Research Article

Etiology of chronic liver disease

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Changes in the etiology of chronic liver disease by referral to a FibroScan center: Increasing prevalence of the nonalcoholic fatty liver disease

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Abstract

Background and Aim: Chronic liver disease (CLD) is a leading cause of morbidity and mortality worldwide with a wide etiological spectrum. FibroScan® is used for follow-up of fibrosis and steatosis. This single-center study aims to review the distribution of indications by referral to FibroScan®.

Materials and Methods: Demographic characteristics, CLD etiologies, and FibroScan® parameters of the patients who were referred to our tertiary care center between 2013 and 2021 were retrospectively evaluated.

Results: Out of 9345 patients, 4946 (52.93%) were males, and the median age was 48 [18–88] years. Nonalcoholic fatty liver disease (NAFLD) was the most common indication (N=4768, 51.02%), followed by hepatitis B (N=3194, 34.18%) and hepatitis C (N=707, 7.57%). Adjusting for age, sex, and CLD etiology, the results revealed that patients with older age (Odds ratio (OR)=2.908; confidence interval (CI)=2.597–3.256; p<0.001) and patients with hepatitis C (OR=2.582; CI=2.168–3.075; p<0.001), alcoholic liver disease (OR=2.019; CI=1.524–2.674, p<0.001), and autoimmune hepatitis (OR=2.138; CI=1.360–3.660, p<0.001) had increased odds of advanced liver fibrosis compared to NAFLD.

Conclusion: NAFLD was the most common indication for referral to FibroScan®.

Keywords: Chronic liver disease; indications; liver fibrosis.

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Introduction

Chronic liver disease (CLD) is a leading cause of mortality and morbidity worldwide. While the disease burden across all countries was characterized as primarily due to communicable etiologies such as chronic viral hepatitis historically, transitions in diet, lifestyle, and medical advancements have caused a paradigm shift in the contribution of different etiologies to the CLD spectrum. Hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-related liver disease (ALD), and nonalcoholic fatty liver disease (NAFLD) are the main contributors to the global CLD burden. NAFLD and ALD are the current challenges due to increasing obesity and alcohol consumption, whereas HBV and HCV have been declining due to the implementation of national vaccination programs and new treatments worldwide.[1]

In Turkiye, the epidemiological transition of CLD has been facilitated by the adoption of healthcare policies concerning communicable diseases while increasing metabolic diseases such as type 2 diabetes mellitus (T2DM) leading to NAFLD.[2–5] Indeed, a recent multicenter study in eight tertiary care centers in Turkiye revealed NAFLD prevalence of 51% by ultrasonography among patients who presented to the gastroenterology clinics with dyspepsia.[6] This was not a surprising finding because Turkiye is the most obese country in Europe, with an obesity prevalence of 32%.[7] Similarly, another multicentric data of apparently healthy subjects at routine check-ups showed an obesity prevalence of 48%.[8] Currently, even though HBV is included in the national immunization program,[9] and patients with HCV are treated effectively,[10] viral hepatitis is still known to be the major contributor to CLD in Turkiye. However, a shift to NAFLD in the near future is inevitable.[4]

Despite the efforts to define the spectrum of CLD in Turkiye,[4] the present data are limited and sparse. In this study, we aimed to describe the distribution of CLD etiologies and associated FibroScan parameters [controlled attenuation parameter (CAP) and liver stiffness measurement (LSM)] among patients referred to our tertiary care center for FibroScan examinations.

Materials and Methods

Patients

The study is a retrospective analysis of 9345 patients with various CLD etiologies and 11 688 FibroScan® examinations conducted in Marmara University Institute of Gastroenterology between January 2013

and September 2021. Electronic database containing demographic information (age at first FibroScan and sex), indication for referral, and FibroScan® data (date, operator, probe type, duration, LSM (kPa), the interquartile range (IQR) of measurements, IQR/median for LSM, and CAP (dB/m) was reviewed. Based on ICD-10 diagnostic codes, CLD etiologies were categorized as HBV, HCV, NAFLD, ALD, autoimmune hepatitis (AIH), cholestatic liver diseases (primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC)), metabolic liver diseases (Wilson's disease, hemochromatosis, and alpha-1 antitrypsin deficiency) and drug-induced liver injury (DILI).

