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ORIGINAL ARTICLE

Simple blood fibrosis tests reduce unnecessary referrals for specialized evaluations of liver fibrosis in NAFLD and ALD patients

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KEYWORDS
eLIFT;
FIB4;
Liver fibrosis;
Referral;
Care pathway

Summary
Background: Liver fibrosis evaluation is mandatory in non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) to decide the patient management. Patients with these diseases are usually under the care of non-liver specialists who refer them to specialized centers where the most accurate fibrosis tests are available. We aimed to evaluate whether simple blood fibrosis tests available to all physicians help to reduce the rate of unnecessary referral of NAFLD and ALD patients without advanced fibrosis.
Methods: NAFLD and/or ALD patients newly referred to our center for a non-invasive evaluation of liver fibrosis were retrospectively included. The FibroMeter^{VCTE} (FM^{VCTE}, combination of blood markers and Fibroscan results) was defined as the reference test for specialized evaluation of liver fibrosis. A FM^{VCTE} result < 0.384 indicated the absence of advanced fibrosis and thus an ''unnecessary referral''.
Results: 558 patients were included (NAFLD: 283, ALD: 156, mixed NAFLD + ALD: 119). FM^{VCTE} was < 0.384 (unnecessary referral) in 58.8% of patients. FIB4 was < 1.30 in 45.2% and eLIFT < 8 in 47.7% of the patients. 84.9% of patients with FIB4 < 1.30 and 85.3% of patients with eLIFT < 8 had also FM^{VCTE} < 0.384. Therefore, using FIB4 or eLIFT as first-line evaluation of liver fibrosis decreased by three-fold the rate of unnecessary referral. The negative predictive value of FIB4 and eLIFT was >80% whatever the underlying cause of chronic liver disease.

Abbreviations: ALD, alcoholic liver disease; eLIFT, easy liver fibrosis test; FM, FibroMeter^{V2G}; FM^{VCTE}, FibroMeter^{VCTE3G}; LSM, liver stiffness measurement; NAFLD, non-alcoholic fatty liver disease.

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Conclusion: The use of eLIFT by non-liver specialists for NAFLD and ALD patients can improve the relevance of referrals for specialized evaluation of liver fibrosis.
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Introduction

Non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) are the two most frequent causes of chronic liver disease [1—4]. Accurate staging of liver fibrosis is mandatory in NAFLD and ALD patients to evaluate the disease severity and decide the patient management [5,6]. In this context of very large populations to evaluate, non-invasive tests of liver fibrosis represent a very attractive option [7,8]. Elastography devices and specialized blood tests including direct markers of liver fibrosis are the most accurate methods for the non-invasive evaluation of liver fibrosis, contributing to a large overflow of patients referred to specialized centers where these tools are available. In clinical practice, decision to refer by non-liver specialists mainly relies on the presence of liver risk factors and/or biochemical abnormalities such as excessive alcohol consumption, liver steatosis, chronically elevated transaminases or hyperferritinemia. However, these conditions are not specific to advanced forms of liver disease. Therefore, many referred patients have no or only mild liver lesions which require only lifestyle modifications without specialized liver management. Such ''unnecessary'' referrals consume healthcare resources and induce costs which would be advantageous to avoid.

Simple blood fibrosis tests, such as the FIB4, include common biological parameters available to all physicians, with calculation at bedside thanks to free websites or smartphone applications [9]. We have recently developed a new simple blood fibrosis test specifically dedicated to non-liver specialists, the easy liver fibrosis tests (eLIFT). Compared to the other blood fibrosis tests, the eLIFT has the advantage to be easily calculated ''at-a-glance'' as it corresponds to the sum of points attributed to simple parameters: age, gender, gamma-glutamyl transferase, aspartate aminotransferase, platelets and prothrombin time (Table 1).

The aim of the present study was to evaluate whether the simple blood fibrosis tests FIB4 and eLIFT can accurately reduce the rate of unnecessary referral for specialized evaluation of liver fibrosis in NAFLD and ALD patients.

Table 1 The easy Liver Fibrosis Test (eLIFT). The eLIFT corresponds to the sum of points attributed to its six composite parameters.

