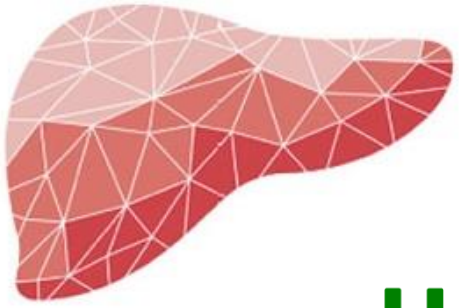
MÁSTER EN HEPATOLOGÍA



UAM
Universidad Autónoma de Madrid

Universidad de Alcalá

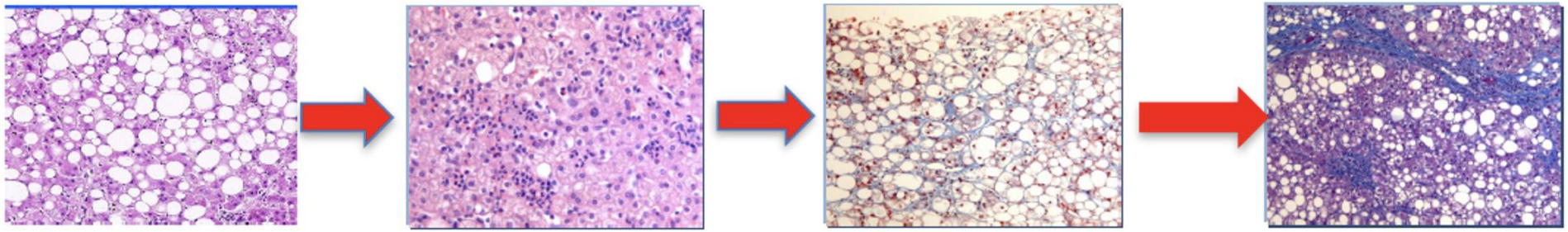
Esteatosis hepática metabólica / NAFLD / MAFLD. Estratificación.

Javier Crespo
Hospital Universitario Marqués de Valdecilla. Santander.
Universidad de Cantabria

Valdecilla Instituto de Investigación Sanitaria IDIVAL

Valdecilla Hospital Universitario Marqués de Valdecilla

Una enfermedad muy heterogénea



Depósito de ácidos grasos libres, triglicéridos y colesterol en el citoplasma del hepatocito, preferentemente en forma macrogotular, sin consumo de alcohol y no asociado a otras enfermedades hepáticas.

Different clinical and histological phenotypes; different disease drivers

Obesity | T2D | High CV risk | Psychotic disorder | Low GH | Psoriatic arthritis | Sarcopenia Frailty | PNPLA3 | Moderate Alcohol

Una enfermedad muy heterogénea

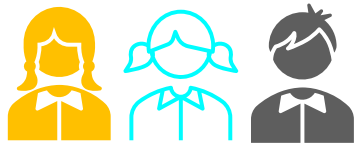
Social and economic factors impact on MAFLD outcomes

Sex

- **Overall: < 70 yo, males had a higher prevalence of cirrhosis**
- **In US: women higher prevalence of NASH-related cirrhosis**
- **NAFLD-related mortality according to sex differs across studies**

Socioeconomic status

- **Low socioeconomic status is associated to higher prevalence of advanced liver disease and HCC rates**
- **In geographic regions with an overall lower socioeconomic position, there is higher cirrhosis prevalence**

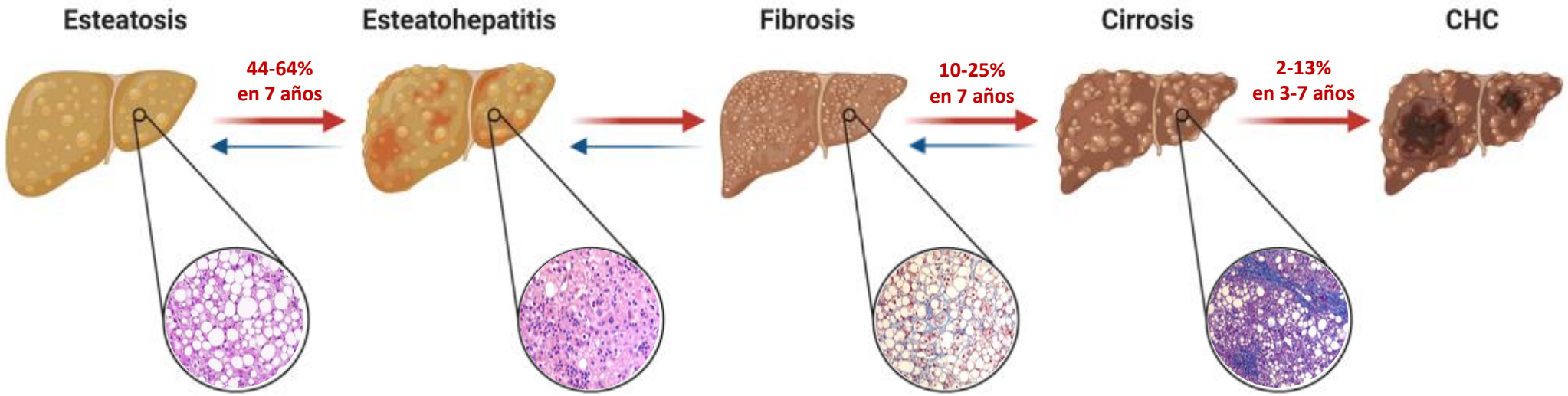


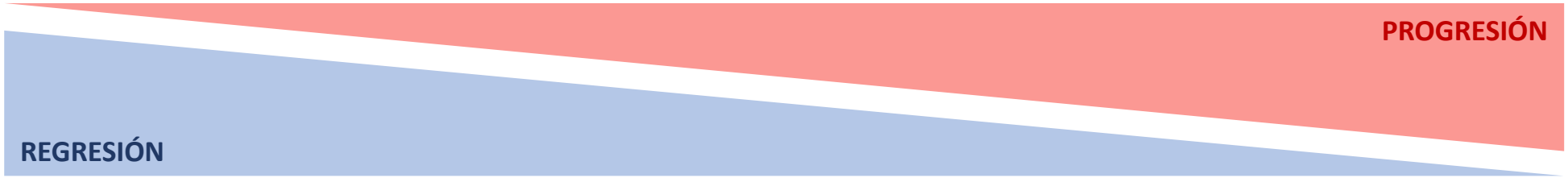
Ethnicity

- **Ethnic inequalities have been observed in NAFLD-related complications**
- **Despite highest NASH prevalence has been seen among Hispanic population, non-Hispanic White patients are more commonly transplanted for NASH compared to Hispanics in the US**

Talens et al. J. Clin. Med. 2021

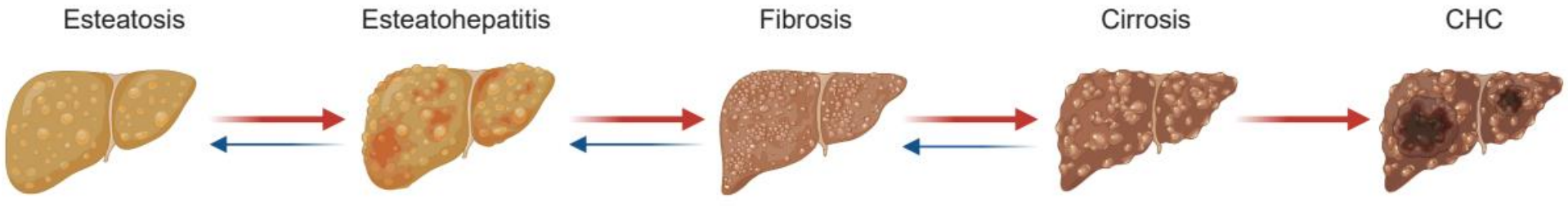
Una enfermedad muy heterogénea





Boon-Bee Goh et al. Dig Dis Sci 2016

Estratificar el riesgo de progresión



Comorbilidades metabólicas

- Diabetes mellitus
- Resistencia a la insulina
- Dislipemia
- Obesidad
- Hipertensión arterial

Factores genéticos

- PNPLA3
- TM6SF2
- GCKR
- MBOAT7
- **HSD17B13**

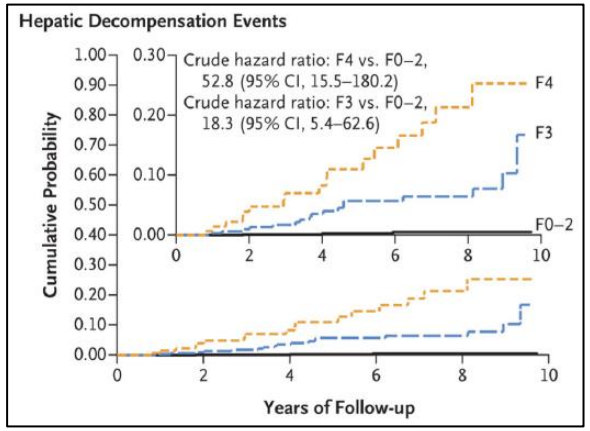
Factores medioambientales

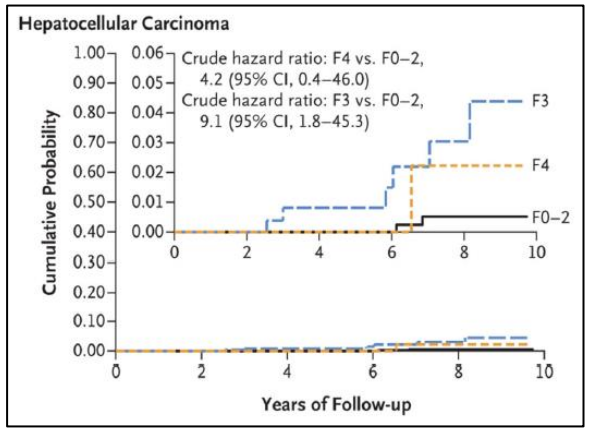
- Fructosa
- Colesterol
- Alcohol
- **Ejercicio**
- **Café**

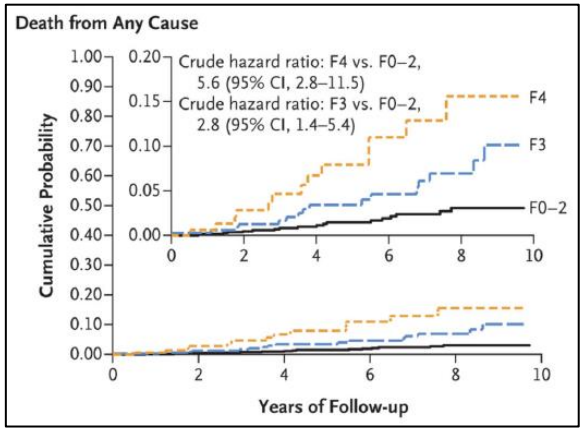
Factores asociados con progresión del NAFLD

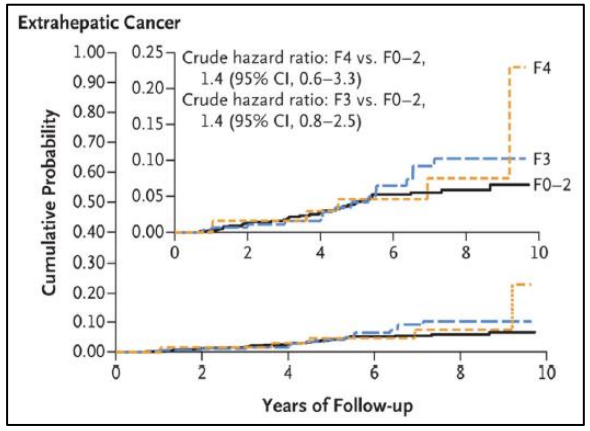
Powell EE et al. Lancet 2021

Estratificar el riesgo de progresión. FIBROSIS.









