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Centro de Investigación Biomédica en Red  
Enfermedades Hepáticas y Digestivas

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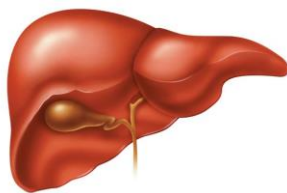


## XIV CURSO EN AVANCES EN INFECCION VIH Y HEPATITIS VIRALES

Vigo, 31 de Enero  
y 1 de Febrero  
de 2020



# Identificación y manejo práctico de la esteatosis hepática metabólica



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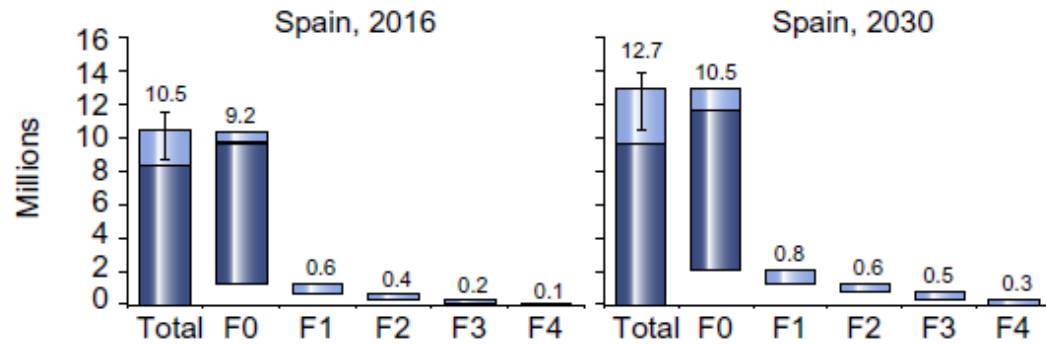


Fig. 1. Distribution of NAFLD population by fibrosis stage - 2016 & 2030.

