Journal of Clinical and Translational Hepatology **2023** vol. 11(6) | 1377–1386
DOI: 10.14218/JCTH.2023.00117

Original Article

A Cross-sectional Real-life Study of the Prevalence, Severity, and Determinants of Metabolic Dysfunction-associated Fatty Liver Disease in Type 2 Diabetes Patients

Quentin Binet[1*], Audrey Loumaye[2], Michel P Hermans[2] and Nicolas Lanthier[1]

[1]*Service d'Hépato-Gastroentérologie, Cliniques universitaires Saint-Luc, UCLouvain, Brussels, Belgium;* [2]*Service d'Endocrinologie et Nutrition, Cliniques universitaires Saint-Luc, UCLouvain, Brussels, Belgium*

Received: 14 March 2023 | **Revised:** 23 April 2023 | **Accepted:** 25 May 2023 | **Published online:** 30 June 2023

Abstract

Background and Aims: Most data on liver assessment in type 2 diabetes mellitus (T2DM) patients are from retrospective cohorts with selection bias. We aimed at appraising the feasibility, results, and benefits of an outpatient systematic noninvasive screening for metabolic dysfunction-associated fatty liver disease (MAFLD) severity and determinants in T2DM patients. ***Methods:*** We conducted a 50-week cross-sectional study enrolling adult T2DM outpatients from a diabetes clinic. An algorithm based on guidelines was applied using simple bioclinical scores and, if applicable, ultrasound and/or elastometry. ***Results:*** Two hundred and thirteen patients were included. Mean age and body mass index were 62 years and 31 kg/m^2 and 29% of patients had abnormal transaminase levels. The acceptance rate of additional liver examinations was 92%. The prevalence of MAFLD, advanced fibrosis and cirrhosis was 87%, 11%, and 4%, respectively. More than half of the cases of advanced fibrosis had not been suspected and were detected by this screening. MAFLD was associated with poor glycemic control, elevated transaminases, low HDL-C and the absence of peripheral arterial disease. Advanced fibrosis was linked to high waist circumference and excessive alcohol consumption, which should be interpreted with caution owing to the small number of patients reporting excessive consumption. ***Conclusions:*** Simple bioclinical tools allowed routine triage of T2DM patients for MAFLD severity, with high adherence of high-risk patients to subsequent noninvasive exams.

Citation of this article: Binet Q, Loumaye A, Hermans MP, Lanthier N. A Cross-sectional Real-life Study of the Prevalence, Severity, and Determinants of Metabolic Dysfunction-associated Fatty Liver Disease in Type 2 Diabetes Patients. J Clin Transl Hepatol 2023;11(6):1377–1386. doi: 10.14218/JCTH.2023.00117.

Keywords: Noninvasive tests; MAFLD; Outpatient; Steatosis; Fibrosis.

Abbreviations: ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; CKD, chronic kidney disease; FIB-4, fibrosis-4 index; FLI, fatty liver index; GGT, gamma-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LSM, liver stiffness measurement; MAFLD, metabolic dysfunction-associated fatty liver disease; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score; NITs, noninvasive tests; T2DM, type 2 diabetes mellitus; VCTE, vibration-controlled transient elastography.

[*]**Correspondence to:** Quentin Binet, Service d'Hépato-Gastroentérologie, Cliniques universitaires Saint-Luc, 10 Avenue Hippocrate, 1200 Bruxelles, Belgium. ORCID: https://orcid.org/0000-0003-3299-2385. Tel: +32-2-7642828, Fax: +32-2-7648927, E-mail: quentin.binet@saintluc.uclouvain.be

Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD) refers to steatosis occurring in the setting of a metabolic risk condition, such as type 2 diabetes mellitus (T2DM),[1,2] and is now recognized as the most prevalent chronic liver disease worldwide.[3] T2DM is an important risk factor for MAFLD and vice-versa, and seems to accelerate the progression of liver disease.[4–8] Despite the high prevalence and serious clinical implications of MAFLD in T2DM patients, it is often overlooked in clinical practice.[4] As MAFLD entails considerable (extra-)hepatic morbidity and mortality, there is a need for increased awareness among all stakeholders (primary care physicians, specialists, and health policy-makers) for adding MAFLD as a frequent end-organ comorbidity of T2DM, along with micro- and macrovascular complications.[4,9]

EASL-EASD-EASO guidelines recommend screening high-risk patients for the presence of MAFLD and assessing the presence of advanced fibrosis using systematic calculation of noninvasive tests (NITs) for steatosis and fibrosis detection.[4,9,10] These tests use readily available bioclinical parameters and can therefore be routinely used by general practitioners and diabetologists to detect patients who might benefit from further investigation. In the case of indeterminate results for fibrosis or suspected advanced fibrosis, patients should undergo one-dimensional ultrasound vibration-controlled transient elastography (VCTE) (Fibroscan; Echosens, Paris, France) for confirmation, and from abdominal Doppler ultrasound to assess liver surface, parenchyma, and vasculature. In the setting of elevated liver enzymes, other causes of liver disease should be ruled out. Few patients would eventually undergo liver biopsy, which remains the gold standard for MAFLD staging.

To demonstrate the feasibility and accuracy of such a systematic approach, there is a crucial need for prospective studies of MAFLD screening in high-risk patients such as those with T2DM. To date, few studies (mainly retrospective) are available,[11–16] and most were focused on nonalcoholic fatty liver disease (NAFLD), thus excluding patients with significant

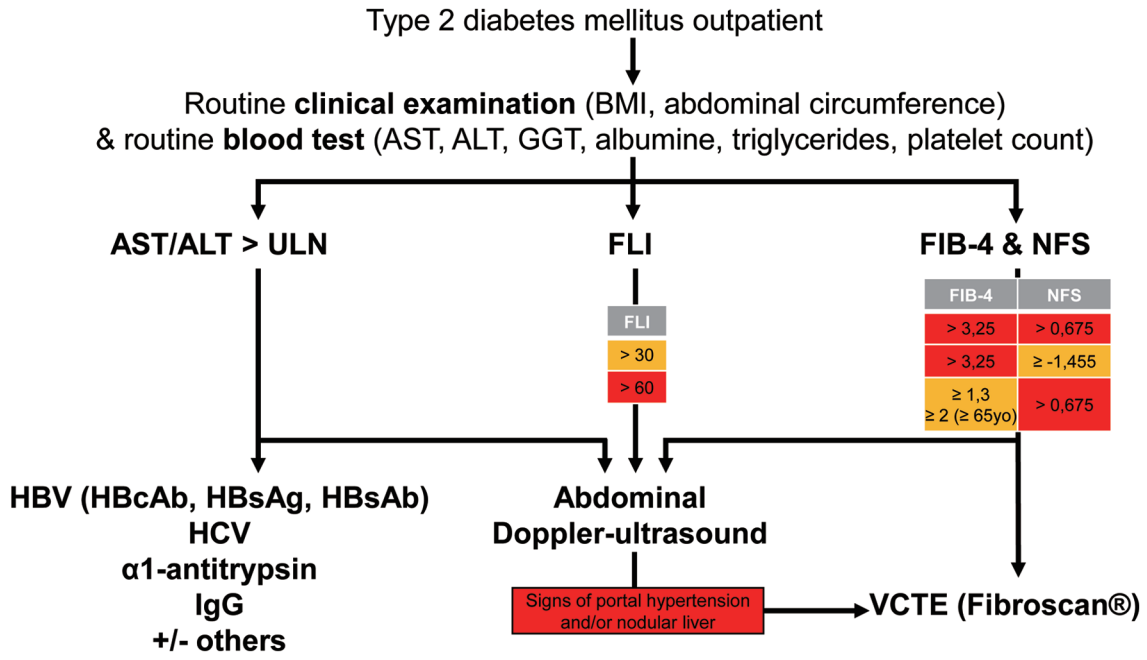

Fig. 1. Study flow chart. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, fibrosis-4 index; GGT, gamma-glutamyl transferase; HBcAb, hepatitis B core antibody; HBsAb & HBsAg, hepatitis B surface antibody & antigen; HBV, hepatitis B virus; IgG, immunoglobulin G dosage; FLI, fatty liver index; NFS, nonalcoholic fatty liver disease fibrosis score; ULN, local laboratory upper limit of normal value; VCTE, vibration-controlled transient elastrography.

alcohol consumption. That may not represent real-life practice. We therefore carried out a cross-sectional study targeting consecutive patients attending diabetes clinic for MAFLD and advanced fibrosis screening on the basis of NITs. Depending on individual results, this initial assessment was followed by abdominal Doppler ultrasound and/or VCTE in high-risk patients.