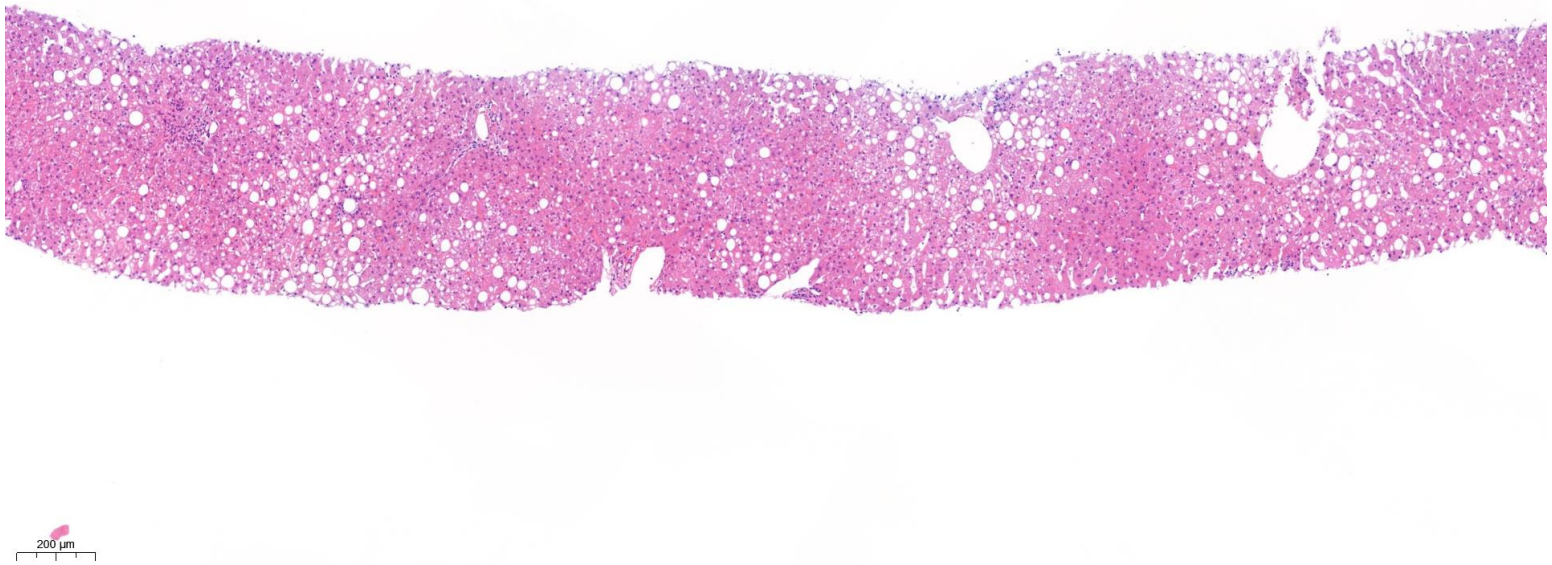
- Estudio prospectivo y multicéntrico de resultados clínicos en 1773 pacientes con NAFLD diagnosticados por biopsia hepática.
- La incidencia de complicaciones relacionadas con el hígado aumentó con el grado de fibrosis.
- La mortalidad por todas las causas aumentó con el aumento de los grados de fibrosis.
- La incidencia de cánceres no hepáticos fue similar en todos los grados de fibrosis.
- **Los grados de fibrosis F3 y F4 se asociaron con un mayor riesgo de complicaciones hepáticas y mortalidad por todas las causas.**

Sanyal AJ et al. N Engl J Med. 2021

Marcador diagnóstico ideal: Biopsia hepática

Courtesy of Dra María Luisa Cagigal

Marcador diagnóstico ideal: Biopsia hepática



Courtesy of Dra María Luisa Cagigal

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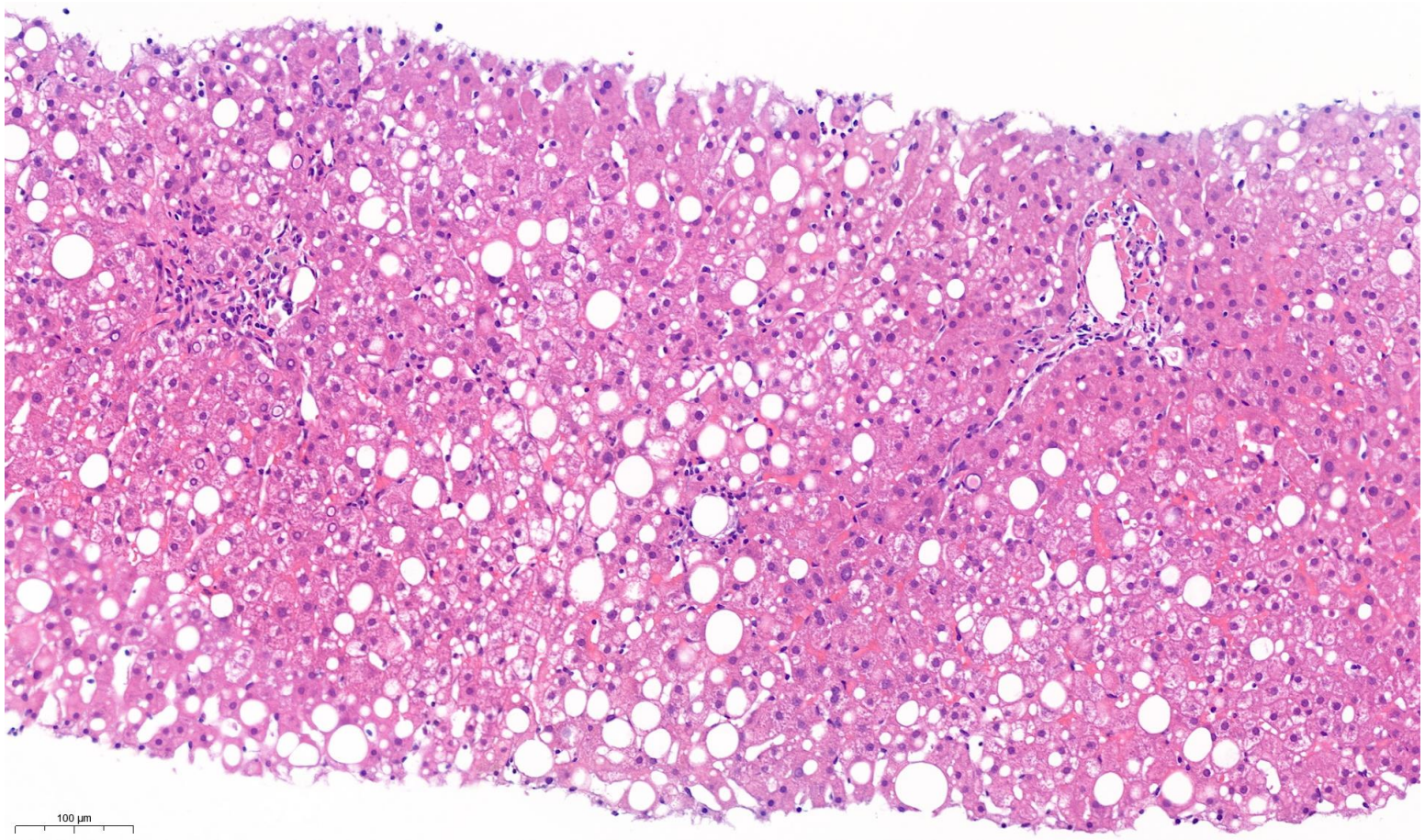

Courtesy of Dra María Luisa Cagigal

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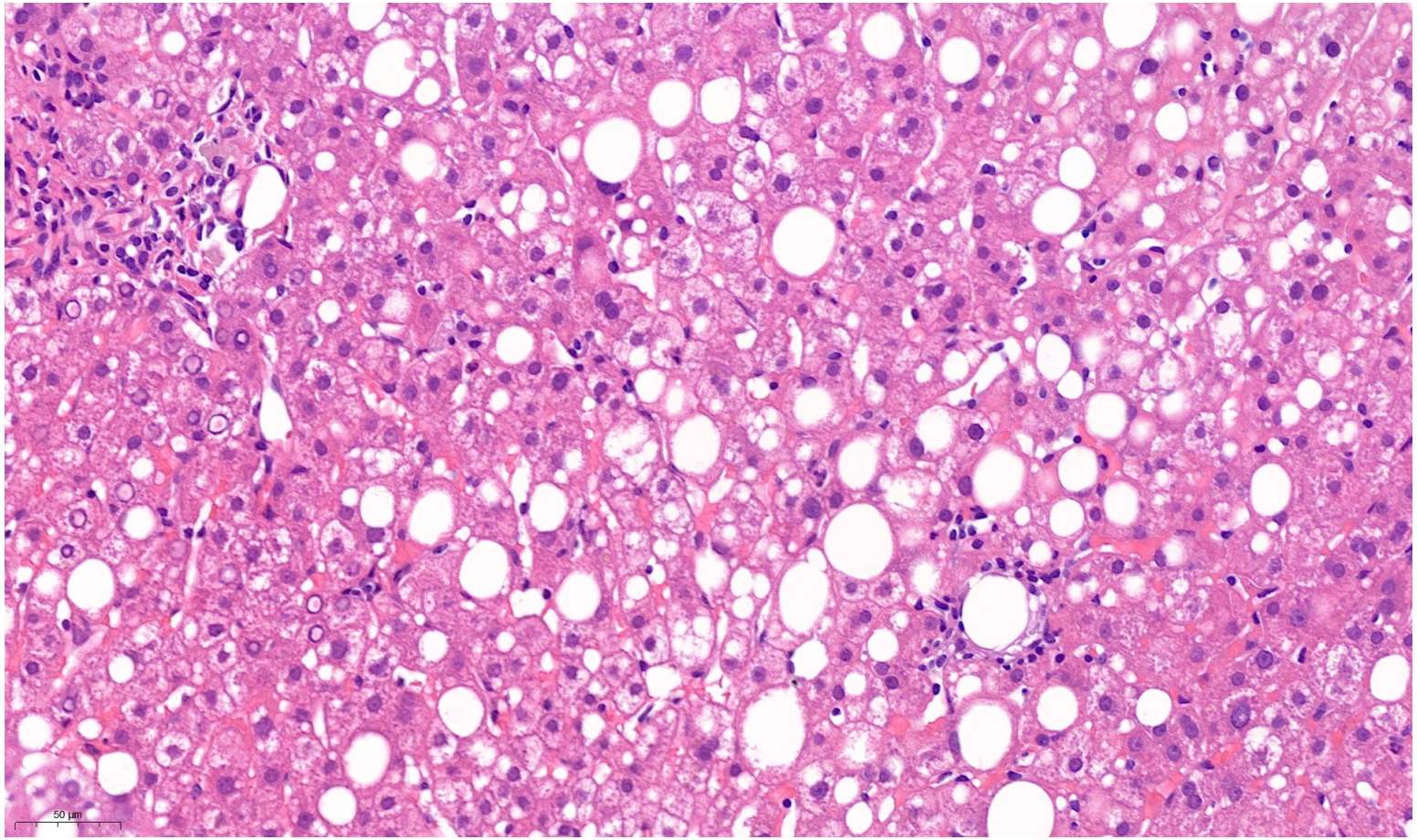
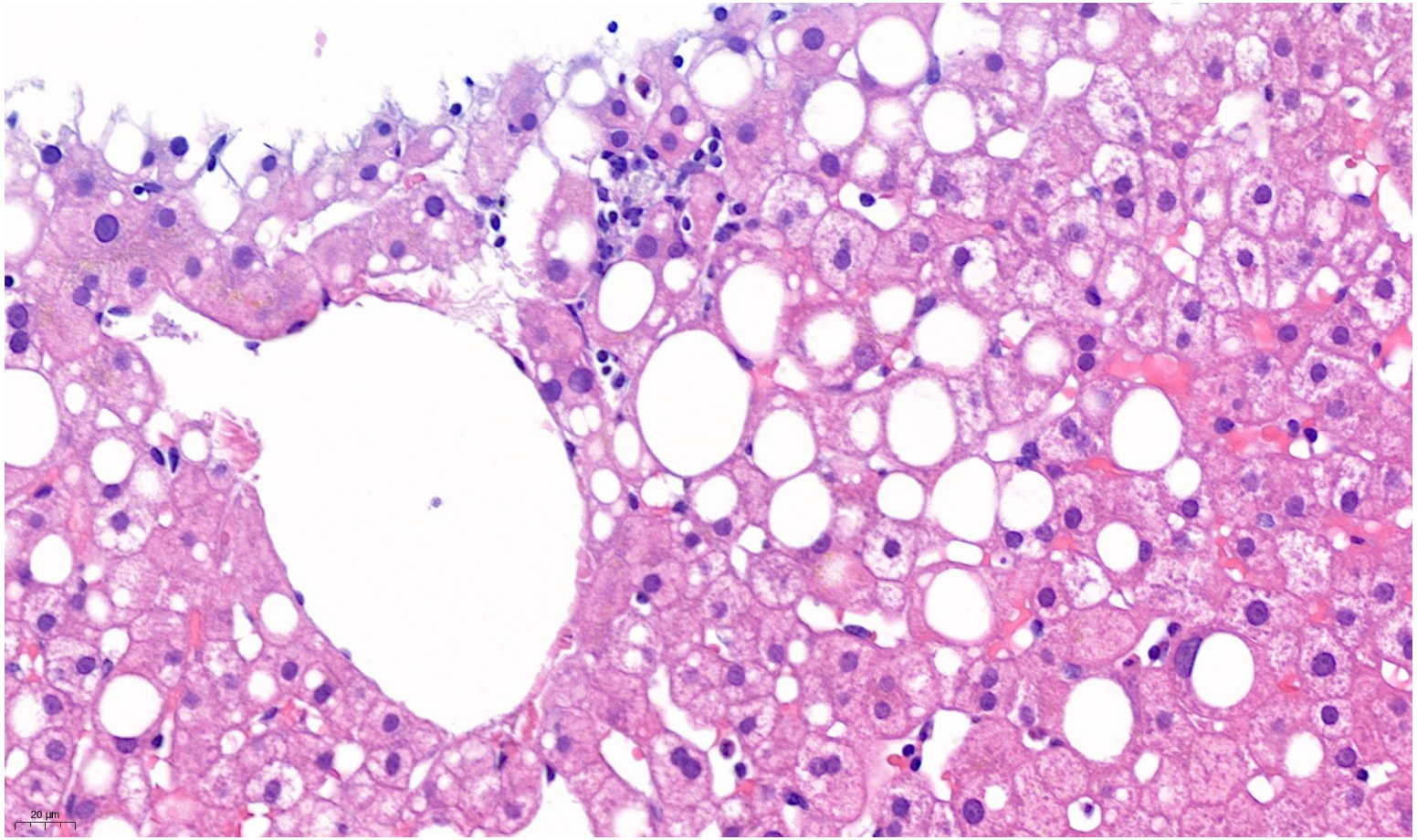