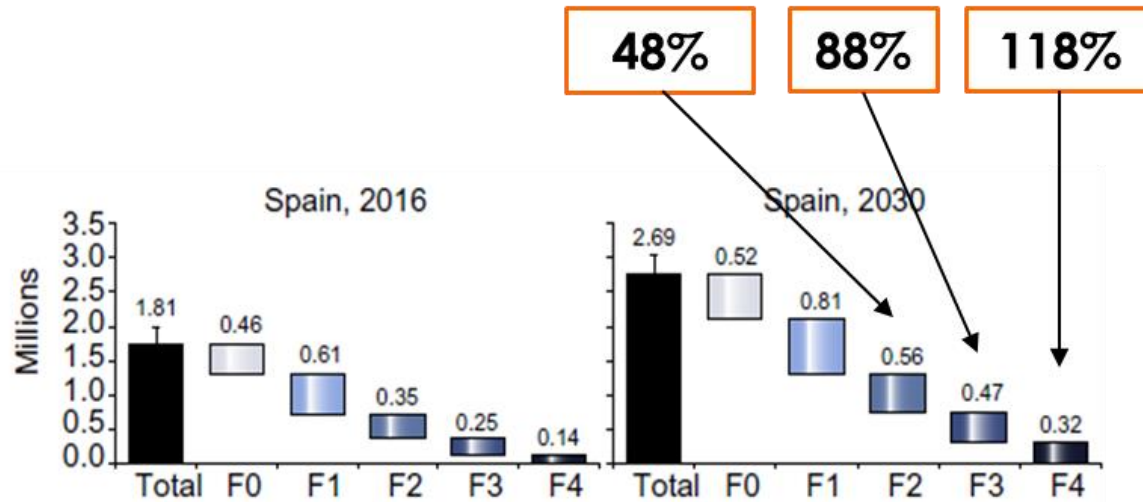
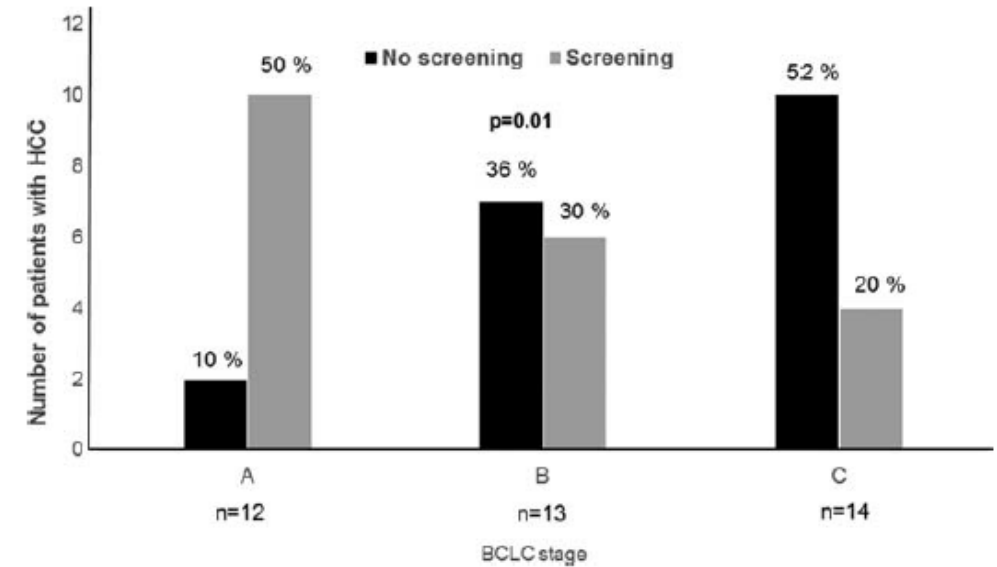
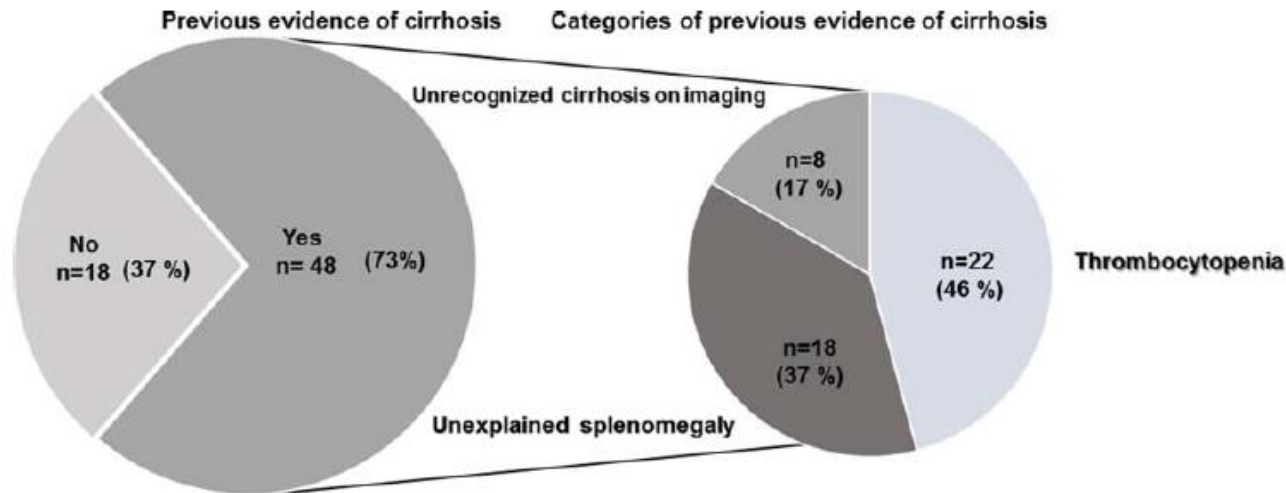
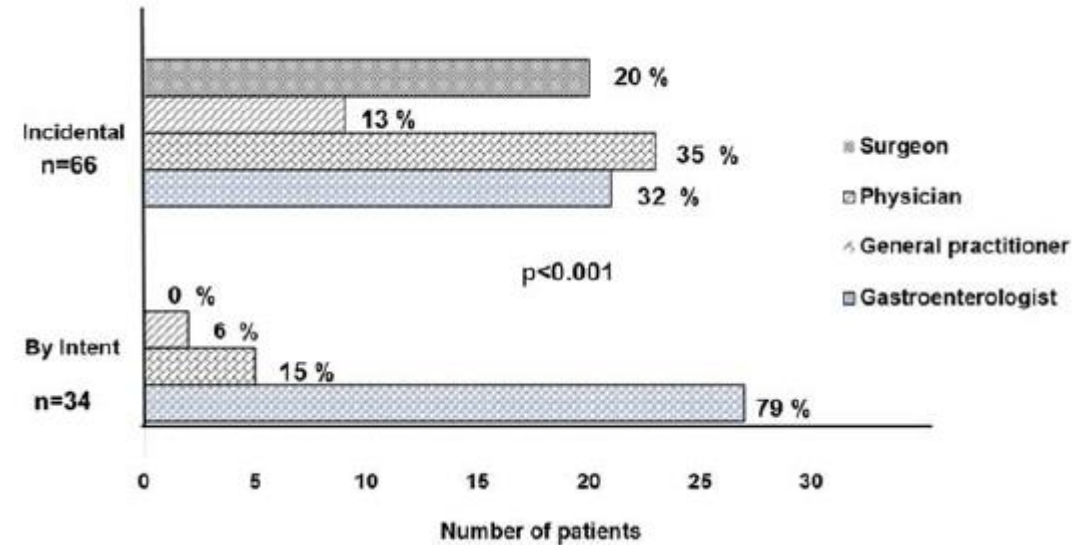
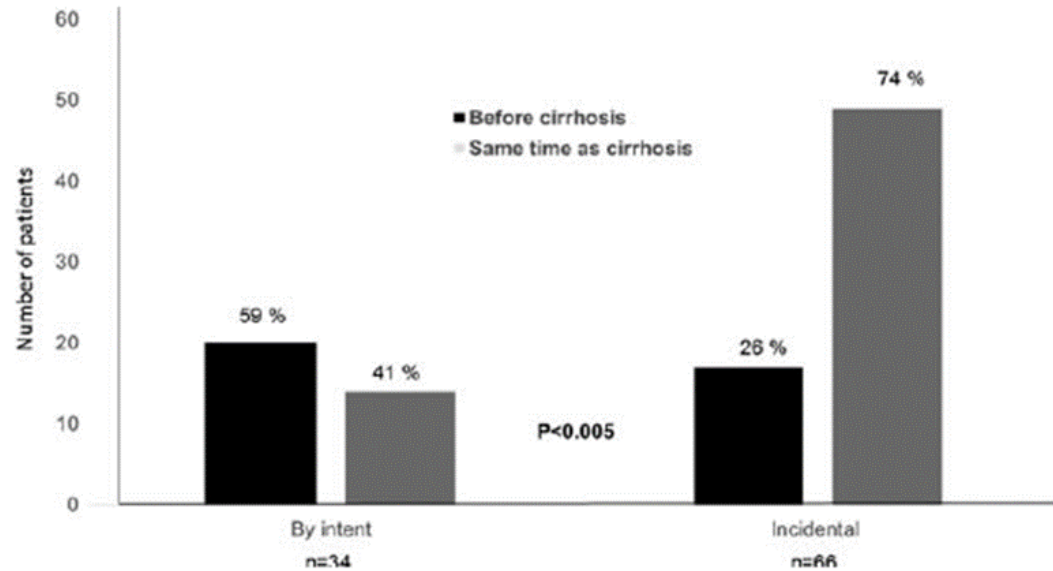
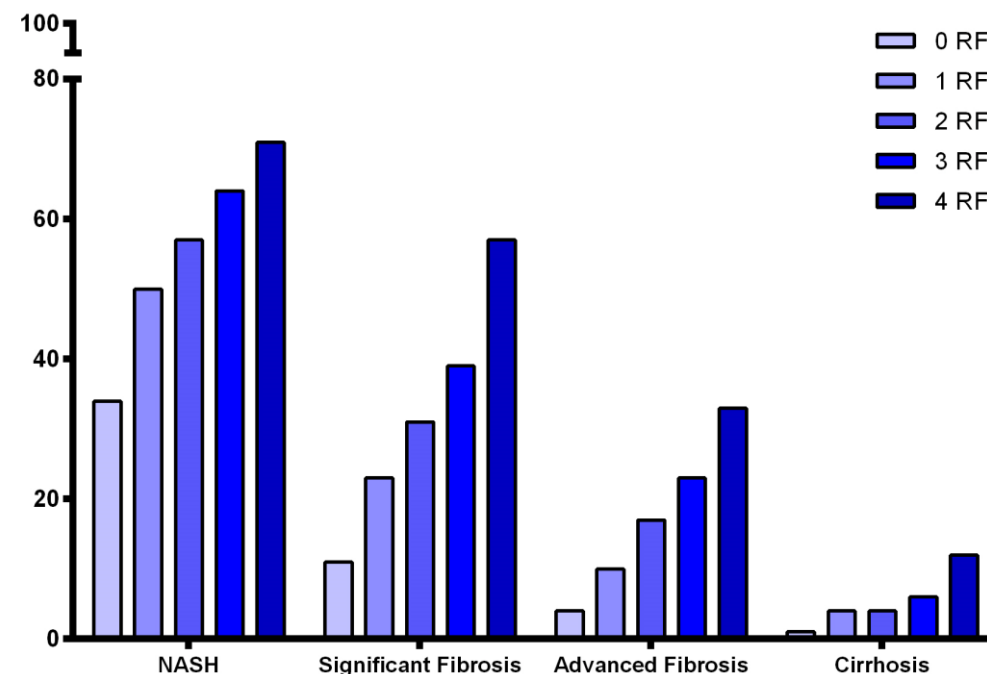
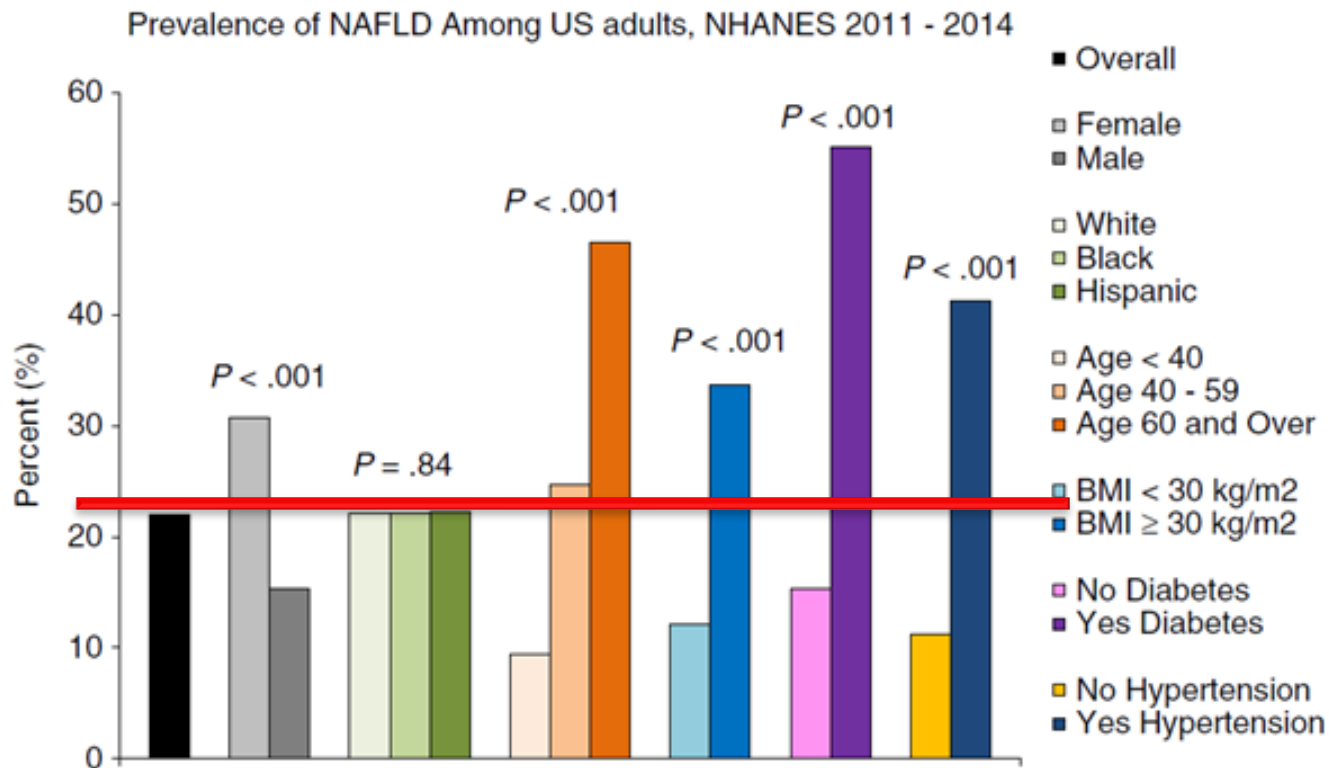
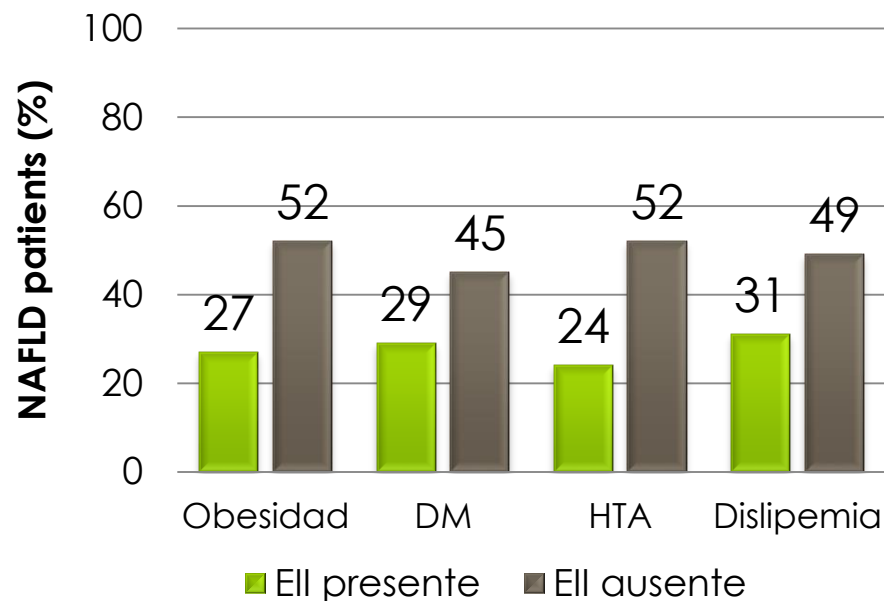
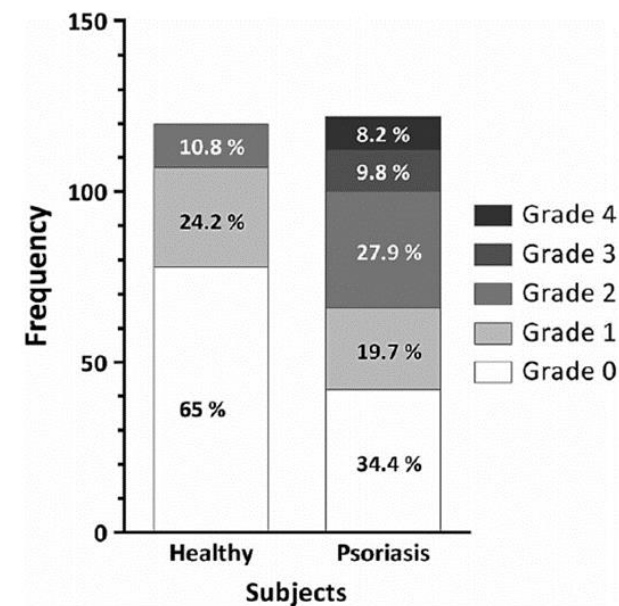
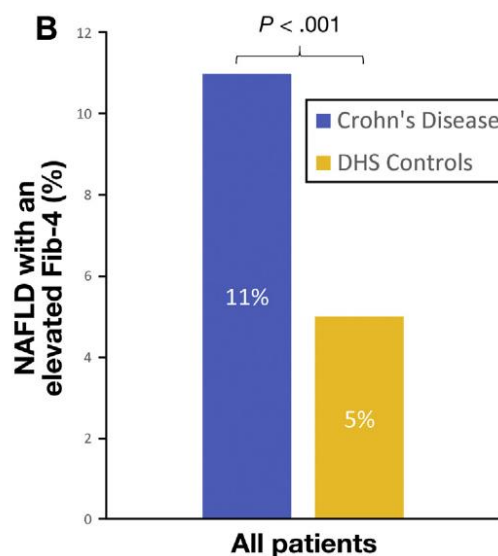
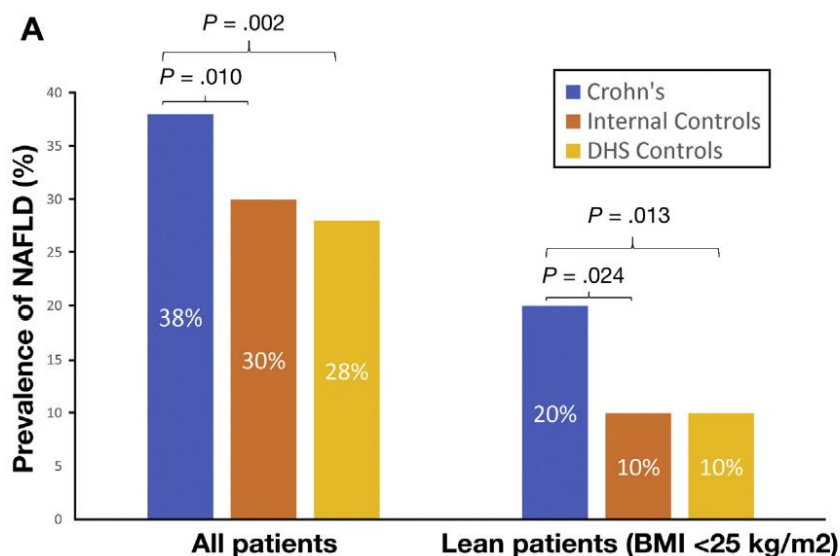


