COMPARISON ANALYSIS OF FIB-4, LIVERFAST (LF) AND LIVER STIFFNESS MEASUREMENT (LSM) WITH TRANSIENT ELASTOGRAPHY (TE) IN SEQUENTIAL AND COMBINATORY PATHWAYS FOR NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Victor De Lédinghen[1], Adèle Delamarre[2], Paul Hermabessière[2], Juliette Foucher[3], Marie Irles-Depe[4], Faiza Chermak[4] and Jean-Baptiste Hiriart[5]

(1) Liver Fibrosis Investigation Center, Bordeaux University Hospital, (2) Bordeaux University Hospital CHU Bordeaux, (3) Hepatology Department, Haut-Lévêque Hospital, (4) Hepatology Unit, Bordeaux University Hospital, Inserm U1053, Bordeaux University, France

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BACKGROUND

The identification of NAFLD bridging liver fibrosis (F3F4) remains challenging. Using non-invasive liver fibrosis tools (NITs) may permit earlier detection of F3F4 for liver specialist review.

To assess the performance for staging bridging fibrosis (F3F4) of sequential (Seq-M) and combinatory models (Combi-M) of several NITs: LIVERFASt, FIB-4, Transient Elastography (TE) taking liver biopsy (LB) as reference.

NAFLD cohort prospectively collected in a hepatology tertiary center (NCT01241227) with concomitant evaluation with liver biopsy (LB), FIB4, LIVERFASt (LF) and transient elastography (TE).

F3F4 cut-offs used were:
- *FIB-4 dual cut-off ||<1.3, >3.25*
- *LIVERFASt scores ≥ 0.58*
- *TE liver stiffness measurement ≥9.7kPa*

For each Seq-M and Combi-M models performance for F3F4 staging was assessed using:
- *Sensitivity (Se), Specificity (Sp), Positive/Negative predictive values (PPV/NPV),*
- *Non-applicability (NA) for TE (IQR/LSM>30% or failure),*
- *FIB-4 indeterminate zone (FIB4-IZ),*
- *Discordant results (DR) rates.*

Different sequential and combinatory scenarios were assessed:

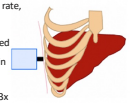
FIB-4 alone scenario (S1) was compared to Sequential models:
- **FIB-4 followed by TE scenario (S2)**
- **FIB-4 followed by LF scenario (S3) only for FIB4-IZ** (scores 1.3-3.25).

Combi-M scenario of FIB-4 + LF + TE (S4) was compared to other scenarios:
- **LF + TE scenario (S5),**
- **FIB-4 + LF scenario (S6)**
- **FIB-4 + TE scenario (S7)** In case of indeterminate zone (FIB4-IZ) or non-applicable TE (TE-NA), the staging relied on the other NIT and, in case of DR, on the most severe score.

Analysis was conducted in-intention-to-diagnose taking into account NA and IZ for the adjustment of the results.

Vibration Controlled Transient Elastography (TE) by Fibroscan (Echosens, Paris, France)

- **Quality criteria:** IQR/median, Success rate, 10 valid LSM
- **Variability** in 531 NAFLD patients paired measurements: one stage difference in 32%, two stages difference in 10%
- **Overestimation: Cytolysis** with ALT > 3x ULN, **non fasting, MetS:** T2D, BMI>30, high-blood pressure



LIVERFASt™ (Fibronostics, Orlando, Florida)

- **AI computer aided biomarker** for assessing **fibrosis, activity and steatosis**
- Constructed **using SAF histological combines** 10 biomarkers including liver-specific fibrosis markers, lipid panel, liver enzymes, BMI, age, and gender

- **Underestimation**: inflammatory syndrome (e.g. ulcerated diabetic foot). **Overestimation risks:** hemolysis

FIB-4 Index

- Algorithm: **platelet count, age, AST and ALT**

$$\text{FIB-4} = \frac{\text{age(years)} \times \text{AS(IU/L)}}{\text{Platelet count } (10^9/\text{L}) \times \text{ALT(IU/L)}^{\frac{1}{2}}}$$

