Liste des abréviations

NAFLD	Non-Alcoholic Fatty Liver Disease
FS	Fibroscan
NFS	NAFLD Fibrosis Score
FM^{V3G}	Fibrometer V3G
VCTE	Vibration Controlled Transient Elastography
FS_M	Fibroscan M probe
FS_{XL}	Fibroscan XL probe
LSM	Liver Stiffness Measurement
AUROC	Area under the receiver operating characteristics
SAFE	Sequential Algorithm for Fibrosis Evaluation
IQR/M	Interquartile Range/Median

Plan

ABSTRACT

Background and Aims

Fibroscan and FibroMeter accurately diagnose advanced liver fibrosis in NAFLD (J Hepatol 2016). However, they have a grey zone where the diagnosis remains undetermined. As already shown in chronic hepatitis C, we aimed to evaluate if combining fibrosis tests reduces this grey zone and thus the need for liver biopsy in NAFLD.

Methods

723 biopsy-proven NAFLD patients with Fibroscan (FS) and blood tests were included. Blood tests evaluated were: NAFLD Fibrosis Score (NFS), FibroMeter^{V3G} (FM^{V3G}), FibroMeter^{VCTE} (FM^{VCTE}: a combination of Fibroscan with the blood markers of FM^{V3G} in a single formula). The primary diagnostic target was advanced fibrosis as defined by NASH CRN fibrosis stage F≥3.

Results

Liver stiffness measurement with the FS M probe (FS_M) failed with no valid measurement in 105 patients. The per-protocol analysis performed in the 618 remaining patients showed that FM^{VCTE} had a significantly higher AUROC (0.861±0.015, p≤0.009) than NFS (0.725±0.020), FM^{V3G} (0.772±0.020) and FS_M (0.831±0016). The rate of patients included in the grey zone between the 90% sensitivity and 95% specificity thresholds was the lowest with the FM^{VCTE} (37.9%, p<0.025 vs other tests). Six test combinations were evaluated: SAFE (Sebastiani, Hepatology 2009), Bordeaux algorithm (BA, Castera J Hepatol 2010), NFS-FS_M (Petta, Liver Int 2015), FM^{VCTE}, FM^{V3G} first then FM^{VCTE} if undetermined diagnosis (FM^{V3G}-FM^{VCTE}), FS_M first then FM^{VCTE} (FS_M-FM^{VCTE}). Diagnostic accuracy and rate of liver biopsy were, respectively: 90.8%/73.8%,

88.0%/43.7%, 96.1%/67.2%, 93.4%/37.9%, 90.3%/29.6%, 90.5%/30.3%. FM^{V3G}-FM^{VCTE} and FS_M-FM^{VCTE} provided thus the lowest rate of liver biopsy ($p<0.001$ vs others) with a high diagnostic accuracy around 90%. The FS XL probe (FS_{XL}) was available in a subset of 371 patients. An intention-to-diagnose analysis was performed in this subgroup by using FS_{XL} in case of FS_M failure (n=67) and liver biopsy in case of FS_{XL} failure (n=7). Diagnostic accuracy and rate of liver biopsy of the five tests combinations (SAFE, BA, NFS-FS, FM^{V3G}-FM^{VCTE}, FS-FM^{VCTE}) were, respectively: 89.5%/71.2%, 86.8%/42.9%, 95.1%/67.9%, 86.8%/29.1%, 88.7%/30.7%.

Conclusions

The synchronous combination of Fibroscan with blood markers in the $FibroMeter^{VCTE}$ improves the non-invasive diagnosis of advanced fibrosis in NAFLD. In clinical practice, the sequential use of fibrosis tests (first: Fibroscan or $FibroMeter^{V3G}$; then, if necessary: $FibroMeter^{VCTE}$) significantly reduce the need for liver biopsy.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), the liver manifestation of the metabolic syndrome linked to obesity and insulin resistance, affects 25% of the general population both in western and developing countries (1). NAFLD encompasses a large spectrum of liver lesions but the patient prognosis is mainly linked to the level of fibrosis which must therefore be accurately evaluated in clinical practice (2-4). In this context, non-invasive tests of liver fibrosis (blood tests, elastography) position as very interesting tools to identify the subset of patients with advanced fibrosis and impaired prognosis among the large NAFLD population. In a recent study, we have shown that liver stiffness measurement (LSM) by Vibration Controlled Transient Elastography (VCTE) and the blood test FibroMeter^{V} were the most accurate among nine fibrosis tests evaluated to diagnose advanced fibrosis in NAFLD (5).

The combination of fibrosis tests significantly improves their diagnostic accuracy (6-8), but this approach remains poorly evaluated in NAFLD. Only one study has evaluated the diagnostic accuracy of an algorithm based on the agreement between VCTE and the blood test NAFLD fibrosis score (NFS) (9). This algorithm provided excellent accuracy for the diagnosis of advanced fibrosis in NAFLD but disagreement between both fibrosis tests occurred in half of the patient who therefore required liver biopsy. Other diagnostic algorithms combining fibrosis tests exist in chronic hepatitis C but they have never been evaluated in NAFLD. The Bordeaux algorithm is based on the agreement between VCTE and the blood test Fibrotest (6). The Sequential Algorithm for Fibrosis Evaluation (SAFE) combines the two blood tests APRI and Fibrotest (7). Such sequential

procedure is relevant for large populations in clinical practice: by using a first-line test, it selects the subgroup of patients who require more complex and accurate procedures. Finally, we have developed the new and accurate FibroMeter^{VCTE} that synchronously combines in a single formula the blood markers of the FibroMeter^{V} with VCTE (10).

The aims of the present study were: to evaluate in a large population of NAFLD patients the diagnostic accuracy of the fibrosis tests combinations previously developed in chronic hepatitis C; to improve the non-invasive diagnosis of advanced fibrosis in NAFLD by combining the best fibrosis tests in new practical algorithms; to evaluate the accuracy of these new algorithms in an intention-to-diagnose analysis.

PATIENTS AND METHODS

Patients

Patients with biopsy-proven NAFLD were included from January 2004 to April 2016 at Angers and Bordeaux University Hospitals. NAFLD was defined as liver steatosis on liver biopsy after exclusion of concomitant steatosis-inducing drugs, excessive alcohol consumption (>210 g/week in men or >140 g/week in women), chronic hepatitis B or C infection, and histological evidence of other concomitant chronic liver disease. Patients were not included if they had liver complications (liver failure, ascites, variceal bleeding, systemic infection or hepatocellular carcinoma).

Liver biopsy

In each center, pathological examinations were performed by a senior expert specialized in hepatology and blinded for patient data. Liver fibrosis was evaluated according to the NASH CRN scoring system (11), F0: no fibrosis; F1: perisinusoidal or portal/periportal fibrosis, F2: perisinusoidal and portal/periportal fibrosis, F3: bridging fibrosis and F4: cirrhosis. Significant fibrosis was defined as F≥2 and advanced fibrosis as F3/4. Because previous longitudinal studies have demonstrated that liver-related prognosis is impaired when advanced fibrosis occurs (2-4, 12), we chose advanced F3/4 fibrosis as our primary diagnostic target.

Blood fibrosis tests

Fasting blood samples were taken the day of or within the week preceding liver biopsy. The following blood fibrosis tests were calculated according to published or patented formulas: NFS (13), FibroMeter^{V2G} (14), FibroMeter^{V3G} (15) and FibroMeter^{VCTE} (10). We

chose NFS because it is the most validated blood fibrosis test in NAFLD, and FibroMeter^{V2G} because it was the most accurate among eight blood tests evaluated in our previous study (5). 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 (15). Finally, FibroMeter^{VCTE} is a new fibrosis test that combines in a single formula the blood markers of the FibroMeter^{V3G} with VCTE. APRI (16) and Fibrotest (17) were also calculated to determine the SAFE algorithm (7). All blood assays were performed in the laboratories of the Angers or Bordeaux centers. We have previously demonstrated the excellent inter-laboratory reproducibility of blood fibrosis tests (18).

