Testes não invasivos de fibrose nas doenças autoimunes do fígado

Mesa Redonda: Avaliação não-invasiva de fibrose nas doenças do fígado

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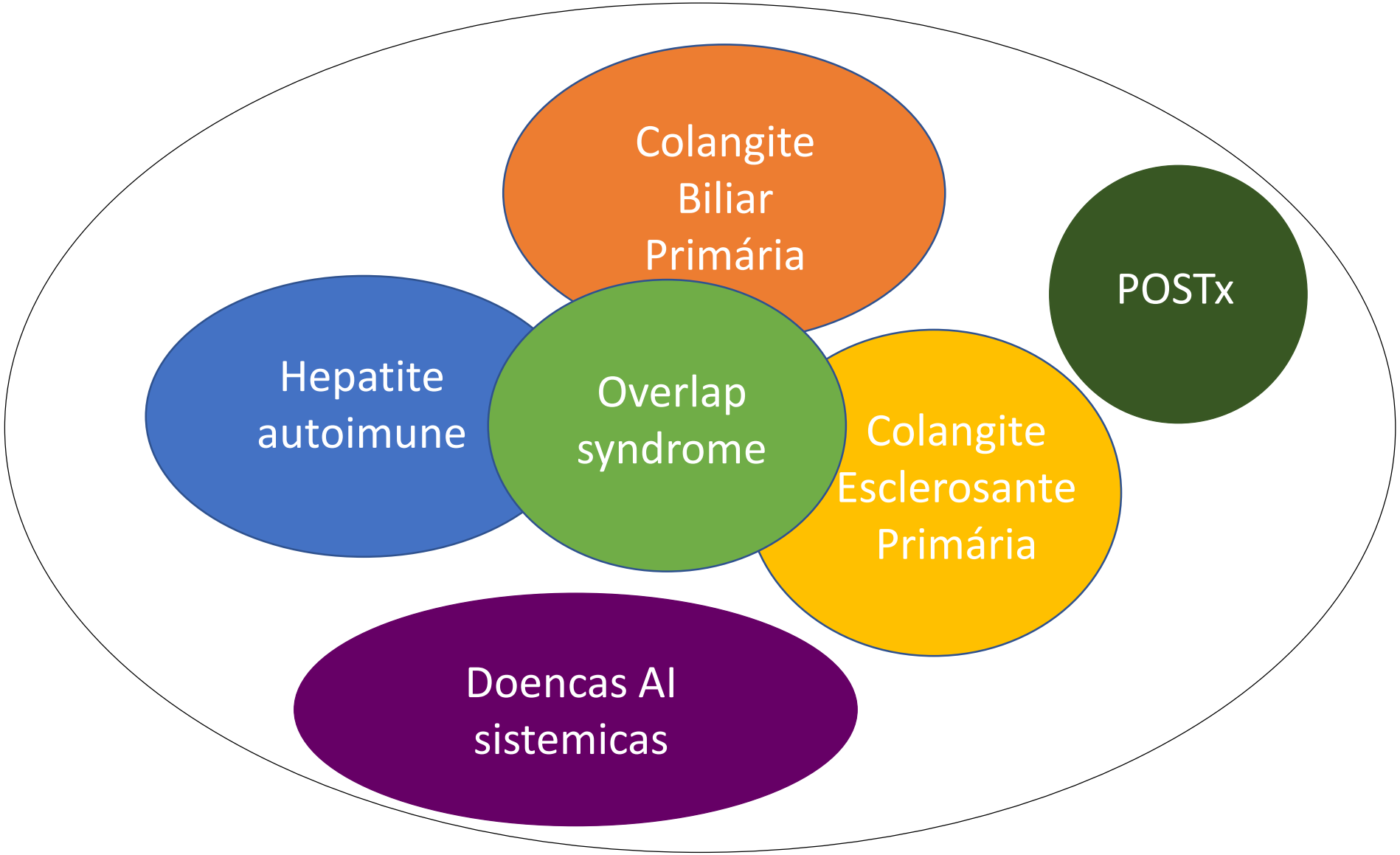
Doenças autoimunes do fígado



Métodos Não Invasivos

EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis

European Association for the Study of the Liver*,
Asociación Latinoamericana para el Estudio del Hígado

reversible in this setting [247,248]. However, specific data of either serum markers of fibrosis or imaging techniques is scarce to make recommendations. Of note, disproportionally high results of TE [249] have been reported in patients with AIH, which is likely related to the inflammatory activity considering that values decreased rapidly upon induction of disease remission.

most of the cases are below 0.8. Thus, current evidence allows the conclusion that no single serum measurement has the ability to differentiate between early and advanced fibrosis in PBC [241]. In the case of PSC, no specific studies are available in this regard.

J Hepatol 2015;63:237-64

Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases

Keith D. Lindor,[1] Christopher L. Bowlus,[2] James Boyer,[3] Cynthia Levy,[4] and Marlyn Mayo[5]

other biliary tract diseases. Transient elastography[80] is a noninvasive tool that has shown a high degree of accuracy in diagnosing advanced fibrosis in patients with PBC.[92] Over a 5-year period, on-treatment liver stiffness appears stable in most noncirrhotic PBC patients, whereas it significantly increases in patients with cirrhosis. Progression of liver stiffness in PBC is predictive of poor outcome,[80,93] and successful medical therapies have been associated with improvement in liver stiffness.[94] The role of serial measurements as an endpoint is being evaluated, as is the value of magnetic resonance elastography.

Hepatology 2018

Caso clinico 1:

IVF, 54 anos, iniciou ha 2 meses com queda do estado geral, nauseas, vomitos e coluria, sem acolia fecal ou prurido. Nega artralgias ou febre.