Methods

Type of study

We conducted a monocentric (tertiary center), cross-sectional study including T2DM outpatients attending the diabetes consultation of the Cliniques universitaires Saint-Luc (Brussels) between June 2021 and May 2022. The study protocol (No. B4032021000065) was in line with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board and ethics committee. All included patients provided written informed consent.

Inclusion and exclusion criteria

In the setting of diabetology consultations, ambulatory patients with T2DM, over the age of 18 years, able to read and understand the information letter, and benefiting from social security in health care were eligible. Patients under supervision or curatorship, deprived of liberty, and those with intercurrent disease with an estimated life expectancy of <6 months and/or inability to present to follow-up consultations or tests were excluded. Of note, to provide reliable results on the prevalence of the condition, patients who had previously been diagnosed with MAFLD were not excluded from the study. Patients with excessive alcohol consumption or other causes of secondary steatosis were also not excluded.

Study design

Informed consent forms were systematically collected during outpatient visits at the diabetes clinic over an enrollment period of 50 weeks. All included patients benefited from an initial bioclinical screening to calculate validated noninvasive scores for steatosis [fatty liver index (FLI),[17] hepatic steatosis index,[18] and NAFLD ridge score],[19] and fibrosis [NAFLD fibrosis score (NFS),[20] fibrosis-4 index (FIB-4),[21,22] and Hepamet fibrosis score],[23] aspartate aminotransferase (AST)-to-platelet ratio index (APRI), and isolated AST.[24] Based on national and international guidelines,[9,10] in those with positive screening for MAFLD using FLI or advanced liver fibrosis by NFS and FIB-4, the two most validated scores in the literature, patients were invited to undergo subsequent diagnostic tests such as abdominal Doppler ultrasound and/or VCTE. Patients with elevated transaminase levels were further assessed to at least exclude viral hepatitis B and C, alpha-1-antitrypsin deficiency, and biological markers of autoimmune hepatitis, i.e. elevated immunoglobulin G (Fig. 1). Further management was clinically guided according to current standards of care.

Analytical assessment

An interview on disease status, personal history of previous diseases, smoking status, alcohol consumption (units/week), and pharmacological therapy was collected on a routine basis. MAFLD was defined as evidence of liver steatosis by the positivity of one score based on laboratory and anthropometric parameters (i.e., FLI) and/or imaging (i.e., liver ultrasound), in the setting of a metabolic risk condition (i.e., T2DM in this study). MAFLD diagnosis is therefore based on positive criteria, as opposed to former NAFLD which, as the name suggests, requires the exclusion of excessive alcohol consumption and other causes of secondary steatosis.[2]

Diabetes was diagnosed by American Diabetes Association criteria.[25] Macroangiopathy or established cardiovascular disease was defined as a composite of coronary artery disease (acute coronary syndromes, revascularization procedures,

or stable angina), cerebrovascular disease (previous stroke, transient ischemic attack, or >35% carotid artery stenosis) and peripheral arterial disease requiring revascularization. Microangiopathy was defined as the presence of diabetic kidney disease, diabetic retinopathy, or diabetic neuropathy. Diabetic kidney disease was defined as chronic kidney disease (CKD) stage ≥3 (defined as a CKD-EPI estimated glomerular filtration rate of <60 mL/min/1.73 m^2) and/or the presence of an altered albumin excretion rate defined as a urine albumin / creatinine ratio of >30 mg/g. Diabetic retinopathy was diagnosed by a dilated eye exam performed by an ophthalmologist.

Height (cm), body weight (kg), waist circumference (cm), systolic and diastolic blood pressure (mmHg) at rest were obtained during the diabetes clinic consultation. Body mass index (BMI) was reported as kg/m^2. Hypertension was defined as taking antihypertensive treatment and/or by a repeated resting systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Plasma/serum creatinine, AST, alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, platelets, white blood cells, and albumin were measured at local laboratories. Low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald's formula. Dyslipidemia was defined as taking lipid-lowering drugs and/or as an LDL-C≥70 mg/dL and/or a non-LDL-C≥100 mg/dL. VCTE quality criteria included a minimum of 10 measurements to obtain the median valid liver stiffness measurement (LSM) and interquartile range (IQR), an IQR / median LSM ratio of ≤0.3 × LSM for values >7 kPa, and a success rate of ≥60% in obtaining the 10 measurements.[26,27] Liver stiffness cutoffs using medium (and extra-large) probes were: F0–F1<7.8 (6.4) kPa; F2 [7.8 (6.4)–12.5 (9.3)] kPa; F3 [12.5 (9.3)–22.3 (16.0)] kPa; and F4≥22.3 (16.0) kPa.[28]

Study endpoints

The primary endpoint was to assess the feasibility of outpatient systematic screening for MAFLD in T2DM patients. To do so, we determined the respective prevalence of steatosis and severe fibrosis using simple noninvasive tools. We estimated patient adherence to more accurate fibrosis screening by VCTE if indicated by bioclinical testing. Secondary endpoints were risk factors and clinical and/or biological criteria associated with steatosis or advanced fibrosis in this T2DM population.

Statistical analysis

The statistical analysis was performed with SPSS v29.0 (IBM Corp., Armonk, NY, USA). Continuous variables were reported as means±standard deviation (SD) and compared using the student unpaired *t*-test; or as medians and IQR and compared using the Wilcoxon rank-sum test. Categorical variables were reported as numbers and percentages and were compared using the chi-square test or Fisher's exact test as appropriate. Logistic regression models were used to identify factors independently associated with MAFLD or advanced fibrosis. *p*-values ≤0.05 were considered significant.

Results

Study population

The baseline characteristics of the 213 T2DM patients who were included are shown in Table 1. Their mean age was 62 years and 67.1% were men. The vast majority of patients were overweight or obese (mean BMI 31.3 kg/m^2), three men (1.4%) reported an alcohol consumption >30 g/day, and no women reported a consumption of >20 g/day. Only 33 patients (15.5%) had been previously evaluated for MAFLD in a hepatology consultation.

NITs for steatosis

A total of 77.0 % of the patients were classified in the high-risk category for steatosis (FLI>60), 18.2% in the indeterminate risk category (30≤FLI≤60), while only 4.8 % were classified as low-risk (FLI<30). When using hepatic steatosis index and NAFLD ridge score, an even lower proportion of patients were ascribed to the low-risk group (Fig. 2).