- **Dual cut-off** for advanced fibrosis (<1.45, >3.25)
- **Over or underestimation**: age range, cytosis, normal ALT and AST (T2D)
- Lower diagnostic performance for cirrhosis in T2D

Disclosures: VDL: Echosens: Speaking and teaching

De Ledinghen V, et al. Hepatology 2020, Castera L, et al. Hepatology 2010; Ratziu V, et al. Gastroenterology. 2005; Nascimbeni F, et al. Clin Gastroenterol Hepatol 2014; McPherson S, Am J Gastroenterol. 2017

Characteristics of included patients

N=588	Median or prevalences (%)
Gender Male	56.4%
Age (median), years	56.4
Type 2 Diabetes	51.4%
BMI, Kg/m2	31.5
Bridging fibrosis (F3F4) prevalences	
• F3F4 Liver Biopsy	45.4%
• LIVERFASt Fibrosis score	39.8%
• FIB-4	15.4%
• Transient Elastography (TE)	43.5%
FIB-4 Indeterminate zone (IZ) (1.3-3.25)	280 (47.6%)
TE Non-Applicable (NA)	67 (11.4%)
Discordance Rate (DR) for F3F4 vs biopsy	
• FIB-4 (indeterminate zone not counted)	16.9%
• TE (not applicable not counted)	24.4%
• LIVERFASt	32.3%
Concordance rate for F3F4 staging	
• All concordant (Te, LIVERFASt, Fib-4)	160 (27.2%)
• At least 2 NITs are concordant	356 (60.5%)

Performance of sequential and combinatory non-invasive models

Model	SE	SP	PPV	NPV	Comments
S1 FIB-4 alone ITD taking into account the IZ					
• YES	26.2%	57.9%	34.2%	48.6%	
• NO	61.9%	95.4%	88.6%	81.2%	
S2 FIB-4 followed by TE	65.2%	81.8%	77.0%	72.4%	TE-NA 32(11.4%)
S3 FIB-4 followed by LIVERFASt	57.0%	81.3%	71.7%	69.4%	With the advantage of higher applicability vs TE
S4 Combination of FIB-4 + LF + TE	52.1%	73.8%	62.3%	64.9%	Palliation of NA-TE by staging with LF or FIB-4
S5 Combination of LF + TE (see Figure 1))	74.6%	84.0%	79.1%	80.9%	Discordance rate between TE and LF 194 (32.9%)
S5 with discordant results integrated as *"the most severe result (either TE or LF) is true"*	83.5%	58.3%	62.5%	81%	Se/NPV increased while Sp/PPV decreased
S6 FIB-4 + LF	57.1%	80%	70.4%	69.2%	
S7 FIB-4 + LF	73.8%	70.8%	68.7%	75.7%	with 32pts (5.4%) in **S7** having both non-applicableTE and indeterminate zone FIB-4.

Figure 1. Combinatory model (Scenario 5) using Transient Elastography and LIVERFASt™

LIVERFASt™ F0-F2 (score ≤0.58) N=354						LIVERFASt™ F3F4 (score >0.58) N=234					
TE F0-F2 <9.7kPa N=194		TE F3F4 ≥9.7kPa N=123		*TE NA* N=37		TE F0-F2 <9.7kPa N=71		TE F3F4 ≥9.7kPa N=133		*TE NA* *N=30*	
LB F0-F2 N=158	**LB F3F4 N=36**	LB F0-F2 N=50	**LB F3F4 N=73**	LB F0-F2 N=29	**LB F3F4 N=8**	LB F0-F2 N=50	**LB F3F4 N=21**	LB F0-F2 N=20	**LB F3F4 N=113**	LB F0-F2 N=14	**LB F3F4 N=16**

TE = Transient elastography; NA= not applicable TE result (IQR/LSM>30% or failure); LB= Liver biopsy; IQR= Interquartile Range; LSM= Liver stiffness measurement

Our study suggested that NITs such as Transient Elastography and LIVERFASt when used in combination:
- outperform sequential approaches, including those integrating FIB4
- could palliate for the non-applicable TE results

If both TE and LF agree on the presence of F3F4, the detection of severe NAFLD is improved.

victor.deledinghen@chu-bordeaux.fr

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