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FIB-4 Outperforms Liver Biopsy in the Assessment of Prognosis in HIV/HCV Coinfection

Berenguer J[1], Zamora FX[2], Carrero A[1], von Wichmann MA[3], López-Aldeguer J[4], Téllez MJ[5], Sanz J[6], Esteban H[7], Bellón JM[1], González-García J[2] , and the GESIDA 3603 Study Group.

[1]Hospital General Universitario Gregorio Marañón/IiSGM, [2]Hospital La Paz/IdiPAZ, [3]Hospital de Donostia, [4]Hospital La Fe, [5]Hospital Clínico San Carlos, [6]Hospital Príncipe de Asturias, [7]Fundación SEIMC/GESIDA, SPAIN.

Background & Aims

- Liver biopsy (LB) is widely considered the gold standard in the assessment of the severity of liver disease [1].
- FIB-4 is a non-invasive test based on platelet count, age, AST, and INR, to estimate fibrosis in HIV/HCV-coinfected patients [2].
- We compared the prognostic abilities of LB and FIB-4 in HIV/HCV coinfected patients from the GeSIDA 3603 Study Cohort [3].

1) Bravo AA, et al. N Engl J Med 2001, 344: 495.
2) Sterling RK, et al. Hepatology 2006; 43: 1317-25
3) Berenguer J, et al. *Clin Infect Dis 2012*; 55(5): 728

Methods

Patients
- From the GESIDA 3603 Study Cohort we selected patients with a baseline assessment of fibrosis by both LB (METAVIR) and FIB-4.

Definitions of fibrosis
- Significant fibrosis: LB F≥2 / FIB-4 ≥1
- Advanced fibrosis: LB F≥3 / FIB-4 ≥3.25

Outcomes
- Overall death
- Liver-related events: Decompensation or hepatocellular carcinoma (HCC), whichever occurred first.

Statistics
- We used ROC curves to determine the ability of LB and FIB-4 to predict outcomes. Comparisons were done by the method of Hanley and McNeil.
- We used adjusted Cox models to test the association of LB and FIB-4 with time to overall death and with time death or liver-related events (whichever occurred first)

Results

Patients
- 903 patients met the inclusion criteria (table 1)

Δt between LB and FIB-4
- The median time (IQR) between LB and FIB-4 was 4.5 (2.2 – 12.0) months

Follow-up
- The median FU time was 63 months

Events
- Frequency of events during FU are shown in table 2
- Accuracy of LB and FIB4 for the prediction of events (AUROCs) are shown in figure 1
- Predictive values and Likelihood ratios of LB and FIB-4 are shown in table 3
- Kaplan-Meier estimates of liver-related events or overall death (whichever occurred first) for LB and FIB-4 are shown in figure 2
- Adjusted hazard ratios (95% CI) of events according to LB and FIB-4 are shown in figure 3

Table 1. Baseline characteristics I

Characteristic	No SVR (n=575)	SVR (n=328)	Total (n=903)
Male sex *	437 (76.3)	241 (73.7)	678 (75.3)
Age – yr #	40 (37 - 43)	40 (37 - 43)	40 (37 - 43)
Prior IDU *	483 (84.7)	283 (86.8)	766 (85.5)
CDC category C *	139 (24.4)	68 (21.1)	207 (23.2)
CD4 + cells/uL nadir #	209 (104 - 322)	231 (140 - 353)	217 (116 - 330)
CD4 + cells/uL baseline#	532 (373 - 728)	527 (402 - 727)	529 (387 - 727)
HIV-RNA < LOQ *	366 (65.7)	213 (66.6)	579 (66)
Ethanol > 50 g/d*	30 (5.8)	8 (2.6) †	38 (4.6)
Methadone use	81 (15.2)	27 (8.8) †	108 (12.9)

*n (%); # median (IQR) † p<.05 with the group No SVR.

Abbreviations: IDU, injection drug use; LOQ, lower limit of quantification; LB, liver biopsy; Rx, treatment with IFN-RBV

Table 1. Baseline characteristics II

Characteristic	No SVR (n=575)	SVR (n=328)	Total (n=903)
HCV genotype*			
1 or 4	442 (76.9)	137 (41.8) †	579 (64.1)
2 or 3	118 (20.5)	183 (55.8) †	301 (33.3)
Unknown	15 (2.6)	8 (2.4)	23 (2.5)
HCV-RNA ≥ 500K IU/mL*	354 (73.4)	179 (61.1) †	533 (68.8)
METAVIR fibrosis score*			
F0, No. (%)	41 (7.1)	30 (9.1)	71 (7.9)
F1, No. (%)	137 (23.8)	105 (32) †	242 (26.8)
F2, No. (%)	147 (25.6)	89 (27.1)	236 (26.1)
F3, No. (%)	161 (28)	75 (22.9)	236 (26.1)
F4, No. (%)	89 (15.5)	29 (8.8) †	118 (13.1)
HBsAg positive*	26 (4.6)	8 (2.5)	34 (3.8)

*n (%); # median (IQR) † p<.05 with the group No SVR.

Table 2. Frequency of events during follow-up

	No SVR (N=575)	SVR (N=328)	Total (N=903)	P
OD*	43 (7.5)	3 (0.9)	46 (5.1)	<.001
DECOMP*	61 (10.6)	3 (0.9)	64 (7.1)	<.001
HCC*	11 (1.9)	2 (0.6)	13 (1.4)	.114
LRE*	67 (11.7)	4 (1.2)	71 (7.9)	<.001
OD/LRE*	83 (14.5)	7 (2.1)	90 (10)	<.001

*n (%)

Abbreviations: OD, overall deaths; DECOMP, decompensation; HCC, hepatocellular carcinoma; LRE, liver-related event.

