The Prevalence of Metabolic Associated Fatty Liver Disease in The Turkish Population: A Multicenter Study

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ABSTRACT

Background and Aim: The aim of the present study was to investigate the prevalence of metabolic associated fatty liver disease (MAFLD) in patients with dyspepsia.

Methods: Between January 2019 and December 2019, a total of 909 consecutive patients with complaint of dyspepsia were included.

Results: Their median age was 47 years. Among them, 30.3% of the patients were obese, 18.8% had type 2 diabetes mellitus, 35.1% had metabolic syndrome, 84.8% had dyslipidemia, and 23.9% had hypertension. The prevalence of MAFLD was found to be 45.5%. Among those patients with MAFLD prevalence of obesity, type 2 diabetes mellitus, metabolic syndrome, dyslipidemia, and hypertension were 43.3%, 24.9%, 52.5%, 92.3% and 31.9%, respectively. MAFLD was significantly associated with all the metabolic comorbidities ($p<0.001$). The median FIB-4 score of the MAFLD patients was 0.88 [0.1-9.5]. Of note, 53 patients with hepatic steatosis did not meet the MAFLD criteria.

In Conclusion, based on the results of the present study, the prevalence of MAFLD is found to be significantly high in daily clinical practice in Turkey. Early diagnosis and prevention efforts should be aimed to reduce disease progression, which highlight application of a region based implementation strategy in our country.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a clinical entity characterized by the presence of hepatic steatosis in individuals without significant alcohol consumption and having a secondary cause of hepatic steatosis. The clinicopathologic spectrum of NAFLD includes non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), hepatic fibrosis, cirrhosis and hepatocellular cancer (HCC). NAFLD is commonly associated with metabolic comorbidities, such as obesity, diabetes mellitus, dyslipidemia and cardiovascular disease (1).

Recently, some studies have reported the lack of clarity in the association between NAFLD and metabolic risk factors; they proposed that a more appropriate nomenclature for the disease would be metabolic (dysfunction) associated fatty liver disease (MAFLD) (2, 3). MAFLD, formerly called NAFLD, is defined as evidence of hepatic steatosis by invasive or noninvasive methods and the presence of at least one of three metabolic dysfunctions, such as overweight or obesity, type 2 diabetes mellitus (T2DM), or evidence of metabolic dysfunction (increased waist circumference and an abnormal glycemic and lipid profile) (2). MAFLD is a heterogeneous entity. Alcohol consumption, regardless of the amount, is not a reference in the diagnosis of MAFLD. Moreover, MAFLD can coexist with other liver diseases. Some studies have reported that MAFLD more accurately reflects the current knowledge of fatty liver diseases associated with metabolic disorders (2,3). Differently from NAFLD which requires "negative" definition, i.e., a diagnosis of exclusion based on the absence of coexisting chronic liver disorders, MAFLD is a positive definition and a focus on metabolic factors as its causative drivers is expected to reduce patient confusion on disease etiology, which can in turn facilitate patient-physician communication and shared decision-making (4, 5). However, it has also been reported that the proposed name-change to MAFLD is premature and requires building a wider consensus (6).

The prevalence of NAFLD varies widely; it affects approximately 25% of individuals across the globe (7, 8). Its relatively high prevalence even in apparently healthy Turkish individuals underlines the importance of early recognition of MAFLD in daily clinical practice (9-12). Unfortunately, early diagnosis of MAFLD constitutes a major clinical challenge owing to its usually asymptomatic presentation.

Dyspepsia is one of the most prevalent symptoms of gastrointestinal disorders; it affects nearly half of the general population. It is characterized by epigastric pain, burning, or abdominal discomfort (13). Thus, the

aim of the present study was to determine the prevalence of MAFLD in patients with dyspepsia in routine clinical practice.

