High Prevalence of Liver Fibrosis Among European Adults With Unknown Liver Disease: A Population-Based Study

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BACKGROUND & AIMS: **Liver fibrosis is the main determinant of long-term outcome in chronic liver diseases. Little is known about the prevalence of liver fibrosis in the general population. The aim of the study was to investigate the prevalence of liver fibrosis in the general adult population with unknown liver disease.**

METHODS: **This was a population-based, cross-sectional study performed in the Barcelona metropolitan area. Subjects aged 18 to 75 years old were identified randomly from citizens included in the primary health care registry. Of 4866 subjects invited, 3076 participated (63.2%). Liver fibrosis was estimated by measuring liver stiffness (LS) with transient elastography (TE). Liver histology was assessed in 92 subjects with increased LS.**

RESULTS: **Prevalence estimates of increased LS (≥6.8, ≥8.0, and ≥9.0 kPa) were 9.0%, 5.8%, and 3.6%, respectively. The etiology of liver disease was mainly nonalcoholic fatty liver disease (NAFLD), followed by alcohol risk consumption (consumption of ≥21 standard drinking units/wk in men and ≥14 standard drinking units/wk in women). Factors independently associated with increased LS were male sex, abdominal obesity, type 2 diabetes, serum glucose, high-density lipoprotein, and triglyceride levels. Subjects without risk factors for NAFLD or without alcohol risk consumption had a very low prevalence of increased LS. The best cut-off value of LS for significant liver fibrosis (F2–F4) was 9.2 kPa, with high sensitivity and specificity. TE was more accurate than alanine aminotransferase, NAFLD fibrosis score, or Fibrosis 4. An algorithm for screening for liver fibrosis using TE in the community setting is proposed.**

CONCLUSIONS: **These findings show a high prevalence of silent liver disease with advanced fibrosis mainly related to NAFLD in adult European subjects without known liver disease. An LS value less than 9.2 kPa predicts the absence of significant liver fibrosis with high accuracy and could be used for screening purposes.**

Keywords: NAFLD; Liver Fibrosis; Cirrhosis; Transient Elastography.

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Abbreviations used in this paper: ALT, alanine aminotransferase; FLI, fatty liver index; LS, liver stiffness; NAFLD, nonalcoholic fatty liver disease; TE, transient elastography.

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Cirrhosis is one of the main causes of death worldwide and one of the leading causes of disability-adjusted life-years.[1] Although the prevalence of cirrhosis resulting from hepatitis C likely will decrease in the coming years, the prevalence of cirrhosis resulting from alcohol consumption and, in particular, nonalcoholic fatty liver disease (NAFLD), is increasing.[2] NAFLD is a particularly alarming health problem because it is associated with metabolic comorbidities, mainly obesity, type 2 diabetes, hyperlipidemia, and metabolic syndrome, the frequency of which is increasing markedly in most areas of the world.[3–5] NAFLD affects approximately 25% of the population worldwide and patients with NAFLD have decreased survival compared with that of the general population.[3–6] It must be emphasized, however, that only a relatively small proportion of patients with NAFLD will progress to develop cirrhosis, the main predictive factor being liver fibrosis. The presence and severity of fibrosis predicts not only cirrhosis development but also long-term survival.[7,8] Epidemiologic studies assessing the prevalence of NAFLD in the general population have been based on evaluation of fat in the liver, as assessed usually by ultrasound, but information on the prevalence of liver fibrosis in the general population is very scarce.[9] This information may be helpful to design screening strategies for an early diagnosis of liver fibrosis, which may allow therapeutic interventions before cirrhosis develops.

Methods

Study Design and Participants

This was a population-based, cross-sectional study aimed at investigating the prevalence of liver fibrosis, as assessed by liver stiffness (LS) measurement using transient elastography (TE), a widely accepted method for noninvasive assessment of liver fibrosis,[10,11] among the adult general population without known liver disease of an urban area of Catalonia, in southwest Europe. The study was conducted in several municipalities in the northern part of the Barcelona metropolitan area between April 2012 and January 2016.

The health system in Catalonia is public and all citizens are included in a health registry and are assigned a primary health care physician who is located in the primary health care center closest to their abode. Participants in the study were identified randomly from a total of 162,950 subjects aged 18 to 75 years from the registries of the primary health care centers of the municipalities included in the study. Randomly identified subjects were contacted by telephone and invited to participate. Those interested in participating were asked to attend their primary health care center where a member of their research team, composed of a primary care physician and a research nurse, explained the study protocol carefully. Patients with a current history of liver disease, including cholestasis, were excluded from the study. Other exclusion criteria were active malignancy, other severe diseases (congestive heart failure New York Heart Assocation $>$ 2, chronic obstructive pulmonary disease Global Initiative for Chronic Obstructive Lung Disease $>$ 2, chronic kidney disease requiring dialysis, previous organ transplantation, and severe neurologic diseases), or admission to long-term nursing homes. After the informed consent was signed, the following steps were taken: (1) a detailed medical history, including alcohol consumption (assessed as drinking units/wk); anthropometric measurements, including body weight, height, and waist circumference; and arterial pressure; (2) blood tests, including liver biochemistry, hepatitis B and C virus markers (hepatitis B surface antigen and anti–hepatitis C virus), glycemia, glycosylated hemoglobin, lipid profile, serum creatinine, and serum ferritin; and (3) a TE with measurement of LS was performed (see later). Subjects with LS $\geq$ 6.8 kPa, which may be indicative of significant liver fibrosis,[12,13] as well as those with LS $<$ 6.8 kPa but with alanine aminotransferase (ALT) levels higher than 2 times the upper limit of normal, were referred for hepatology consultation. The remaining subjects did not undergo any further evaluation. The hepatology consultation consisted of a comprehensive evaluation of the stage and cause of liver disease, and included a liver biopsy in patients who agreed to undergo the procedure.

Procedures

TE was performed using the Fibroscan system (402; Echosens, Paris, France), as described in the Supplementary Materials section. Only the M probe was used because the XL probe was not available.

A liver biopsy was performed percutaneously with the Tru-Cut biopsy needle using a standard procedure. Liver histology was assessed by 2 liver pathologists (N.O. and A.D.) who were not aware of the results of LS measurement and was graded from F0 to F4.[14] NAFLD and alcoholic liver disease were defined using standard diagnostic criteria.