Abdominal Doppler ultrasound

Doppler ultrasound was offered to patients with an intermediate or high FLI. Eighteen patients declined and one patient with a high FLI died from cardiac arrest following food aspiration before further liver assessment. When evaluated by abdominal Doppler ultrasound, the hepato-renal echogenicity gradient was increased in 80.6% of patients at high or indeterminate risk (an FLI of >30) and in 84.0% of high-risk patients (an FLI of >60). Using a sequential combination of FLI and ultrasound (if the FLI was >30), a total of 185 patients (86.9%) were diagnosed with MAFLD. Twenty-two patients had dysmorphic liver and/or signs of portal hypertension and were offered a further assessment by VCTE. Two patients were suspected to have a hemangioma, which was confirmed by magnetic resonance imaging (MRI). None of the patients presented with liver lesions compatible with hepatocellular carcinoma.

NITs for fibrosis

In contrast to steatosis, the prevalence of scores consistent with advanced fibrosis varied greatly, ranging from 3.8% (FIB-4), 4.6% (Hepamet fibrosis score), and 19.0% (NFS). Whereas NFS seemingly classified a majority of T2DM patients in the intermediate risk group (59.0 %), the FIB-4 with age-adjusted cutoffs classified most patients in the low-risk group (75.1%; Fig. 2). Using sequential FLI and the combination of NFS and FIB-4 with age-adjusted cutoffs as recommended by the guidelines led to referring 29 patients (13.6%) who were offered further evaluation by VCTE.

VCTE

VCTE was offered to patients with dysmorphic liver features or signs of portal hypertension on abdominal Doppler ultrasound, as well as to patients with positive fibrosis screening by both NFS and FIB-4. Of 43 patients, three declined and one died from cardiac arrest after food aspiration and before VCTE evaluation. The acceptance rate for this additional testing was therefore very high (92.3%). Of 39 VCTE measurements, 37 met the quality criteria. In that select population, the mean controlled attenuation parameter was 325±47 dB/m and the LSM was 17.0±12.8 kPa. The spread of the elasticity module results is shown in Figure 3. Overall, 24 patients were classified as having advanced fibrosis, nine of whom were diagnosed with cirrhosis, i.e. F4 and dysmorphic liver or signs of portal hypertension. Of the 24 patients with VCTE-confirmed advanced fibrosis, 13 (54.2%) had never previously been evaluated by a hepatologist and therefore had newly diagnosed MAFLD that was already at an advanced stage.

Assessment for other causes of elevated transaminases

Sixty-one patients (28.6%) had elevated transaminases (local reference range, AST>36 and/or ALT>35 UI/L). Besides

Table 1. Patients' characteristics for the total population, by MAFLD status and by advanced fibrosis status

Population variable	Total (*n*=213)	No MAFLD (*n*=28)	MAFLD (*n*=185)	*p*-value	No advanced fibrosis (*n*=189)	Advanced fibrosis (*n*=24)	*p*-value
Demographic							
Age in years, mean±SD	62±12	67±12	61±12	0.035	62±13	62±11	0.982
Female sex, n (%)	70 (32.9)	7 (25)	63 (34.1)	0.342	65 (34.4)	5 (20.8)	0.183
Weight in kg, mean±SD	91±18	77±12	93±18	<0.001	90±17	99±20	0.027
Height in cm, mean±SD	170±10	169±10	171±9	0.555	170±10	170±8	0.774
BMI in kg/m^2, mean±SD	31±5	27±3	32±5	<0.001	31±5	34±7	0.033
Waist circumference in cm, mean±SD	109±13	97±8	110±12	<0.001	108±12	116±14	0.004
Lifestyle, *n* (%)							
Alcohol consumption >30 g/d in M	3 (1.4)	0	3 (1.6)	0.497	1 (0.5)	2 (8.3)	0.002
Alcohol consumption >20 g/d in F	0	0	0		0	0	
Smoking history	81 (38.0)	11 (39.3)	73 (39.5)	0.700	70 (37.0)	14 (58.3)	0.079
History / comorbidities, *n* (%)							
Hypertension	146 (68.5)	15 (57.1)	130 (70.3)	0.163	128 (67.7)	18 (75.0)	0.470
Dyslipidemia	177 (83.1)	23 (82.1)	154 (83.2)	0.885	158 (83.6)	19 (79.2)	0.585
Coronary artery disease	41 (19.2)	7 (25.0)	34 (18.4)	0.408	37 (19.6)	4 (16.7)	0.733
Cerebrovascular disease	14 (6.6)	3 (10.7)	11 (5.9)	0.343	14 (7.4)	0	0.168
Peripheral arterial disease	17 (8.0)	5 (17.9)	12 (6.5)	0.039	15 (7.9)	2 (8.3)	0.946
Diabetic kidney disease	63 (29.6)	16 (57.1)	57 (70.3)	0.311	56 (29.6)	7 (29.2)	0.963
Chronic kidney disease, stage ≥3	35 (16.4)	16 (57.1)	29 (70.3)	0.444	33 (17.5)	2 (8.3)	0.256
Microalbuminuria, AER>30 mg/g creatinine	46 (21.6)	4 (14.3)	42 (22.7)	0.313	40 (21.2)	6 (25)	0.667
Diabetic retinopathy	23 (10.8)	4 (14.3)	19 (10.3)	0.478	19 (10.1)	4 (16.7)	0.330
Diabetic neuropathy	19 (8.9)	0	19 (10.3)	0.076	16 (8.5)	3 (12.5)	0.514
Sleep apnea syndrome	31 (14.6)	1 (3.6)	30 (16.2)	0.077	26 (13.8)	5 (20.8)	0.354
Bariatric surgery	8 (3.8)	1 (3.6)	7 (3.8)	0.952	6 (3.2)	2 (8.3)	0.213
Diabetes medications, *n* (%)							
Metformin	180 (84.5)	22 (78.6)	158 (85.4)	0.352	159 (84.1)	21 (87.5)	0.667
SGLT2-i	50 (23.5)	8 (28.6)	42 (22.7)	0.495	45 (23.8)	5 (20.8)	0.746
DPP4-i	26 (12.2)	4 (14.3)	130 (70.3)	0.718	26 (13.8)	0	0.052
GLP1-RA	43 (20.2)	2 (7.1)	41 (22.2)	0.065	35 (18.5)	8 (33.3)	0.089
Sulfonylurea	48 (22.5)	5 (17.9)	43 (23.2)	0.525	40 (21.2)	8 (33.3)	0.179
Glitazone	3 (1.4)	0	3 (1.6)	0.497	3 (1.6)	0	0.534

(continued)