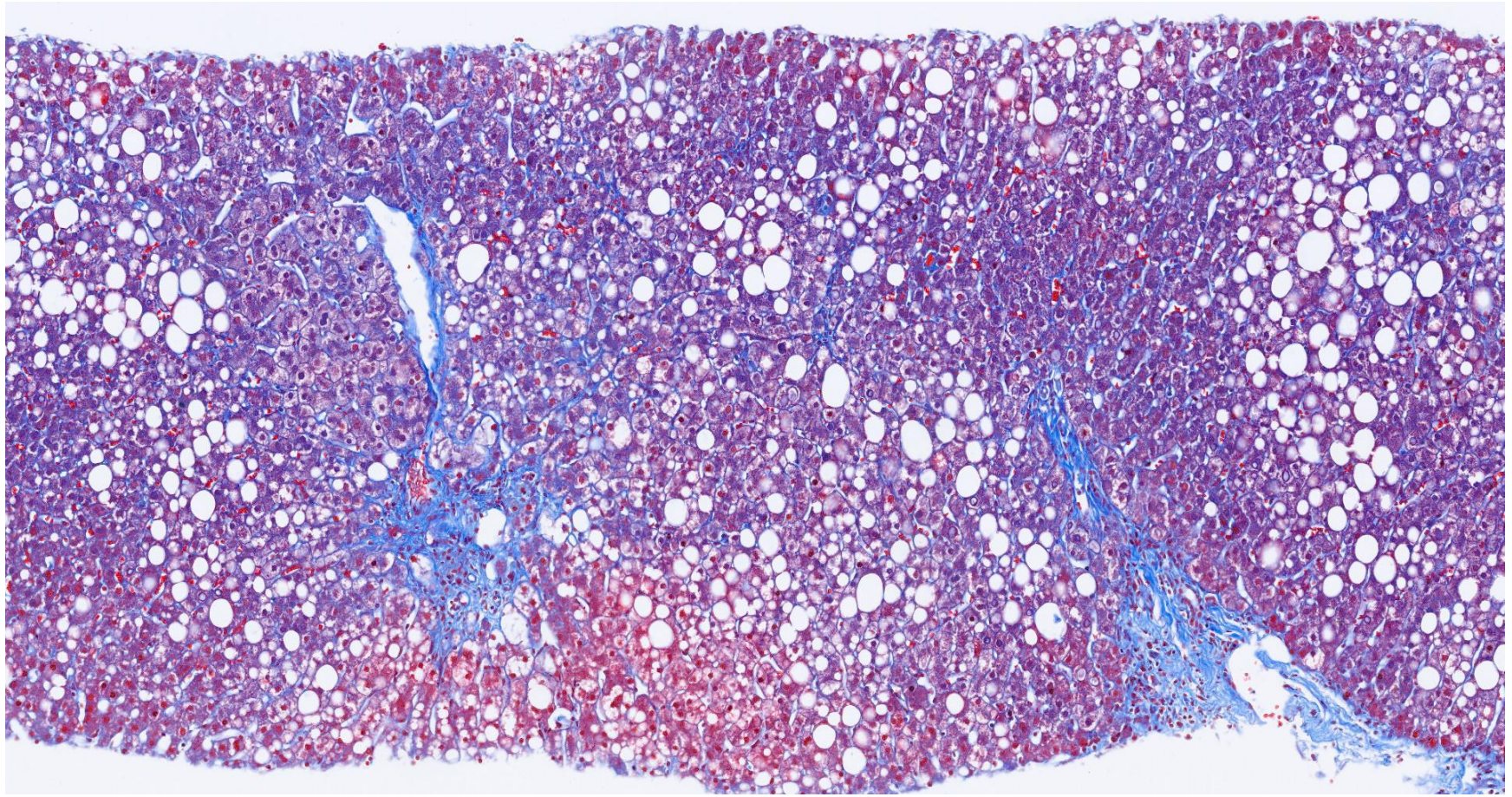
Courtesy of Dra María Luisa Cagigal

Marcador diagnóstico ideal: Biopsia hepática



Courtesy of Dra María Luisa Cagigal

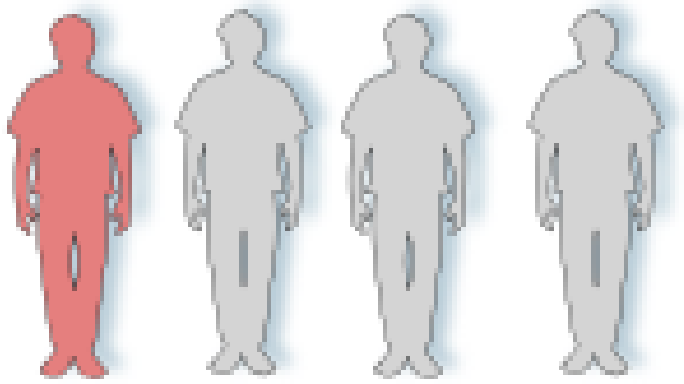
Marcador diagnóstico ideal: Biopsia hepática



Courtesy of Dra María Luisa Cagigal

Marcador diagnóstico ideal: Biopsia hepática…pero es totalmente inviable.

- NAFLD is estimated to affect 25% of adults globally:
  - The Middle East and South America have the highest prevalence at 32 and 30%, respectively.
  - Africa has the lowest prevalence at 13%.



- NAFLD progresses to NASH in about 20% of cases.

- A modeling study of China, France, Germany, Italy, Japan, Spain, the United Kingdom and the United States forecasted the prevalence of NAFLD and NASH to increase by up to 30 and 56%, respectively, from 2016 to 2030.

Younossi ZM, et al. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016;64(1):73-84. Estes, C, et al. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology* 2018;67(1):123-33. Estes C, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. *Journal of Hepatology* 2018;69(4):896-904.

Limitations of liver biopsy as gold standard: progression over the time

Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis…
N=108 mean follow-up 6.6 years

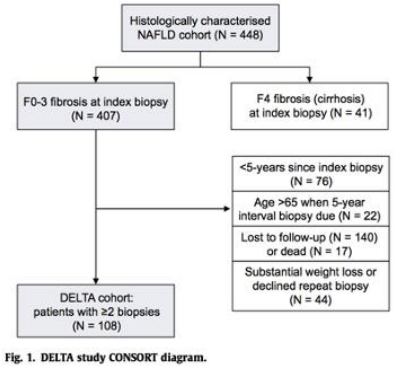
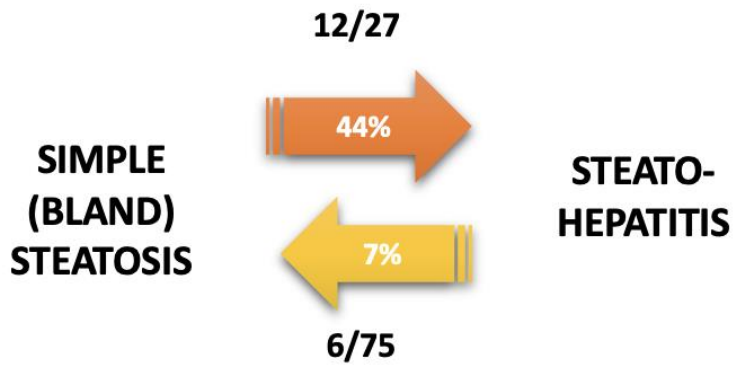
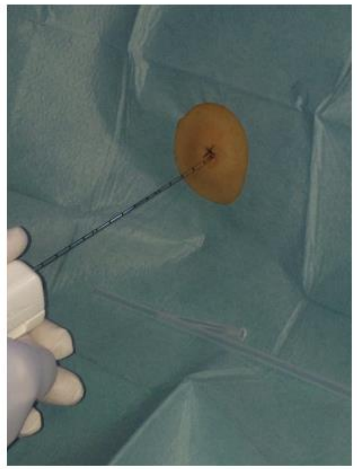


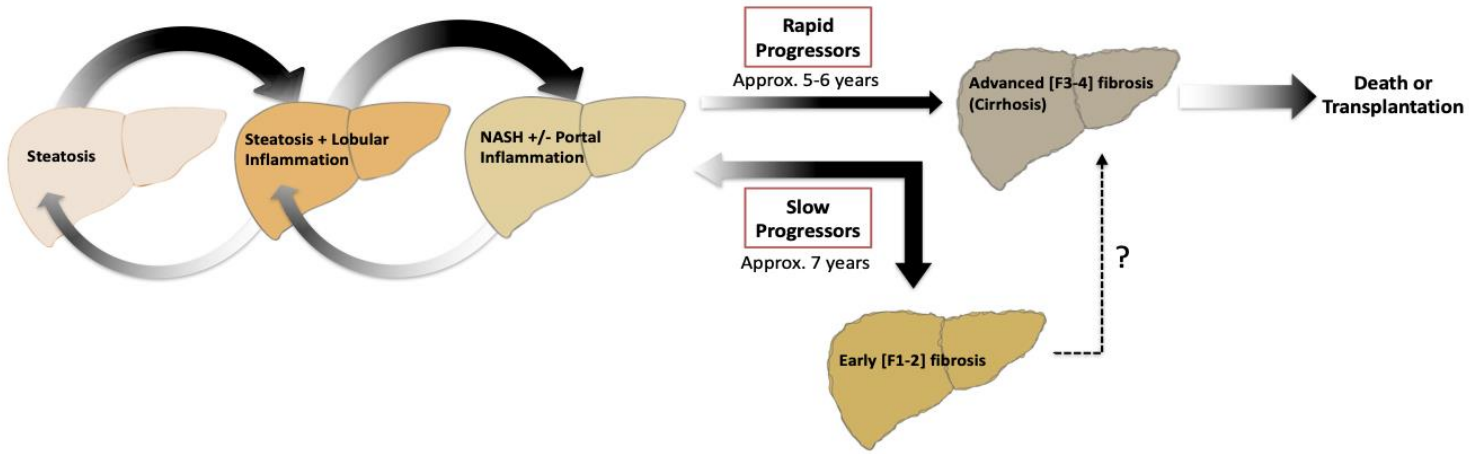
Fig. 1. DELTA study CONSORT diagram.





McPherson S et al. J Hepatol 2015

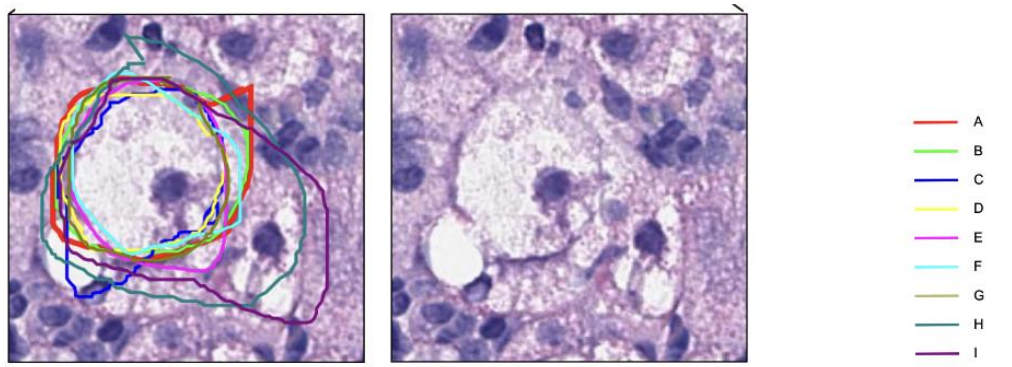
Dynamic changes: steatosis, steatohepatitis & fibrosis

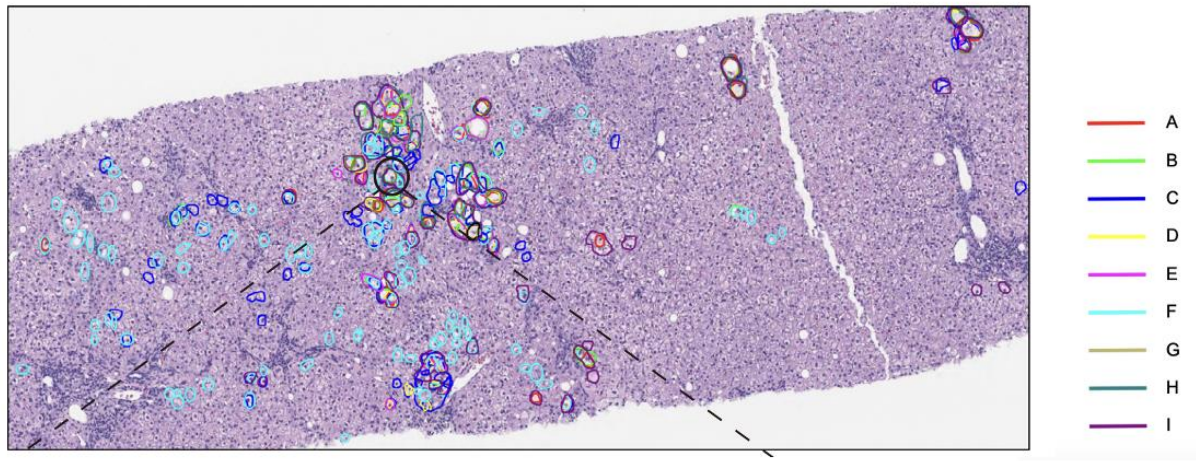


Histological diagnosis of steatohepatitis: Ballooning & inflammation

Pathologist	Minority call	Digital image # 1	2	3	4	5	6	7	8	9	10
A	1/10	NASH	NASH	NASH	NASH	NASH	NASH	NASH	Not NASH	NASH	NASH
B	3/10	Not NASH	NASH	NASH	NASH	NASH	NASH	NASH	NASH	NASH	NASH
C	2/10	NASH	NASH	NASH	NASH	NASH	Not NASH	NASH	Not NASH	Not NASH	Not NASH
D	2/10	Not NASH	NASH	NASH	NASH	NASH	Not NASH	NASH	Not NASH	Not NASH	NASH
E	1/10	NASH	Not NASH	NASH	NASH	NASH	NASH	NASH	Not NASH	Not NASH	NASH
F	1/10	NASH	NASH	NASH	NASH	NASH	NASH	NASH	NASH	Not NASH	NASH
G	2/10	NASH	NASH	NASH	NASH	NASH	Not NASH	Not NASH	Not NASH	Not NASH	NASH
H	7/10	Not NASH	Not NASH	Not NASH	Not NASH	NASH	Not NASH	Not NASH	Not NASH	Not NASH	Not NASH
I	2/10	NASH	NASH	NASH	NASH	NASH	NASH	NASH	NASH	NASH	NASH
Concordance		6/9	7/9	8/9	7/9	9/9	5/9	7/9	6/9	6/9	7/9
		NASH	NASH	NASH	NASH	NASH	NASH	NASH	Not NASH	Not NASH	NASH

Fig. 5. Comparison of 'non-NASH NAFL' *vs.* 'NASH' diagnostic call by pathologist and image. Table cells are coloured blue through to red as a heat map indicating the relative number of ballooned hepatocytes identified by each pathologist (dark blue denotes cases for which a given pathologist has indicated that no ballooned hepatocytes were present at Phase 1. Colour changes through light blue to white and then red as the number of ballooned cells identified increases, with darker red indicating that many ballooned cells were seen). The non-NASH NAFL *vs.* NASH diagnosis at Phase 2 made independently by each pathologist is shown, along with the degree of concordance for this decision (as a fraction out of 9 pathologists) and the majority decision for each digital image. Where NASH is shown in red text, this denotes a NASH diagnosis call by a pathologist at Phase 2 despite previously reporting that no ballooned hepatocytes were present in the digital image during Phase 1. NAFL, non-alcoholic fatty liver; NASH, non-alcoholic steatohepatitis.