Variables	Points
Age (years)	
≥40	3
Gender	
Male	1
AST (IU/L)	
35—69	2
≥70	4
Gamma-GT (IU/L)	
35—89	1
≥90	2
Platelets (G/L)	
170—249	1
<170	4
Prothrombin time (%)	
84—96	2
<84	4

Methods

Patients

All patients with NAFLD and/or ALD newly referred to our department for liver stiffness measurement between October 2014 and March 2017 were retrospectively included. All patients with a previous history of hepatocellular carcinoma or cirrhosis decompensation (liver failure, encephalopathy, ascites, variceal bleeding) were excluded. ALD was defined by excessive alcohol consumption, i.e., >210 g/week in men or >140 g/week in women. Patients were considered to have mixed NAFLD and ALD (NAFLD + ALD) when they fulfilled all the following conditions: 1/excessive alcohol consumption, 2/overweight (BMI ≥25 kg/m^2), and 3/antidiabetic and/or antihypertensive and/or lipid-lowering drugs. The study protocol conformed to the ethical guidelines of the current Declaration of Helsinki and was approved by the local Ethics Committee.

Liver stiffness measurement

Liver stiffness measurement (LSM) was performed using a Fibroscan 502 Touch device (Echosens, Paris, France) by a specialized nurse experienced with the procedure (>500 examinations) and blinded to patient data. Examination conditions were those recommended by the manufacturer [10]. LSM was stopped when 10 valid measurements were recorded, and their median was calculated thereafter to establish the result, expressed in kilopascals. Fibroscan's XL probe was used in cases of M probe LSM failure.

Blood fibrosis tests

Blood samples were taken the day of LSM and used to calculate four blood fibrosis tests according to patent or published formula: FIB4, eLIFT, FibroMeter^{V2G}, and FibroMeter^{VCTE3G} [9,11—13]. FibroMeter^{V2G} (FM) is a specialized blood fibrosis test including indirect (aspartate aminotransferase, platelets, prothrombin time, urea) and direct (hyaluronate, apha2macroglobulin) markers of liver fibrosis in association with age and sex [13]. FibroMeter^{VCTE3G} (FM^{VCTE}) is an innovative combination of FM blood markers (aspartate

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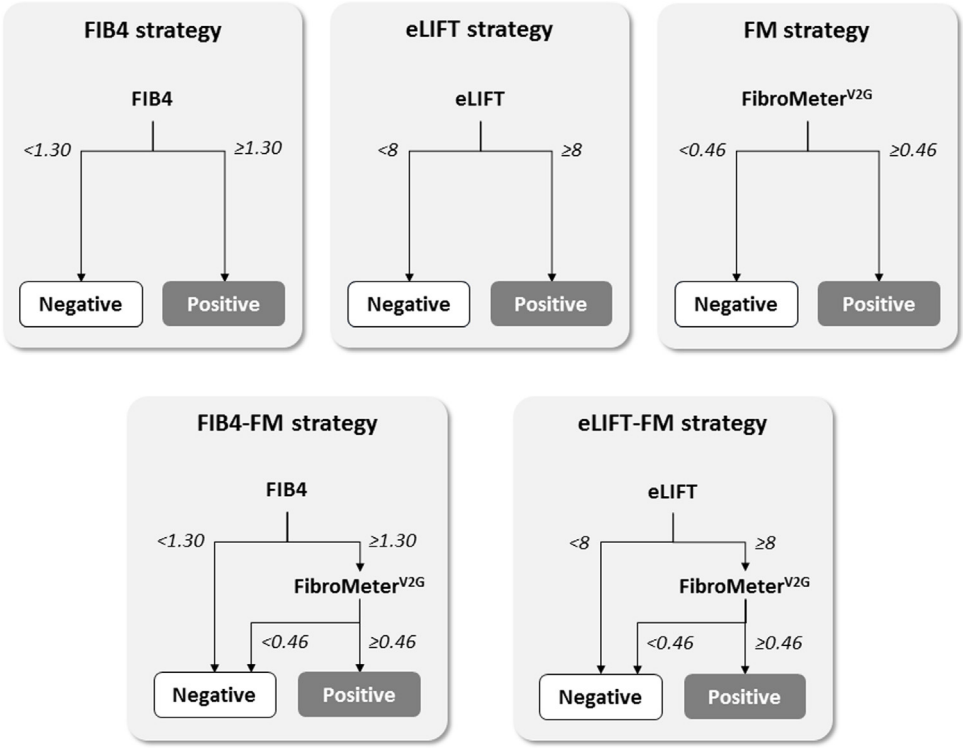

Figure 1 Five strategies tested for the first-line evaluation of liver fibrosis.

aminotransferase, gamma-GT, platelets, prothrombin time, alpha2macroglobulin) with LSM result in a single diagnostic test [11].