Statistical Analysis

The main outcome variable was the prevalence of liver fibrosis, as assessed by increased LS ($\geq$6.8 kPa). This cut-off value was used as the main outcome variable in the analysis because it was predetermined in the study protocol. Nonetheless, because the optimal cut-off level of LS to define significant liver fibrosis changed since the study protocol was written, 2 other values also were used, 8.0 kPa and 9.0 kPa, which have been shown to predict significant liver fibrosis in large populations of patients, mostly with NAFLD.[15,16] Statistical methods are reported in the Supplementary Materials section.

Results

Characteristics of the Study Population

Of the 4866 eligible subjects, 3076 accepted to participate in the study (success rate, 63.2%). Fifty-two

Table 1. Baseline Characteristics of the 3014 Subjects Included in the Study

	(n = 3014)
Male, n (%)	1289 (43)
Age, *y*	54 ± 12
Caucasian, n (%)	2818 (95)
Body mass index, *kg/m²*	28 ± 5
Overweight, ≥25 to <30 kg/m², n (%)	1251 (42)
Obesity, ≥30 kg/m², n (%)	933 (31)
Abdominal obesity,[a] n (%)	1485 (50)
Waist circumference of all subjects, *cm*	94 ± 13
Waist circumference of males, *cm*	99 ± 11
Waist circumference of females, *cm*	90 ± 12
Alcohol risk consumption,[b] n (%)	275 (9)
Arterial hypertension, n (%)	791 (26)
Type 2 diabetes, n (%)	308 (10)
Hypercholesterolemia, n (%)	1128 (37)
Hypertriglyceridemia, n (%)	321 (11)
Metabolic syndrome,[c] n (%)	817 (28)
Glucose level, *mg/dL*	101 ± 26
Glycosylated hemoglobin level, %	5.7 ± 0.7
Total cholesterol level, *mg/dL*	213 ± 39
HDL level, *mg/dL*	55 ± 13
LDL level, *mg/dL*	134 ± 35
Triglyceride level, *mg/dL*	124 ± 81
AST level, *U/L*	24 ± 9
ALT level, *U/L*	24 ± 14
AST and/or ALT > ULN,[d] n (%)	251 (9)
GGT level, *U/L*	23 (17–35)
HBsAg positive, n (%)	23 (1)
Anti HCV positive, n (%)	9 (0.3)
FLI,[e] n (%)	
<30	934 (33)
30–60	823 (29)
≥60	1062 (38)

NOTE. Data are n (%) or means (±SD), except for γ-glutamyltransferase, which is median (interquartile range).
AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ULN, upper limit of normal.
[a]Waist circumference ≥102 cm in men or ≥88 cm in women.
[b]See Supplementary Materials for definition.
[c]See Supplementary Materials for definition.
[d]ULN was 40 U/L.
[e]The FLI estimates the amount of fat in the liver and includes body mass index, waist circumference, and serum γ-glutamyltransferase and triglycerides.

patients were excluded: 46 (1.5%) for unreliable LS measurements and 16 for other reasons. Therefore, the study population consisted of 3014 subjects (Supplementary Figure 1).The characteristics of the population are shown in Table 1.

Prevalence of Increased Liver Stiffness: Relationship With Risk Factors for Chronic Liver Disease

The prevalence of increased LS (≥6.8 kPa) in the whole series was 9.0% (95% CI, 8.0%–10.1%). When higher cut-off values for LS were used (≥8.0 kPa and ≥9.0 kPa), the prevalence of LS was 5.8% (5.0%–6.7%) and 3.6% (2.9%–4.3%), respectively. In the whole series, the mean value of LS was 5 kPa (range, 2–46.4 kPa). The distribution of LS values in the whole population is shown in Supplementary Figure 2. There was a relationship between LS values and age, male sex, and a number of risk factors of chronic liver diseases (Supplementary Table 1). In multivariate analysis, factors associated with increased LS were male sex, abdominal obesity, type 2 diabetes, serum glucose level, high-density lipoprotein, and triglyceride levels, as well as increased aspartate aminotransferase or ALT levels. Factors were identical regardless of the cut-off level of LS used, 6.8, 8.0, or 9.0 kPa (Table 2). When subjects with high-risk alcohol consumption or anti–hepatitis C virus or hepatitis B surface antigen–positive were excluded from the analysis (n = 304), the prevalence of increased LS was 8.3%, 5.3%, and 3.3% for the cut-off values 6.8, 8.0, and 9.0 kPa, respectively, values slightly lower than those observed in the whole population. Multivariate analysis in this patient population yielded very similar results to those in the overall population (Supplementary Table 2). When only subjects with increased alcohol risk consumption were considered (n = 273), the prevalence of increased LS was 16.1% (12.0–21.0), 10.3% (6.9–14.5), and 6.6% (4.0–10.2) for the 3 different cut-off values, respectively.

Prevalences of LS according to different risk factors are shown in Figure 1 and Supplementary Table 3. Moreover, there was a relationship between steatosis, as estimated by fatty liver index (FLI) and LS. The prevalence of increased LS in patients with severe steatosis (FLI ≥ 60) was 20.3%, 13.7%, and 8.9% with the cut-off values of 6.8, 8.0, and 9.0 kPa, respectively. Corresponding values in patients with FLI < 60 were 2.6%, 1.2% and 0.4%, respectively ($P < .001$, for all).

Fibrosis in Liver Biopsy: Relationship With Liver Stiffness and Biological Scores

A hepatology consultation was offered to 300 subjects (10% of the whole population; 271 because of LS ≥ 6.8 kPa and 29 because of ALT > 2 upper limit of normal), and 179 accepted. Ninety-two of these 179 subjects consented to undergo a liver biopsy (31% of all eligible patients). Of the 92 patients, 81 had NAFLD and 7 had alcoholic liver disease. The remaining 4 patients had no histologic abnormalities. LS was slightly higher in patients in whom a liver biopsy was performed compared with those in whom it was not (10.1 ± 5.3 vs 8.9 ± 3.5 kPa, respectively; $P = .024$).

