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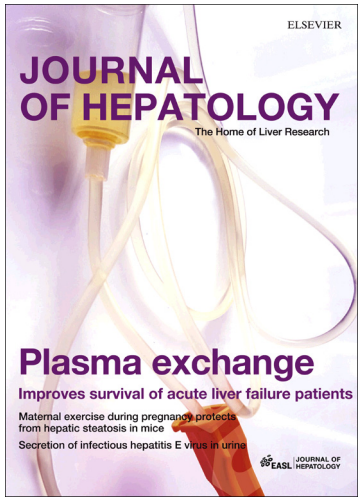


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# A stepwise algorithm using a at-a-glance first-line test for the non-invasive diagnosis of advanced liver fibrosis and cirrhosis

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**Author Contributions:**

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Jérôme Boursier: study concept and design, acquisition of data, statistical analysis, analysis and interpretation of data, drafting of the manuscript, obtained funding, study supervision; Victor de Ledinghen: acquisition of data, critical revision of the manuscript for important intellectual content; Vincent Leroy: acquisition of data, critical revision of the manuscript for important intellectual content; Rodolphe Anty: acquisition of data, critical revision of the manuscript for important intellectual content; Sven Francque: acquisition of data, critical revision of the manuscript for important intellectual content; Dominique Salmon: acquisition of data; Adrien Lannes: acquisition of data; Sandrine Bertrais: statistical analysis; Frederic Oberti: acquisition of data; Isabelle Fouchard-Hubert: acquisition of data; Paul Calès: acquisition of data, critical revision of the manuscript for important intellectual content, obtained funding

**Abbreviations:** CLD, Chronic Liver Disease; NAFLD: Non-Alcoholic Fatty Liver Disease; HCC: HepatoCellular Carcinoma; LSM: Liver Stiffness Measurement; AUROC: Area Under the Receiving Operating Characteristics

**Clinical trial registration:** no registration (analysis of pooled data from previously published diagnostic studies)

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**ABSTRACT**

**Background & Aims.** Chronic liver diseases (CLD) are highly frequent and thus mainly managed by non-hepatologists. Because they lack access to the best non-invasive tests of liver fibrosis, these physicians cannot accurately determine the disease severity and the need for referral to a hepatologist. We aimed to implement an algorithm, comprising a new first-line test usable by all physicians, for the detection of advanced liver fibrosis in all CLD patients.

**Methods.** Diagnostic study: 3,754 CLD patients with liver biopsy were 2:1 randomized into derivation and validation sets. Prognostic study: longitudinal follow-up of 1,275 CLD patients with baseline fibrosis tests.

**Results**: Diagnostic study: the *e*asy *LI*ver *F*ibrosis *T*est (eLIFT), an "at-a-glance" sum of points attributed to age, gender, gamma-GT, AST, platelets and prothrombin time, was developed for the diagnosis of advanced fibrosis. In the validation set, eLIFT and FIB4 had the same sensitivity (78.0% vs 76.6%, p=0.470) but eLIFT gave less false-positive results, especially in patients ≥60 years old (53.8% vs 82.0%, p<0.001), and was thus more suitable as screening test. FibroMeter$^{VCTE}$ was the most accurate among the eight fibrosis tests evaluated. The sensitivity of the eLIFT-FM$^{VCTE}$ algorithm (first-line eLIFT, second-line FibroMeter$^{VCTE}$) was 76.1% for advanced fibrosis and 92.1% for cirrhosis. Prognostic study: patients diagnosed as having "no/mild fibrosis" by the algorithm had excellent liver-related prognosis with thus no need for referral to a hepatologist.

**Conclusion:** The eLIFT-FM$^{VCTE}$ algorithm extends the detection of advanced liver fibrosis to all CLD patients and reduces unnecessary referrals of patients without significant CLD to hepatologists.

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**LAY SUMMARY**

Blood fibrosis tests and transient elastography accurately diagnose advanced liver fibrosis in the large population of patients having chronic liver disease, but these non-invasive tests are currently available only in specialized centers. We have developed an algorithm including as first-line procedure the *e*asy *LI*ver *F*ibrosis *T*est (eLIFT), a new simple and widely available blood test, that selects at-risk patients who need further evaluation with the FibroMeter$^{VCTE}$, an accurate fibrosis test combining blood markers and transient elastography result. This new algorithm, called the eLIFT-FM$^{VCTE}$, accurately identifies the patients with advanced chronic liver disease who need referral to a specialist, and those with no or mild liver lesions who can remain under the care of their usual physician.

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**INTRODUCTION**

Chronic liver diseases (CLD) are very common: worldwide, an estimated 160 million people have chronic hepatitis C (1), 240 million have chronic hepatitis B (2), and 25% of the general population has non-alcoholic fatty liver disease (NAFLD) (3). CLD can lead to a progressive accumulation of fibrosis in the liver which progressively evolves to cirrhosis and its life-threatening complications such as hepatocellular carcinoma (HCC), liver failure, variceal bleeding, or renal insufficiency. In 2012, driven by the growing worldwide burden of CLD, cirrhosis was responsible for more than 35 million years of lost life and thus became the eleventh leading cause of mortality among non-communicable diseases (4). Additionally, HCC has become the sixth leading incident cancer and the second leading cause of cancer-related death worldwide (4).

Both the prognosis and the management of CLD patients are closely linked to the level of liver fibrosis. Treatment of the cause of CLD is mandatory in patients who develop advanced septal fibrosis to prevent further progression to cirrhosis and its complications (1, 2, 5). In cirrhotic patients, screening procedures are required for early detection of HCC and identification of large esophageal varices. Liver biopsy is the reference procedure for liver fibrosis evaluation but its invasive nature makes it unsuitable as first-line procedure in the large number of CLD patients. Blood tests and liver stiffness measurement (LSM) by elastography have been recently developed for the non-invasive evaluation of liver fibrosis and provide an exciting alternative to biopsy (6). However, the high cost of the most accurate blood fibrosis tests limits their widespread use, and liver elastometry is only accessible in specialized centers.

CLD patients are numerous and thus not all of them can be referred to the few specialized hepatology clinics. In practice, most CLD patients are managed by non-hepatologists who encounter challenges in the evaluation of the liver disease that remains silent for many years with normal physical examination and normal routine diagnostic tests. In addition, non-hepatologists have very limited access to the best non-invasive liver fibrosis tests. Resultantly, liver fibrosis is unevaluated in many CLD patients with progressive fibrosis.

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These patients are finally diagnosed too late when they have reached the stage of cirrhosis complications with an impaired short-term prognosis.

Therefore, in the present work, we aimed to develop and validate a stepwise algorithm that can be easily instigated by all physicians to facilitate the widespread detection of advanced liver fibrosis in all CLD patients. Such an algorithm should prove very helpful in the regulation of the large flow of CLD patients between primary care and specialized centers, and especially in the identification of CLD patients who needs referral to specialized hepatologists and those who do not.

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## PATIENTS AND METHODS

The study protocol conformed to the ethical guidelines of the current Declaration of Helsinki. All patients included in the cross-sectional population and the longitudinal cohort gave informed written consent for their participation.