Ao exame fisico: BEG, consciente, orientada, bpp, acianotica, ictericia +1/4, edema +1/4 MMII. PA=120/80mmHg, FR=18irpm, FC=68ppm

Hb/Hto=13,5/40,6	AST=169(35)	FAN=1/1280 (nucleo)
Leuco=4680(2181)	ALT=116(35)	AntMit/LKM1/citosol= negativo
Plaquetas= 209000	GGT=247(50) / FA=191(100)	Anti-DNA=negativo
RNI=1,14	BT/BD=2,89/2,39	HLA-B1=duvidoso
Creat=0,7	IGG=2.680/gamaglob=2,08	Anti-RNP=12 (positivo)

APRI	**2,379**
FIB4	4,05
LSM	8,8kPa

Score para HAI= +11 (sem biopsia)

Seguimento:

Biopsia hepatica: aumentada celularidade portal, composto por infiltrado misto, predominio de linfocitos e polimorfonucleares, com presenca de frequentes plasmocitos. Hepatite de Interface: presente; Pseudorosetas: ausentes; Colestase leve.

Pre-tratamento:

Score para HAI sem biopsia= +11
Scores para HAI com biopsia=+15
Score pos-tratamento= +17

HEPATITE AUTOIMUNE

3 meses apos tratamento	
AST	22(35)
ALT	17(35)
IGG	1250
gama	1,8
FAN	negativo
APRI	0,319
FIB4	1,46
LSM	6,5kPa

Questoes para Reflexao:

1) Qual a interpretacao podemos fazer com relacao aos marcadores nao invasivos de fibrose na HAI?
   a. Os 3 MNI utilizados sao concordantes quanto a presenca de FA/CH, portanto, podemos assumir tal resultado como verdadeiro;
   b. A elastografia hepatica pode auxiliar no seguimento da HAI sendo importante marcador de resposta ao tto;
   c. Na HAI os marcadores se comportam de forma descoordenada devido a inflamacao e colestase hepatica e nao devem ser valorizados isoladamente nessa fase, sendo necessaria a BX hepatica com esse fim
   d. A interpretacao dos valores da elastografia deve ser realizada com cautela nessa fase inicial pre-tratamento da HAI.

Systematic review: diagnostic accuracy of non-invasive tests for staging liver fibrosis in autoimmune hepatitis

Shanshan Wu[1] · Zhirong Yang[2,3] · Jialing Zhou[1] · Na Zeng[1] · Zhiying He[1] · Siyan Zhan[4] · Jidong Jia[1,5] · Hong You[1,5]

N=16 estudos (867 pacientes)
- TE=10
- FIB4=6
- APRI=8
- ARFI=2

72% feminino
Mediana idade=46 anos
ALT=56U/L
Status tratamento:
- 39% não tratados
- 35% tratados
- 26% inconclusivo

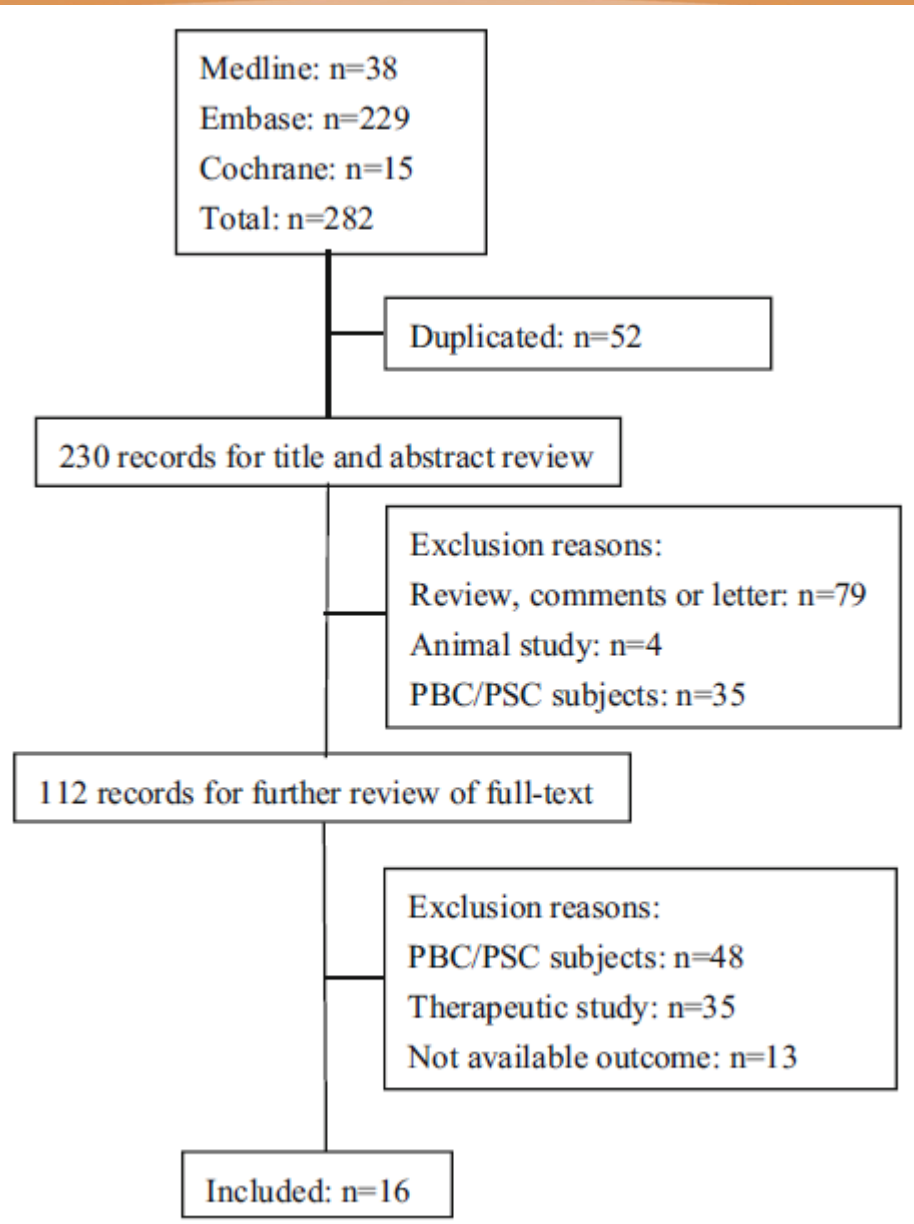
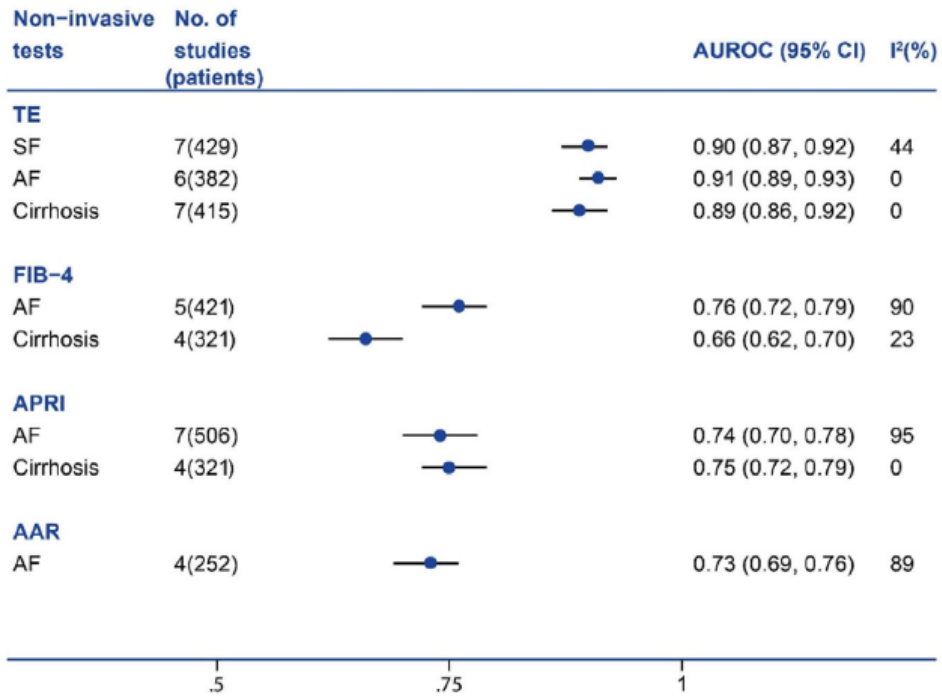


