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Prognostic Utility of Transient Elastography In HIV-Infected Patients With Liver Cirrhosis

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INTRODUCTION

- Liver cirrhosis is an important cause of mortality in HIV-infected subjects.
- After the first hepatic decompensation survival decreases sharply.
- Early diagnosis of liver cirrhosis and optimal management are essential to decrease the risk of hepatic decompensations and to improve prognosis in HIV-infected subjects.
- Transient elastograhy (TE) has been incorporated to the routine management of HIV-infected subject with liver cirrhosis to measure liver stiffness (LS).
- TE beside the good performance for the diagnosis of liver cirrhosis is a sensitive test to detect changes in the liver damage and portal hypertension.
- It is not known if liver stiffness measurements could predict hepatic mortality in HIV-infected subjects with chronic hepatitis.

OBJECTIVE

- To assess the performance of TE to predict hepatic decompensation and mortality in HIV cirrhotic subjects.

PATIENTS AND METHODS

- From the GESIDA prospective cohort of HIV-infected patients with confirmed liver cirrhosis in Spain with follow-up between 2004-2012 we selected all subjects who had a TE measurement at least 6 month before the last visit.
- Combined primary endpoint: death or hepatocarcinoma or liver transplant.
- Episodes of hepatic decompensation at baseline and during follow-up were collected.
- We evaluated by univariate/multivariate Cox proportional hazard models the prognostic value to predict hepatic decompensation or a combined endpoint (death, hepatocarcinoma or liver transplant) of LS measurement, CD4+ (nadir, baseline and <200 at baseline), ART, history of anti-HCV treatment, sustained viral response (SVR) to anti-HCV treatment, concomitant chronic hepatitis B, current Child-Pugh score (CPS), MELD, FIB4 score, APRI score.
- The sensitivity, specificity, PPV, NPV, positive likelihood ratio (LH+) and negative likelihood ratio (LH-) were calculated. LS measurement cutoff point was selected using ROC curve.

RESULTS

- 160 subjects had one TE measurement with at least 6 months of follow-up later in the cohort. Baseline characterisitcs are referred to the characteristic collected in the visit when TE measurement was performed (table 1).
- The median of follow-up was 36 months. 19 primary outcomes and 21 hepatic decompensation occurred during follow-up (table 2).
- Variables associated to combined endpoint were analyzed through univariate and multivariate methods. Two different models of multivariate analysis were conducted including or excluding hepatic decompensation variable (table 3 and 4).
- TE measurement of 44 Kpa had the best diagnostic performance and was selected.
- Survival analysis showed significant differences in subjects with TE measurement higher than 44 kpa and hepatic decompensation at baseline (figures 1 and 2).
- TE measurement performance for predicting clinical outcomes are shown in table 5.
- TE measurement for combined endpoint and death AUROC had a high performance (figure 3 and 4).

BASELINE CHARACTERISTICS

Table 1

Mean age, years (SD)	45 (6.7)
Female (%)	39 (24.4)
Cirrhosis diagnosis	
- Biopsy (%)	127 (79.4)
- Bonacini Score >8 (%)	21 (13.1)
Cirrhosis etiology	
- Hepatitis C (%)	152 (95.6)
- Genotypes 2,3 (%)	41 (28.7)
- Hepatitis B (%)	12 (8.4)
- Prior alcohol abuse (%)	40 (25.0)
Child Pugh score	
- CP A (%)	83 (55)
- CP B, C (%)	67 (45)
Compensated liver cirrhosis (%)	138 (86.3)
Median duration HIV infection (years), (IQR)	17.8 (12.6- 20.8)
Median duration HCV infection (years) (IQR)	11.7 (8.6- 14.2)
Transmission route IVDU (%)	139 (86.9)
CDC stage C (%)	52 (32.7)
Receiving ART at baseline (%)	151 (94.4)
HIV RNA load < 50 copies/mL (%)	138 (86.8)
Median CD4 cell count (IQR)	
- Baseline	448 (303-642)
- Nadir	184 (69.5-268)
Previous therapy against HCV (%)	125 (82.2)
- Sustained virological response (%)	34 (27.2)
- Still receiving HCV treatment (%)	5 (4.0)
- Non responders or relapsers (%)	86 (68.8)
Median Alanine aminotransferase , IU/L (IQR)	51 (30.0-79.5)
Median Aspartate aminotransferase, IU/L (IQR)	49 (32.0-83)
Median Total bilirubin, mg/dL (IQR)	0.9 (0.5-1.6)
Median Platelet count, mm3 (IQR)	118 (81.0-182.0)
MELD score	
- < 14	82 (96.5)
- > 14	3 (3.5)
Median Liver stiffness, kPa (IQR)	16.9 (9.5-26.3)
Liver stiffness, kPa (%)	
- < 21	100 (62.5)
- 21-39.9	38 (23.8)
- > 40	22 (13.8)
APRI score	
- < 0.5	42 (26.6)
- 0.5-1.5	53 (33.5)
- > 1.5	63 (39.9)
FIB4 score	
- < 1.45	43 (27.4)
- 1.45-3.25	53 (33.8)
- > 3.25	61 (38.9)