PATIENTS AND METHODS

Patients: This multi-center, prospective cohort study included 932 consecutive patients with complaint of dyspepsia who admitted eight different tertiary care centers in Turkey between January 2019 and December 2019. Dyspepsia was defined based on the clinical guidelines (13). All the patients underwent clinical, laboratory, and radiological examinations. Data were collected from the outpatient visit charts. This study was approved by the local ethical committee of the XXX. This study was funded by Turkish Association for the Study of the Liver (TASL).

The exclusion criteria were as followings: presence of viral hepatitis, drug-induced liver disease, significant alcohol consumption [>21 units of alcohol per week in men and >14 units of alcohol per week in women], autoimmune hepatitis, genetic liver diseases, and Wilson's disease. The patients with significant transaminase levels, which can be explained by liver pathologies other than MAFLD were referred for further diagnosis and excluded from the current analysis. We also excluded the patients with missing data for liver transaminases.

Methods: Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), bilirubin, fasting glucose, cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL) levels, and complete blood cell counts were measured by the local laboratories at the participating centers.

All the patients underwent abdominal ultrasonography (US) to rule out any abdominal pathology. The abdominal US was performed by experienced radiologists who were blinded to the patients' clinical history. Hepatic steatosis was evaluated comparing its echogenicity to the kidney based on standard criteria. Hepatic steatosis was graded as mild, moderate, and severe. Mild fatty liver was defined as slightly diffuse increased echogenicity in the hepatic parenchyma and normal visualization of the diaphragm, hepatic, and portal veins borders. Moderate fatty liver was defined as diffuse increased echogenicity in the hepatic parenchyma with slightly impaired appearance of the intrahepatic vessels and the diaphragm. Severe fatty liver was defined as

marked increased echogenicity with poor or no visualization of the intrahepatic vessel borders, the diaphragm, and the posterior right lobe of the liver (14, 15).

Definitions: T2DM was defined based on American Diabetes Association criteria (16) and metabolic syndrome was defined according to the Adult Treatment Panel III criteria (17). Dyslipidemia was defined as elevated triglycerides and/or LDL or low HDL levels (18). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Obesity was defined based on World Health Organization criteria, with a BMI of 25-29.9 kg/m^2 defined as overweight, and a BMI ≥30 kg/m^2 defined as obesity (19).

MAFLD was defined as evidence of hepatic steatosis by sonography and the presence of at least one of the following three criteria:

- BMI ≥25 kg/m^2;
- T2DM;
- At least two of the metabolic dysfunction criteria for individuals with a BMI ≤25 kg/m^2.

Metabolic dysfunction indicated the presence of at least two of the following criteria (2,3):

1) Waist circumference ≥102/88 cm in men and women;

2) Blood pressure ≥130/85 mmHg, or specific drug treatment;

3) Plasma triglyceride level ≥150 mg/dL, or specific drug treatment;

4) Plasma HDL level <40 mg/dL for men and <50 mg/dL for women, or specific drug treatment;

5) Prediabetes (i.e., fasting glucose levels 100 to 125 mg/dL, or 2-hour post-load glucose levels 140 to 199 mg/dL, or glycated hemoglobin 5.7% to 6.4%;

6) Homeostasis model assessment (HOMA)-insulin resistance score ≥2.5; and

(7) Plasma high-sensitivity C-reactive protein level (hs-CRP) level >2 mg/L (2).

FIB-4 were calculated on the day when abdominal US was performed as follows:

Fibrosis-4 (FIB-4) scores were calculated on the day when abdominal US was performed as follows:

FIB-4: Age (years) x AST (U/L) / ALT (U/L)$^{1/2}$ x platelets x10^9/L (20).

The FIB-4 index gives values ranging between 0.2 and 10. A score of <1.3 indicates a low risk for fibrosis; a score >2.67 indicates a high risk for advanced fibrosis (21, 22).

Statistical analysis Means and standard deviations, medians and ranges, and frequencies and percentages were used for the descriptive statistics. Comparisons between two groups were assessed with Student's t-test or the Mann-Whitney U test, depending on the distribution of the data. Categorical variables were assessed with the chi-square test or Fisher's exact test. The normality of distribution was analyzed with the Kolmogorov-Smirnov test. A p value of less than 0.05 was considered to be statistically significant.

