Nonalcoholic Fatty Liver Disease as a Risk Factor for Severe Cholangitis

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ABSTRACT **Background:** Nonalcoholic fatty liver disease (NAFLD) is one of the most prevalent chronic liver disorders. Acute cholangitis (AC) is a life-threatening illness.

Objective: To determine whether NAFLD is a risk factor for the severity of AC.

Methods: We retrospectively studied hospitalized patients with a diagnosis of AC over 5 years. Patients were divided into a NAFLD group and a non-NAFLD group. We compared the two groups with regard to demographic characteristics, co-morbidities, laboratory data, and severity of AC (including Charlson Comorbidity Index [CCI] and Tokyo Consensus meeting criteria).

Results: In all, 298 of 419 hospitalized patients diagnosed with AC met the inclusion criteria. Of these, 73/298 (24.5%) were in the NAFLD group. NAFLD group patients were younger and more likely to be diabetic and obese than the non-NAFLD group. Participants in the NAFLD presented with higher serum C-reactive protein and higher liver enzymes ($P < 0.05$, for each parameter) and with more events of organ dysfunction ($P < 0.001$) and bacteremia ($P < 0.005$). Regarding the severity of AC according to Tokyo Consensus, among the NAFLD group more patients presented with Grade II (39.7 vs. 33.3%, $P < 0.001$) and Grade III (23.3 vs. 18.3, $P < 0.001$) cholangitis. More Grade I cholangitis was found among the non-NAFLD group (48.4 vs. 37%, $P < 0.001$). Multivariate logistic regression analysis showed that NAFLD was independently associated with severe AC, Grade III (odds ratio 3.25, 95% confidence interval 1.65–6.45, $P = 0.038$).

Conclusions: NAFLD is an independent risk factor for the severity of AC.

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Nonalcoholic fatty liver disease (NAFLD) is one of the most prevalent chronic liver disorders worldwide [1]. This entity encompasses a wide spectrum of hepatic damage in which steatosis with inflammation progresses to nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and ultimately, hepatocellular carcinoma [1,2]. Biliary and pancreatic manifestations have been reported in patients with NAFLD. NAFLD has been positively found to be associated with pancreatitis and its severity [3,5].

NAFLD is associated with metabolic syndrome and is considered the hepatic manifestation of the metabolic syndrome. Moreover, NAFLD is linked with several components of the metabolic syndrome, primarily diabetes mellitus and obesity [6,7]. Importantly, a pathogenetic link between NAFLD and imbalance of the gut microbiome has been observed. Recent studies have indicated that changes in the gut microbiome are associated with NAFLD and progression to NASH [8,9].

Acute cholangitis (AC) is a clinical syndrome characterized by fever, jaundice, and abdominal pain that develops as a result of stasis and infection in the biliary tract. It is also referred to as ascending cholangitis. Cholangitis was first described by Charcot's triad as a serious and life-threatening illness; however, it is now recognized that the severity can range from mild to life-threatening [10].

As in NAFLD, the gut microbiome plays a crucial role in the pathogenesis of acute cholangitis via an interesting recently described gut-liver axis and inflammasome activation in cholangiocyte pathophysiology [11].

There are no data on the incidence, clinical course, and outcomes of cholangitis in this fast-growing NAFLD population. The question remains, how does gut microbiome change in NAFLD impact susceptibility to cholangitis. We aimed to determine whether NAFLD is a risk factor for the severity of AC.