LS increased progressively with the degree of fibrosis in the liver biopsy, from 8.4 ± 1.9 in patients with F0 to F1 to 10.7 ± 1.5, 14.2 ± 1.6, and 30.8 ± 10.8 kPa in patients with F2, F3, and F4, respectively ($P < .001$) (Supplementary Table 4). Comparison of demographic and clinical characteristics of patients with F0 to F1 and those of patients with F2 to F4 showed only statistically significant differences in the proportion of patients with type 2 diabetes (19% vs 43%, respectively; $P = .0015$). Table 3 shows the relationship between LS values and the severity of liver fibrosis in the 88 patients who had an

Table 2. Multivariate Analysis of Factors Associated With Increased Liver Stiffness Using 3 Different Cut-Off Values

	6.8 kPa				8.0 kPa				9.0 kPa			
	OR	95% CI		*P* value	OR	95% CI		*P* value	OR	95% CI		*P* value
Male sex	3.01	2.25	4.05	.000	2.71	1.90	3.87	.000	3.26	2.06	5.16	.000
AST and/or ALT > ULN[a]	2.15	1.48	3.12	.000	1.95	1.26	3.03	.003	2.91	1.76	4.80	.000
Abdominal obesity[b]	3.84	2.75	5.34	.000	4.28	2.78	6.59	.000	4.19	2.42	7.24	.000
Glucose level ≥100 mg/dL	1.63	1.18	2.24	.003	2.06	1.38	3.07	.000	2.20	1.29	3.73	.004
Low HDL[c]	1.51	1.10	2.07	.011	1.68	1.16	2.44	.006	1.67	1.05	2.66	.030
Triglyceride level ≥150 mg/dL	1.63	1.21	2.19	.001	1.73	1.21	2.47	.003	1.41	0.90	2.20	.137
Type 2 diabetes	2.13	1.49	3.05	.000	2.00	1.33	3.01	.001	2.28	1.40	3.74	.001

AST, aspartate aminotransferase; HDL, high-density lipoprotein; OR, odds ratio; ULN, upper limit of normal.
[a]ULN was 40 U/L.
[b]Waist circumference was ≥102 cm in men or ≥88 cm in women.
[c]HDL was <40 mg/dL in men or <50 mg/dL in women.

abnormal liver biopsy. The proportion of patients diagnosed with significant liver fibrosis (≥F2) increased with the cut-off level used. With LS ≥ 6.8 kPa, 32% of patients had significant liver fibrosis, a percentage that increased to 45% and 65% with the cut-off values of 8.0 kPa and 9.0 kPa, respectively. Interestingly, only 2 of the 52 subjects (3.8%) with LS < 9.0 kPa had significant liver fibrosis.

The value of LS that best predicted the presence of significant liver fibrosis was 9.2 kPa, with a sensitivity of 93%, a specificity of 78%, and a predictive accuracy of 83%. The predictive accuracy of LS in the detection of significant liver fibrosis was significantly better than that of ALT levels, and NAFLD fibrosis score and Fibrosis 4, 2 scores that have been shown to correlate with liver fibrosis (Supplementary Figure 3).

Development of an Algorithm for Screening for Liver Fibrosis in the Community Setting

We next sought to develop an algorithm that could be useful for screening for liver fibrosis in subjects in the community using TE as a screening method. The cut-off level used was 9.2 kPa because this value had the highest predictive accuracy for significant liver fibrosis, with a very high negative predictive value and a reasonably high positive predictive value.

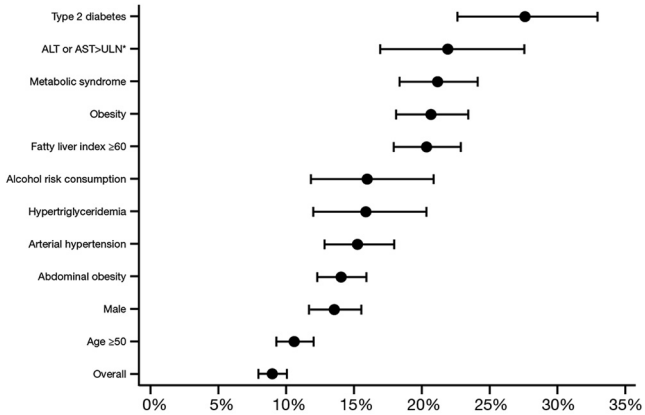

Figure 1. Prevalence and 95% CI of liver stiffness ≥ 6.8 kPa in subjects classified according to several risk factors of liver disease. AST, aspartate aminotransferase.

We first analyzed the prevalence of significant liver fibrosis in subjects categorized according to the presence or absence of risk factors for liver fibrosis (obesity, type 2 diabetes, hyperlipidemia, arterial hypertension, metabolic syndrome, or alcohol risk consumption). Overall, 57.9% of subjects had 1 or more risk factors. Remarkably, the prevalence of LS ≥ 9.2 kPa in patients without risk factors was only 0.4%, compared with 5.0% in patients with 1 or more risk factors ($P < .001$). We then analyzed whether some laboratory variables or scores could be useful to rule out significant liver fibrosis in the subset of patients with risk factors. Of the 4 variables analyzed (transaminase levels, NAFLD fibrosis score, FIB-4, and FLI), FLI had the highest negative predictive value and the best area under the receiver operating characteristic curve for the prediction of significant liver fibrosis (Figure 2 and Supplementary Table 5).

On this basis, a 3-step algorithm for screening for liver fibrosis in primary care was developed (Figure 3). The first step consists of assessment of risk factors for liver fibrosis (metabolic syndrome or its components and alcohol risk consumption). Subjects without risk factors should not undergo screening because of a very low risk of liver fibrosis. The second step consists of calculation of FLI in subjects with risk factors. Patients with a value of FLI less than 60 should not be screened because of a very low risk of liver fibrosis. Finally, in the third step, a TE should be performed in subjects with risk factors and FLI ≥ 60. The prevalence of LS ≥ 9.2 kPa in this high-risk group is 8.7%. With this approach, approximately two thirds of the population from 18 to 75 years would not require screening for liver fibrosis. The algorithm performed equally well in subjects ages 45 to 75 years and if subjects with alcohol risk consumption were excluded (data not shown).