Fig 1. Accuracy of LB and FIB4 for the prediction of events

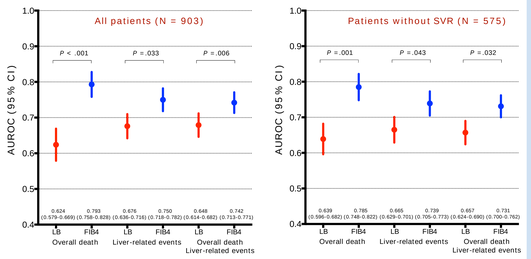


Figure 2. Kaplan Meier estimates of OD/LRE

(Overall deaths or liver-related event whichever occurred first)

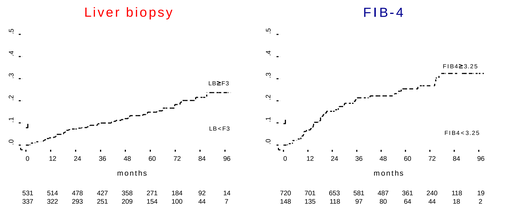


Table 3. Predictive values & Likelihood ratios of LB & FIB-4

Liver-related events			
Cut-off	Event	No event	Total
LB≥F3	45	309	354
LB<F3	26	523	549
Total	71	832	903
FIB4≥3.25	34	124	158
FIB4<3.25	37	708	745
Total	71	832	903

	LB	FIB-4
PPV % (95% CI)	12.7 (9.1;16.3)	21.5 (14.8;28.2)
NPV % (95% CI)	95.3 (93.4;97.1)	95.0 (93.4;96.7)
LR+ (95% CI)	1.71 (1.40;2.08)	3.21 (2.40;4.30)
LR- (95% CI)	0.58 (0.43;0.80)	0.61 (0.49;0.77)
Well classified	63%†	82%†

†P<.001

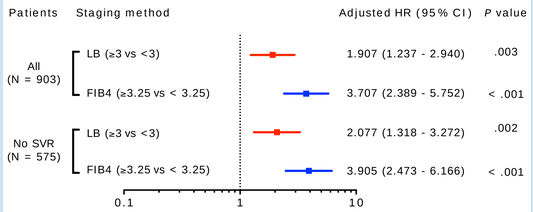
Overall deaths/Liver-related events			
Cut-off	Event	No event	Total
LB≥F3	54	300	354
LB<F3	36	513	9
Total	90	813	903
FIB4≥3.25	40	118	158
FIB4<3.25	50	695	745
Total	90	813	903

	LB	FIB-4
PPV % (95% CI)	15.2 (11.4;19.1)	25.3 (18.2;32.4)
NPV % (95% CI)	93.4 (91.3;95.6)	93.3 (91.4;95.1)
LR+ (95% CI)	1.63 (1.34;1.97)	3.06 (2.30;4.07)
LR- (95% CI)	0.63 (0.49;0.82)	0.65 (0.54;0.78)
Well classified	63%†	81%†

†P<.001

Figure 3. Adjusted HR (95% CI) of OD/LRE according to absence or presence of advanced fibrosis LB vs. FIB-4

(Overall deaths or liver-related event whichever occurred first)



Adjusted by Age, Sex, HIV transmission category, CDC clinical category, CD4+ cell nadir, HCV genotype, HCV RNA

Conclusions

① We found that FIB-4 outperformed LB as a predictor of both overall death and liver-related events

② It must be taken into consideration that liver biopsy makes it possible to evaluate liver structure but not function, whereas FIB-4 enables us to evaluate liver function.

③ Our results call into question the role of liver biopsy as a gold standard for assessing prognosis in HIV/HCV coinfection.

The GeSIDA 3603 Team

Principal Investigators: J Berenguer, J Gonzalez
Study Coordinators: E Barquilla, H Esteban
Statistician: JM Bellón

H. Gregorio Marañón, Madrid
T Aldámiz, JM Bellón, J Cosín, I Gutiérrez, JC López, P Miralles, B Padilla, A Carrero, F Tejerina, C Díez, M Ramírez, M Sánchez-Conde, J Berenguer,

H. 12 de Octubre, Madrid
MA Hernando, F Pulido, V Rodríguez, R Rubio

H. Clínic, Barcelona
P Callau, JM Gatel, J Mallolas, JM Miro

H. Clínico Univ de Valencia, Valencia
A Ferrer, MJ Galindo

H. Clínico San Carlos, Madrid
MJ Téllez, J Vergas

H. Donostia, San Sebastián
J Arrizabalaga, JA Iribarren, MA Von Wichmann

H. General de Valencia, Valencia
E Ortega, L Ortiz

H. La Paz, Madrid
J Alvarez, JR Arribas, I Bernardino, M Mora, F Pascual, JM Peña, E Rodríguez, I Valero, F Zamora, J González,

H. Germans Trias i Pujol Badalona
B Clotet, A Jou, C Tural

H. Getafe, Madrid
G Gaspar, G Pérez

H. Guadalajara, Guadalajara
M Rodríguez, ML Montes

H. La Fe, Valencia
S Cuellar, J López-Aldeguer

H. La Princesa, Madrid
I Santos, J Sanz

H. Móstoles, Madrid
C Barros, E Condés

Fund SEIMC-GESIDA, Madrid
E Aznar, E Barquilla, H Esteban, B Moyano

H. Príncipe Asturias, Madrid
A Arranz, J de Miguel, J Sanz

H. Ramón y Cajal, Madrid
A Moreno, S Moreno, C Quereda, MA Sanfrutos

H. Santa Creu i Sant Pau Barcelona
P Domingo, JM Guardiola

H. Severo Ochoa, Madrid
M Cervero, JJ Jusdado, R Torre

H. Vall d´Hebron, Barcelona
M Crespo, E Van den Eynde

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