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Abstract 76-OR

LIVERFASt Has Similar Performance to Liver Biopsy for the Screening of NASH Fibrosis in Type 2 Diabetes Mellitus (T2D)

Victor de Lédinghen[1], Adèle Delamarre[1], Brigitte Lebail[1], Hortense Marraud-Des-Grottes[1], Marie Irlès-Depé[1], Marie Decraecker[1], Juliette Foucher[1], Jean-Baptiste Hiriart[1], Ronald Quiambao[2], Mona Munteanu[2,3], Imtiaz Alam[4,5]

(1) Liver Fibrosis Investigation Center, Hepatology Department, University Hospital of Bordeaux, France; (2) Medical Affairs Department, Fibronostics, Orlando, Florida, US; (3) University Paris Rene-Descartes Paris, France; (4) Dell Medical School, Austin, TX, US (5) Austin Hepatitis Center, TX, US

CHU Hôpitaux de Bordeaux

Presenter Disclosures

Mona Munteanu

Fibronostics

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Background

ADA: Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes—2021

"T2D is associated with the development of NAFLD, including NASH, liver fibrosis, cirrhosis, and hepatocellular carcinoma."

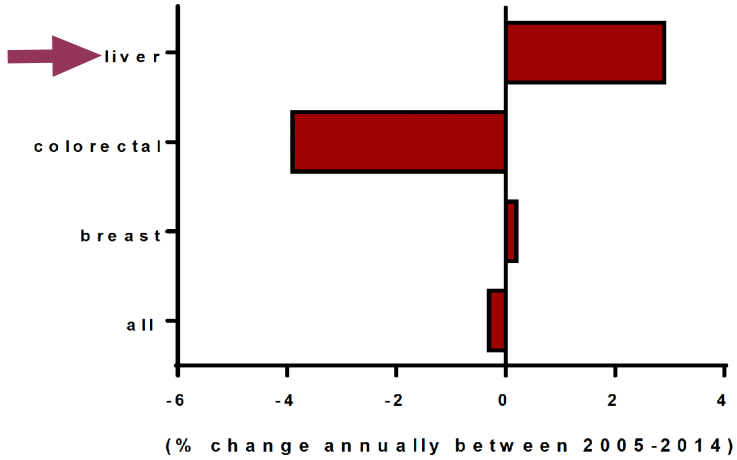
Diabetes Care 2021

High prevalence of NAFLD among T2D

- **56%** of patients with T2D have **NAFLD**
- **37%** of patients with T2D have **NASH**
- **17%** of patients with **T2D** and **NAFLD** who undergo liver biopsy, have **advanced fibrosis**

Younossi ZM, et al. J Hepatol. 2019

Liver cancer rate related to obesity is increasing 3% annually



El-Serag HB, Gastroenterology 2004
Steele, Morbidity and Mortality Weekly Report 2017

"Given that liver biochemistries can be normal in patients with NAFLD, they may not be sufficiently sensitive to serve as screening test, while, liver ultrasound or TE are potentially more sensitive, but their utility as screening tools is unproven"