### Cross-sectional population

The cross-sectional population was used to develop and validate the new stepwise algorithm. This population was obtained by pooling the data of seven published studies that evaluated non-invasive liver fibrosis tests using liver biopsy as the reference (7-13). We provide here the main inclusion/exclusion criteria and methods of these seven studies.

#### *Patients*

All included patients had CLD without decompensated cirrhosis or HCC. Patient duplication between studies was corrected so as to ensure that all patients were included only once in the statistical analysis for the present work.

#### *Liver biopsy*

All patients had a liver biopsy taken and used as the reference for liver fibrosis evaluation. Pathological examinations were performed in each center by senior experts specialized in hepatology and blinded for patient data. Liver fibrosis was evaluated according to NASH CRN staging in patients with NAFLD, and METAVIR staging in patients with other causes of CLD. Although the two semi-quantitative scoring systems comprise stages from F0 to F4, they do not completely correspond (**Supplementary Table s1**). For the present study, we defined "no/mild fibrosis" as NASH CRN F0-2 or METAVIR F0-1, "septal fibrosis" as NASH CRN F3 or Metavir F2-3, and "cirrhosis" as NASH CRN F4 or METAVIR F4. Advanced fibrosis, which was defined as NASH CRN F≥3 or Metavir F≥2 (**Table s1c**), was the primary diagnostic target of the study.

#### *Blood fibrosis tests*

Fasting blood samples were taken the day of or within the three months before or after liver biopsy. The data available from the seven studies enabled the calculation of six blood

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fibrosis tests according to published or patented formulas: APRI (14), FIB4 (15), Hepascore (16), FibroMeter$^{V2G}$ (17), FibroMeter$^{V3G}$ (18), and FibroMeter$^{VCTE}$ (19). FibroMeter$^{V3G}$ is the same blood fibrosis test than FibroMeter$^{V2G}$ but hyaluronate, a costly and difficult-to-obtain marker, has been replaced by the gammaGT. We have previously shown that FibroMeter$^{V2G}$ and FibroMeter$^{V3G}$ have comparable diagnostic accuracy in chronic hepatitis C (18). FibroMeter$^{VCTE}$ is a fibrosis test that combines in a single formula both the blood markers of the FibroMeter$^{V3G}$ with the Fibroscan result. We have previously shown that FibroMeter$^{VCTE}$ was significantly more accurate than FibroMeter$^{V2G}$ and Fibroscan in chronic hepatitis C (19). In the present study, APRI and FIB4 were considered as "simple fibrosis tests" since they use common, inexpensive variables and easy-to-calculate formulas. The other fibrosis tests include more expensive parameters in complex equations that require computerized calculation.

***Fibroscan***

LSM with Fibroscan was performed in each center by an experienced operator blinded for patient data using the standard M probe. LSM was performed in fasting conditions, the day of or within the three months before or after liver biopsy. Examination conditions were those recommended by the manufacturer (20). LSM result (kilo Pascal: kPa) corresponded to the median value of the 10 valid measurements recorded.

**Longitudinal cohort**

The prognostic longitudinal cohort was used to validate the clinical significance of the new stepwise algorithm developed in the cross-sectional population. We used a previously-established local database that retrospectively included all consecutive CLD patients seen in the Hepatology Department of the Angers University Hospital for a non-invasive evaluation of liver fibrosis between January 2005 and December 2009 (19). Exclusion criteria for the present study were: prothrombin time <70% or serum bilirubin ≥30 µmol/L (i.e., no need for a fibrosis test to diagnose advanced fibrosis), missing LSM or blood test results, and an interval between blood fibrosis tests and LSM >6 months. Follow-up started the day of the non-invasive evaluation of liver fibrosis and ended January 1$^{st}$, 2011. Dates and causes of death were obtained from the computerized National Registry of Individuals (CepiDC-Inserm, France). For those patients who could not be matched individually within the

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national registry, mortality data were obtained from the hospital database, or from the concerned general practitioner.

**Statistics**

In the cross-sectional population, the diagnostic accuracies of the fibrosis tests were mainly expressed as the area under the receiver operating characteristics (AUROC) and compared using the Delong test (21). In the longitudinal cohort, the prognostic accuracies of fibrosis tests were evaluated using the Harrell C-index, as previously described (22). Briefly, the Harrell C-index is an extension of the AUROC for time-to-event (survival) data; it evaluates the concordance between the predicted risk of the event and the observed survival time (discriminative ability). Its results vary from 0 to 1, with a value of 1 indicating a perfect concordance. Survival curves were determined using the Kaplan-Meier method and compared with the log rank test. Statistical analyses were performed using SPSS version 18.0 software (IBM, Armonk, NY, USA) and SAS 9.1 (SAS Institute Inc., Cary, NC, USA). This study was reported in accordance with the recently published LiverFibroSTARD statements (23).

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## RESULTS

### Cross-sectional population: derivation and validation of the new algorithm

#### *Patient characteristics*

The cross-sectional population included 3,754 patients with CLD. Patient characteristics at inclusion are detailed in **Table 1**. 56.6% of patients were male and mean age was 49.5±13.1 years. The main causes of CLD were chronic hepatitis C (45.5%) and NAFLD (34.2%). Mean biopsy length was 25±10 mm (median: 23mm; 1$^{st}$ quartile: 17mm; 3$^{rd}$ quartile: 30mm). The prevalence of advanced fibrosis was 46.0% and cirrhosis 13.2%. The 3,754 patients were 2:1 randomly divided into derivation and validation sets (**Supplementary Figure s1**), the characteristics of which were not significantly different (**Table 1**).

#### *Determination of the first-line "simple" fibrosis test*

*Evaluation of APRI and FIB4*

Because they are simple fibrosis tests available to all physicians, we evaluated APRI and FIB4 for the first-line test of the new algorithm. FIB4 had significantly higher AUROCs than APRI for the diagnosis of advanced fibrosis or cirrhosis (**Table s2**). As calculated in the derivation set, the 80% sensitivity thresholds of APRI and FIB4 for advanced fibrosis were respectively 0.40 and 1.20. Using these thresholds in the validation set, FIB4 and APRI had similar sensitivity for advanced fibrosis (respectively 76.6% vs 75.8%, p=0.688), but FIB4 had significantly better sensitivity for cirrhosis (93.1% vs 86.7%, p=0.035). The rate of patients with FIB4 <1.20 was significantly higher than the rate of patients with APRI <0.40 (44.7% vs 41.3%, p=0.010). Taken together, these results suggested that FIB4 should be better than APRI as a first-line test in the new algorithm. However, the FIB4 equation includes age and **Figure 1** shows that the rate of false positives (i.e., the rate of FIB4 ≥1.20 among patients with no/mild fibrosis) dramatically rose with age. In patients ≥60 years old, the false positive rate was 82.0%, which limited the interest of FIB4 as a first-line screening test.