Table 1. *(continued)*

Population variable	Total (*n*=213)	No MAFLD (*n*=28)	MAFLD (*n*=185)	*p*-value	No advanced fibrosis (*n*=189)	Advanced fibrosis (*n*=24)	*p*-value
Glinide	12 (5.6)	1 (3.6)	11 (5.9)	0.612	10 (5.3)	2 (8.3)	0.543
Insulin	90 (42.3)	15 (53.6)	75 (40.5)	0.193	80 (42.3)	10 (41.7)	0.951
Cardiovascular medications, *n* (%)							
ACE inhibitor / sartan	120 (56.3)	16 (57.1)	104 (56.2)	0.927	106 (56.1)	14 (58.3)	0.834
Thiazide / indapamide	53 (24.9)	4 (14.3)	47 (25.4)	0.650	48 (25.4)	5 (20.8)	0.626
Loop diuretic	13 (6.1)	2 (7.1)	11 (5.9)	0.811	11 (5.8)	2 (8.3)	0.633
Betablocker	60 (28.2)	4 (14.3)	54 (29.2)	0.395	54 (28.6)	6 (25.0)	0.714
Calcium channel blocker	41 (19.2)	2 (7.1)	39 (21.1)	0.081	38 (20.1)	3 (12.5)	0.373
Statin	153 (71.8)	20 (71.4)	133 (71.9)	0.959	136 (72.0)	17 (70.8)	0.908
Ezetimibe	44 (20.7)	3 (10.7)	41 (22.2)	0.163	39 (20.6)	5 (20.8)	0.982
Fibrate	34 (16.0)	1 (3.6)	33 (17.8)	0.055	28 (14.8)	6 (25.0)	0.199
Acetylsalicylic acid	82 (38.5)	14 (50.0)	68 (36.8)	0.180	76 (40.2)	6 (25.0)	0.149
Amiodarone	3 (1.4)	0	3 (1.6)	0.497	3 (1.6)	0	0.534
Biological, median (IQR)							
HbA1c as %	7.0 (1.4)	6.8 (0.9)	7.1 (1.5)	0.045	7.0 (1.3)	6.7 (1.8)	0.494
White blood cells/mm^3	7.20 (2.65)	6.54 (2.63)	7.23 (2.64)	0.137	7.22 (2.55)	6.38 (2.74)	0.218
Platelet count as × 10^3/mm^3	239 (91)	231 (54)	242 (93)	0.200	243 (88)	175 (69)	<0.001
Albumin in g/L	45 (4)	43 (5)	46 (4)	0.088	45 (4)	45 (7)	0.603
AST in U/L	22 (13)	19 (5)	23 (13)	0.001	21 (9)	43 (29)	<0.001
ALT in U/L	24 (18)	16 (8)	26 (20)	<0.001	22 (17)	35 (32)	<0.001
GGT in U/L	26 (33)	15 (7)	28 (33)	<0.001	24 (27)	70 (83)	<0.001
Total cholesterol in mg/dL	144 (59)	139 (49)	145 (60)	0.117	144 (58)	146 (56)	0.715
HDL-cholesterol in mg/dL	42 (16)	50 (20)	41 (15)	0.003	43 (16)	41 (18)	0.266
Triglycerides in mg/dL	136 (101)	91 (74)	138 (104)	<0.001	135 (95)	138 (147)	0.228

In this type 2 diabetes mellitus population, MAFLD was defined by a fatty liver index (FLI) >60 or >30 with an increased hepatorenal echogenicity gradient. Advanced fibrosis (F3–F4) was defined as a liver stiffness measurement ≥12.5 kPa (medium probe) or ≥9.3 kPa (extra-large probe). Results are means±SD, median (IQR), or number (%). Means were compared by *t*-tests. Medians were compared by Wilcoxon rank sum tests. Categorical variables were compared by chi-square or Fisher's exact tests. *p*-values <0.05 were significant. ACE, angiotensin-converting enzyme; AER, albumin excretion rate; ALT, alanine aminotransferase;

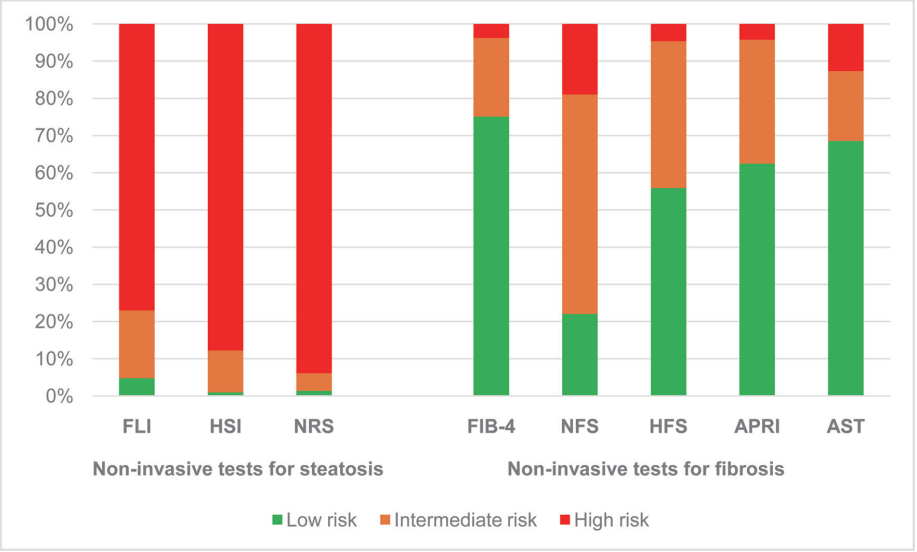

Fig. 2. Risk stratification for steatosis and fibrosis in type 2 diabetes mellitus patients based on various noninvasive tests. APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase with cutoffs of 26 and 40 IU/L;[24] FIB-4, fibrosis-4 index with age-adjusted cut-offs; FLI, fatty liver index; HFS, Hepamet fibrosis score; HSI, hepatic steatosis index; NFS, nonalcoholic fatty liver disease fibrosis score; NRS, nonalcoholic fatty liver disease ridge score.

two patients whose excessive alcohol consumption might underlie elevated liver tests, none of the patients were found to have liver conditions other than MAFLD. Two patients had slightly decreased serum alpha-1-antitrypsin levels, and were subsequently asked to undergo phenotype determination of the protein.

Association of MAFLD and/or advanced fibrosis with demographic, clinical, and biochemical characteristics

Besides waist circumference, BMI, triglycerides, and GGT, all used for FLI calculation and thus collinear variables, there was a significant association between MAFLD status and lower age, absence of peripheral arterial disease, glycemic control (HbA1c), transaminase levels, and low HDL-C (Table 1). In multivariable models adjusted for age and sex, high HbA1c, high transaminases, and low HDL-c remained linked to MAFLD. In multivariable models adjusted for age, sex, BMI, smoking status, hypertension, and dyslipidemia (factors known to be associated with vascular disease), peripheral arterial disease was associated with decreased odds of MAFLD [OR 0.197 (95% CI: 0.040–0.963), p=0.045; Table 2].

In addition to the parameters used for FIB-4 and NFS calculation (age, BMI, AST, ALT, platelet count, and albumin), there was a significant association between advanced fibrosis and excessive alcohol consumption (chi-square test, Table 1; univariate logistic regression, and multivariable regression adjusted for age and sex, Table 3). In multivariable models adjusted for age and sex, high waist circumference was also associated with increased odds of advanced fibrosis [OR 1.047 (95% CI: 1.011–1.084), p=0.010; Table 3].

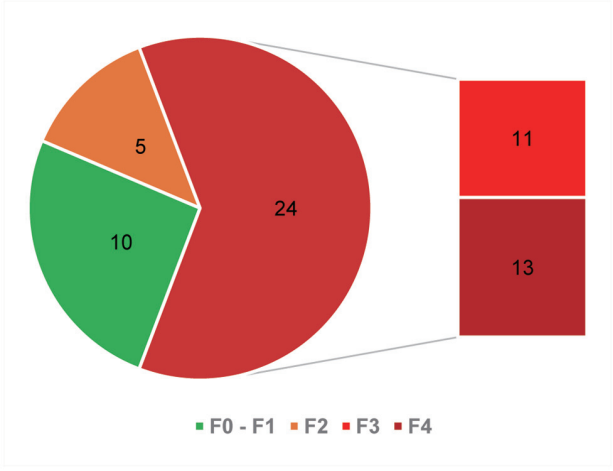

Fig. 3. Fibrosis stage based on liver stiffness measurements in type 2 diabetes mellitus patients at high risk of advanced fibrosis on the basis of abdominal Doppler ultrasound results and the combination of two noninvasive tests (FIB-4 and NFS). Liver stiffness cutoffs using the M (and XL) probes were: F0–F1<7.8 (6.4) kPa; F2 [7.8 (6.4)–12.5 (9.3)] kPa; F3 [12.5 (9.3)–22.3 (16.0)] kPa; and F4≥22.3 (16.0) kPa.[28] FIB-4, fibrosis-4 index with age-adjusted cutoffs; NFS, nonalcoholic fatty liver disease fibrosis score.