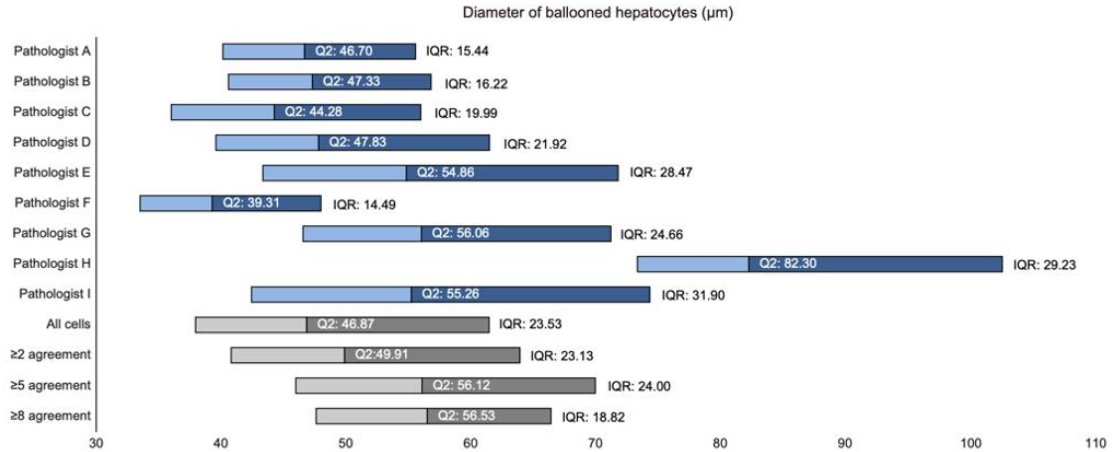


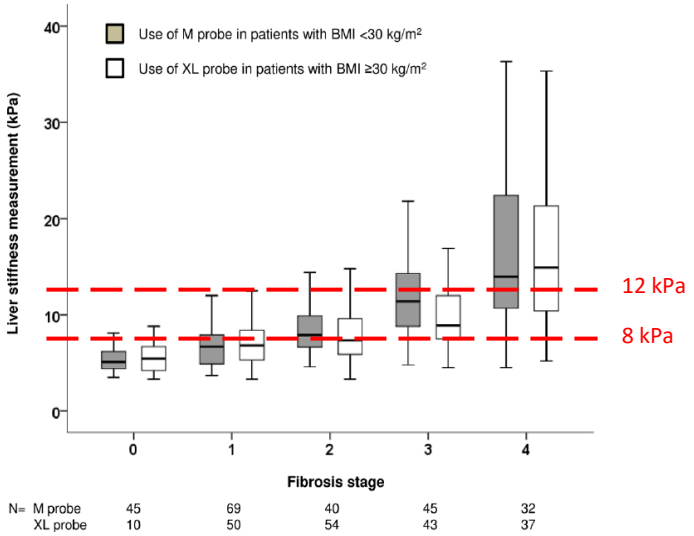
Fig. 4. Ballooned hepatocyte diameter by pathologist. Chart based on the lower quartile, median and upper quartile of the 9 pathologists and their agreements after removing large clusters. The median and IQR of all ballooned hepatocytes identified by each pathologist.

Brunt et al. J Hepatol 2022;76:1030-1041

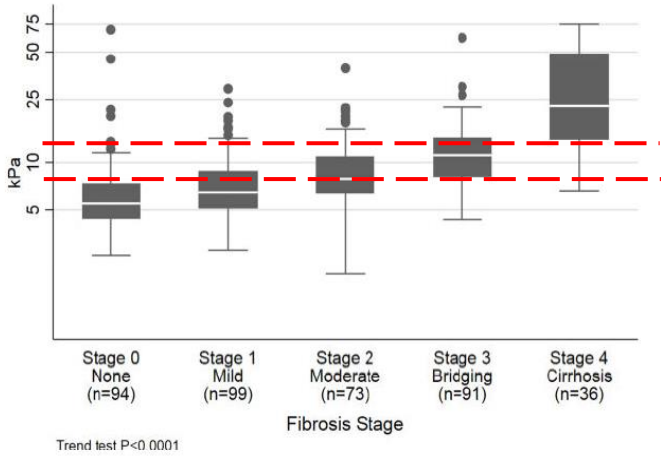
Métodos de evaluación del grado de fibrosis

Elastografía de transición (ET)

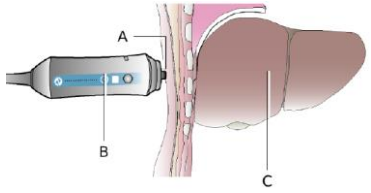
- Cuantificación de la rigidez hepática. Medida en una región de 10 x 40 mm de longitud.
- **Limitaciones:** Obesidad, espacio intercostal estrecho, ascitis
- **Resultado influido por**: Congestión venosa por fallo cardíaco, hipertensión biliar secundaria a colestasis extrahepática, hepatitis aguda, hepatitis crónica con elevada inflamación o necrosis, esteatosis hepática.



Wong V et al. Gut 2019



Siddiqui MS et al. Clin Gastroenterol Hepatol. 2019



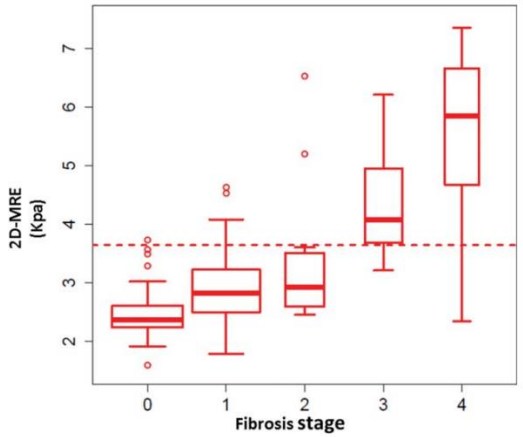
Tapper EB et al. Nat Rev Gastroenterol Hepatol 2018
Carrión JA. Gastroenterol Hepatol 2009

- **ET < 8 kPa:** Descarta fibrosis avanzada
- **ET > 12 kPa:** Indica cirrosis

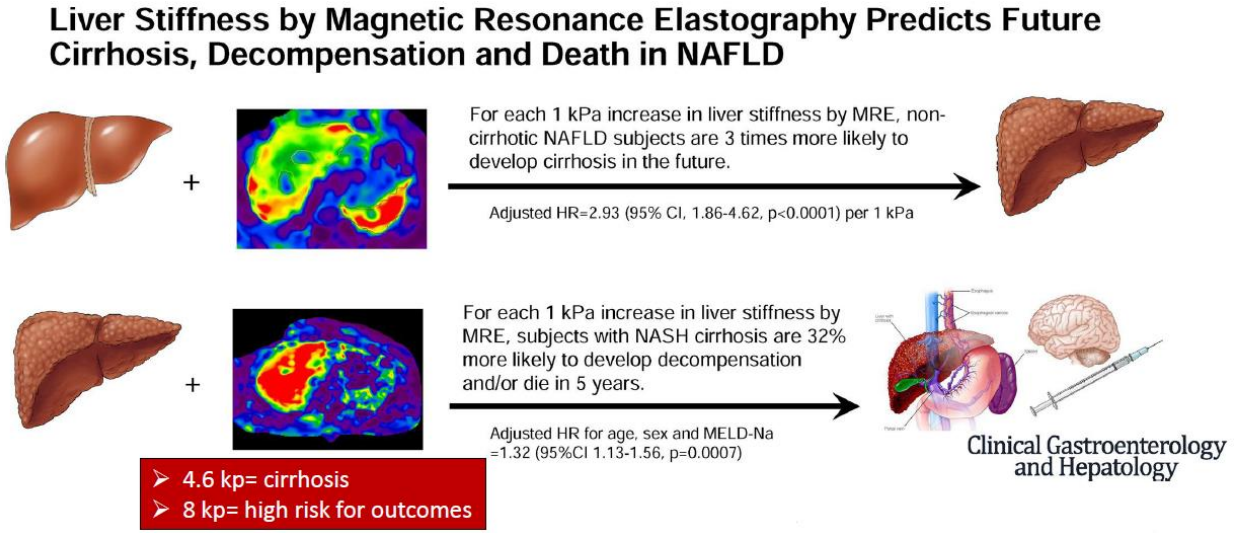
Métodos de evaluación del grado de fibrosis

Elastografía por Resonancia Magnética (MRE)

- Valora el parénquima hepático en su totalidad.
- **Operador independiente**, altamente reproducible, no afectado por obesidad, esteatosis o ascitis.
- **Depende de factores de paciente**: Incapacidad de retener la respiración, sobrecarga hepática de hierro (crea "ruido" en la señal).
- AUROC de 0,90 para todos los grados de fibrosis.
- Alto coste y prolongado tiempo de adquisición.



Loomba R et al. Hepatology 2014



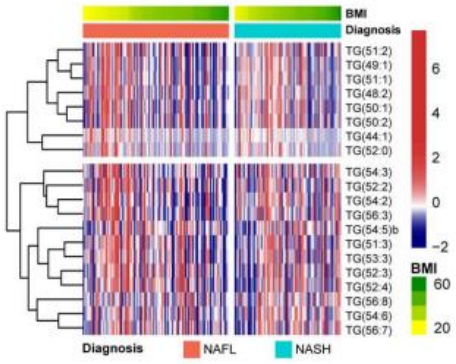
- Estudio retrospectivo con pacientes NAFLD con MRE entre 2007 y 2019.
- N = 829 pacientes, 639 sin cirrosis.
- Seguimiento desde la fecha de la primera MRE hasta la muerte, el último encuentro clínico o el final del estudio (mayo de 2019).
- **En pacientes sin cirrosis, MRE es un predictor independiente del desarrollo de cirrosis. En pacientes con cirrosis, MRE es un predictor independiente de descompensación y muerte**

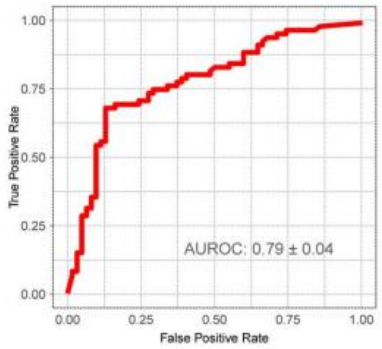
Gidener T et al. Clin Gastroenterol Hepatol 2021

Métodos de evaluación del grado de fibrosis

Metabolómica

Firma metabolómica en suero para el diagnóstico de NASH





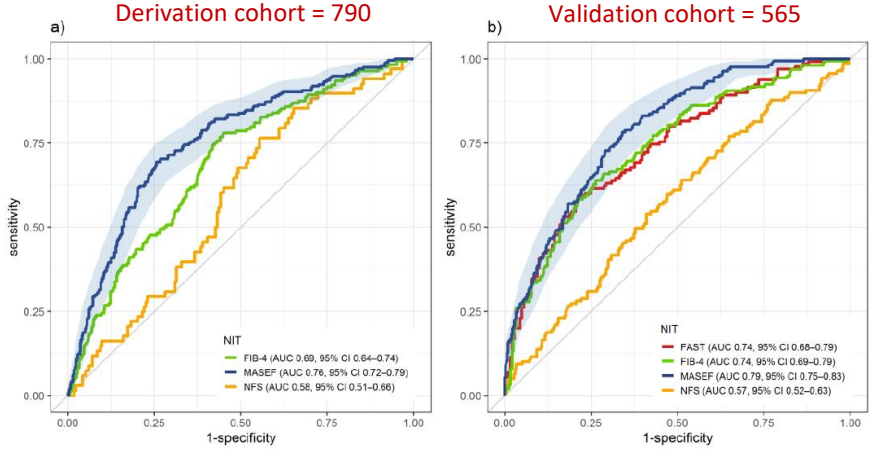
El test lipidómico evaluado distingue esteatosis simple de NASH con alta precisión.