*Development of a new first-line "simple" fibrosis test*

We decided to develop a new fibrosis test to circumvent the previously identified limitations while improving ease-of-use and availability for all physicians. Toward this, we chose the clinical and blood parameters commonly assessed in CLD patients: age, gender, gamma-GT,

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ALT, AST, platelet count, and prothrombin time. Continuous variables were transformed into qualitative and ordinal variables according to the thresholds corresponding to 33% and 66% prevalence for advanced fibrosis (see **Figure s2** for more details). By multivariate analysis in the derivation set, all variables except ALT were independent predictors of advanced fibrosis (**Table s3**). The β coefficients of the multivariate analysis (β coefficients x3, rounded) were used to determine a new, simple and user-friendly liver fibrosis score: the *e*asy *LI*ver *F*ibrosis *T*est (eLIFT, **Table 2**). To keep AST from weighing too heavily in the score, it was capped at four points, as were platelets and prothrombin time. In the derivation set, the 80% sensitivity threshold of eLIFT was calculated at eight.

This new eLIFT was then evaluated in the validation set versus FIB4. Significant differences between the AUROCs of eLIFT and FIB4 were observed neither for advanced fibrosis (respectively, 0.781±0.013 vs 0.789±0.013, p=0.421) nor for cirrhosis (0.853±0.015 vs 0.844±0.015, p=0.424). There was no significant difference in accuracy between eLIFT ≥8 and FIB4 ≥1.20: their sensitivities for advanced fibrosis were respectively 78.0% and 76.6% (p=0.470), for cirrhosis 94.2% and 93.1% (p=0.791), and the rates of patients with negative results were 43.5% and 44.7% (p=0.383). However, eLIFT was less influenced by age (**Figure s3**), providing a significantly lower rate of false positives in patients ≥60 years old: 53.8% vs 82.0% with FIB4 (p<0.001). This latter result, in addition to the test's "at-a-glance" ease of calculation, placed eLIFT as a better choice than FIB4 for the first-line test in our algorithm.

***Determination of the second-line "diagnostic" fibrosis test***

Blood fibrosis tests (APRI, FIB4, eLIFT, Hepascore, FibroMeter$^{V2G}$, FibroMeter$^{V3G}$), LSM by Fibroscan, and FibroMeter$^{VCTE}$ were all available in a core group of 1,946 patients. This core group had more severe liver disease than the other 1,808 patients (**Table s4**). The core group comprised 1,282 patients from the derivation set and 664 from the validation set (**Figure s1**), with no significant differences between these two subsets (**Table s4**).

FibroMeter$^{VCTE}$ had significantly highest AUROC for the diagnosis of advanced fibrosis compared to the seven other fibrosis tests evaluated in the core group (**Table s5**). It also had significantly highest AUROC for the diagnosis of cirrhosis compared to the six blood fibrosis tests (**Table s6**). Consequently, we chose FibroMeter$^{VCTE}$ as the second-line test for our

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algorithm. Two FibroMeter$^{VCTE}$ thresholds for 90% sensitivity (0.384) and 90% specificity (0.715) for advanced fibrosis were calculated in the 1,282 patients from the derivation set. These two thresholds delineated three patient subgroups with the following diagnoses: <0.384: no/mild fibrosis, ≥0.384 and <0.715: undetermined (grey zone), ≥0.715: advanced fibrosis. Using liver biopsy in the grey zone, this patient classification had 89.5% diagnostic accuracy in the derivation set vs 88.3% in the 664 patients from the validation set (p=0.399, **Figure s4**).

***New algorithm***

The first-line "simple" eLIFT was combined with the second-line "diagnostic" FibroMeter$^{VCTE}$ into a new stepwise algorithm called eLIFT-FM$^{VCTE}$ (**Figure 2**). When applied to the validation set (n=664 patients), eLIFT-FM$^{VCTE}$ diagnosed 32.7% of the patients as having no/mild fibrosis at the first step (negative eLIFT <8) and 13.7% at the second (positive eLIFT ≥8 but negative FibroMeter$^{VCTE}$ <0.384). Thus, there was no need for referral to a hepatologist for 46.4% of the patients. Of the remaining patients, 19.4% were included in the grey zone and 34.2% were diagnosed as having advanced fibrosis. Using liver biopsy in the grey zone, the diagnostic accuracy of eLIFT-FM$^{VCTE}$ was 83.3%, sensitivity and specificity for advanced fibrosis were respectively 76.1% and 92.2%, and sensitivity and specificity for cirrhosis were respectively 92.1% and 76.2% (**Table 3**, see **Table s7** for detailed results).

Compared to the other causes of chronic liver disease, eLIFT ≥8 had higher sensitivity and lower specificity in the alcohol subgroup (**Figure s5**). Interestingly, these differences were erased after the use of the FibroMeter$^{VCTE}$: sensitivity and specificity for advanced fibrosis as well as the rate of well-classified patients were not significantly different between etiologies by using the eLIFT-FM$^{VCTE}$ algorithm. By multivariate analysis performed in the whole population, we evaluated the influence of age, sex, CLD cause, derivation/validation set, biopsy length and LSM IQR/median ratio on the diagnostic accuracy of the eLIFT-FM$^{VCTE}$. None of these parameters were independently associated with the rate of well-classified patients by the algorithm.

We finally compared the eLIFT-FM$^{VCTE}$ to strategies using FIB4 or FibroMeter$^{V2G}$ alone. We chose FIB4 as it was the best "simple" test compared to APRI for the diagnosis of advanced fibrosis, and FibroMeter$^{V2G}$ because it was the most accurate among all blood tests evaluated (**Table s5**). Results in the validation set showed that the eLIFT-FM$^{VCTE}$ had the

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same diagnostic accuracy than blood tests alone, but it had the strong advantage to require significantly less liver biopsies (**Table s8**).

**Longitudinal cohort: evaluation of the prognostic significance of the new algorithm**

The aim of the prognostic study was to evaluate the prognostic significance of the algorithm, especially in the subgroup of patients diagnosed as "no/mild fibrosis" as it can include false negative results.

***Patient characteristics***

The longitudinal cohort included 1,275 patients. Their characteristics at baseline are detailed in the **Table s9**. Mean age was 52.8±14.7 years and 66.8% were male. One hundred and twenty-eight patients died during the median follow-up period of 2.9 years (interquartile range: 1.9-4.2 years; 3,807 person-years). Death was related to liver complications in 43 patients. According to the eLIFT-FM$^{VCTE}$ algorithm, 60.1% of patients were diagnosed as having no/mild fibrosis (46.8% with eLIFT <8, and 13.3% with eLIFT ≥8 but FibroMeter$^{VCTE}$ <0.384), 12.8% were included in the grey zone, and 27.1% were diagnosed as having advanced fibrosis.

***Prognostic accuracy of fibrosis tests***

The Harrell C-indexes of eLIFT and FIB4 for the prediction of all-cause mortality were not significantly different (**Table 4**). However, the discriminative ability of eLIFT was significantly better than that of FIB4 for the prediction of death related to liver complications, thus reinforcing our choice to use it rather than FIB4 as the first-line test in our new algorithm. FibroMeter$^{VCTE}$ had the significantly highest Harrell C-index for the prediction of death related to liver complications compared to the seven other fibrosis tests evaluated, confirming its use as the second-line test in the algorithm.

