Prospective screening for significant liver fibrosis by fibrosis-4 in primary care patients without known liver disease

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Background Fibrosis-4 test (FIB-4) is one of the simplest, free of charge, noninvasive scoring tests. We aimed to prospectively measure the prevalence of liver fibrosis in adults with no previously known liver disease and who consulted a general practitioner by FIB-4 score; compare this test to an NAFLD Fibrosis Score (NFS) and Fibrometer (FM); explore the prevalence of risk factors (obesity, diabetes, alcohol, and hypertension) and reconsider a possible cause of liver disease in patients recognized as FIB-4-positive.

Methods Over a 6-month period, 40 general practitioners (GPs) offered all their consecutive adult primary care patients with no previously known liver pathology and a liver fibrosis screening via a blood test of three scores.

Results Among the consecutive 2121 patients included in the study, 39% had a BMI greater than 25 kg/m^2, 13% had an alcohol consumption greater than 100 g/week, 10% had type 2 diabetes, and 29% had hypertension. The prevalence of significant liver fibrosis by FIB-4, according to age was 19.1% (95% confidence interval: 17.5–20.9%). By comparison, prevalence was 16.8% (15.0–18.5%) by the NFS and 8.2% (6.9–9.6%) by the FM. A significant relationship was observed between FIB-4 fibrosis risk stages and NFS and FM scores. GPs identified the cause of disease in 2/3 of FIB-4-positive cases, mainly nonalcoholic steatohepatitis.

Conclusion Liver fibrosis was suspected by FIB-4 score in 19.1% of patients with no previously known liver disease. The detection of significant fibrosis by the FIB-4 allowed the GP to suspect liver disease. The FIB-4 score that can be automatically generated should allow earlier recognition of liver disease in the general population. Eur J Gastroenterol Hepatol 33: e986–e991

Introduction

Chronic liver disease (CLD) can lead to a progressive accumulation of fibrosis in the liver which may progress to cirrhosis and hepatocellular carcinoma (HCC). The burden of CLD worldwide is substantial, with approximatively 2 million deaths annually attributed to cirrhosis and HCC, caused mainly by nonalcoholic fatty liver disease (NAFLD), alcohol-related liver disease, or viral hepatitis, in addition to other important but less common causes of CLD [1–6].

Both the prognosis and the management of CLD patients are closely linked to liver fibrosis. Treating the cause of CLD is mandatory to prevent further progression of fibrosis to cirrhosis and its complications [3–6]. Liver biopsy is the reference procedure for a liver fibrosis

Key Points

Liver fibrosis was suspected by FIB-4 score in 406 of 2121 (19.1%) patients with previously unknown hepatic pathology, who consult a general practitioner. A significant relationship was observed between FIB-4 fibrosis risk stages (low, intermediate, and high risk) and significant fibrosis defined by two other more accurate but more costly scores, namely NAFLD score and Fibrometer. The detection of significant fibrosis by this simple FIB-4 blood test allowed the general practitioner to suspect a chronic liver disease and to define its cause in 2/3 of cases. The FIB-4 score is automatically generated as soon as the transaminases and platelets levels are measured and allows earlier recognition and management of chronic liver disease.

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Keywords: fibrosis-4 test, general practice, liver fibrosis, noninvasive tests, screening

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evaluation, but its invasive nature makes it unsuitable as a first-line procedure. Blood tests and liver stiffness measurement (LSM) by transient elastography have been recently developed for the noninvasive evaluation of liver fibrosis and provide an exciting alternative to biopsy [7]. However, the high cost of the most accurate blood fibrosis test (Fibrosure, Fibrometer [8–10]) limits its widespread use and liver elastometry is only accessible in specialized centers. Other scores, simple and usable in current medical practice, are based on a simple and free calculation of commonly measured biomarkers: FIB-4 [11] Aspartate aminotransferase to Platelets Ratio Index [12], NAFLD Fibrosis Score (NFS) [13]. Among these noninvasive simple indexes, FIB-4 and NFS offer the best diagnostic performance for detecting significant fibrosis [5,6,14].

In practice, most CLD patients are seen and managed by general practitioners (GPs) who encounter challenges in evaluating a liver disease that remains silent for many years with normal routine diagnostic tests. In addition, GPs have very limited access to the best noninvasive liver fibrosis tests. Consequently, CLD remains unrecognized in many patients with progressive fibrosis. Thus, the liver conditions in these patients are diagnosed too late when they have reached the stage of cirrhosis.