Unreliable measurements (<10 valid measurements obtained and/or LSM IQR/median >30%), age less than 18 years at initial referral to FibroScan examination, use of small size probe, having non-CLD indications (e.g., psoriasis, T2DM, isolated liver enzyme elevations, inflammatory bowel disease, hepatosplenomegaly, and having bariatric surgery) as the cause of referral, absent steatosis measurements, performed examinations other than by YY were exclusion criteria. A total of 4465 (32.33%) patients and 6077 measurements (34.21%) were excluded from the final analysis. The exclusion process is shown in Figure 1.

After the exclusion criteria were applied, 9345 patients with 11 688 examinations were suitable for final analysis. If a patient had multiple FibroScan® exams over a 9-year period, only the first exam was included in the study. Cases were considered duplicates if their first name, last name, and date of birth matched. The matching cases were sorted by the FibroScan examination dates.

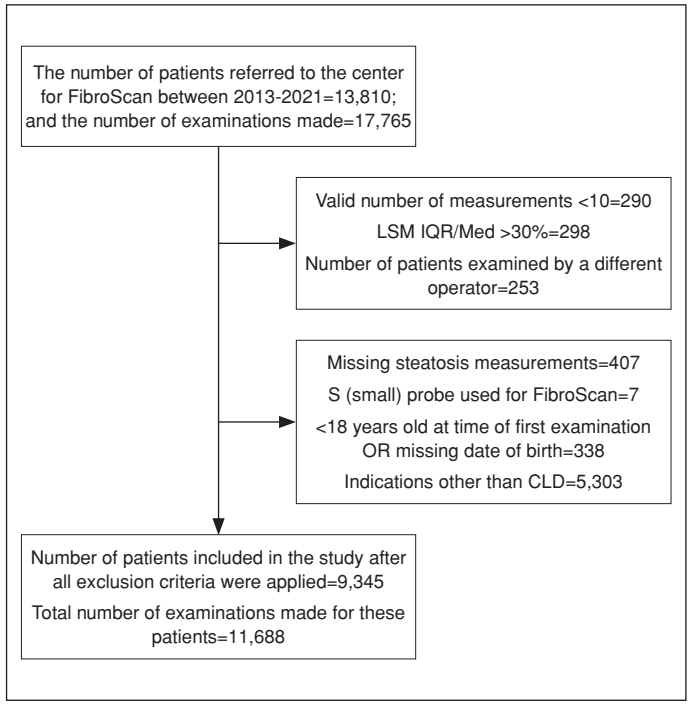

Figure 1. Exclusion criteria.

LSM: Liver stiffness measurement; IQR: Interquartile range; OR: Odds ratio; CLD: Chronic liver disease.

FibroScan Examinations

A single experienced operator, YY, performed the FibroScan® during outpatient visits. All measurements were performed using FibroScan® 502 (Echosens, France). All the examinations were started with the M probe (frequency: 3.5 Hz). Prompted by the automatic probe selection tool, the probe was switched to XL (frequency: 2.5 Hz) automatically. An attempt was made to obtain at least 10 valid measurements. The median value of these measurements was recorded as LSM, and the IQR of the measurements was calculated and recorded by the engine. LSM values derived from at least 10 valid measurements that have an IQR/median value of ≤30% were considered reliable.[11–13]

The cutoff values for CAP and LSM were derived from the literature (F0: ≤6.0 kPa, F1: 6.1–7.0 kPa, F2: 7.1–9.9 kPa, F3: 10.0–13.9 kPa, F4: ≥14.0 kPa; S0: <238 dB/m (<5%), S1: 238–258 dB/m (5%–33%), S2: 259–289 dB/m (34%–66%), S3: >290 dB/m (>66%).[14–16]

Statistical Analysis

Patient characteristics and the FibroScan® results were summarized using descriptive statistics. The distribution of variables was evaluated using the Kolmogorov–Smirnov normality test. Normally distributed data were presented as mean±standard deviation (SD), nonnormally distributed data as median [minimum–maximum]. Categorical data were expressed as counts and proportions. Independent samples t-test and ANOVA were used for the comparison of mean LSM of gender and age groups. Categorical data were compared with the Chi-squared test. Logistic regression was used to analyze the relationship between age group, gender, CLD etiology, and having advanced liver fibrosis. Statistical analysis was done with Statistical Package for Social Sciences version 28 (IBM Corp., Armonk, NY, USA) for Windows software and was reported with 95% confidence intervals.