***Prognostic accuracy of the new algorithm***

**Figure 3a** shows overall survival and **Figure 3b** survival free of death related to liver complications as a function of the four patient subgroups defined by the eLIFT-FM$^{VCTE}$ algorithm. Interestingly, there were no significant differences in prognosis between patients

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diagnosed as having no/mild fibrosis with a negative eLIFT (<8) and those diagnosed as no/mild fibrosis with a positive eLIFT (≥8) but a negative FibroMeter$^{VCTE}$ (<0.384). Patients diagnosed as having no/mild fibrosis by the eLIFT-FM$^{VCTE}$ had an excellent liver-related prognosis with only two of them who died from liver-related complication during the follow-up. Finally, as expected, patients diagnosed as having advanced fibrosis according to eLIFT-FM$^{VCTE}$ had the worse prognosis among the four subgroups.

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**DISCUSSION**

Despite the recommendation of early management for patients with CLD by all international guidelines, it is estimate that two thirds of cirrhosis cases are diagnosed belatedly when liver-related complications appear and the short-term prognosis is already impaired (24, 25). This demonstrates a crucial need for simple and accurate tools able of identifying the subset of CLD patients who require specific management by specialized physicians. In this setting, the non-invasive diagnosis of liver fibrosis is a rapidly growing field of research; blood fibrosis tests, liver elastometry, and their combinations are improving continuously and thus supplying constant increases in diagnostic accuracy (6). Recently, a new three-dimensional magnetic resonance elastography technique showed an almost perfect AUROCs of 0.971 and 0.979 for the diagnoses of advanced liver fibrosis and cirrhosis, respectively (26). However, the best means for the non-invasive evaluation of liver fibrosis are currently available only in specialized tertiary centers, which creates a dilemma. First, in chronic liver diseases, where NAFLD patients alone represent at least 25% of the general population (3), there are simply not enough of these centers to screen all CLD patients for advanced fibrosis. Second, even if we could do so, this would result in an incredibly high rate of unnecessary evaluations; indeed, a large proportion of CLD patients have alcoholic liver disease or NAFLD with no or mild liver fibrosis and thus do not require the "firepower" of a tertiary center or specific management by hepatologists.

FIB4 is a simple and widely available blood fibrosis test whose published diagnostic cut-offs are 1.45 and 3.25 (15). The low cut-off has been calculated to exclude severe fibrosis (Ishak ≥4) with 90% negative predictive value in the princeps study conducted in HIV-HCV co-infected patients (15). In our work, FIB4 >1.45 had only 67.2% sensitivity for the diagnosis of advanced fibrosis. As we aimed 80% sensitivity for the first-line test, we determined the corresponding FIB4 threshold that was calculated at 1.20. Using this cut-off, 90% of all the patients who were ≥60 years old had a positive FIB4 leading unsuitable this test for the screening of advanced fibrosis in elderly patients. We acknowledge that a lower cut-off has amplified the deleterious effect of age on FIB4 accuracy already observed by others teams (27). However, this finally demonstrates the limits of FIB4 for the screening of advanced fibrosis: either the FIB4 threshold is low to ensure a good sensitivity but then increasing age

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induces rapidly a high rate of false positive results; or the FIB4 threshold is higher with less influence of age but then the sensitivity is low and insufficient.

We demonstrated here that it is possible to organize an accurate and generalized detection of advanced liver fibrosis and cirrhosis in all CLD patients. Our process starts with eLIFT, a new test designed for use by all physicians, as it is based on parameters commonly assessed in CLD. Compared to FIB4, the new eLIFT has two main advantages. First, while the FIB4 needs a computer for calculation, eLIFT is very easily calculated at-a-glance and in one's head. This makes eLIFT easier and faster to use in clinical practice than FIB4. More importantly, because the age is capped at 40 years, the rate of false positive results with eLIFT is much lower in elderly patients. In clinical practice, the purpose of eLIFT is to be used by any physician to identify patients at risk of advanced fibrosis who require further evaluation with a more accurate fibrosis test, i.e. FibroMeter$^{VCTE}$. Together, they compose the eLIFT-FM$^{VCTE}$ algorithm. We showed here that eLIFT-FM$^{VCTE}$ had excellent sensitivity for detecting cirrhotic patients and good sensitivity for detecting patients with advanced fibrosis. The strength of our cross-sectional diagnostic study was the large size of the population where eLIFT-FM$^{VCTE}$ was derived and validated.

eLIFT ≥8 was more sensitive and less specific for advanced fibrosis in the subgroup of patients with alcoholic disease (**Figure s5**). False positive results linked to increased AST and GGT in the context of chronic excessive alcohol consumption could have participated to this lack of specificity. Interestingly, the differences observed with eLIFT between etiologies were erased after the use of FibroMeter$^{VCTE}$ as second line test in the eLIFT-FM$^{VCTE}$ algorithm. This suggested that the eLIFT-FM$^{VCTE}$ could be used for the screening of advanced fibrosis in alcoholic patients but at the cost of a higher rate of patients requiring a second-line test. Due to the small rate of alcoholic patients included in our work, further studies evaluating the eLIFT-FM$^{VCTE}$ specifically in this population are required.

An important strength of our work is the use of a longitudinal cohort "from the real life" to validate the prognostic significance of eLIFT-FM$^{VCTE}$. Indeed, following the eLIFT-FM$^{VCTE}$ algorithm, patients diagnosed as having no/mild fibrosis are not referred to a specialized hepatologist (**Figure 2**). The results obtained in the longitudinal cohort validated this management approach: the no/mild fibrosis patients had an excellent liver-related prognosis

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with only two deaths related to liver complication during the follow-up. Additionally, we have previously shown in chronic hepatitis C that the patient prognosis is linked to the evolution of the results of the non-invasive liver fibrosis tests (28). Thus, in patients diagnosed as having no/mild fibrosis, the non-invasive tests can be repeated in the follow-up and, should the results change, spark the second-line test or a referral to a hepatologist. Finally, as shown in **Figure 2**, eLIFT-FM$^{VCTE}$ clearly defines a pathway (algorithm) and the actors in that pathway (first-line non-hepatologist physicians, second-line platforms for FibroMeter$^{VCTE}$ realization, and finally specialized hepatologists for patients needing them). In this way, it will minimize unnecessary referrals of CLD patients with no/mild fibrosis to specialized centers, and especially increase the detection of CLD patients with advanced fibrosis who need specialized management. A recent study showed that CLD patients with access to ambulatory gastrointestinal subspecialty care had improved survival (29). In this setting, thanks to an increase in the detection of CLD patients with advanced fibrosis, we expect that the eLIFT-FM$^{VCTE}$ algorithm can improve the global CLD patient care.

Our algorithm is limited by the presence of a subgroup with undetermined diagnosis. Further works will be needed to see if a more accurate non-invasive fibrosis tests, such as magnetic resonance elastography (26), can provide a more precise diagnosis in this subgroup. Our study has included large populations with diagnostic and prognostic analyses, but it was performed in patients referred to hepatology units from tertiary centers. Further works are now required to validate the relevance of the eLIFT-FM$^{VCTE}$ for the screening of advanced liver fibrosis and cirrhosis in at-risk populations (diabetics, alcoholics, psychiatric patients, etc.) and in primary care settings. These works should include cost-effectiveness analyses to evaluate if the costs induced by the eLIFT-FM$^{VCTE}$ algorithm are counterbalanced by a better patient management and less expenses linked to decompensated liver diseases.

