Liver stiffness measurement predicts clinical outcomes in autoimmune hepatitis

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Table S1. Predictive factors of cirrhosis development during the follow-up in non-cirrhotic patients at baseline treated with azathioprine.

Variable	Cirrhosis development			Univariate analysis		
	No (n=197)	Yes (n=10)	*p* value	Wald	HR (IC 95%)	*p* value
Age at entry(years)	5744-66)	56(43-63)	0.925			
Female sex (n, %)	145 (87%)	11 (61%)	0.256			
AST (U/L)	535 (128 -1064)	783 (408-1232)	0.195			
ALT (U/L)	633 (200-1350)	821 (415 – 1275)	0.526			
Total bilirubin (mg/dL)	2.26 (0.85 – 8.90)	7.2 (1.05 – 14.8)	0.122			
ALP (x ULN)	1.08 (0.77 – 1.52)	1.39 (1 – 2.63)	0.044	7.894	1.970 (1.228 – 3.163)	0.05
γ-GT (U/L)	160 (66 – 275)	157 (87 – 380)	0.416			
IgG (g/L)	17 (13.9 – 22.1)	21 (15.05 – 36.6)	0.075			
INR	1.10 (1.03 – 1.22)	1.2 (1.01 – 1.28)	0.415			
Platelets (x 10^3/L)	227 (176 – 276)	200 (147 – 276)	0.169			
mHAI						
Grade	8 (6 – 11)	10.5 (9.5 – 12)	0.007	2.127	1.119 (0.962 – 1.301)	0.145
Stage	1(0-1)	1 (1-3)	0.047	3.455	1.409 (0.982 - 2.023)	0.063
Fibrosis (n, %)	96 (49%)	12 (67%)	0.075			
Advanced fibrosis (n, %)	14 (7.1%)	5 (27.7%)	0.002	6.572	4.318 (1.411 – 13.125)	0.010
ANA (n, %)	152 (77%)	16 (89%)	0.277			
SMA (n, %)	148 (75%)	15 (83%)	0.476			

Anti-SLA/LP (n, %)	7 (3.6%)	1 (5.5%)	0.675			
Anti-LKM-1 (n, %)	1 (0.5%)	0 (0%)	0.756			
BLSM (kPa)	5.3 (4.3 – 7)	10.65 (8.65 – 15.93)	<0.001	29	1.309 (1.187 – 1.443)	<0.001
BR at BLSM (n, %)	164 (83%)	10 (56%)	<0.001	7.164	0.254 (0.093 – 0.693	0.007
Time from diagnosis to BLSM (years)	2.05 (1.16 – 3.81)	1.75 (1.25 -5.73)				

Data are expressed as median (IQR).

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, γ-glutamyl transferase; IgG, immunoglobulin G; mHAI, modified hepatitis activity index; ANA, antinuclear antibodies; SMA, smooth muscle antibodies; anti-SLA/LP, anti-soluble liver antigen/liver pancreas antibodies; anti-LKM1, anti-liver kidney microsomal antibodies; Cs, corticosteroids; AZA, azathioprine; MMF, mycophenolate mofetil; BLSM, first liver stiffness measurement after 6 months of treatment initiation; BR, biochemical response.

Table S2. Predictive factors of cirrhosis development during follow-up in non-cirrhotic patients at baseline treated with mycophenolate.

Variable	Cirrhosis development			Univariate analysis		
	No (n=102)	Yes (n=4)	*p* value	Wald	HR (IC 95%)	*p* value
Age at entry (years)	52 (37 – 62)	53 (46 - 61)	0.696			
Female sex (n, %)	69 (68%)	3 (75%)	0.757			
AST (U/L)	119 (53- 478)	498 (139 – 1059)	0.214			
ALT (U/L)	200 (73 – 757)	837 (266 – 1441)	0.187			
Total bilirubin (mg/dL)	1.06 (0.6 – 3.66)	7.65 (1.2 – 13)	0.135			
γ-GT (U/L)	82 (36 - 182)	128 (79 -237)	0.273			
IgG (g/L)	15.6 (12 – 20.3)	23.6 (14.2 – 38.4)	0.135			
INR	1.05 (0.97 – 1.16)	1.45 (1.05 – 1.86)	0.050			
Platelets (x 10^9/L)	233 (192 – 273)	222 (66 – 285)	0.570			
mHAI						
Grade	6 (4 – 8)	8 (6 – 13)	0.176			
Stage	1 (1-2)	3 (0-4)	0.188			
ANA (n, %)	44 (43%)	4 (10%)	0.025			
SMA (n, %)	94 (92%)	3 (75%)	0.227			
Anti-SLA/LP (n, %)	11 (11%)	0 (0%)	0.488			
Anti-LKM-1 (n, %)	8 (8%)	0 (0%)	0.560			
BLSM (kPa)	5.3 (4.4 – 6.8)	12.9 (5.9 – 21.7)	0.030	6.930	1.216 (1.051 – 1.406)	0.008
BR at BLSM (n, %)	80 (80%)	0 (0%)	0.000	1.084	0.003 (0.000- 174.616)	0.298
Time from diagnosis to BLSM (years)	2.78 (1.33 – 5.32)	1.92 (1.02 – 9.77)	0.703			