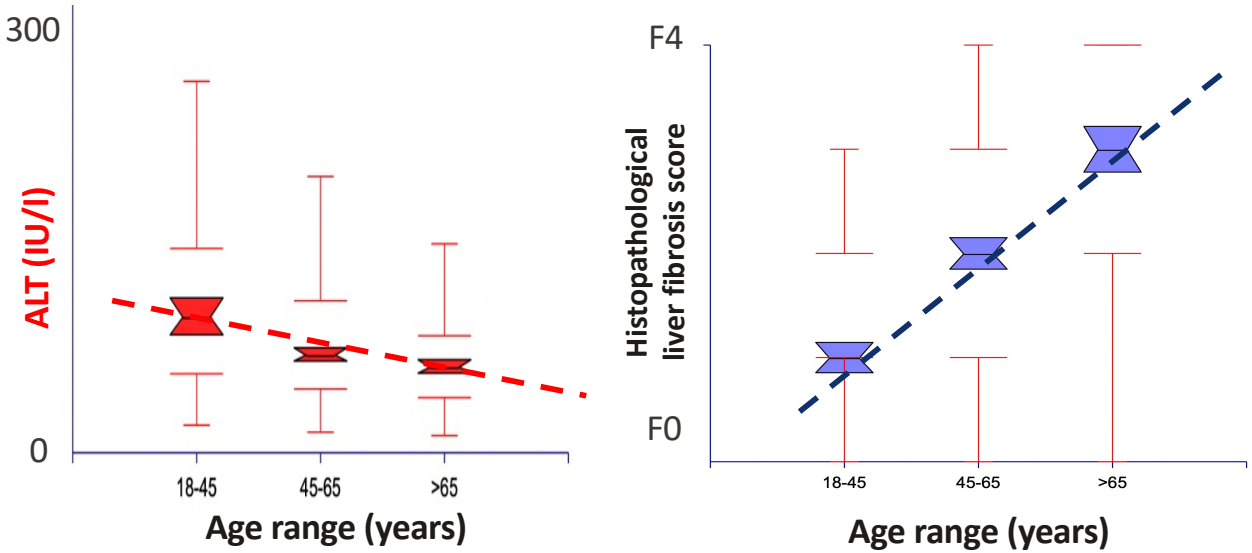
Chalassani N. et al. Hepatology 2018

Standards of Medical Care in Diabetes—2021

"Patients with T2D or prediabetes and elevated ALT or fatty liver on ultrasound should be evaluated for presence of NASH and liver fibrosis. "

Diabetes Care 2021

Opposite correlation of ALT and liver fibrosis with age ranges



De Ledinghen V, et al. Hepatology 2020
Mofrad P, et al. Hepatology. 2003
Fracanzani AL, et al. Hepatology 2008
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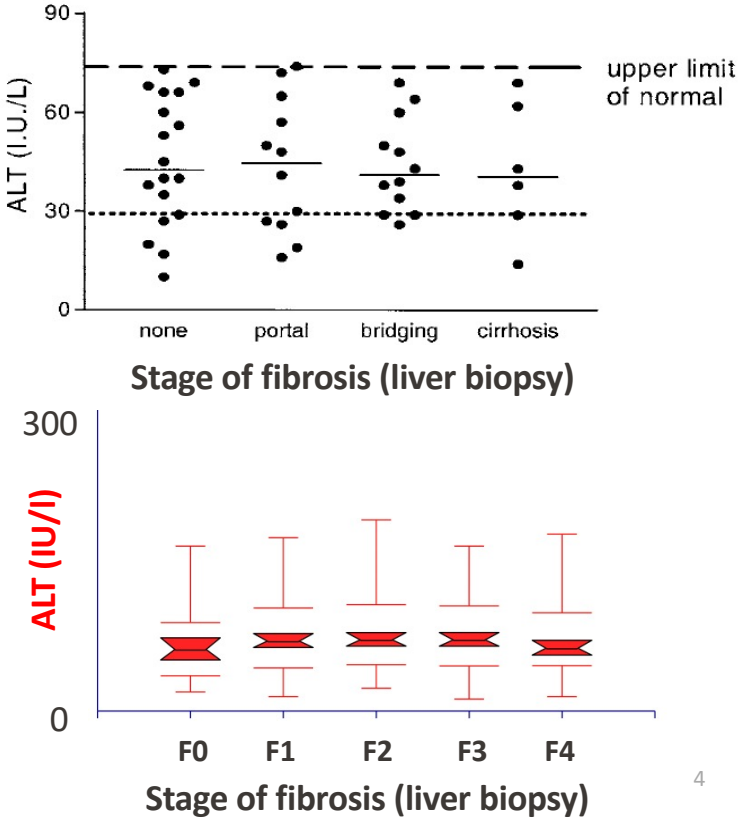
ALT lacks sensitivity for discriminating fibrosis staging



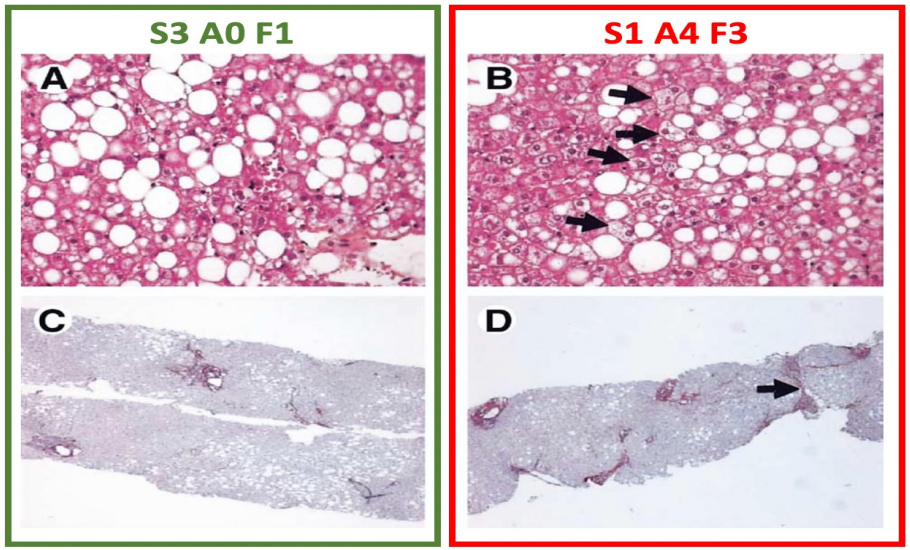
What tests to use to screen for NAFLD?