Table 1. Distribution of FibroScan measurements and number of patients by year

Years	Number of patients	Number of examinations
2013	319	413
2014	569	656
2015	932	1038
2016	1103	1259
2017	1485	1799
2018	1650	2017
2019	1522	2020
2020	936	1362
2021	829	1124
Total	9345	11 688

Ethics

This study was approved by the Marmara University Medical School Ethics Committee (Protocol number: 09.2021.1245, approval date: November 5, 2021). Due to the retrospective nature of the study, the informed consent was waived. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

The distribution of the number of patients referred to this clinic for FibroScan and the number of examinations conducted each year is given in Table 1. Out of 17 765 measurements before exclusion, 520 (2.93%) examinations were classified as unreliable.

Table 2. Summary of FibroScan findings and demographic characteristics of the study population

Category, Median [Min–Max]	
Liver stiffness measurement (kPa)	6.10 [1.8–75]
Controlled attenuation parameter (db/m)	283 [0–400]
IQR	0.8 [0–19.1]
Number of valid measurements	10 [10–34]
Probe size, n (%)	
Medium	6685 (71.5)
XL	2660 (28.5)
Category, Mean±SD	
IQR/med (%)	14.36±6.949
Exam duration (seconds)	102.56±63.97
Age group, n (%)	
18–35	1815 (19.4)
36–55	4958 (53.1)
56–88	2572 (27.5)
Median age [min–max]	48 [18–88]
Sex, n (%)	
Male	4946 (52.9)
Female	4399 (47.1)

Min: Minimum; Max: Maximum; IQR/med: Interquartile range/median; SD: Standard deviation.

Two hundred and nighty (55.77%) out of 520 were unreliable because of failing the 10 valid measurement criteria (males: 94 (32.41%), mean age: 52±14 years, mean body mass index (BMI): 38±9 kg/m^2). Two hundred and nighty-eight patients (57.31%) were excluded due to IQR/median >30% (males: 109 (36.58%), mean age: 52±17 years, mean BMI: 35.9±8.2 kg/m^2). Sixty-eight (13.08%) were excluded for having both less than 10 valid measurements and IQR/median >30%.

Out of 9345 patients in the study population, 6685 (71.5%) patients were examined with M probe and 2660 (28.5%) with XL probe. In the final analysis, 4946 (52.9%) were males. The median age was 48 [18–88] years. Of the total patients, 1815 (19.4%) patients were young adults (18–35 years), 4958 (53.1%) were middle-aged (36–55 years), and 2572 (27.5%) were older-aged (over 55 years) (Table 2). The mean LSM value was 8.34±7.97 kPa for females and 8.65±8.77 kPa for males without significance (p=0.077). The mean LSM was 11.34±11.67 kPa in the older-aged, 7.79±7.07 kPa in the middle-aged, and 6.45±4.12 kPa in the young adults. The mean value of LSM was significantly different between younger- and middle-aged groups (p<0.001, 95% CI=[-1.879, -0.801]); younger- and older-aged groups (p<0.001, 95% CI=[-5.491, -4.286]); and middle- and older-aged groups (p<0.001, 95% CI=[-4.025, -3.071]).

NAFLD was the most frequent indication for FibroScan referral (N=4768, 51.02%), followed by HBV (N=3194, 34.18%), HCV (N=707, 7.57%), ALD (N=275, 2.94%), DILI (N=169, 1.81%), AIH (N=97; 1.04%), PBC and PSC (94, 1.01%), and metabolic liver diseases (41, 0.44%). The number of patients with each indication is listed in Table 3. There was a transition in disease etiology frequencies for FibroScan referral over the study period. The change in disease etiology frequencies from 2013 to 2021 is depicted in Table 4. Notably, the percentage of patients with HCV referred for FibroScan® decreased from 24.8% in 2013 to 2.5% in 2021.

Table 3. Distribution of the chronic liver disease etiology

Etiology	Total, n (%)
NAFLD	4768 (51.02)
HBV	3194 (34.18)
HCV	707 (7.57)
ALD	275 (2.94)
DILI	169 (1.81)
AIH	97 (1.04)
PSC/PBC	94 (1.0)
Metabolic liver diseases	41 (0.44)
Total	9345 (100)

NAFLD: Nonalcoholic fatty liver disease; HCV: Hepatitis C virus; HBV: Hepatitis B virus; DILI; Drug-induced liver injury; PSC/PBC: Primary sclerosing cholangitis and primary biliary cirrhosis; ALD: Alcoholic liver disease; AIH: Autoimmune hepatitis.