Liver stiffness measurement

In all patients, LSM by VCTE (Fibroscan, Echosens, Paris, France) was performed using the standard M probe by an experienced observer (>500 examinations) blinded for patient data. LSM was performed in fasting condition, the day of or no more than three months before or after liver biopsy. Examination conditions were those recommended by the manufacturer (19). LSM was stopped when 10 valid measurements were recorded and the result (kilo Pascal: kPa) was expressed as the median of these valid measurements. LSM failure was defined as LSM with no or only one valid measurement. The VCTE XL probe, specifically dedicated for LSM in obese patients, is available since October 2009 in Bordeaux center and June 2013 in Angers center. Since these dates, all patients included in the present study had LSM with both M and XL probes. LSM with the XL probe was performed in the same time and in the same conditions than with the M probe.

Diagnostic algorithms

The following diagnostic algorithms combining non-invasive fibrosis tests were determined (**Figure s1** in Supplementary Material): SAFE, Bordeaux algorithm and Palermo algorithm (6, 7, 9). As Metavir F≥2 corresponds to septal fibrosis and thus to NASH CRN F≥3 fibrosis, we used the SAFE and Bordeaux algorithms for Metavir F≥2 to diagnose advanced fibrosis in the present study. The SAFE is a sequential algorithm which includes APRI as first-line test and Fibrotest as second-line procedure. The Bordeaux and Palermo algorithms are based on the agreement between VCTE and a blood fibrosis test, respectively Fibrotest and NFS.

Statistical analysis

Diagnostic indexes **–** Diagnostic accuracy of fibrosis tests was mainly expressed as the area under the receiver operating characteristics (AUROC) and the Obuchowski index. The Obuchowski index is a multinomial version of the AUROC adapted to ordinal references such as pathological fibrosis staging (20). With N (=5: F0 to F4) categories of the gold standard outcome and AUROCst, it estimates the AUROC of diagnostic tests differentiating between categories s and t. The Obuchowski index is a weighted average of the N(N-1)/2 (=10) different AUROCst corresponding to all the pair-wise comparisons between two of the N categories. In addition, the Obuchowski index was assessed using a penalty function proportional to the difference in fibrosis stages, i.e., a penalty of 1 when the difference between stages was 1, 2 when the difference was 2, 3 when the difference was 3, and 4 when the difference was 4. Finally, the result can be interpreted as the probability that the non-invasive test will correctly rank two randomly chosen patients with different fibrosis stages.

Per-protocol and intention-to-diagnose analysis – All patients included in the study had blood fibrosis tests and LSM with the M probe. We first performed a per-protocol analysis where patient having LSM failure with the M probe were excluded. We then aimed to take into account LSM failure and to evaluate the diagnostic algorithms in the context of current clinical practice. An intention to diagnose analysis was thus performed in the subgroup of patients for whom LSM with both M and XL probes was available: the XL probe result was used in case of M probe failure, and liver biopsy was used if LSM failed with both probes.

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 (21).

RESULTS

Patients

723 patients were included in the study, 314 in Angers and 409 in Bordeaux. 105 patients had LSM failure with the M probe. The characteristics of the 618 remaining patients included in the per-protocol analysis are detailed in **Table 1**. 59.1% were male, mean age was 55.2±12.5 years and mean BMI was 31.0±5.5 kg/m^2. Mean biopsy length was 27±11 mm (median: 25 mm; 1st quartile: 20 mm; 3rd quartile: 33 mm) and 89.1% of liver biopsies had ≥15 mm length. Median LSM was 9.1 Kpa (1st quartile: 6.3 kPa; 3rd quartile: 14.0 kPa). Correlation and agreement between FibroMeter^{V2G} and FibroMeter^{V3G} were excellent with, respectively, Spearman coefficient = 0.933 ($p<0.001$) and intra-class correlation coefficient = 0.939 ($p<0.001$) (**Figure s2**).

Comparison of fibrosis tests

FibroMeter^{VCTE} outperformed the other fibrosis tests (**Table 2**): it provided significantly higher AUROCs for advanced fibrosis and cirrhosis, significantly higher Obuchowski index than blood tests, and higher Obuchowski index than VCTE with borderline significance.

For each fibrosis test, we calculated the 90% sensitivity and 95% specificity thresholds for advanced fibrosis (**Table s1**). These two cut-offs defined three diagnostic intervals: a lower interval where the diagnosis was F0-2 (≥90% sensitivity for advanced fibrosis), a higher interval where the diagnosis was advanced fibrosis (≥95% specificity), and an intermediate grey zone between the two thresholds where the diagnosis remained undetermined. As we have previously shown it is the main determinant of LSM reliability, we then evaluated the diagnostic accuracy of VCTE and FibroMeter^{VCTE} as a

function of the interquartile range/median (IQR/M) ratio in the lower and the higher intervals (**Table s2**). Whereas it had no influence in the lower interval, IQR/M >0.30 was associated with a significant decrease in diagnostic accuracy in the higher interval. Therefore, patients with unreliable results (i.e., IQR/M >0.30 in the higher interval) were reclassified in the intermediate grey zone. Finally, FibroMeter^{VCTE} provided the lowest rate of patients included in the intermediate grey zone (37.9%, p ≤0.001 vs other fibrosis tests; **Table s1**).

New diagnostic algorithms

We first evaluated the five fibrosis tests used with their diagnostic intervals followed by liver biopsy in case of undetermined diagnosis (**Figure s3a**). All fibrosis tests provided similar accuracy and an excellent 93% rate of well-classified patients (**Table 3**). However, the rate of liver biopsy requirement was high, ranging from 40% to 60%.

Despite it provided the best compromise between an excellent diagnostic accuracy (93.4%) and the lowest rate of liver biopsy requirement (37.9%), FibroMeter^{VCTE} could appear quite difficult to perform in clinical practice as it requires both blood markers and VCTE, the latter being available only in specialized centers. We thus evaluated four sequential algorithms using a first-line fibrosis test (NFS, FibroMeter^{V2G}, FibroMeter^{V3G} or VCTE), followed by FibroMeter^{VCTE} in case of undetermined diagnosis, and finally liver biopsy as last-line procedure if the diagnosis remained undetermined (**Figure s3b**). Compared to blood tests or VCTE alone, these sequential algorithms strongly reduced the rate of liver biopsy requirement by 33-50% at the price of a slight 3% decrease in diagnostic accuracy.

We finally selected two algorithms: the VCTE-FibroMeter^{VCTE} algorithm (VCTE-FM^{VCTE}) and the FibroMeter^{V3G}-FibroMeter^{VCTE} algorithm (FM$^{V3G\text{-}VCTE}$, **Figure s4**). These two algorithms appeared the most relevant for clinical practice according to the following reasons: first, as first-line test, VCTE gives an immediate result and induced the lowest rate of second-line FibroMeter^{VCTE} requirement (**Table 3**). Second, compared to FibroMeter^{V2G}, FibroMeter^{V3G} is free of hyaluronate that is a costly and difficult-to-obtain blood marker. Finally, compared to NFS, FibroMeter^{V3G} and VCTE have the advantage to be included in the FibroMeter^{VCTE} and to require only one additional method (blood markers or VCTE) to calculate the second line-test of the sequential algorithm.

