)	330 (90.9)	0.63 (0.41 - 0.98)	0.04
Nationality	Qatari	37 (10.9)	301 (89.1)	1.00 (Reference)	
	Non-Qatari	71 (12.4)	504 (87.6)	1.15 (0.75 - 1.75)	0.52
Diagnosis	UC	63 (11.9)	467 (88.1)	1.00 (Reference)	
	CD	45 (11.7)	338 (88.3)	0.99 (0.66 - 1.48)	0.95
Level of UC	E1	13 10.7%)	108 (89.3)	1.00 (Reference)	
	E2	33 (13.0)	221 (87.0)	1.24 (0.63 -2.45)	0.54
	E3	17 (11.1)	136 (88.9)	1.04 (0.48 - 2.23)	0.93
Location of CD	L1	20 (12.8)	136 (87.2)	1.0 (Reference)	
	L2	6 (12.2)	43 (87.8)	0.95 (0.36 - 2.52)	0.92
	L3	13 (9)	132 (91.0)	0.67 (0.32 - 1.40)	0.29
	L4	1 (7.7)	12 (92.3)	0.57 (0.07, 4.60)	0.60
Severity of IBD	Mild	24 (85.7)	4 (14.3)	1.00 (Reference)	
	Moderate	25 (89.3)	3 (10.7)	1.34 (0.28 - 6.87)	0.69
	Severe	14 (87.5)	2 (12.5)	1.17 (0.19 - 7.21)	0.87
BMI	BMI <=25	26 (7.1)	338 (92.9)	1.00 (Reference)	
	BMI >25 to 30	35 (11.9)	259 (88.1)	1.76 (1.03 - 2.99)	0.04
	BMI >30	42 (18.1)	190 (81.9)	2.87 (1.71 - 4.84)	0.001
NAFLD Score Category	No fibrosis	82 (10.8)	676 (89.2)	1.00 (Reference)	
	Fibrosis	2 (10.5)	17 (89.5)	0.97 (0.22 - 4.27)	0.97
	Intermediate	19 (18.8)	82 (81.2)	1.91 (1.10 - 3.31)	0.02
Medication	Non-Biologicals	75 (11.8)	559 (88.2)	1.00 (Reference)	
	Biologicals	33 (11.8)	246 (88.2)	1.00 (0.65 - 1.55)	0.99
Surgery	Yes	19 (11.4)	147 (88.6)	1.04 (0.67 - 1.60)	0.86
Comorbidities*	Hypertension	20 (19.4)	83 (80.6)	1.98 (1.16 - 3.38)	0.01
	Diabetes Mellitus	28 (25.2)	83 (74.8)	3.05 (1.87 - 4.95)	0.001
	Coronary artery disease (CAD)	4 (17.4)	19 (82.6)	1.59 (0.53 - 4.76)	0.40
	Chronic kidney disease (CKD)	0 (0.0)	5 (100.0)	-	0.41
Smoking*	Yes	15 (9.9)	137 (90.1)	0.79 (0.44 - 1.40)	0.41

The data of some of the variables like Level of UC, Location of CD, Severity of IBD, BMI, NAFLD scores were not available in all patients during retrospective data/chart review.

*Absence of comorbidities and no smoking groups were taken as reference groups respectively.

The overall prevalence of NAFLD was 11.8% (108 of 913 IBD patients; 95% CI 9.9, 14.1). The prevalence of NAFLD does not differ significantly between CD and UC patients (11.7% vs 11.9%; P=0.949). Overall, patients who developed NAFLD were older at baseline (42.6±12.5 vs 36.2 ±13.1 years; P<0.001), higher BMI (29.3±5.7 vs 26.6±6.1; P<0.001) and had higher prevalence of diabetes (26% vs 10.3%; P<0.001) and hypertension (19% vs 10.3%; P=0.011). Crohn's disease does not differ significantly between NAFLD and non-NAFLD patients (P>0.05).