PATIENTS AND METHODS

STUDY POPULATION, DATA COLLECTION & PROTOCOL DESIGN

This retrospective cohort study was conducted at the Shaare Zedek Medical Center, Jerusalem, Israel. We reviewed the hospital records of all consecutive adult patients hospitalized over 5 years (January 2015 to December 2019) at Shaare Zedek Medical Center. Included were adult patients (≥ 18 years) hospitalized for AC. The clinical diagnosis of AC was made based on the clinical findings, such as the Charcot triad, in combination with the laboratory data and imaging findings in patients who underwent abdominal ultrasonography examinations during hospitalization. Patients diagnosed with gastrointestinal infections other than AC were excluded. Furthermore, patients with a known history of heavy alcohol use (defined as patients who had a history of alcohol consumption of more than 30 grams a day for at least 5 years) and those diagnosed with chronic viral hepatitis or patients with a history of other known liver disease were excluded. Patients with other hepatic pathology or autoimmune phenotypes, such as alcoholic liver disease, drug-induced liver injury, autoimmune hepatitis, viral hepatitis, cholestatic liver disease, and metabolic/genetic liver disease were also excluded using specific clinical, laboratory, radiological, and/or histological criteria/tests. The current study received ethics approval from the local hospital ethics committee and was conducted according to the Helsinki Declaration and its subsequent amendments. Data were coded to preserve the anonymity of the patients. Informed consent was waived because of the non-interventional study design.

DEFINITIONS

NAFLD was diagnosed by abdominal ultrasonography based on the presence of fatty liver (hepatic parenchymal brightness, visualization of portal and hepatic borders, liver-to-kidney contrast, deep beam attenuation, and bright vessel walls) [12].

CCI predicts 10-year survival/mortality of patients with several co-morbidities based on its scoring system. The CCI score is composed of 17 categories including (age, myocardial infarction, congestive heart failure, peripheral vascular disease, stroke or transient ischemic ischemia, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes, hemiplegia, chronic kidney disease, solid tumors, leukemia, lymphoma, and acquired immunodeficiency syndrome) [13].

AC was defined according to the new diagnostic criteria and severity assessment of acute cholangitis in revised Tokyo Classification as:

A. Systemic inflammation
- A-1: Fever and/or shaking chills
- A-2: Laboratory data: evidence of inflammatory response

B. Cholestasis
- B-1: Jaundice
- B-2: abnormal liver function tests

C. Imaging
- C-1: Biliary dilatation
- C-2: Evidence of the etiology on imaging (e.g., stricture, stone, stent)

A suspected diagnosis includes one item in A in addition to one item in either B or C. A definite diagnosis includes one item in A, one item in B, and one item in C. The Tokyo Consensus meeting defines the severity of AC in 3 grades: Grade I is mild with no onset of organ dysfunction and with a good response to initial antibiotic treatment. Grade II is moderate with no onset of organ dysfunction but without response to initial antibiotic treatment, and Grade III is severe and defined as the onset of organ dysfunction and without response to initial antibiotic treatment [14].

STATISTICAL ANALYSIS

Before commencing any statistical processing and analysis, data were visually inspected and checked for outliers. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA). Categorical variables were tested using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were examined using Student's *t*-test if normally distributed and Mann–Whitney test if not. We performed univariate analysis to identify variables associated with the severity of AC. Variables that were significantly associated ($P < 0.1$) with the primary outcome (severe cases of AC) were entered into the multivariate logistic regression model. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the severity of AC were calculated. $P < 0.05$ was considered statistically significant.

RESULTS

Of the 419 patients aged ≥ 18 years who were hospitalized during the studied period, a total of 121 patients were excluded: 97 did not meet inclusion criteria (indefinite diagnosis of cholangitis or presence of other gastrointestinal active infection on or inflammation) and 24 patients had exclusion criteria (significant alcohol intake in 7, chronic viral hepatitis in 6, cirrhosis in 2, and hepatotoxic medications in 9 patients). In total, 298 patients were included in the study. Based on the results of abdominal ultrasound, the patients were divided into two groups: patients with NAFLD (73, 24.5%) and those without NAFLD (225, 75.5%).

The demographic, clinical, and laboratory data are shown in Table 1. The patients in the NAFLD group were younger and predominantly male (53.4% vs. 50.2%, $P = 0.07$) with a median age of 71.8 ± 20.9 years vs. 73.6 ± 19.3 years in the non-NAFLD group ($P = 0.035$). Obesity and diabetes mellitus

were more frequent among the NAFLD group (mean body mass index [BMI] 29.7 ± 7.1 vs. 26.3 ± 6.3, P=0.020; and 29 (39.7%) vs. 74 (32.8%), P = 0.049, respectively). There were no significant differences in other co-morbidities between the two study groups.