New FM$^{V3G\text{-}VCTE}$ and VCTE-FM^{VCTE} versus previously published algorithms

Our results validated the diagnostic accuracy of the SAFE, Bordeaux and Palermo algorithms in NAFLD (**Table 4**). The Palermo algorithm provided the highest diagnostic accuracy (96.1%, $p<0.001$ vs others), but it also required the highest rate of liver biopsy (67.2%, $p\leq0.013$ vs others). Compared to SAFE and Bordeaux algorithms, the FM$^{V3G\text{-}VCTE}$ and the VCTE-FM^{VCTE} provided similar 90% diagnostic accuracy, but the rate of liver biopsy was significantly lower with, respectively, 29.6% and 30.3% vs 43.7% with the Bordeaux algorithm ($p<0.001$) and 73.8% with the SAFE ($p<0.001$). Therefore, by showing an excellent diagnostic accuracy and the lowest rate of liver biopsy requirement, our FM$^{V3G\text{-}VCTE}$ and VCTE-FM^{VCTE} algorithms positioned as the most relevant procedures for the diagnosis of advanced fibrosis in NAFLD.

Intention-to-diagnose analysis

371 patients had LSM with both M and XL probes. Their characteristics are detailed in **Table s3**. 67 patients had LSM failure with the M probe of whom 60 had result with the XL probe and 7 had LSM failure with both probes. Patients with LSM failure were kept in the intention-to-diagnose analysis as follow: XL probe result was used in case of M probe failure, and liver biopsy was used if LSM failed with both probes. The five diagnostic algorithms (SAFE, Bordeaux, Palermo, $FM^{V3G\text{-}VCTE}$ and $VCTE\text{-}FM^{VCTE}$) evaluated in an intention-to-diagnose basis showed similar accuracy than in the per-protocol analysis (**Table 4**). **Figure 1** summarizes how to accurately diagnose advanced fibrosis in NAFLD in clinical practice.

DISCUSSION

As in the other causes of chronic liver diseases, an accurate evaluation of liver fibrosis is mandatory in NAFLD to decide the patient management. Liver biopsy remains the reference exam for this purpose but, because of its invasiveness, it can't be proposed as first-line procedure to all NAFLD patients who represents 25% of the general population (1). Several non-invasive methods exist with their own interests and disadvantages. Blood fibrosis tests can be performed by all physicians but the most accurate include specialized and costly blood markers. VCTE is very accurate, gives an immediate result while the consultation, but remains available only in specialized centers. Other elastography methods included in Doppler-ultrasonographic devices have been developed but few data about their diagnostic accuracy and the best diagnostic cut-offs has been published. In the present work, we have developed two algorithms for the practical diagnosis of advanced fibrosis in NAFLD. We though these algorithms by considering the resources available for the physicians (either VCTE or only blood tests as first-line examination) to ensure their feasibility in clinical practice and thus their broad application. The strengths of our work are: 1/ the large number of patients included, 2/ the direct comparison for the first time in NAFLD of the previously published algorithms (SAFE, Bordeaux algorithm, Palermo algorithm), and 3/ the intention-to-diagnose analysis that takes into account LSM failure and thus evaluates algorithms in the "real life" conditions. Finally, by giving the best compromise between an excellent diagnostic accuracy and the lowest rate of liver biopsy required, the new $FM^{V3G\text{-}VCTE}$ and VCTE-FM^{VCTE} algorithms position as the best procedures for the non-invasive diagnosis of advanced fibrosis in NAFLD.

Health care systems must to be strongly organized if we want to achieve a broad and accurate evaluation of liver fibrosis in all patients of the very large NAFLD population. Because it starts with a blood fibrosis test, the $FM^{V3G\text{-}VCTE}$ algorithm has the advantage it can be initiated by every physicians. If the result falls in the grey zone of the $FibroMeter^{V3G}$, the patient is referred to a specialized center for VCTE examination. Therefore, as it combines VCTE with the blood markers of the $FibroMeter^{V3G}$, the $FibroMeter^{VCTE}$ can be calculated immediately without any additional blood sampling. For those centers where VCTE is available, the VCTE-FM^{VCTE} algorithm provides two advantages: it allows the highest rate of patients with a diagnosis since the first step of the algorithm, and this with an immediate result during the consultation. Finally, our two new algorithms adapt to the available resources and the daily clinical practice, therefore proposing the most practical solution for the accurate non-invasive diagnosis of advanced liver fibrosis in NAFLD.

Combination of fibrosis tests have been previously published in chronic hepatitis C (SAFE and Bordeaux algorithm) and in NAFLD (Palermo algorithm). Our results confirmed the excellent diagnostic accuracy of the Palermo algorithm (9), but this was at the price of a high rate of liver biopsy which was required in more than two third of the patients. The Bordeaux algorithm provided the same diagnostic accuracy than $FM^{V3G\text{-}VCTE}$ and VCTE-FM^{VCTE} but it induced 50% more liver biopsies. It must also be emphasized that, on the contrary of $FM^{V3G\text{-}VCTE}$, the Bordeaux and Palermo algorithms necessarily require VCTE, which limits their widespread utilization in all NAFLD patients. As $FM^{V3G\text{-}VCTE}$ and VCTE-FM^{VCTE}, the SAFE is a sequential algorithm combining a first-line fibrosis test and a more complex procedure as second-line exam. This strategy appears

particularly attractive for the screening of advanced fibrosis in large populations such as NAFLD patients. Our results confirmed in NAFLD those previously obtained for the SAFE in chronic hepatitis C (7, 8): it has an excellent 90% diagnostic accuracy but it requires a too high rate of liver biopsy (> 70%) for a wide use in clinical practice. Taken together, all these results indicate the new $FM^{V3G\text{-}VCTE}$ and VCTE-FM^{VCTE} are more relevant for clinical practice than the previously published algorithms.

Most of the studies that have evaluated elastography excluded LSM failure from their statistical analysis. Because physicians must deal with these failures, we performed an intention-to-diagnose evaluation in which XL probe was used in case of M probe failure, and liver biopsy in case of both probes failure. Finally, the results obtained in this intention-to-diagnose analysis were similar to those of the per-protocol analysis.

$FM^{V3G\text{-}VCTE}$ and VCTE-FM^{VCTE} are still limited by the need for a liver biopsy in a small subgroup of patients. Magnetic resonance elastography has recently shown excellent diagnostic accuracy for liver fibrosis evaluation in chronic liver diseases (24). Further works will have to evaluate if the use of this technology as third-line exam in our algorithms will allow even more reducing the need for liver biopsy in NAFLD patients.

In conclusion, the $FM^{V3G\text{-}VCTE}$ and VCTE-FM^{VCTE} algorithms accurately discriminate NAFLD patients having advanced liver fibrosis from those having no or mild fibrosis while limiting the rate of liver biopsy in contrast to the previous algorithms.

