Growing burden of nonalcoholic fatty liver disease in Turkey: A single-center experience

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ABSTRACT

Background/Aims: Nonalcoholic fatty liver disease (NAFLD), which consists of nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH), is a growing epidemic in Turkey, considering the recent alarming prevalence of 48.3%. Patients with NASH and/or liver fibrosis are more likely to progress to advanced liver disease. In this single-center study, we sought to describe the clinical and histological characteristics of a sample of Turkish patients with biopsy-proven NAFLD, who were enrolled over a 4-year period.

Materials and Methods: This is a retrospective analysis of prospectively collected data from a total of 468 patients (224 males, 244 females; median age, 47 [18-71]. The study cohort consisted of patients with biopsy-proven NAFLD who were followed up at our outpatient clinic from 2009 to 2010 and from 2017 to 2018. Histological classification of the biopsies was performed according to the Steatosis, Activity and Fibrosis (SAF) scoring allowing the use of Fatty Liver Inhibition of Progression (FLIP) algorithm and the NAFLD Activity Score (NAS) scoring system.

Results: Based on the SAF scoring, most patients (90.4%) had biopsy-proven NASH, whereas the NAFL was much rarer (9.6%). The prevalence of significant fibrosis (≥F2), advanced fibrosis (≥F3), and cirrhosis (F=4) was 35.0%, 17.5%, and 3.8%, respectively. The percentage of lean, overweight, and obese patients with NAFLD was 6.4%, 32.6%, and 61%, respectively. Metabolic syndrome was prevalent in 63% of the patients and Type 2 diabetes mellitus in 33.5%.

Conclusion: The growing burden of NAFLD as a public health problem in Turkey is underscored by its marked histological severity in terms of NASH and fibrosis. Well-conducted clinical trials will be essential for slowing down the NASH progression.

Keywords: Nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic fatty liver, Turkey

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is defined as the fat accumulation (more than 5% of the liver weight) in hepatocytes, and it is diagnosed by either using imaging methods or liver biopsy in patients without a secondary cause for hepatic fat accumulation. It can be roughly divided into two types: nonalcoholic fatty liver (NAFL), which is considered to be the benign NAFLD subtype, and nonalcoholic steatohepatitis (NASH), which may progress to hepatic fibrosis and cirrhosis. Therefore, NASH is more likely to be associated with liver-related morbidity and mortality (1).

Nonalcoholic fatty liver disease represents a major public health burden, considering its estimated worldwide prevalence of 25% (2). In parallel to the growing obesity epidemic, an increased prevalence of Type 2 diabetes mellitus (T2DM) and metabolic syndrome (MS), NAFLD is estimated to increase in the upcoming years (3). In this scenario, according to a recent model, the progressive subtype of NAFLD, NASH, is predicted to increase the number of liver-related deaths until 2030 by 178% (4). For this reason, NASH represents an important group of patients, and it is the main therapeutic target. However, NASH and the stage of the fibrosis can only be diagnosed by liver biopsy, the reference standard in the diagnosis of NAFLD that remains an invasive procedure (5). Therefore, it is problematic to conduct studies that involve liver biopsy.

According to the few published prevalence studies in Turkey, the NAFLD prevalence is 10.6%-23.2% (6-8). However, recent unpublished data revealed an alarming prevalence of 48.3% (9). This datum possibly represents the Turkish population more accurately, considering the high prevalence of obesity (32.2%) in Turkey according to the 2016 World Health Organization data (10). Despite the emerging prevalence of NAFLD in Turkey, there are no systemic researches that have investigated the

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characteristics of biopsy-proven NAFLD patients. In this study, we sought to describe the clinical and histological characteristics of a sample of Turkish patients with biopsy-proven NAFLD enrolled over a 4-year period from a single center.

MATERIALS AND METHODS

Patients

This is a retrospective analysis of prospectively collected data of 468 biopsy-proven adult patients with NAFLD who were diagnosed and followed up at the Marmara University Gastroenterology Outpatient Facilities over a period of 4 years, between 2009 and 2010 and between 2017 and 2018. The Turkish NAFLD biobank electronic database of Marmara University Institute of Gastroenterology was reviewed, and demographic (age at the time of biopsy, gender); clinical (height, weight, body mass index [BMI], waist circumference, systolic and diastolic blood pressures); and laboratory (fasting blood glucose, liver function test, lipid profile) data of the patients were collected. Patients with viral hepatitis, drug-induced liver disease, autoimmune hepatitis, metabolic/genetic liver diseases, or a low platelet count (<100.000/mL) were excluded from the study. All patients underwent ultrasonographic liver examination prior to the liver biopsy.