Discussion

The current study showed a high prevalence of liver fibrosis, as estimated by increased LS measured with TE,

Table 3. Relationship Between Liver Stiffness and Grading of Fibrosis in Liver Biopsy Using 3 Different Cut-Off Values: 6.8 kPa, 8.0 kPa, and 9.0 kPa

	LS of 6.8 kPa					LS of 8.0 kPa					LS of 9.0 kPa				
	<6.8 kPa		≥6.8 kPa		*P*	<8.0 kPa		≥8.0 kPa		*P*	<9.0 kPa		≥9.0 kPa		*P*
Fibrosis					.719					<.001					<.001
F0	3	(75%)	48	(55%)		24	(75%)	27	(45%)		35	(73%)	16	(36%)	
F1	1	(25%)	12	(14%)		7	(22%)	6	(10%)		11	(23%)	2	(5%)	
F2	0	(0%)	21	(24%)		1	(3%)	20	(33%)		2	(4%)	19	(43%)	
F3–F4	0	(0%)	7	(8%)		0	(0%)	7	(12%)		0	(0%)	7	(16%)	

in a cohort of 3014 European subjects aged 18 to 75 years with previously unknown liver disease randomly identified from the general population. Strengths of the current investigation were as follows: (1) population-based study; (2) high rate of participation of eligible subjects (almost two thirds); and (3) correlation between LS findings and liver fibrosis assessed by liver biopsy in almost one third of subjects with increased LS.

There are very few studies investigating the prevalence of liver fibrosis in the general population. A precise cut-off value of LS in this population has not been defined; therefore, prevalence estimates vary depending of the value of LS chosen. Koehler et al[17] reported a prevalence of liver fibrosis of 5.6% with a cut-off value of 8.0 kPa in 3040 subjects older than age 45 years from Rotterdam. In a study from Hong Kong, the estimated prevalence among 922 subjects aged 18 to 72 years was 2%, with a cut-off of 9.6 kPa.[18] No liver biopsies were performed in these 2 studies; therefore, an ideal cut-off of LS could not be established. Finally, in a study from France including 1358 subjects older than age 45 years, the estimated prevalence was 7%, with a predefined cut-off value of 8 kPa.[15] Liver fibrosis was confirmed histologically in some subjects with increased LS. In all 3 studies, the most common cause of liver disease was NAFLD.

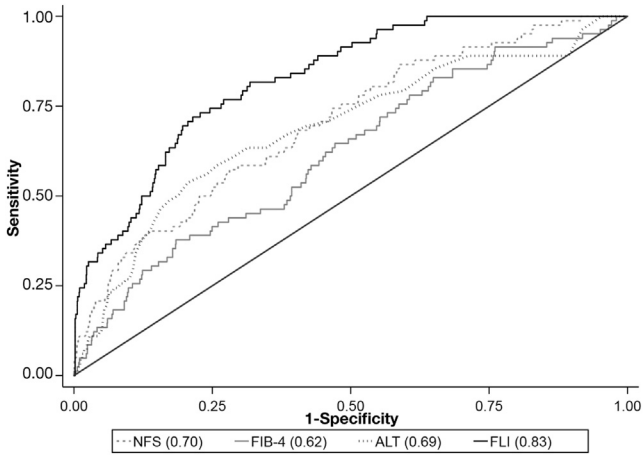

Figure 2. Comparison of area under the receiver operating characteristic curves for significant liver fibrosis according to a LS measurement ≥ 9.2 kPa, as estimated by transient elastography, FLI, ALT level, NAFLD fibrosis score (NFS), and FIB-4 in the whole population of subjects.

In the current study, prevalence estimates of significant liver fibrosis ranged from 9% with the cut-off value of 6.8 kPa, to 5.8% with 8.0 kPa, and 3.6% with 9.0 kPa. The highest rates were observed among subjects with risk factors for NAFLD and subjects with increased alcohol consumption. Independent predictive factors associated with increased LS were male sex and components of the metabolic syndrome. Estimates from the current study (excluding potential false-positive results) indicate that the prevalence of significant liver fibrosis (F2–F4) among the European population of Caucasian origin, aged 18 to 75 years, without known liver disease, is 2.61%, and the prevalence of cirrhosis is 0.4%. Extrapolation of these data to the whole European population (738 million in 2016)[19] indicates that approximately 10 million European citizens with unknown liver disease have significant liver fibrosis and approximately 1.5 million have silent cirrhosis.

An important distinct feature of the current investigation compared with previous population-based studies is the assessment of the relationship between LS and liver fibrosis as determined by histologic examination. The best cut-off level for a diagnosis of significant liver fibrosis was 9.2 kPa, with a sensitivity of 93%, a specificity of 78%, and 83% of cases diagnosed correctly. Almost two thirds of subjects with LS ≥ 9.2 kPa had significant liver fibrosis, while almost all subjects (95.8%) with LS below this value had only F0 or F1. This value is similar to the 8.7 kPa reported in a recent investigation in patients with NAFLD.[20] Our results therefore suggest that TE is a valuable method for detecting significant liver fibrosis in subjects without known liver disease and is useful for screening for liver fibrosis in the community. The cut-off value of 9.2 kPa seems accurate enough to define significant liver fibrosis; however, because it was derived from a relatively low number of subjects with liver histology, it should be validated in future prospective population-based studies before it is implemented in clinical practice for screening purposes.

The findings of the current study show that TE has higher predictive accuracy compared with NAFLD fibrosis score or FIB-4, which suggests that these surrogate fibrosis markers are not useful for the detection of significant liver fibrosis in the general population. This