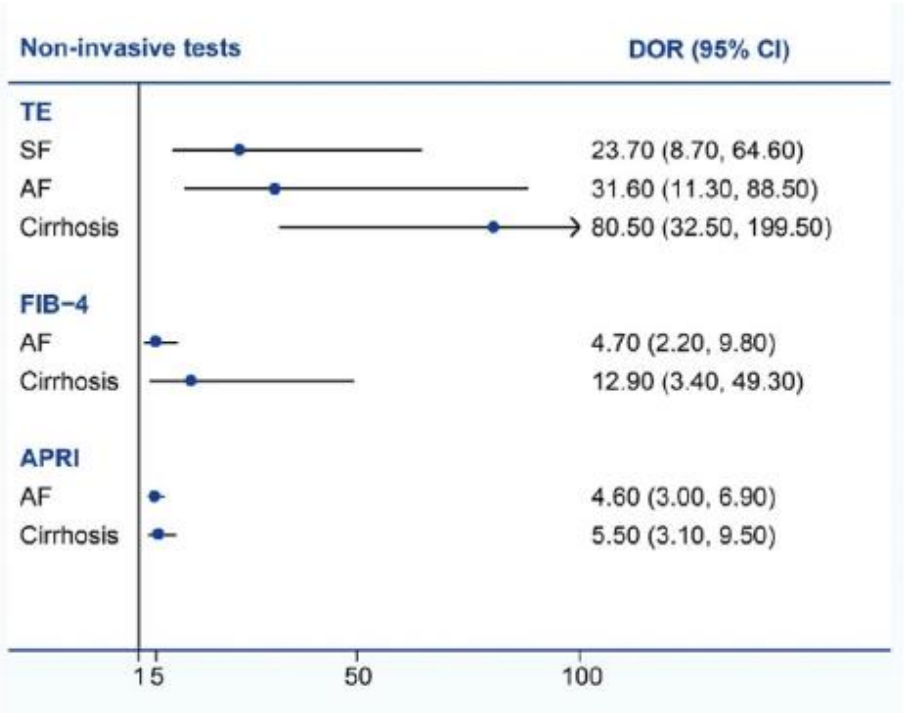
Fig. 1 Flowchart for study selection in the meta-analysis

Wu S et al, Hepatol Int 2018

Panel 2. Summary AUROC of TE, FIB-4, APRI and AAR in detecting SF, AF and cirrhosis.



Panel 2. Pooling DOR of TE, FIB-4 and APRI in detecting SF, AF and cirrhosis.



Wu S et al, Hepatol Int 2018

Transient elastography in autoimmune hepatitis: Timing determines the impact of inflammation and fibrosis

Johannes Hartl[1,†], Ulrike Denzer[1,2,†], Hanno Ehlken[1,2], Roman Zenouzi[1], Moritz Peiseler[1], Marcial Sebode[1], Sina Hübener[1], Nadine Pannicke[1], Christina Weiler-Normann[1], Alexander Quaas[3], Ansgar W. Lohse[1], Christoph Schramm[1,*]

Table 1. Clinical characteristics of patients with AIH included in the prospective and validation study at the time of liver stiffness measurement.

Parameter	Prospective pilot study (n = 34)	Validation cohort (n = 60)
Age, years	53 ± 17 (21-74)	52 ± 21 (21-79)
Female, n	28 (82%)	50 (83%)
ALT, U/L	48.5 ± 45.0 (8-244)	35.0 ± 40.1 (25-196)
IgG, U/L	13.7 ± 5.1 (8.3-35.3)	12.9 ± 3.6 (8.9-22.7)
GGT, U/L	85.0 ± 84 (10-468)	41.5 ± 80 (20-320)
AP, U/L	86 ± 124 (38-369)	69 ± 41 (40-200)
Bilirubin, mg/dl	0.6 ± 0.6 (0.3-2.0)	0.6 ± 0.4 (0.3-1.8)
Platelet count (10^3/mm^3)	253 ± 58 (140-416)	241 ± 88 (78-388)
Albumin (g/L)	44.0 ± 4.1 (35-51)	41 ± 4.8 (36-49)
Liver stiffness (kPa)	6.8 ± 6.6 (2.5-33.3)	6.6 ± 11.9 (3.8-74)
Histological staging, Desmet and Scheuer		
F0	6 (18%)	14 (23%)
F1	6 (18%)	12 (20%)
F2	11 (32%)	12 (20%)
F3	5 (15%)	8 (13%)
F4	6 (18%)	14 (23%)
Histological grading, Desmet and Scheuer		
G0-1	17%	36%
G2	26%	46%
G3 *	32%	10%
G4	14%	8%

*$p = 0.01$.