Predictors of development of NAFLD by univariate and multivariate logistic regression analysis

The results of univariate and multivariate logistic regression analysis testing for each predictor or potential risk factor and their possible association with NAFLD among IBD patients are presented in Table 2. Age >50 years was significantly associated with an increased risk for NAFLD (OR 3.34; 95% CI 1.82, 6.14; P=0.001), whereas gender female associated with significantly decreased risk for NAFLD (OR 0.63; 95% CI 0.41, 0.98; P=0.04). In patients having a BMI >30 kg/m^2 (OR 2.87; 95% CI 1.71, 4.84; P=0.001), the presence of hypertension (OR 1.98; 95% CI 1.16, 3.38; P=0.01) and diabetes mellitus (OR 3.05; 95% CI 1.87, 4.95; P=0.001), were all positively and significantly associated with an increased risk for NAFLD.

In multivariable logistic regression analysis controlling for all other potential predictors and covariates such as age, gender, BMI, diagnosis, comorbidity, and biological and non-biological medications, it was observed that age >40 to 50 years (adjusted OR 2.98; 95% CI 1.62, 5.48; P=0.001), age >50 years (adjusted OR 2.03; 95% CI 1.03, 4.0; P=0.04), BMI > 30 kg/m^2 (adjusted OR 2.24; 95% CI 1.28, 3.91; P=0.01) and diabetes mellitus (adjusted OR 1.98; 95% CI 1.15, 3.4; P=0.02) remained independently and significantly associated with an increased risk of NAFLD. Gender female showed protective effect and have decreased risk (adjusted OR 0.58; 95% CI 0.36, 0.93; P = 0.02) significantly associated with NAFLD (Table 4).

Table 4: Multivariate analysis of factors associated with NAFLD

Variables	Categories	Adjusted Odds ratio (95% CI)	P-Value
Age	Age <= 30 years	1.00 (Reference)	
	Age > 30 to 40 years	1.18 (0.61- 2.27)	0.62
	Age > 40 to 50 years	2.98 (1.62 - 5.48)	0.001
	Age >50 years	2.03 (1.03 – 4.00)	0.04
Sex	Male	1.00 (Reference)	
	Female	0.58 (0.36 -0.93)	0.02
BMI	BMI <=25	1.00 (Reference)	
	BMI >25 to 30	1.46 (0.84 - 2.52)	0.18
	BMI >30	2.24 (1.28 - 3.91)	0.01
Comorbidities*	Diabetes Mellitus	1.98 (1.15 - 3.4)	0.02

*Absence of comorbidities taken as a reference group.

Predictors of significant steatosis-logistic regression analysis:

The results of logistic regression analysis testing for each predictor or potential risk factor and their possible association with significant steatosis are presented in Table 3.