Specialized and first-line evaluations of liver fibrosis, decision to refer

Specialized evaluation of liver fibrosis

We recently showed that FM^{VCTE} was the most accurate non-invasive test of liver fibrosis in a large series of 1,964 patients with biopsy-proven chronic liver disease [11]. Therefore, FM^{VCTE} was chosen as the reference test for specialized evaluation of liver fibrosis in our study. FM^{VCTE} is interpreted using two diagnostic cut-offs: <0.384 to rule out advanced fibrosis with 90% sensitivity, and ≥ 0.715 to rule in advanced fibrosis with 90% specificity [11]. In the present work, FM^{VCTE} result ≥ 0.384 defined patients ''at-risk of advanced fibrosis'', and FM^{VCTE} result ≥ 0.715 the patients with ''confirmed advanced fibrosis''.

First-line evaluation of liver fibrosis

The cut-offs used to rule-out advanced liver fibrosis with blood fibrosis tests were those previously published: <1.30 for FIB4, <8 for eLIFT, and <0.46 for FM [7,11,14]. Five strategies were tested for the first-line evaluation of liver fibrosis (Fig. 1): 1/FIB4 strategy: positive if FIB4 ≥ 1.30; 2/eLIFT strategy: positive if eLIFT ≥ 8; 3/FM strategy: positive if FM ≥ 0.46; 4/FIB4-FM strategy: positive if FIB4 ≥ 1.30 then FM ≥ 0.46; and 5/eLIFT-FM strategy: positive if eLIFT ≥ 8 then FM ≥ 0.46.

Adequacy of the decision to refer

''Correct decision to refer'' was defined by a positive result with the first-line evaluation of liver fibrosis confirmed by a positive result with the specialized liver evaluation (Table 2). ''Correct decision to not refer'' was defined by a negative first-line evaluation confirmed by a negative specialized liver evaluation. ''Missed referral'' was defined by a negative result with the first-line evaluation despite positive result with the specialized liver evaluation. ''Unnecessary referral'' was defined by a positive first-line evaluation but negative result with the specialized liver evaluation.

Statistics

Quantitative variables were expressed as means $\pm$ standard deviations or medians with 1st and 3rd quartiles as appropriate and compared using the Mann—Whitney or the Wilcoxon test. Qualitative variables were expressed as percentages and compared using the Fisher exact test or the McNemar test. Statistical analyses were performed using SPSS version 18.0 software (IBM, Armonk, NY, USA).

Results

Patients

During the study period, 866 patients with NAFLD and/or ALD underwent a first LSM with Fibroscan in our department. A history of hepatocellular carcinoma or decompensated cirrhosis was present in 23 patients, who were thus excluded. Another 285 patients had missing blood markers for blood

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Table 2 Adequacy of the decision to refer by using the study first line-strategies.

Specialized evaluation of liver fibrosis	First-line strategy	
	Negative	Positive
Negative	Correct decision to not refer	Unnecessary referral
Positive	Missed referral	Correct decision to refer

Table 3 Patient characteristics at inclusion.

	All ($n = 558$)	NAFLD ($n = 283$)	ALD ($n = 156$)	Mixed NAFLD + ALD ($n = 119$)	P
Age (years)	57.5 ± 12.2	56.5 ± 12.7	55.5 ± 11.5	62.4 ± 10.4	< 0.001
Male sex (%)	68.6	53.4	78.8	91.6	< 0.001
Diabetes treatment (%)	30.1	38.1	5.4	43.5	< 0.001
BMI (kg/m^2)	30.8 ± 6.9	32.9 ± 6.6	25.6 ± 5.1	32.4 ± 6.4	< 0.001
AST (IU/l)	35 (26–50)	33 (25–44)	37 (26–57)	40 (29–59)	0.002
ALT (IU/l)	39 (25–64)	42 (29–69)	31 (22–52)	39 (25–57)	< 0.001
Gamma-GT (IU/l)	76 (40–161)	53 (33–107)	95 (47–197)	109 (55–271)	< 0.001
Bilirubin (μmol/l)	10 (8–15)	10 (7–13)	10 (8–16)	12 (8–17)	0.062
Prothrombin time (%)	99 (88–109)	101 (93–109)	95 (85–109)	93 (78–105)	< 0.001
Platelets (G/l)	225 (181–275)	238 (193–286)	223 (177–277)	196 (152–254)	< 0.001
LSM result (kPa)	7.2 (5.4–15.5)	6.8 (5.0–12.0)	6.9 (5.1–18.8)	11.2 (6.2–21.5)	< 0.001
FM^{VCTE} (%)					< 0.001
< 0.384	58.8	67.5	57.1	40.3	
0.384-0.714	11.5	11.7	12.2	10.1	
≥ 0.715	29.7	20.8	30.8	49.6	

BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LSM: liver stiffness measurement with Fibroscan; FM^{VCTE}: FibroMeter^{VCTE}.

fibrosis tests calculation. The characteristics of the 558 remaining patients are summarized in Table 3. The mean age of the patients was 57.5 ± 12.2 years, 68.6% were male, mean BMI was 30.8 ± 6.9 kg/m^2, 30.1% were diabetic, and median LSM was 7.2 kPa (1st and 3rd quartiles: 5.4–15.5). The cause of chronic liver disease was NAFLD in 283 patients, ALD in 156, and NAFLD + ALD in 119. Patients with NAFLD + ALD had more severe liver disease with significantly higher LSM results, lower prothrombin times, and lower platelet counts than patients with NAFLD or ALD alone.

FM^{VCTE} was ≥ 0.384 and the specialized evaluation of liver fibrosis concluded to ''at-risk of advanced liver fibrosis'' in 230 patients (41.2%). FM^{VCTE} was ≥ 0.715 and the specialized evaluation of liver fibrosis concluded to ''confirmed advanced liver fibrosis'' in 166 patients (29.7%). FIB4, eLIFT, FM, FIB4-FM, and eLIFT-FM strategies had a positive result in, respectively: 306 (54.8%), 292 (52.3%), 238 (42.7%), 206 (36.9%), and 197 (35.3%) patients.

Identification of patients at-risk of advanced liver fibrosis (FM^{VCTE} ≥ 0.384)

The negative results of the first-line evaluation were confirmed by a negative result with the specialized liver evaluation (FM^{VCTE} < 0.384) in 83–86% of the cases whatever the strategy used (see negative predictive values in Table 4). The positive results of the first-line evaluation were confirmed by a positive result with the specialized liver evaluation (FM^{VCTE} ≥ 0.384) in > 80% of the cases using sequential FIB4-FM and eLIFT-FM strategies, 78% using FM strategy, and 63-65% using FIB4 and eLIFT strategies (see positive predictive values in Table 4). The rate of unnecessary referral was decreased by three-fold using FIB4 or eLIFT strategy, six-fold using FM strategy, and ten-fold using FIB4-FM or eLIFT-FM strategy (Fig. 2a). However, this was at a price of a decrease in the detection rate of patients at-risk of advanced fibrosis: 73% of the patients with FM^{VCTE} ≥ 0.384 had positive first-line evaluation using FIB4-FM or eLIFT-FM strategy versus 80–84% using FIB4, eLIFT or FM strategy ($P \leq 0.002$, see sensitivities in Table 4). The rate of negative results with the first-line evaluation confirmed by a negative FM^{VCTE} < 0.384 was > 80% whatever the underlying cause of chronic liver disease (Figure s1a in Supplementary Material). Compared to patients correctly referred (positive first-line evaluation confirmed by FM^{VCTE} ≥ 0.384), patients with missed referral (negative first-line evaluation despite FM^{VCTE} ≥ 0.384) were younger, more female, more obese, and as expected had lower serum transaminases and better liver function (Table s1).

Identification of patients with confirmed advanced liver fibrosis (FM^{VCTE} ≥ 0.715)

The negative results of the first-line evaluation were confirmed by a negative result with the specialized liver evaluation (FM^{VCTE} < 0.715) in 92–95% of the cases whatever the

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Table 4 Accuracy of the five first-line strategies for the identification of patients at-risk of advanced liver fibrosis (i.e., with FibroMeter^{VCTE3G} $\geq$ 0.384).

	Strategy					
	Current practice	FIB4	eLIFT	FM	FIB4-FM	eLIFT-FM
Positive result (%)	100.0[a]	54.8	52.3	42.7	36.9	35.3
Sensitivity (%)	100.0	83.5	83.0	80.4	73.9	73.0
Specificity (%)	0.0	65.2	69.2	83.8	89.0	91.2
NPV (%)	-	84.9	85.3	85.9	83.0	82.8
PPV (%)	41.2	62.7	65.4	77.7	82.5	85.3

FM: FibroMeter^{V2G}; NPV: negative predictive value; PPV: positive predictive value.
[a] By definition, all patients included in our study were referred to the specialized center.