RESULTS

From 932 consecutive patients, 9 patients were excluded due to significantly elevated transaminases and referred for further diagnosis. We excluded 14 patients due to missing data for transaminase levels. Finally, a total of 909 patients (male/female: 344/565) with dyspepsia were included in the analysis. Most of the patients were female (62.2%). Their median age was 47 years [18-91]. Of the 909 patients, 30.3% of the patients were obese, 18.8% had T2DM, 35.1% had metabolic syndrome, 84.8% had dyslipidemia, and 23.9% had hypertension, 28% were active smokers and 5.6% were social alcohol drinkers. At the time of the evaluation, median serum AST, ALT, and GGT levels were 22 U/L [8-196], 22 U/L [2-238], and 24 U/L [6-292] respectively. The characteristics of the study population are summarized in Table 1. The association of MAFLD with the comorbidities is presented in Figure 1.

During sonographic examination, 467 patients (51.4%) showed hepatic steatosis. Among them, 288 patients (61.7%) had mild steatosis, 151 (32.3%) had moderate steatosis and 28 (6%) had severe steatosis. The median FIB-4 score of the patients with hepatic steatosis was 0.88 [0.1-9.5]. Eighty one percent of the patients had low fibrosis score (<1.3) and 2.8% presented with high risk for advanced fibrosis (FIB-4 > 2.67).

MAFLD was diagnosed in 45.5% of the 909 dyspeptic patients (n=414) and 88.7% of the patients with hepatic steatosis. Most of the patients were female (56.8% vs. 43.2%, p=0.002). MAFLD was the most prevalent in the fifth decade of life (P<0.001). MAFLD was diagnosed in 71.3% of the obese patients (P<0.001), in 60.2% of the diabetic patients (p<0.001), in 69.3% of the patients with metabolic syndrome (p<0.001), in 60.8% of the hypertensive patients (p<0.001), and 52.4% of the patients with dyslipidemia (p<0.001). The median FIB-4 score of the patients with MAFLD was 0.88 [0.1-9.5]. In all, 81.4% of the patients had a low

fibrosis score, and 2.9% presented with high risk for advanced fibrosis according to the FIB-4 score. The distribution of MAFLD according to the patients' FIB-4 score and age is summarized in Table 2 and Figure 2, respectively.

The prevalence of metabolic comorbidities is depicted in Table 3 in comparison between patients with MAFLD and NAFLD.

Of note, 53 dyspeptic patients (5.8%) with hepatic steatosis did not meet the MAFLD criteria.

DISCUSSION

The present study determined the prevalence of MAFLD in patients with dyspepsia at eight different tertiary care centers in Turkey. This study found that half of the dyspeptic patients (51.4%) were diagnosed with hepatic steatosis by abdominal US. Interestingly, 38.3% of them had moderate and severe steatosis. Patients with dyspepsia had relatively high comorbid conditions. We found that the prevalence of obesity, T2DM, metabolic syndrome, dyslipidemia and hypertension were 30.3%, 18.8%, 35.1%, 84.8%, and 23.9%, respectively. These findings are compatible with the results reported in previous studies (7-10), indicating that NAFLD is a growing public health problem worldwide as well as in Turkey.

The diagnostic approach of MAFLD plays a significant role in the prediction of its prevalence. The chosen diagnostic method can lead to over- or underestimation of the disease. Abdominal US, computerized tomography, magnetic resonance imaging (MRI), controlled attenuation parameter (CAP) by transient elastography (TE), and MRI-derived proton density fat fraction (PDFF-MRI) are the noninvasive imaging methods for prediction of hepatic steatosis (22-24). Although abdominal US has low sensitivity of, it is still routinely and widely used in daily clinical practice due to its availability and cost-effectiveness (25). In the present study, we found that around half of the dyspeptic patients were diagnosed with MAFLD using abdominal US. Most of the MAFLD patients were female. There was a relationship between the patient's age and the prevalence of MAFLD ($P<0.001$). The highest prevalence of MAFLD was observed at the fifth decade of life. MAFLD was associated with metabolic disorders. In the present study, approximately more than half of

the obese patients, diabetic patients, patients with metabolic syndrome, hypertensive patients and patients with dyslipidemia had a diagnosis of MAFLD.