Table 4. Change in disease etiology frequencies from 2013 to 2021

Indications	2013 (%)	2021 (%)	Rate of change (%)
NAFLD	44.8	56.2	25.44
HCV	24.8	2.5	-89.91
HBV	23.1	33.3	44.16
Metabolic liver diseases	0.6	0.5	-16.67
DILI	1.3	1.4	7.69
PSC/PBC	0.9	1.4	55.56
ALD	0.3	3.6	1100
AIH	3.1	1.0	-67.74

NAFLD: Nonalcoholic fatty liver disease; HCV: Hepatitis C virus; HBV: Hepatitis B virus; DILI: Drug-induced liver injury; PSC/PBC: Primary sclerosing cholangitis and primary biliary cirrhosis; ALD: Alcoholic liver disease; AIH: Autoimmune hepatitis.

Among NAFLD patients, 22.9% (N=1094) had T2DM. The proportion of advanced fibrosis was 17.1% (N=814) among patients with NAFLD regardless of the T2DM status. On the other hand, NAFLD patients with T2DM had significantly higher rates of advanced fibrosis (28.7%, N=314) (p<0.001).

The distribution of steatosis grades and fibrosis stages by CLD etiology is presented in Tables 5 and 6. Overall, 2453 (26.2%) patients had no steatosis (S0; CAP <238 db/m) and 4526 (48.4%) had no fibrosis (F0; ≤6.0 kPa) at baseline. The prevalence of patients with grade 0, 1, 2, and 3 steatosis was 26.2% (N=2453), 11.0% (N=1032), 16.2% (N=1516), and 46.6% (N=4344), respectively (Table 5). Hepatic steatosis was not confirmed for 417 patients (8.7%) by FibroScan®, who were referred to our center because of ultrasonographically detected steatosis (US-NAFLD). The prevalence of patients with stage 0, 1, 2, 3, and 4 fibrosis was 48.4% (N=4526), 15.2% (N=1423), 18.3% (N=1710), 7.7% (N=721), and 10.3% (N=965), respectively (Table 6). The prevalence of advanced fibrosis was 18% (N=1686). The proportion of patients with advanced liver fibrosis (>10.0 kPa; F3–F4) was highest in the HCV group (N=283, 40%) (p<0.001).

Logistic regression was used to analyze the impact of age, sex, and CLD etiology on advanced liver fibrosis development in CLD patients. The dependent variable was dichotomously categorized as the presence of advanced fibrosis (stages 3–4) (N=1686, 18.1%) or no advanced fibrosis

Table 5. Distribution of steatosis grades by chronic liver disease etiology

Etiology	Steatosis grades among patients, n (%)				Total, n (%)
	S0	S1	S2	S3	
NAFLD	417 (8.7)	356 (7.5)	775 (16.3)	3220 (67.5)	4768 (100.0)
HCV	370 (52.3)	89 (12.6)	123 (17.4)	125 (17.7)	707 (100.0)
HBV	1457 (45.6)	505 (15.8)	500 (15.7)	732 (22.9)	3194 (100.0)
Metabolic liver diseases	19 (46.3)	7 (17.1)	6 (14.6)	9 (22.0)	41 (100.0)
DILI	42 (24.9)	15 (8.9)	28 (16.6)	84 (49.7)	169 (100.0)
PSC/PBC	48 (51.1)	15 (16.0)	17 (18.1)	14 (14.9)	94 (100.0)
ALD	46 (16.7)	30 (10.9)	57 (20.7)	142 (51.6)	275 (100.0)
AIH	54 (55.7)	15 (15.5)	10 (10.3)	18 (18.6)	97 (100.0)
Total	2453 (26.2)	1032 (11.0)	1516 (16.2)	4344 (46.6)	9345 (100.0)

NAFLD: Nonalcoholic fatty liver disease; HCV: Hepatitis C virus; HBV: Hepatitis B virus; DILI: Drug-induced liver injury; PSC/PBC: Primary sclerosing cholangitis and primary biliary cirrhosis; ALD: Alcoholic liver disease; AIH: Autoimmune hepatitis.