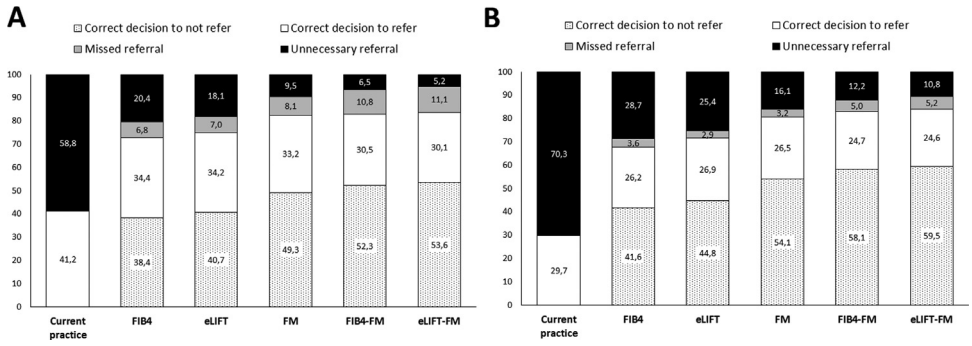

Figure 2 Rate of correct decision to not refer, correct decision to refer, missed referral, and unnecessary referral for each of the five first-line strategies. a: The objective is the identification of patients at-risk of advanced fibrosis (FM^{VCTE} $\geq$0.384); b: The objective is the identification of patients with confirmed advanced fibrosis (FM^{VCTE} $\geq$0.715).

Table 5 Accuracy of the five first-line strategies for the identification of patients with confirmed advanced liver fibrosis (i.e., with FibroMeter^{VCTE3G} $\geq$ 0.715).

	Strategy					
	Current practice	FIB4	eLIFT	FM	FIB4-FM	eLIFT-FM
Positive result (%)	100.0[a]	54.8	52.3	42.7	36.9	35.3
Sensitivity (%)	100.0	88.0	90.4	89.2	83.1	82.5
Specificity (%)	0.0	59.2	63.8	77.0	82.7	84.7
NPV (%)	-	92.1	94.0	94.4	92.0	92.0
PPV (%)	29.7	47.7	51.4	62.2	67.0	69.5

FM: FibroMeter^{V2G}; NPV: negative predictive value; PPV: positive predictive value.
[a] By definition, all patients included in our study were referred to the specialized center.

strategy used (see negative predictive values in Table 5). The positive results of the first-line evaluation were confirmed by a positive result with the specialized liver evaluation (FM^{VCTE} $\geq$ 0.715) in 67—70% of the cases using sequential FIB4-FM and eLIFT-FM strategies, 62% using FM strategy, and 48-51% using FIB4 and eLIFT strategies (see positive predictive values in Table 5). The rate of unnecessary referral was decreased by 2.5 to 3-fold using eLIFT of FIB4 strategy, 4.5-fold using FM strategy, and 6-fold using FIB4-FM or eLIFT-FM strategy (Fig. 2b). However, this was at a price of a decrease in the detection rate of patients with confirmed advanced fibrosis: 83% of the patients with FM^{VCTE} $\geq$ 0.715 had positive first-line evaluation using FIB4-FM or eLIFT-FM strategy versus 88-90% using FIB4, eLIFT or FM strategy ($P < 0.05$, see sensitivities in Table 5). The rate of negative results with the first-line evaluation confirmed by a negative FM^{VCTE} < 0.715 was > 90% whatever the underlying cause of chronic liver disease (Figure s1b in Supplementary Material).

Discussion

Worldwide, cirrhosis has become the eleventh leading cause of death due to non-communicable diseases and hepatocellular carcinoma the second leading cause of death due to cancer [15]. At the time of diagnosis, 75% of patients with

cirrhosis are already decompensated with poor short-term survival and 66% of those with hepatocellular carcinoma are already at the palliative stage [16—18]. These data underline the crucial need for widespread diagnosis and early management of advanced forms of chronic liver diseases, especially in the two main causes of them: NAFLD and ALD. Given the high prevalence of NAFLD and ALD in the general population, achieving this ambitious goal will require close collaboration between hepatologists and many other practitioners, including primary care physicians and specialists in addiction or diabetes. Our study shows that very simple blood fibrosis tests, using common parameters and easily deployable by any physician, improves the identification of patients truly needing referral for specialized evaluation of liver fibrosis. A negative FIB4 < 1.30 or eLIFT < 8 indicates a very high probability of a no/mild fibrosis diagnosis by a specialized test, and therefore no need for referral to a hepatologist.