Fig. 2. Distribution of NASH population by fibrosis stage - 2015 & 2030.

Spain	
2016 Country population (000)	46,100
2030 Country population (000)	45,900
Adult obesity prevalence (BMI) $\geq 30$ kg/m <sup>2</sup>	
2016	18.0%
2030	18.9%
NAFLD	
2016 Total cases	10,532,000
2016 Prevalence (all ages)	22.9%
2030 Total cases	12,653,000
2030 Prevalence (all ages)	27.6%
NAFL	
2016 Total cases	8,728,000
2016 Prevalence (all ages)	18.9%
2030 Total cases	9,966,000
2030 Prevalence (all ages)	21.7%
NASH	
2016 Total cases	1,803,700
2016 Prevalence (all ages)	3.9%
2030 Total cases	2,687,300
2030 Prevalence (all ages)	5.9%
Incident NAFLD	
2016 Total cases	337,000
2016 Prevalence (all ages)	7.3
2030 Total cases	330,500
2030 Prevalence (all ages)	7.2
NASH mortality	
2016 Total cases	3,260
2016 Prevalence (all ages)	4,530
2030 Total cases	7,590
2030 Prevalence (all ages)	7,850



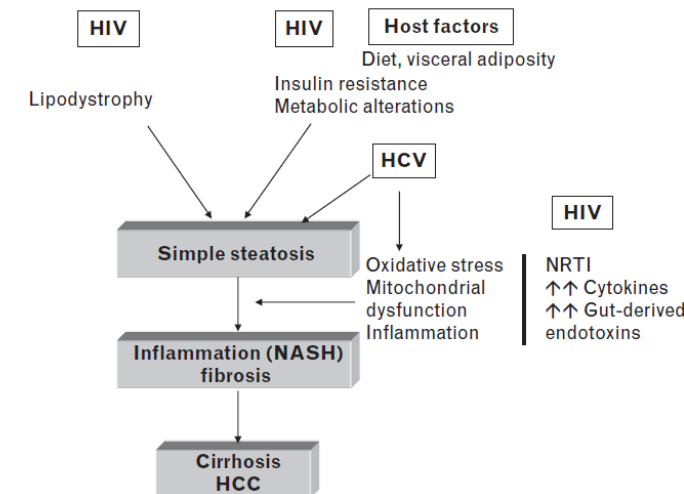




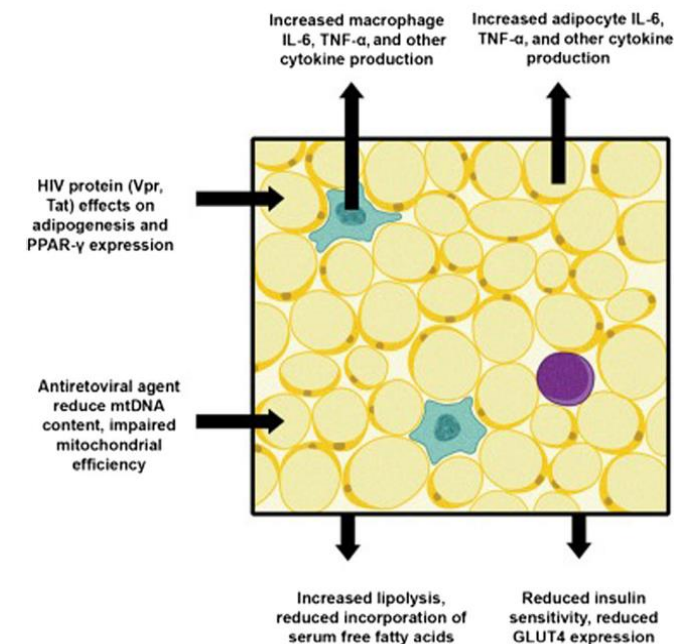
## NAFLD y Hidradenitis supurativa

	OR (95% CI)*	P
Male gender	0.25 (0.09-0.69)	0.007
Abdominal perimeter, cm	1.15 (1.08-1.21)	<0.001
Hidradenitis	7.75 (2.54-23.64)	<0.001
ALT, U/L	1.03 (1.003-1.07)	0.03

	Patient population	Number of patients with HIV mono-infection	NAFLD diagnostic assay	NAFLD prevalence in patients with HIV mono-infection	Predictors of NAFLD in patients with HIV mono-infection
Hadigan et al (2007) <sup>19</sup>	Consecutive patients with HIV who did not abuse alcohol	33	MRS	42.0%	High HOMA-IR, visceral adiposity, high BMI, and high plasma ALT and triglyceride concentrations
Guaraldi et al (2008) <sup>20</sup>	Patients with HIV who did not abuse alcohol or have viral hepatitis	225	Liver-to-spleen attenuation on CT	36.9%	Male sex and large waist circumference
Ingiliz et al (2009) <sup>21</sup>	Patients with chronic elevation in liver test results that had no genetic cause and had no HCV, HBV, or autoimmune disease	30	Liver biopsy	Of the total patient cohort, 60.0% had steatosis and 53.0% had NASH	High fasting plasma glucose concentration
Crum-Cianflone et al (2009) <sup>20</sup>	Patients with HIV who did not have HCV or HBV	267	Ultrasound and 55 liver biopsies	31.0% of patients assessed by ultrasound had NAFLD; 36.0% of patients assessed by biopsy had NAFLD and 20.0% had NASH	Large waist circumference, and high plasma triglyceride and LDL concentrations
LiVecchi et al (2012) <sup>22</sup>	Patients with HIV mono-infection or HIV-HCV co-infection	57	Ultrasound and transient elastography	54.0%	Lipodystrophy, high plasma triglyceride concentration, metabolic syndrome, high plasma cholesterol concentration, and ART use for more than 1 year
LiVecchi et al (2013) <sup>23</sup>	Patients with HIV mono-infection or HIV-HCV co-infection	69	Ultrasound and transient elastography	46.3%	High plasma triglyceride concentrations and diabetes
Sterling et al (2013) <sup>24</sup>	Patients with HIV who did not have HCV or HBV, did not abuse alcohol, and did not have diabetes mellitus or elevated liver test results	14	Liver biopsy	Of the total patient cohort, 65.0% had steatosis and 26.0% had NASH	High HOMA-IR and serum GGT concentrations, which predict steatosis
Nishijima et al (2014) <sup>25</sup>	Patients with HIV who did not have HBV or HCV, and did not abuse alcohol	435	Ultrasound	31.0%	High BMI and dyslipidaemia
Price et al (2014) <sup>26</sup>	Multicenter AIDS Cohort Study: patients with HIV who did not abuse alcohol	465	Liver-to-spleen attenuation on CT	13.0%	PNPLA3 genotype and cumulative dideoxynucleoside exposure
Macias et al (2014) <sup>27</sup>	Patients with HIV in a walk-in clinic	505	Transient elastography with CAP	40.0%	High BMI, and high fasting plasma glucose and plasma triglyceride concentrations
Sulyok et al (2015) <sup>28</sup>	Outpatients with HIV mono-infection or HIV-HCV co-infection	136	Transient elastography with CAP	49.5%	High BMI, diabetes, and hypertension
Morse et al (2015) <sup>29</sup>	Patients with HIV who had elevated serum ALT concentrations for 6 months, were on ART, and did not have chronic liver disease	62	Liver biopsy	Of the total patient cohort, 55.0% had NASH and 18.0% had bridging fibrosis	Diabetes, obesity, and PNPLA3 genotype
Lui et al (2016) <sup>30</sup>	Patients with HIV who did not have HBV or HCV	80	Transient elastography and MRS	28.7%	High BMI, metabolic syndrome, high fasting glucose and serum triglyceride concentrations