Mayo R et al. Hepatol Commun 2018

Rendimiento diagnóstico de **Metabolomics-Advanced Steatohepatitis Fibrosis Score (MASEF)** en la identificación de pacientes NASH de riesgo (NAS ≥ 4 + ≥ F2)

Derivation cohort = 790

Validation cohort = 565



Score	Sample	AUC (95% CI)	Cutoff	Sensitivity	Specificity	PPV	NPV
MASEF	Derivation	0.756	0.33	69.4%	74.4%	53.4%	85.2%
	Validation	0.789	0.33	78.2%	65.2%	48.1%	87.9%
FIB-4	Derivation	0.687	1.107	78.0%	55.1%	86.5%	40.3%
	Validation	0.740	1.107	81.0%	50.3%	85.9%	41.4%
NFS	Derivation	0.584	-1.033	75.0%	44.6%	84.8%	30.2%
	Validation	0.574	-1.033	74.8%	36.5%	77.7%	32.9%
FAST	Validation	0.736	0.637	58.5%	79.0%	66.7%	72.6%

Noureddin M et al. Hepatology (accepted)

Métodos de evaluación del grado de fibrosis

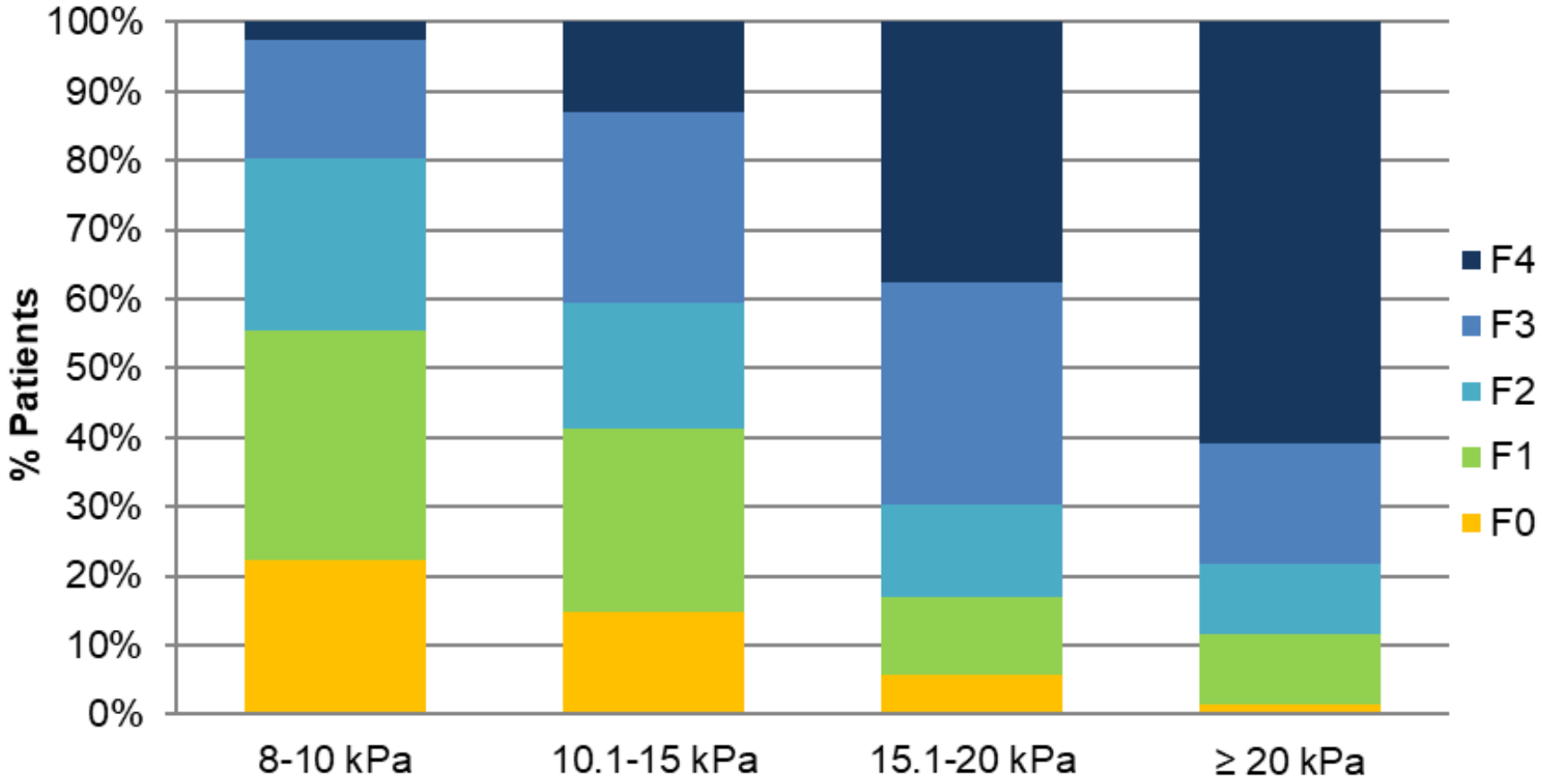
Métodos indirectos

Model	Components and regression equation	Cut-offs for advanced fibrosis	Clinical benefits and limitations	
NAFLD fibrosis score	−1.675 + 0.037 × **Age** (yrs) + 0.094 × **BMI** (kg/m^2) + 1.13 × **IFG/diabetes** (yes = 1, no = 0) + 0.99 × **AST/ALT ratio** − 0.013 × **Platelet** (×10^9/L) −0.66 × **Albumin** (g/dl)	<−1.45 (low) – NPV: 88–93% >0.67 (high) – PPV: 78–90% Age >65 yrs <0.12 (low) – 81–98%	Cheap and reproducible Sensitivity to exclude F ≥3 Specificity to diagnose F ≥3 Influenced by age Allows predict clinical outcomes	Yes High Modest Yes Yes
FIB-4 index	**Age** (yrs) × **AST** [U/L]/(**Platelet** [10^9/L] × (**ALT** [U/L])$^{1/2}$)	<1.30 (low) – NPV: 90–95% >3.25 (high) – PPV: 75% Age >65 yrs <2.0 (low) – 82–98%	Cheap and reproducible Sensitivity to exclude F ≥3 Specificity to diagnose F ≥3 Influenced by age Allows predict clinical outcomes	Yes High Modest Yes Yes
BARD score	**AST/ALT ratio** ≥0.8 = 2 points **BMI** ≥28 = 1 point **Presence of diabetes** = 1 point Score ranges from 0 to 4 points	Single cut-off = 2 NPV: 95–97%, PPV: 27%	Cheap and reproducible Sensitivity to exclude F ≥3 Specificity to diagnose F ≥3 Influenced by age Allows predict clinical outcomes	Yes High Low Unknown Yes
APRI	(AST [IU/L])/(AST upper limit of normal [IU/L])/(Platelet [10^9/L])	Single cut-off = 1 NPV: 84%, PPV: 37%	Cheap and reproducible Sensitivity to exclude F ≥3 Specificity to diagnose F ≥3 Influenced by age Allows predict clinical outcomes	Yes High Low Unknown Yes
Hepascore	Y = exp [−4.185818 − (0.0249 × **Age**) + (0.7464 × **Sex**) + (1.0039 × **α2-macroglobulin**) + (0.0302 × **Hyaluronic acid**) + (0.0691 × **Bilirubin**) − (0.0012 × GGT)] *Hepascore* = Y/(1 + Y)	Single cut-off = 0.37 NPV: 92%, PPV: 57%	Cheap and reproducible Sensitivity to exclude F ≥3 Specificity to diagnose F ≥3 Influenced by age Allows predict clinical outcomes	Yes High Modest Unknown Yes

Vilar-Gomez. J Hepatol. 2018.

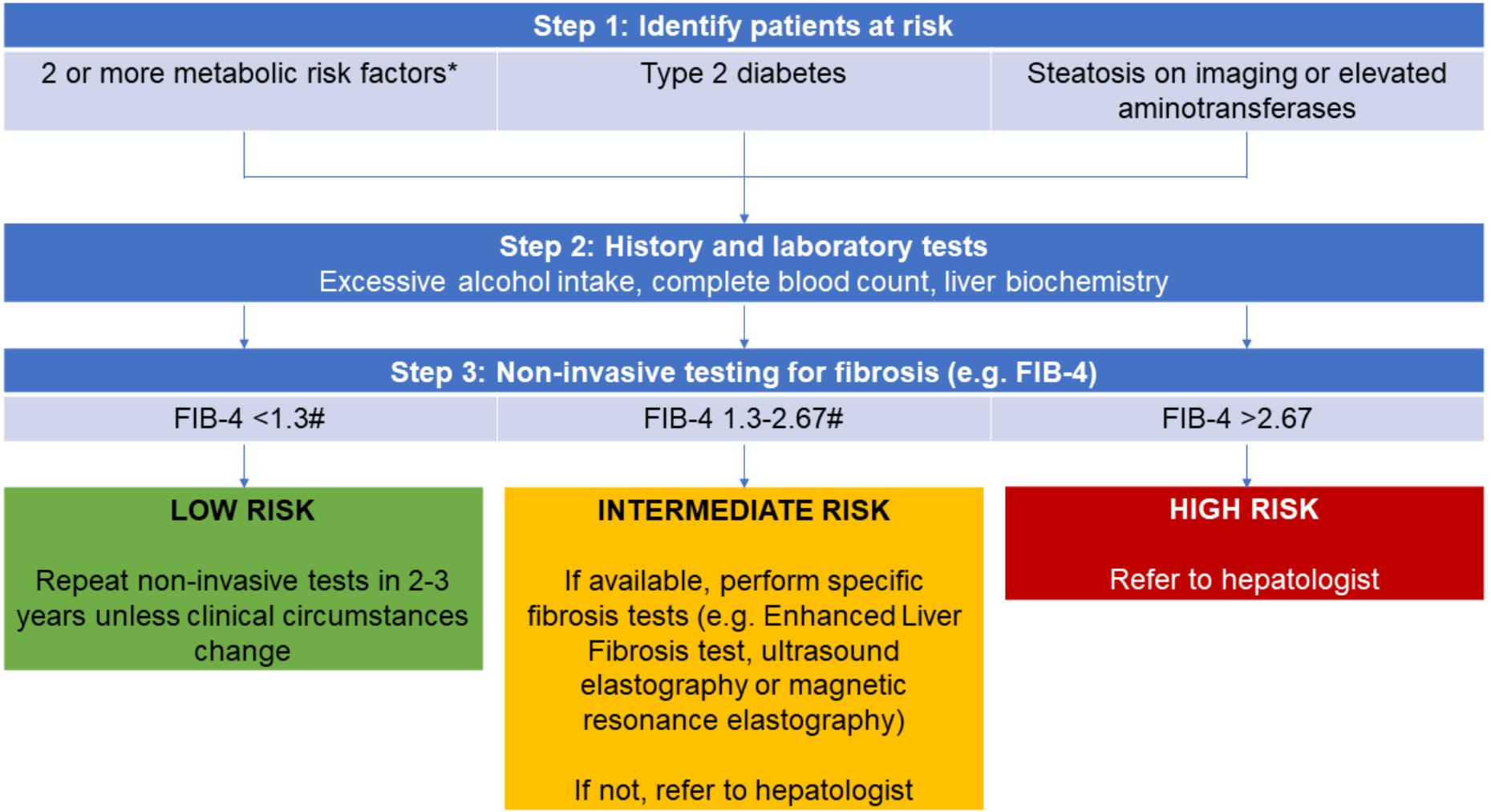
Recordad: todos los métodos tienen limitaciones

The proportion of patients with advanced fibrosis increased at each LSM interval, but even at the highest interval (LSM ≥ 20 kPa), there was a substantial proportion of patients without cirrhosis (39%).



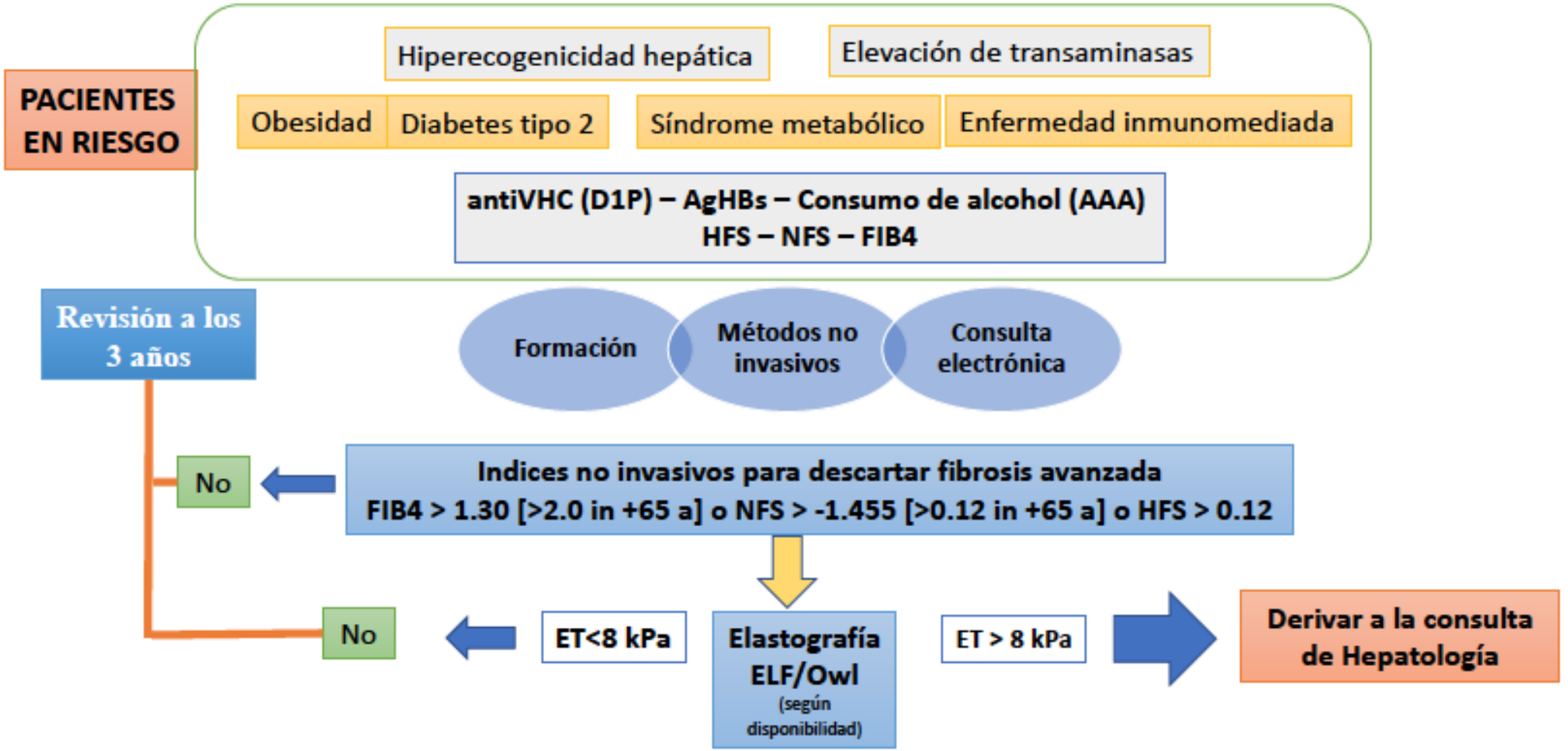
Calleja JL, ….Crespo J. Prevalence estimation of significant fibrosis because of NASH in Spain combining transient elastography and histology. Liver Int. 2022; 42: 1783-1792.