Liver histology

Liver biopsy was performed under the following conditions: 1) evidence of hepatic steatosis on ultrasound; 2) abnormal liver enzymes or hepatomegaly or splenomegaly confirmed by ultrasound, computer tomography, or magnetic resonance imaging; and 3) the absence of secondary causes of hepatic fat accumulation (e.g., significant alcohol consumption [>21 units of alcohol per week for men and >14 units of alcohol per week for women] and previous history of steatogenic drugs use). Hepatic fat accumulation >5% was diagnosed as NAFLD, as documented in the literature (11,12).

The liver biopsy specimens were scored according to the NAFLD activity (NAS) scoring system (NASH-Clinical Research Network [NASH-CRN] classification), categorized into non-NASH, borderline NASH, and definite NASH (13), and the Steatosis, Activity and Fibrosis (SAF)/Fatty Liver Inhibition of Progression (FLIP) histological algorithm, categorized into non-NASH and NASH (14) by a pathologist expertized in liver. The NAS scoring was performed evaluating the following three parameters: steatosis (0-3), lobular inflammation (0-3), and hepatocellular ballooning (0-2). The final score was a summation of those parameters ranging between 0 and 8. Following this, a NAS<3 was categorized as non-NASH, 3-4 as borderline NASH, and >4 as definite NASH. The SAF algorithm created by scoring the grade of the steatosis (S), activity (A) and fibrosis (F) required at least the presence of Grade 1 steatosis in addition to any grade of hepatocellular ballooning and lobular inflammation to classify a specimen as NAFLD. As for the activity grade, which shows the summation of the scores for ballooning and lobular (acinar) inflammation, A1 was considered mild activity, A2 moderate activity, and A>2 severe activity. Grading each of these three parameters as at least 1, the specimen was considered as NASH. According to the SAF score, the NAFLD severity was considered mild when the activity grade was <2 and the fibrosis stage <2. When the activity grade was >2 and/or the fibrosis stage >2, the severity of the disease was considered to be significant (15).

Statistical analysis

The characteristics of the patients were described using descriptive statistics. Continuous data were stated as mean, standard deviation (SD), median, and minimum-maximum. The distribution normality of the variables was calculated using the Kolmogorov-Smirnov or Shapiro-Wilk test. Categorical data were expressed as counts and proportions. A statistical analysis was performed using the Statistical Package for Social Sciences for Windows software version 24 (IBM Corp.; Armonk, NY, USA) for Windows software and was reported with 95% confidence intervals.

Ethics

The Turkish NAFLD biobank electronic database of Marmara University Institute of Gastroenterology used in this study. This study was approved by the Marmara University School of Medicine Medical Ethics Committee (Protocol number: 09.2019.182, date of approval: 02/01/2019). Informed consent was waived due to the retrospective nature of this study. The study was in adherence to the principles of the Declaration of Helsinki.

RESULTS

A total of 468 biopsy-proven NAFLD (224 males, 244 females; median age: 47 [18-71]) were included in the study. In general, the study population consisted of obese and overweight adults. Notably, 30 patients (6.4%) from the cohort were lean; these cases represented the so-called lean NAFLD, which is currently a hot topic in the field. Two hundred and ninety-five of them had MS (63%), and more than one-third (n=157) had T2DM (33.5%). Generally, the patients had increased transaminase levels. The general characteristics of the patients are depicted in Table 1.

Table 1. General characteristics of the patients (n=468)

Age, median [minimum–maximum], years	47 [18–71]
Gender, male/female, n	224/244
BMI, median [minimum–maximum], kg/m^2	31.06 [18.29–56.0]
Lean/overweight/obese, %	6.4/32.6/61.0
Metabolic syndrome, %	63.0
Type 2 diabetes mellitus, %	33.5
Systolic blood pressure, mean±SD, mmHg	127.77±17.32 CI*[126.07–129.45]
Diastolic blood pressure, mean±SD, mmHg	82.30±10.87 CI [81.24–83.36]
Waist circumference, mean±SD, cm	104.18±10.48 CI [103.92–105.13]
Weight, mean±SD, kg	85.69±14.23 CI [84.4–87.0]
AST, median [minimum–maximum], U/l / increased AST, %	42.0 [15–302]/61.2
ALT, median [minimum–maximum], U/l / increased ALT, %	66.0 [12–483]/76.9
Total cholesterol, mean±SD, mg/dL	212.59±46.07 CI [208.24–216.61]
Triglycerides, mean±SD, mg/dL	190.77±109.73 CI [180.62–200.62]
HDL cholesterol, median [minimum–maximum], mg/dL	44.0 [18–96]
Platelets, mean±SD, x10^3 per microliter	242±67 CI [236–249]
Hemoglobin, mean±SD, mg/dL	14.35±1.61 CI [14.21–14.51]
Uric acid, mean±SD, mg/dL	6.33±1.56 CI [6.06–6.60]
Glucose, median [minimum–maximum], mg/dL	101.0 [66–307]
HbA1c, median [minimum–maximum], %	5.7 [3.52–61.5]
HOMA-IR, mean±SD	4.38±2.96 CI [4.06–4.67]
HOMA-IR>2.7, %	73.1

