Research Article

MAFLD in Turkish primary care

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Prevalence, determinants, and fibrosis risk stratification of metabolic-associated fatty liver disease in a Turkish primary care setting: A retrospective study

Ayse Yazan Arslan[1], Sultannur Celik[2], Fatuhulah Amin[2], Ilayda Caylak[2], Irem Kesapli[2], Ibrahim Berke Kilic[2], Serdar Karakullukcu[3], Cuneyt Ardic[1], Yusuf Yilmaz[4]

[1]Department of Family Medicine, Recep Tayyip Erdogan University, School of Medicine, Rize, Turkiye; [2]Recep Tayyip Erdogan University, School of Medicine, Rize, Turkiye; [3]Department of Public Health, Karadeniz Technical University, Faculty of Medicine, Trabzon, Turkiye; [4]Department of Gastroenterology, Recep Tayyip Erdogan University, School of Medicine, Rize, Turkiye

Abstract

Background and Aim: Metabolic-associated fatty liver disease (MAFLD) is a condition that frequently goes unnoticed as it typically remains asymptomatic until progressing to an advanced stage. As a result, it is essential to implement opportunistic screening initiatives within family medicine practices to accurately identify and refer selected at-risk patients to specialized care. This study aims to investigate the prevalence of MAFLD and advanced hepatic fibrosis among primary care patients in Turkiye by utilizing non-invasive tests.

Materials and Methods: We performed a retrospective analysis of prospectively collected data from February 1, 2022, to April 14, 2023, at a Family Medicine Outpatient Clinic. The Hepatic Steatosis Index (HSI) was used to identify fatty liver cases, followed by established MAFLD criteria for diagnosis. Patients were then categorized based on advanced fibrosis risk using the fibrosis-4 (FIB-4) index.

Results: Among the 450 patients who sought primary care during the study period (286 women and 164 men; mean age: 48.2±13.7 years), 295 (65.6%) were diagnosed with MAFLD using HSI values and established criteria. Diabetes mellitus emerged as the sole independent predictor of MAFLD. FIB-4 values classified 242 (82%) and 53 (18%) patients with MAFLD at low and intermediate risk of advanced fibrosis, respectively, with none at high risk.

Conclusion: MAFLD exhibits a notable prevalence among Turkish patients who presented at a Family Medicine Outpatient Clinic. Given the growing impact of metabolic diseases, primary care providers and non-liver specialists should actively participate in MAFLD screening programs.

Keywords: Family medicine; fibrosis; metabolic-associated fatty liver disease; non-invasive tests; screening.

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Corresponding author: Yusuf Yilmaz; Recep Tayyip Erdogan Universitesi Tip Fakultesi, Gastroenteroloji Anabilim Dali, Rize, Turkiye
Phone: +90 533 440 39 95; **e-mail:** dryusufyilmaz@gmail.com

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Introduction

Non-alcoholic fatty liver disease (NAFLD) has become the predominant liver disease worldwide, with a surge in new cases, especially in Middle Eastern countries.[1,2] In 2020, metabolic-associated fatty liver disease (MAFLD) was introduced as a refined nomenclature for NAFLD, addressing the drawbacks of a diagnosis based solely on excluding excessive alcohol consumption and other liver conditions.[3–5] This updated terminology permits the identification of metabolically complex fatty liver conditions that may coexist with chronic liver disease or alcoholism, while excluding cases unrelated to metabolic dysfunction.[6] For a MAFLD diagnosis, fatty liver detection must occur through histology (biopsy), imaging, or blood biomarker testing, alongside meeting one of the following criteria: Overweight/obesity, Type 2 diabetes mellitus (DM), or evidence of metabolic dysregulation.[3]

Although research on the epidemiology of MAFLD is limited,[7] a previous study reported an alarming prevalence rate of 45.5% in Turkiye,[8] highlighting the urgent need for increased awareness and effective interventions for MAFLD screening across diverse clinical settings, including primary care. For most of the Turkish population, primary care physicians serve as frontline care providers who, through their long-term experience, become familiar with the population's health-care needs.[9] In Turkiye's health-care system, family medicine outpatient clinics act as gatekeepers, positioning them advantageously for preventive activities.[10] In family medicine settings, opportunistic screening refers to the responsibility of family medicine physicians in utilizing frequent contacts with the general population for preventing common non-communicable diseases.[11] Nevertheless, in the field of MAFLD, this potential has yet to be comprehensively examined and investigated thus far. Moreover, it is essential to incorporate fibrosis screening for identified patients, as the degree of hepatic fibrosis is a critical factor influencing adverse clinical outcomes in MAFLD patients.[12] While liver biopsy remains the reference standard for assessing liver fibrosis, it has several drawbacks, such as invasiveness, costs, risk of bleeding, interobserver variability, and patient reluctance.[13] Given the vast MAFLD population, there is an urgent need for non-invasive tests (NITs) to screen for fibrosis without requiring hepatic biopsy. Among the numerous available NITs, the fibrosis-4 (FIB-4) index – which incorporates factors such as age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count – stands out as a highly efficient and cost-effective option that can be easily utilized in a screening environment.[14]