	Prospective pilot study (n = 34)			Validation cohort (n = 60)		
Histologic staging	F ≥2	F ≥3	F = 4	F ≥2	F ≥3	F = 4
Optimal cut-off	5.8	10.4	16.0	5.8	10.4	16.0
AUROC	0.77	0.82	0.92	0.89	0.96	0.97
Sensitivity	0.82	0.73	0.83	0.94	0.89	0.92
Specificity	0.67	0.91	1.00	0.75	1.00	1.00
PPV	0.82	0.80	1.00	0.83	1.00	1.00
NPV	0.67	0.88	0.97	0.95	0.95	0.98

J Hepatol 2016;65:769-775

Table 3. Characteristics of patients with different time intervals between start of treatment and TE measurement.

	Time interval between TE and initiation of immunosuppression		
	<3 months (n = 34) Group 1	6-18 months (n = 25) Group 2	>4 years (n = 27) Group 3
ALT, U/L*	70 ± 51 (8-191)	37 ± 43 (15-108)	38 ± 47 (15-94)
IgG, g/L	15.7 ± 2.9 (10-21)	13.4 ± 4.7 (9-27)	13.0 ± 5.3 (9.6-23)
Grading, according to Desmet and Scheuer **	2.8 (3)	1.8 (2)	1.7 (2)
Correlation TE and grading, Spearman coefficient	ρ = 0.558, *p* = 0.001	ρ = 0.404, *p* = 0.062	ρ = 0.422, *p* = 0.045
Correlation TE and staging, Spearman coefficient	ρ = 0.399, *p* = 0.19	ρ = 0.809, *p* <0.0001	ρ = 0.850, *p* <0.0001

Table 4. Diagnostic performance of TE according to the time interval between TE measurement and initiation of immunosuppressive treatment.

	Histological fibrosis stage		
	F ≥2 (≥5.8 kPa)	F ≥3 (≥10.5 kPa)	F = 4 (≥16.0 kPa)
<3 months (n = 34) Group 1			
AUROC	0.68	0.80	0.71
Sensitivity	0.71	0.60	0.60
Specificity	0.66	0.88	0.93
Positive predictive value	0.65	0.75	0.60
Negative predictive value	0.58	0.85	0.93
6-12 months (n = 25) Group 2			
AUROC	0.97	1.00	1.00
Sensitivity	0.94	1.00	1.00
Specificity	0.88	1.00	1.00
Positive predictive value	0.94	1.00	1.00
Negative predictive value	0.88	1.00	1.00
>4 years (n = 27) Group 3			
AUROC	0.94	0.96	1.00
Sensitivity	1.00	0.95	1.00
Specificity	0.77	0.94	1.00
Positive predictive value	0.80	0.80	1.00
Negative predictive value	0.88	0.94	1.00

Comparison of AUROCs: F ⩾2: group 1 *vs.* group 2: $p = 0.027$, group 1 *vs.* group 3: $p = 0.012$; F ⩾3: group 1 *vs.* group 2: $p = 0.029$, group 1 *vs.* group 3: $p = 0.12$; F ⩾4: group 1 *vs.* group 2: $p = 0.036$, group 1 *vs.* group 3: $p = 0.036$.

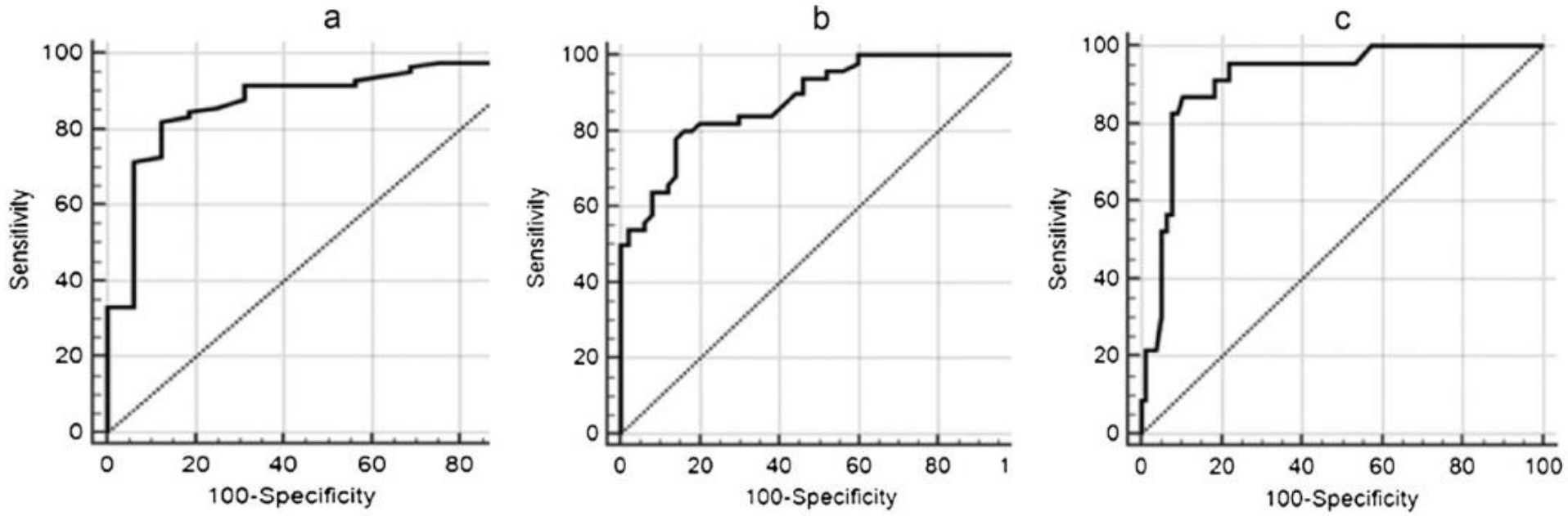
Hatl J, J Hepatol 2016;65:769-775

Evaluate of transient elastography in assessing liver fibrosis in patients with autoimmune hepatitis