The FIB-4 score appears as a new screening tool for hepatic fibrosis, which is simple, based on biomarkers of current practice, free of charge, and usable 'at a glance' by all physicians, who may or may not be specialized in hepatology. FIB-4 can be automatically generated as soon as the transaminases and platelets levels are measured. Earlier detection and management of CLD would be possible by detecting significant fibrosis through the use of FIB-4 in primary care.

Objective and methods

The main objective of the study was to evaluate the pertinence of systematically screening hepatic fibrosis by FIB-4 test in the population of adult subjects consulting in general medicine, outside of emergency or acute pathologies, and with no previously known liver disease. Patients screened with an FIB-4 score predictive of significant fibrosis would receive appropriate diagnostic and therapeutic management, according to the usual procedures implemented by GPs. The secondary objectives were to estimate the prevalence of comorbidities, overweight, diabetes, hypertension, and alcohol consumption; to compare the results of FIB-4 score with another simple score (NFS) and with a more accurate score Fibrometer; to identify independent risk factors for significant hepatic fibrosis among the comorbidities identified; and to reconsider the main causes of liver damage, if applicable.

Over a 6-month period, from 1 October 2018 to 31 March 2019, 2121 patients from 40 GPs in the French Alpes Maritimes were included. Inclusion criteria were adult primary care patients, with no previously known liver pathology and liver fibrosis screening via a simple blood test allowing calculation of the noninvasive fibrosis scores. Details of the formulas and cutoffs for the tests under investigation are shown in Table 1. Previously published cutoffs were used to exclude and diagnose significant fibrosis for each score [9–11,13,15]. New thresholds for FIB-4 and NFS were used in patients aged greater than 65 years [16]. Referral to a specialist of the FIB-4-positive subjects was left to the GP's discretion. Transient elastography performed by the specialist was considered in our study as the reference test for the detection of hepatic fibrosis.

Statistical methods

Continuous data were expressed as mean and SD, whereas categorical data were expressed as frequency and percentages. Univariate analysis used the chi-square test and was followed by a multivariate logistic regression with a stepwise selection model on univariate significant parameters. A multivariate logistic regression with a stepwise selection model (with 0.05 significance level for entering effects and 0.10 for removing effects) was assessed on univariate significant parameters. The effect of significant risk factors of fibrosis was expressed using an odds ratio (OR; Oregon) and a 95% confidence interval (95% CI). All *P* values were considered significant at an alpha level less than 0.05. All calculations were performed using STATA MP11 (StataCorp LP, College Station, Texas, USA) and SAS V9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Among the 2121 consecutive patients included [sex ratio M/F 0.62, mean age 62 years (SD 10)], 39% had a BMI greater than 25 kg/m^2 and 13% BMI greater than 30 kg/m^2, 13% had an alcohol consumption greater than 100 g/week, 10% had type 2 diabetes, and 29% had hypertension (Table 2). Increased aspartate aminotransferase rate was found in 6.8%, alanine aminotransferase in 6.1%, and gamma glutaryl transferase in 15% of cases. The prevalence of significant hepatic fibrosis defined as an FIB-4 greater than or equal to 1.3 (for <65 years) and greater than or equal to 2 (for >65 years) was 19.1% (406/2121) (95% CI 17.5–20.9%). Among these 406 FIB-4-positive patients, 37 (1.7%) had an FIB-4 greater than 2.67, indicating a high risk of liver fibrosis [15]. By comparison, the prevalence was 16.8% (290/1728) (15.0–18.5%) by the NFS defined as NFS greater than or equal to –1.455 (for <65 years) and greater than or equal to 0.12 (for ≥65 years), and the prevalence was 8.2% (138/1707) (6.9–9.6 %) as measured by the Fibrometer.

Univariate analyses showed that all risk factors are significantly associated with fibrosis irrespective of the scores, except the diabetes factor which is not significant for FIB-4 testing (Table 3). Multivariate analyses showed that male sex and hypertension are significant factors of fibrosis when NFS testing: ORs 1.5 (1.1–1.9) $P < 0.01$ and 1.7 (1.3–2.2) $P < 0.001$, respectively. Hypertension, alcohol consumption, and diabetes are significant factors of fibrosis when Fibrometer testing: ORs 1.8 (1.2–2.8) $P < 0.01$ for hypertension and 2.4 (1.4–3.9) $P < 0.01$ for alcohol consumption. An important relationship was observed between FIB-4 fibrosis risk stages (low, intermediate, and high risk) and significant fibrosis defined by NFS and Fibrometer (Table 4): 10% of patients with FIB-4 low fibrosis risk were observed with NFS significant