Table 3: Univariate analysis of factors associated with significant steatosis

Variables	Categories	Severe steatosis N (%) 24 (22.22)	Mild to moderate steatosis N (%) 84 (77.77)	Unadjusted Odds ratio (95% CI)	P-Value
Age	Age <= 30 years	4 (20)	16 (80)	1.00 (Reference)	
	Age > 30 to 40 years	3 (13.6)	19 (86.4)	0.63 (0.12 - 3.25)	0.58
	Age > 40 to 50 years	10 (26.3)	28 (73.7)	1.43 (0.39 - 5.31)	0.59
	Age >50 years	7 (25)	21 (75)	1.33 (0.33- 5.35)	0.68
Sex	Male	20 (26.7)	55 (73.3)	1.00 (Reference)	
	Female	4 (12.1)	29 (87.9)	0.38 (0.12 - 1.22)	0.09
Nationality	Qatari	6 (16.2)	31 (83.8)	1.00 (Reference)	
	Non-Qatari	18 (25.4)	53 (74.6)	1.76 (0.63 - 4.89)	0.28
Diagnosis	UC	13 (20.6)	50 (79.4)	1.00 (Reference)	
	CD	11 (24.4)	34 (75.6)	1.25 (0.50 - 3.10)	0.64
Level of UC	E1	3 (23.1)	10 (76.9)	1.00 (Reference)	
	E2	5 (15.2)	28 (84.8)	0.59 (0.12 - 2.96)	0.53
	E3	5 (29.4)	12 (70.6)	1.39 (0.26 - 7.30)	0.69
Location of CD	L1	7 (35)	13 (65.0)	1.00 (Reference)	
	L2	2 (33.3)	4 (66.7)	0.93 (0.14 -6.40)	0.94
	L3	2 (15.4)	11 (84.6)	0.34 (0.06 – 1.97)	0.23
	L4	0 (0.0)	1 (100)	0.00 (0.00 -)	1.00
Severity of IBD	Mild	5 (20.8)	19 (79.2)	1.00 (Reference)	
	Moderate	4 (16)	21 (84.0)	0.72 (0.17 - 3.10)	0.66
	Severe	3 (21.4)	11 (78.6)	1.04 (0.21- 5.20)	0.97
BMI	BMI <=25	3 (11.5)	23 (88.5)	1.00 (Reference)	
	BMI >25 to 30	9 (25.7)	26 (74.3)	2.65 (0.64 - 11.01)	0.18
	BMI >30	12 (28.6)	30 (71.4)	3.07 (0.77 - 12.15)	0.11
NAFLD Score Category	No fibrosis	16 (19.5)	66 (80.5)	1.00 (Reference)	
	Fibrosis	1 (50.0)	1 (50.0)	4.13 (0.25 - 69.56)	0.33
	Intermediate	7 (36.8)	12 (63.2)	2.41 (0.82 – 7.09)	0.11
Medication	Non- Biologicals	19 (25.3)	56 (74.7)	1.00 (Reference)	
	Biologicals	5 (15.2)	28 (84.8)	0.53 (0.18 -1.56)	0.24
Surgery	Yes	5 (26.3)	14 (73.7)	1.32 (0.42- 4.11)	0.64
Comorbidities*	Hypertension	10 (50.0)	10 (50.0)	5.28 (1.86 - 15.05)	0.001
	Diabetes Mellitus	13 (46.4)	15 (53.6)	5.44 (2.04 - 14.46)	0.001
	Coronary artery disease (CAD)	1 (25.0)	3 (75.0)	1.17 (0.12 - 11.83)	0.89
	Chronic kidney disease (CKD)	24 (22.2)	84 (77.8)	-	
Smoking*	Yes	5 (33.3)	10 (66.7)	1.95 (0.60 - 6.38)	0.27

The data of some of the variables like Level of UC, Location of CD, Severity of IBD, BMI, NAFLD scores were not available in all patients during retrospective data/chart review. *Absence of comorbidities and no smoking groups were taken as reference groups respectively.

Patients presented with hypertension (OR 5.28; 95% CI 1.86, 15.05; P=0.001) and diabetes mellitus (OR 5.44; 95% CI 2.04, 14.46; P=0.001) had a significant and increased risk associated with significant steatosis. Patients with older age, higher BMI, smoking, fibrosis and intermediate fibrosis and severity of IBD were found to have an increased risk associated with significant steatosis, however, this difference was statistically insignificant (P>0.05). In multivariable logistic regression analysis controlling for all other potential predictors and covariates such as age, gender, BMI, diagnosis, comorbidity, and medications, it was observed that only diabetes mellitus (adjusted OR 5.04; 95% CI 1.89, 13.44; P=0.001) was found to be independently and significantly associated with an increased risk of significant steatosis. The sample size was small and confidence intervals were wide in the above statistical comparisons, suggesting that a larger study with more statistical power is needed to detect statistically significant differences if any.

ROC analysis for determining suitable and optimum cut-off of NAFLD score for significant steatosis:

The discriminative ability of the NAFLD was found to be good with an area under the ROC curve value of 0.70 (95% CI 0.57, 0.80). The sensitivity and specificity values at a cut-off NAFLD score point of ≥ -1.67 were 61% and 65% with positive likelihood ratio value 1.72, respectively (Table 5 and Figure 1).