Caract. Gerais	
Participantes	100
Idade (anos)	45,0±12,8
Feminino (%)	81
ALT (U/L)	131,5±135,7
AST (U/L)	122,5±149,9
FA (U/L)	100,9±41,8
IgG (g/L)	19,3±5,8
APRI	1,62±1,90
FIB4	2,58±2,52
LSM (kPa)	11,2±8,2

Caract. Histológicas	N=100
Fibrose	
F0	6
F1	10
F2	34
F3	27
F4	23
Atividade	
A0	0
A1	9
A2	36
A3	55

Xu, Q et al J Gastroenterol Hepatol 2017;32:639-644



Fibrose	AUROC (95IC)	Cutoff (kPa)	S%	E%	VPP%	VPN%
≥F2 (a)	0,88 (0,79-0,97)	6,45	82	87,2	97,1	98,6
≥F3 (b)	0,88 (0,82-0,95)	8,75	80	84	83,6	80,5
F4 (c)	0,91 (0,85-0,98)	12,5	87	89,6	71,3	95,9

Xu, Q et al J Gastroenterol Hepatol 2017;32:639-644

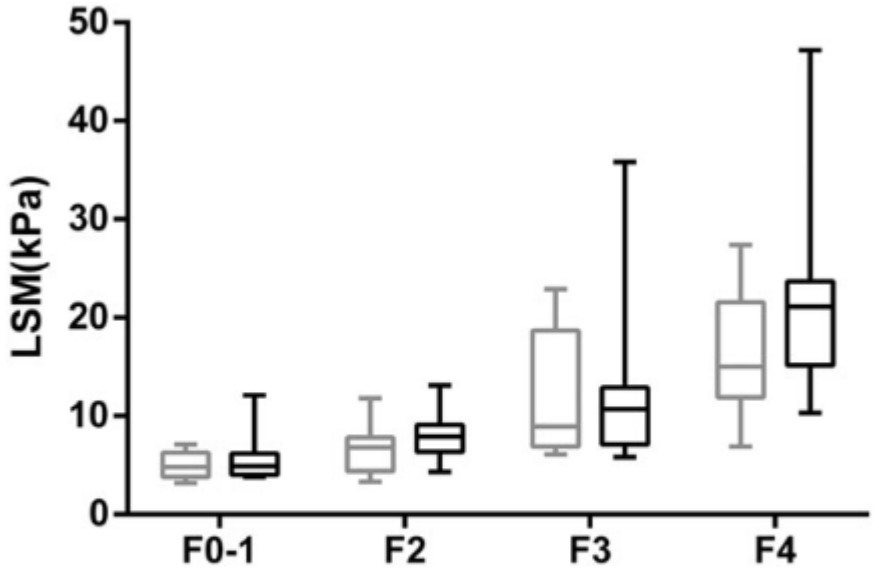


Figure 4 Impact of the serum ALT levels on LSM determination. AIH patients were divided into two subgroups according to the serum ALT levels in each fibrosis stage. ▭, ALT ≤ 2 ULN; ▭, ALT > 2 ULN.