*"Noninvasive tests, such as **elastography** or **fibrosis biomarkers**, may be used to assess risk of fibrosis, but referral to a liver specialist and **liver biopsy** may be required for definitive diagnosis"*

Diabetes Care 2021; Chalasani N, et al. Hepatology 2018

Liver biopsy: NASH-CRN or SAF

Sampling variability in paired NAFLD specimens

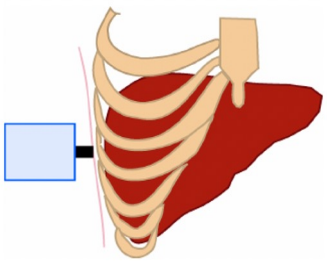


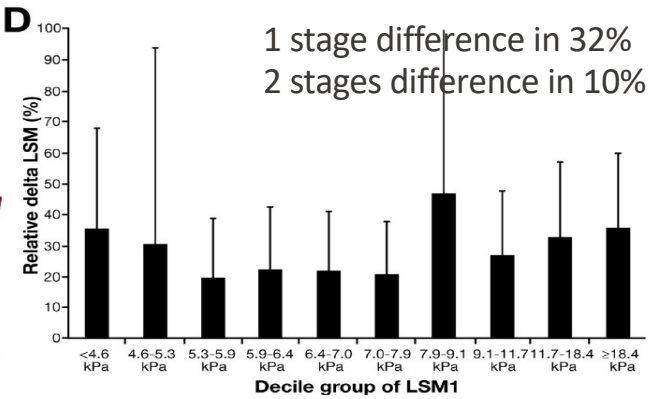
- Invasive, expensive, morbi-mortality, variability, patient's refusal…

Ratziu V, et al. Gastroenterology. 2005
Bedossa P, et al. Hepatology 2012

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





- **Overestimation**: **Cytolysis** with ALT > 3x ULN, **non-fasting**
  MetS: T2D, BMI>30, high-blood pressure

www.echosens.com

Nascimbeni F, et al. Clin Gastroenterol Hepatol 2014;
Castera L, et al. Hepatology 2010; Roulot D et al. J Hepatol 2008

What tests to use to screen for NAFLD?

*"Noninvasive tests, such as **elastography** or **fibrosis biomarkers**, may be used to assess risk of fibrosis, but referral to a liver specialist and **liver biopsy** may be required for definitive diagnosis"*

Diabetes Care 2021; Chalasani N, et al. Hepatology 2018

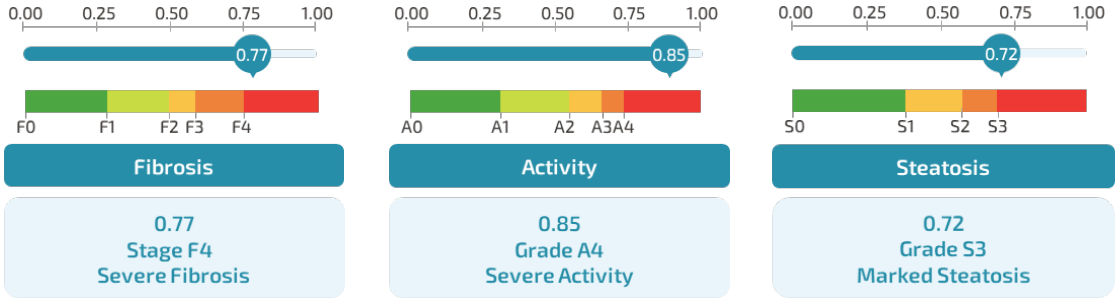
FIB-4 Index

- Algorithm : **platelet count, age, AST, and ALT**
- **Dual cut-off** for advanced fibrosis (<1.45, >3.25)
- **Over- or underestimation** : age range, cytolysis, normal ALT and AST (T2D)

Mallet V, et al. Presse Med. 2019;
Kaswala DH, et al. Dig Dis Sci 2016;
Imajo K, et al. Gastroenterology 2016;
McPherson S, Am J Gastroenterol. 2017;
De Ledinghen V, et al. Hepatology 2020

LIVERFASt™ (Fibronostics, Orlando, Florida)

- **AI computer aided biomarker** constructed **using SAF** and combining:
- **For LIVERFASt fibrosis score:** age, gender with **5 liver-specific** biomarkers: apolipoprotein A1, haptoglobin, alpha-2 macroglobulin, GGT, bilirubin
- **For Steatosis** and **Activity scores:** ALT, AST, lipid panel, glucose and BMI
- **CPT 0166U** for LIVERFASt fibrosis, activity and steatosis scores