Discussion

Given the increasing prevalence of MAFLD, routine referral of all patients to specialized hepatologists is neither feasible nor sustainable. Clinicians are therefore challenged to identify a select target population at high risk of advanced MAFLD. Systematic screening with a simple algorithm of NITs including routine bioclinical parameters followed by readily available confirmatory imaging techniques such as Doppler ultrasound and/or VCTE, prospectively identified 86.9% of MAFLD, 11.3% of advanced fibrosis, and 4.2% cirrhosis patients in a population of 213 T2DM outpatients attending a diabetes clinic in a tertiary care center.

Our study is, to the best of our knowledge, the first to prospectively include consecutive outpatients with real-life use of NITs for systematic steatosis and fibrosis screening in a regular T2DM population. Few retrospective studies using NITs for steatosis and fibrosis assessment from T2DM population databases are available.[11–15] Limitations of those studies mainly include their retrospective design. Consequently noninvasive scores may not have been appropriately calcu-

Table 2. Logistic regression model comparing the prevalence of population variables with or without MAFLD

Population variable	MAFLD Odds ratio (95% CI)	*p*-value
Demographic and biochemical		
Age in years	0.961 (0.927–0.998)	0.037
Female sex, yes/no	1.549 (0.625–3.840)	0.345
Waist circumference in cm	1.134 (1.076–1.196)	<0.001
BMI in kg/m^2	1.406 (1.223–1.618)	<0.001
Obesity, BMI≥30 kg/m^2, yes/no	7.557 (2.748–20.785)	<0.001
Peripheral arterial disease, yes/no	0.319 (0.103–0.988)	0.048
HbA1c as %	1.534 (1.018–2.310)	0.041
AST in U/L	1.088 (1.020–1.161)	0.010
ALT in U/L	1.098 (1.040–1.159)	<0.001
GGT in U/L	1.062 (1.021–1.104)	0.003
HDL-C in mg/dL	0.955 (0.926–0.984)	0.003
Multivariable adjustment		
Age, sex-adjusted	0.963 (0.928–0.999)	0.042
Waist circumference, age- and sex-adjusted	1.164 (1.095–1.236)	<0.001
BMI, age- and sex-adjusted	1.384 (1.202–1.592)	<0.001
Obesity, age- and sex-adjusted	7.280 (2.628–20.164)	<0.001
Peripheral arterial disease, age-, sex-, BMI-, smoking history-, hypertension-, and dyslipidemia-adjusted	0.197 (0.040–0.963)	0.045
HbA1c, age- and sex-adjusted	1.557 (1.010–2.400)	0.045
AST, age- and sex-adjusted	1.085 (1.016–1.159)	0.015
ALT, age- and sex-adjusted	1.097 (1.037–1.161)	0.001
GGT, age- and sex-adjusted	1.059 (1.018–1.101)	0.005
HDL-C, age- and sex-adjusted	0.951 (0.922–0.981)	0.002

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; MAFLD, metabolic dysfunction-associated fatty liver disease. Level of significance, $p<0.05$.

lated in all patients owing to lack of crucial information (e.g., abdominal circumference for FLI) or nonconcomitant collection of anthropometric and biological parameters. Secondly, those studies did not systematically assess the presence of other etiologies of steatosis or elevated liver tests such as excessive alcohol consumption or other causes of liver disease (e.g., viral infection). Finally, intermediate or high-risk noninvasive scores did not lead to medical counseling or further testing (e.g., imaging studies or liver biopsy) as per the guidelines. Therefore, the acceptance and applicability of these measures were not recorded.

A recent prospective study by Ajmera *et al*.[16] assessed the prevalence of NAFLD, advanced fibrosis, and hepatocellular carcinoma in a population of 524 patients recruited in primary care or endocrinology clinics. The value of their study lies in the carrying out of MRI (proton density fat fraction, and elastography) in the vast majority of patients, which allowed for optimal noninvasive assessment of the degree of steatosis and fibrosis and for highlighting advanced fibrosis and even hepatocellular carcinoma in patients with low FIB-4 scores.[29] However, their study has some limitations including possible recruitment bias, limited real-life availability of MRI, questionable usefulness of hepatic fat quantification, and possible bias resulting from exclusion of patients with excessive alcohol consumption.[30]

Large retrospective studies reported similar positivity rates of various NITs for steatosis and therefore a prevalence of MAFLD similar to that in our population.[11–15] We confirmed the presence of hepatic steatosis in the majority of regular T2DM patients, which seems reasonable given the pathophysiology of these two interrelated comorbidities.[4] Overall, the prevalence of MAFLD is higher than that of T2DM in the general population, and insulin resistance measured with the gold standard euglycemic-hyperinsulinemic clamp, is already present in patients with steatosis prior to T2DM onset.[31] Mediators produced by the steatotic liver (hepatokines such as fetuin-A) may contribute to peripheral insulin resistance.[32,33] The role of insulin resistance in the worsening of steatosis following the onset of T2DM is also well described.[34]

As NITs would classify nearly all T2DM patients at high or intermediate risk for steatosis, with the caveat of missing a subgroup of patients with low BMI, abdominal circumference and/or triglycerides due to more severe liver disease (cirrhosis or hepatocellular carcinoma), one might rather skip the NITs for steatosis and go directly to performing Doppler ultrasonography. Despite its lower sensitivity versus NITs for detecting hepatic steatosis (defined as >5% macrovesicular steatosis) because the sonographic hepatorenal index does not always significantly increase in mild steatosis (5–10% liver fat),[9,35] liver ultrasound can yield invaluable additional information regarding the liver surface, parenchyma, and vasculature, alongside other abdominal organs of interest, in

Table 3. Logistic regression model comparing the prevalence of population variables with or without advanced fibrosis

Population variable	Advanced Fibrosis Odds ratio (95 % CI)	*p*-value
Demographic and biochemical		
Age in years	1.000 (0.966–1.034)	0.982
Female sex, yes/no	0.502 (0.179–1.406)	0.190
Waist circumference in cm	1.049 (1.014–1.086)	0.005
BMI in kg/m^2	1.118 (1.036–1.207)	0.004
Obesity, BMI≥30 kg/m^2, yes/no	2.559 (0.973–6.731)	0.057
Alcohol consumption in units/week	1.055 (0.995–1.119)	0.073
Excessive alcohol consumption, yes/no	17.091 (1.489–196.231)	0.023
Insulin, yes/no	0.973 (0.411–2.303)	0.951
Platelet count as ×10^3/mm^3	0.978 (0.969–0.987)	<0.001
AST in U/L	1.057 (1.031–1.083)	<0.001
ALT in U/L	1.020 (1.005–1.035)	0.009
GGT in U/L	1.015 (1.008–1.022)	<0.001
Multivariable adjustment		
Waist circumference, age- and sex-adjusted	1.047 (1.011–1.084)	0.010
BMI, age- and sex-adjusted	1.118 (1.035–1.208)	0.004
Obesity, age- and sex-adjusted	2.637 (0.994–6.992)	0.051
Alcohol consumption, age- and sex-adjusted	1.051 (0.992–1.114)	0.094
Excessive alcohol consumption, age- and sex-adjusted	16.646 (1.367–202.640)	0.027
Platelet count, age- and sex-adjusted	0.977 (0.968–0.987)	<0.001
AST, age- and sex-adjusted	1.061 (1.034–1.089)	<0.001
ALT, age- and sex-adjusted	1.024 (1.006–1.043)	0.009
GGT, age- and sex-adjusted	1.015 (1.008–1.023)	<0.001

Excessive alcohol consumption was defined as a mean >30 g/day in men and >20 g/day in women. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase. Level of significance, $p<0.05$.

particular the spleen and splenic vein.