The primary aim of this retrospective study was to determine the prevalence of MAFLD among primary care patients in Turkiye. To achieve this, we initially utilized the Hepatic Steatosis Index (HSI) – a diagnostic tool that combines the ALT-to-AST ratio, body mass index (BMI), and additional factors for women and individuals diagnosed with DM[15] – to identify fatty liver cases. Subsequently, we applied the established criteria for MAFLD[3] to achieve the diagnosis. Once identified, patients with MAFLD were categorized based on their advanced fibrosis risk, employing the FIB-4 results for classification.

Materials and Methods

Study Design and Participants

This research involves a retrospective analysis of information gathered prospectively from February 1, 2022, to April 14, 2023, at the Family Medicine Outpatient Clinic of Recep Tayyip Erdogan University Training and Research Hospital, Rize, Turkiye. To be eligible for inclusion, consecutive patients had to be at least 18 years old. Those with chronic kidney disease, cancer, or incomplete data were excluded from the study. The investigation adhered to the guidelines established in the Declaration of Helsinki and received approval from the local ethics board (reference number: 2023/129). Due to the study's retrospective nature and data de-identification for evaluation, obtaining informed consent from participants was considered unnecessary and waived by the ethics committee.

Data collection

The data collected from all participants included age, sex, smoking habits, alcohol consumption, routine laboratory tests, metabolic syndrome diagnosis (based on International Diabetes Federation criteria), BMI, chronic disease presence, HSI, and FIB-4. BMI was determined by dividing weight (in kg) by the square of height (in meters). HSI calculations incorporated laboratory and anthropometric measurements, including ALT, AST, and BMI, using the formula: HSI=8 × (ALT/AST ratio) + BMI (+2 for DM, +2 for females).[15] The presence of DM was identified by a fasting glucose level of ≥126 mg/dL or the use of anti-diabetic medication. Finally, FIB-4 was calculated using the equation: [age × AST (IU/L)]/[platelets ($\times 10^9$) × √ALT (IU/L)].[14]

Identification of Patients with MAFLD

HSI values below 30 served as a basis for excluding fatty liver cases, whereas values greater than or equal to 36 indicated their presence.[15] Patients were deemed to have MAFLD if they exhibited HSI values higher than 36 in conjunction with at least one of the following criteria: overweight or obesity, Type 2 DM, or signs of metabolic dysregulation.[3]

Screening of Advanced Fibrosis

Utilizing previously defined cutoffs,[14] patients exhibiting FIB-4 values under 1.30 were categorized as having a low risk for advanced fibrosis. In contrast, FIB-4 values surpassing 2.67 were interpreted as indicating a high risk for advanced fibrosis. Finally, FIB-4 values within the range of 1.30–2.67 were regarded as signifying an intermediate risk for advanced fibrosis.[14]

Statistical Analysis

To evaluate the normality of continuous variables, we utilized the Shapiro–Wilk test. Continuous variables with normal and skewed distribu-

Table 1. General characteristics of the study patients (n=450)

Parameter	Total, n (%)
Demographics	
Age (years), mean±standard deviation	48.2±13.7
Women	286 (63.6)
Men	164 (36.4)
Lifestyle factors	
Smoking	
Non-smokers	317 (70.4)
Ex-smokers	53 (11.8)
Current smokers	80 (17.8)
Alcohol use	
Non-drinkers	432 (96.2)
Current drinkers	17 (3.8)
Laboratory parameters	
ALT (U/L)	20.8±12.2
AST (U/L)	20.3±6.7
Platelet count ($x10^3$ U/L)	259.1±65.5
GGT (U/L)	25.6±20.0
Fasting blood glucose (mg/dL)	102.4±33.1
LDL cholesterol (mg/dL)	135.6±37.0
Non-HDL cholesterol (mg/dL)	165.2±107.4
Metabolic syndrome	
Yes	161 (35.8)
No	289 (64.2)
Body mass index (kg/m^2)	29.0±5.7
Chronic diseases	
Diabetes mellitus	
Yes	72 (16.0)
No	378 (84.0)
Hypertension	
Yes	136 (30.2)
No	314 (69.8)
Cardiovascular disease	
Yes	56 (12.4)
No	394 (87.6)
Cerebrovascular disease	
Yes	4 (0.9)
No	446 (99.1)
HSI, mean±standard deviation	61.9±57.9
HSI categories	
<30	33 (7.3)
30–36	90 (20.0)
≥36	327 (72.7)
FIB-4, mean±standard deviation	0.94±0.57
FIB-4 categories	
Low risk (<1.30)	379 (84.2)
Intermediate risk (1.30–2.67)	71 (15.8)
High risk (>2.67)	0 (0)

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, HSI: Hepatic steatosis index, FIB-4: fibrosis-4 index. Unless otherwise indicated, data are presented as counts and percentages.