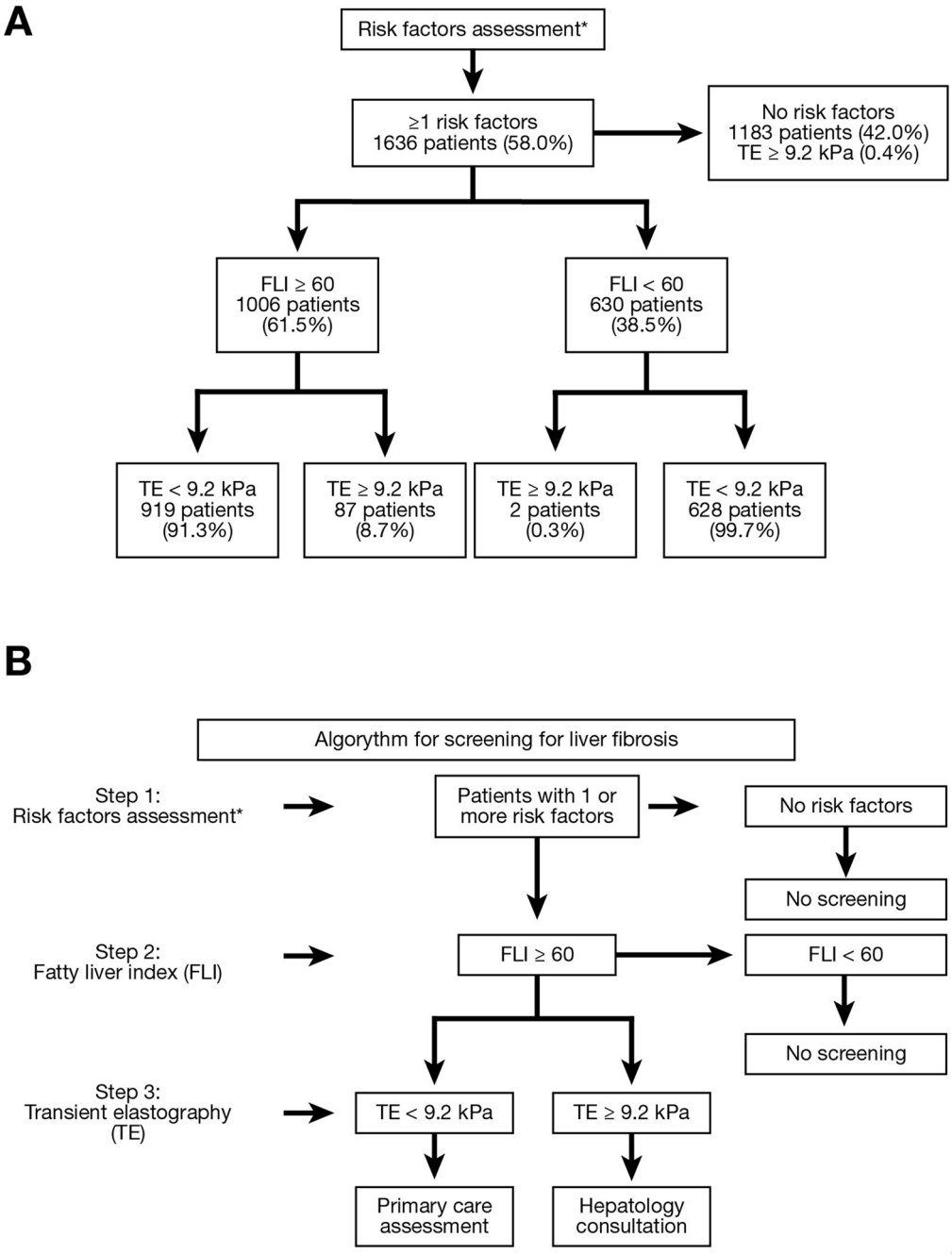

Figure 3. (*A*) Prevalence of LS $\geq$ 9.2 kPa according to risk factors for liver fibrosis and FLI values. (*B*) Proposed algorithm for screening for liver fibrosis in the community. The asterisk (*) indicates if one of the following risk factors is present: obesity, Type 2 diabetes, hyperlipidemia, arterial hypertension, metabolic syndrome, or alcohol risk consumption.

was somehow expected because these tests were derived to diagnose/exclude advanced fibrosis and their performance for significant liver fibrosis is limited. Liver enzymes (aspartate aminotransferase/ALT) also have been proposed to screen for liver disease in subjects with suspected NAFLD.[10] Our findings show that almost 75% of subjects with LS $\geq$ 9.2 kPa had normal ALT levels, indicating that many subjects with significant liver fibrosis could be missed if liver enzyme levels were used for screening of liver fibrosis.

Based on the findings of the current study, an algorithm for screening for liver fibrosis in the community setting was proposed, which includes 3 steps: (1) identification of subjects with risk factors for liver fibrosis; (2) assessment of FLI; and (3) TE to measure LS. The prevalence estimate of liver fibrosis among subjects without risk factors for NAFLD or without alcohol risk consumption was very low (0.4%); therefore, according to our results, subjects without risk factors should not be screened. The second step should be applied to subjects with risk factors and consists of using a scoring system with a high negative predictive value to identify subjects with a very low likelihood of significant liver fibrosis who would not require screening. In this regard, the best score was FLI, a score that provides a noninvasive assessment of the amount of fat in the liver,[21] whereas NAFLD fibrosis score and FIB-4 performed less well. Finally, the third step consists of performing a TE in all subjects (age, 18–75 y) with risk factors for liver fibrosis and FLI $\geq$ 60. The

lower threshold of age could be increased to 40 to 50 years because of the low prevalence of liver fibrosis in subjects younger than this age according to our findings. Subjects with LS $<$ 9.2 kPa should not be referred for a hepatology consultation because of a very low likelihood of significant liver fibrosis. These subjects should be managed in primary care by general practitioners and nurses and enrolled in specific lifestyle modification programs.[3,4,22,23] By contrast, subjects with LS $\geq$ 9.2 kPa should be referred to a hospital for a hepatology consultation. A cost-effectiveness analysis of this proposed algorithm for screening in the general population was not performed. Nonetheless, the feasibility of such a public health intervention depends solely on the targeted group. If applied to a general population setting, the number of subjects needed to scan to correctly diagnose one new case of significant fibrosis is approximately 36.7 individuals. However, with the current prevalence estimates and within the proposed algorithm, this number decreases to 13.8, which represents an efficiency gain of 2.65-fold with respect to the first scenario.

This study had some limitations that should be mentioned. First, the population studied was mainly of Caucasian origin, with only 5% of subjects from other ethnic origins. Therefore, we do not know if the results found apply to other ethnic groups. Second, the XL probe was not available in this study. The use of this probe could reduce the number of unreliable measurements of LS, particularly among obese subjects, and also perhaps the number of false-positive results. Moreover, it would have been interesting to quantify the amount of fat in the liver by using a controlled attenuation parameter, a system that is coupled to LS measurement[24]; however, this tool was not available. Finally, as mentioned previously, it would have been ideal to have a higher number of subjects with a liver histology assessment; however, a 31% rate of liver biopsy is rather high for a population-based study in asymptomatic subjects with previously unknown liver disease.

In conclusion, the findings of this population-based study show an unexpectedly high prevalence of significant liver fibrosis, mainly related to NAFLD, in a European urban population aged 18 to 75 years with previously unknown liver disease of almost exclusive Caucasian origin. These data highlight the relevance of NAFLD as a major health issue and suggest that effective screening and preventive and therapeutic measures should be taken to reduce the present and future impact of this disease in the population.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2017.12.048.