In conclusion, eLIFT is a new, user-friendly, at-a-glance fibrosis test available to all physicians, whether specialized in hepatology or not, who manage CLD patients in their daily clinical practice. The eLIFT-FM$^{VCTE}$ algorithm, which sequentially combines eLIFT and FibroMeter$^{VCTE}$, can discriminate patients having no or mild fibrosis with excellent prognosis from those who have advanced CLD with impaired prognosis and need specialized care. Finally, the sequential eLIFT-FM$^{VCTE}$ algorithm defines a pathway that will help to regulate the large flow

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of CLD patients between primary care and specialized centers: patients with no or mild liver lesions will remain under the care of their usual physician whereas those with advanced CLD will be redirected to hepatologists for specialized management.

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**Table 1: Patient characteristics at inclusion in the cross-sectional population**

| | All (n=3,754) | Derivation (n=2,503) | Validation (n=1,251) | p |
|---|---|---|---|---|
| Age (years) | 49.5 ± 13.1 | 49.6 ± 13.1 | 49.4 ± 13.1 | 0.798 |
| Male gender (%) | 56.6 | 56.5 | 56.8 | 0.889 |
| Cause of CLD (%): | | | | 0.355 |
| - Alcohol | 7.7 | 7.6 | 8.0 | |
| - HCV | 45.5 | 45.0 | 46.4 | |
| - HBV | 3.2 | 2.8 | 3.9 | |
| - Co-infection HBV/HCV-HIV | 5.0 | 5.2 | 4.7 | |
| - NAFLD | 34.2 | 34.8 | 32.9 | |
| - Others | 4.4 | 4.6 | 4.1 | |
| Fibrosis (%) | | | | 0.513 |
| - No/mild fibrosis | 54.0 | 54.7 | 52.8 | |
| - Septal fibrosis | 32.8 | 32.4 | 33.4 | |
| - Cirrhosis | 13.2 | 12.9 | 13.8 | |
| Biopsy length (mm) | 25 ± 10 | 25 ± 10 | 25 ± 10 | 0.557 |
| AST (IU/L) | 57 ± 58 | 57 ± 61 | 56 ± 51 | 0.654 |
| ALT (IU/L) | 79 ± 86 | 79 ± 88 | 78 ± 81 | 0.963 |
| GGT (IU/L) | 122 ± 201 | 124 ± 198 | 119 ± 207 | 0.730 |
| Bilirubin (µmol/L) | 13 ± 16 | 12 ± 13 | 13 ± 20 | 0.063 |
| Platelets (G/L) | 221 ± 74 | 221 ± 75 | 220 ± 73 | 0.499 |
| Prothrombin time (%) | 93 ± 12 | 93 ± 12 | 93 ± 12 | 0.378 |
| APRI | 0.75 ± 0.96 | 0.75 ± 1.01 | 0.73 ± 0.85 | 0.620 |
| FIB4 | 1.84 ± 1.89 | 1.83 ± 1.87 | 1.84 ± 1.94 | 0.767 |

CLD: chronic liver disease; HCV: hepatitis C virus; HBV: hepatitis B virus; Co-infection HBV/HCV-HIV: co-infection with hepatitis B or C virus and human immunodeficiency virus

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**Table 2: The *e*asy *LI*ver *F*ibrosis *T*est (eLIFT)**

| ITEM | POINTS |
|---|---|
| ***Age (years)*** | |
| - <40 | 0 |
| - ≥40 | 3 |
| ***Gender*** | |
| - Female | 0 |
| - Male | 1 |
| ***AST (IU/L)*** | |
| - <35 | 0 |
| - 35 – 69 | 2 |
| - ≥70 | 4 |
| ***Gamma-GT (IU/L)*** | |
| - <35 | 0 |
| - 35 – 89 | 1 |
| - ≥90 | 2 |
| ***Platelets (G/L)*** | |
| - 250 ≤ | 0 |
| - 170 – 249 | 1 |
| - <170 | 4 |
| ***Prothrombin time (%)*** | |
| - 97 ≤ | 0 |
| - 84 – 96 | 2 |
| - <84 | 4 |

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**Table 3: Accuracy of the eLIFT-FM$^{VCTE}$ algorithm for the diagnosis of advanced fibrosis in the core group of the cross-sectional population.**

| | All (n=1,946) | Derivation (n=1,282) | Validation (n=664) | p |
|---|---|---|---|---|
| DA | 84.4 | 84.9 | 83.3 | 0.357 |
| Se | 78.2 | 79.4 | 76.1 | 0.238 |
| Spe | 91.4 | 90.9 | 92.2 | 0.615 |
| NPV | 78.8 | 80.4 | 75.6 | - |
| PPV | 91.1 | 90.4 | 92.4 | - |
| -LR | 0.24 | 0.23 | 0.26 | - |
| +LR | 9.0 | 8.8 | 9.8 | - |
| OR | 37.9 | 38.6 | 37.6 | - |
| LB | 19.3 | 19.3 | 19.4 | 0.952 |

DA: diagnostic accuracy (rate of well-classified patients, %); Se: sensitivity (%); Spe: specificity (Spe); NPV: negative predictive value (%); PPV: positive predictive value (%); -LR: negative likelihood ratio; +LR: positive likelihood ratio; OR: Odds Ratio; LB: rate of liver biopsy required (%)

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**Table 4: Pairwise comparison (p value) of Harrell C-indexes for overall survival or survival free of death related to liver complications in the longitudinal cohort**

| Endpoint | Fibrosis test | Harrell C-index | FIB4 | eLIFT | HS | $FM^{V2G}$ | $FM^{V3G}$ | LSM | $FM^{VCTE}$ |
|---|---|---|---|---|---|---|---|---|---|
| Overall survival | APRI | 0.560 [0.509-0.618] | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| | FIB4 | 0.684 [0.638-0.730] | - | 0.322 | 0.295 | 0.004 | 0.036 | 0.379 | 0.049 |
| | eLIFT | 0.702 [0.657-0.746] | - | - | 0.686 | 0.042 | 0.361 | 0.761 | 0.120 |
| | Hepascore | 0.712 [0.660-0.762] | - | - | - | 0.203 | 0.823 | 0.944 | 0.352 |
| | $FibroMeter^{V2G}$ | 0.732 [0.690-0.771] | - | - | - | - | 0.056 | 0.351 | 0.921 |
| | $FibroMeter^{V3G}$ | 0.716 [0.674-0.756] | - | - | - | - | - | 0.796 | 0.423 |
| | LSM | 0.708 [0.659-0.757] | - | - | - | - | - | - | 0.091 |
| | $FibroMeter^{VCTE}$ | 0.730 [0.682-0.773] | - | - | - | - | - | - | - |
| Survival free of death related to liver complications | APRI | 0.663 [0.585-0.744] | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| | FIB4 | 0.788 [0.726-0.843] | - | 0.043 | <0.001 | <0.001 | 0.029 | <0.001 | <0.001 |
| | eLIFT | 0.826 [0.782-0.869] | - | - | 0.019 | 0.034 | 0.628 | 0.005 | <0.001 |
| | Hepascore | 0.882 [0.833-0.926] | - | - | - | 0.466 | 0.137 | 0.660 | 0.083 |
| | $FibroMeter^{V2G}$ | 0.867 [0.822-0.907] | - | - | - | - | 0.069 | 0.386 | 0.029 |
| | $FibroMeter^{V3G}$ | 0.837 [0.783-0.878] | - | - | - | - | - | 0.108 | 0.003 |
| | LSM | 0.892 [0.841-0.935] | - | - | - | - | - | - | 0.030 |
| | $FibroMeter^{VCTE}$ | 0.917 [0.887-0.946] | - | - | - | - | - | - | - |

