Changes in the Etiology of Chronic Liver Disease by Referral to a Fibroscan Center: Rising Prevalence of the Non-Alcoholic Fatty Liver Disease

Running head: Etiology of chronic liver disease

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Abstract

Background and Aim: Chronic liver disease (CLD) is a leading cause of morbidity and mortality worldwide with 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 9,345 patients, 4,946 (52.9%) were male, and median age was 48 [18-88]. Non-alcoholic fatty liver disease (NAFLD) was the most common indication (N= 4,768, 51.02%) followed by hepatitis B (N=3,194, 34.18%) and hepatitis C (N=707, 7.57%). Adjusting for age, sex, 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), 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 non-alcoholic fatty liver disease (NAFLD) are the main contributors to 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 Turkey, the epidemiological transition of CLD has been facilitated by adoption of healthcare policies concerning communicable diseases, on the other hand, 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 Turkey revealed NAFLD prevalence of 51% by ultrasonography among patients who presented to the gastroenterology clinics with dyspepsia (6). This was not a surprising finding, since Turkey is the most obese country in Europe with an obesity prevalence of 32% (7). Similarly, another multi-centric data of apparently healthy subjects at routine check-up 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 Turkey. However, a shift to NAFLD in the near future is inevitable (4).

The efforts for defining the spectrum of CLD in Turkey notwithstanding (4), present data are limited and sparse. In this study, we aimed to describe the distribution of CLD etiologies and

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associated Fibroscan parameters (controlled attenuation parameter (CAP) and liver stiffness measurement (LSM)) among patients referred to our tertiary care center for Fibroscan examinations.

Material and methods

Patients

This is a retrospective analysis of 9,345 patients with various CLD etiologies, and 11,688 FibroScan® examinations conducted in XX Institute of XX 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, liver stiffness measurement (LSM) (kPa), the interquartile range of measurements (IQR), IQR/median for LSM, and controlled attenuation parameter (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 (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 <18 years at initial referral to Fibroscan examination, use of small size probe, having non-CLD indications (psoriasis, T2DM, isolated liver enzyme elevations, inflammatory bowel disease, hepatosplenomegaly, having a bariatric surgery, etc.) as the cause of referral, absent steatosis measurements, performed examinations other than by XX were exclusion criteria. A total of 4,465 (32.33%) patients, and 6,077 measurements (34.21%) were excluded from the final analysis. The exclusion process is shown in **Figure 1**.

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After the exclusion criteria were applied, 9,345 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 were matching, and matching cases were sorted by the Fibroscan examination dates.

Fibroscan examinations

A single experienced operator, XX, performed the FibroScan® during outpatient visits. All measurements were performed with FibroScan® 502 (Echosens, France). All the examinations were started with the M probe (3.5 Hz frequency). Prompted by the automatic probe selection tool, the probe was switched to XL (2.5 Hz frequency) automatically. An attempt was made to obtain at least 10 valid measurements. Median value of these measurements was recorded as LSM, and the IQR of the measurements were 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 cut-off values for CAP and LSM were derived from the literature. Those cut-off values were as follows: 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 and 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).

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Statistical analysis

Patient characteristics and the FibroScan® results were summarized using descriptive statistics. Distribution of variables was evaluated by the Kolmogorov-Smirnov normality test. Normally distributed data were presented as mean±standard deviation (SD), non-normally 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 Chi-Square 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.

Ethics

This study was approved by the XX University Medical School Ethics Committee (Protocol number: 09.2021.1245, approval date: 05/11/2021). Due to the retrospective nature of the study, the informed consent was waived. The study was in adherence to the principles of the Declaration of Helsinki.

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Results

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

Two hundred and nighty (55.77%) out of 520 were unreliable because of failing the 10 valid measurement criteria (94 males (32.4%), mean age of 52 ± 14 years, mean body mass index (BMI): 38 ± 9 kg/m2). Two hundred and nighty eight patients (57.31%) were excluded due to IQR/median > 30% (109 males (36.6%), mean age= 52 ± 17 years, mean BMI: 35.9 ± 8.2 kg/m2). Sixty eight (13.08%) were excluded for having both less than 10 valid measurements and IQR/median >30%.

Out of 9,345 patients in the study population, 6,685 (71.5%) patients were examined with M probe, and 2,660 (28.5%) with XL probe**.** In the final analysis, 4,946 (52.9%) were male. Median age was 48 [18-88] years. 1,815 (19.4%) patients were young adults (18-35 years), 4,958 (53.1%) were middle-aged (36-55 years), and 2,572 (27.5%) were older-aged (over 55 years) **(Table 2).** Mean LSM value was 8.34±7.97 kPa for females, and 8.65±8.77 kPa for males without significance (p=0.077). 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. Mean value of LSM was significantly different between younger and middle age 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= 4,768, 51.02%), followed by HBV (N=3,194, 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

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(41, 0.44%). 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. 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.