Regarding the severity of AC according to Tokyo Classification, among the NAFLD group 27 patients (37%) presented with Grade I compared to 109 (48.4%) in the non-NAFLD group (P < 0.005), 29 (39.7%) presented with Grade II compared to 75 (33.3%) in non-NAFLD patients (P < 0.005), and 17 NAFLD (23.3%) presented with Grade III cholangitis, compared to 41 (18.3%) in the non-NAFLD group (P < 0.005) [Figure 1].

Table 1. Demographics, clinical and laboratory characteristics of 298 patients included in each of the study groups

Parameters	NAFLD group, n=73	Non-NAFLD group, n=225	*P*-value
Age (years), mean ± SD	71.8 ± 20.9	73.6 ±19.3	0.034
Male sex, n (%)	39 (53.4)	113 (50.2)	0.076
Body mass index, mean ± SD	29.7 ± 7.1	26.3 ± 6.3	0.020
Ischemic heart disease, n (%)	12 (16.4)	39 (17.3)	0.782
Diabetes mellitus, n (%)	29 (39.7)	74 (32.8)	0.049
Chronic renal failure, n (%)	14 (19.1)	39 (17.3)	0.843
Smoking history, n (%)	13 (17.8)	42 (18.6)	0.616
CRP mg/dl, mean ± SD	37.8 ± 18.6	19.6 ± 12.2	0.019
Creatinine mg/dl, mean ± SD	1.57 ± 1.1	1.21 ± 0.8	0.037
AST U/L, mean ± SD	74 ± 12.8	64.23 ± 9.43	< 0.005
ALT U/L, mean ± SD	61.43 ± 9.36	49.23 ± 8.24	< 0.005
GGT U/L, mean ± SD	252.3 ± 73.3	143.25 ± 91.42	< 0.005
Direct bilirubin mg/dl, mean ± SD	6.35 ± 2.56	2.63 ± 3.15	< 0.001
Albumin g/dl, mean ± SD	2.6 ± 1.33	3.2 ± 1.21	< 0.005
Charlson Comorbidity Index > 4, n (%)	38 (16.8)	21 (28.7)	< 0.005
Other at least one organ dysfunction, n (%)	19 (26.0)	23 (10.2)	< 0.001
Bacteremia, n (%)	26 (11.1)	17 (23.2)	< 0.005
Tokyo classification, n (%)			
Grade I	27 (37)	109 (48.4)	< 0.001
Grade II	29 (39.7)	75 (33.3)	< 0.001
Grade III	17 (23.3)	41 (18.3)	< 0.001

ALT = alanine transaminase, AST = aspartate transaminase, BMI = body mass index, CRP = C-reactive protein, GGT = gamma-glutamyl transferase, NAFLD = nonalcoholic fatty liver disease, SD = standard deviatio

With regard to laboratory features, the NAFLD group patients had higher serum CRP levels compared to the non-NAFLD group (37.8 mg/dl vs. 19.6 mg/dl, P = 0.019). NAFLD patients also had higher serum creatinine levels (1.57 ± 1.1 vs. 1.21 ± 0.8 mg/dl, P = 0.037), higher mean aspartate transaminase levels (74.2 ± 12.8 vs. 64.23 ± 9, P < 0.005), mean alanine transaminase levels (from 61.43 ± 9.36 compared to 49.23 ± 8.24, P < 0.005), mean gamma-glutamyl transferase (GGT) levels (252.3 ± 73.8 among the NAFLD group vs. 143.25 ± 91.42, P < 0.005). Furthermore, a similar trend was found with direct bilirubin levels. The mean direct bilirubin levels at admission were 6.35 ± 2.56 mg/dl among the NAFLD group compared to 2.63 ± 3.15 mg/dl in the non-NAFLD group (P < 0.001).

Last, patients in the NAFLD group had lower mean serum albumin levels (2.6 ± 1.33 vs, 3.2 ± 1.21, P < 0.005, respectively), higher frequency of CCI > 4 points (28.7% vs. 16.8%, P < 0.005), more events of at least one organ dysfunction (19/73 (26%) vs. 23/225(10.2%), P < 0.001), and more frequent bacteremia (23% vs. 11.1%, P < 0.005) when compared to the non-NAFLD group.