LSM: liver stiffness measurement by Fibroscan



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**FIGURE LEGEND**

**Figure 1: Rate of patients with FIB4 results ≥1.20 as a function of age and the presence of advanced fibrosis in the whole cross-sectional population.** Patients were ranked by age and categorized into 20 equally-populated, consecutive subgroups (5.0% percentiles). Then, the prevalence of FIB4 ≥1.20 was determined in each of these 20 subgroups, both in patients with no/mild fibrosis and in patients with advanced fibrosis.

**Figure 2: New eLIFT-FM$^{VCTE}$ algorithm that combines the eLIFT (first-line "simple" test) and the FibroMeter$^{VCTE}$ (second-line "diagnostic" test) in a stepwise manner**

**Figure 3: Overall survival (panel 3a) and survival free of death related to liver complications (panel 3b) as a function of the four subgroups defined by the eLIFT-FMVCTE algorithm in the longitudinal cohort**

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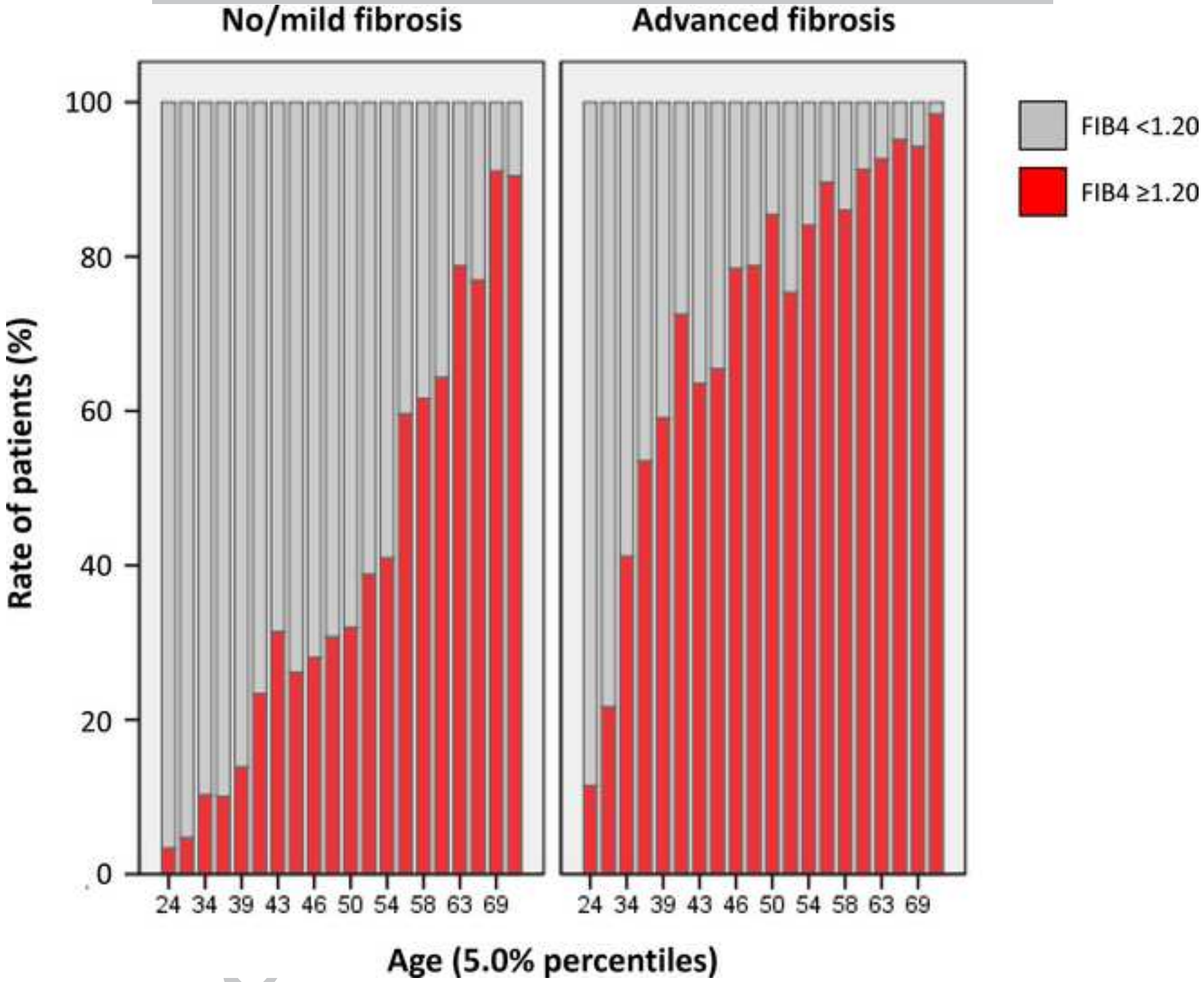