The increasing prevalence of MAFLD is associated with the increasing prevalence of obesity and T2DM, worldwide (2, 3). Moreover, the increasing prevalence of MAFLD was even considered the reflection of increasing prevalence of obesity and T2DM (26). In the present study, the prevalence of obesity and T2DM in dyspeptic patients was 30.3% and 18.8%, respectively. The obesity rate was not significantly different from 2016 data of World Health Organization as 32.1% (27). Epidemiological studies, such as Turkish Diabetes Epidemiological Study 1 (TURDEP I) (28) and TURDEP II (29), have found the prevalence of T2DM increased 90% over the course of 12 years impacting 16.5% of the Turkish population (28, 29). Therefore, we believe we minimalized the effects of comorbidities to our reported prevalence for defining population based prevalence.

Considering the recent estimation models applied to different countries, in the next decade, MAFLD and the severity of MAFLD are expected to increase worldwide with the increasing rate of comorbidities, such as T2DM, obesity and metabolic syndrome (30-32). This indicates that the evidence of high comorbidity rates in Turkey creates a need for region specific implementation to effectively manage MAFLD.

Several noninvasive biochemical-based biomarkers, including the FIB-4 score, and imaging methods, such as TE and magnetic resonance elastography (MRE) are widely used to assess of liver fibrosis in routine clinical practice (33). For the stratification of risk for advanced fibrosis we calculated FIB-4 score for the patients with MAFLD as recommended in the guidelines of European Association for the Study of the Liver (32) and American Association for the Study of the Liver Diseases (1). Our study population was appropriate for the risk assessment of advanced liver fibrosis with FIB-4, since both FIB-4 and NAFLD Fibrosis Score (NFS) were shown to perform adequately in different clinical settings including among diabetic and non-diabetic patients or patients with elevated and normal transaminase levels (34, 35). However, in light of the previous studies there may be some diagnostic inaccuracies in lean and morbidly obese patients (36) and patients younger than 35 years or older than 65 years (37). In our study, we chose to calculate FIB-4 score over NFS. As shown previously, although FIB-4 performed only slightly better than NFS, FIB-4 was clinically more practical due to including fewer parameters (35). The diagnostic utility of those tests lies in their ability to exclude patients without advanced fibrosis owing to their high negative predictive value (32, 38). In our study, more than 80% of the study population was classified as low risk of advanced fibrosis, which indicates a need for referring to secondary or tertiary care centers of those remaining 20% for further diagnostics (39-41).

The strength of this study lies in the large cohort sample provided by eight different tertiary care centers in Turkey. We believe our patient selection preference was able to reflect the general population, due to the fact that the majority of the patients applied to the eight gastroenterology outpatient clinics with complaint of dyspepsia without known any known liver disease. Moreover, we used a heterogeneous group in terms of comorbidities. Consequently, this study also highlighted the general characteristics of the patient profile of our daily routine clinical practice. However, our study must be evaluated in light of its limitations. First, since the dyspeptic patients did not have any symptoms and/or liver test abnormalities, we did not perform a liver biopsy. The severity of liver disease was assessed based on the FIB-4 test. Second, abdominal US examinations were performed by a different radiologist at the respective center. This might have caused the heterogeneity of the sonography findings.

In conclusion, based on the results of the present study, we highlight the high prevalence of MAFLD in our daily clinical practice. It is expected that the disease burden of MAFLD on the Turkish Health Care System may increase in the future. We suggest that implementation of region-specific guidelines is necessary to effectively manage MAFLD.

