Combination of LIVERSTAT (LST) and Fibroscan (LSM) Outperforms FIB-4 and LSM for MASLD Advanced Fibrosis (AF) F3F4

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INTRODUCTION

- Metabolic dysfunction-associated liver disease (MASLD) affects one in four subjects and can progress undetected from simple steatosis to advanced fibrosis and cirrhosis, especially in patients with type 2 diabetes (T2D).
- Given the limitations of liver biopsy and the scarce availability of transient elastography (TE), there is a growing need for non-invasive, cost-effective blood- based tests for liver fibrosis assessment
- Clinical care pathways integrating AI-based blood tests like the STRATIFICATION test, LiverSTAT, and staging at-risk MASH patients ,LIVERFASt, offer a promising approach to identifying advanced fibrosis in patients with MASLD.
- AASLD clinical practice guidelines stated that the primary risk assessment could be done with FIB- 4 and those with advanced fibrosis risk should be referred for secondary risk assessment with either a standard-of-care, liver stiffness measurement (LSM) with Fibroscan, or other noninvasive testing.

  Rinella M. et al. Hepatology 2023
- We previously developed LIVERFASt (CPT code 0166U) that demonstrated a high PPV for advanced fibrosis in secondary care in T2D MASLD patients

	Overall MASLD population, N=399		Patients with T2D N=235	
	Number	Biopsy confirms both NITs	Number	Biopsy confirms both NITs
LIVERFASt & LSM agree for F3F4	74	**70/74 (94.6%)**	56	**53/56 (94.6%)**

deLedinghen J Hepatol Suppl. 2024 (EASL 2024 poster2448

- LIVERFAST is a particularly useful blood NIT for the identification of at-risk MASH patients for drug therapy by and provides assessment of activity (NAS≥4) along with fibrosis.

CONTACT INFORMATION

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DISCLOSURES

N.Alkhouri: Advisory Panel; ; Madrigal Pharmaceuticals, Inc., 89bio, Inc., Altimmune Inc., Novo Nordisk, Consultant; ; Boehringer-Ingelheim, Speaker's Bureau; ; Alexion Pharmaceuticals, Inc., Gilead

Sciences, Inc.. A. Kohli: none. R.Nadeem: None. P.Leff: None. P.Mantry: None. Yong Wen Leow: None. Wah KheongChan: None. R.Quiambao: Other Relationship; ; Fibronostics USInc.. I. Alam: Advisory Panel. J.Dupuy: None. M.Munteanu: Employee; ; Fibronostics. V.Deledinghen: Advisory Panel; ; Fibronostics.

AIMS

To retrospectively compare the efficacy of two combinations in one-step approach : LiverSTAT & LSM versus FIB-4 & LSM, for the identification of advanced fibrosis (F3F4) in a multicenter multiethnic meta-dataset of MASLD patients.

METHODS

- Retrospective data from 5 hepatology centers from MASLD patients that underwent liver biopsy (LB) along with LSM with Fibroscan , FIB-4 and LiverSTAT.
- Efficiency has been assessed using:
  - Concordance rates between noninvasive tests and biopsy,
  - Number needed to screen (NNS) to detect one subject with LB F3F4.
- Cut-offs for advanced fibrosis were:
  - **LSM*:** 12kPa (to rule-in F3-F4)
  - **FIB-4*:** 1.3 and 2.67 to rule out/rule in F3F4;
  - **LiverSTAT** cut-off of 0.59.

  *recommended by AASLD clinical practice guidelines

NON-INVASIVE TESTS (NITs)

LiverSTAT (Fibronostics, Florida, US), fibronostics.com

- AI computer aided proprietary algorithm, assess fibrosis and steatosis for MASLD category determination
- Combines seven blood biomarkers and anthropometrics to generate a category of fibrosis/steatosis for the STRATIFICATION of MASLD subjects

LIVERFASt (Fibronostics, Florida, US), fibronostics.com, CPT code 0166U

- Combines biochemistry blood biomarkers and anthropometrics to generate scores correlated to biopsy fibrosis, activity and steatosis staging
- Has similar performance in patients with T2D as in patients without T2D
- LIVERFASt Activity and Fibrosis test can identify AT-RISK MASH patients with fibrosis F2F3 and NAS≥4 facilitating selection for drug therapy

Fibroscan (TE, Echosens, paris, France)

- TE quality criteria: IQR/median<30%, Success rate≥60%, 10 valid LSM
- FibroScan LSM variates with paired measurements in MASLD with differences of 1-stage (32%) and 2-stages (10%). Overestimation with Cytolysis with ALT>3x ULN, non fasting, MetS: T2D, BMI>30, high BP

FIB-4 (Free calculator Algorithm: platelet count, age, AST and ALT)
Dual cut-off for advanced fibrosis (<1.3, >2.67), Over/underestimation factors: age, cytolysis, T2D,

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

RESULTS

Characteristics of Included Patients with (n=786)