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

www.fibronostics.com

De Ledinghen V, et al. Hepatology 2020; Aravind A, et al. JILSA 2020

Noninvasive Comparative Performances for Cirrhosis in patients with or without T2D taking liver biopsy as gold standard

ITD analysis in N=301 T2D (prevalence of cirrhosis 20.0%)

	AUROC (95%CI)
LIVERFASt Fibrosis Score	**0.774 (0.702 - 0.831)**
LSM FibroScan (M/XL probes)	0.720 (0.629 - 0.791)
FIB-4	0.676* (0.584 - 0.751)

LIVERFASt P= ns vs LSM FibroScan and *p<0.01 vs FIB-4

ITD analysis in N=282 Non-T2D (prevalence of cirrhosis 10.4%)

	AUROC (95%CI)
LIVERFASt Fibrosis Score	**0.824 (0.732 - 0.887)**
LSM FibroScan (M/XL probes)	0.768 (0.647 - 0.852)
FIB-4	0.855 (0.732 - 0.924)

LIVERFASt P= ns vs FibroScan LSM and FIB-4

- LIVERFASt has similar performance for cirrhosis to LSM by Fibroscan with better applicability and without failure
- In T2D population, LIVERFASt outperforms FIB-4

ITD Intention to diagnose

De Ledinghen V, et al. Hepatology 2020

Aim of the study

To demonstrate that LIVERFASt Fibrosis score (LF-Fib) is a surrogate to liver biopsy (LB) for the estimation of the transition rate to fibrosis, F1 stage or more (TRF1), in type 2 diabetic (T2D) patients with better performances than liver stiffness measurement (LSM) by transient elastography and than FIB-4 index.