Table 5. Performance of NAFLD score for the diagnosis of severe steatosis

NAFLD score cut-off	AUC (95% CI)	Accuracy	Sensitivity	Specificity	PPV	NPV	LR+	LR-
-1.665	0.69 (0.57-0.80)	63.73 (54.05-72.4)	60.87% (40.79-77.84)	64.56% (53.56-74.2)	33.33% (21.01-48.45)	85% (73.89-91.9)	1.72 (1.46-2.02)	0.6 (0.48-0.77)

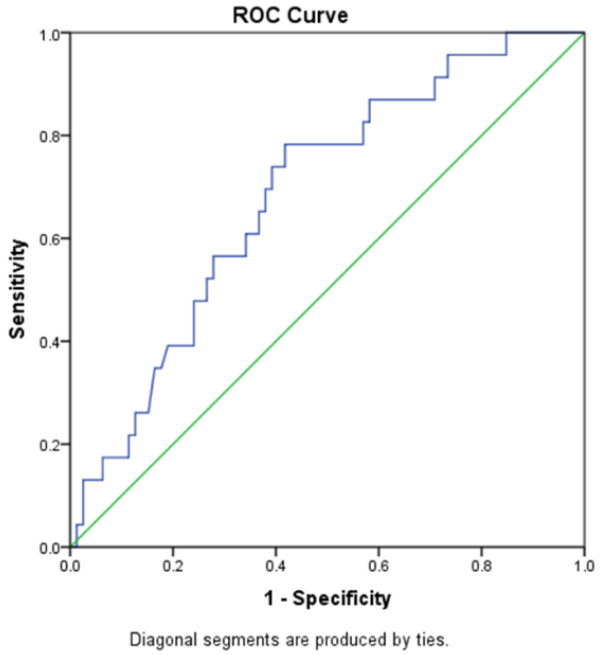

Fig 1. ROC curve showing suitable and optimum cut-off of NAFLD score for significant steatosis

The predicted cut-off NAFLD score derived using ROC analysis was found to co-relate well and had good predictive ability (accuracy index value 64%) in predicting significant steatosis.

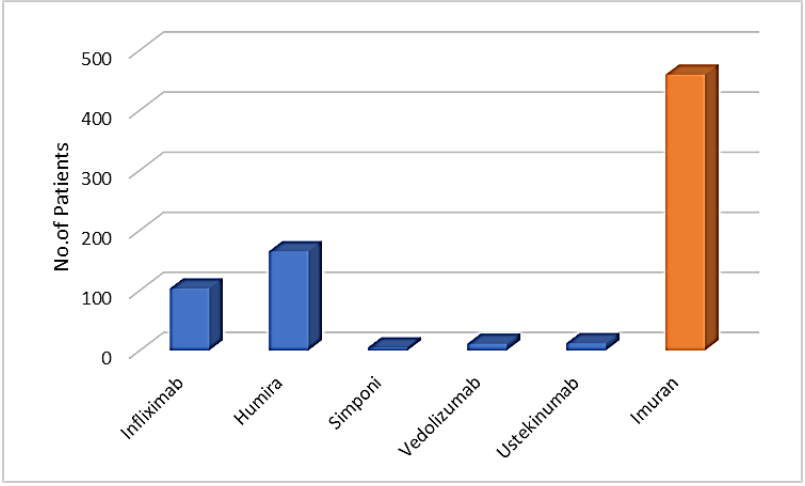

Figure 2 represents the Biological (Infliximab, Humira, Simponi, Vedolizumab, Ustekinumab) and Non-Biological (Imuran) medications in IBD patients.

Discussion

IBD may commonly have liver involvement due to different factors such as autoimmune disorders, primary sclerosing cholangitis, liver toxicity of some drugs and fatty liver [14]. In the present study, we analyzed NAFLD phenotype in patients with IBD by assessing the ultra-sonographic grade of steatosis. The prevalence of NAFLD in IBD patients was 11.8% in Qatar, though it was ranging between 6.2% to 40% globally [4,15-16]. In a recent meta-analysis containing 19 studies including 5620 patients, the overall prevalence of NAFLD in the IBD population was 27.5% [17]. However, could not find any significant difference in the prevalence of NAFLD among CD and UC patients which is similar to the previous findings [18].

NAFLD is dramatically increasing in Gulf countries including Qatar, where there is already an epidemic of obesity and diabetes mellitus exist [19-20]. It was found that by 2030, the NAFLD population was projected to increase 48% in Saudi Arabia and 46% in UAE, with overall prevalence rates estimated at 31.7% and 30.2%, suggested that advanced liver disease and mortality attributable to NAFLD will increase across the gulf countries [21].