Table 1. An overview of the simple noninvasive fibrosis markers under investigation (FIB-4, NFS, and Fibrometer scores) [7,9–11,13,17]

Tests	Calculation method	Lower cutoff	Upper cutoff
FIB-4 score	$\frac{\text{Age} \times \text{AST (IU/L)}}{\text{Platelet Count } (\times 10^9/\text{L}) \times \sqrt{\text{ALT (IU/L)}}}$	<1.3 (<65 years) <2 (≥65 years)	≥ 1.3 (<65 years) ≥ 2 (≥65 years)
NFS	$-1.675 + 0.037 \times \text{Age (years)} + 0.094 \times \text{BMI (kg/m}^2\text{)} + 1.13 \times \text{Fasting Glycaemia or Diabetes (Yes=1, No=0)} + 0.99 \times (\text{AST/ALT}) + 0.013 \times \text{Platelet Count } (10^9/\text{L}) - 0.66 \times \text{Albumin (g/dl)}$	<–1.455 (<65 years) <0.12 (≥65 years)	0.676
Fibrometer	Patented formula including age, prothrombin index, AST, ALT, urea, GGT, A2MG, and platelet count	<F2 (F1–F3)	≥F2 (F1–F3)

A score below the lower cutoff is used to exclude significant fibrosis with reasonable accuracy and a score above the upper cutoff is suggestive of the presence of significant fibrosis.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; A2MG, alpha-2-macroblobulin; F, fibrosis stage; FIB-4, fibrosis 4; GGT, gamma glutaryl transferase; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score.

Table 2. Characteristics of the 2121 patients

	Patients (*N* = 2121)
Sex ratio M/F	0.62
Age; mean (SD) (years)	62 (10)
Age; *n* (%) (years)	
45–54	521 (25)
55–64	653 (31)
≥65	947 (45)
BMI; mean (SD) (kg/m^2)	26 (5)
BMI; *n* (%) (kg/m^2)	
Underweight (<18.5)	77 (4)
Normal weight (18.5 to <25)	1220 (58)
Overweight (25 to <30)	556 (26)
Obesity (≥30)	268 (13)
Alcohol, *n* (%) (g/week)	
≤10	1842 (87)
>10	279 (13)
Diabetes; *n* (%)	214 (10)
Hypertension; *n* (%)	610 (29)
AST > IU/L; *n* (%)	147 (7)
ALT > IU/L; *n* (%)	127 (6)
GGT > IU/L; *n* (%)	318(15)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; F, female; GGT, gamma glutaryl transferase; M, male.

fibrosis (144/1405), 42% of FIB-4 intermediate fibrosis risk (125/295), and 75% of FIB-4 high fibrosis risk (21/28) ($P < 0.001$) (and 5, 16, and 54% were observed also with Fibrometer significant fibrosis, respectively, among FIB-4 low, intermediate, and high fibrosis risk, $P < 0.001$).

GPs defined the cause of liver damage in 193 (i.e. 65%) patients among the 295 out of 406 FIB-4-positive patients in which this information could be analyzed – NAFLD: 97, alcohol: 48, both: 24, other: 24 cases. Referral to a specialist was left to the GP's discretion. Specialized advice was requested by the GP for only 65 out of 406 FIB-4-positive patients. Among these, 62 patients had interpretable LSMs by transient elastography: 13 (21%) had an LSM greater than 7 kPa with a fibrosis stage F2 (7–9.5 kPa) for 9, F3 (9.5–14.5 kPa) for 2, and F4 greater than 14.5 kPa for 2. Among the 37 subjects with FIB-4 greater than 2.67, liver stiffness was measured in 11 subjects (29.7%). Significant fibrosis at the 7-kPa threshold was demonstrated in 8 of the 11 subjects. A cause of CLD was found in all patients with LSM greater than 7 kPa and in 41% of patients with LSM less than 7 kPa ($P < 0.05$). The percentage of significant fibrosis according to the 7-kPa threshold was significantly higher in patients with FIB-4 greater than 2.67 [62 % (8/13)] than in those with FIB-4 less than 2.67 [6% (3/49)] $P < 0.001$ (Table 5). This percentage was also higher in patients with a cause of CLD [39% (13/33)] as compared with those without cause of CLD [0% (0/29)] $P < 0.01$.