RESULTS

Table 2: clinical events during follow-up

	N	%
Follow-up, median (IQR) months	36 (20-47)	-
Lost to follow-up	5	3
Endpoints,		
Any	19	12
Death	14	8.8
Hepatocarcinoma	6	3.8
Transplant	3	1.9
Deaths,		
Hepatic causes	8	5
Other	6	3.7
Unknown	0	-
Decompensation during follow-up,		13
First decompensation	13	8
New decompensation	8	5

VARIABLES ASSOCIATED TO COMBINED ENDPOINT

Table 3: model 1 excluding hepatic decompensation

	Univariate analysis HR (CI 95%)	P	Multivariate analysis	P
Age (cuantitative)	1.02 (0.94-1.11)	0.58	-	-
Female	1.06 (0.38-2.94)	0.91	-	-
HCV sustained virological response	0.17 (0.02-1.4)	0.10	-	-
Receiving ART at baseline	1,19 (0.16-8.9)	0.86	-	.
HIV RNA BLQ at baseline	0.75 (0.2-2.6)	0.65	-	-
CD4<200 cel/µL at baseline	5.8 (2.6-14.8)	<0.000	2.7 (1.01-7.5)	0.047
- Child Pugh score B,C at baseline	1.3 (0.5-3.3)	0.6	-	-
- Platelets (cuantitative)	0.98 (0.96-0.99)	0.001	ns	-
- Platelets <120.000 cel/mL	20.2(2.66-154)	0.004		
MELD > 14	0.05 (0-400)	0.66	-	-
APRI (cuantitative)	1.5 (1.25-1.8)	<0.000	ns	-
APRI > 1.5	5.5 (1.8-16)	0.003		
FIB4 (cuantitative)	1.35 (1.2-1.5)	0.000	-	-
FIB4 > 3.25	14.3 (3.2-62)	0.000	6.3 (1.2-32)	0.03
TE measure (cuantitative)	1.05 (1.03-1.07)	0.000		
TE measure > 44 Kpa	12 (4.6-32)	0.000	4.2 (1.5-12)	0.008

Table 4: model 2 including hepatic decompensation

	Univariate analysis HR (CI 95%)	P	Multivariate analysis	P
Age (cuantitative)	1.02 (0.94-1.11)	0.58	-	-
Female	1.06 (0.38-2.94)	0.91	-	-
HCV sustained virological response	0.17 (0.02-1.4)	0.10	-	-
Receiving ART at baseline	1,19 (0.16-8.9)	0.86	-	.
HIV RNA BLQ at baseline	0.75 (0.2-2.6)	0.65	-	-
CD4<200 cel/µL at baseline	5.8 (2.6-14.8)	<0.000	ns	-
- Child Pugh score B,C at baseline	1.3 (0.5-3.3)	0.6	-	-
- Platelets (cuantitative)	0.98 (0.96-0.99)	0.001	ns	-
- Platelets <120.000 cel/mL	20.2(2.66-154)	0.004		
Decompensation at baseline	9.4 (3.6 – 25)	<0.001	4.5 (1.6 -13)	0.005
MELD > 14	0.05 (0-400)	0.66	-	-
APRI (cuantitative)	1.5 (1.25-1.8)	<0.000	ns	-
APRI > 1.5	5.5 (1.8-16)	0.003		
FIB4 (cuantitative)	1.35 (1.2-1.5)	0.000	-	-
FIB4 > 3.25	14.3 (3.2-62)	0.000	8.2 (1.7-40)	0.009
TE measure (cuantitative)	1.05 (1.03-1.07)	0.000		
TE measure > 44 Kpa	12 (4.6-32)	0.000	3 (1.03-9)	0.04