### Effects of HIV and Antiretroviral Therapy on Adipose Tissue Biology



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## Editorial: looking for patients at risk of cirrhosis in the general population—many needles in a haystack

Hidden cirrhosis is a common oversight in clinical practice. In fact, it is not unusual to find cirrhosis during routine laparoscopic surgery (Figure 1). Apart from signs and symptoms of cirrhosis, which are scarce in clinical practice, serum aminotransaminase elevation remains the hallmark signal that raises suspicion of liver disease in

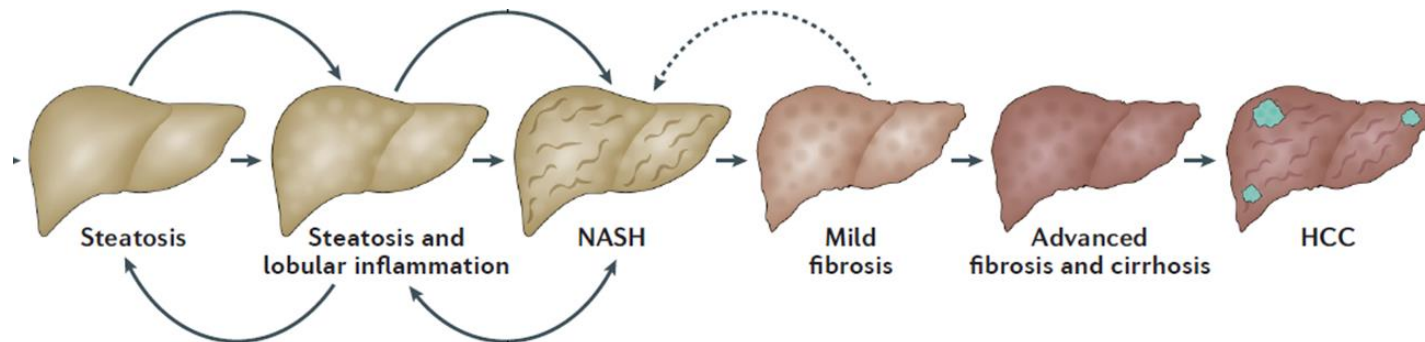
primary care.<sup>1</sup> However, Harman et al observed that more than two-thirds of cirrhotic patients showed normal AST/ALT levels,<sup>2</sup> probably because necroinflammatory reactions usually disappear as the liver progresses to cirrhosis ("burn-out cirrhosis"). Thus, general practitioners and hepatologists have to begin to adjust their thought process

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Variable	Alcohol and normal LSM (n = 316)	Alcohol and elevated LSM (n = 75)	T2DM and normal LSM (n = 371)	T2DM and elevated LSM (n = 171)	Both risks and normal LSM (n = 40)	Both risks and elevated LSM (n = 24)
Age (y)	55 (43-64)	61 (52-66) <sup>a</sup>	64 (56-74)	65 (54-71)	64.5 (57.5-72.5)	63 (56-67)
Male Gender n (%)	238 (75.3%)	65 (86.7%)	221 (59.6%)	115 (67.3%)	35 (87.5%)	22 (91.7%)
Body mass index (kg/m <sup>2</sup> )	25.7 (22.8-28.7)	28.7 (26.5-33.3) <sup>a</sup>	28.9 (25.9-32.0)	32.45 (29.0-36.3) <sup>b</sup>	28.05 (26.0-31.7)	32.75 (27.85-35.9) <sup>c</sup>
Hazardous alcohol use n (%)	—	—	40 (10.8%)	24 (14.0%)	—	—
Current alcohol (units/week)	28 (21-42)	30 (23-60)	0.5 (0-6)	1 (0-7)	25 (20-30)	29 (20.5-46)
Type 2 diabetes n (%)	40 (12.7%)	24 (32.0%) <sup>a</sup>	—	—	—	—
Raised ALT level n (%)	42 (13.3%)	25 (33.3%) <sup>a</sup>	28 (7.6%)	46 (26.9%) <sup>b</sup>	4 (10.0%)	6 (25.0%)
Obesity n (%)	63 (20.3%)	33 (44.0%) <sup>a</sup>	157 (42.6%)	116 (67.8%) <sup>b</sup>	16 (40.0%)	14 (58.3%)
Ischaemic heart disease n (%)	18 (5.7%)	10 (13.3%) <sup>a</sup>	55 (14.8%)	31 (18.1%)	5 (12.5%)	3 (12.5%)
Hypertension n (%)	78 (24.8%)	38 (50.7%) <sup>a</sup>	209 (56.3%)	101 (59.1%)	22 (55.0%)	16 (66.7%)
Hyperlipidaemia n (%)	143 (45.3%)	40 (53.3%)	318 (85.7%)	149 (87.1%)	34 (85.0%)	17 (70.8%)
Metabolic syndrome n (%)	28 (8.9%)	20 (26.7%) <sup>a</sup>	157 (42.3%)	109 (63.7%) <sup>b</sup>	15 (37.5)	12 (50.0%)
Liver stiffness median (kPa)	4.8 (4.1-5.75)	10.9 (9.0-15.7) <sup>a</sup>	5.3 (4.4-6.4)	11.3 (9.0-15.8) <sup>b</sup>	5.1 (4.4-6.4)	12.85 (9.1-17.65) <sup>c</sup>

**Table 2.** Proportions of patients meeting process measures

	N (%) <sup>a</sup>
<i>All patients</i>	251
<i>Review of primary care records</i>	
Elevation of transaminases	99 (39.4)
Consideration of NAFLD/NASH	54 (21.5)
Referral to GI/hepatology	26 (10.4)
Recommendation for lifestyle modification	37 (14.7)
Receipt of any NAFLD care	99 (39.4)
<i>Patients with high NFS scores</i>	37 (14.7)
<i>Review of primary care records</i>	
Elevation of transaminases	11 (29.7)
Consideration of NAFLD/NASH	6 (16.2)
Referral to GI/hepatology	1 (2.7)
Recommendation for lifestyle modification	5 (13.5)
Receipt of any NAFLD care	11 (29.7)



NASH CRN	SAF
Steatosis grade 0-3 0: < 5% <sup>a</sup> 1: 5-33% 2: 34-66% 3: > 66%	Steatosis grade (S) 0-3 S <sub>0</sub> : < 5% <sup>b</sup> S <sub>1</sub> : 5-33% S <sub>2</sub> : 34-66% S <sub>3</sub> : > 66%
Hepatocyte ballooning 0-2 0: None 1: Mild, few 2: Moderate-marked, many	Hepatocyte ballooning 0-2 0: None 1: Clusters of hepatocytes with rounded shape and pale and/or reticulated cytoplasm 2: Same as score 1 with enlarged hepatocytes (>2× normal size)
Lobular (acinar) inflammation 0-3 0: None 1: <2 foci/20× field 2: 2-4/20× field 3: >4/20× field	Lobular (acinar) Inflammation 0-2 0: None 1: ≤ 2 foci per 20× field 2: > 2 foci per 20× field
NAFLD activity score (NAS): 0-8 Sum of scores for steatosis, ballooning and lobular inflammation	Activity grade (A): 0-4 A <sub>1</sub> (A = 1): mild activity A <sub>2</sub> (A = 2): moderate activity A <sub>3</sub> & A <sub>4</sub> (A > 2): severe activity
Fibrosis stage 0: No significant fibrosis 1: 1a mild (delicate) zone 3 PSF (requires collagen stain to identify) 1b moderate (dense) zone 3 PSF 1c portal fibrosis only 2: Zone 3 PSF with periportal fibrosis 3: Bridging fibrosis 4: Cirrhosis	Fibrosis stage (F) F <sub>0</sub> : No significant fibrosis F <sub>1</sub> : 1a mild zone 3 PSF 1b moderate zone 3 PSF 1c portal fibrosis only F <sub>2</sub> : Zone 3 PSF with periportal fibrosis F <sub>3</sub> : Bridging fibrosis F <sub>4</sub> : Cirrhosis