Table 2. General characteristics of the patients with and without MAFLD

Parameter	Patients without MAFLD (n=155)	Patients with MAFLD (n=295)	p
Demographics			
Age (years), median (IQR)	43 (31–51)	51 (43–59)	<0.001
Women, n (%)	103 (66.5)	183 (62.0)	0.35
Lifestyle factors			
Current smokers, n (%)	31 (20.0)	49 (16.6)	0.22
Current drinkers, n (%)	3 (1.9)	14 (4.7)	0.14
Clinical and laboratory parameters			
ALT (U/L)	14 (11–19)	20 (15–27)	<0.001
AST (U/L)	18 (16–22)	20 (17–23)	0.02
Platelet count (x10^3 U/L)	242 (207–283)	257 (218–306)	0.03
GGT (U/L)	17 (13–23)	24 (18–32)	<0.001
Fasting blood glucose (mg/dL)	91 (85–99)	98 (91–109)	<0.001
LDL cholesterol (mg/dL), mean±SD	127.9±37.0	139.7±36.4	0.001
Non-HDL cholesterol (mg/dL), median (IQR)	147 (117–174)	167 (140–192)	<0.001
Metabolic syndrome, n (%)	21 (13.5)	140 (47.5)	<0.001
Body mass index (kg/m2), median (IQR)	23.9 (21.6–26.0)	30.8 (28.6–34.3)	<0.001
Diabetes mellitus, n (%)	6 (3.9)	66 (22.4)	<0.001
Hypertension, n (%)	21 (13.5)	115 (39.0)	<0.001
Cardiovascular disease, n (%)	11 (7.1)	45 (15.3)	0.01
Cerebrovascular disease, n (%)	0 (0)	4 (1.4)	0.30
FIB-4, mean±SD	0.84 (0.54–1.15)	0.87 (0.62–1.17)	0.23
FIB-4 categories			0.21
Low risk (<1.30), n (%)	137 (88.4)	242 (84.2)	
Intermediate risk (1.30–2.67), n (%)	18 (11.6)	53 (15.8)	
High risk (>2.67), n (%)	0 (0)	(0)	

MAFLD: Metabolic-associated fatty liver disease, IQR: İnterquartile range, SD: Standard deviation, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, HSI: Hepatic steatosis index, FIB-4: Fibrosis-4 index. Unless otherwise indicated, data are presented as counts and percentages.

tions were presented as the mean with standard deviation and median with interquartile range, respectively. We reported categorical variables as frequencies and percentages. When comparing patients with and without MAFLD, the Student's t-test was applied to normally distributed continuous variables, whereas the Mann–Whitney U test was used for skewed continuous data. We examined categorical variables with the Chi-squared test. For identifying independent predictors of MAFLD, we conducted a multivariable logistic regression analysis, including all variables from Table 1 as potential predictors or covariates. The results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). All statistical analyses were performed using the SPSS software (version 20.0; IBM, Armonk, NY, USA). A two-tailed P value of less than 0.05 was considered statistically significant.

Results

General Characteristics of the Study Participants

We examined a total of 450 patients (286 women and 164 men; mean age: 48.2±13.7 years) who sought treatment at a Family Medicine Outpatient Clinic located in Turkiye. The demographic information and general characteristics of the study participants are summarized in Table 1. Notably, 327 patients (72.7%) exhibited HSI values equal to or greater than 36, suggesting the presence of fatty liver.

Prevalence of MAFLD

After evaluating the HSI values and applying the established diagnostic criteria,[3] 295 patients (65.6%) were identified as having MAFLD. They were found to be older and had higher values for AST, ALT, platelet count, gamma-glutamyl transferase, fasting blood glucose, low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and BMI compared to those who did not meet the criteria for MAFLD. As anticipated, these patients more frequently met the diagnostic criteria for metabolic syndrome and had a higher prevalence of DM, hypertension, and cardiovascular disease (Table 2). In multivariable logistic regression analysis, DM was identified as the only independent variable associated with the diagnosis of MAFLD (OR=4.03; 95% CI=3.03–16.9; $p < 0.001$).

Screening of Advanced Fibrosis

In the entire study cohort (n=450), 379 patients (84.2%) displayed FIB-4 values below 1.30, indicating a low risk for advanced fibrosis. The remaining 71 patients (15.8%) had FIB-4 values ranging from 1.30 to 2.67, suggesting an intermediate risk. Notably, no patients exhibited FIB-4 values exceeding 2.67, which would denote a high risk for advanced fibrosis. On examining the subgroup of patients diagnosed with MAFLD (n=295), the FIB-4 values exhibited the

following distribution: Below 1.30, n=242 (82%); within the range of 1.30–2.67, n=53 (18%). Consequently, the distribution of FIB-4 results did not demonstrate a significant difference between patients with and without MAFLD (p=0.21).