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TABLE 1 The characteristics of the study population

Characteristics	n= 909
Age, years	47 [18-91]
Gender, male/female	344 (37.8%) / 565 (62.2%)
BMI, kg/m^2	27.3 [15.7-58.8]
Waist circumference, cm	95 [41-137]
Systolic blood pressure, mmHg	125 [85-189]
Diastolic blood pressure, mmHg	79 [50-120]
Smoking, yes/no	170 (28.0%) / 438 (72.0%)
Alcohol, yes/no	50 (5.6%) / 848 (94.4%)
Platelet, per μL	260 [75-731]
Type 2 DM, yes/no	171 (18.8%) / 738 (81.2%)
Hypertension, yes/no	217 (23.9%) / 691 (76.1%)
Dyslipidemia, yes/no	687 (84.8%) / 123 (15.2%)
Metabolic syndrome, yes/no	313 (35.1%) / 580 (64.9%)
Obesity, yes/no	223 (30.3%) / 512 (69.7%)
MAFLD, yes/no	414 (45.5%) / 495 (54.5%)
Albumin, mg/dL	4.3 [2.0-6.3]
AST, U/L	22 [8-196]
ALT, U/L	22 [2-238]
GGT, U/L	24 [6-292]
Fasting blood glucose, mg/dL	95 [52-351]
LDL, mg/dL	119 [24-410]
HDL, mg/dL	45 [10-231]
Triglycerides, mg/dL	129 [11-626]
Insulin, U/L	9.4 [2.03-142.27]

Continuous data were presented as median [minimum-maximum]. Abbreviations; MAFLD: Metabolic associated fatty liver disease, AST: Aspartate aminotransferase, ALT: Alanine aminotransfarese, GGT: Gama glutamyl transferase, LDL: low-density lipoprotein, HDL: high-density lipoprotein

TABLE 2. The classification of risk for advanced fibrosis according to FIB-4 score

FIB-4 score indicating low, indeterminate and high risk of advanced fibrosis	N (%)
FIB-4<1.3 low risk of advanced fibrosis, FIB-4>2.67 high risk of advanced fibrosis	
Patients with MAFLD (n=414), low/indeterminate/high risk	337 (81.4)/ 65 (15.7) /12 (2.9)
Patients with evidence of hepatic steatosis (n=467), low/indeterminate/high risk	378 (80.9) /76 (16.3) /13 (2.8)

Abbreviations; FIB-4: Fibrosis-4 Index, MAFLD: metabolic associated fatty liver disease

TABLE 3. Comparison of comorbidity prevalence between patients with MAFLD and NAFLD

Comorbidity	**MAFLD (N=414)**	**NAFLD (N=467)**
Obesity	159/366 (43.4%)	159/386 (41.2%)
Type 2 diabetes mellitus	103/414 (24.9%)	103/467 (22.1%)
Metabolic syndrome	217/413 (52.5%)	217/466 (46.6%)
Dyslipidemia	360/390 (92.3%)	386/430 (89.8%)
Hypertension	132/414 (31.9%)	134/467 (28.7%)

Abbreviations; MAFLD: metabolic associated fatty liver disease, NAFLD: non-alcoholic fatty liver disease