Esteatosis hepática*						
	F0	F1	F2	F3	F4	P value
Pacientes	75,6%	86,9%	92,6%	92,5%	86,2%	<0.0001
Balonización hepática*						
	F0	F1	F2	F3	F4	P value
Pacientes	43,7%	70,7%	78,9%	76,5%	63,5%	<0.0001
Inflamación lobulillar*						
	F0	F1	F2	F3	F4	P value
Pacientes	50,7%	77,6%	87,5%	85,3%	76,7%	<0.0001
NAS score*						
Media ± DT	F0	F1	F2	F3	F4	P value
	2.4±1.7	3.5±1.7	4.2±1.7	3.9±1.5	3.4±1.7	<0.0001
NASH (NAS score ≥4)*						
	F0	F1	F2	F3	F4	P value
Pacientes	25,8%	49,1%	64,4%	63,2%	45,9%	<0.0001
NASH (SAF score)*						
	F0	F1	F2	F3	F4	P value
Pacientes	31%	56,5%	69,1%	65,5%	52,8%	<0.0001



## Hepatic Steatosis Index (HSI)

Fórmula:  $8 * (\text{ALT/AST}) \text{ ratio} + \text{BMI} + 2 \text{ (if DM)} + 2 \text{ (if female)}$

Interpretación: HSI<30: No NAFLD; HSI>36 NAFLD

HEPATIC STEATOSIS INDEX		
AST		U/L
ALT		U/L
SEXO FEMENINO		SI/NO
DIABETES TIPO 2		SI/NO
PESO		kg
TALLA		m
IMC (kg/m <sup>2</sup> )		Kg/m <sup>2</sup>
HSI		

FATTY LIVER INDEX		
Triglicéridos		mg/dl
GGT		U/L
Perímetro abdominal		cm
PESO		kg
TALLA		m
IMC (kg/m <sup>2</sup> )		Kg/m <sup>2</sup>
FLI		

## Fatty Liver Index (FLI)

Fórmula:

$100 / (1 + \text{EXP}((1) * (0.953 * \text{Ln}(\text{Tg})) + (0.139 * \text{BMI}) + (0.718 * \text{Ln}(\text{GGT})) + (0.053 * (\text{WC})) - 15.475))$

Interpretación: FLI<30: No NAFLD; FLI>60 NAFLD

## Ultrasonography

Sensitivity 60-70%, Specificity 90-95%

Do not detect mild fat infiltration < 30%!!!!

## Controlled Attenuation Parameter (CAP)

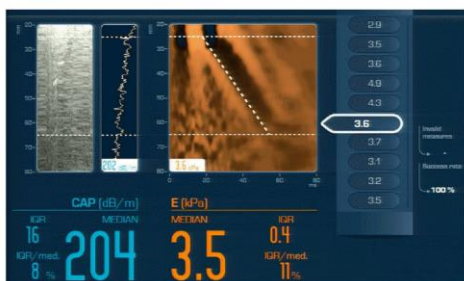
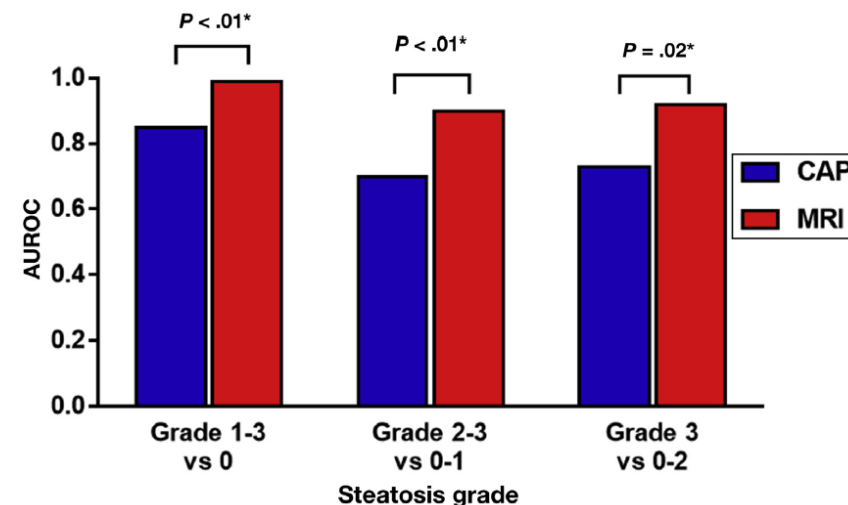
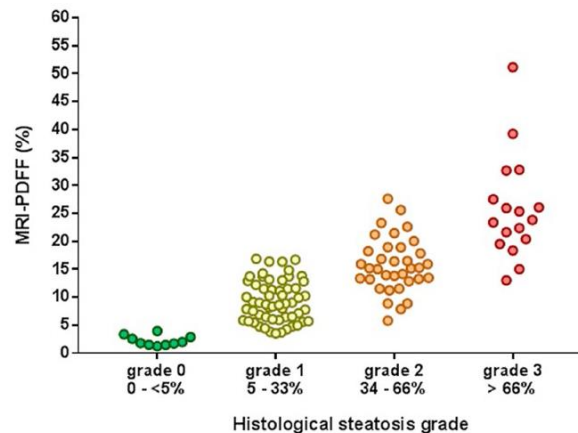
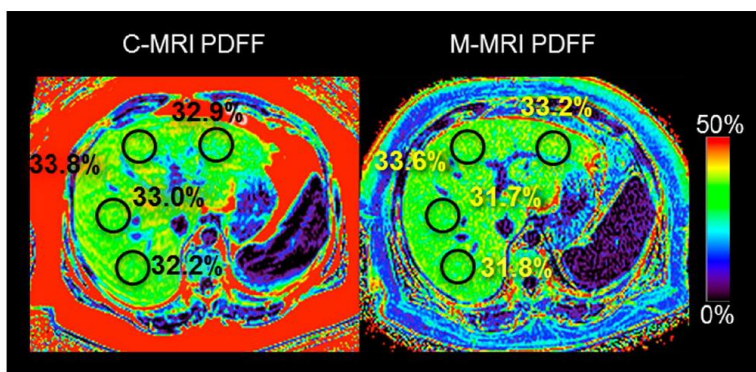


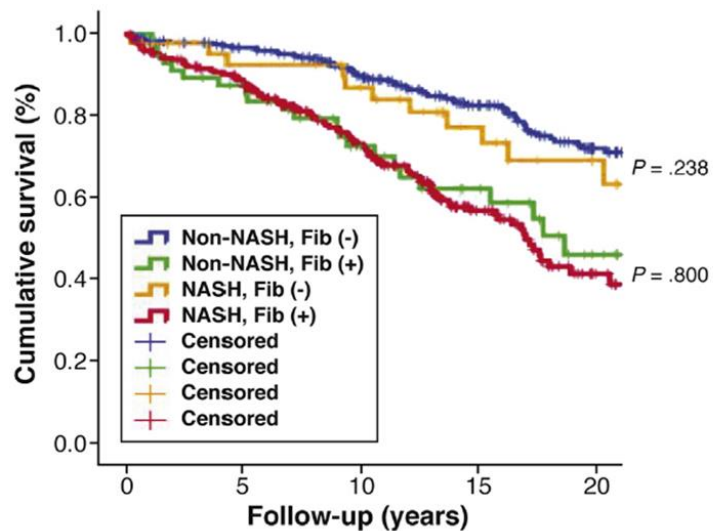
Table 1. Comparison between commonly used modalities for liver fat quantification.

Modality	Cost	Accuracy	Point of care	Quantitative
CUS	+	++	Yes	No
CAP	+	++	Yes	Yes, but not linear in higher liver fat content
CT	++	++	No	Semi-quantitative
MRI-PDFF	++	+++	No	Yes

	S0 vs. S1-S3	S0-S1 vs. S2-S3	S0-S2 vs. S3*
AUC	0.823 (0.809-0.837)	0.865 (0.850-0.880)	0.882 (0.858-0.906)
Sensitivity	0.688 (0.600-0.750)	0.773 (0.690-0.838)	0.882 (0.765-0.956)
False negative rate (1-sensitivity)	0.312 (0.250-0.400)	0.227 (0.162-0.310)	0.118 (0.044-0.235)
Specificity	0.822 (0.761-0.897)	0.812 (0.749-0.879)	0.776 (0.720-0.821)
False positive rate (1-specificity)	0.178 (0.103-0.239)	0.188 (0.121-0.251)	0.224 (0.179-0.280)
Optimal cut-off, dB/m	248 (237-261)	268 (257-284)	280 (268-294)

## Proton Density Fat Fraction (MRI-PDFF)

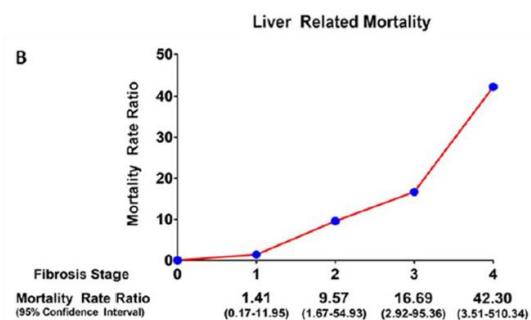
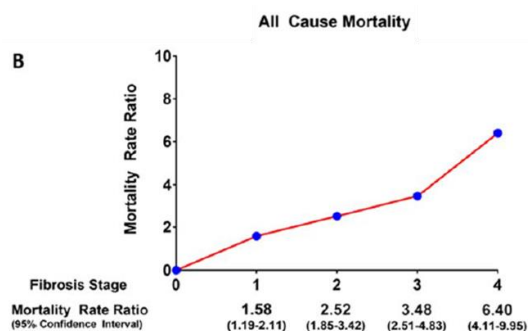