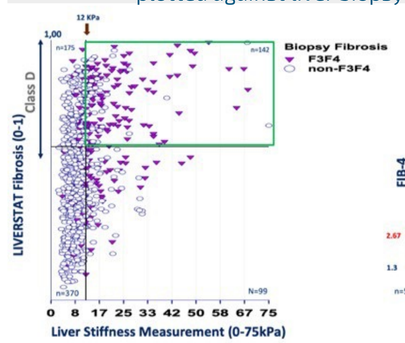
Characteristics	No (%), prevalence or Median (range)
Cohort origin US / Malaysia / France	174 (22%) / 304 (38%) / 304 (38%)
Gender Female	428 (54.5%)
Age, years	57.1 (18-85)
ALT / AST, IU/L	52 (9-371) / 39 (12-335)
BMI, Kg/m2	31.4 (21.4-83.0)
Platelets (*10³)	240 (10-632)
FIB-4 score	1.52 (0-18.7)
FIB-4 category	
<1.3	422 (53.7%)
Intermediate	273 (34.7%)
>2.67	91 (11.6%)
LiverSTAT score	0.52 (0.05-0.99)
LiverSTAT Fibrosis Staging	
Presumed F0	123 (16%)
Presumed F1F2	346 (44%)
Presumed F3F4	317 (40%)
LSM by Fibroscan, kPa	9.5 (2.7-75)
LSM presumed F3F4	454 (57.8%)
LSM no presumed F3F4	332 (42.2%)
NASH-CRN Fibrosis Staging at biopsy	
Stages F0 / F1 / F2	123 (15.6%) / 242 (30.8%) / 163 (20.7%)
Stages F3 / F4	189 (24.0%) / 69 (8.8%)

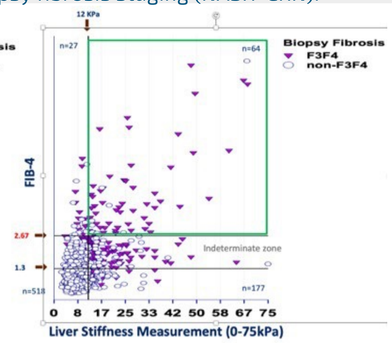
Agreement for advanced fibrosis of LiverSTAT and LSM with liver biopsy, respectively, according to FIB-4 group

N=786	N=422 FIB-4 < 1.3 NO Presumed advanced fibrosis	N=273 FIB-4 1.3-2.67 (indeterminate zone)	FIB-4 ≥2.68 No Presumed advanced
	Concordance rate with LB staging F3F4 according to FIB-4 class		
LiverSTAT	70.3%	56.0%	70.1%
LSM	61.8%	43.2%	76.9%

The combination LiverSTAT & LSM identifies twice more patients with advanced fibrosis than the combination FIB-4 & LSM

Scatterplots of the combinations LiverSTAT and LSM and FIB-4 and LSM plotted against liver biopsy fibrosis staging (NASH-CRN).





N=512/786 (65%) MASLD patients, LiverSTAT and LSM agree

LiverSTAT & LSM agree	Number	Biopsy confirms both NITs	Biopsy disagrees with both NITs
LiverSTAT & LSM agree for F3F4 (LiverSTAT≥0.59 and LSM ≥12kPa)	**142**	**107/142 (75%)**	**35 double false positives** (4.5% of the whole cohort and 6.8% of the cohort with LSM and LiverSTAT agreement)
LiverSTAT & LSM agree for F0-F2 (LiverSTAT<0.59 and LSM <12kPa)	**370**	**315/370 (85%)**	**55 double false negatives** (7% of the whole cohort and 10.7% of the cohort with LSM and LiverSTAT agreement)

N=582/786 (74%) MASLD patients, FIB-4 and LSM agree

FIB-4 & LSM agree	Number	Biopsy confirms both NITs	Biopsy disagrees with both NITs
FIB-4 & LSM agree for F3F4 (FIB-4>2.67 and LSM ≥12kPa)	**64**	**54/64 (84%)**	**10 double false positives** (1.3% of the whole cohort and 1.7% of the cohort with LSM and FIB-4 agreement)
FIB-4 & LSM agree for F0-F2 (FIB-4<1.3 and LSM <12kPa)	**518**	**429/518 (83%)**	**89 double false negatives** (11.3% of the whole cohort and 15.3% of the cohort with LSM and FIB-4 agreement)

In the subgroup with ≥2 cm liver biopsy samples size, when LiverSTAT and LSM agreed:
- The confirmation rate for F3F4 increased from 75% to 86% (43/50) and
- The number needed to screen (NNS*) for one additional patient to be confirmed as F3F4 decreased from 1.8 to 1.6

In the subgroup with ≥2 cm liver biopsy samples size, when FIB-4 and LSM agreed for F3F4:
- The confirmation rate for F3F4 increased from 84% to 91% (30/33)
- The number needed to screen (NNS*) for one additional patient to be confirmed as F3F4 decreased from 2.2 to 1.8

LiverSTAT & LSM identifies & can help for the identification of F3F4 among patients with FIB-4 ≤ 2.67

LiverSTAT along with LSM can help in the identification of F3F4 among FIB-4 scores ≤2.67

- 191/258 (74%) of patients with biopsy F3F4 have FIB-4 ≤ 2.67
- 132/191 (70%) of patients had a FIB-4 " intermediate zone"
- 59/191 (30%) of patients with LB F3F4 had FIB-4 <1.3

LiverSTAT & LSM agree for F3F4 in 95 pts with FIB-4 ≤2.67 Biopsy confirms F3F4 in 64/95 (67%)

54/64 (84%) patients with agreement for fibrosis F3F4 between LiverSTAT &LSM and biospsy had FIB-4 in the intermediate zone

CONCLUSIONS

Initial MASLD assessment with LiverSTAT instead of FIB-4 along with Fibroscan

- **Correctly identified twice more F3F4**
- **Does not miss F3F4 patients because of a "grey zone"**
- **Can work as an upfront screening for F3F4 before referral to more complex assessments**