FIGURE LEGENDS

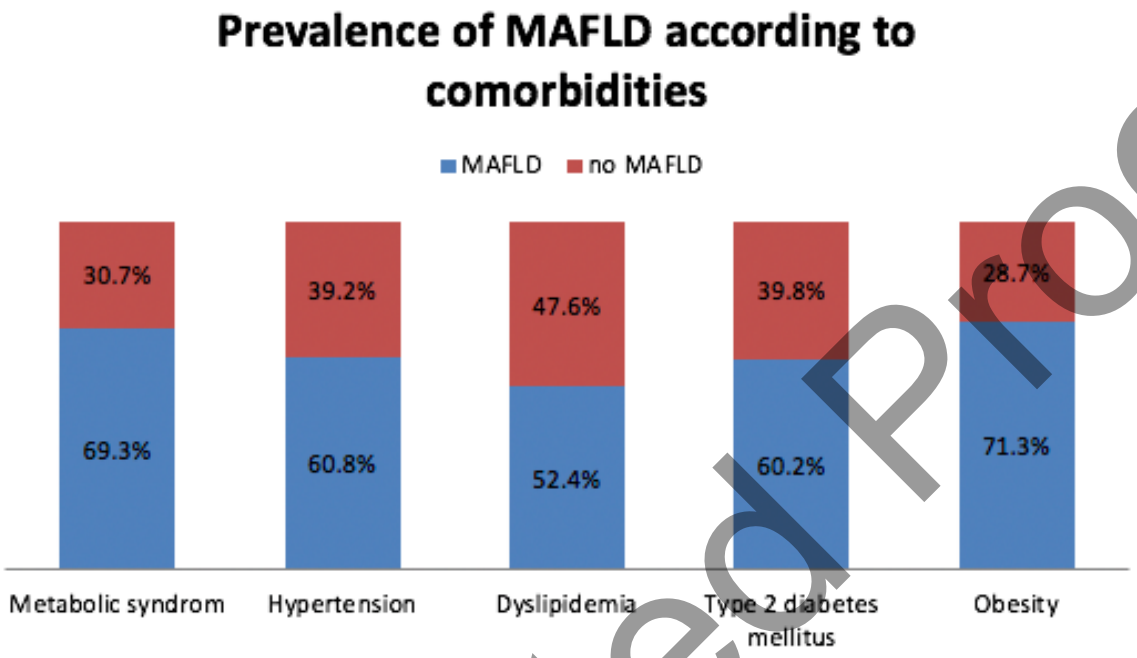

Figure 1 The association of MAFLD with comorbidities

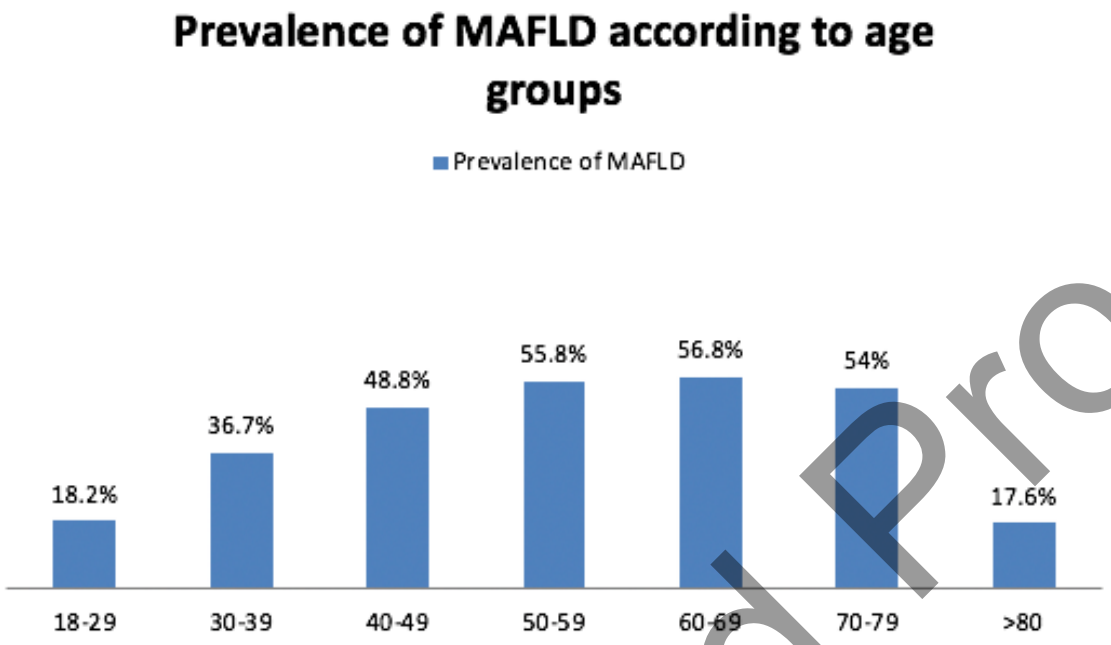

Figure 2 Prevalence of MAFLD according to age groups