On one hand, we found a statistically-significant association between MAFLD and poor glycemic control, elevated transaminases and low HDL-C, which is consistent with available literature.[36–40] We also found an association between MAFLD and absence of peripheral arterial disease. The latter is compatible with the paradoxical ocular protection of steatosis in T2DM patients,[41,42] as there is an established association between lower-extremity arterial disease and diabetic retinopathy.[43] Moreover, recent data from large cohorts indicate that patients with high visceral fat and low liver fat suffer from higher cardiovascular risk.[44] However, that is contrary to other previous reports.[45] A confounding factor for this association was the lower age of the MAFLD group, as shown by multivariable adjustments. Another confounding hypothesis was a more severe fibrosis level in patients without MAFLD, because the degree of steatosis may decrease with advanced fibrosis or cirrhosis,[46] but has been invalidated as neither FIB-4, NFS, nor Hepamet fibrosis score were significantly higher than in the MAFLD group. On the other hand, we did not confirm the association that previous retrospective studies reported between liver steatosis and cardiovascular disease,[47,48] (micro)albuminuria,[12] or CKD.[49,50] Moreover, we could not settle the puzzling results of previous retrospective studies about the association of steatosis and diabetic retinopathy.[41,49] Neither could we show an association between certain glucose-lowering drugs and the absence of MAFLD. However, it is important to note that our study did not include long-term prospective follow-up. In the future, our database will allow us to study the evolution of MAFLD in patients particularly according to their treatments.

The prevalence of advanced fibrosis using NITs varied from 3.8% (FIB-4) and 4.2% (APRI) to 19.0% (NFS), which is similar to previous retrospective studies.[12] When assessing LSM using available cutoffs[28] in patients with a high risk combination of FIB-4 and NFS, or abnormal abdominal Doppler ultrasound (liver dysmorphism, signs of portal hypertension), we found 11.3 % advanced fibrosis and 4.2 % cirrhosis in T2DM patients. As VCTE was only performed in patients with a combination of high NITs results, we were not able to evaluate and compare the diagnostic performance of the scores. We confirmed the known association between a higher BMI and more severe MAFLD with advanced fibrosis.[16] In our population, alcohol consumption in units per week tended to be higher in patients with liver fibrosis, and excessive alcohol consumption was a risk factor for advanced fibrosis, confirming previous data suggesting that alcohol use was a significant risk factor for the progression of liver disease in MAFLD.[51,52] Although because concerning a small number of patients, this should be interpreted with much caution. Finally, we did not confirm the previously described association between liver fibrosis and CKD, cardiovascular disease, or

insulin use in T2DM patients.[12,16]

The discrepancy of positivity rates between NITs shows that there are serious limitations of the sole use of a NIT for detection of liver fibrosis. First of all, NITs seem to perform best for detecting fibrosis in older, nonobese and nondiabetic patients.[53] There are several potential reasons why NITs would underperform in T2DM.[24,53,54] Indeed, patients with T2DM may only represent a relatively small part of the whole spectrum of MAFLD severity, resulting in potential spread effect. Moreover, certain glucose-lowering agents (e.g., glucagon-like peptide 1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, glitazones) or lipid-lowering drugs (e.g., fibrates) could be potential confounders by modulating liver fat accumulation and/or measurements used to calculate the scores (e.g., ALT, AST, triglycerides, or BMI). In addition, many of the diagnostic tools were developed and validated in Caucasian populations and might not necessarily apply to other ethnicities. Finally, observational studies are always prone to selection bias that can affect generalizability of the study results. Specifically, there were concerns regarding use of NFS in T2DM because the algorithm included the presence of diabetes, leading to spectrum bias with an increase in the score for all patients and a decreased positive predictive value.[54] In addition, it requires assessment of serum albumin, which is not a routine test at diabetes clinics. Conversely, an FIB-4 of <1.3 has been shown to have modest negative predictive value and might not accurately classify T2DM people as at low risk of advanced fibrosis.[54] An option to reduce indeterminate results rate is therefore to combine different biomarkers of liver fibrosis.[24,55] Second, an approach that solely bases referrals on fibrosis stage is insufficient. Indeed, it is likely to miss out on a subset of patients with nonalcoholic steatohepatitis (NASH) and early fibrosis who still need referral to a specialist because they are at high risk of developing advanced fibrosis or cirrhosis in the short term. That underlines the need for reliable noninvasive biomarkers of NASH that are currently not available for clinical routine use.[24]

Elevated transaminases were found in 28.6% of patients. That subgroup was further assessed for other liver diseases but eventually were confirmed as having only MAFLD or MAFLD and alcohol-related liver disease (two patients). However, we noticed that the majority of those patients had never been tested to rule out viral hepatitis B and C, alpha-1-antitrypsin deficiency, or signs of auto-immune hepatitis. We consider that elevated transaminases should not be trivialized in T2DM patients, and should at least once be subject to further assessment.

In conclusion, using simple bioclinical noninvasive tools to routinely triage T2DM patients with potentially severe liver disease is feasible. There is wide adherence of high-risk patients to noninvasive complementary testing with abdominal Doppler ultrasound and VCTE. The usefulness of noninvasive scores for steatosis detection in T2DM is questionable, as the vast majority of patients were classified as at high or indeterminate risk of steatosis, meaning that nearly all T2DM patients presented with MAFLD. A baseline abdominal Doppler ultrasound seems therefore appropriate in all T2DM patients to assess the liver surface, parenchyma, and vascularization. Systematic combined use of NFS and FIB-4, although having multiple shortcomings, allowed for detecting a significant number of patients with previously undiagnosed cirrhosis and/or advanced fibrosis. In particular, the study showed that the majority of patients could be managed by their treating physicians.

Acknowledgments

We thank the UCLouvain platform "Support en méthodologie et calcul statistique" and more specifically Céline Bugli for their advice regarding statistical analyses.

Funding

The authors declare that they received no financial support for the present study. NL has a mandate of Clinical Researcher from the Fonds de la Recherche Scientifique (FNRS, Belgium).

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Collected the data, performed the analyses, interpreted the data and wrote the manuscript (QB), recruited the patients to the study and critically reviewed the manuscript (AL, MPH), conceived, designed and supervised the study, and critically reviewed the manuscript (NL). All authors approved the final version of the manuscript.

Ethical statement

The study protocol (No. B4032021000065) was in line with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board and ethics committee. All included patients provided written informed consent.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