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; HDL: high-density lipoprotein; HbA1c: Hemoglobin A1c; HOMA-IR: homeostatic model assessment of insulin resistance; SD: standard deviation. *Confidence interval

According to the liver ultrasonography, the prevalence of steatosis Grade 1, Grade 2, and Grade 3 were 25%, 55%, and 20%, respectively. As far as the liver histology was concerned, we found that >90% of the patients had NASH according to the SAF/FLIP algorithm. Only 45 (9.6%) of the patients had NAFL. Similar results were obtained when we applied the NAS score, according to which 313 (66.9%) of the patients had definite NASH, 134 (28.6%) were borderline NASH, and only 21 (4.5%) had simple steatosis. Based on the SAF score, 95.9% of the patients had severe disease, whereas only 4.1% of those had mild form of the disease. Significant fibrosis (≥F2), advanced fibrosis (≥F3), and cirrhosis (F=4) were prevalent in 164 (35%), 82 (17.5%), and 18 (3.8%) of the patients, respectively. Liver biopsy characteristics according to the NAS score and SAF classification are listed in Table 2.

We classified patients into two groups as NAFL and NASH. In both of the groups rate of comorbidities were similar. For both groups, more than 60% of the patients suffered from hyperlipidemia, obesity, and MS. More than one-third had hypertension and T2DM (Figure 1). Figure 2 depicts the relationships between fibrosis grades and histological activity (Figure 2).

Compared to the period between 2009 and 2010 (n=326), fibrosis severity showed an increased pattern between 2017

Table 2. Liver biopsy characteristics of the patients (n=468)

Grade of activity (A) according to SAF score A0 / A1 / A2 / A3 / A4, n	9 (1.9%) / 32 (6.8%) / 103 (22.1%) / 160 (34.2%) / 164 (35.0%)
Stage of fibrosis (F) according to SAF score F0 / F1/ F2 / F3 / F4, n	159 (34.0%) / 145 (31.0%) / 82 (17.5%) / 64 (13.7%) / 18 (3.8%)
NASH/NAFL according to SAF classification, n	423 (90.4%) / 45 (9.6%)
NAFLD activity score NAS score (NASH–CRN), mean±SD	5.18±1.59
NAFLD activity score (NAS) <3, n	21 (4.5%)
NAFLD activity score (NAS)=3–4, n	134 (28.6%)
NAFLD activity score (NAS) >4, n	313 (66.9%)

SAF: Steatosis, Activity and Fibrosis; NASH: Non-alcoholic steatohepatitis; NAFL: Non-alcoholic fatty liver; NAFLD: Non-alcoholic fatty liver disease; SD: standard deviation