Discussion

The first two studies on screening for significant liver fibrosis in general practice were conducted by measuring liver stiffness using transient elastography. The liver elasticity threshold used in these two studies was 7 kPa. These two studies showed a prevalence of 17% of significant fibrosis in subjects who consulted in general practice [17,18]. However, screening for hepatic fibrosis by measuring hepatic elasticity in subjects who consult a GP is difficult to achieve in general practice in France. We have, therefore, used the simplest and most widely used fibrosis blood test, the FIB-4 Fibrosis score, to prospectively define the prevalence of significant fibrosis in a population of 2121 consecutive subjects consulting a GP with no previously known hepatic disease. Most other studies in general practice have considered a higher threshold of fibrosis, referred to as advanced fibrosis [19,20], to distinguish patients to be referred to specialists from those who could continue to be followed in general practice. Some have proposed an algorithm using FIB-4 and then a specialized enhanced liver fibrosis test in FIB-4-positive subjects to refine the search for subjects with advanced fibrosis [21]. This succession of tests

Table 3. Uni- and multivariate analyses of risk factors associated with fibrosis according to FIB-4, nonalcoholic fatty liver disease fibrosis score, and Fibrometer

	FIB-4 (*N* = 2121)					NFS (*N* = 1728)					Fibrometer (*N* = 1687)				
	Univariate			Multivariate		Univariate			Multivariate		Univariate			Multivariate	
Parameters	No fibrosis (*N* = 1715)	Fibrosis (*N* = 406)	*P* value	Odds ratio (95 % CI)	*P* value	No fibrosis (*N* = 1438)	Fibrosis (*N* = 290)	*P* value	Odds ratio (95 % CI)	*P* value	No fibrosis (*N* = 1549)	Fibrosis (*N* = 138)	*P* value	Odds ratio (95 % CI)	*P* value
Hypertension	519 (30%)	91 (22%)	<0.01	0.7 (0.5–2.3)	<0.01	387 (27%)	112 (39%)	<0.001	1.7 (1.3–2.2)	<0.001	413 (27%)	72 (52%)	<0.001	1.8 (1.2–2.8)	<0.01
Alcohol			<0.05					<0.05					<0.001		
≤10	1503 (88%)	339 (84%)		-	NS	1263 (88%)	239 (82%)				1376 (89%)	96 (70%)			
>10	212 (12%)	67 (17%)		-	NS	175 (12%)	51 (18%)			NS	173 (11%)	42 (30%)		2.4 (1.4–3.9)	<0.01
BMI			<0.001					<0.001[a]					<0.001		
Underweight	30 (2%)	10 (3%)			NS	63 (4%)	3 (1%)		-	-	28 (2%)	0		-	NS
Normal weight	732 (43%)	215 (53%)			NS	902 (63%)	106 (37%)		-	-	708 (46%)	42 (30%)		-	NS
Overweight	606 (35%)	123 (30%)			<0.01	349 (24%)	94 (32%)		-	-	527 (34%)	58 (42%)		-	NS
Obesity	347 (20%)	58 (14%)		0.7 (0.5–2.3)		124 (9%)	87 (30%)		-	-	286 (19%)	38 (28%)		-	NS
Diabetes	182 (11%)	32 (8%)	NS	-	NS	69 (5%)	95 (33%)	<0.001[a]			129 (8%)	31 (23%)	<0.001	2.4 (1.4–3.9)	<0.01

FIB-4, fibrosis 4; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score.
[a]BMI and diabetes are constitutive parameters of NAFLD score,NFS, thus these were not included in multivariate analysis.

Table 4. Relationship between the fibrosis-4 test, nonalcoholic fatty liver disease fibrosis score, and the Fibrometer scores for the three risk classes (low, intermediate, and high) of the fibrosis-4 test score

	FIB-4			
Tests	FIB-4 Low risk of fibrosis <1.3 (<65 years) <2 (≥65 years)	FIB-4 intermediate risk of fibrosis ≥1.3 to ≤2.67 (<65 years) ≥2 to ≤2.67 (≥65 years)	FIB-4 high risk of fibrosis >2.67	*P* value[a]
NFS significant fibrosis (≥−1.455 in patients <65 years) (≥0.12 in patients ≥65 years)	144/1405 (10%)	125/295 (42%)	21/28 (75%)	<0.001
Fibrometer Significant Fibrosis	71/1369 (5%)	46/290 (16%)	15/28 (54%)	<0.001

FIB-4, fibrosis 4; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score.
[a]Chi-square test.