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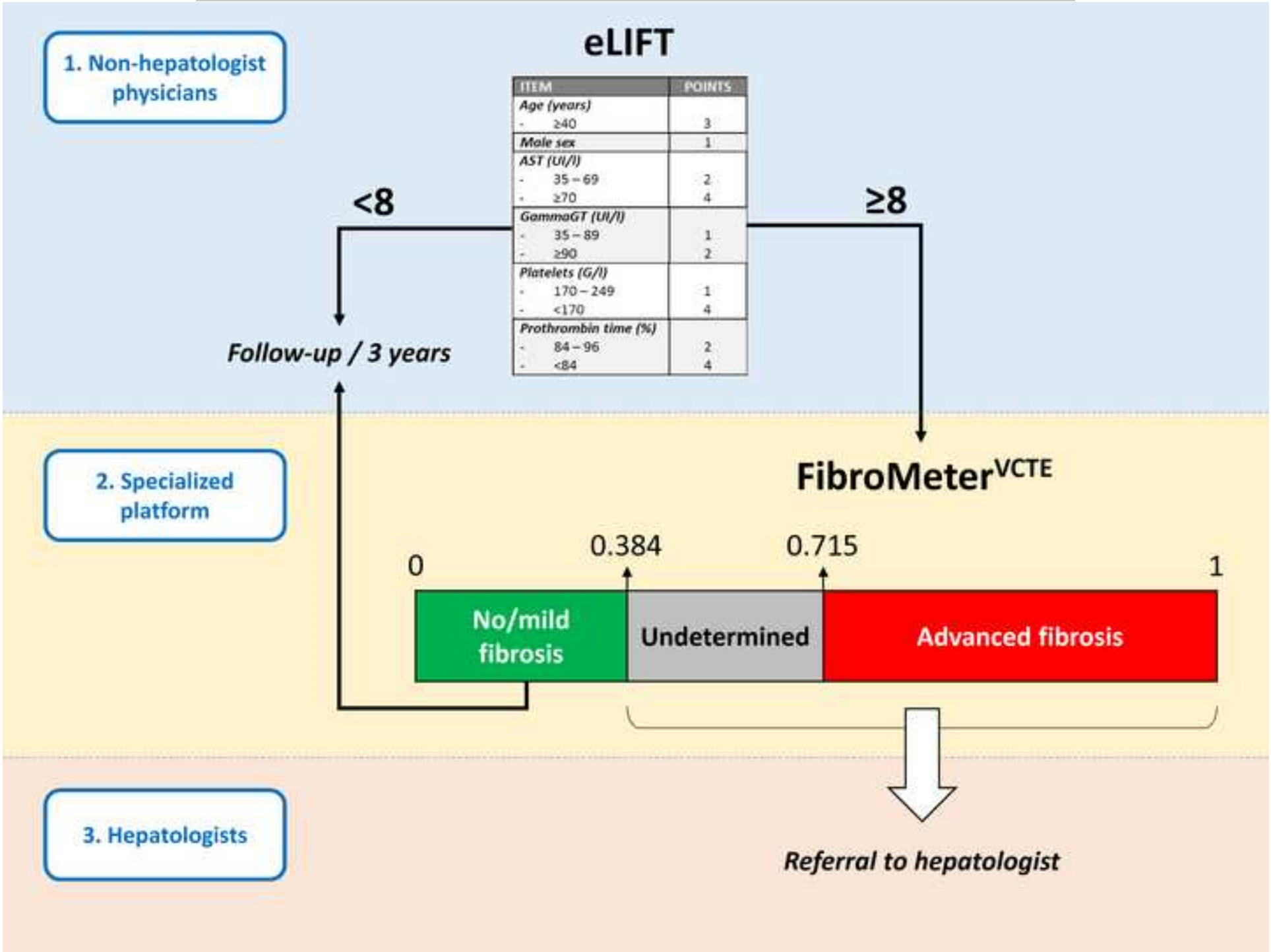
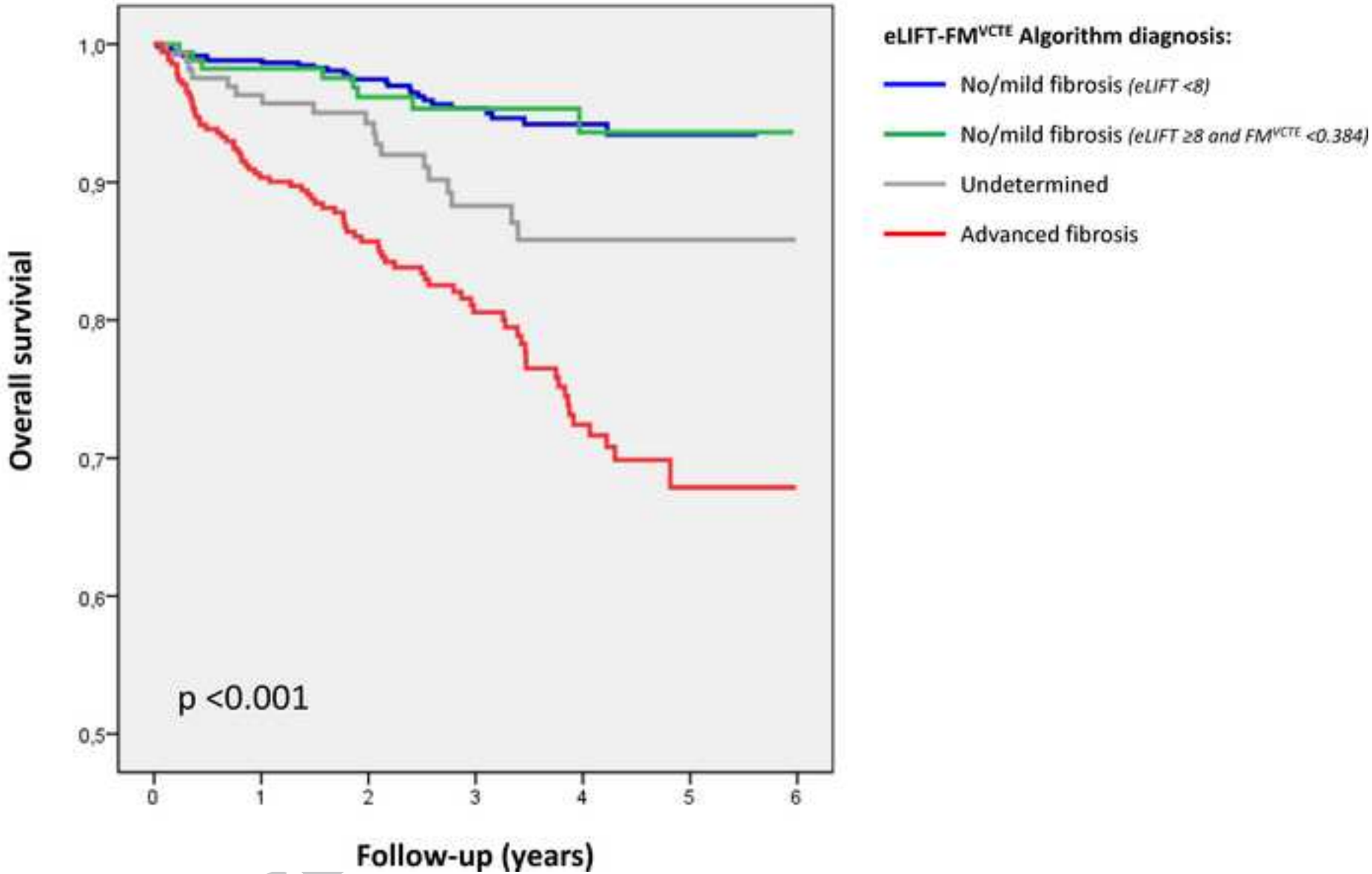
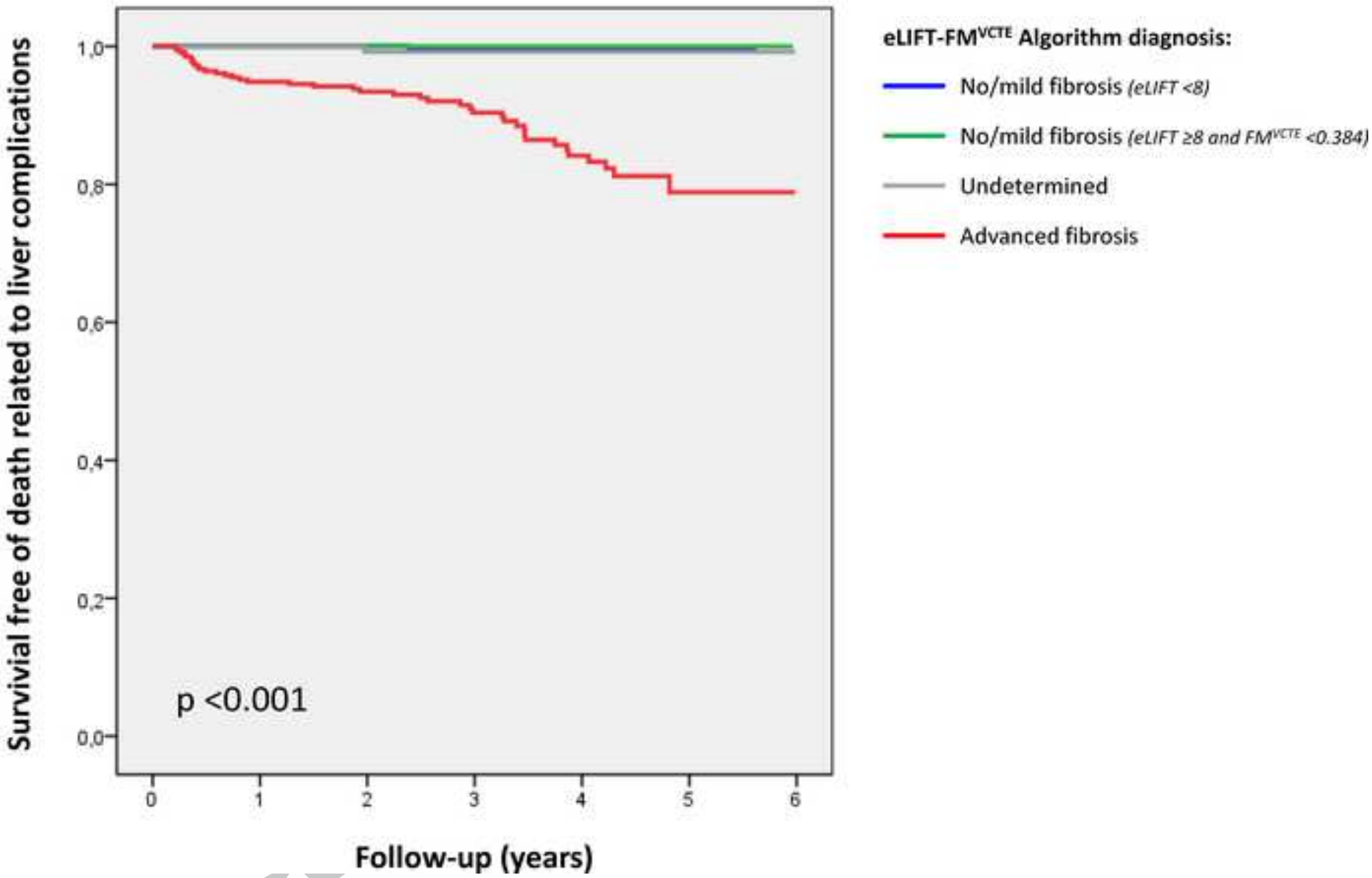