279	241	197	137	72	<b>Non-NASH, Fib (-)</b>
56	46	30	19	7	<b>Non-NASH, Fib (+)</b>
43	35	31	20	12	<b>NASH, Fib (-)</b>
241	197	124	58	18	<b>NASH, Fib (+)</b>

	Hepamet Score	NAFLD Fibrosis Score	FIB-4
Edad	✓	✓	✓
Sexo	✓		
IMC		✓	
AST	✓	✓	✓
ALT		✓	✓
Plaquetas	✓	✓	✓
DM	✓	✓	
HOMA	✓		
Albúmina	✓	✓	

NIT	Factors	Lower Threshold to Rule Out Advanced Fibrosis	Upper Threshold to Rule in Advanced Fibrosis
FIB-4	$FIB-4 = \text{age (years)} \times \text{AST [U/L]} / (\text{platelets [10}^9\text{/L]} \times \text{ALT [U/L]}^{1/2})$	1.3	2.67
NFS	$NFS = -1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2) + 1.13 \times \text{impaired fasting glucose/diabetes (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet (} \times 10^9\text{/L)} - 0.66 \times \text{albumin (g/dL)}$	-1.455	0.676



Variable	NFS (n = 2,417)		FIB-4 (n = 3,123)	
Prevalence of F3-F4	80%		71%	
AUROC (95% CI)	0.74 (0.74, 0.74)		0.78 (0.78, 0.78)	
Thresholds	<-1.455	≥0.676	<1.3	≥2.67
Sensitivity*	89 (88, 91)	38 (36, 40)	82 (81, 84)	36 (34, 38)
Specificity*	37 (33, 42)	89 (86, 92)	57 (54, 60)	93 (91, 94)
PPV*	85 (84, 87)	93 (91, 95)	83 (81, 84)	93 (91, 94)
NPV*	46 (41, 51)	26 (24, 29)	56 (53, 60)	37 (35, 39)
Misclassified*	21 (20, 23)	52 (50, 54)	25 (23, 26)	47 (46, 49)

**Table 3.** Discrimination Ability of the Hepamet Fibrosis Score Compared With NAFLD Fibrosis Score and FIB-4 in the Estimation and Validation Cohorts

	Hepamet Fibrosis Score	NAFLD Fibrosis Score	FIB-4
<b>Estimation cohort (n = 758)</b>			
Advanced fibrosis (F0–F2 vs F3–F4)	0.850 (0.807–0.893)	0.775 (0.723–0.828); .0025	0.772 (0.713–0.832); .0002
<b>Validation cohort (n = 1694)</b>			
Advanced fibrosis (F0–F2 vs F3–F4)	0.844 (0.819–0.869)	0.789 (0.764–0.814); <.0001	0.801 (0.776–0.826); <.0001
<b>Overall cohort (n = 2452)</b>			
Advanced fibrosis (F0–F2 vs F3–F4)	0.848 (0.826–0.869)	0.778 (0.756–0.801); <.0001	0.802 (0.780–0.825); <.0001

**HFS SCORE:**  
Introduzca todos los valores

Sexo ▼

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Edad

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Diabetes ▼

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Glucosa (mg/dL)

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Insulina (μU/mL)

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HOMA

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AST (U/L)

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Albumina (g/dL)

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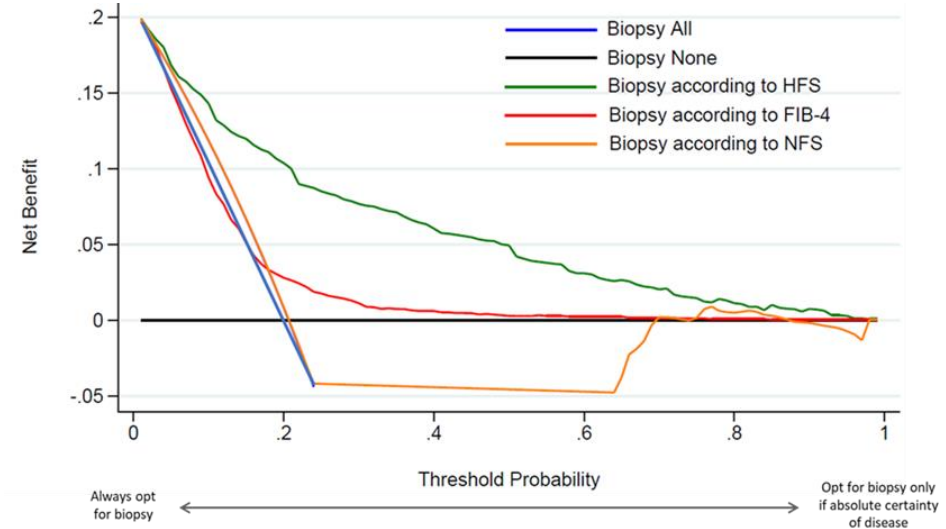
Plaquetas (x 10<sup>9</sup>)

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CALCULAR

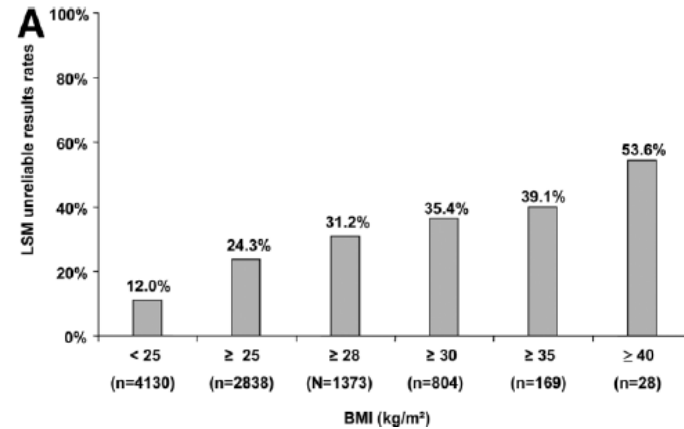
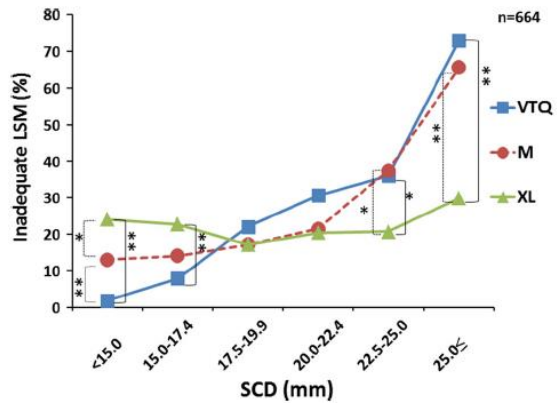
  

RESET



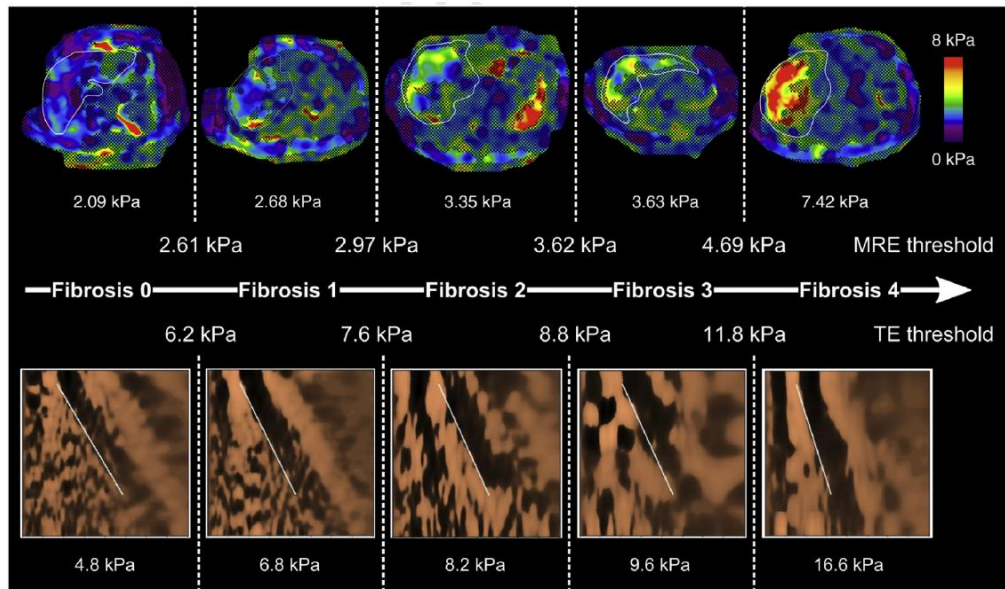
Hepamet Fibrosis Score	Fibrosis significativa (F2-F4)	Fibrosis avanzada (F3-F4)	Cirrosis (F4)
Riesgo bajo (<0.12)	23,6%	8,1%	0,9%
Riesgo intermedio (0.12-0.47)	57,1%	33,7%	7,4%
Riesgo alto (≥0.47)	86,4%	76,3%	35,5%