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Conflicts of interest
The authors disclose no conflicts.

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Supplementary Materials

Transient Elastography

TE was performed using the Fibroscan system (402; Echosens). This method estimates the LS, which is known to have a good correlation with the severity of liver fibrosis.[1–3] The basis and characteristics of TE can be found elsewhere.[4] Measurements were performed on the right lobe of the liver after a minimum of a 6-hour fast. The final value given was the average of 10 measurements. Criteria for exclusion were an inability to obtain 10 valid measurements and/or an interquartile range/liver stiffness measurement ratio greater than 30%. All procedures were performed by trained nurses with the same machine using the M probe, the only probe available at the time of study initiation. The Fibroscan system was freely provided by the manufacturing company (Echosens). Echosens did not participate in the design or development of the study, had no access to the database, and was neither involved in the analysis of the results nor in writing the manuscript.

Liver Histology

Fibrosis was staged from 0 to 4: F0, no fibrosis; F1, portal fibrosis; F2, periportal fibrosis; F3, bridging fibrosis; and F4, cirrhosis, according to criteria published elsewhere.[5]

Statistical Analysis

The study was planned to have a sample size of 3000 patients to detect, with a significance of 5%, a prevalence of LS $\geq$ 6.8 kPa of 8% with 1% accuracy. This sample also allowed detection of an odds ratio $\geq$ 2.0 for a factor present in the 7% of subjects with LS $<$ 6.8 kPa and 80% statistical power. Descriptive analysis used frequencies and percentages (categoric variables), means and SD (symmetric distributed continuous variables), and median and interquartile range (skewed continuous variables). Bivariate comparisons of high/low LS (using the mentioned cut-off values) with potential explanatory variables was performed using chi-squared tests (percentages, using the exact version when appropriate), *t* tests (means), and Mann–Whitney tests (medians). In the case of comparisons of more than 2 means, analysis of variance was used. Multivariate logistic regression was used to assess the relationship between high/low LS (dependent variable) and mutually adjusted risk factors (plus age). Only variables with a *P* value less than .05 odds ratios were included in the models. Receiver operating characteristic curves were drawn to show the performance of different methods assessing fibrosis (using the histologic examination F2–F4 as the gold standard). The area under the receiver operating characteristic curve values were compared using the DeLong et al[6] method. All comparisons were bilateral and the significance was 0.05. Stata v14 (Data Analysis and Statistical Software; Stata Corp LLC, TX) was used to analyze data. The protocol was approved by the Ethics Committee of the Fundació Goli Gorina (P11/58) (Barcelona, Spain), and all subjects provided written informed consent to participate in the study.

Definition of Risk Alcohol Consumption

Alcohol risk consumption was defined as a consumption of $\geq$21 standard drinking units/wk in men and $\geq$14 standard drinking units/wk in women.

Definition of Metabolic Syndrome

Metabolic syndrome was defined according to the National Cholesterol Education Programme Adult Treatment Panel III criteria: waist circumference $>$102 cm in males and $>$88 cm in females, arterial hypertension ($\geq$135 mm Hg/$\geq$85 mm Hg), basal glycemia $\geq$110 mg/dL, high-density lipoprotein cholesterol $<$50 mg/dL in women and $<$40 mg/dL in men, and triglyceride level $\geq$150 mg/dL. A patient must have 3 or more of these components to be considered as having metabolic syndrome.

Supplementary References

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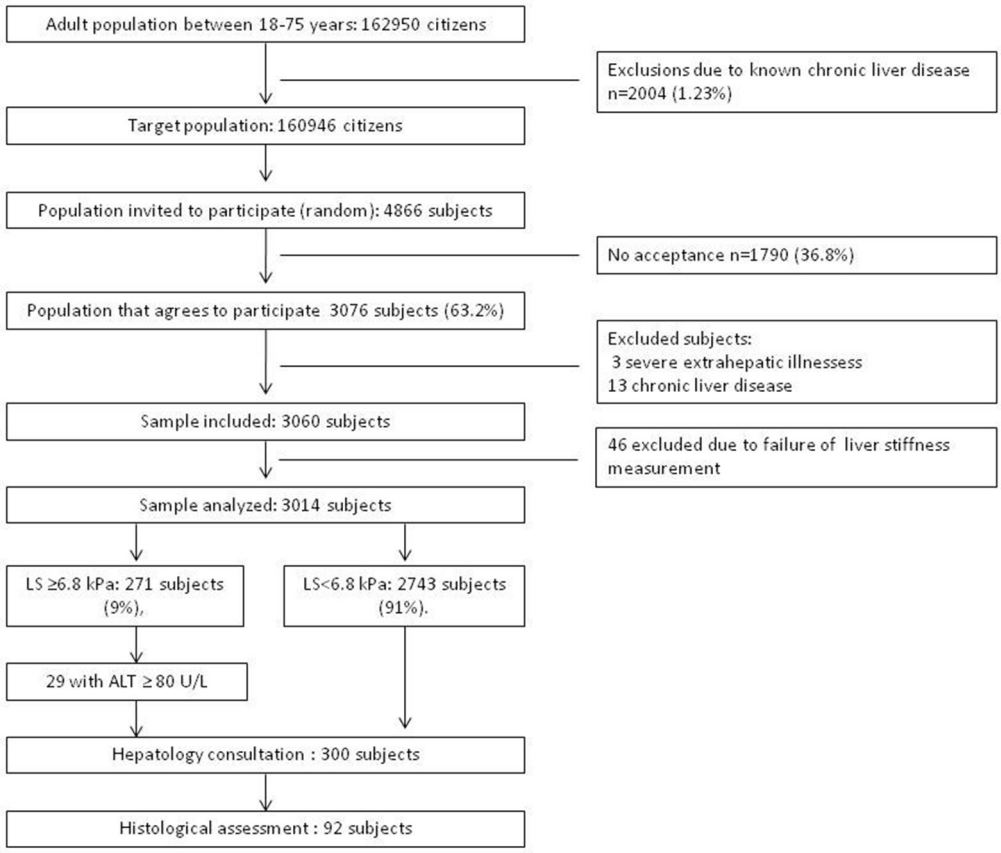
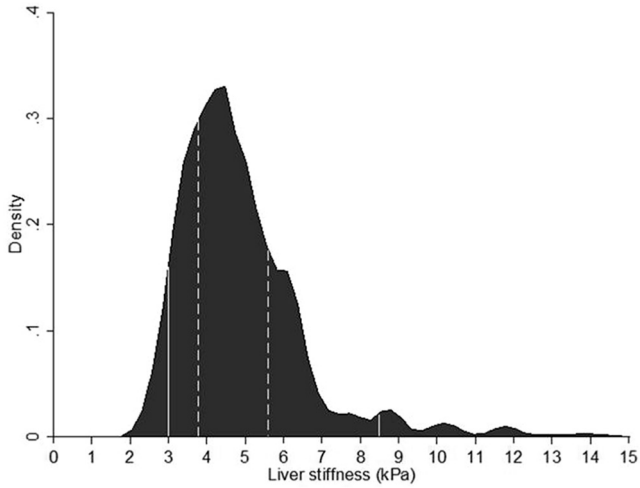
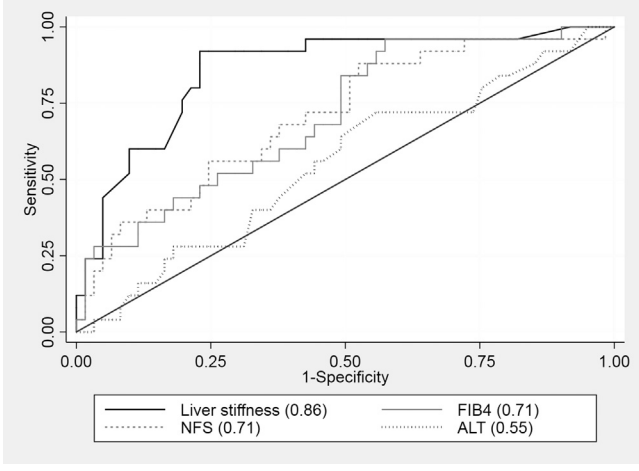