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TABLES

Table I : Patient characteristics at inclusion

	Liver stiffness measurement with VCTE M probe			p
	All (n=723)	Available (n=618)	Failure (n=105)	
Angers center (%)	43.4	43.7	41.9	0.751
Age (years)	55.7 ± 12.3	55.2 ± 12.5	58.3 ± 10.4	0.016
Male sex (%)	57.1	59.1	45.7	0.014
Diabetes (%) [a]	50.3	48.1	63.8	0.003
BMI (kg/m^2)	31.9 ± 6.0	31.0 ± 5.5	36.6 ± 6.4	<0.001
Biopsy length (mm)	26 ± 11	27 ± 11	25 ± 12	0.038
NAFLD Activity Score	4.0 ± 1.6	4.0 ± 1.6	3.6 ± 1.5	0.027
Fibrosis stage (%):				0.258
- 0	9.0	8.9	9.5	
- 1	25.2	26.4	18.1	
- 2	26.8	27.0	25.7	
- 3	26.0	25.6	28.6	
- 4	13.0	12.1	18.1	
Fibrosis F3/4 stages (%)	39.0	37.7	46.7	0.084
AST (IU/L)	49 ± 32	49 ± 33	44 ± 28	0.029
ALT (IU/L)	68 ± 49	71 ± 50	53 ± 37	<0.001
Total bilirubin (µmol/L)	12 ± 8	12 ± 8	11 ± 7	0.139
Prothrombin time (%)	96 ± 15	96 ± 14	94 ± 21	0.832
Platelets (G/L)	218 ± 71	220 ± 71	209 ± 67	0.132

BMI: body mass index; NAFLD: nonalcoholic fatty liver disease; AST: aspartate aminotransferase; ALT: alanine aminotransferase

[a] either anti-diabetic treatment or fasting glycemia ≥126 mg/dl

Table II : AUROC and Obuchowski index of non-invasive fibrosis tests

Fibrosis test	AUROC			Obuchowski
	F ≥2	F ≥3	F4	
NFS	0.712 ± 0.021	0.725 ± 0.020	0.756 ± 0.028	0.721 ± 0.017
FibroMeter^{V2G}	0.754 ± 0.019	0.800 ± 0.018	0.829 ± 0.025	0.780 ± 0.014
FibroMeter^{V3G}	0.725 ± 0.020	0.772 ± 0.020	0.807 ± 0.027	0.752 ± 0.015
VCTE	0.823 ± 0.018	0.831 ± 0.016	0.856 ± 0.021	0.826 ± 0.013
FibroMeter^{VCTE}	0.825 ± 0.017	0.861 ± 0.015	0.891 ± 0.017	0.842 ± 0.011
Comparison (p)				
NFS vs FibroMeter^{V2G}	0.058	<0.001	0.017	<0.001
NFS vs FibroMeter^{V3G}	0.545	0.030	0.110	0.079
NFS vs VCTE	<0.001	<0.001	0.001	<0.001
NFS vs FibroMeter^{VCTE}	<0.001	<0.001	<0.001	<0.001
FibroMeter^{V2G} vs FibroMeter^{V3G}	0.006	<0.001	0.025	<0.001
FibroMeter^{V2G} vs VCTE	0.004	0.148	0.300	0.009
FibroMeter^{V2G} vs FibroMeter^{VCTE}	<0.001	<0.001	0.002	<0.001
FibroMeter^{V3G} vs VCTE	<0.001	0.006	0.107	<0.001
FibroMeter^{V3G} vs FibroMeter^{VCTE}	<0.001	<0.001	<0.001	<0.001
VCTE vs FibroMeter^{VCTE}	0.893	0.009	0.010	0.098

NFS: NAFLD fibrosis score; VCTE: Vibration Controlled Transient Elastography

Table III : Accuracy of fibrosis tests and new study algorithms for the diagnosis of advanced fibrosis

Procedure	1st test	2nd test	DA	Se	Spe	NPV	PPV	-LR	+LR	OR	LB	FM^{VCTE}
Fibrosis	NFS	-	92.9	88.0	95.8	92.9	92.8	0.13	21.2	168.9	58.4	-
test [a]	$FibroMeter^{V2G}$	-	93.4	89.4	95.8	93.8	92.7	0.11	21.1	191.4	54.5	-
	$FibroMeter^{V3G}$	-	93.4	89.7	95.6	93.9	92.5	0.11	20.3	188.5	59.5	-
	VCTE	-	93.7	89.7	96.1	93.9	93.3	0.11	23.0	214.8	44.5	-
	$FibroMeter^{VCTE}$	-	93.4	89.7	95.6	93.9	92.5	0.11	20.3	188.5	37.9	-
Sequential	NFS	$FibroMeter^{VCTE}$	88.3	81.5	92.5	89.2	86.8	0.20	10.8	54.2	27.0	58.4
algorithm	$FibroMeter^{V2G}$	$FibroMeter^{VCTE}$	90.4	85.5	93.4	91.5	88.6	0.16	12.9	83.0	29.1	54.5
	$FibroMeter^{V3G}$	$FibroMeter^{VCTE}$	90.3	85.8	93.0	91.6	88.1	0.15	12.2	80.4	29.6	59.5
	VCTE	$FibroMeter^{VCTE}$	90.5	84.5	94.0	91.0	89.5	0.16	14.2	86.1	30.3	44.5

DA: diagnostic accuracy (i.e., rate of well classified patients, %); Se: sensitivity (%); Spe: specificity (%); NPV: negative predictive value (%); PPV: positive predictive value (%); -LR: negative likelihood ratio; +LR: positive likelihood ratio; OR: odd ratio; LB: rate of liver biopsy required (%); FM^{VCTE}: rate of second-line $FibroMeter^{VCTE}$ required (%)

[a] used with their diagnostic intervals followed by liver biopsy in case of undetermined diagnosis

Table IV : new $FM^{V3G\text{-}VCTE}$ and VCTE-FM^{VCTE} versus previously published algorithms

Analysis	Algorithm	1st line test(s)	2nd line test	DA	Se	Spe	NPV	PPV	-LR	+LR	OR	LB [a]	2nd line rate
Per protocol	SAFE (7)	APRI	Fibrotest	90.8 [b]	100.0	85.2	100.0	80.3	0.00	6.8	NA	73.8	39.6
(n=618)	Bordeaux (6)	Fibrotest + VCTE	-	88.0	96.1	83.1	97.3	77.5	0.05	5.7	122.5	43.7	100.0
	Palermo (9)	NFS + VCTE	-	96.1 [c]	95.7	96.4	97.4	94.1	0.04	26.3	590.9	67.2	100.0
	$FM^{V3G\text{-}VCTE}$	$FibroMeter^{V3G}$	$FibroMeter^{VCTE}$	90.3	85.8	93.0	91.6	88.1	0.15	12.2	80.4	29.6	59.5
	VCTE-FM^{VCTE}	VCTE	$FibroMeter^{VCTE}$	90.5	84.5	94.0	91.0	89.5	0.16	14.2	86.1	30.3	44.5
Intention to	SAFE (7)	APRI	Fibrotest	89.5	100.0	82.7	100.0	78.8	0.00	5.8	NA	71.2	38.3
diagnose	Bordeaux (6)	Fibrotest + VCTE	-	86.8	95.9	81.0	96.8	76.4	0.05	5.0	98.6	42.9	100.0
(n=371)	Palermo (9)	NFS + VCTE	-	95.1 [c]	96.6	94.2	97.7	91.5	0.04	16.8	458.8	67.9	100.0
	$FM^{V3G\text{-}VCTE}$	$FibroMeter^{V3G}$	$FibroMeter^{VCTE}$	86.8	83.4	88.9	89.3	82.9	0.19	7.5	40.5	29.1	55.0
	VCTE-FM^{VCTE}	VCTE	$FibroMeter^{VCTE}$	88.7	84.1	91.6	90.0	86.5	0.17	10.0	57.8	30.7	46.4

DA: diagnostic accuracy (i.e., rate of well classified patients, %); Se: sensitivity (%); Spe: specificity (%); NPV: negative predictive value (%); PPV: positive predictive value (%); -LR: negative likelihood ratio; +LR: positive likelihood ratio; OR: odd ratio; LB: rate of liver biopsy required (%); 2nd line rate: rate of second-line test required (%)