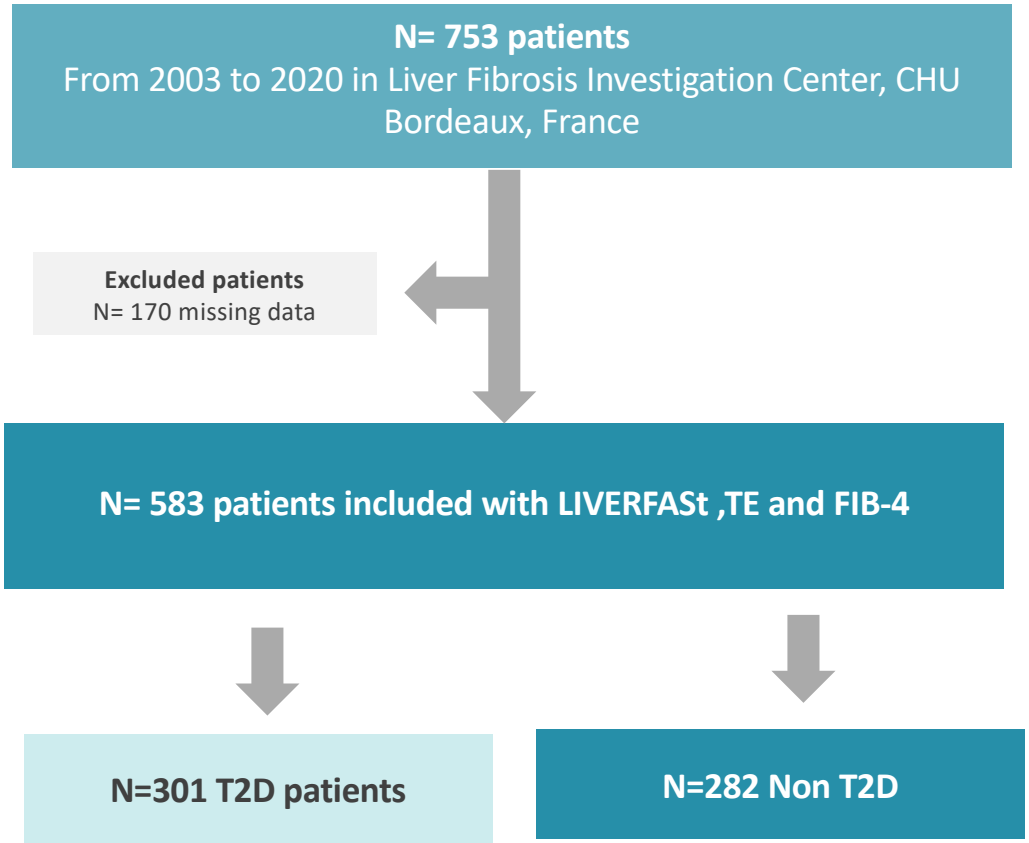
Methods

- **Prospectively** collected NAFLD patients from a tertiary Liver Center in Bordeaux University Hospital (CHU), France
- **Concomitant LB** and LIVERFASt, TE, FIB-4
- **Transition rate to any fibrosis (TRF1)** evaluated using modelling of hazard from birth to the age of the liver fibrosis estimator
- **Cut-offs** (highest sensitivity for minimal fibrosis, F1 stage) :
    - LB : Stage F1 perisinusoidal zone 3 or portal fibrosis (*SAF by Bedossa P, et al. Hepatology 2012*)
    - TE: 5.6 kPa (*Roulot D et al. J Hepatol 2008*)
    - LF-Fib: 0.28 (*Aravind A, et al. JILSA 2020*)
    - FIB-4: 1.45 (*Mallet V, et al. Presse Med. 2019*)

- **Statistics**: Cox Mantel Hazard Ratios [HR (95%CI), logrank comparison p value between groups]
  Logistic regression, Odds Ratio (Wald probability level)

Results: NAFLD patients from the Liver Fibrosis Investigation Center (CHU of Bordeaux, France) (NCT01241227)

Cohort Flow Chart



Characteristics of included patients

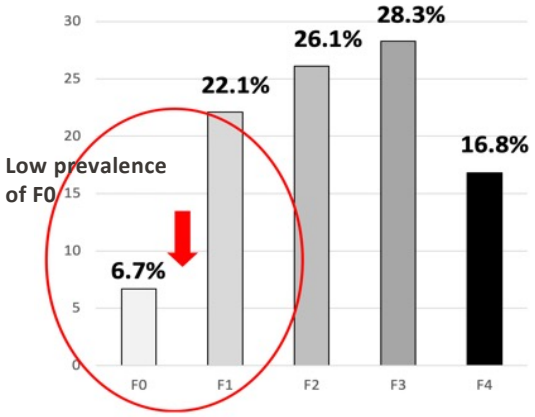
Characteristics N=583	Prevalence , median (SE or range)
Male Gender	**56.4%**
Age, years	**59.5 (18-85)**
BMI, Kg/m2	31.5 (20.1-54.0)
Obesity BMI≥30 , Kg/m2	**59%**
ALT, IU/L	55 (0.5)
AST, IU/L	59 (0.12)
HbA1c,%	6.6 (0.14)
Total cholesterol, mmol/l	5.14 (0.54)
Triglycerids, mmol/l	1.58 (0.43)

Non-invasive tests	Median (SE) scores
LIVERFASt Fibrosis score	0.48 (0.01)
LIVERFASt Activity score	0.41 (0.01)
LIVERFASt Steatosis score	0.74 (0.01)
FibroScan LSM **CAP**	9.6 (0.5) kPa 324 (2.6) dB/m
FIB-4	1.55 (0.08)
Time lapse between LB and NIT	1.7 (0.4) months.

Prevalence of NAFLD features at liver biopsy

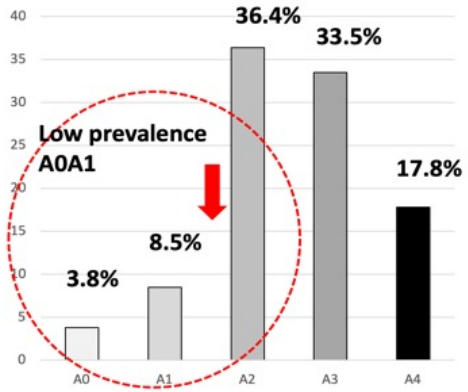
Liver Biopsy	
Biopsy length, mm Biopsy no. fragments	25 (11-95)mm 3 (1-25)
NAS score (Kleiner) **0-2** **3-4** **5-8**	 **8% (39)** **33% (162)** **59% (285)**

Biopsy staging of FIBROSIS



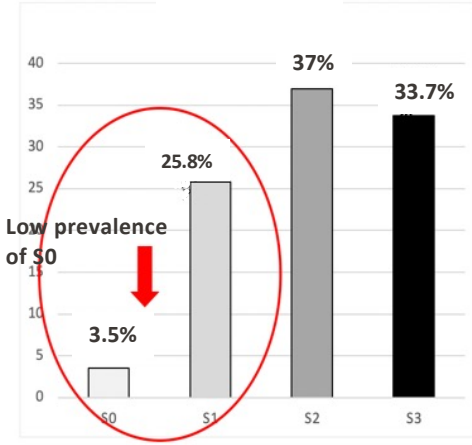
LB Fibrosis staging

Biopsy grading ACTIVITY (SAF)