Table 5. Relationship between liver stiffness measurement, fibrosis-4 test, and cause of chronic liver disease

LSM (*n* = 62)	≥7 kPa (*n* = 13)	<7 kPa(*n* = 49)
FIB-4 ≥ 2.67	8	3
Cause of CLD	13 (NASH 7; alcohol 5; both 1)	20 (NASH 15; alcohol 4; both 1)

Specialized advice was requested for 65/406 FIB-4-positive patients, with 62/65 interpretable liver stiffness measurement.
CLD, chronic liver disease; FIB-4, fibrosis-4 test; LSM, liver stiffness measurement; NASH, nonalcoholic steatohepatitis.

is costly and difficult to implement in general practice. We based our study on FIB-4 by taking a blood sample for NFS and Fibrometer tests. Using the recommended FIB-4 thresholds based on age, we observed a rate of significant fibrosis of 19.1%, close to the one reported with transient elastography. Comparable rates were observed with the NFS, which is more complicated to perform than the FIB-4 one as it requires two additional tests: blood glucose and albumin levels. Comparison of the three serum biomarkers of liver fibrosis showed a significant correlation between the FIB-4 risk score and the NFS and Fibrometer scores for the three risk classes of FIB-4 (low, intermediate, and high risk). As the risk of fibrosis determined by FIB-4 increases, the percentage of fibrosis determined by NFS and Fibrometer increases ($P < 0.001$), especially in patients with a high-risk FIB-4 fibrosis score greater than 2.67. The prevalence of a high risk of fibrosis greater than 2.67 detected in the general population by the FIB-4 was 1.7% in our study. In several studies, this percentage is about 7% [22]. The reason why our results diverge from other studies is that we included subjects without known liver disease. Respectively, NFS and Fibrometer scores confirmed 75% and 54% of patients with a high risk of fibrosis FIB-4 score greater than 2.67 (Table 4). As expected, the specialized Fibrometer test showed the best independent correlation with three risk factors (hypertension, alcohol consumption, and diabetes). However, the high cost of one of the most accurate blood fibrosis tests, Fibrometer, limits its widespread screening use. It should be noted in our study that 39% of the subjects who consulted a GP were overweight, with 20% being obese. The elevation of transaminases that allows the suspicion of liver disease was found in 6% of cases, that is, about 1/3 of that observed with FIB-4. Provided with a positive FIB-4 test in subjects who were unknown to have liver disease, GPs were able to find a cause for significant liver fibrosis in 2/3 of the cases and mainly nonalcoholic steatohepatitis in 1/3 of the cases. Thus, one important finding of this

work is that running a test as simple as the FIB-4 could make it possible to identify a previously unknown CLD in general medicine. The positivity of this test may also increase the patient's awareness of a liver disease risk factor (overweight and excessive alcohol consumption). Referral to the specialist was left to the GP's discretion, which explains why only 65 of the 406 FIB-4-positive subjects were referred to the specialist who performed transient elastography. However, NFS or Fibrometer second-line specialized tests were available in almost 80% of FIB-4-positive patients. Significant fibrosis was confirmed by transient elastography in 21% of cases. The percentage of significant fibrosis according to the 7-kPa threshold was significantly higher in patients with FIB-4 greater than 2.67 (as NAFLD and Fibrometer score) and in those with a cause of liver disease risk factor. Subjects recognized as FIB-4-positive that can be confirmed as a priority are therefore those with FIB-4 greater than 2.67 with a cause of liver disease (Table 5). However, a cause of the liver disease was found in 41% of patients without significant fibrosis by LSM. Thus, the FIB-4 score allow the tecognition of a CLD without fibrosis. It is important to act on the liver disease risk factor for patients without significant fibrosis to avoid the development of liver fibrosis. This work allowed us to convince all the clinical laboratories in the French department of the Alpes Maritimes, that is, 120 clinical laboratories, to systematically carry out an FIB-4 calculation as soon as transaminases and platelets were prescribed, as of 1 October 2020. The detection of liver disease through a biological test prompts GPs to look for risk factors and to act on these factors. Confirmation of FIB-4 positivity by another fibrosis test should be a priority in patients with a risk factor for liver disease. In addition, the FIB-4 score can be repeated over time, and may encourage patients to adopt a healthier lifestyle.

In conclusion, systematic screening by FIB-4 test in primary care is useful. Detecting a risk of fibrosis by this simple blood test allowed the GPsto suspect a CLD and to define its cause in 2/3 of cases. Subjects recognized as FIB-4-positive can be confirmed as those with FIB-4 greater than 2.67 with a risk factor of liver disease. FIB-4 could be automatically generated as soon as the transaminases and platelets levels are measured. Our study strongly supports this easy-to-implement strategy using a simple FIB-4 measure as a marker of liver disease. This may represent an initial step to enhance the recognition and management of CLD in the general population.

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Conflicts of interest

There are no conflicts of interest.

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