Overall, 28 (9.3%) patients developed biliary pancreatitis, the majority of which were in the NAFLD group 19 (67.85%) vs. 9 (32.14%) in the control group (P < 0.001). Overall, successful endoscopic decompression by Endoscopic retrograde cholangiopancreatography (ERCP) was performed in 252 (84.56%) patients. Failed ERCP was due to technical difficulties was observed in 12 (4.02%) patients. ERCP was waived in 34 (11.40%) patients due to sepsis and other serious conditions. Percutaneous transhepatic cholangiography (PTC) was performed for decompression instead. The majority of patients who underwent PTC due to hemodynamic instability or serious illness were from the NAFLD group (29 [85.3%] vs. 5 [14.7%], P < 0.001).

To identify potential risk factors for the severity of AC, multivariate logistic regression analysis was performed [Table 2]. After adjustment for potential confounders, a Charlson Comorbidity Index of more than 4 points, (odds ratio [OR] 3.85, 95% confidence interval [95%CI] 1.42–6.5), GGT > 60 (OR 3.85,

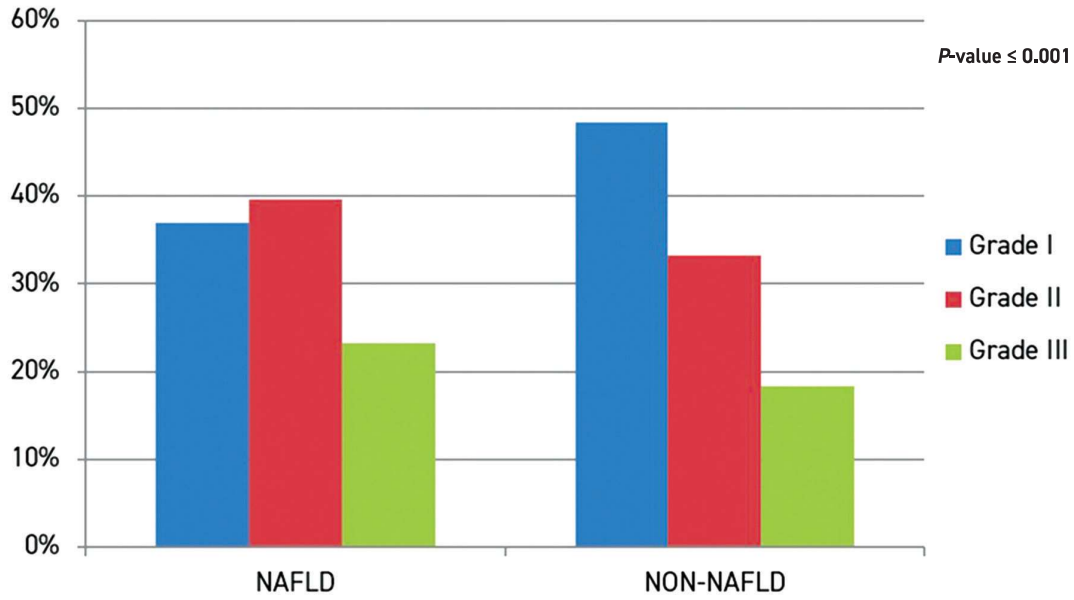
Table 2. Multivariate logistic regression analysis to identify potential risk factors for severe acute cholangitis of Grade III

Variable	Odds ratio	95% confidence interval	*P*-value
Charlson Comorbidity Index > 4	3.85	1.42–6.5	0.015
GGT > 60	3.85	2.12–7.54	0.039
Serum albumin < 2.5	2.35	1.18–7.36	0.042
NAFLD	3.25	1.65–6.45	0.038
BMI >30 kg/m^2	4.47	2.53–7.15	0.006

BMI = body mass index, GGT = gamma-glutamyl transferase, NAFLD = nonalcoholic fatty liver disease

Figure 1. The association between NAFLD and the severity of cholangitis; measured by Tokyo Classification

NAFLD = nonalcoholic fatty liver disease



95%CI 2.12–7.54), serum albumin < 2.5 (OR 2.35, 95%CI 1.18–7.36), NAFLD (OR 3.25, 95%CI 1.65–6.45), and BMI > 30 kg/m^2 (OR 4.47, 95%CI 2.53–7.15) were all independently associated with severe cholangitis (Grade III). Interestingly, diabetes mellitus was not associated with cholangitis in our model.