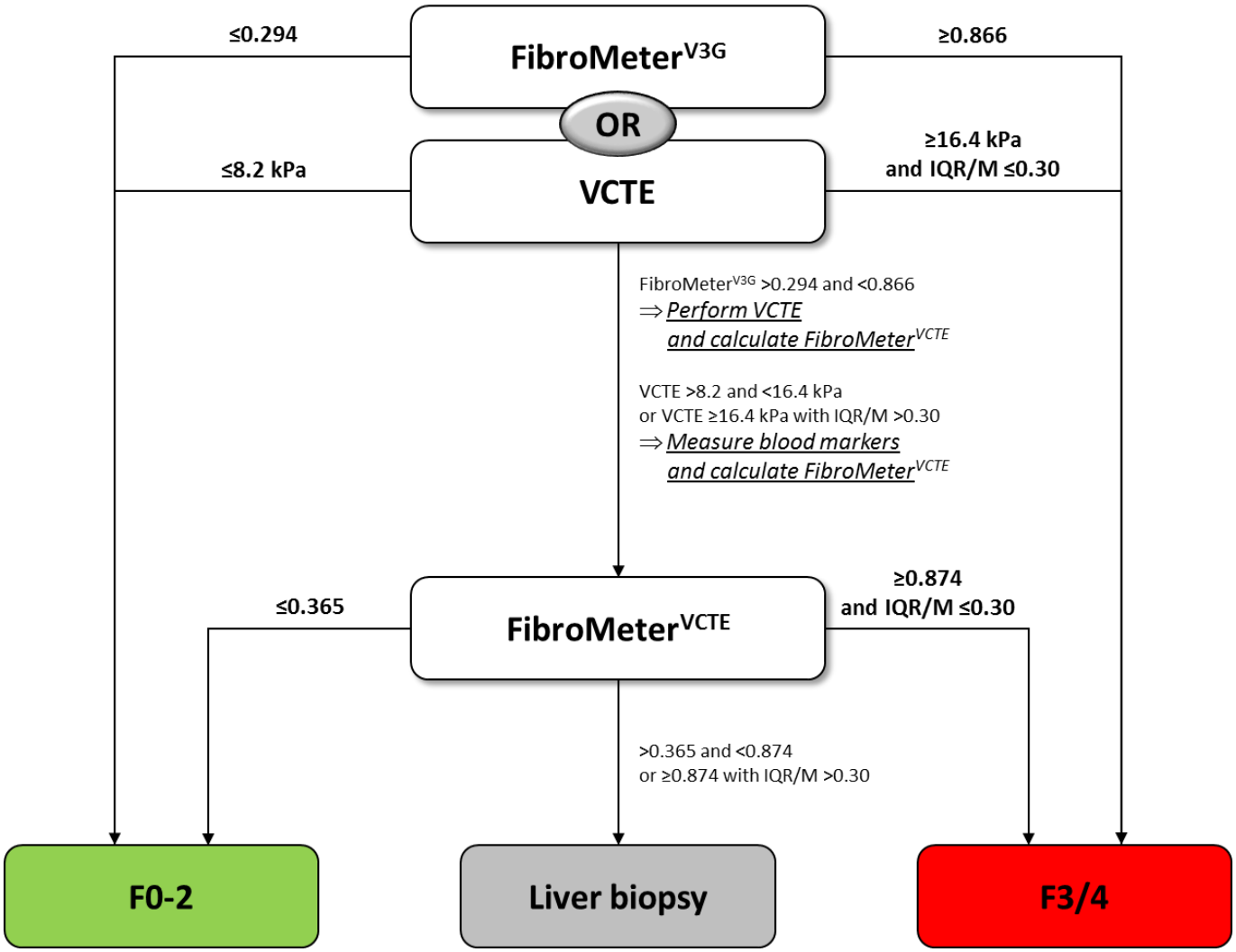
Comparison between algorithms:

[a] all $p \leq 0.013$ excepted $FM^{V3G\text{-}VCTE}$ vs VCTE-FM^{VCTE}, and SAFE vs Palermo only in the intention-to-diagnose analysis

[b] $p < 0.050$ vs Bordeaux

[c] $p \leq 0.003$ vs others

Figure 1: New algorithm for the diagnosis of advanced fibrosis in NAFLD



LISTE DES TABLEAUX

LISTE DES FIGURES

TABLE DES MATIERES

SUPPLEMENTARY MATERIAL

Table s1: Thresholds of 90% sensitivity (Se) and 95% specificity (Spe) for advanced fibrosis and rates of patients included in the diagnostic intervals of fibrosis tests

Fibrosis test	Thresholds		Rate of patients (%)		
	90% Se	95% Spe	≥90% Se interval	Intermediate zone	≥95% Spe interval
NFS	≤ -1.603	≥ 1.003	31.7	58.4	9.9
FibroMeter^{V2G}	≤ 0.252	≥ 0.799	31.9	54.5	13.6 [a]
FibroMeter^{V3G}	≤ 0.294	≥ 0.866	28.8	59.5	11.7
VCTE [b]	≤ 8.2	≥ 16.4	41.1 [c]	44.5 [c]	14.4 [d]
FibroMeter^{VCTE} [b]	≤ 0.365	≥ 0.874	44.8 [c]	37.9 [c]	17.3 [c]

NFS: NAFLD Fibrosis Score; VCTE: Vibration Controlled Transient Elastography

[a] p≤0.020 vs others excepted vs VCTE (p=0.610)

[b] patients with unreliable result (VCTE ≥16.4 kPa with IQR/M >0.30 or FibroMeter^{VCTE} ≥0.874 with IQR/M >0.30, see Table s2) were reclassified in the intermediate grey zone

[c] p<0.025 vs others

[d] p≤0.007 vs NFS and FibroMeter^{VCTE}

Table s2: Diagnostic accuracy of VCTE and FibroMeter^{VCTE} as a function of the interquartile range/median (IQR/M) ratio

		≥90% sensitivity interval	≥95% specificity interval
VCTE result:		***≤ 8.2 kPa***	***≥ 16.4 kPa***
Diagnostic accuracy (%)	All	90.6	80.0
	IQR/M ≤0.30	90.0	83.1
	IQR/M >0.30	96.0	54.5
	p	*0.485*	*0.040*
FibroMeter^{VCTE} result:		***≤ 0.365***	***≥ 0.874***
Diagnostic accuracy (%)	All	91.3	81.7
	IQR/M ≤0.30	91.2	84.1
	IQR/M >0.30	92.9	61.5
	P	*1.000*	*0.061*

Table s3: Baseline characteristics of the patients included in the intention-to-diagnose (ITD) analysis

	All (n=723)	**ITD [a] (n=371)**	**Others (n=352)**	**p**
Angers centre (%)	43.4	31.0	56.5	<0.001
Age (years)	55.7 ± 12.3	55.3 ± 12.7	56.0 ± 11.8	0.921
Male sex (%)	57.1	56.1	58.2	0.599
Diabetes (%) [b]	50.3	53.9	46.6	0.053
BMI (kg/m^2)	31.9 ± 6.0	32.4 ± 5.9	31.3 ± 6.0	0.016
Biopsy length (mm)	26 ± 11	25 ± 10	28 ± 12	0.005
NAFLD Activity Score	4.0 ± 1.6	4.2 ± 1.6	3.8 ± 1.5	<0.001
Fibrosis stage (%):				0.788
- 0	9.0	9.7	8.2	
- 1	25.2	26.1	24.1	
- 2	26.8	25.1	28.7	
- 3	26.0	26.4	25.6	
- 4	13.0	12.7	13.4	
Fibrosis F3/4 stages (%)	39.0	39.1	38.9	1.000
AST (IU/L)	49 ± 32	51 ± 37	47 ± 27	0.928
ALT (IU/L)	68 ± 49	69 ± 48	68 ± 50	0.829
Total bilirubin (µmol/L)	12 ± 8	12 ± 9	11 ± 7	0.002
Prothrombin time (%)	96 ± 15	97 ± 17	94 ± 13	<0.001
Platelets (G/L)	218 ± 71	214 ± 63	223 ± 77	0.105

BMI: body mass index; NAFLD: nonalcoholic fatty liver disease; AST: aspartate aminotransferase; ALT: alanine aminotransferase