[1] Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, *et al*. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020;73(1):202–209. doi:10.1016/j.jhep.2020.03.039, PMID:32278004.
[2] Lanthier N, Vanuytsel T. Metabolic dysfunction-associated fatty liver disease: a new clearer nomenclature with positive diagnostic criteria. Acta Gastroenterol Belg 2020;83(4):513–515. PMID:33321005.
[3] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64(1):73–84. doi:10.1002/hep.28431, PMID:26707365.
[4] Binet Q, Loumaye A, Preumont V, Thissen JP, Hermans MP, Lanthier N. Noninvasive screening, staging and management of metabolic dysfunction-associated fatty liver disease (MAFLD) in type 2 diabetes mellitus patients: what do we know so far? Acta Gastroenterol Belg 2022;85(2):346–357. doi:10.51821/85.2.9775, PMID:35709779.
[5] Watt MJ, Miotto PM, De Nardo W, Montgomery MK. The Liver as an Endocrine Organ—Linking NAFLD and Insulin Resistance. Endocr Rev 2019;40(5):1367–1393. doi:10.1210/er.2019-00034, PMID:31098621.
[6] Gastaldelli A, Cusi K. From NASH to diabetes and from diabetes to NASH: Mechanisms and treatment options. JHEP Reports 2019;1(4):312–328. doi:10.1016/j.jhepr.2019.07.002, PMID:32039382.
[7] Lanthier N, Leclercq IA. Liver and systemic insulin resistance. Hepatology 2014;60(3):1113–1114. doi:10.1002/hep.27017, PMID:24452327.
[8] Stefan N, Cusi K. A global view of the interplay between non-alcoholic fatty liver disease and diabetes. Lancet Diabetes Endocrinol 2022;10(4):284–296. doi:10.1016/S2213-8587(22)00003-1, PMID:35183303.
[9] Francque S, Lanthier N, Verbeke L, Reynaert H, Van Steenkiste C, Vonghia L, *et al*. The Belgian Association for Study of the Liver Guidance Document on the Management of Adult and Paediatric Non-Alcoholic Fatty Liver Disease. Acta Gastroenterol Belg 2018;81(1):55–81. PMID:29562379.
[10] EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64(6):1388–1402. doi:10.1016/j.jhep.2015.11.004, PMID:27062661.
[11] Ciardullo S, Sala I, Perseghin G. Screening strategies for nonalcoholic fatty liver disease in type 2 diabetes: Insights from NHANES 2005–2016. Diabetes Res Clin Pract 2020;167:108358. doi:10.1016/j.diabres.2020.108358, PMID:32745698.