The exact pathogenesis of NAFLD in the IBD population is not clear. It was reported two-fold higher mortality in hospitalized patients affected by IBD together with the concomitant chronic liver disease compared to those suffering only from IBD [22]. IBD patients with NAFLD had a higher number of metabolic risk factors than those with IBD alone [23]. In the present study, we found that IBD patients with NAFLD were older than those without NAFLD. This could reflect a similar trend seen in population-based studies, where an increase in the prevalence of metabolic risks leading to NAFLD increased with age [24]. We also found that patients who had developed NAFLD were having higher BMI and had a higher prevalence of diabetes and hypertension than the non-NAFLD IBD patients. Glassner et al reported that the presence of NAFLD in IBD patients was associated with older age, high BMI, obesity, and increased risk of diabetes [18]. Similar to the previous findings of Arieira et al [25], we also found that gender female showed protective effect and have decreased risk associated with NAFLD.

NAFLD has seen in lean as well as severely underweight subjects and the prevalence of liver steatosis was higher among underweight IBD patients [26]. Despite expected malnourishment in patients with severe IBD, there is still the risk of developing fatty liver. The chronic inflammation in IBD is associated with dysbiosis and compositional and functional alterations of gut microbiota, in the form of reduced microbiota diversity. The compositional and functional alterations of gut microbiota are associated with the development and progression of several liver

diseases including NAFLD [27]. Also, in patients with IBD, the presence of metabolic syndrome (MetS) would be a significant risk factor for increased NAFLD severity [28]. It is reported that in both CD and UC patients, NAFLD Fibrosis Score (NFS) was significantly higher in MetS patients [28]. Few other studies demonstrated that the causal relationship of diseases affecting the gut is impacting the liver. The blood from the GI tract drains to the liver via the hepatic portal system. The bacterial products, cytokines and various biological signal molecules present in the gut could create a disease state in the liver [29]. Recently a signaling molecule Sphingosine-1-phosphate (S1P) has been demonstrated to be a potent activator of various cellular signaling through its S1P receptors (S1PRs) and emerges as one of the key players in metabolic diseases, various liver pathologies including NAFLD, non-alcoholic steatohepatitis (NASH) and liver fibrosis, and gastrointestinal diseases such as inflammatory bowel disease (IBD) [30]. However, in our study, we found that patients with hypertension and diabetes mellitus had a significant and increased risk associated with significant steatosis. Other factors such as older age, higher BMI, smoking, fibrosis and intermediate fibrosis and severity of IBD were also found to have an increased risk associated with steatosis, though could not establish the statistical significance. A possible explanation of this increased fatty liver among IBD- Qatari patient may probably due to their genetic predisposition. A recent study found that there is co-existence of common genes related to NAFLD and IBD and seven key genes are related to these two diseases [31].

In this study, we did not find any significant association between the medications used and the progression to NAFLD in IBD patients which suggests a complex, multifactorial relationship between the diseases than the scope of current pharmacological intervention. Anti-TNF-α drug infliximab and adalimumab showed a potential role in protecting IBD patients from developing NAFLD in the animal model [32]. TNF- α inhibitors are often used in moderate to severe cases of IBD and have proven to be highly efficacious in producing remission. On the other hand, some studies suggested that anti-TNF drugs may increase the chance of progression to NAFLD, through promoting healing of the intestinal mucosa and in turn, absorption of nutrients leading to weight gain and development of metabolic syndrome [33]. Also, longer disease duration of IBD is associated with increased risk of progression to NAFLD and TNF-α inhibitors are generally not used as first-line treatments, and they tend to be used later along the course of IBD. Therefore, patients who receive TNF-α inhibitors may already be in a pool of high-risk patients [34]. These factors may explain why some patients treated with TNF-α inhibitors still progress to NAFLD despite adequate treatment of their IBD. Progression to NAFLD in patients with IBD is likely to be complex and multifactorial.