Data are expressed as median (IQR).

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, γ-glutamyl transferase; IgG, immunoglobulin G; mHAI, modified hepatitis activity index; ANA, antinuclear antibodies; SMA, smooth muscle antibodies; anti-SLA/LP, anti-soluble liver antigen/liver pancreas antibodies; anti-LKM1, anti-liver kidney microsomal antibodies; Cs, corticosteroids; AZA, azathioprine; MMF, mycophenolate mofetil; BLSM, first liver stiffness measurement after 6 months of treatment initiation; BR, biochemical response.

Table S3. Predictive factors of cirrhosis development during the follow-up in patients on BR at the time of BLSM

Variable	Cirrhosis development			Univariate analysis			Multivariate analysis		
	No (n=288)	Yes (n=10)	*p* value	Wald	HR (IC 95%)	*p* value	Wald	HR (IC 95%)	*p* value
Age at entry (years)	55 (44-66)	60 (50-63)	0.805						
Females (n, %)	203 (71%)	7 (70%	0.974						
AST (U/L)	349 (98-1001)	834 (462-1651)	0.070						
ALT (U/L)	485 (147-1243)	951 (483-1240)	0.281						
Total bilirubin (mg/dL)	1.8 (0.8-8)	12.7 (3.-15.3)	0.024						
ALP (x ULN)	0.97 (0.61 – 1.40)	1.55 (1.27-3.35)	0.010	7.674	1.759 (1.189-2.623)	0.006	7.67	1.762 (1.180-2.631)	0.006
γ-GT (U/L)	129 (51-253)	148 (98-349)	0.322						
IgG (g/L)	16.6 (12.8-21)	23 (13.4-38.5)	0.085						
INR	1.10 (1.00-1.22)	1.07 (1.23-1.69)	0.082						
Platelets (x 10^9/L)	227 (178-275)	196 (137-248)	0.106						
mHAI									
Grade	8 (6-10)	11 (8-11)	0.026	2.999	1.217 (0.974-1.521)	0.083			
Stage	0 (0-2)	0 (0-2)	0.789						
Advanced fibrosis (n, %)	31 (10.8%)	1 (10%)	0.908						
ANA (n, %)	198 (68.9%)	9 (90%)	0.163						
SMA (n, %)	213 (74.%)	9(90%)	0.272						
Anti-SLA/LP (n, %)	16 (5.6%)	1 (10%)	0.559						
Anti-LKM-1 (n, %)	8 (2.8%)	0 (0%)	0.587						
Cs + AZA (n, %)	164 (56.9%)	8 (80%)	0.147						

Cs + MMF (n, %)	80 (27.8%)	0 (0%)	0.051						
BLSM (kPa)	5.1 (4.3-6.8)	9.8 (6.43-12.48)	0.000	18.430	1.300 (1.153-1.465)	<0.001	12.147	1.291 (1.18 – 1.490)	<0.001
∆LSM (kPa)	-0.4 (-1.35 – 0.95)	-0.45 (-5.6 -1.55)	0.609						
Time from diagnosis to BLSM (years)	2.22 (1.24-4.91)	2.12 (1.21-6.06)	0.909						

Data are expressed as median (IQR).

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, γ-glutamyl transferase; IgG, immunoglobulin G; mHAI, modified hepatitis activity index; ANA, antinuclear antibodies; SMA, smooth muscle antibodies; anti-SLA/LP, anti-soluble liver antigen/liver pancreas antibodies; anti-LKM1, anti-liver kidney microsomal antibodies; Cs, corticosteroids; AZA, azathioprine; MMF, mycophenolate mofetil; BLSM, first liver stiffness measurement after 6 months of treatment initiation; BR, biochemical response.