Estratificar la gravedad de la enfermedad



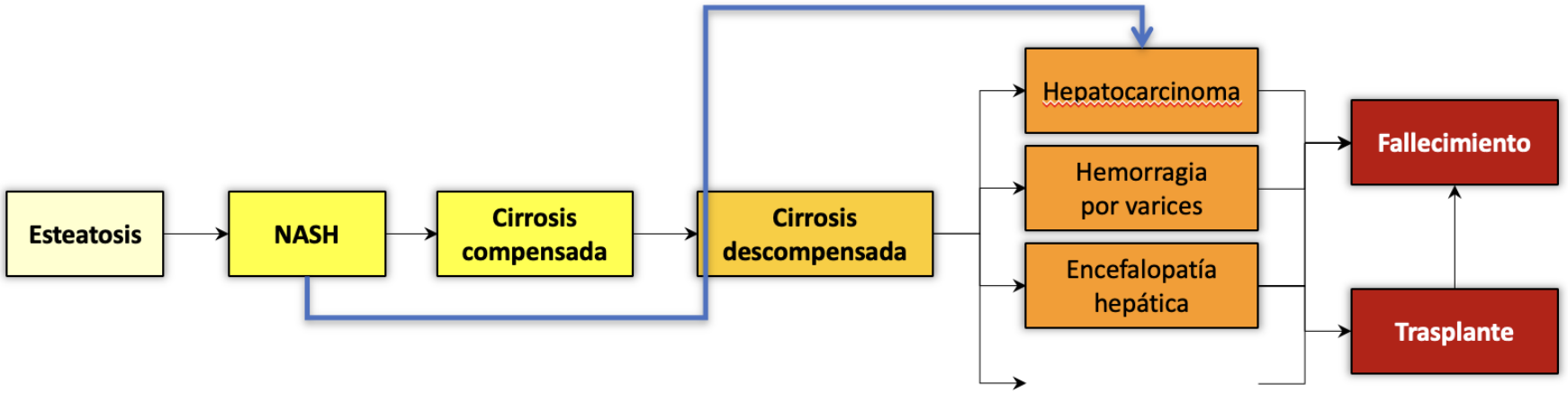
Wong VW, Zelber-Sagi S, Cusi K, Carrieri P, Wright E, Crespo J, Lazarus JV. Review article Management of NAFLD in primary care settings. Liver Int. 2022 Aug 20.

Estratificar la gravedad de la enfermedad



Romero-Gómez M, Aller R, Ampuero J, Fernández Rodríguez C, Augustín S, Latorre R, Rivera-Esteban J, Martínez Urroz B, Gutiérrez García ML, López SA, Albillos A, Hernández M, Graupera I, Benlloch S, Olveira A, Crespo J, Calleja JL. Consensus about detection and referral of hidden prevalent liver diseases. Gastroenterol Hepatol. 2022

¿Solo debemos evaluar la fibrosis hepática?



- Estilo de vida
- Edad
- Factores genéticos
- Factores inmunológicos

ENFERMEDAD CARDIOVASCULAR

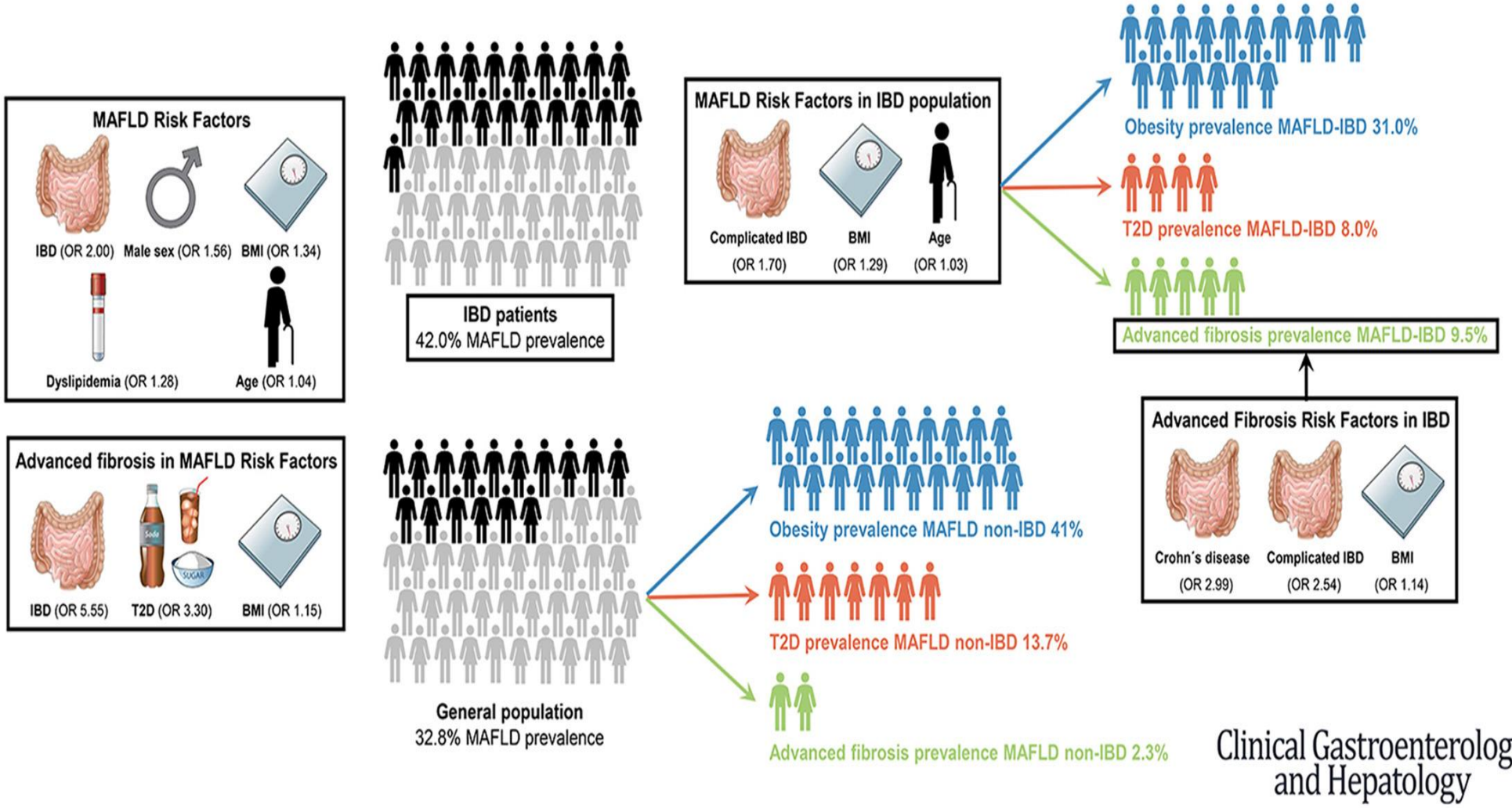
- Resistencia insulina
- Disfunción endotelial
- Dislipemia aterogénica
- Estado pro-inflamatorio

Manifestaciones extrahepáticas

Morbimortalidad secundaria al incremento del riesgo cardiovascular

Incremento del riesgo de cáncer

Estratificar en función del tipo de pacientes. IBD.

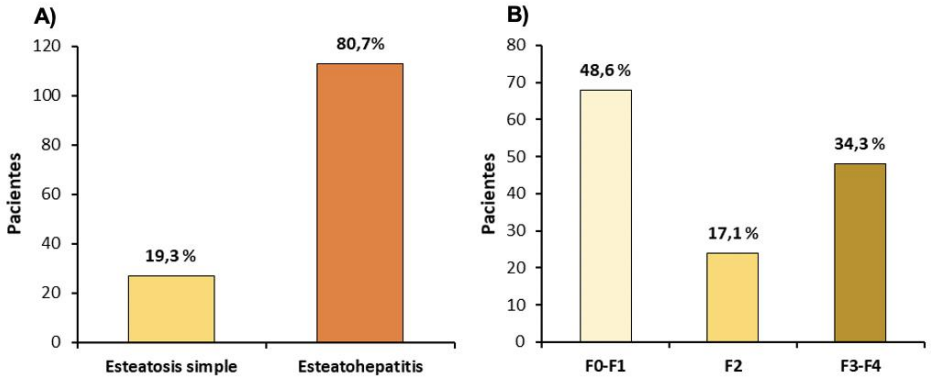


Rodriguez-Duque JC, Arias-Loste MT, …et al.. Increased risk of MAFLD and Liver Fibrosis in Inflammatory Bowel Disease Independent of Classic Metabolic Risk Factors. Clin Gastroenterol Hepatol. 2022 Feb 3:S1542-3565(22)00093-3. doi: 10.1016/j.cgh.2022.01.039. Epub ahead of print. PMID: 35124272.

Estratificar en función del tipo de pacientes. DMII.

Analítica completa, fibroscan + FIB-4
(biopsia y analítica < 1 año)

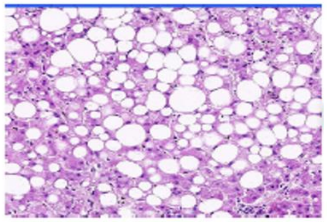
N = 124

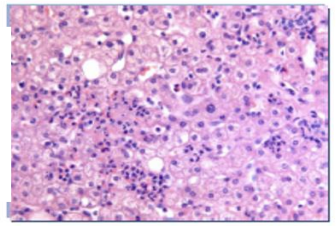


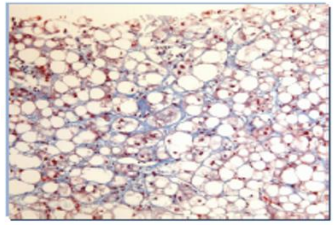
NAFL
N = 23 (18,6%)

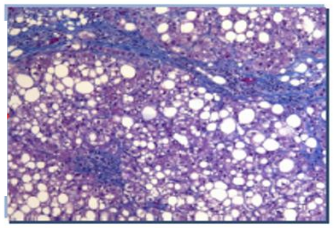
NASH (F0-F1)
N = 35 (28,2%)

NASH (F2-F4)
N = 66 (53,2%)