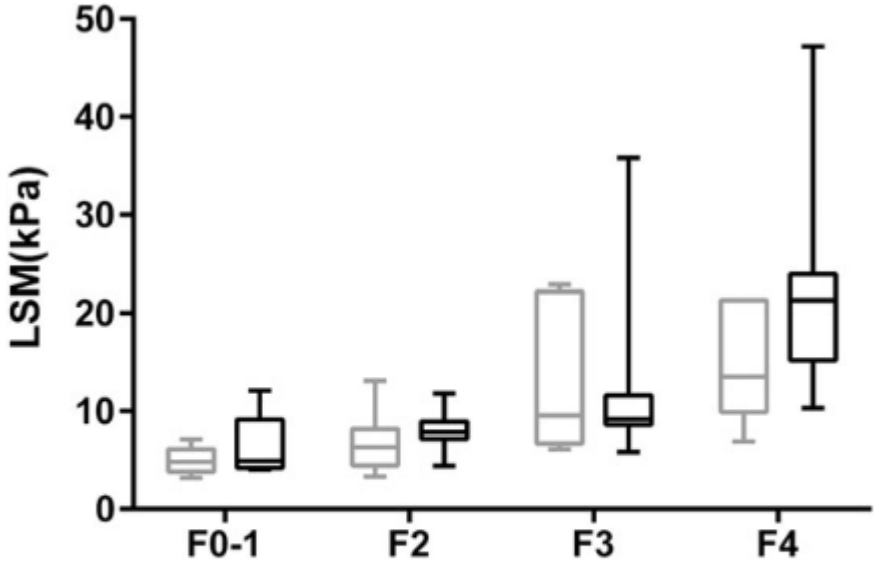


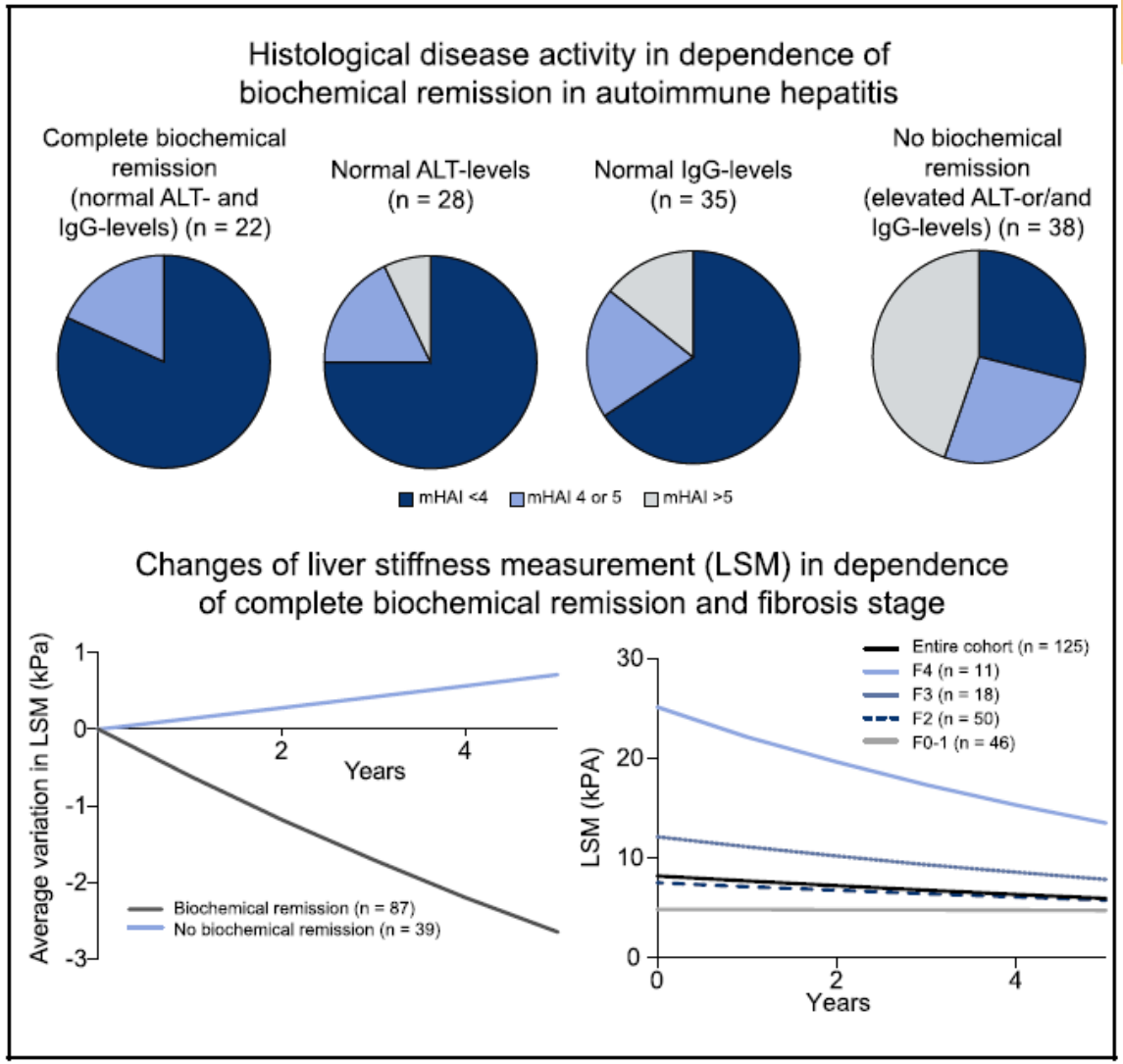
Figure 5 Impact of hepatic inflammatory activity on LSM determination. AIH patients were divided into two subgroups according to the degree of hepatic inflammatory activity in each fibrosis stage. ▭, A ≤ 2; ▭, A > 2.

Xu, Q et al J Gastroenterol Hepatol 2017;32:639-644

Usefulness of biochemical remission and transient elastography in monitoring disease course in autoimmune hepatitis

Johannes Hartl[1,*], Hanno Ehlken[1,2], Marcial Sebode[1], Moritz Peiseler[1], Till Krech[3], Roman Zenouzi[1], Johann von Felden[1], Christina Weiler-Normann[1,4], Christoph Schramm[1,4,†], Ansgar W. Lohse[1,†]

	Remissão bioquímica (n=86)	Sem Remissão bioquímica (n=39)	Valor P
ALT 1ª LSM	26±14	40±21	0,001
IgG 1ª LSM	12,2±3,4	14,1±3,6	-
ALT ult LSM	24±11	43±1,6	<0,0001
IgG ult LSM	11±2,7	16±4,1	<0,0001
LSM 1ª	8,2±6,7	8,1±5,8	-
LSM ult	6,4±3,2	9,2±9,1	0,06
Mudanca LS (%/ano)	-7,5 (-11,0 – 2,0)	+1,7 (-6,0 - 12,2)	<0,0001
Mudanca LS 1º ano e follow up	-0,60±0,48	+0,14±0,09	<0,0001



Harlt, J et al J Hepatol 2018;68:754-763

Caso clinico 2:

SNFS. 47 anos, vem em consulta devido a prurido intenso pelo corpo ha 3 anos. Nega coluria, acolia fecal, febre, uso de medicamentos.

Hb/Hto=13,0/39,3	AST=37(40)	FAN=1/1280 (nucleo e citoplasma)
Leuco=8200(3181)	ALT=85(65)	Anti-Mitocondria= 1/320
Plaquetas= 285000	GGT=965(50) / FA=599(100)	Anti-DNA=negativo
RNI=0,9	BT/BD=0,9/0,5	LKM1/citosol= negativo
Creat=0,9	gamaglob= 1,07	Virus= negativos

APRI	**0,325**
FIB4	0,66
LSM	7,7 kPa

Biopsia hepatica	Doenca hepatobiliar com moderada atividade, com nitida agressao a ductos interlobulares e moderada colestase. Tratos portais com fibrose emitindo septos (F2)

Questoes para reflexao:

1) Qual a interpretacao podemos fazer com relacao aos marcadores nao invasivos de fibrose na CBP/CEP?

   a. Os 2 biomarcadores concordam em afastar FA/CH, porem a elastografia mostrou resultado em Zona Cinza, sendo necessaria a BX
   b. A utilizacao dos MNI, tanto biomarcadores quanto elastografia, nao estao indicados na CBP/CEP por falta de validacao externa na literatura;
   c. Na CBP/CEP os marcadores se comportam de forma descoordenada devido a colestase hepatica e nao devem ser valorizados isoladamente nessa fase, sendo necessaria a BX hepatica com esse fim
   d. Apenas a elastografia deve ser valorizada nessa fase, por conta de interferencia da colestase hepatica nos biomarcadores.