Supplementary Figure 1. Flow chart of the study.



Supplementary Figure 2. Distribution of liver stiffness values in the whole population studied.



Supplementary Figure 3. Comparison of the area under the receiver operating characteristic curves for significant liver fibrosis (≥F2) according to liver biopsy and LS measurement, NAFLD fibrosis score (NFS), FIB-4, and ALT levels.

Supplementary Table 1. Characteristics of Subjects Included in the Study. Categorized Into 2 Groups According to a Cut-Off Level of Liver Stiffness of 6.8 kPa

	<6.8 kPa (n = 2743)	≥6.8 kPa (n = 271)	*P* value
Male, n (%)	1114 (41)	175 (65)	<.001
Age, *y*	54 ± 12	58 ± 10	<.001
Caucasian, n (%)	2562 (94)	256 (94)	.442
Body mass index			
Overweight, ≥25 to <30 kg/m^2, n (%)	1193 (44)	58 (21)	<.001
Obesity, ≥30 kg/m^2, n (%)	740 (27)	193 (71)	
Abdominal obesity,[a] n (%)	1276 (47)	209 (78)	<.001
Alcohol risk consumption,[b] n (%)	231 (8)	44 (16)	<.001
Arterial hypertension, n (%)	670 (24)	121 (45)	<.001
Type 2 diabetes, n (%)	223 (8)	85 (31)	<.001
Hypercholesterolemia, n (%)	992 (36)	136 (50)	<.001
Hypertriglyceridemia, n (%)	270 (10)	51 (19)	<.001
Metabolic syndrome,[c] n (%)	644 (25)	173 (65)	<.001
Glucose level, *mg/dL*	99 (23)	119 (40)	<.001
Glycosilated hemoglobin, %	5.6 ± 0.6	6.2 ± 1.1	<.001
Total cholesterol level, *mg/dL*	213 (39)	206 (40)	.005
HDL level, *mg/dL*	56 (13)	48 (12)	<.001
LDL level, *mg/dL*	135 (34)	126 (38)	<.001
Triglyceride level, *mg/dL*	118 (70)	181 (136)	<.001
AST level, *U/L*	23 (8)	28 (15)	<.001
ALT level, *U/L*	23 (14)	31 (18)	<.001
AST and/or ALT >ULN,[d] n (%)	196 (7)	55 (21)	<.001
GGT level, *U/L*	22 (16–33)	36 (25–62)	<.001
HBsAg positive, n (%)	22 (1)	1 (0.4)	.423
Anti-HCV positive, n (%)	8 (0.3)	1 (0.4)	.838
FLI,[e] n (%)			
<30	910 (36)	24 (9)	<.001
30–60	802 (31)	21 (8)	
≥60	846 (33)	216 (83)	

NOTE. Data are n (%) or means (±SD), except for γ-glutamyltransferase, which is median (interquartile range). *P* value was for a *t* test (continuous variables) or chi-squared test (categoric variables). The Mann–Whitney test was used when medians are presented.
AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ULN, upper limit normal.
[a]Waist circumference ≥102 cm in men or ≥88 cm in women.
[b]≥21 standard drinking units/wk for men and ≥14 standard drinking units/wk for women.
[c]Metabolic syndrome (National Cholesterol Education Programme Adult Treatment Panel III): >102 cm in males and >88 cm in females, arterial hypertension (≥135 mm Hg/≥85 mm Hg), basal glycemia ≥110 mg/dL, HDLc < 50 mg/dL in women and <40 mg/dL in men, and triglyceride level ≥150 mg/dL. A patient must have 3 or more of these components to be considered as having metabolic syndrome.
[d]ULN was 40 U/L.
[e]The FLI estimates the amount of fat in the liver, including body mass index, waist circumference, and serum γ-glutamyltransferase and triglycerides.