DISCUSSION

Our study results indicate that NAFLD is strongly associated with severe cholangitis (defined as Tokyo Classification Grade III). To the best of our knowledge, no previous studies have studied the relationship between NAFLD and severe cholangitis, although a wide array of pancreaticobiliary manifestations are commonly found among patients with NAFLD [15].

Several recent studies have shown the association between NAFLD and bacterial infections [16-18]. Although the exact mechanism is yet to be revealed, alteration of the immune system function with involvement of the dynamic gut-liver axis seems like the most plausible explanation, presumably through the NLRP3 inflammasome activation and its recently described role in cholangiocyte pathophysiology [11]. Other possible contributors within this recently described axis are the gut barrier dysfunction and intestinal immune defects that may overburden the liver's defense mechanisms, allowing bacteria to freely circulate [19]. More cases of bacteremia and organ dysfunction were documented among the NAFLD group when compared to the non-NAFLD group in our study.

The mechanisms by which NAFLD may induce severe cholangitis have not been elucidated. An increasing body of evidence points toward an increased level of proinflammatory cytokines in patients with NAFLD and NASH, with higher oxidative stress and abnormal lipoprotein metabolism was also implicated [20]. Furthermore, NAFLD is closely associated with metabolic syndrome and obesity, which is now seen as a chronic low-grade inflammatory state as the adipocytes have been shown to secrete a variety of cytokines like interleukin-6 and tumor necrosis factor-alpha, which promote inflammation [21]. Interestingly, in our study, NAFLD is independently related to the occurrence of severe cholangitis, regardless of obesity. NAFLD has also been shown to independently correlate with the risk of developing severe pancreatitis, presumably through similar mechanisms [3].

In our study, patients in the NAFLD group presented with significantly higher CRP levels. This finding is consistent with the results reported from earlier studies where a positive correlation between CRP and NAFLD has been demonstrated [22]. Furthermore, patients in the NAFLD group had higher Charlson Comorbidity Index scores, lower albumin levels, and higher GGT levels, which are all predictors of short-term and long-term mortality [13,23]. NAFLD has been well established as a predictor of increased all-cause mortality in a recently conducted comprehensive meta-analysis [24]. Similarly, Nseir et al. [25] demonstrated an increase in the all-cause 30-day mortality among NAFLD patients who presented with community-acquired pneumonia.

Our study has several limitations, including the inherent limitations of a retrospective design, a single-center study, and a relatively small sample size. Another main limitation is the absence of liver biopsies for the diagnosis of NAFLD. Thus, we did not correlate with the degree of inflammation in NAFLD patients, and no distinction was made between hepatic steatosis or NASH. However, to the best of our knowledge, our study is the first to describe the association between NAFLD and severe cholangitis.

CONCLUSIONS

Patients with NAFLD are at an increased risk for developing severe cholangitis with a higher incidence of bacteremia and organ dysfunction. Given the high prevalence of NAFLD and the substantial morbidity and mortality attributed to severe cholangitis, it is imperative to better understand this association to take appropriate measures to reduce the risk of cholangitis in patients with NAFLD.

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I look at the world and I notice it's turning / While my guitar gently weeps / With every mistake we must surely be learning / Still my guitar gently weeps.

George Harrison (1943–2001), English musician, singer-songwriter, and music and film producer who achieved international fame as the lead guitarist of the Beatles

Conscience is a man's compass, and though the needle sometimes deviates, though one often perceives irregularities when directing one's course by it, one must still try to follow its direction.

Vincent van Gogh (1853–1890), Dutch Post-Impressionist painter