[a] Patients for whom liver stiffness measurement with both M and XL was available

[b] either anti-diabetic treatment or fasting glycemia ≥126 mg/dl

Figure s1: Previously published diagnostic algorithms combining non-invasive fibrosis tests

Fibrosis stage corresponds to the NASH CRN staging system. ***Panel s1a:*** Sequential Algorithm for Fibrosis Evaluation combining the blood tests APRI and Fibrotest (7); ***Panel s1b:*** Bordeaux algorithm based on the agreement between VCTE and the blood test Fibrotest (6); ***Panel s1c:*** Palermo algorithm based on the agreement between VCTE and the blood test NAFLD fibrosis score (9)

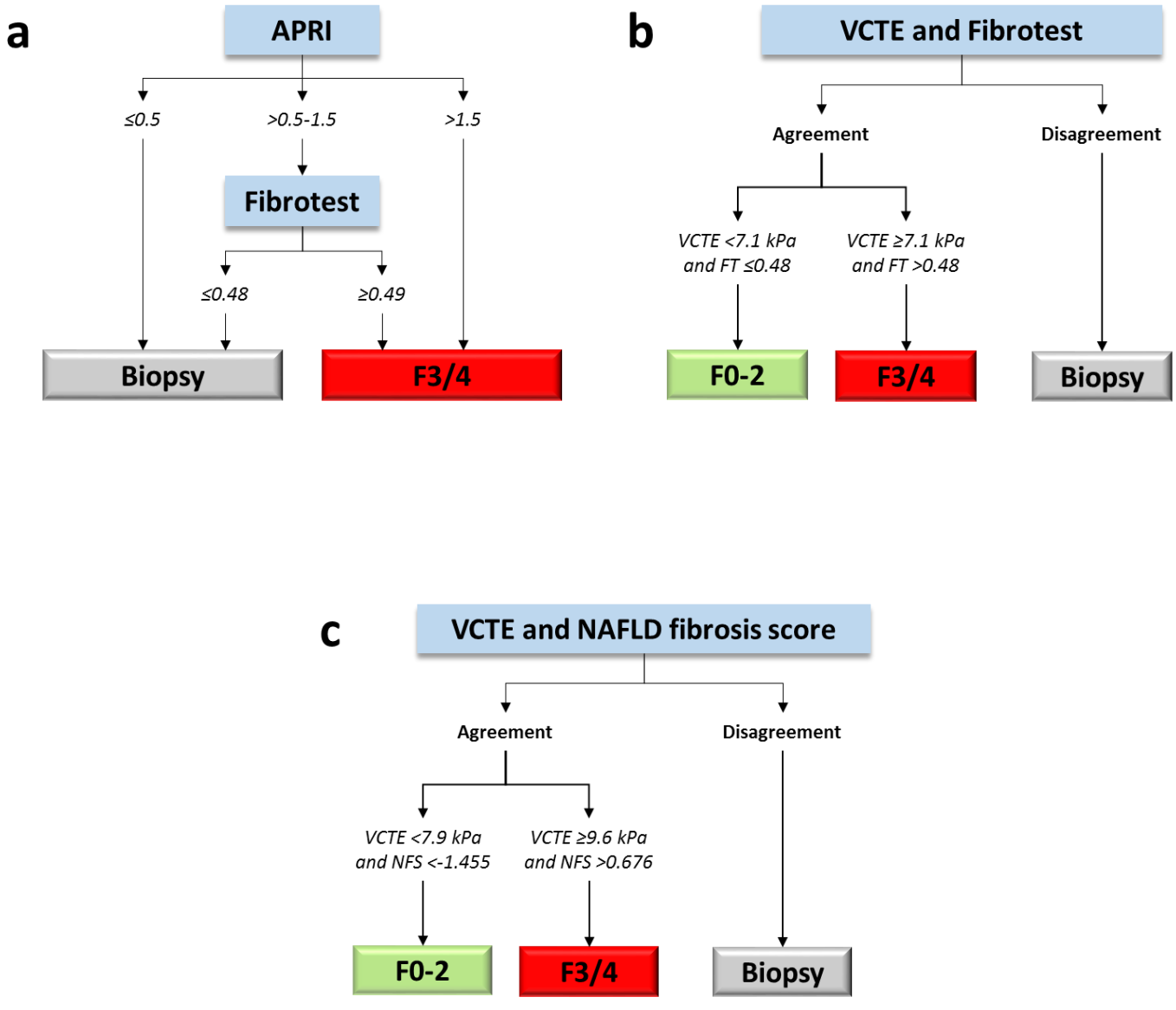


Figure s2: Correlation between FibroMeter^{V2G} and FibroMeter^{V3G}

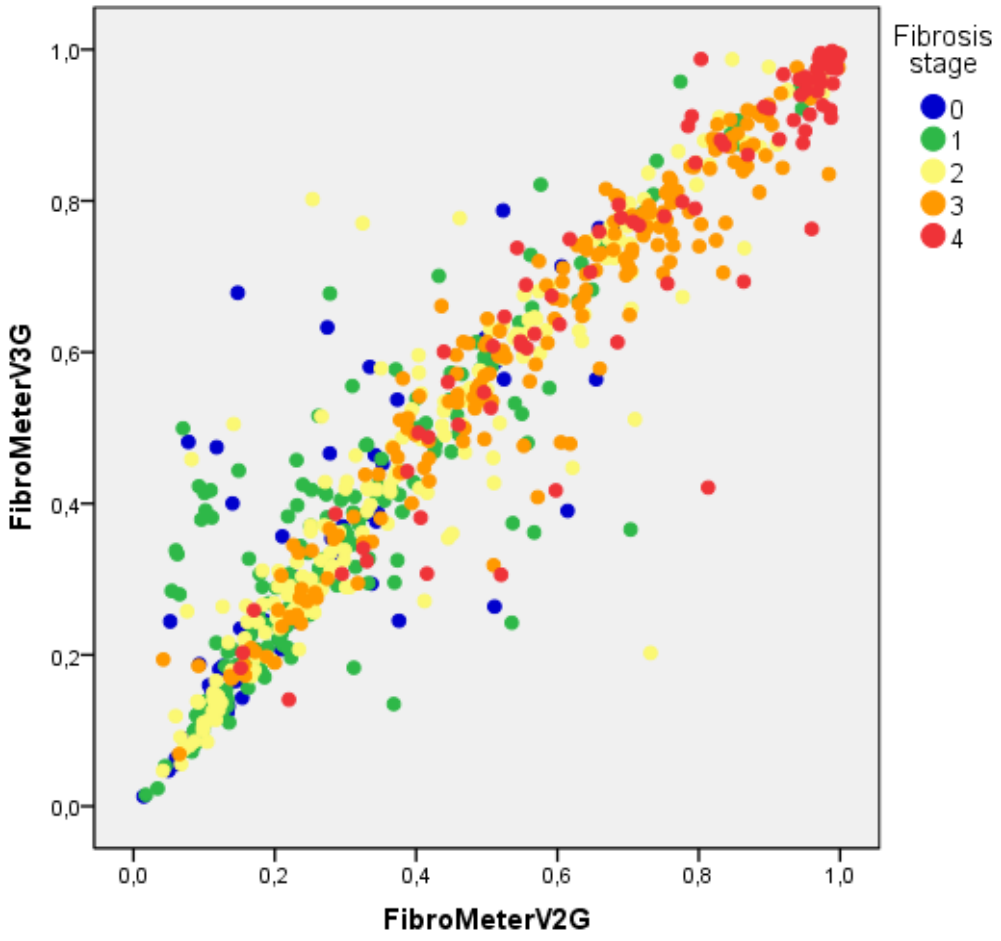
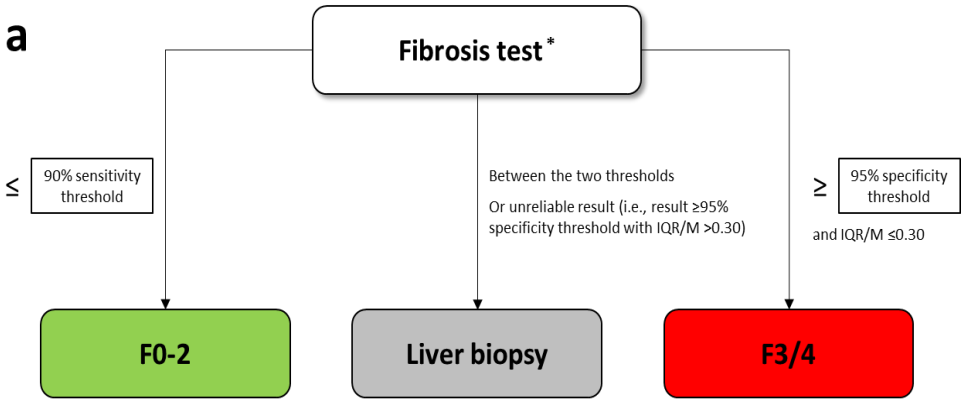