Schroder et al reported that fatty liver represents a risk factor, promoting liver injury, for the development of drug-related hepatotoxicity in IBD patients under immunosuppressive treatment [35]. Though used as a part of conventional treatment, corticosteroids were identified to be an important risk factor for weight gain and in turn, increase the risk of developing fatty liver [36]. Another study reported that drugs including glucocorticoids and immune-modulators increase the risk of progression to NAFLD in IBD patients [37]. Similar to the findings of Arieira et al [25], where there was no difference found between the groups with or without hepatic steatosis in terms of the frequency of previous use of corticosteroids, and biological therapy, our study also did not find any such relation between the drug and the progression of NAFLD in IBD patients.

Liver biopsy is still considered as the gold standard for liver fibrosis measurement in patients with NAFLD though it has many drawbacks such as sampling error, cost, and risk of complications [38]. It is an invasive technique and not feasible to perform on all NAFLD patients. Currently, the ultrasound-based quanti-tative imaging techniques are increasingly used

for the diagnosis of fatty liver because of their easy availability, lower-cost and wide-spread use [39]. However, the diagnostic accuracy of ultrasound in detecting hepatic steatosis has varied among different studies depending on the definition of the disease. In the current study, we used hepatic steatosis ultrasonography using a four-point grading scale which is the most widely used system to evaluate hepatic steatosis in clinical practice. The ultrasound can provide a fair accuracy with 90% sensitivity and 95% specificity for detecting the moderate to severe hepatic steatosis in patients without concomitant chronic liver disease but has limited diagnostic accuracy for detecting mild degree hepatic steatosis for the evaluation of NAFLD [40]. An accurate, non-invasive biomarker discriminating different disease stages or an innovative non-invasive imaging technique to quantify steatosis is highly needed for screening NAFLD patients. There is no such specific serum marker available till date to assess hepatic steatosis as most of them needed further validation on cohorts with patients including several different ethnicities and various co-existing disease like IBD for choosing the best cut-off value. Some non-invasive scoring systems consisting of routinely measured clinical and laboratory variables have been proposed for predicting advanced fibrosis in patients with NAFLD [13]. NAFLD fibrosis score (NFS) is one among those scoring systems to discriminate patients with NAFLD with or without advanced liver fibrosis [41]. In our study, we found a cut-off value of more than or equal to -1.67 for NAFLD score with 61% sensitivity and 65% specificity which showed that NAFLD score has a good predictive ability in predicting significant steatosis.

Conclusion:

The prevalence of NAFLD among IBD patients is dramatically increasing in Gulf countries including Qatar. Older age, high BMI and diabetes mellitus increase the risk of NAFLD in patients with IBD. Such patients who are at high risk for NAFLD needs to be monitored closely and considered for early interventions which can limit the use of more hepatotoxic drugs and can achieve early remission of the disease. The non-invasive screening of IBD patients with NAFLD fibrosis score could discriminate patients with NAFLD with or without advanced liver fibrosis. So, our findings suggest that the NAFLD score has been shown to have prognostic value for hepatic complications and mortality in patients with NAFLD/IBD coexistence.

References

[1]. Benedict M, Zhang X. Non-alcoholic fatty liver disease: An expanded review. WJH. 2017;9(16): 715 -732.

[2]. Sayiner M, Koenig A, Henry L, Younossi ZM. Epidemiology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis in the United States and the Rest of the World. Clinics in Liver Disease. 2016;20(2):205 -214.

[3]. Sartini A, Gitto S, Bianchini M, Verga MC, Di Girolamo M, Bertani A, et al. Non-alcoholic fatty liver disease phenotypes in patients with inflammatory bowel disease. Cell Death Dis. 2018;9(2):87.

[4]. Bargiggia S, Maconi G, Elli M, Molteni P, Ardizzone S, Parente F, et al. Sonographic prevalence of liver steatosis and biliary tract stones in patients with inflammatory bowel disease: study of 511 subjects at a single center. Journal of Clinical Gastroenterology.2003;36(5): 417 - 420.

[5]. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes: Hepatology. 2016;64(1):73 - 84.

[6]. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases:Hepatology. 2018;67(1):328 - 357.

[7]. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2018;15(1):11 - 20.