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 Table 5 and 6. Overall, 2,453 (26.2%) of patients had no steatosis (S0; CAP < 238 db/m), and 4,526 (48.4%) had no fibrosis (F0; ≤ 6.0kPa) at baseline. Prevalence of patients with grade 0, 1, 2 and 3 steatosis were 26.2% (N=2,453, 11.0% (N=1,032), 16.2% (N=1,516), and 46.6% (N=4,344) 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). Prevalence of patients with stage 0, 1, 2, 3, and 4 fibrosis were 48.4% (N=4,526), 15.2% (N=1,423), 18.3% (N=1,710), 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) were highest in 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 presence of advanced fibrosis (stage 3-4) (N=1,686, 18.1%), or no advanced fibrosis (N=7,659, 81.9%). Independent variables (age, gender, etiology) were also

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transformed into dichotomous/polychomotous variables for the analysis. Patients ≤ 55 years are categorized as age group 1 (N= 6,773, 72.5%), and patients >55 years as age group 2 (N=2,572, 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 older age group had odds of having advanced liver fibrosis that was 2.908 times 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 were 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 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).**

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Discussion

In this retrospective cross-sectional study, data of 9,345 patients were analyzed. To the best of our knowledge, this was the first single-center study investigating the epidemiology of CLD in Turkey 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 multi-systemic disease. Therefore, collaboration with primary care and endocrinology is a very important step in the 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 of advanced fibrosis in this group is recommended (17). 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.

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FibroScan® is an accurate, non-invasive 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 a Fibroscan exam reliability of 97.25%, measurement error rate of 2.75%. The same operator performed the exams and investigated 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 derived from more than 30,000 examinations performed to date by the highly experienced single operator in this study. Having one operator perform the measurements increases 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 by 89.91% of HCV patient referral for Fibroscan from 2013 to 2021. 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%). The studies from India show that HBV is the most common CLD etiology, but NAFLD has recently surpassed HBV. 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, 3) general population's increased awareness

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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, 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 Turkey shows a decline by 35% in HCV infection (45). The promising decline in HCV prevalence notwithstanding, 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 is the most cost effective approach (46). Decreasing number of Fibroscan referrals for patients with HCV is promising; efforts should be made to detect and treat the disease early for best outcomes.

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 were saved as text format were not matched to our main data. Retrieving such information for 9,345 was not possible due to time limitations.

In line with the growing obesity pandemics, 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. Presence of NAFLD should be suspected especially in patients with metabolic risk factors such as central obesity, T2DM, dyslipidemia, metabolic syndrome. Referral of those patients at higher risk for developing NAFLD related complications should be considered. National and international strategies to prevent transmission of communicable diseases have proven to be powerful. However, there is

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still a long way to go for eradicating HBV and HCV. Providing health education, interrupting transmission routes, ensuring equitable access to vaccination, testing and treatment are of utmost importance to achieve this aim.

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Tables

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	1,038
2016	1,103	1,259
2017	1,485	1,799
2018	1,650	2,017
2019	1,522	2,020
2020	936	1,362
2021	829	1,124
Total	**9,345**	**11,688**

Uncorrected Proof

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

Category	Median [Minimum-Maximum]
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	6,685 (71.5)
XL	2,660 (28.5)
Category	**Mean ± SD**
IQR/Med (%)	14.36 ± 6.949
Exam Duration	102.56 ± 63.97
Age Group	**N (%)**
18-35	1,815 (19.4)
36-55	4,958 (53.1)
56-88	2,572 (27.5)
Median age [minimum-maximum]	48 [18-88]
Sex	**N (%)**
Male	4,946 (52.9)
Female	4,399 (47.1)

Abbreviations: IQR/med, interquartile range/median

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Table 3: Distribution of the chronic liver disease etiology

Etiology	Total N (%)
NAFLD	4,768 (51.02)
HCV	707 (7.57)
HBV	3,194 (34.18)
Metabolic liver diseases	41 (0.44)
DILI	169 (1.81)
PSC/PBC	94 (1.0)
ALD	275 (2.94)
AIH	97 (1.04)
Total	**9,345 (100)**

Abbreviations: NAFLD, non-alcoholic fatty liver disease; HCV, hepatitis C virus; HBV, hepatitis B virus, DILI; drug induced liver injury, PSC/PBC; primary biliary cholangitis and primary biliary cirrhosis, ALD; alcoholic liver disease

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

	Years		
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

Abbreviations: NAFLD, non-alcoholic fatty liver disease; HCV, hepatitis C virus; HBV, hepatitis B virus, DILI; drug induced liver injury, PSC/PBC; primary biliary cholangitis and primary biliary cirrhosis, ALD; alcoholic liver disease

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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)

Abbreviations: NAFLD, non-alcoholic fatty liver disease; HCV, hepatitis C virus; HBV, hepatitis B virus, DILI; drug induced liver injury, PSC/PBC; primary biliary cholangitis and primary biliary cirrhosis, ALD; alcoholic liver disease

Uncorrected Proof

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)

Abbreviations: NAFLD, non-alcoholic fatty liver disease; HCV, hepatitis C virus; HBV, hepatitis B virus, DILI; drug induced liver injury, PSC/PBC; primary biliary cholangitis and primary biliary cirrhosis, ALD; alcoholic liver disease

Uncorrected Proof

Table 7. Logistic regression analysis for developing advanced liver fibrosis

	OR	95% CI		P-value
		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, CLD etiology				

Abbreviations: NAFLD, non-alcoholic fatty liver disease; HCV, hepatitis C virus; HBV, hepatitis B virus, DILI; drug induced liver injury, PSC/PBC; primary biliary cholangitis and primary biliary cirrhosis, ALD; alcoholic liver disease

Figure legend

Figure 1. Exclusion criteria

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