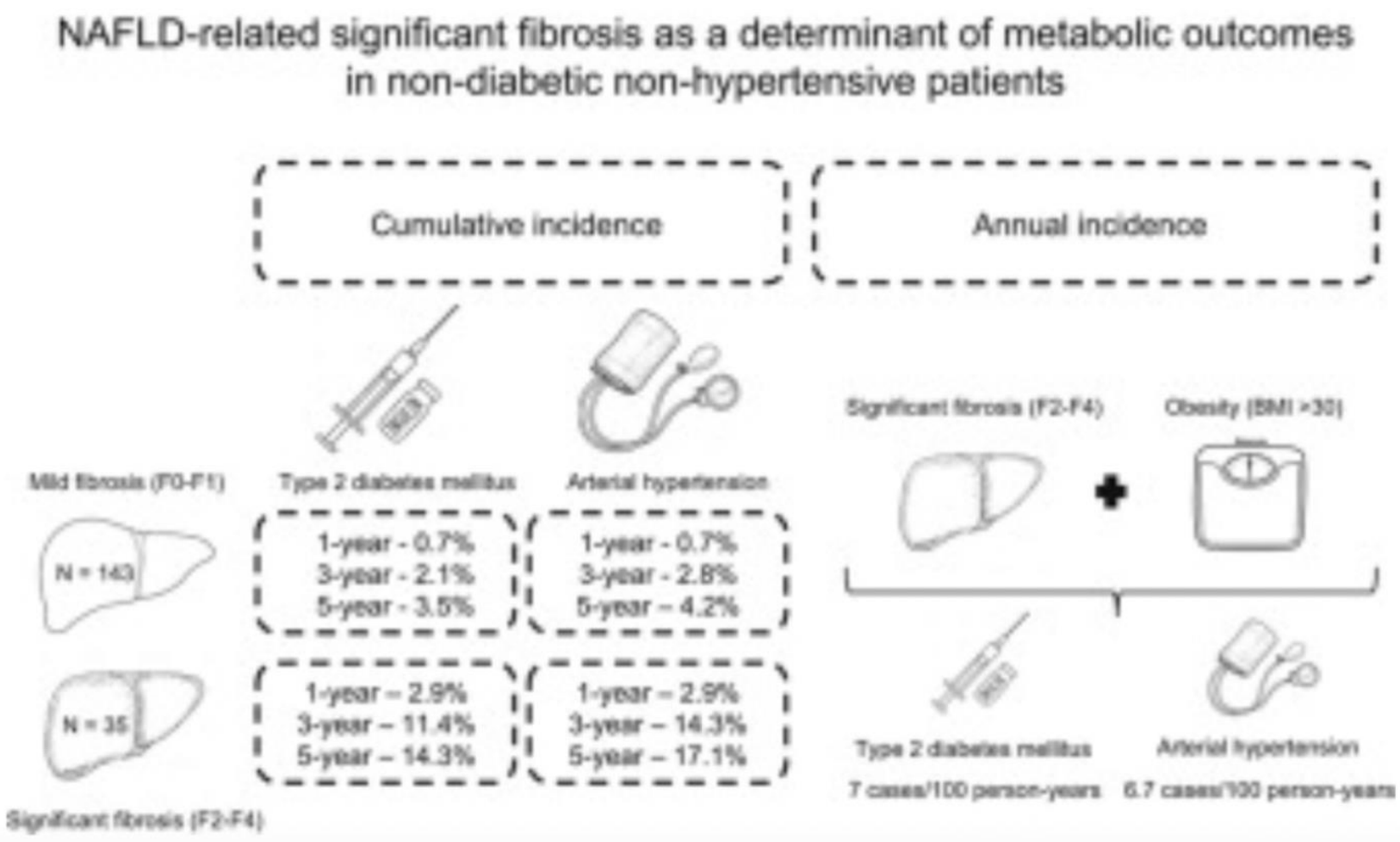






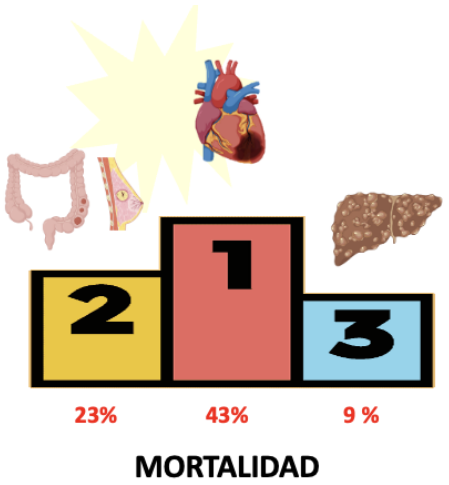
Iruzubieta et al. NASH registry 2022; submitted.

¿Evaluamos solo la fibrosis?



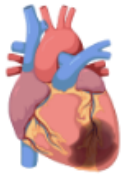
Ampuero J, Aller R, Gallego-Durán R, Crespo J, Calleja JL, García-Monzón C, et al; HEPAmet Registry. Significant fibrosis predicts new-onset diabetes mellitus and arterial hypertension in patients with NASH. J Hepatol. 2020 Jul;73(1):17-25. doi: 10.1016/j.jhep.2020.02.028. Epub 2020 Mar 6. Erratum in: J Hepatol. 2020 Sep;73(3):740-741. PMID: 32147361.

Estratificar su riego vascular

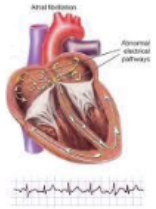


MORTALIDAD

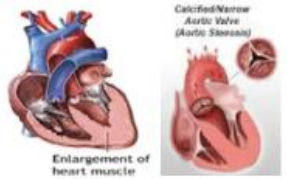
Riesgo eventos CV (fatales y no fatales)



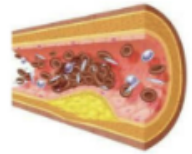
- AC x FA
- Tastornos ritmo

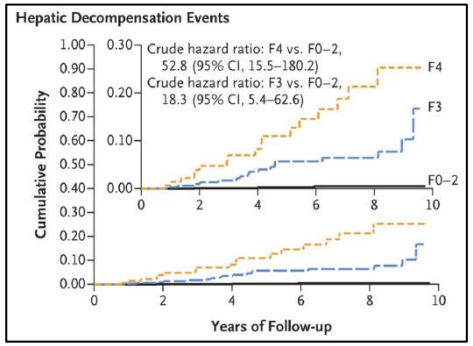


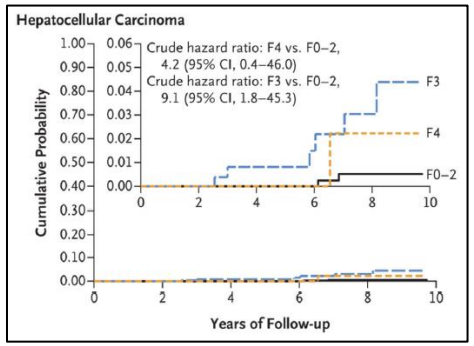
- Disfunción diastólica
- Esclerosis Ao

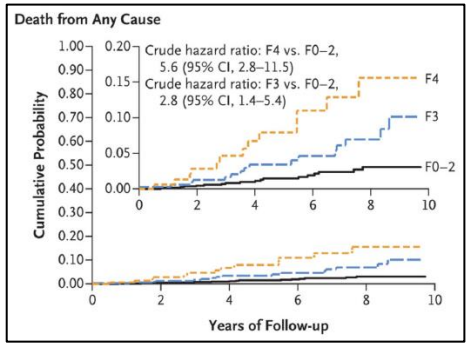


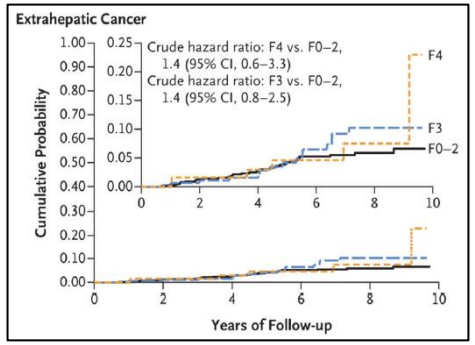
- Calcificación coronaria
- Rigidez arterial
- Íntima-media carótida
- Disfunción endotelial



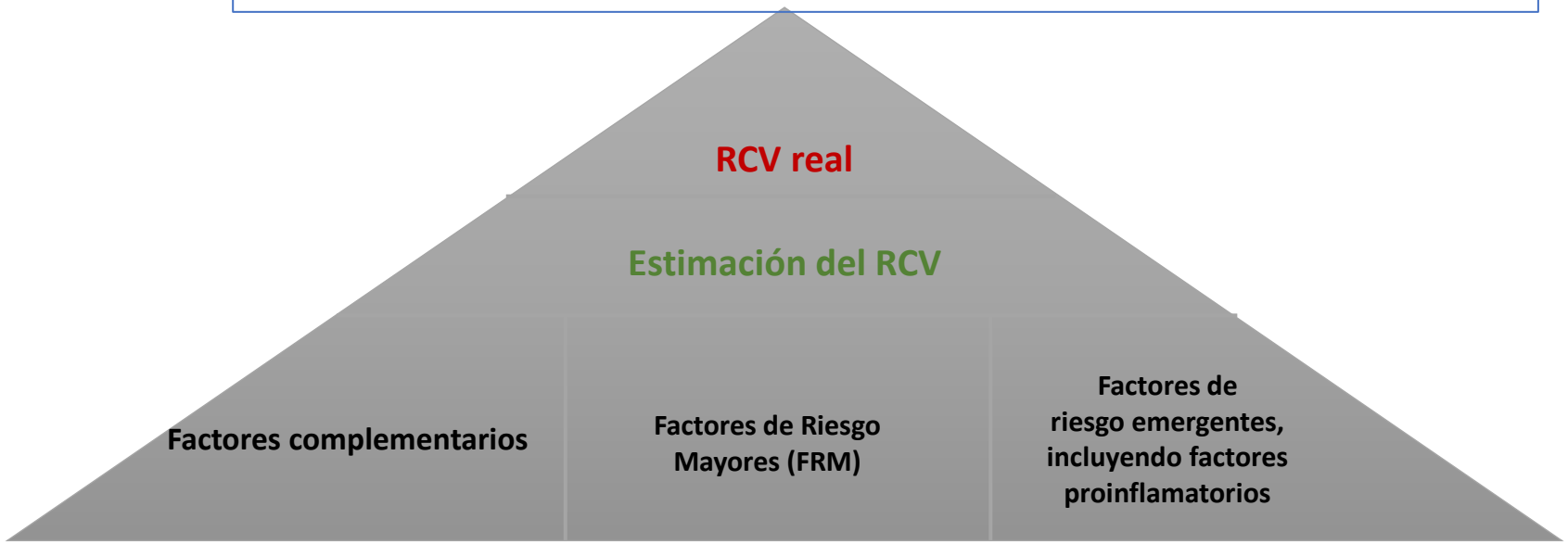






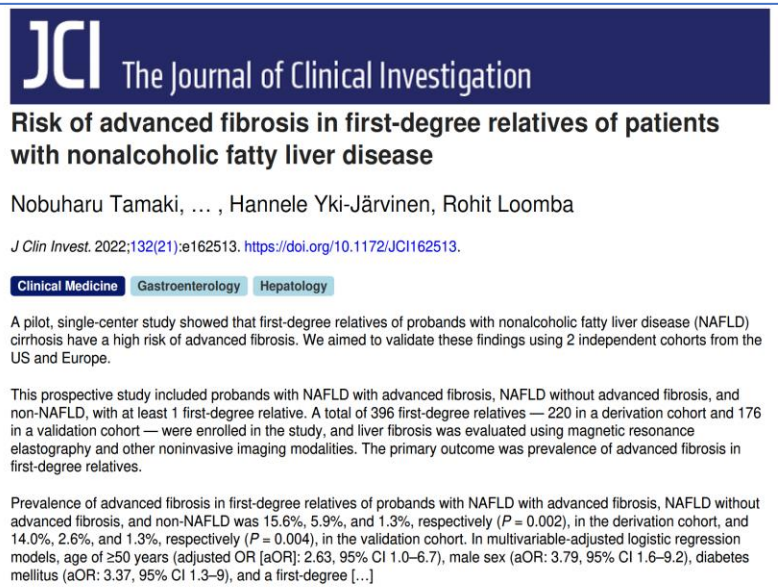


Estratificar su riego vascular



Amnanesis detallada	Exploración física	Historia vascular propia y de los familiares I grado	Variables analíticas	Factores de riesgo emergentes
• Dislipemia y tto. • DMII y tto • HTA y tto • Tabaco • Comorbilidades • Otros	• Sexo, • Edad • Peso • Talla • Perímetro cintura abdominal • TAS / TAD	• MACEs: IAM, Ictus, Muerte súbita • Otros eventos vasculares: Angina inestable, Arritmia grave, Shock cardiogénico, IC grave, Cirugía de revascularización cardiaca, Hipertrofia VI y EA	• HOMA • HbA1c, • Micro albuminuria • Metabolismo lipídico	• hsPCR • Homocisteína • Lp(a) • PON1 • PCSK9 • Pentraxina3

Estratificar su riego vascular



JCI The Journal of Clinical Investigation

Risk of advanced fibrosis in first-degree relatives of patients with nonalcoholic fatty liver disease

Nobuharu Tamaki, … , Hannele Yki-Järvinen, Rohit Loomba

J Clin Invest. 2022;132(21):e162513. https://doi.org/10.1172/JCI162513.

Clinical Medicine | Gastroenterology | Hepatology

A pilot, single-center study showed that first-degree relatives of probands with nonalcoholic fatty liver disease (NAFLD) cirrhosis have a high risk of advanced fibrosis. We aimed to validate these findings using 2 independent cohorts from the US and Europe.

This prospective study included probands with NAFLD with advanced fibrosis, NAFLD without advanced fibrosis, and non-NAFLD, with at least 1 first-degree relative. A total of 396 first-degree relatives — 220 in a derivation cohort and 176 in a validation cohort — were enrolled in the study, and liver fibrosis was evaluated using magnetic resonance elastography and other noninvasive imaging modalities. The primary outcome was prevalence of advanced fibrosis in first-degree relatives.