[8]. Arab JP, Karpen SJ, Dawson PA, Arrese M, Trauner M. Bile acids and nonalcoholic fatty liver disease: Molecular insights and therapeutic perspectives. Hepatology. 2017;65(1):350 - 362.

[9]. Bringiotti R. Intestinal microbiota: The explosive mixture at the origin of inflammatory bowel disease? WJGP. 2014;5(4):550-559.

[10]. Miele L, Valenza V, La Torre G, Montalto M, Cammarota G, Ricci R, et al. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. Hepatology. 2009;49(6):1877-1887.

[11]. Anderson EL, Howe LD, Jones HE, Higgins JPT, Lawlor DA, Fraser A. The Prevalence of Non-Alcoholic Fatty Liver Disease in Children and Adolescents: A Systematic Review and Meta-Analysis. PLoS ONE. 2015;10(10):e0140908.

[12]. Chao CY, Battat R, Al Khoury A, Restellini S, Sebastiani G, Bessissow T. Co-existence of non-alcoholic fatty liver disease and inflammatory bowel disease: A review article. WJG. 2016;22 (34):7727-7734.

[13]. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: A noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007;45(4):846 - 854.

[14]. Khan N, Abbas AM, Whang N, Balart LA, Bazzano LA, Kelly TN. Incidence of Liver Toxicity in Inflammatory Bowel Disease Patients Treated with Methotrexate: A Meta-Analysis of Clinical Trials: Inflammatory Bowel Diseases. 2012;18(2): 359 - 367.

[15]. Gisbert JP, Luna M, González-Lama Y, Pousa ID, Velasco M, Moreno-Otero R, et al. Liver injury in inflammatory bowel disease: Long-term follow-up study of 786 patients: Inflammatory Bowel Diseases. 2007;13(9):1106 -1114.

[16]. Sourianarayanane A, Garg G, Smith TH, Butt MI, McCullough AJ, Shen B. Risk factors of non-alcoholic fatty liver disease in patients with inflammatory bowel disease. Journal of Crohn's and Colitis. 2013;7(8):e279 - e285.

[17]. Zou ZY, Shen B, Fan J G. Systematic Review with Meta-analysis: Epidemiology of Nonalcoholic Fatty Liver Disease in Patients with Inflammatory Bowel Disease. Inflammatory Bowel Diseases. 2019;25(11):1764 -1772.

[18]. Glassner K, Malaty HM, Abraham BP. Epidemiology and Risk Factors of Nonalcoholic Fatty Liver Disease Among Patients with Inflammatory Bowel Disease: Inflammatory Bowel Diseases. 2017;23(6):998 -1003.

[19]. DeNicola E, Aburizaiza OS, Siddique A, Khwaja H, Carpenter DO. Obesity and public health in the Kingdom of Saudi Arabia. Reviews on Environmental Health. 2015;30(3):191-205.

[20]. Abuyassin B, Laher I. Diabetes epidemic sweeping the Arab world. WJD. 2016;7(8):165-174.

[21]. Alswat K, Aljumah A, Sanai F, Abaalkhail F, Alghamdi M, Al Hamoudi W, et al. Nonalcoholic fatty liver disease burden-Saudi Arabia and United Arab Emirates, 2017–2030. Saudi J Gastroenterol. 2018;24(4):211 - 219.

[22]. Henao-Mejia J, Elinav E, Thaiss CA, Licona-Limon P, Flavell RA. Role of the intestinal microbiome in liver disease. Journal of Autoimmunity. 2013; 46:66 -73.

[23]. Park SH, Kim PN, Kim KW, Lee SW, Yoon SE, Park SW, et al. Macrovesicular Hepatic Steatosis in Living Liver Donors: Use of CT for Quantitative and Qualitative Assessment. Radiology. 2006;239 (1):105-112.

[24]. Saroli Palumbo C, Restellini S, Chao C-Y, Aruljothy A, Lemieux C, Wild G, et al. Screening for Nonalcoholic Fatty Liver Disease in Inflammatory Bowel Diseases: A Cohort Study Using Transient Elastography. Inflammatory Bowel Diseases. 2019;25(1):124 -133.