## Transient Elastography

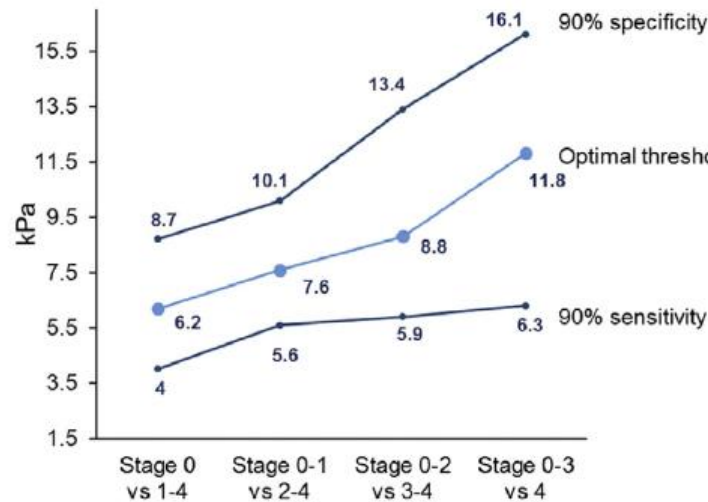


LSM (kPa) Fibrosis stage	XL+ Probe		M+ Probe		Mean
	n	BMI-Adjusted Mean	n	BMI-Adjusted Mean	
0	132	5.4	112	6.5	-1.0
1	136	6.4	106	7.2	-0.9
2	90	7.2	57	7.8	-0.5
3	137	11.3	70	13.7	-2.4
4	57	21.3	30	26.2	-4.8
Total	552	8.0	375	8.8	-0.8

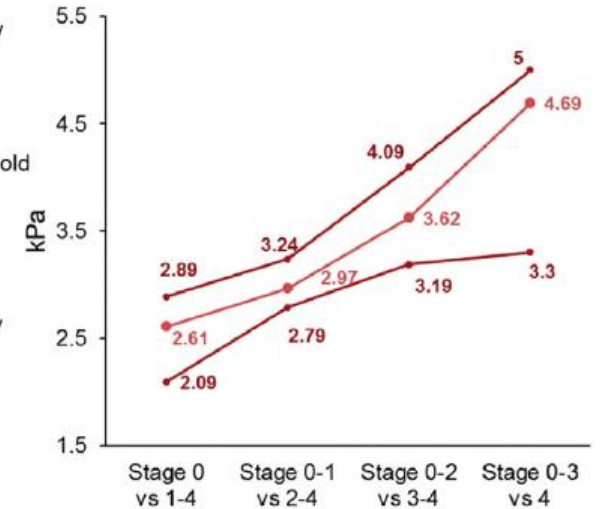
## MR Elastography

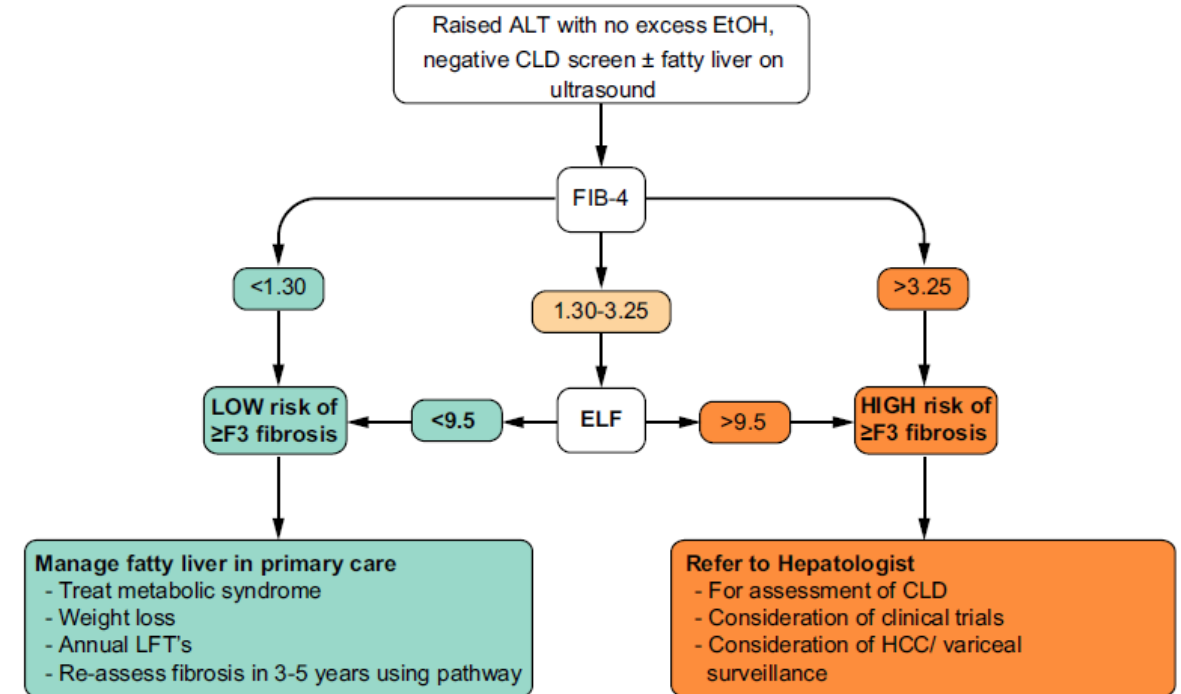
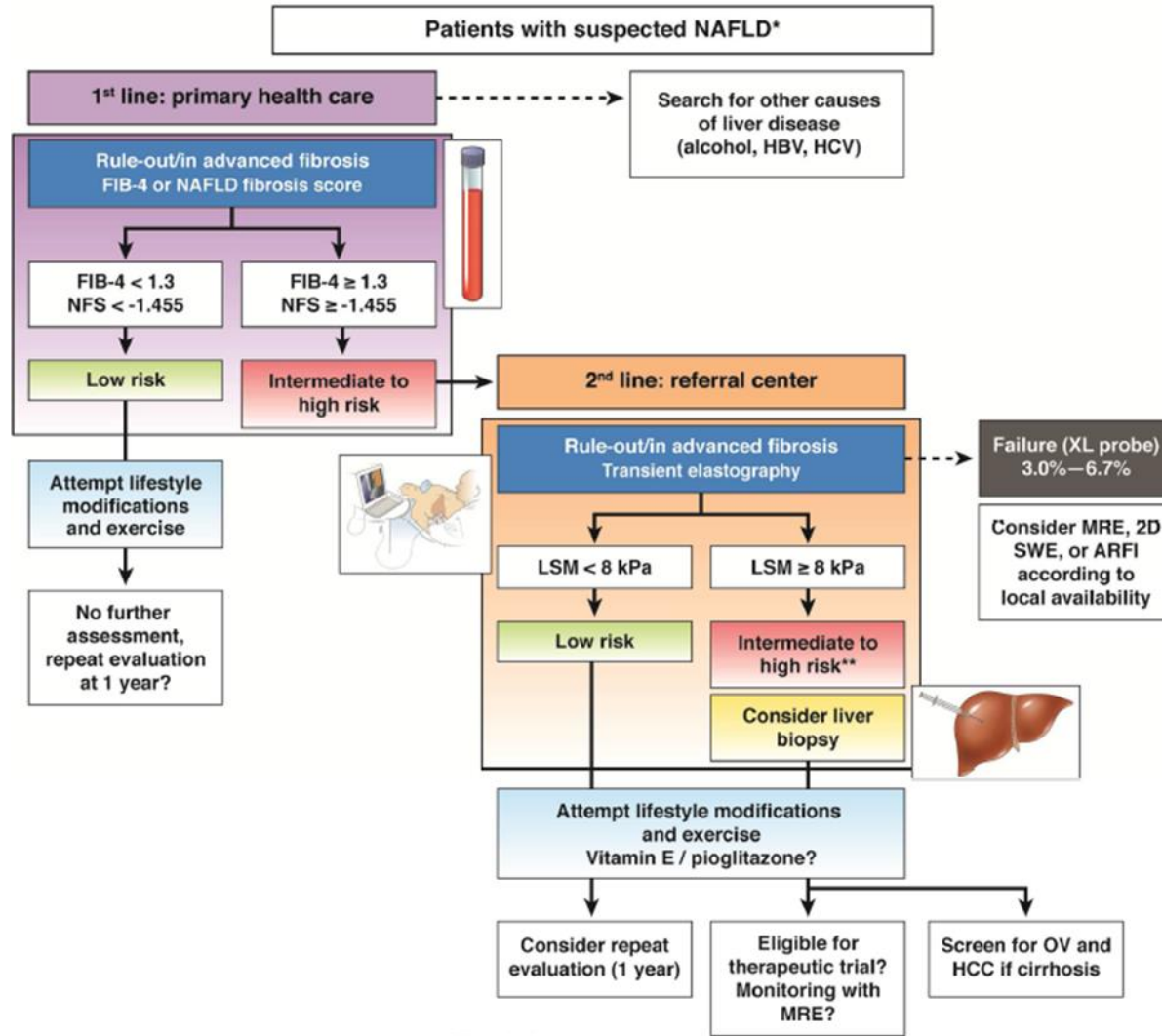