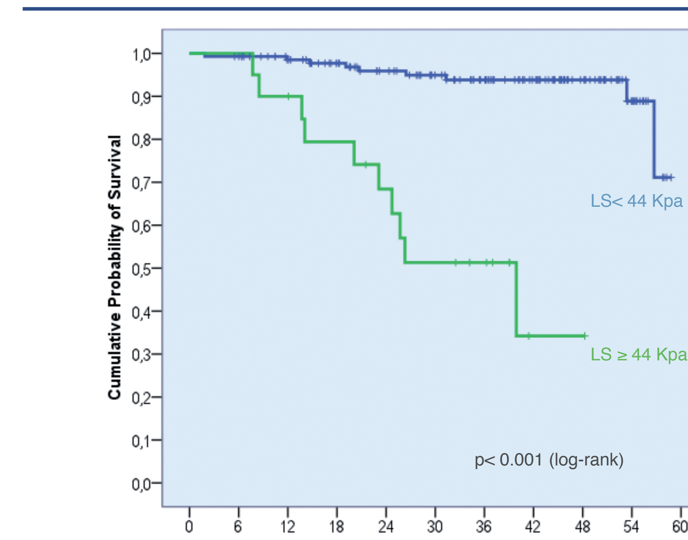
VARIABLES ASSOCIATED TO HEPATIC DECOMPENSATION

Table 5

	Univariate analysis HR (CI 95%)	P	Multivariate analysis	P
Age (cuantitative)	1.02 (0.94-1.11)	0.58	-	-
Female	0.65 (0.22-1.93)	0.4	-	-
HCV sustained virological response	0.03 (0.00-6.2)	0.2	-	-
Receiving ART at baseline	0.25 (0.07-0.9)	0.03	-	.
HIV RNA BLQ at baseline	0.33 (0.1-0.9)	0.04	ns	-
Chronic hepatitis B	6.4 (1.2-35)	0.03	ns	
CD4<200 cel/µL at baseline	4.24 (1.6-11)	<0.003	2.8 (1.06-7.8)	0.04
- Child Pugh score B,C at baseline	0.67 (0.25-1.8)	0.4	-	-
- Platelets (cuantitative)	0.98 (0.97-1)	0.005	ns	-
- Platelets <120.000 cel/mL	5.46(1.6-19)	0.008	ns	-
Esophageal varices/PH*	3.6 (1.1-12)	0.03	-	ns
MELD > 14	0.05 (0-400)	0.66	-	-
APRI (cuantitative)	1.4 (1.2-1.7)	<0.001	ns	-
APRI > 1.5	4.9 (1.7-13)	0.002	ns	-
FIB4 (cuantitative)	1.3 (1.1-1.4)	<0.001	-	-
FIB4 > 3.25	9 (2.5-31)	0.001	4.7 (1.1-19)	0.032
TE measure (cuantitative)	1.04 (1.02-1.06)	<0.001		
TE measure > 44 Kpa	6.4 (2.4-17)	<0.001	3.6 (1.32-10)	0.01

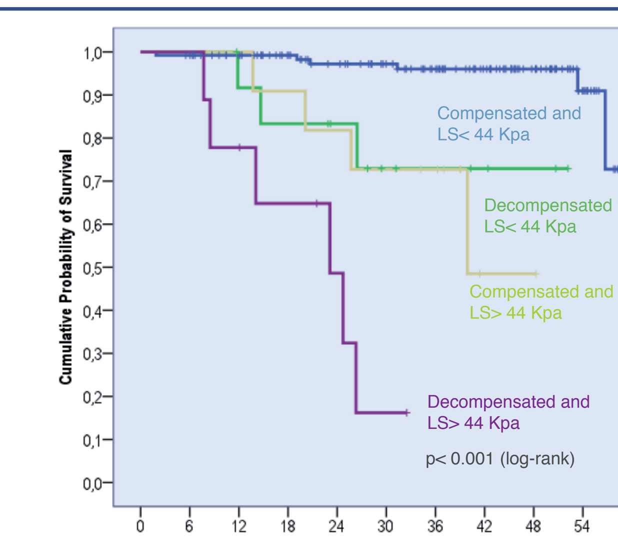
* PH: portal hypertension

COMBINED ENDPOINT AND LS MESAUREMENT


Cumulative Probability of Survival
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
LS< 44 Kpa
LS ≥ 44 Kpa
p< 0.001 (log-rank)
0 6 12 18 24 30 36 42 48 54 60
Months

LS< 44 Kpa	N	140	138	126	113	101	88	76	59	38	15
LS > 44 Kpa		20	20	18	15	1 2	9	7	1	1	-

COMBINED ENDPONT BY HEPATIC DECOMPENSATION AND LS MESAUREMENT


Cumulative Probability of Survival
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
Compensated and LS< 44 Kpa
Decompensated and LS< 44 Kpa
Compensated and LS> 44 Kpa
Decompensated and LS> 44 Kpa
p< 0.001 (log-rank)
0 6 12 18 24 30 36 42 48 54 60
Months