Our work showed that 59% of the NAFLD/ALD patients referred to our tertiary center for a specialized evaluation of liver fibrosis had a final diagnosis of no/mild liver fibrosis (FM^{VCTE} < 0.384) with no need for further specialized liver management. This result emphasizes the suboptimal nature of classical liver risk factors or abnormal liver function tests as criteria for patient referral by non-liver specialists. In contrast, using simple blood fibrosis tests, such as FIB4 or eLIFT, as the referral criterion would have halved the number of referrals to our tertiary center, and reduced by three-fold the rate of ''unnecessary referrals''. As a result, we could have doubled our capacity to manage patients with advanced liver disease over the same period. Similarly, a recent work showed that using eLIFT in patients with type 2 diabetes would spare two-thirds of specialized evaluations of liver fibrosis [19]. Using FIB4 or eLIFT for patient referral would have missed 10% of patients with $FM^{VCTE} \geq 0.715$. However, it has been previously shown that the middle-term liver-related prognosis of patients with FIB4 < 1.30 or eLIFT < 8 is excellent [11,20]. Thus, we think that simple blood fibrosis tests can be repeated as a monitoring tool in patients with negative initial result; any subsequent swing above the threshold would spark a referral for specialized liver evaluation. Further longitudinal studies with long-term follow-up and repeated measurements of blood fibrosis tests are required to validate this attitude in clinical practice.

Simple blood fibrosis tests are inexpensive and widely available but complex blood fibrosis tests outperform them in terms of accuracy [7,8]. Using FM as a first-line test instead of FIB4 or eLIFT would have even more reduced the rates of referrals to 43% and decreased by six-fold the rate of unnecessary referrals. However, FM is more expensive than simple blood fibrosis tests. Whether the increase in costs linked to the use of FM as first-line evaluation is counterbalanced by the saved costs thanks to the subsequent decrease in specialized evaluations of liver fibrosis will have to be determined in further studies. For now, in France, FM is reimbursed for patients with chronic hepatitis C but not for those with NAFLD or ALD. These latter patients must therefore pay for the online calculation of the test. In such a context, using the simple and free FIB4 and eLIFT as a first-line test will most likely be preferred by patients and physicians.

In the very large population of NAFLD and ALD patients, only a minority develop advanced liver fibrosis. Beyond this ''needle in a haystack'' aspect, the diagnosis of advanced liver fibrosis is very difficult in these patients because they frequently have no symptoms, normal physical examinations, and usually only non-specific biological or radiological abnormalities. We show here that FIB4 and eLIFT are very simple and attractive solution in this setting for non-liver specialists. With it, they can identify NAFLD and ALD patients with no need for referral to specialized liver evaluation because they are highly likely to have no or only mild fibrosis, and those who do because of an increased risk of advanced liver fibrosis. Compared to the FIB4, the eLIFT has the advantage to be very easily calculated, at a glance by head, without any computer. However, very recent surveys have shown that most non-liver specialists do not use non-invasive tests for their patients with liver risk factors [21,22]. Therefore, education programs to familiarize them with the concept and the use of these tests in their daily clinical practice are highly required.

In conclusion, referral of NAFLD and ALD patients for specialized evaluation of liver fibrosis is overloaded by patients without advanced fibrosis. The use of simple blood fibrosis tests, such as FIB4 or eLIFT, as first-line evaluation will limit unnecessary referrals of patients who don't need a specialized liver management and therefore spare the resources of healthcare systems.

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University Hospital of Angers.

Authors' Contributions

Study design: J. Boursier.

Data acquisition: T. Broussier, A. Lannes, F. Zuberbuhler, F. Oberti, I. Fouchard-Hubert, P. Cales, J. Boursier.

Analysis: T. Broussier, G. Hunault, J. Boursier.

Drafting/critical revision: T. Broussier, A. Lannes, F. Oberti, J. Boursier.

Disclosure of interest

Paul Calès owns patent of the FibroMeterV2G. Paul Calès and Jerome Boursier own patent of the FibroMeterVCTE. The other authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.clinre.2019.07.010.

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