Supplementary Table 2. Multivariate Analysis of Factors Associated With Increased LS Using 3 Different Cut-Off Values Excluding Patients With Alcohol Risk Consumption and/or Hepatitis B Virus/Hepatitis C Virus Positive (n = 2710)

	6.8 kPa				8.0 kPa				9.0 kPa			
	OR	95% CI		*P* value	OR	95% CI		*P* value	OR	95% CI		*P* value
Male sex	2.86	2.08	4.05	.000	2.74	1.87	4.03	.000	3.49	2.12	5.72	.000
AST and/or ALT >ULN[a]	2.18	1.44	3.29	.000	1.91	1.16	3.14	.011	3.27	1.87	5.72	.000
Abdominal obesity[b]	4.06	2.81	5.88	.000	4.95	3.02	8.11	.000	5.12	2.71	9.66	.000
Glucose ≥100 mg/dL	1.63	1.15	2.32	.030	2.02	1.30	3.15	.002	2.35	1.30	4.25	.004
Low HDL level[c]	1.46	1.04	2.05	.030	1.77	1.18	2.60	.006	1.66	1.00	2.77	.052
Triglyceride level ≥150 mg/dL	1.60	1.15	2.22	.005	1.75	1.18	2.60	.006	1.29	0.78	2.13	.329
Type 2 diabetes	2.41	1.63	3.55	.000	2.07	1.32	3.25	.001	2.30	1.33	3.98	.003

NOTE. Logistic multivariate regression using dichotomized liver stiffness as a dependent variable. All variables mutually adjusted for age and sex.
AST, aspartate aminotransferase; HDL, high-density lipoprotein; OR, odds ratio; ULN, upper limit of normal.
[a]ULN was 40 U/L.
[b]Waist circumference ≥102 cm in men or ≥88 cm in women.
[c]HDL<40 mg/dL in men or <50 mg/dL in women.

Supplementary Table 3. Prevalences of Increased LS According to Different Risk Factors in Patients Categorized Using 3 Different Cut-Off Values

		LS prevalence					
		6.8 kPa		8.0 kPa		9.0 kPa	
	n	Prevalence	95% CI	Prevalence	95% CI	Prevalence	95% CI
Sex							
Male	1289	14%	(12%–16%)	9%	(7%–10%)	6%	(5%–7%)
Female	1725	6%	(5%–7%)	4%	(3%–5%)	2%	(1%–3%)
Age, *y*							
<50	983	6%	(4%–7%)	3%	(2%–4%)	2%	(1%–3%)
≥50	2031	11%	(9%–12%)	7%	(6%–8%)	5%	(4%–6%)
Body mass index							
Normal, <25 kg/m^2	813	2%	(2%–4%)	1%	(0%–2%)	0%	(0%–1%)
Overweight, ≥25 to <30 kg/m^2	1251	5%	(4%–6%)	3%	(2%–4%)	2%	(1%–3%)
Obesity, ≥30 kg/m^2	933	21%	(18%–23%)	14%	(12%–16%)	9%	(7%–11%)
Abdominal obesity[a]							
No	1498	4%	(3%–5%)	2%	(1%–3%)	1%	(1%–2%)
Yes	1485	14%	(12%–16%)	9%	(8%–11%)	6%	(5%–7%)
Alcohol consumption							
Never/former/mild drinker	2737	8%	(7%–9%)	5%	(5%–6%)	3%	(3%–4%)
Alcohol risk consumption[b]	275	16%	(12%–21%)	10%	(7%–14%)	7%	(4%–10%)
Arterial hypertension							
No	2223	7%	(6%–8%)	4%	(3%–5%)	2%	(2%–3%)
Yes	791	15%	(13%–18%)	10%	(8%–13%)	7%	(5%–9%)
Type 2 diabetes							
No	2706	7%	(6%–8%)	4%	(3%–5%)	2%	(2%–3%)
Yes	308	28%	(23%–33%)	20%	(16%–25%)	14%	(11%–19%)
Hypertriglyceridemia							
No	2693	8%	(7%–9%)	5%	(4%–6%)	3%	(3%–4%)
Yes	321	16%	(12%–20%)	11%	(8%–15%)	7%	(4%–10%)
Transaminases, AST/ALT							
Transaminase levels ≤ULN[c]	2654	8%	(7%–9%)	5%	(4%–6%)	3%	(2%–4%)
Transaminase levels >ULN	251	22%	(17%–28%)	14%	(10%–19%)	12%	(8%–16%)
Metabolic syndrome[d]							
No	2069	5%	(4%–6%)	3%	(2%–3%)	1%	(1%–2%)
Yes	817	21%	(18%–24%)	14%	(12%–17%)	9%	(7%–11%)
FLI[e]							
<30	934	3%	(2%–4%)	1%	(0%–1%)	0%	(0%–1%)
30–60	823	3%	(2%–4%)	2%	(1%–3%)	1%	(0%–2%)
≥60	1062	20%	(18%–23%)	14%	(12%–16%)	9%	(7%–11%)

AST, aspartate aminotransferase; ULN, upper limit of normal.

[a]Waist circumference ≥102 cm in men or ≥88 cm in women.

[b]≥21 standard drinking units/wk men and ≥14 standard drinking units/wk women.

[c]ULN was 40 U/L.

[d]Metabolic syndrome (National Cholesterol Education Programme Adult Treatment Panel III): >102 cm in males and >88 cm in females, arterial hypertension (≥135 mm Hg/≥85 mm Hg), basal glycemia ≥110 mg/dL, HDLc <50 mg/dL in women and <40 mg/dL in men, and triglycerides ≥150 mg/dL. A patient must have 3 or more of these components to be considered as having metabolic syndrome.

[e]The FLI estimates the amount of fat in the liver, including body mass index, waist circumference, and serum γ-glutamyltransferase and triglycerides.

Supplementary Table 4. Liver Stiffness Values in Patients Classified According to. Fibrosis Severity in the Liver Biopsy

	LS, *kPa*				
Fibrosis	n	Mean	SD	Minimum	Maximum	*P* value
F0–F1	64	8.4	1.9	3.5	14.3	<.001
F2	21	10.7	1.5	6.9	13.9	
F3	3	14.2	1.6	12.8	16	
F4	4	30.8	10.8	21.3	46.4	

NOTE. F0–F4 according to METAVIR classification. *P* value is for analysis of variance *t* test.

Supplementary Table 5. Number of Patients With Liver Stiffness ≥ 9.2 kPa

	LS ≥9.2 kPa					
	No	Yes	Sensitivity	Specificity	PPV	NPV
NFS						
Mild/high	721	63	75%	52%	8%	97
Low	774	21				
FIB-4						
Mild/high	578	42	48%	62%	7%	95
Low	943	45				
FLI						
High	919	87	98%	41%	9%	99.7%
Low/mild	628	2				
AST/ALT						
>40	160	27	29%	90%	14%	96%
≤40	1430	66				

NOTE. Sensitivity, specificity, positive predictive value, and negative predictive value according to values of NFS, FIB-4, FLI, and transaminases values.
AST, aspartate aminotransferase; NFS, NAFLD fibrosis score; NPV, negative predictive value; PPV, positive predictive value.