Table 6. Distribution of fibrosis stages by chronic liver disease etiology

Etiology	Fibrosis stages among patients, n (%)					Total, n (%)
	F0	F1	F2	F3	F4	
NAFLD	2264 (47.5)	726 (15.2)	964 (20.2)	384 (8.1)	430 (9.0)	4768 (100.0)
HCV	197 (27.9)	95 (13.4)	132 (18.7)	89 (12.6)	194 (27.4)	707 (100.0)
HBV	1764 (55.2)	515 (16.1)	499 (15.6)	183 (5.7)	233 (7.3)	3194 (100.0)
Metabolic liver diseases	17 (41.5)	5 (12.2)	9 (22.0)	5 (12.2)	5 (12.2)	41 (100.0)
DILI	97 (57.4)	21 (12.4)	22 (13.0)	14 (8.3)	15 (8.9)	169 (100.0)
PSC/PBC	32 (34.0)	17 (18.1)	24 (25.5)	10 (10.6)	11 (11.7)	94 (100.0)
ALD	127 (46.2)	26 (9.5)	39 (14.2)	26 (9.5)	57 (20.7)	275 (100.0)
AIH	28 (28.9)	18 (18.6)	21 (21.6)	10 (10.3)	20 (20.6)	97 (100.0)
Total	4526 (48.4)	1423 (15.2)	1710 (18.3)	721 (7.7)	965 (10.3)	9345 (100.0)

NAFLD: Nonalcoholic fatty liver disease; HCV: Hepatitis C virus; HBV: Hepatitis B virus; DILI: Drug-induced liver injury; PSC/PBC: Primary sclerosing cholangitis and primary biliary cirrhosis; ALD: Alcoholic liver disease; AIH: Autoimmune hepatitis.

(N=7659, 81.9%). Independent variables (age, gender, and etiology) were also transformed into dichotomous/polychotomous variables for the analysis. Patients ≤55 years are categorized as age group 1 (N=6773, 72.5%) and patients >55 years as age group 2 (N=2572, 27.5%). Age group 1, male sex, and NAFLD etiology were used as reference categories for analysis. After adjusting for sex and CLD etiology, patients in the older age group had odds of having advanced liver fibrosis that was 2.908 times that of patients with younger age (CI: 2.597–3.256, p<0.001). After adjusting for age and sex, patients with HCV, ALD, and AIH had odds of having advanced fibrosis that was 2.582 (CI=2.168–3.075, p<0.001), 2.019 (CI=1.524–2.674, p<0.001), and 2.138 (CI=1.360–3.660, p<0.001) times that of patients with NAFLD, respectively. Patients with HBV had a decreased odds for developing advanced liver fibrosis by 20% compared to patients with NAFLD (OR=0.800; CI=2.168–3.075, p<0.001) (Table 7).

Discussion

In this retrospective cross-sectional study, the data of 9345 patients were analyzed. To the best of our knowledge, this was the first single-center study investigating the epidemiology of CLD in Turkiye using FibroScan®.

NAFLD was the etiology with the highest prevalence, affecting nearly half of the study population. Given that NAFLD affects the majority of the population,[6] examining each patient with FibroScan® is neither possible nor cost-effective. A stepwise approach with a blood-based panel followed by FibroScan is recommended to reduce unnecessary liver biopsies.[17,18] NAFLD is a multisystemic disease. Therefore, collaboration with primary care and endocrinology is a very important step in disease management.

Nearly 50% increase in NASH and liver-related mortality and morbidity is expected by 2030.[19,20] In our previous single-center biopsy-proven NAFLD study, we showed a similar tendency.[5] NAFLD is also highly prevalent among young adults, which would increase the burden of the disease in the upcoming years.[20,21] NAFLD constitutes a global public health issue with its increasing prevalence and severity through the years. Poor glycemic control and insulin resistance are associated with an increased risk of advanced fibrosis for NAFLD patients.[22] NAFLD patients with T2DM had a significantly higher number of advanced fibrosis compared to those without T2DM in this study. Since NAFLD patients with T2DM constitute a vulnerable group for having advanced fibrosis, screening for advanced fibrosis in this group is recommended.[17]

Table 7. Logistic regression analysis for developing advanced liver fibrosis

	OR	95% CI		p
		Lower	Upper	
Age [younger age group (ref.)]	2.908	2.597	3.256	<0.001
Sex [male (ref.)]	0.998	0.891	1.118	0.972
NAFLD (ref.)				
HCV	2.582	2.168	3.075	<0.001
HBV	0.800	0.702	0.911	<0.001
Metabolic liver diseases	1.893	0.912	3.928	0.087
DILI	0.955	0.630	1.447	0.826
Cholestatic liver diseases	1.392	0.840	2.307	0.200
ALD	2.019	1.524	2.674	<0.001
AIH	2.138	1.360	3.660	<0.001

Variables included in the model: advanced fibrosis, gender, age, and CLD etiology. OR: Odds ratio; CI: Confidence interval; NAFLD: Nonalcoholic fatty liver disease; HCV: Hepatitis C virus; HBV: Hepatitis B virus; DILI: Drug-induced liver injury; PSC/PBC: Primary sclerosing cholangitis and primary biliary cirrhosis; ALD: Alcoholic liver disease; AIH: Autoimmune hepatitis.