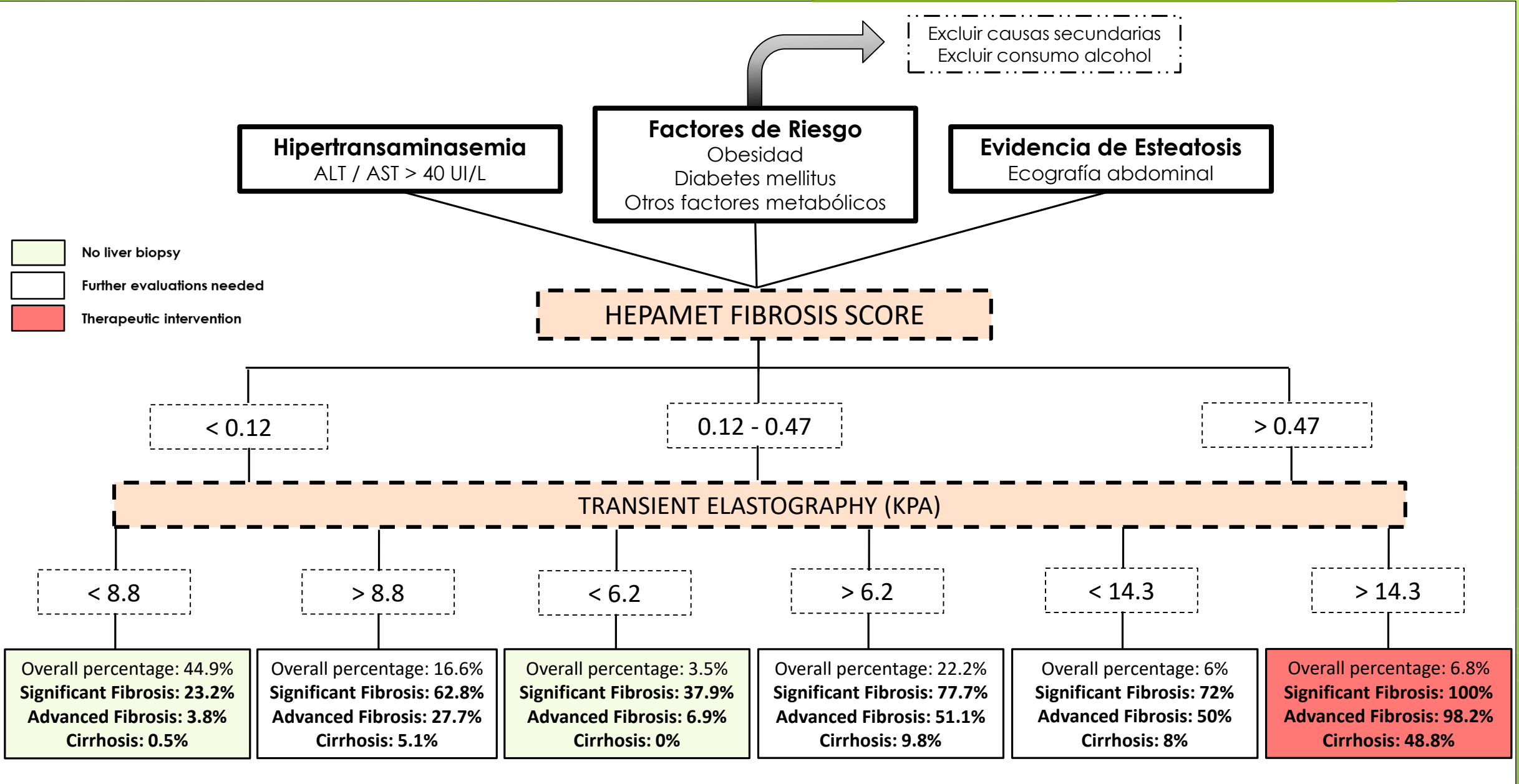
### A Transient elastography



### B MR elastography







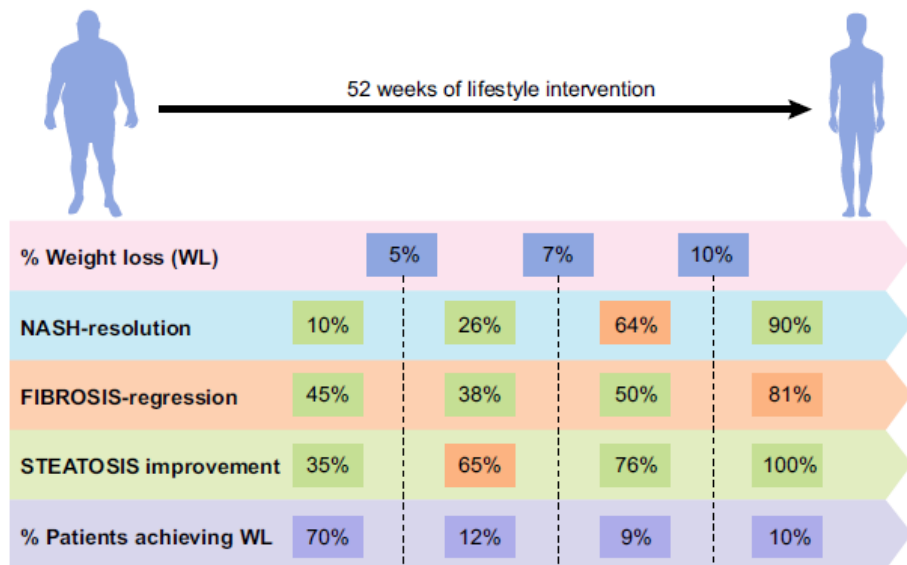
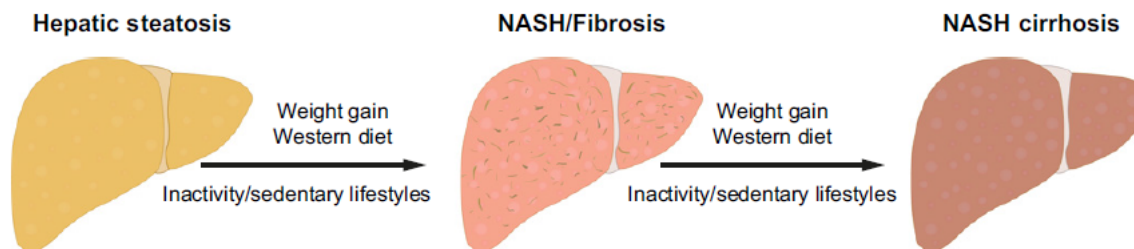
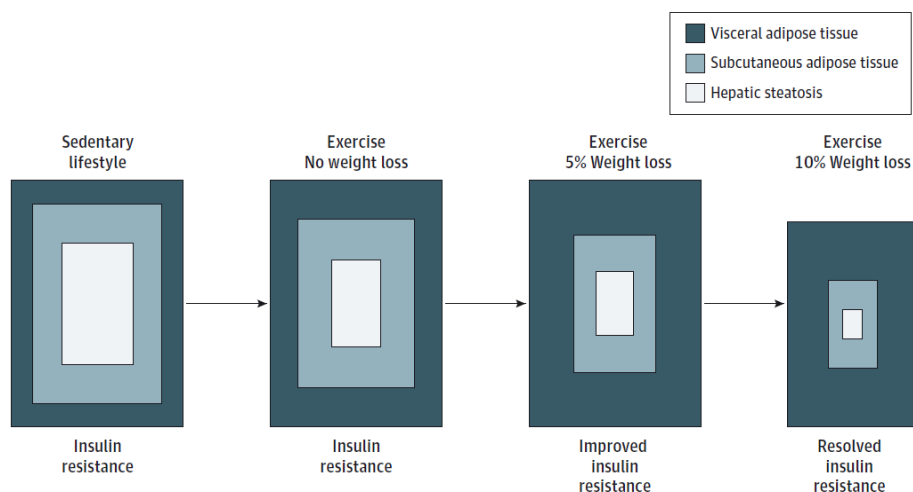


Figure. Benefits of Exercise and Weight Loss on Adipose Tissue Compartments and Insulin Resistance



	Weight loss	Dietary options	Physical activity exercise options
<b>Weight loss</b>	Weight loss $\geq 5\%$	Mediterranean diet Encourage a regular meal pattern Avoid snacking Reduce alcohol intake (if relevant)	Increase daily physical activity levels (aim for 10,000 steps/day if appropriate) Decrease total sedentary time and break up sedentary time Aerobic or resistance exercise (aiming for 150 min/week of moderate intensity exercise)
	Minimum 7-10% weight loss	Mediterranean diet Encourage a regular meal pattern Avoid snacking Reduce alcohol intake (if relevant) Reduction in fructose/glucose intake (especially sugar-containing drinks) and processed foods	
	Modest caloric restriction 500-800 kcal/day (overweight/obese patients) Increase weight loss targets in well-compensated obese patients	Protein intake 1.2-1.5 g/kg/day Small frequent meals Encourage abstinence from alcohol Reduction in fructose/glucose intake (especially sugar-containing drinks) and processed foods	



- La **esteatosis hepática** puede estar presente pero, en ocasiones, puede ser **difícil identificarla**.
- El **principal** determinante pronóstico en la **EHmet** es la **fibrosis hepática**.
- La medición de **enzimas hepáticas** no es un buen indicador de daño hepático, por lo que **no debería** ser usado para **guiar nuestras decisiones** en la **EHmet**.
- Los **métodos no invasivos**, basados en parámetros bioquímicos, deben ser utilizados como **primer paso** en la evaluación de la **EHmet**.
- En ausencia de fármacos disponibles (y cuando vengan), la **intervención** más relevante es **sobre el estilo de vida**.