Diagnostic performance of a point shear wave elastography (pSWE) for hepatic fibrosis in patients with autoimmune liver disease

Dong Won Park[1☯], Yoon Jin Lee[2☯], Won Chang[2], Ji Hoon Park[2], Kyoung Ho Lee[2], Young Hoon Kim[2], Nam Kyu Kang[1], Jung Wha Chung[1], Hee Yoon Jang[1], Soomin Ahn[3], Haeryoung Kim[4], Sook-Hyang Jeong[1], Jin-Wook Kim[1], Eun Sun Jang[1*]

FIBROSE	F0	F1	F2	F3	F4
HAI (N=49)	12 (24,5%)	6 (12,2%)	10 (20,4%)	10 (20,4%)	11 (22,4%)
CBP (N=41)	8 (19,5%)	22 (53,7%)	8 (19,5%)	2 (4,9%)	1 (2,4%)

	Cutoff	AUROC (IC)	S	E	VPP	VPN	LR+	LR-
HAI								
≥F2	4,47	0,70(0,56-0,83)	93,6	44,4	74,4	80,0	1,68	0,15
≥F3	7,11	0,76(0,62-0,67)	66,7	78,6	70,0	75,9	3,11	0,42
F4	9,28	0,75(0,61-0,87)	63,6	86,8	58,3	89,2	4,84	0,42
CBP								
≥F2	5,56	0,81(0,65-0,90)	81,8	73,3	52,9	91,7	3,07	0,25
≥F3	6,04	0,91(0,75-0,96)	100	81,6	30,0	100	5,43	0

PlosOne 2019

Acoustic Radiation Force Impulse (ARFI) Elastography in Autoimmune and Cholestatic Liver Diseases

Table 2. ARFI point shear wave elastography of the liver in patients with AIH, Overlap syndrome, PBC and PSC .

	All	AIH	Overlap syndrome	PBC	PSC
N	85	31	12	26	16
Number of measurements	9.1 ± 1.82 (5-12)	9.0 ± 1.9 (5-12)	9.8 ± 1.3 (7-12)	9.2 ± 1.6 (5-11)	8.8 ± 2.3 (5-12)
Measurement depth [cm]	4.0 ± 1.1 (2-7.2)	4.1 ± 1.2 (2.2 7.1)	4.3 ± 1.3 (2.69-7.2)	3.7 ± 0.8 (2.5-5.6)	4.0 ± 1.1 (2-6.3)
Median [m/s]	1.79 ± 0.87 (0.73-4.02)	2.07 ± 1.03 (0.84-4.02)	2.16 ± 0.85 (0.90-3.40)	1.37 ± 0.6 (0.73-3.48)	1.65 ± 0.55 (0.88-2.68)
Mean ARFI [m/s]	1.80 ± 0.84 (0.74-3.98)	2.09 ± 1.00 (0.84-3.98)	2.18 ± 0.84 (0.9- 3.35)	1.37 ± 0.58 (0.74-3.2)	1.66 ± 0.52 (0.88-2.61)
Standard deviation (SD)	0.31 ± 0.31 (0.03-1.42)	0.32 ± 0.31 (0.03-1.42)	0.38 ± 0.20 (0.08-0.65)	0.31 ± 0.39 (0.04-1.38)	0.26 ± 0.21 (0.03-0.69)
Interquartile range (IQR) [m/s]	0.39 ± 0.45 (0.01-2.53)	0.36 ± 0.39 (0.05-1.64)	0.49 ± 0.29 (0.06-0.92)	0.40 ± 0.61 (0.01-2.53)	0.35 ± 0.34 (0.03-1.22)
ARFI correlation with fibrosis	r = 0.510 p < 0.001	r = 0.653 p < 0.001	r = 0.813 p = 0.001	r = 0.019 p = 0.927	r = 0.588 p = 0.017

Detecção de cirrose (F≥5 Ishak):
AUROC=87,2% (77,8-96,6)
S=90%; E=74,7%

Goertz RS et al. An Hepatol 2019;18:23-29

Retrospective Study

Magnetic resonance elastography is accurate in detecting advanced fibrosis in autoimmune hepatitis

Jin Wang, Neera Malik, Meng Yin, Thomas C Smyrk, Albert J Czaja, Richard L Ehman, Sudhakar K Venkatesh

N=36 HAI 2007-2015
51,6±20,6 anos

- F≥1=32 (88,9%)
- F≥2=27 (75%)
- F≥3=19 (32,8%)
- F=4 13 (36,1%)

Table 3 Area under the receiver operating characteristic curves of magnetic resonance elastography and laboratory tests for prediction of advanced fibrosis and cirrhosis in autoimmune hepatitis

	Advanced fibrosis			Cirrhosis		
	AUC	SE	95%CI	AUC	SE	95%CI
LS	0.966	0.0278	0.845-0.998	0.980	0.0175	0.867-1.000
ALT	0.526	0.0998	0.354-0.695	0.582	0.1010	0.406-0.744
AST	0.618	0.0964	0.441-0.774	0.691	0.0909	0.515-0.834
AST/ALT	0.681	0.0904	0.505-0.826	0.736	0.0860	0.563-0.868
APRI	0.728	0.0932	0.554-0.862	0.776	0.0789	0.606-0.898
FIB_4	0.786	0.0760	0.618-0.905	0.803	0.0750	0.636-0.916
INR	0.770	0.0770	0.596-0.891	0.800	0.0880	0.635-0.915
Platelet	0.802	0.0780	0.636-0.916	0.763	0.0904	0.592-0.888