LB Activity grading

Biopsy grading STEATOSIS

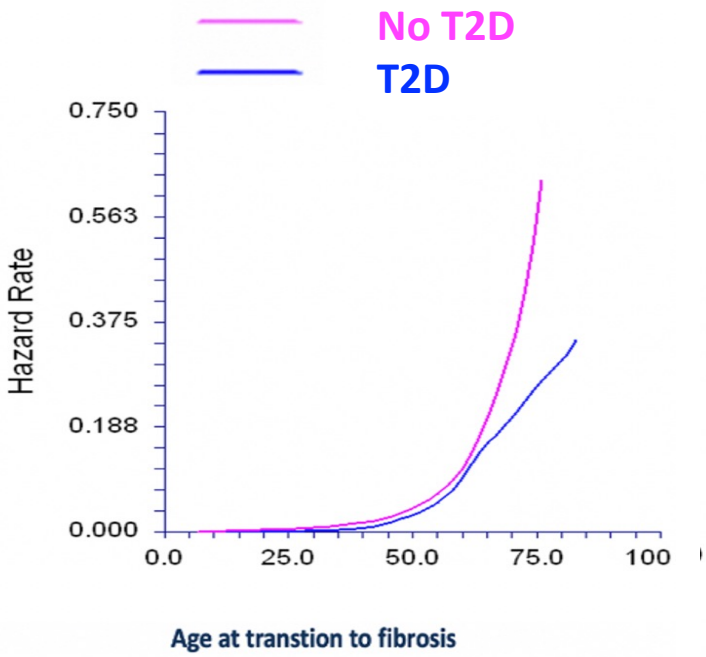


LB Steatosis grading

De Ledinghen V., et al. Hepatology 2020.

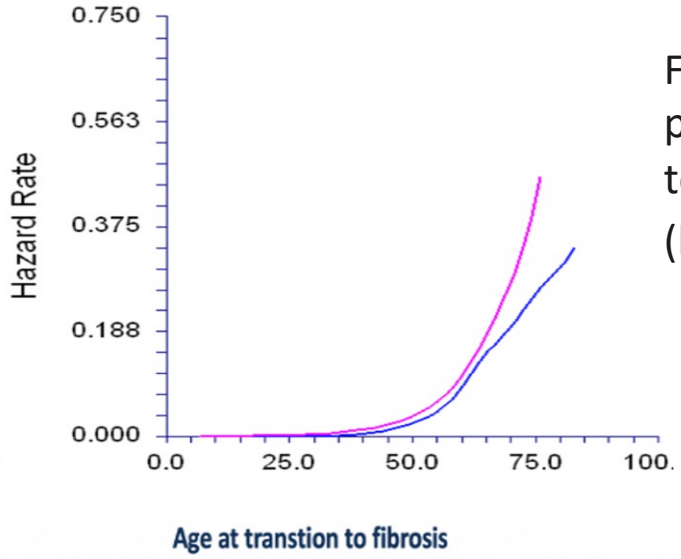
The Transition rate to fibrosis (TRF1) [HR Plot (95%CI), logrank] as per LIVERFASt-Fibrosis was similar to that of LB in both populations with or without T2D

Liver Biopsy Fibrosis stage



Cox Mantel HR (95%CI)
Non T2DM 1.50 (1.26-1.78)
T2DM 0.67 (0.56-0.80)
p<0.0001

LIVERFASt Fibrosis score

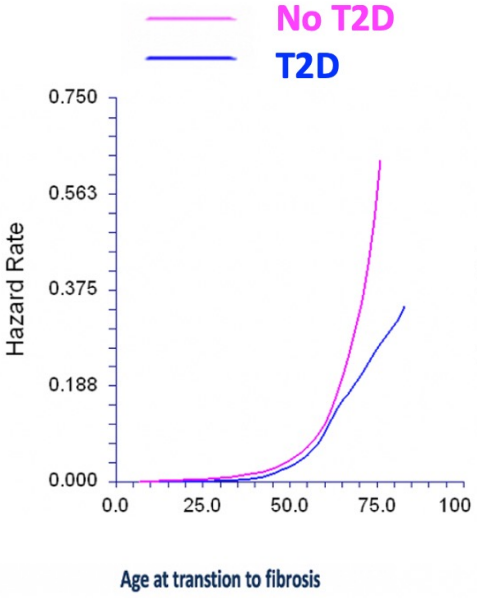


Cox Mantel HR (95%CI)
Non T2DM 1.54 (1.27-1.86)
T2DM 0.65 (0.54-0.79)
p<0.0001

Faster transition rate to F1 in patients without T2D compared to patients with T2D (logrank p<0.0001)