**A**


Overall survivial
1,0
0,9
0,8
0,7
0,6
0,5
p <0.001
0
1
2
3
4
5
6
Follow-up (years)
eLIFT-FM^VCTE Algorithm diagnosis:
No/mild fibrosis (eLIFT <8)
No/mild fibrosis (eLIFT ≥8 and FM^VCTE <0.384)
Undetermined
Advanced fibrosis

**B**


Survivial free of death related to liver complications
1,0
0,8
0,6
0,4
0,2
0,0
p <0.001
0
1
2
3
4
5
6
Follow-up (years)
eLIFT-FM^VCTE Algorithm diagnosis:
No/mild fibrosis (eLIFT <8)
No/mild fibrosis (eLIFT ≥8 and FM^VCTE <0.384)
Undetermined
Advanced fibrosis

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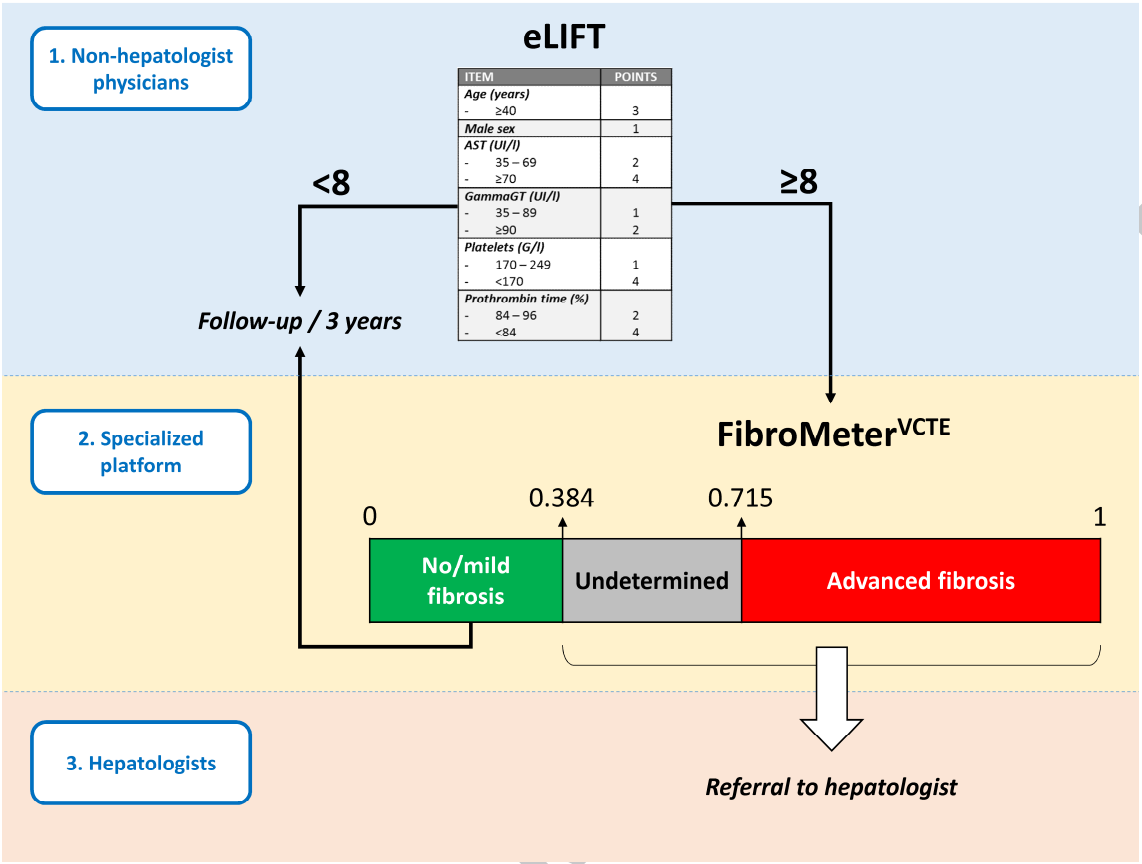


Graphical abstract