Similarly, in our logistic regression analysis, patients with HBV had lower odds of advanced fibrosis compared to our NAFLD population, which indicates the significant burden of NAFLD.

FibroScan® is an accurate, noninvasive diagnostic method for hepatic steatosis and fibrosis.[23–26] It is more sensitive for detecting lower amounts of hepatic steatosis compared to ultrasonography.[27] XL probe emerged as a useful tool for obese individuals to reduce diagnostic inaccuracies.[28] In this study, we reached FibroScan exam reliability of 97.25% and a measurement error rate of 2.75%. The same operator performed the exams and investigated the feasibility of FibroScan® for obese patients in another study and found a measurement error rate of 3%.[29] Similar studies report measurement error rates of 5%–10%, which are well above the measurement error rate in our study. Highly reliable results in this study were derived from more than 30 000 examinations performed to date by a highly experienced single operator. Having one operator perform the measurements increases the reproducibility of results and decreases variation between measurements. BMI > 30 kg/m² is recognized as a significant drawback for obtaining reliable FibroScan results.[29] We were able to collect only a limited number of BMI data of the patients due to time constraints. Therefore, we could not extrapolate whether high BMI and LSM failure were significantly correlated.

Our results showed a decline of 89.91% of HCV patient referrals for FibroScan from 2013 to 2021. The epidemiologic transition from viral hepatitis to NAFLD is associated with growing metabolic disturbances.[8,30–32] Same transition was observed in Lebanon,[33] India,[34–36] and Mexico.[37] Comparable to the results of our study, the study from Lebanon reported that NAFLD was the leading etiology (58.3%), followed by HBV (11.1%) and HCV (7.7%). Studies from India show that HBV is the most common CLD etiology, but NAFLD has recently surpassed HBV. The shift from HCV to NAFLD was reported by a study from Mexico. The decline in HCV may have been impacted by (1) highly successful antiviral treatment, (2) routine screening tests since 1992 before blood transfusions, and (3) general population's increased awareness about transmission and prevention.[38–40] A cohort study surveyed the US United Network for Organ Sharing database during 2014–2019 for liver disease etiologies among liver transplant candidates. HCV prevalence was in decline, and NASH and ALD were the most common etiologies of CLD among transplant candidates.[41] Studies from Italy also reported a declining HCV prevalence.[42–44] Current evidence from Turkiye shows a decline of 35% in HCV infection.[45] Despite the promising decline in HCV prevalence, the highest ratio of patients with advanced fibrosis was found in the HCV group in this study. A study investigating the cost-effectiveness of early treatment of HCV based on liver fibrosis stage in a treatment-naive population suggests that treating patients with HCV as early as any level of fibrosis is detected to be the most cost-effective approach.[46] The decreasing number of FibroScan referrals for patients with HCV is promising; efforts should be made to detect and treat the disease early for the best outcomes.

The database used in our study included retrospectively recorded patient information. There were limited data on factors predicting clinical progression. Waist circumference, BMI, laboratory data, liver biopsy, and patients' comorbidity data saved in text format were not matched with our main data. Retrieving such information for 9345 patients was not possible due to time limitations.

In line with the growing obesity pandemic, NAFLD represents a significant number of patients with CLD. Physicians should be aware of the epidemiological characteristics of CLD to reduce unnecessary laboratory examinations and referrals. The presence of NAFLD should be suspected especially in patients with metabolic risk factors such as central obesity, T2DM, dyslipidemia, and metabolic syndrome. Referral of those patients at higher risk for developing NAFLD-related complications should be considered. National and international strategies to prevent the transmission of communicable diseases have proven to be powerful. However, there is still a long way to go in eradicating HBV and HCV. Providing health education, interrupting transmission routes, ensuring equitable access to vaccination, and testing and treatment are of utmost importance in achieving this aim.

Ethics Committee Approval: The Marmara University School of Medicine Clinical Research Ethics Committee granted approval for this study (date: 05.11.2021, number: 09.2021.1245).

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