Table S4. Variation in liver stiffness measurements during the follow-up in the entire cohort and in different subpopulations.

Variable	Overall (n=371)	Cirrhosis at BLSM		p	Poor outcomes		p	Cirrhosis during follow-up		p
		Yes (n=48)	No (n=323)		Yes (n=5)	No (n=366)		Yes (n=24)	No (n=299)	
BLSM (kPa)	6 (4.5-8.5)	11.3 (7.6 – 16.05)	5.6 (4.4 -7.7)	<0.001	15.2 (10.9 – 28.4)	6.1 (4.50 – 8.50)	0.001	10.7 (8.52 – 15.40)	5.5 (4.3 – 7.3)	<0.001
Last LSM (kPa)	5.6 (4.4-7.3)	8.8 (6.1 – 14.25)	5.3 (4.3 -7.4)	<0.001	17.1 (14 -24.75)	5.6 (4.4 -7.23)	<0.001	8.4 (6.85 -14.30)	5.3 (4.2 – 6.5)	<0.001
∆ (kPa)	-0.55 (-2 – 0.9)	-1.4 (-4.05 – 1.00)	-0.50 (-1.7 – 1.00)	0.078	1.70 (-4.55 – 4.10)	-0.60 (-2.00 – 0.90)	0.121	-0.45 (-5.18 – 5.75)	-0.5 (-1.6 – 0.83)	0.798
∆LSM/year	-0.13 (-0.63 – 0.28)	-0.51 (-1.56 – 0.26)	-0.11 (-0.55 – 0.29)	0.014	0.42 (-1.37 – 1.64)	-0.13 (-0.61 – 0.28)	0.155	-0.08 (-0.75 – 1.62)	-0.11 (-0.54 – 0.26)	0.478
Time from BLSM to last LSM (years)	3.50 (1.94-5.78)	3.02 (1.82 – 4.81)	2.57 (1.94 -5.95)	0.211	3.46 (2.44 – 4.64)	3.51 (1.94 – 5.81)	0.774	5.11 (2.45 – 7.10)	3.52 (1.89 – 5.79)	0.052

Data are expressed as the median (IQR).

Abbreviations: LSM; liver stiffness measurement; BLSM, first liver stiffness measurement after 6 months of treatment initiation); ∆, variation in LSM from BLSM and last LSM; ∆LSM/year, variation in LSM per year

Fig. S1. Discriminative capacity of platelet count, mHAI, and ALT for predicting poor clinical outcomes.