World J Gastroenterol 2017;23:859-868

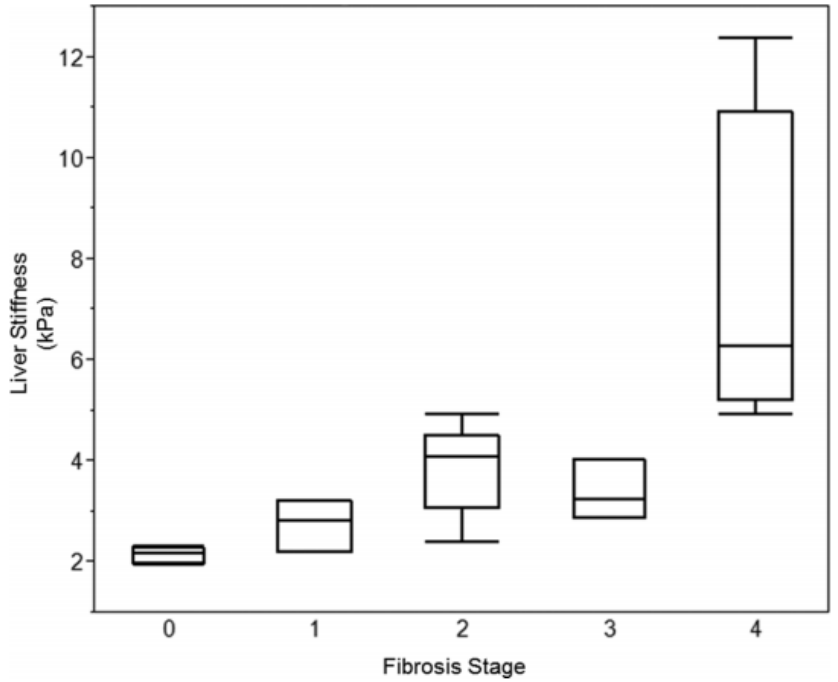
Performance of Magnetic Resonance Elastography in Primary Sclerosing Cholangitis

John E. Eaton, M.D.[1,4], Bogdan Dzyubak[2], Sudhakar K. Venkatesh, M.D.[2], Thomas C. Smyrk, M.D.[3], Gregory J. Gores, M.D.[1], Richard L. Ehman, M.D.[2], Nicholas F. LaRusso, M.D.[1], Andrea A. Gossard, A.P.R.N., C.N.P.[1], and Konstantinos N. Lazaridis, M.D.[1]

N=266 CEP seguimento médio de 2,05 anos (1,43 – 2,74 anos)

N= 20 CEP com biópsia hepática

- F0= 4
- F1= 3
- F2= 6 (LSM=2,41kPa)
- F3= 3 (LSM=3,26 kPa)
- F4= 4 (LSM=4,93 kPa)



LSM correlacionou positivamente com fibrose na CEP (r=0,84; p<0,001)
CIRROSE: S=100%; E=94%

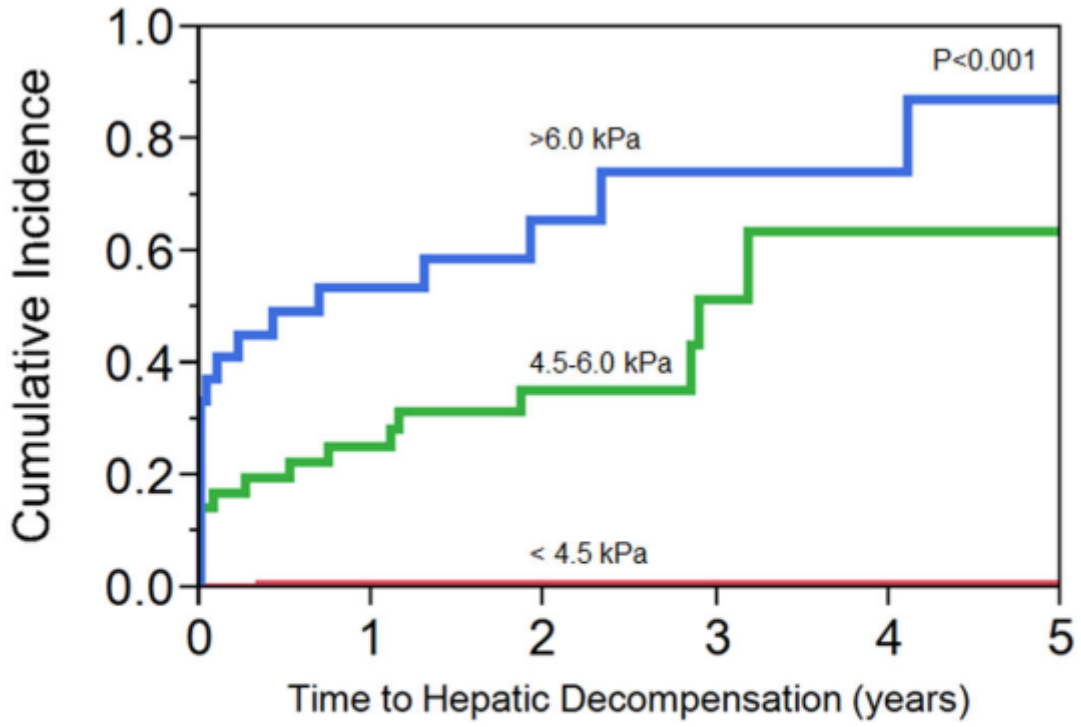
J Gastroenterol Hepatol, 2016;31:1184-1190

N=266 CEP seguimento médio de 2,05 anos (1,43 – 2,74 anos)

N=36 (14 descompensaram)

LSM= 5,99 x 2,76 kPa; p<0,001 (descompensaram x não)

HR=1,55 (95%IC 1,41-1,70)



Number at Risk:

>6.0 kPa	27	11	6	3	3	2
4.5-6.0 kPa	42	26	18	6	3	2
<4.5 kPa	197	163	107	45	24	17

Figure 2.
Time to Hepatic Decompensation

Eaton et al. J Gastroenterol Hepatol, 2016;31:1184-1190

Mensagens finais

- Os estudos com marcadores não invasivos de fibrose nas doenças hepáticas autoimunes são ainda escassos, com números pequenos de pacientes;
- Biomarcadores têm performance apenas marginal na avaliação de fibrose nessa população e não é recomendado pelos principais guidelines;
- Métodos físicos parecem promissores na avaliação da fibrose, particularmente na HAI e CBP, com especial atenção para a elastografia transitória (maior número de estudos);
- A ET têm se mostrado útil no seguimento dos pacientes portadores de DAI, porém merece atenção a possível interferência de fatores confundidores na interpretação dos resultados (colestase e elevação ALT, AST).

Obrigada!

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