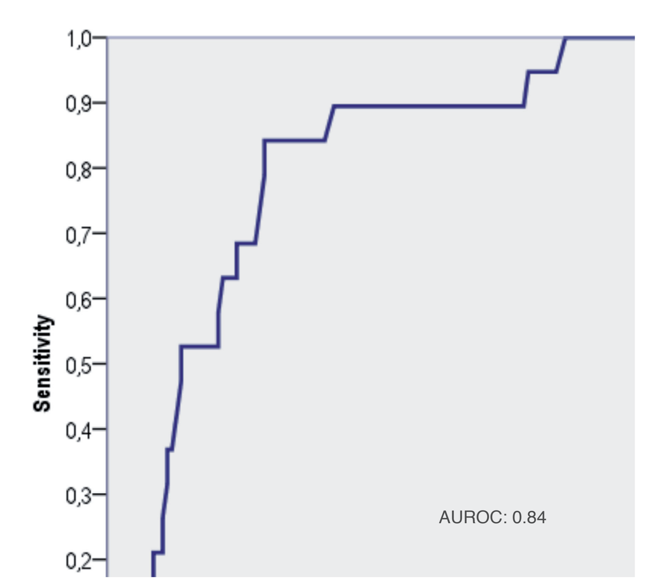
Compensated and LS< 44 Kpa	N	127	125	115	103	93	83	72	56	36	15	-
Decompensated and LS< 44 Kpa	N	13	13	11	10	8	5	4	3	2	-	-
Compensated and LS> 44 Kpa	N	11	11	11	10	9	8	7	1	1	-	-
Decompensated and LS> 44 Kpa	N	9	9	7	5	3	1	-	-	-	-	-

TE MEASUREMENT DIAGNOSIS PERFORMANCE

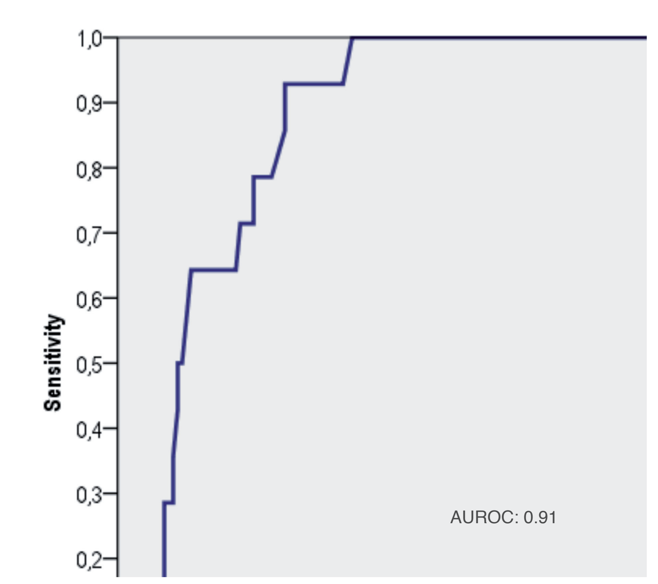
Table 6

	LS >44 for combined endpoint	LS >44 for death
AUROC	0.85 (0.76-0.94)	0.91 (0.85-0.96)
SENSITIVITY	52.6% (28.9-75.6)	64.3% (35.1-87.2)
SPECIFICITY	92.9% (87.3-96.6)	92.5% (86.9-96.2)
POSITIVE PREDICITVE VALUE	50% (27.2-72.8)	45% (23.1-68.5)
NEGATIVE PREDICTIVE VALUE	93.5 (88.2-97.0)	96.4 (91.9-98.8)
POSITIVE LIKELYHOOD RATIO	7.4 (3.2-5.5)	8.6 (3.8-15.2)
NEGATIVE LIKELYHOOD RATIO	0.5 (0.3-0.8)	0.4 (0.16-0.69)

AUROC FOR COMBINED ENDPOINT


Sensitivity
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
AUROC: 0.84

AUROC FOR DEATH


Sensitivity
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
AUROC: 0.91

CONCLUSIONS

- LS measurement accurately predicts survival, risk for development of hepatocarcinoma and/or liver transplantation in HIV infected subjects with liver cirrhosis.
- LS measurement predict hepatic decompensation.
- LS measurement appears to be the best prognostic test for predicting ESLD events in HIV-infected subjects with liver cirrhosis.

DISCUSSION

- Our study has some limitations:
 - » Low number of clinical events
 - » Follow-up not long enough
- These limitations might preclude showing a possible survival benefit for coinfected patients with liver cirrhosis who achieve SVR.
- Every effort should be made to identify progression of cirrhosis in HIV patients.

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