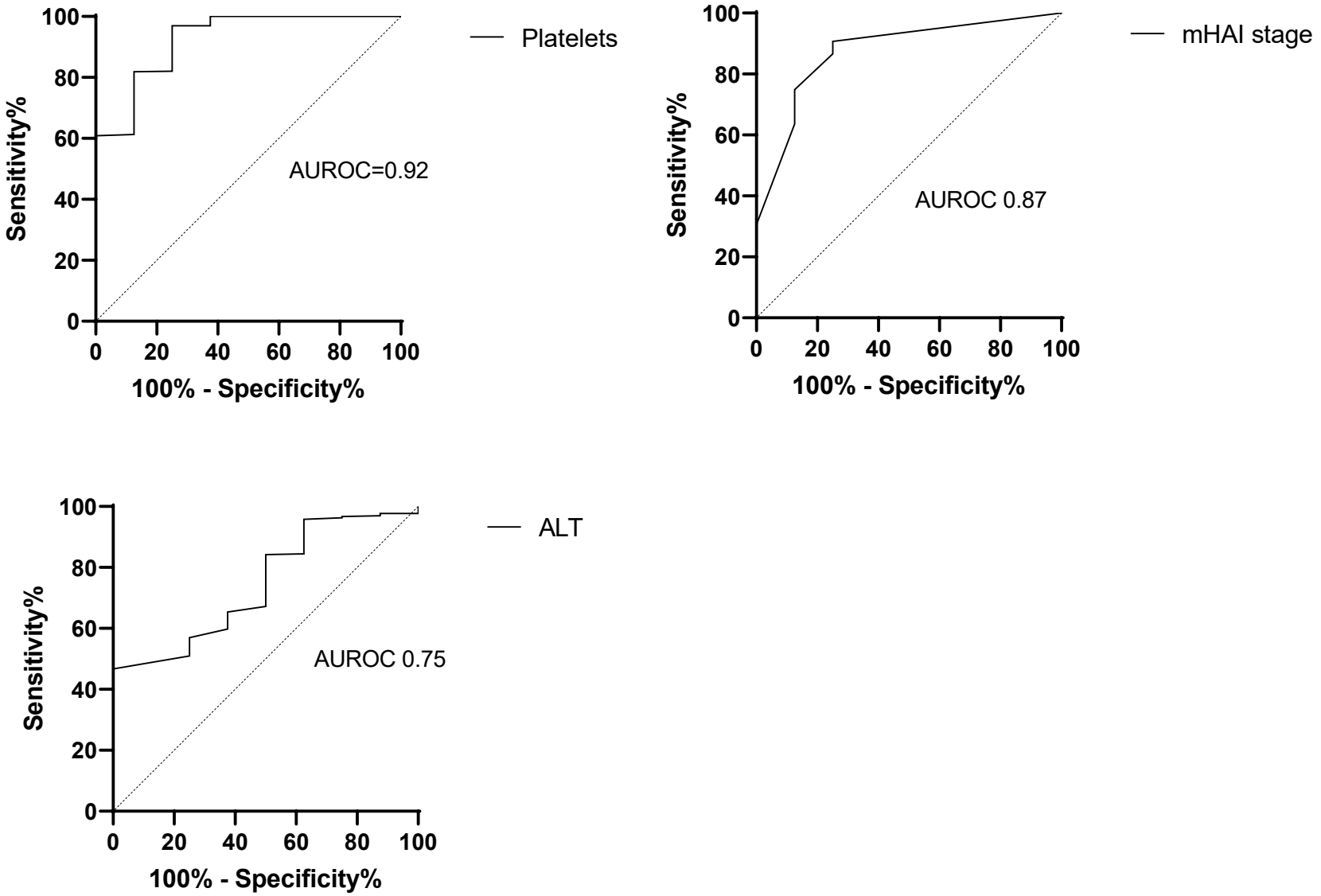

Fig. S2. Lack of impact of time between diagnosis and BLSM and IgG at baseline in the risk of developing cirrhosis.

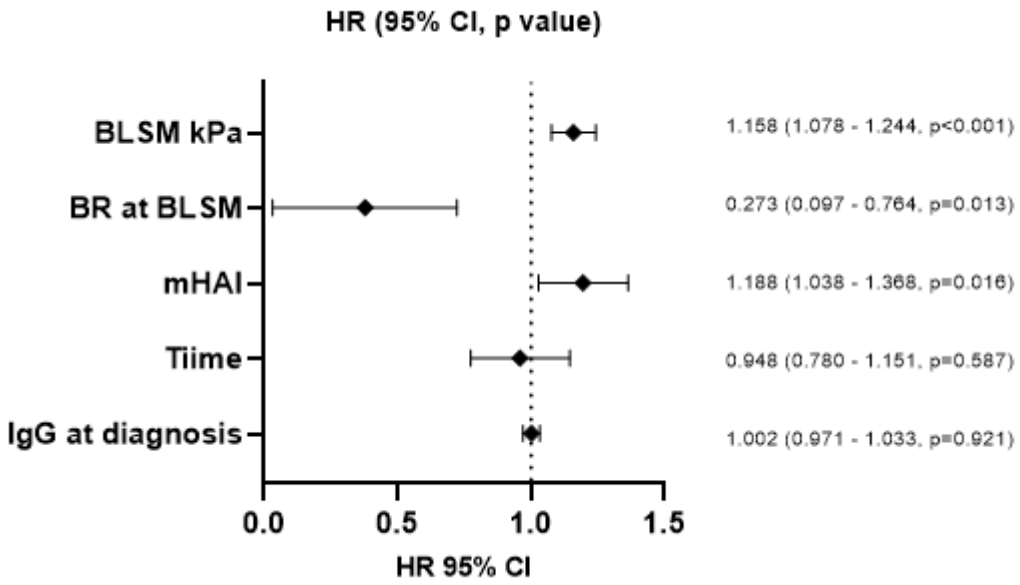

Fig. S3. Maximally selected rank statistics confirm the 8.5 kPa cutoff point in the prediction of cirrhosis development.