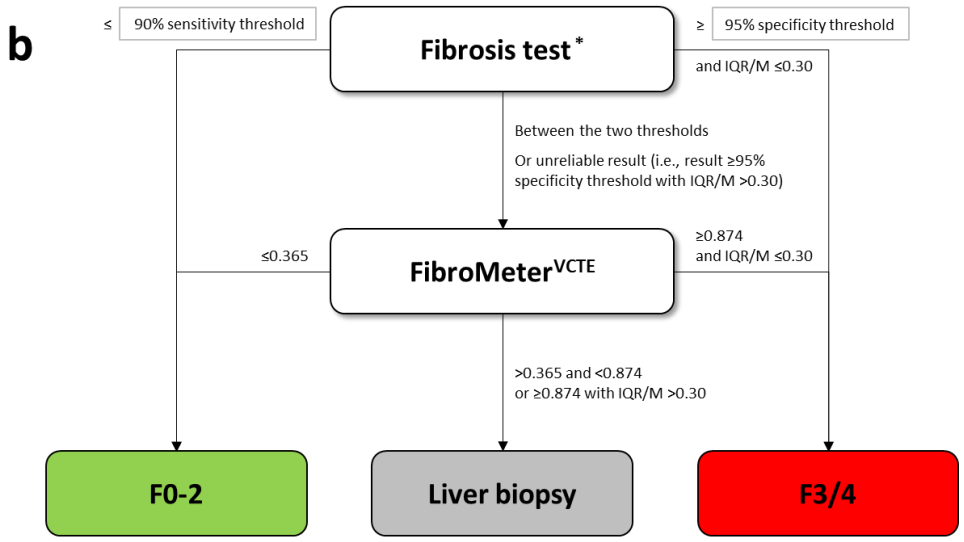
Figure s3: Diagnostic procedures evaluated in the study

Panel s3a: Diagnostic intervals of fibrosis tests. The 90% sensitivity and 95% specificity thresholds defined three diagnostic intervals: a lower interval where the diagnosis was F0-2 (≥90% sensitivity for advanced fibrosis), a higher interval where the diagnosis was advanced fibrosis (≥95% specificity), and an intermediate grey zone requiring liver biopsy.

Panel s3b: Sequential algorithm using a first-line fibrosis test, followed by the combinatorial test FibroMeter^{VCTE} in case of undetermined diagnosis, and finally liver biopsy as last-line procedure if the diagnosis remained undetermined.

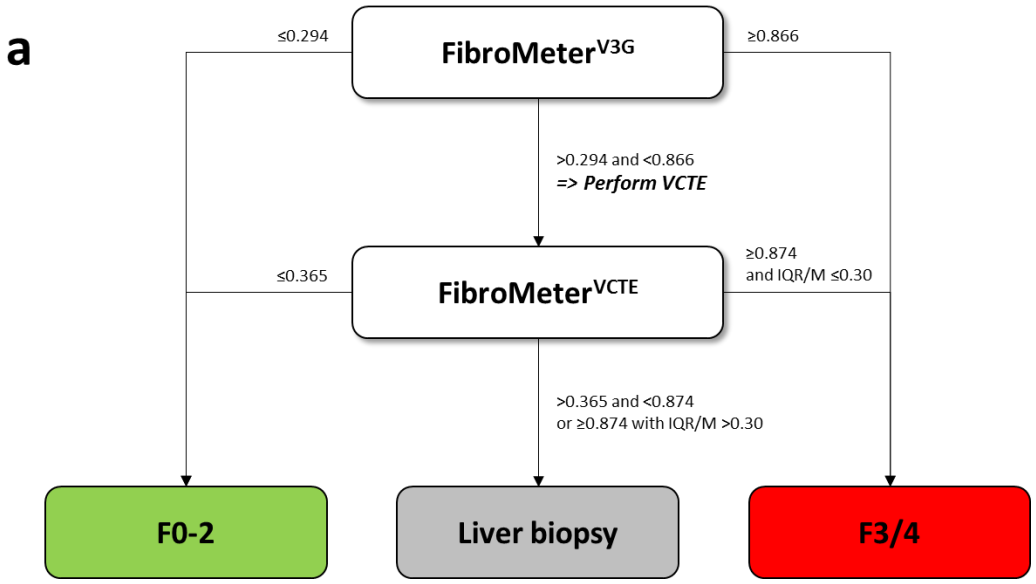


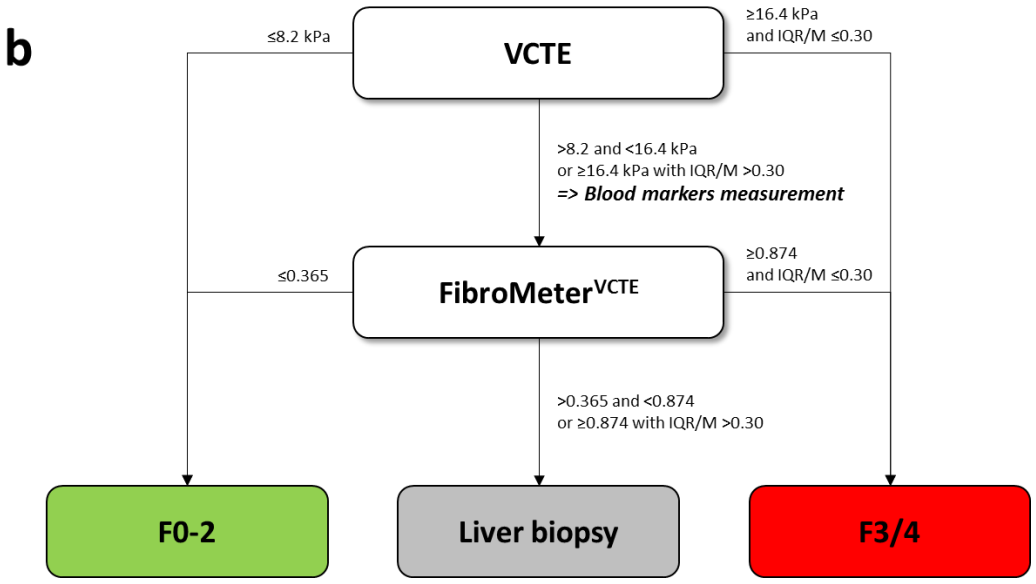
* NAFLD fibrosis score, FibroMeter^{V2G}, FibroMeter^{V3G}, VCTE or FibroMeter^{VCTE}
IQR/M: interquartile range/median ratio of the liver stiffness measurement by VCTE



* NAFLD fibrosis score, FibroMeter^{V2G}, FibroMeter^{V3G} or VCTE
IQR/M: interquartile range/median ratio of the liver stiffness measurement by VCTE

Figure s4: The FM$^{V3G\text{-}VCTE}$ (*panel 1a*) and the VCTE-FM^{VCTE} (*panel 1b*) algorithms.