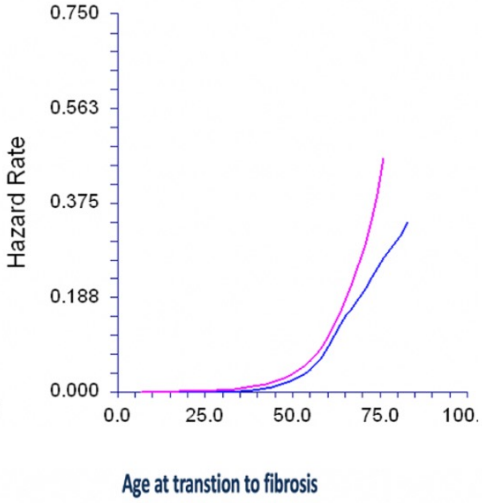
The Transition rates to fibrosis (TRF1) [HR Plot (95%CI), logrank] as estimated using TE and FIB-4 were less similar to that of LB in both populations with or without T2D

Liver Biopsy Fibrosis stage



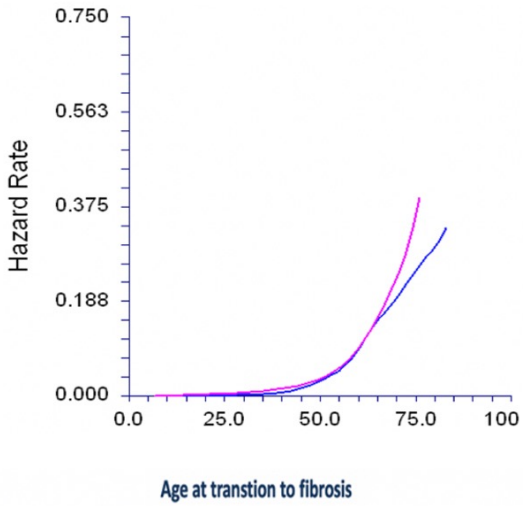
Cox Mantel HR (95%CI)
Non T2DM 1.50 (1.26-1.78)
T2DM 0.67 (0.56-0.80)
p<0.0001

LIVERFASt Fibrosis score



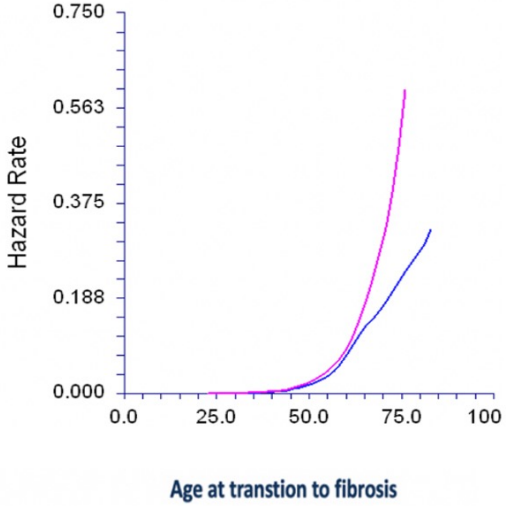
Cox Mantel HR (95%CI)
Non T2DM 1.54 (1.27-1.86)
T2DM 0.65 (0.54-0.79)
p<0.0001

Liver Stiffness Measurement (TE)