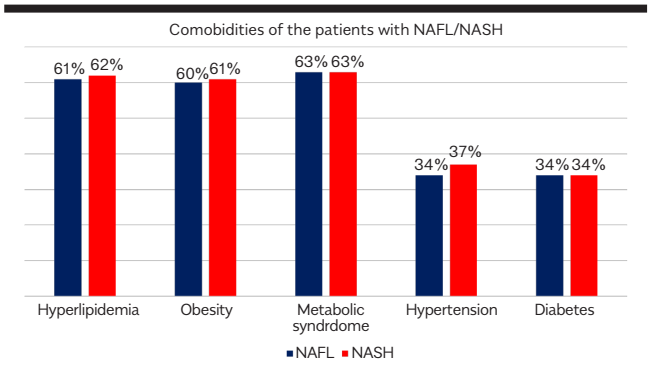

Figure 1. Comorbidities of patients with NAFL and NASH

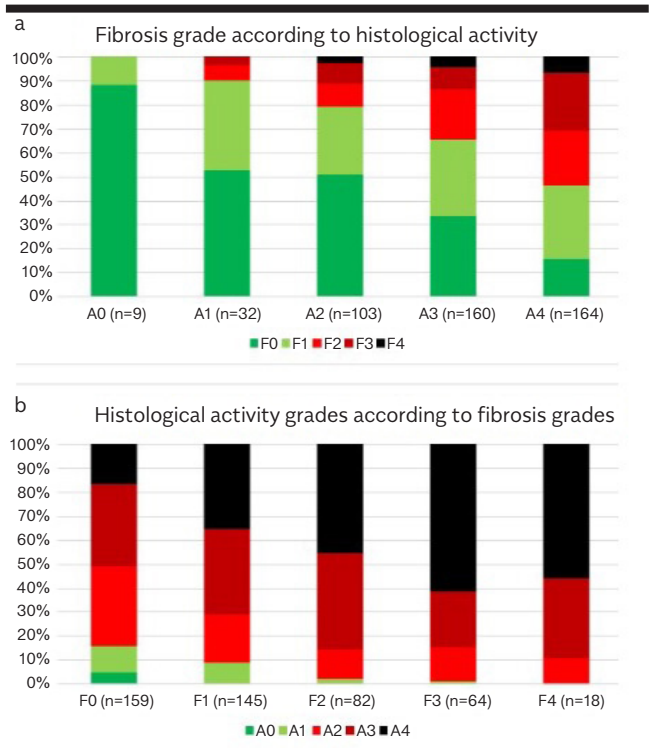

Figure 2. a, b. Fibrosis grade according to histological activity (a). Histological activity according to fibrosis grade (b)

and 2018 (n=142). During the 2009-2010 period, the prevalence of significant fibrosis, advanced fibrosis, and cirrhosis were 25.1%, 9.8%, and 1.2%, respectively. Between 2017 and 2018, the values were 58.8%, 36.1%, and 9.9%, respectively. In addition, the NASH rate increased from 88.1% to 95.7% between 2009 and 2010 and 2017 and 2018.

DISCUSSION

In this study, we presented the general characteristics of a sample of Turkish adult population diagnosed with NAFLD. Overall, in a sample of 468 biopsy-proven NAFLD patients, we found a high rate of NASH with a prevalence of 90.4%. In addition, comorbidity rates of the patients were relatively high considering the obesity, MS, and T2DM prevalence with 61%, 63%, and 33.5%, respectively. Showing similarities to our study, a large Indian cohort (n=1000) with biopsy-proven NAFLD patients revealed that, according to the NASH-CRN classification, 61.8% of the patients had definite NASH, whereas according to the SAF score, 88.3% were classified as NASH (15). In a Spanish cohort of 1058 patients, despite a relatively high comorbidity prevalence (T2DM [30.6%], hypertension [45.9%], dyslipidemia [40.5%], hypertriglyceridemia [38%]), NASH was present in 52.2% of the population when the SAF algorithm was considered for classifying the NAFLD type (16). However, in an Australian cohort, (17) liver biopsy was performed during bariatric surgery in 216 patients. T2DM was present in 26%, hypertension in 46%, and dyslipidemia in 20.1% of patients, and 74.1% were diagnosed with NAFLD and 17.1% with NASH. This prevalence of NASH is relatively low. Howev-

er, in our study, the NAS scoring was used for classifying the NAFLD. Additionally, since the study population was completely obese, this study did not represent general NAFLD patients' characteristics. The classification used for differentiation NAFLD represents an important issue, in terms of determining an accurate prevalence of NASH.