[25]. Arieira C, Monteiro S, Xavier S, Dias de Castro F, Magalhães J, Moreira MJ, et al. Hepatic steatosis and patients with inflammatory bowel disease: when transient elastography makes the difference. European Journal of Gastroenterology & Hepatology. 2019;31(8):998 -1003.

[26]. Adams LC, Lübbe F, Bressem K, Wagner M, Hamm B, Makowski MR. Non-alcoholic fatty liver disease in underweight patients with inflammatory bowel disease: A case-control study. PLoS ONE. 2018;13(11):e0206450.

[27]. Betrapally NS, Gillevet PM, Bajaj JS. Gut microbiome and liver disease. Translational Research. 2017; 179:49 - 59.

[28]. Carr RM, Patel A, Bownik H, Oranu A, Kerner C, Praestgaard A, et al. Intestinal Inflammation Does Not Predict Nonalcoholic Fatty Liver Disease Severity in Inflammatory Bowel Disease Patients. Dig Dis Sci. 2017;62(5):1354 -1361.

[29]. Paolella G. Gut-liver axis and probiotics: Their role in non-alcoholic fatty liver disease. WJG. 2014;20(42):15518 - 15531.

[30]. Kwong EK, Zhou H. Sphingosine-1-phosphate signaling and the gut-liver axis in liver diseases. Liver Research. 2019;3(1):19 -24.

[31]. Karbalaei R, Piran M, Rezaei-Tavirani M, Asadzadeh-Aghdaei H, Heidari MH. A systems biology analysis protein-protein interaction of NASH and IBD based on comprehensive gene information. Gastroenterol Hepatol Bed Bench. 2017;10(3):194 -201.

[32]. Yalcin M, Akarsu M, Celik A, Sagol O, Tunali S, Ertener O, et al. A comparison of the effects of infliximab, adalimumab, and pentoxifylline on rats with non-alcoholic steatohepatitis. Turk J Gastroenterol. 2015;25(1):167-175.

[33]. Lapumnuaypol K, Kanjanahattakij N, Pisarcik D, Thongprayoon C, Wijarnpreecha K, Cheungpasitporn W. Effects of inflammatory

bowel disease treatment on the risk of nonalcoholic fatty liver disease: a meta-analysis. European Journal of Gastroenterology & Hepatology. 2018;30(8):854 -860.

[34]. Girardin M, Manz M, Manser C, Biedermann L, Wanner R, Frei P, et al. First-Line Therapies in Inflammatory Bowel Disease. Digestion. 2012;86(s1):6-10.

[35]. Schröder T, Schmidt KJ, Olsen V, Möller S, Mackenroth T, Sina C, et al. Liver steatosis is a risk factor for hepatotoxicity in patients with inflammatory bowel disease under immunosuppressive treatment: European Journal of Gastroenterology & Hepatology. 2015;27(6): 698 -704.

[36]. Candelli M, Nista EC, Pignataro G, Zannoni G, de Pascalis B, Gasbarrini G, et al. Steatohepatitis during methylprednisolone therapy for ulcerative colitis exacerbation. J Intern Med. 2003;253(3): 391-392.

[37]. Gisbert JP, González-Lama Y, Maté J. Thiopurine-Induced Liver Injury in Patients With Inflammatory Bowel Disease: A Systematic Review. Am J Gastroenterology. 2007;102(7): 1518 -1527.

[38]. Sumida Y. Limitations of liver biopsy and non-invasive diagnostic tests for the diagnosis of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. WJG. 2014;20(2):475 - 485.

[39]. Das C, Baruah M, Singh D. Imaging of nonalcoholic fatty liver disease: A road less travelled. Indian J Endocr Metab. 2013;17(6):990 - 995.

[40]. Lee DH. Imaging evaluation of non-alcoholic fatty liver disease: focused on quantification. Clin Mol Hepatol. 2017;23(4):290 - 301.

[41]. Peleg N, Issachar A, Sneh-Arbib O, Shlomai A. AST to Platelet Ratio Index and fibrosis 4 calculator scores for non-invasive assessment of hepatic fibrosis in patients with non-alcoholic fatty liver disease. Digestive and Liver Disease. 2017;49(10):113