[12] Ciardullo S, Muraca E, Perra S, Bianconi E, Zerbini F, Oltolini A, *et al*. Screening for non-alcoholic fatty liver disease in type 2 diabetes using non-invasive scores and association with diabetic complications. BMJ Open Diabetes Res Care 2020;8(1):e000904. doi:10.1136/bmjdrc-2019-000904, PMID:32049637.
[13] Morieri ML, Vitturi N, Avogaro A, Targher G, Fadini GP. Prevalence of hepatic steatosis in patients with type 2 diabetes and response to glucose-lowering treatments. A multicenter retrospective study in Italian specialist care. J Endocrinol Invest 2021;44(9):1879–1889. doi:10.1007/s40618-021-01501-y, PMID:33432553.
[14] Bergram M, Nasr P, Iredahl F, Kechagias S, Rådholm K, Ekstedt M. Low awareness of non-alcoholic fatty liver disease in patients with type 2 diabetes in Swedish Primary Health Care. Scand J Gastroenterol 2022;57(1):60–69. doi:10.1080/00365521.2021.1984572, PMID:34618619.
[15] Singh A, Le P, Peerzada MM, Lopez R, Alkhouri N. The Utility of Noninvasive Scores in Assessing the Prevalence of Nonalcoholic Fatty Liver Disease and Advanced Fibrosis in Type 2 Diabetic Patients. J Clin Gastroenterol 2018;52(3):268–272. doi:10.1097/MCG.0000000000000905, PMID:28787358.
[16] Ajmera V, Cepin S, Tesfai K, Hofflich H, Cadman K, Lopez S, *et al*. A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes. J Hepatol 2023;78(3):471–478. doi:10.1016/j.jhep.2022.11.010, PMID:36410554.
[17] Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, *et al*. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol 2006;6(1):33. doi:10.1186/1471-230X-6-33, PMID:17081293.
[18] Lee J-H, Kim D, Jung KH, Lee CH, Yang JI, Kim W, *et al*. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis 2010;42(7):503–508. doi:10.1016/j.dld.2009.08.002, PMID:19766548.
[19] Yip TC-F, Ma AJ, Wong VW-S, Tse Y-K, Chan H L-Y, Yuen P-C, *et al*. Laboratory parameter-based machine learning model for excluding non-alcoholic fatty liver disease (NAFLD) in the general population. Aliment Pharmacol Ther 2017;46(4):447–456. doi:10.1111/apt.14172, PMID:28585725.
[20] Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, *et al*. The NAFLD fibrosis score: A noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45(4):846–854. doi:10.1002/hep.21496, PMID:17393509.
[21] Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, *et al*. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43(6):1317–1325. doi:10.1002/hep.21178, PMID:16729309.
[22] McPherson S, Hardy T, Dufour J-F, Petta S, Romero-Gomez M, Allison M, *et al*. Age as a Confounding Factor for the Accurate Non-Invasive Diagnosis of Advanced NAFLD Fibrosis. Am J Gastroenterol 2017;112(5):740–751. doi:10.1038/ajg.2016.453, PMID:27725647.
[23] Ampuero J, Pais R, Aller R, Gallego-Durán R, Crespo J, García-Monzón C, *et al*. Development and Validation of Hepamet Fibrosis Scoring System–A Simple, Noninvasive Test to Identify Patients With Nonalcoholic Fatty Liver Disease With Advanced Fibrosis. Clin Gastroenterol Hepatol 2020;18(1):216–225.e5. doi:10.1016/j.cgh.2019.05.051, PMID:31195161.
[24] Bril F, McPhaul MJ, Caulfield MP, Clark VC, Soldevilla-Pico C, Firpi-Morell RJ, *et al*. Performance of Plasma Biomarkers and Diagnostic Panels for Nonalcoholic Steatohepatitis and Advanced Fibrosis in Patients With Type 2 Diabetes. Diabetes Care 2020;43(2):290–297. doi:10.2337/dc19-1071, PMID:31604692.
[25] Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2013;36(Suppl 1):S67–S74. doi:10.2337/dc13-S067, PMID:23264425.
[26] Petta S, Wong VW-S, Cammà C, Hiriart JB, Wong GLH, Marra F, *et al*. Improved noninvasive prediction of liver fibrosis by liver stiffness measurement in patients with nonalcoholic fatty liver disease accounting for controlled attenuation parameter values. Hepatology 2017;65(4):1145–1155. doi:10.1002/hep.28843, PMID:27639088.
[27] Boursier J, Zarski J-P, de Ledinghen V, Rousselet MC, Sturm N, Lebail B, *et al*. Determination of reliability criteria for liver stiffness evaluation by transient elastography. Hepatology 2013;57(3):1182–1191. doi:10.1002/hep.25993, PMID:22899556.
[28] Myers RP, Pomier-Layrargues G, Kirsch R, Pollett A, Duarte-Rojo A, Wong D, *et al*. Feasibility and diagnostic performance of the FibroScan XL probe for liver stiffness measurement in overweight and obese patients. Hepatology 2012;55(1):199–208. doi:10.1002/hep.24624, PMID:21898479.
[29] Park CC, Nguyen P, Hernandez C, Bettencourt R, Ramirez K, Fortney L, *et al*. Magnetic Resonance Elastography vs Transient Elastography in Detection of Fibrosis and Noninvasive Measurement of Steatosis in Patients With Biopsy-Proven Nonalcoholic Fatty Liver Disease. Gastroenterology 2017;152(3):598–607.e2. doi:10.1053/j.gastro.2016.10.026, PMID:27911262.
[30] Binet Q, Hermans MP, Lanthier N. Screening for NAFLD and its severity in type 2 diabetic patients: value of magnetic resonance imaging and outstanding issues. J Hepatol 2023;78(5):e166–e167. doi:10.1016/j.jhep.2022.12.004, PMID:36528235.
[31] Albhaisi S, Chowdhury A, Sanyal AJ. Non-alcoholic fatty liver disease in lean individuals. JHEP Reports 2019;1(4):329–341. doi:10.1016/j.jhepr.2019.08.002, PMID:32039383.
[32] Etienne Q, Lebrun V, Komuta M, Navez B, Thissen JP, Leclercq IA, *et al*. Fetuin-A in Activated Liver Macrophages Is a Key Feature of Non-Alcoholic Steatohepatitis. Metabolites 2022;12(7):625. doi:10.3390/metabo12070625, PMID:35888749.
[33] Lanthier N, Lebrun V, Molendi-Coste O, van Rooijen N, Leclercq IA. Liver Fetuin-A at Initiation of Insulin Resistance. Metabolites 2022;12(11):1023. doi:10.3390/metabo12111023, PMID:36355106.
[34] Armandi A, Rosso C, Caviglia GP, Bugianesi E. Insulin Resistance across the Spectrum of Nonalcoholic Fatty Liver Disease. Metabolites 2021;11(3):155. doi:10.3390/metabo11030155, PMID:33800465.
[35] Tran B Van, Ujita K, Taketomi-Takahashi A, Hirasawa H, Suto T, Tsushima Y. Reliability of ultrasound hepatorenal index and magnetic resonance imaging proton density fat fraction techniques in the diagnosis of hepatic steatosis, with magnetic resonance spectroscopy as the reference standard. PLoS One 2021;16(8):e0255768. doi:10.1371/journal.pone.0255768, PMID:34383812.
[36] Alexopoulos A, Crowley MJ, Wang Y, Moylan CA, Guy CD, Henao R, *et al*. Glycemic Control Predicts Severity of Hepatocyte Ballooning and Hepatic Fibrosis in Nonalcoholic Fatty Liver Disease. Hepatology 2021;74(3):1220–1233. doi:10.1002/hep.31806, PMID:33724511.
[37] Hall A, Covelli C, Manuguerra R, Luong TV, Buzzetti E, Tsochatzis E, *et al*. Transaminase abnormalities and adaptations of the liver lobule manifest at specific cut-offs of steatosis. Sci Rep 2017;7(1):40977. doi:10.1038/srep40977, PMID:28106158.
[38] Lanthier N, Rodriguez J, Nachit M, Hiel S, Trefois P, Neyrinck AM, *et al*. Microbiota analysis and transient elastography reveal new extra-hepatic components of liver steatosis and fibrosis in obese patients. Sci Rep 2021;11(1):659. doi:10.1038/s41598-020-79718-9, PMID:33436764.
[39] Zou Y, Zhong L, Hu C, Zhong M, Peng N, Sheng G. LDL/HDL cholesterol ratio is associated with new-onset NAFLD in Chinese non-obese people with normal lipids: a 5-year longitudinal cohort study. Lipids Health Dis 2021;20(1):28. doi:10.1186/s12944-021-01457-1, PMID:33766067.
[40] Wang D, Wang L, Wang Z, Chen S, Ni Y, Jiang D. Higher non-HDL-cholesterol to HDL-cholesterol ratio linked with increased nonalcoholic steatohepatitis. Lipids Health Dis 2018;17(1):67. doi:10.1186/s12944-018-0720-x, PMID:29615042.
[41] Gninkoun CJ, Ahn SA, Amoussou-Guenou KD, Bouenizabila E, Rousseau MF, Hermans MP. Fatty Liver Linked to Reduced Frequency of Ocular Complications in T2DM. J Diabetes Mellit 2020;10(03):154–168. doi:10.4236/jdm.2020.103013.
[42] Hermans MP, Bouenizabila E, Daniel Amoussou-Guenou K, Jules Gninkoun C, Ahn SA, Rousseau MF. Fatty liver and atherogenic dyslipidemia have opposite effects on diabetic micro- and macrovascular disease. Diabetes Metab Syndr Clin Res Rev 2022;16(10):102613. doi:10.1016/j.dsx.2022.102613, PMID:36116326.
[43] Foussard N, Saulnier P-J, Potier L, Ragot S, Schneider F, Gand E, *et al*. Relationship Between Diabetic Retinopathy Stages and Risk of Major Lower-Extremity Arterial Disease in Patients With Type 2 Diabetes. Diabetes Care 2020;43(11):2751–2759. doi:10.2337/dc20-1085, PMID:33055101.
[44] Tejani S, McCoy C, Ayers CR, Powell-Wiley TM, Després JP, Linge J, *et al*. Cardiometabolic Health Outcomes Associated With Discordant Visceral and Liver Fat Phenotypes: Insights From the Dallas Heart Study and UK Biobank. Mayo Clin Proc 2022;97(2):225–237. doi:10.1016/j.mayocp.2021.08.021, PMID:34598789.
[45] Zou Y, Li X, Wang C, Wang J, Wang F, Ma L, *et al*. Association between non-alcoholic fatty liver disease and peripheral artery disease in patients with type 2 diabetes. Intern Med J 2017;47(10):1147–1153. doi:10.1111/imj.13549, PMID:28696562.
[46] Tiniakos DG. Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis: histological diagnostic criteria and scoring systems. Eur J Gastroenterol Hepatol 2010;22(6):643–50. doi:10.1097/MEG.0b013e32832ca0cb, PMID:19478676.
[47] Zhou Y-Y, Zhou X-D, Wu S-J, Hu XQ, Tang B, van Poucke S, *et al*. Synergistic increase in cardiovascular risk in diabetes mellitus with nonalcoholic fatty liver disease. Eur J Gastroenterol Hepatol 2018;30(6):631–636. doi:10.1097/MEG.0000000000001075, PMID:29351115.
[48] Liu H-H, Cao Y-X, Jin J-L, Guo YL, Zhu CG, Wu NQ, *et al*. Metabolic-associated fatty liver disease and major adverse cardiac events in patients with chronic coronary syndrome: a matched case–control study. Hepatol Int 2021;15(6):1337–1346. doi:10.1007/s12072-021-10252-0, PMID:34626331.
[49] Targher G, Bertolini L, Rodella S, Zoppini G, Lippi G, Day C, *et al*. Non-alcoholic fatty liver disease is independently associated with an increased prevalence of chronic kidney disease and proliferative/laser-treated retinopathy in type 2 diabetic patients. Diabetologia 2008;51(3):444–450. doi:10.1007/s00125-007-0897-4, PMID:18058083.
[50] Wang T-Y, Wang R-F, Bu Z-Y, Targher G, Byrne CD, Sun DQ, *et al*. Association of metabolic dysfunction-associated fatty liver disease with kidney disease. Nat Rev Nephrol 2022;18(4):259–268. doi:10.1038/s41581-021-00519-y, PMID:35013596.
[51] Ntandja Wandji LC, Gnemmi V, Mathurin P, Louvet A. Combined alcoholic and non-alcoholic steatohepatitis. JHEP Reports 2020;2(3):100101. doi:10.1016/j.jhepr.2020.100101, PMID:32514497.
[52] Idalsoaga F, Kulkarni A V, Mousa OY, Arrese M, Arab JP. Non-alcoholic Fatty Liver Disease and Alcohol-Related Liver Disease: Two Intertwined Entities. Front Med 2020;7:448. doi:10.3389/fmed.2020.00448, PMID:32974366.
[53] Ito T, Nguyen VH, Tanaka T, Park H, Yeh ML, Kawanaka M, *et al*. Poor Diagnostic Efficacy of Noninvasive Tests for Advanced Fibrosis in Obese or Younger Than 60 Diabetic NAFLD patients. Clin Gastroenterol Hepatol 2023;21(4):1013–1022.e6. doi:10.1016/j.cgh.2022.05.015, PMID:35654298.
[54] Gracen L, Hayward KL, Irvine KM, C VP, Powell EE. Low accuracy of FIB-4 test to identify people with diabetes at low risk of advanced fibrosis. J Hepatol 2022;76(5):1013–1020. doi:10.1016/j.jhep.2022.06.016, PMID:35764234.
[55] Srivastava A, Gailer R, Tanwar S, Trembling P, Parkes J, Rodger A, *et al*. Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease. J Hepatol 2019;71(2):371–378. doi:10.1016/j.jhep.2019.03.033, PMID:30965069.