Discussion

Since MAFLD frequently exhibits no noticeable symptoms until reaching more advanced stages, the need for early detection and screening for this condition, along with its primary prognostic indicator (i.e., liver fibrosis), is becoming increasingly vital.[16] To address this growing concern, in the present study, we proposed to integrate opportunistic screening initiatives within the scope of family medicine practices. This is particularly relevant considering the general population's limited awareness of this condition, coupled with the persistent rise in the prevalence of metabolic diseases.[6] Our study demonstrates that among a large cohort of Turkish patients visiting a Family Medicine Outpatient Clinic, the prevalence of MAFLD based on current consensus criteria is remarkably high at 65.6%. Of the numerous factors examined, DM was the sole predictor with a significant independent association with this condition. In a primary care environment, timely identification of patients with MAFLD at the greatest risk of complications, particularly those with the highest likelihood of fibrosis, would enable family practitioners to refer these individuals to hepatologists and specialized centers for further evaluation and treatment.[17] However, our findings reveal that only 18% of patients meeting the MAFLD diagnostic criteria displayed an intermediate risk of advanced fibrosis. In contrast, the remaining 82% showed a low risk, as indicated by FIB-4 values below 1.30. Collectively, these results suggest that within a Turkish family medicine setting, the severity of MAFLD tends to be relatively mild, despite its high occurrence.

By leveraging the wealth of clinical and laboratory data that are routinely gathered for various purposes in family medicine, opportunistic screening of MAFLD and fibrosis through NITs – such as HSI and FIB-4 – presents an opportunity for early identification of liver-related conditions that carry a substantial risk of future complications, particularly in high-risk individuals with DM.[18] As artificial intelligence-driven advancements continue to accelerate in the health-care sector, the potential for rapid computation of NITs and automated risk stratification using easily accessible clinical data may soon become a tangible reality. The considerable benefits of this approach are further magnified by the vast number of laboratory tests conducted within Family Medicine Outpatient Clinics for a diverse range of clinical indications. On identification of MAFLD and considering the results from the FIB-4 assessment, a step-wise strategy can be employed to determine the most effective referral pathways for newly diagnosed patients in the primary care setting.[19] Subjects exhibiting an FIB-4 score below 1.30 are considered to be at a low risk for advanced fibrosis and can remain under primary care supervision. In contrast, patients with an FIB-4 score exceeding 2.67 are at a high risk for advanced fibrosis, warranting referral to secondary care specialists. However, it is important to note that no high-risk cases were identified in the present study. For patients with FIB-4 scores within the gray zone, supplementary testing, such as transient elastography (TE), can be utilized to more accurately assess their risk for advanced fibrosis.[19] The question of whether adding TE can significantly reduce unnecessary referrals to secondary care and improve the identification of patients with advanced fibrosis in Turkish primary care settings remains unanswered. However, this approach will also require a thorough evaluation of its cost-effectiveness.

The interpretation of our findings should consider certain limitations. First, the study's single-center design might potentially lead to selection bias, which highlights the importance of validating the results through independent investigations. Second, although we did not employ histological analysis, ultrasound, or TE-established controlled attenuation parameter to evaluate steatosis, our screening methodology utilizing NITs can be considered suitable within the context of the general population. However, it is essential to note that the positive predictive values of NITs are only moderate, and their performance may be less reliable for patients with DM.[20] Finally, our study lacks follow-up information on patients with MAFLD at intermediate risk for advanced fibrosis, who, within the cohort, were most likely to develop complications.

Conclusion

Our study highlights a notable prevalence of MAFLD among Turkish patients attending a Family Medicine Outpatient Clinic, with DM identified as the sole independent risk factor. Given the escalating impact of metabolic diseases in Turkiye, it is crucial for primary care providers and non-liver specialists to be involved in MAFLD screening programs. An urgent call for a comprehensive, collaborative management strategy between primary and secondary healthcare providers is essential, along with well-defined referral pathways. Undoubtedly, this approach will yield long-term clinical advantages by alleviating both hepatic and extra-hepatic consequences of MAFLD.

Ethics Committee Approval: The Recep Tayyip Erdogan University Clinical Research Ethics Committee granted approval for this study (date: 25.05.2023, number: 2023/129).

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Conflict of Interest: YY has disclosed receiving consultancy fees, speaker honoraria, and/or participating in clinical trials sponsored by Zydus, Cymabay, Novo Nordisk, and Echosens. The remaining authors have declared no competing interests.

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