ZUBERBUHLER FLORAINE

La combinaison du Fibroscan et des tests sanguins avec le Fibromètre ^{VCTE} diminue significativement l'utilisation de la biopsie hépatique pour l'évaluation de la fibrose avancée dans la NAFLD

RÉSUMÉ

Contexte et objectifs : Le Fibroscan et le Fibromètre diagnostiquent avec précision la fibrose avancée dans la NAFLD (J Hepatol 2016). Cependant, ils ont une zone grise où le diagnostic reste indéterminé. Comme nous l'avons déjà démontré dans l'hépatite C chronique, nous voulions évaluer si la combinaison de tests non invasifs réduisait cette zone grise et donc le recours à la biopsie hépatique dans la NAFLD.

Méthode : 723 patients ayant une NAFLD prouvée histologiquement, et qui ont eu une évaluation par Fibroscan et tests sanguins, ont été inclus. Les tests sanguins évalués étaient : NAFLD Fibrosis Score (NFS), FibroMètre^{V3G} (FM^{V3G}), FibroMètre^{VCTE}. La cible diagnostique était la fibrose avancée, définie par le NASH CRN system, comme un stade F≥3.

Résultats : La mesure de l'élasticité hépatique avec la sonde FS M(FS_M) a été un échec chez 105 patients. L'analyse per protocole réalisée chez les 618 patients restants a mis en évidence que le FM^{VCTE} avait une AUROC significativement supérieure (0.861±0.015, p≤0.009) à celle du NFS (0.725±0.020), du FM^{V3G} (0.772±0.020) et FS_M (0.831±0016). Le nombre de patients inclus dans la zone grise, entre les seuils de sensibilité à 90% et de spécificité à 95%, était le plus faible avec le FM^{VCTE} (37.9%, p<0.025 vs les autres tests). Six combinaisons de tests ont été évalués : SAFE (Sebastiani, Hepatology 2009), l'algorithme de Bordeaux (BA, Castera J Hepatol 2010), NFS-FS_M (Petta, Liver Int 2015), FM^{VCTE}, FM^{V3G} en première ligne puis FM^{VCTE} si le diagnostic était indéterminé (FM^{V3G}-FM^{VCTE}), FS_M en premier puis FM^{VCTE} (FS_M-FM^{VCTE}). La précision diagnostique et le taux de biopsies hépatiques étaient respectivement : 90.8%/73.8%, 88.0%/43.7%, 96.1%/67.2%, 93.4%/37.9%, 90.3%/29.6%, 90.5%/30.3%. FM^{V3G}-FM^{VCTE} et FS_M-FM^{VCTE} ont le taux le plus bas de biopsies hépatiques (p<0.001 vs les autres) avec une précision diagnostique élevée, aux alentours de 90%. Le Fibroscan avec la sonde XL a été fait chez 371 patients. Une analyse en intention de diagnostiquer a été réalisée dans ce sous-groupe, en utilisant le FS_{XL} dans les cas d'échecs du FS_M (n=67) et la biopsie hépatique lorsque le FS_{XL} échouait (n=7). La précision diagnostique et le taux de biopsie hépatique de cinq combinaisons de tests (SAFE, BA, NFS-FS, FM^{V3G}-FM^{VCTE}, FS-FM^{VCTE}) étaient, respectivement : 89.5%/71.2%, 86.8%/42.9%, 95.1%/67.9%, 86.8%/29.1%, 88.7%/30.7%.

Conclusion La combinaison du Fibroscan et des tests sanguins avec le FibroMètre^{VCTE} améliore le diagnostic non invasif de la fibrose avancée dans la NAFLD. En pratique clinique, l'utilisation séquentielle des tests (premièrement : Fibroscan ou FibroMeter^{V3G} ; puis, si nécessaire : FibroMeter^{VCTE}) diminue significativement la nécessité de recours à la biopsie hépatique.

Mots-clés : Fibrose hépatique, cirrhose, tests non invasifs, algorithmes, biopsie hépatique

The combination of Fibroscan with blood markers in the FibroMeter^{VCTE} significantly reduces the use of liver biopsy for the assessment of advanced fibrosis in NAFLD

ABSTRACT

Background and Aims: Fibroscan and FibroMeter accurately diagnose advanced liver fibrosis in NAFLD (J Hepatol 2016). However, they have a grey zone where the diagnosis remains undetermined. As already shown in chronic hepatitis C, we aimed to evaluate if combining fibrosis tests reduces this grey zone and thus the need for liver biopsy in NAFLD.

Methods: 723 biopsy-proven NAFLD patients with Fibroscan (FS) and blood tests were included. Blood tests evaluated were: NAFLD Fibrosis Score (NFS), FibroMeter^{V3G} (FM^{V3G}), FibroMeter^{VCTE} (FM^{VCTE}: a combination of Fibroscan with the blood markers of FM^{V3G} in a single formula). The primary diagnostic target was advanced fibrosis as defined by NASH CRN fibrosis stage F≥3.

Results: Liver stiffness measurement with the FS M probe (FS_M) failed with no valid measurement in 105 patients. The per-protocol analysis performed in the 618 remaining patients showed that FM^{VCTE} had a significantly higher AUROC (0.861±0.015, p≤0.009) than NFS (0.725±0.020), FM^{V3G} (0.772±0.020) and FS_M (0.831±0016). The rate of patients included in the grey zone between the 90% sensitivity and 95% specificity thresholds was the lowest with the FM^{VCTE} (37.9%, p<0.025 vs other tests). Six test combinations were evaluated: SAFE (Sebastiani, Hepatology 2009), Bordeaux algorithm (BA, Castera J Hepatol 2010), NFS-FS_M (Petta, Liver Int 2015), FM^{VCTE}, FM^{V3G} first then FM^{VCTE} if undetermined diagnosis (FM^{V3G}-FM^{VCTE}), FS_M first then FM^{VCTE} (FS_M-FM^{VCTE}). Diagnostic accuracy and rate of liver biopsy were, respectively: 90.8%/73.8%, 88.0%/43.7%, 96.1%/67.2%, 93.4%/37.9%, 90.3%/29.6%, 90.5%/30.3%. FM^{V3G}-FM^{VCTE} and FS_M-FM^{VCTE} provided thus the lowest rate of liver biopsy (p<0.001 vs others) with a high diagnostic accuracy around 90%. The FS XL probe (FS_{XL}) was available in a subset of 371 patients. An intention-to-diagnose analysis was performed in this subgroup by using FS_{XL} in case of FS_M failure (n=67) and liver biopsy in case of FS_{XL} failure (n=7). Diagnostic accuracy and rate of liver biopsy of the five tests combinations (SAFE, BA, NFS-FS, FM^{V3G}-FM^{VCTE}, FS-FM^{VCTE}) were, respectively: 89.5%/71.2%, 86.8%/42.9%, 95.1%/67.9%, 86.8%/29.1%, 88.7%/30.7%.

Conclusions: The synchronous combination of Fibroscan with blood markers in the FibroMeter^{VCTE} improves the non-invasive diagnosis of advanced fibrosis in NAFLD. In clinical practice, the sequential use of fibrosis tests (first: Fibroscan or FibroMeter^{V3G}; then, if necessary: FibroMeter^{VCTE}) significantly reduce the need for liver biopsy.

Keywords: Liver fibrosis ; Cirrhosis ; Non-invasive tests ; Algorithms ; Liver biopsy

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