A recent model for NAFLD (18), which showed estimated data from 2016 and included China and Japan from Asia; France, Germany, Italy, Spain, and the United Kingdom from Europe; and the United States, showed the estimated prevalence was the highest in the United States (26.3%) followed by Italy (25.4%), Spain (22.9%), Germany (22.9%), United Kingdom (21.9%), France (21.6%), Japan (17.9%) and China (17.6%). Among those NAFLD patients, 20.3%, 17.1%, 17.1%, 18%, 18.5%, 16.5%, 16.6%, and 13.4% respectively had NASH. In another study (19), the same model was applied for the 2017 data from Saudi Arabia and the United Arab Emirates and an estimated NAFLD prevalence of 25.7% and 25%, respectively, was obtained. In these NAFLD patients, NASH rates were 16.2% and 16.4%, respectively. The low prevalence for NASH in those studies compared to ours can be explained by the fact that their data represented estimated prevalence from all age groups, including pediatric populations, with and without comorbidities. All in all, our data consisted of adult NAFLD patients with a high comorbidity prevalence. Additionally, in both models, an increased prevalence of NASH has been estimated until 2030 (18,19). In our data, we also observed the progress in NASH cases when the patients underwent liver biopsy in 2009-2010 (88.1%) versus those from 2017-2018 (95.7%), which also supports a tendency to have an increase in the disease severity in the upcoming decades. However, this difference can be explained with the use of FibroScan in our outpatient clinic, which helped us get information about liver fibrosis, and we selected only the patients with a high risk for fibrosis for biopsy. In fact, we did not perform a FibroScan assessment on our patients from the 2009-2010 period, and we did not follow a definite algorithm to perform liver biopsy according to the FibroScan results. However, we can state that we had the tendency to perform liver biopsy in patients whose FibroScan results suggested a high risk of fibrosis.

It is known that severe obesity significantly increases the risk of developing both NAFLD and T2DM (20). In obese patients who underwent bariatric surgery, it has been proven that fibrosis caused by NAFLD strongly correlates with the presence of T2DM (21). However, a recent study has shown that people of black race with T2DM were more likely to be free of NAFLD compared to white race, which shows the role of ethnicity in the prevalence of disease (22). In normal-weight Asian populations, NAFLD severity is even greater than in any other race with normal weight, even though their BMI is lower. In a study conducted in China, majority of the study population had Stage 1 fibrosis, and 10% had advanced fibrosis, which might be related to the higher visceral obesity rate among Asians compared to other races (23). Our study, in which significant fibrosis was detected in 35% of the patients, contributes to the literature providing data from a sample of the Turkish population.

It has been confirmed that obesity is a major risk factor for the development of NAFLD. Additionally, it has been found that obese NAFLD patients had a higher risk of developing NASH. Also their NAS and fibrosis scores were higher compared to nonobese NAFLD patients (24,25). However, a recent meta-analysis (26) suggested that obesity should not be considered as a major risk factor for the development of NASH and advanced fibrosis. According to the findings of this study, NAFLD can progress both in lean and obese individuals and therapy should be considered independently from the presence of obesity. We also conducted a study (27) in our clinic and compared lean (7.9%) and obese and overweight patients (92.1%) with NAFLD. Our results showed that fibrosis stage was milder in lean patients, although steatosis, lobular inflammation, ballooning, portal inflammation, and the NASH score were not significantly different from obese and overweight patients with NAFLD. In addition, considering the clinical characteristics, lean patients with NAFLD were younger and had a lower blood pressure and higher hemoglobin levels; MS was less prevalent in them. In the current study population, only 6.4% of patients were lean, the rest were overweight or obese. Our prevalence of significantly higher obesity, NASH and significant fibrosis support the hypothesis of the strong relationship between obesity and the severity of NAFLD. However, more systemic studies are needed to investigate the features of lean NAFLD patients and the relationship between NAFLD and obesity.

It is well known that another major risk factor for developing NAFLD and it progressing to steatohepatitis is the presence of MS (28,29). In a Turkish study (30), this relationship has been confirmed considering the higher frequency of NASH among NAFLD patients with MS. However, in that study, fibrosis showed similar prevalence among NAFLD patients with and without MS. The common presence of the high rate of NASH and MS in our study group supports the association between the NAFLD severity and MS.

Our omission to depict the characteristics of the general population may be considered a limitation to our study. In addition, the liver biopsy was performed in high-risk patients in a tertiary center, which adds bias to the study. Moreover, in 2017-2018, we tended to perform liver biopsy after a primary elimination by FibroScan, which may cause the selection bias increasing the severity of NAFLD. As mentioned in the methods, we excluded the patients with a platelet count <100.000/mL. Had we not excluded them, we could have found a higher cirrhosis prevalence in our study. On the other hand, our study consists of only biopsy-proven patients evaluated by the same pathologist. In addition, data used here are prospectively collected retrospective data without any missed data, which makes a positive contribution to the power of the study.

In conclusion, the growing burden of NAFLD as a public health problem in Turkey is underscored by its marked histological severity in terms of NASH and fibrosis. Well-conducted clinical trials will be needed to slow down the NASH progression.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Marmara University School of Medicine (Protocol number: 09.2019.182, date of approval: 02/01/2019).

Informed Consent: Informed consent was waived due to the retrospective nature of this study.

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