Cox Mantel HR (95%CI)
Non T2DM 1.34 (1.12-1.60)
T2DM 0.75 (0.63-0.89)
p<0.001

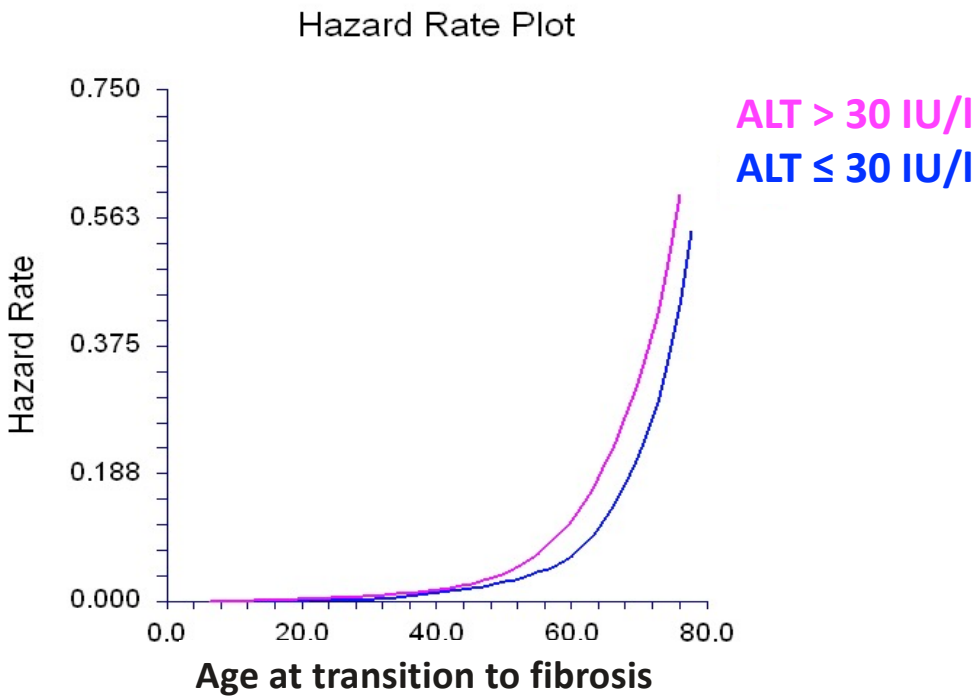
FIB-4



Cox Mantel HR (95%CI)
Non T2DM 1.26 (1.01-1.59)
T2DM 0.79 (0.63-0.99),
p=0.04

Abnormal ALT (>30IU/l) is driving the transition to fibrosis in patients without T2D and has no impact in T2D

Non-T2DM

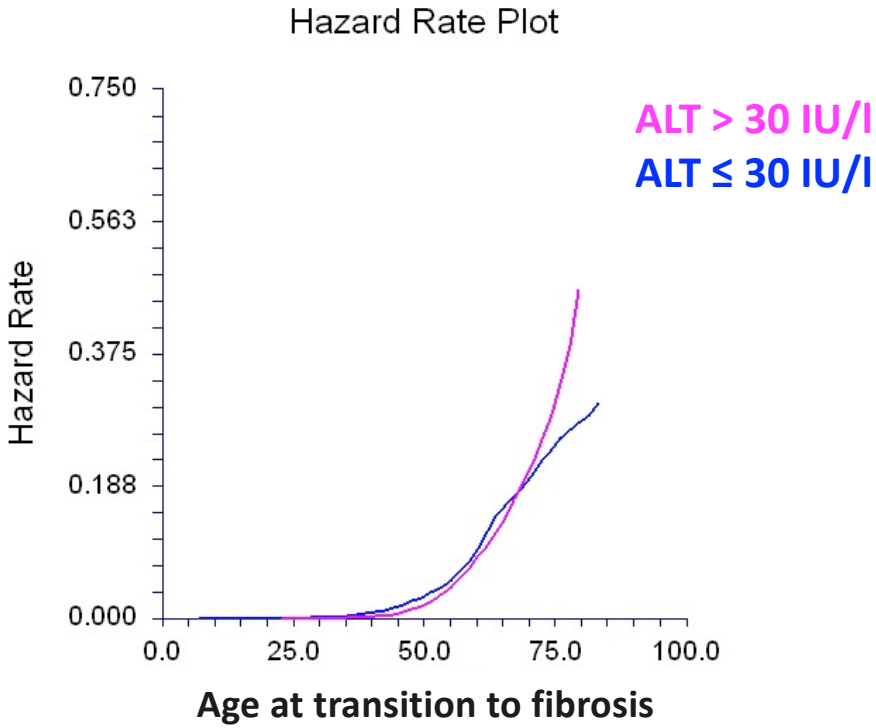


Cox Mantel HR (95% CI)

ALT > 30 2.13 (1.55-2.95)

ALT ≤ 30 0.47 (0.34-0.65), logrank p<0.001

T2DM



Cox Mantel HR (95% CI)

ALT > 30 1.28 (0.93-1.75)

ALT ≤ 30 0.78 (0.57-1.07), logrank p=ns

Multivariate analysis

In T2D NAFLD patients, LIVERFASt FAS, FIB-4, high blood pressure, BMI≥35 and male gender were independently associated to the histological transition to fibrosis

Parameter	T2D patients	Non- T2D patients
LIVERFASt Fibrosis	**P<0.0001**	**P<0.0001**
LIVERFASt Activity	**P<0.0001**	**P<0.0001**
LIVERFASt Steatosis	**P<0.0001**	**P<0.0001**
LSM (TE by Fibroscan)	ns	ns
FIB-4	**P<0.0001**	ns
Blood Pressure (=high)	**P<0.0001**	**P<0.0001**
HbA1c	ns	ns
BMI≥35 Kg/m^2	**P<0.0001**	ns
Gender (=male)	**P<0.01**	**P<0.05**

Conclusions

Liver-specific AI-based blood biomarkers, such as LIVERFASt, allow:

- Detection of progression from simple NAFL to NASH fibrosis, similar to liver histology
- Better and earlier screening strategy for stratifying high-risk patients for NASH, as T2D aged ≥45 years or having co-morbidities as obesity or arterial hypertension
- Improved estimation of elementary liver lesions with noninvasive standard-of-care

Thank you very much for your attention!