Prevalence of advanced fibrosis in first-degree relatives of probands with NAFLD with advanced fibrosis, NAFLD without advanced fibrosis, and non-NAFLD was 15.6%, 5.9%, and 1.3%, respectively ($P = 0.002$), in the derivation cohort, and 14.0%, 2.6%, and 1.3%, respectively ($P = 0.004$), in the validation cohort. In multivariable-adjusted logistic regression models, age of ≥50 years (adjusted OR [aOR]: 2.63, 95% CI 1.0–6.7), male sex (aOR: 3.79, 95% CI 1.6–9.2), diabetes mellitus (aOR: 3.37, 95% CI 1.3–9), and a first-degree […]

Anamnesis detallada	Exploración física	Historia vascular propia y de los familiares I grado	Variables analíticas	Factores de riesgo emergentes
• Dislipemia y tto. • DMII y tto • HTA y tto • Tabaco • Comorbilidades • Otros	• Sexo, • Edad • Peso • Talla • Perímetro cintura abdominal • TAS / TAD	• MACEs: IAM, Ictus, Muerte súbita • Otros eventos vasculares: Angina inestable, Arritmia grave, Shock cardiogénico, IC grave, Cirugía de revascularización cardiaca, Hipertrofia VI y EA	• HOMA • HbA1c, • Micro albuminuria • Metabolismo lipídico	• hsPCR • Homocisteína • Lp(a) • PON1 • PCSK9 • Pentraxina3

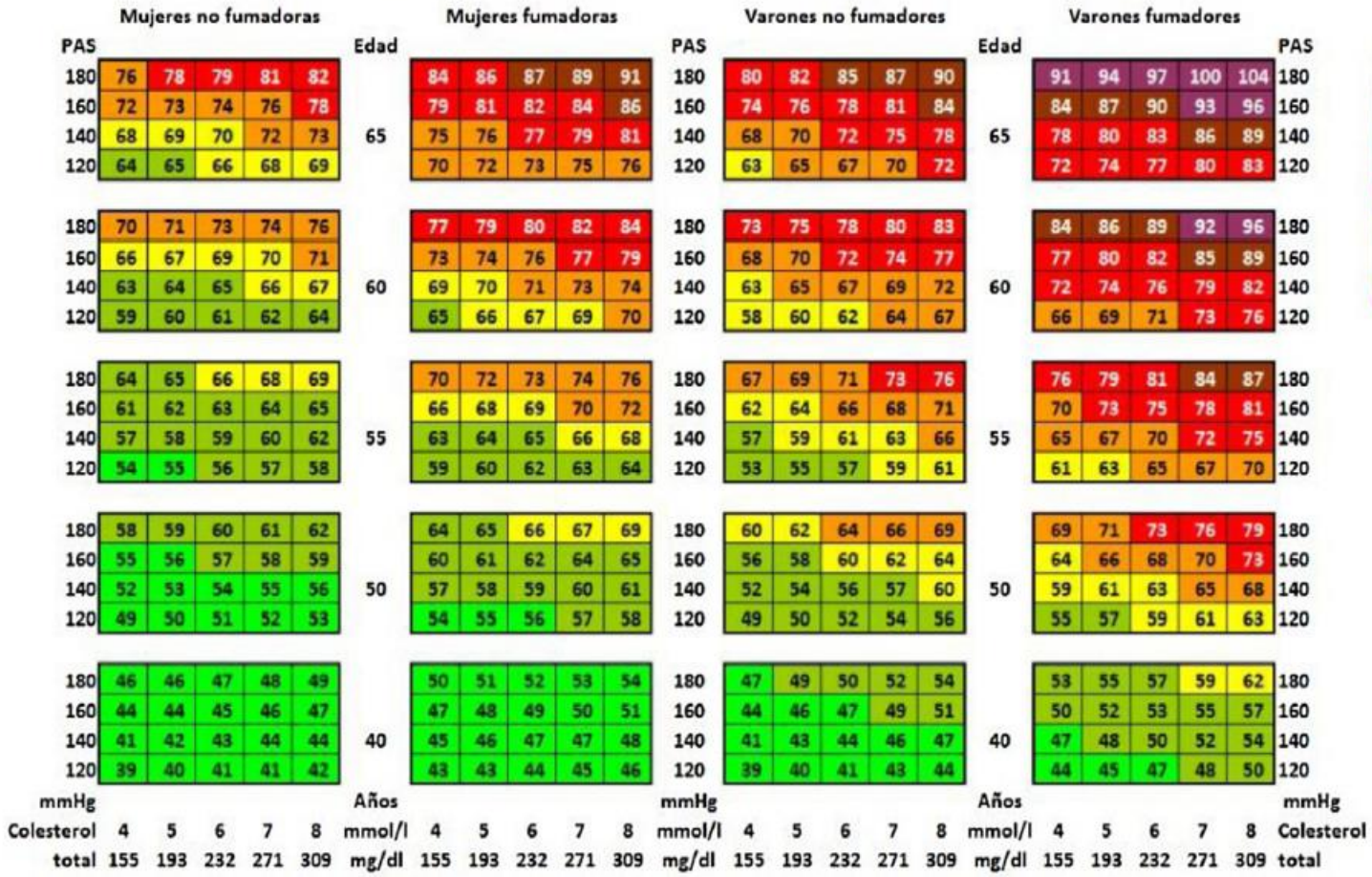
Evaluación del riesgo vascular. Calculadoras.

Tabla de riesgo relativo

Presión arterial sistólica (mmHg)	No fumador					Fumador				
180	3	3	4	5	6	6	7	8	10	12
160	2	3	3	4	4	4	5	6	7	8
140	1	2	2	2	3	3	3	4	5	6
120	1	1	1	2	2	2	2	3	3	4
	4	5	6	7	8	4	5	6	7	8

Colesterol (mmol/l)

Edad vascular para países de bajo riesgo



Mach F et al. Eur Heart J 2020

Estratificar en función del riesgo genético

FUNCIÓN	GENES	SNPs
Metabolismo lípidos	PNPLA3	rs738409
	PNPLA3	rs2294918
	TM6SF2	rs58542926
	MBOAT7	rs641738
	LYPLAL1	rs12137855
	LPIN1	rs13412852
Diferenciación adipocitos	FTO	rs1421085
	LPIN1	rs13412852
Homeostasis glucosa y resistencia a la insulina	ENPP1	rs1044498
	GCKR	rs1260326
	GCKR	rs780094
	FNDC5	rs3480
	LOC157273	rs4240624
	LYPLAL1	rs12137855
Respuesta inmune e inflamación	IL28B	rs12979860
	FTO	rs1421085
	MERTK	rs4374383
	PNPLA3	rs738409
	PNPLA3	rs2294918
Senescencia	CDKN1A	rs762623
Estrés oxidativo	SOD2	rs4880
Fibrogénesis	KLF6	rs3750861

Valdecilla Instituto de Investigación Sanitaria IDIVAL

Estratificar en función del IMC. Lean MAFLD.

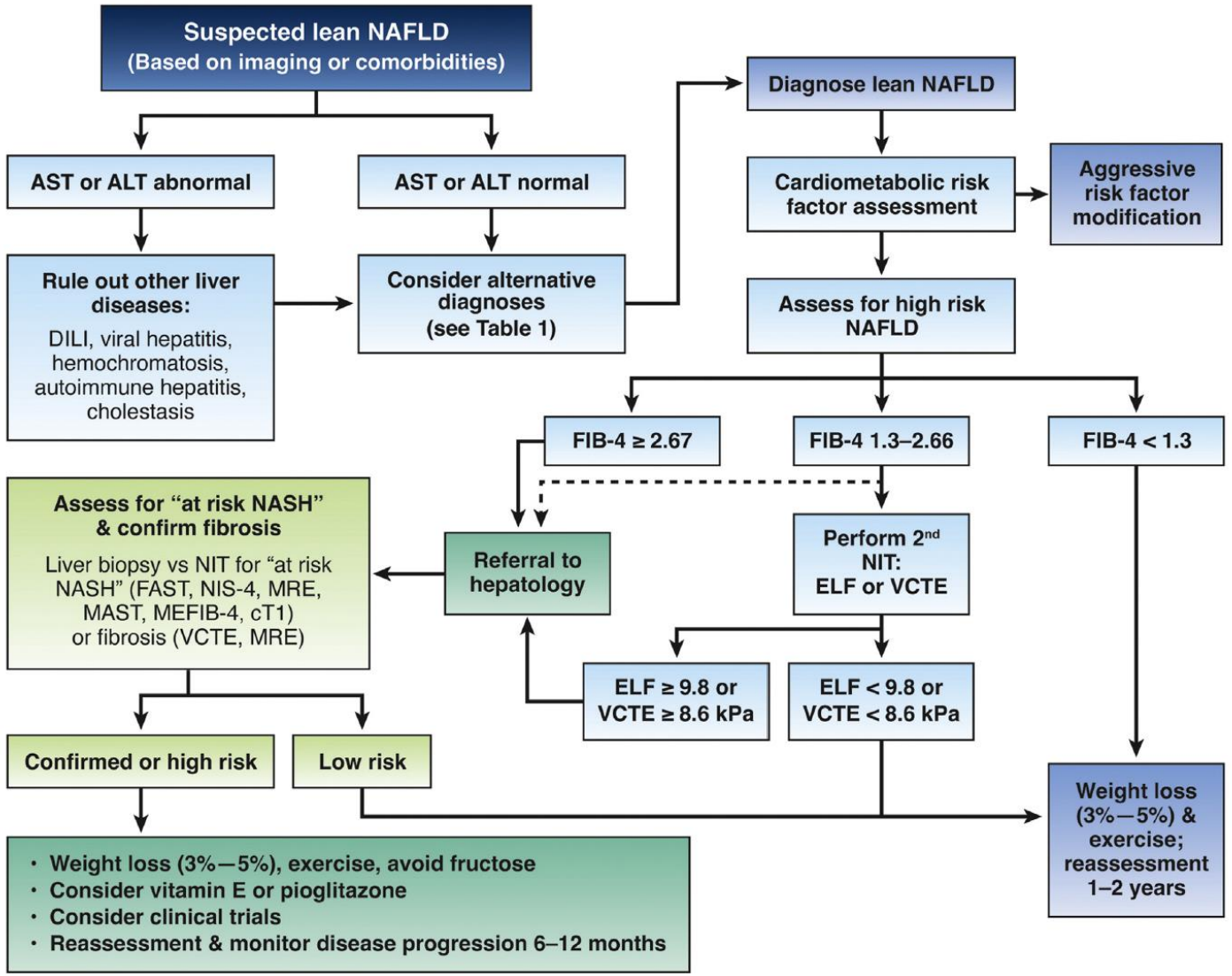


Figure 1. Management and treatment algorithm in patients with suspected lean NAFLD.

Valdecilla
Hospital Universitario Marqués de Valdecilla

Long MT, Noureddin M, Lim JK. AGA Clinical Practice Update: Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Lean Individuals: Expert Review. Gastroenterology. 2022 Sep;163(3):764-774.e1. doi: 10.1053/j.gastro.2022.06.023. Epub 2022 Jul 14. PMID: 35842345; PMCID: PMC9398982.

Estratificar en función del IMC. Lean MAFLD.

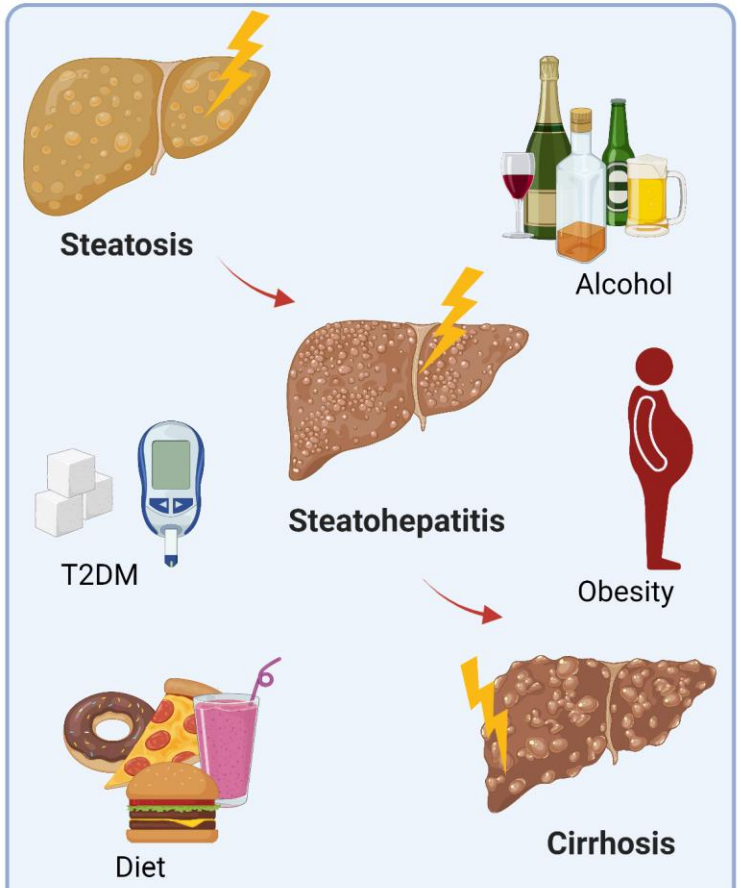
Table 1. Potential Secondary Causes of Fatty Liver in Lean Individuals

Liver-related	Systemic
Specific liver conditions	Endocrine
Chronic hepatitis C (especially genotype 3)	Hypothyroidism
Wilson's disease	Hypopituitarism
A1 antitrypsin	Polycystic ovary syndrome
Liver diseases of pregnancy	Growth hormone insufficiency
Acute fatty liver of pregnancy	Other genetic disorders
HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome	Lysosomal acid lipase deficiency
Drug-induced liver injury	Familial hypobetalipoprotein B
Methotrexate, amiodarone, corticosteroids, valproic acid, tetracycline, and amphetamines	Abetalipoproteinemia
HIV medications (cART: didanosine, stavudine, and zidovudine)	Urea cycle disorders
	Hereditary fructose intolerance
	Glycogen storage disease
	Fatty acid oxidation disorders
	Autosomal recessive carbamoyl phosphate synthetase I deficiency
	Environmental toxins
	Metal: Arsenic, cadmium, mercury, lead
	Chloroalkenes: (vinyl chloride, trichloroethylene, perchloroethylene)
	Herbicides, pesticide Nutritional effects
	Total parenteral nutrition
	Malnutrition/Kwashiorkor disease
	Acute weight loss (eg, bariatric surgery, prolonged fasting)
	Short bowel syndrome
	Celiac disease

Long MT, Noureddin M, Lim JK. AGA Clinical Practice Update: Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Lean Individuals: Expert Review. Gastroenterology. 2022 Sep;163(3):764-774.e1. doi: 10.1053/j.gastro.2022.06.023. Epub 2022 Jul 14. PMID: 35842345; PMCID: PMC9398982.

Estratificar el consumo de alcohol

Fatty Liver Disease



Dual diagnosis: MAFLD/NAFLD +/- ALD

Questionnaire **Sample collection**

SCR for alcohol consumption

+ metabolic characterization

Results & Conclusions

Moderate to excessive alcohol consumption in

28.6% of NAFLD patients
25.0% of MAFLD patients

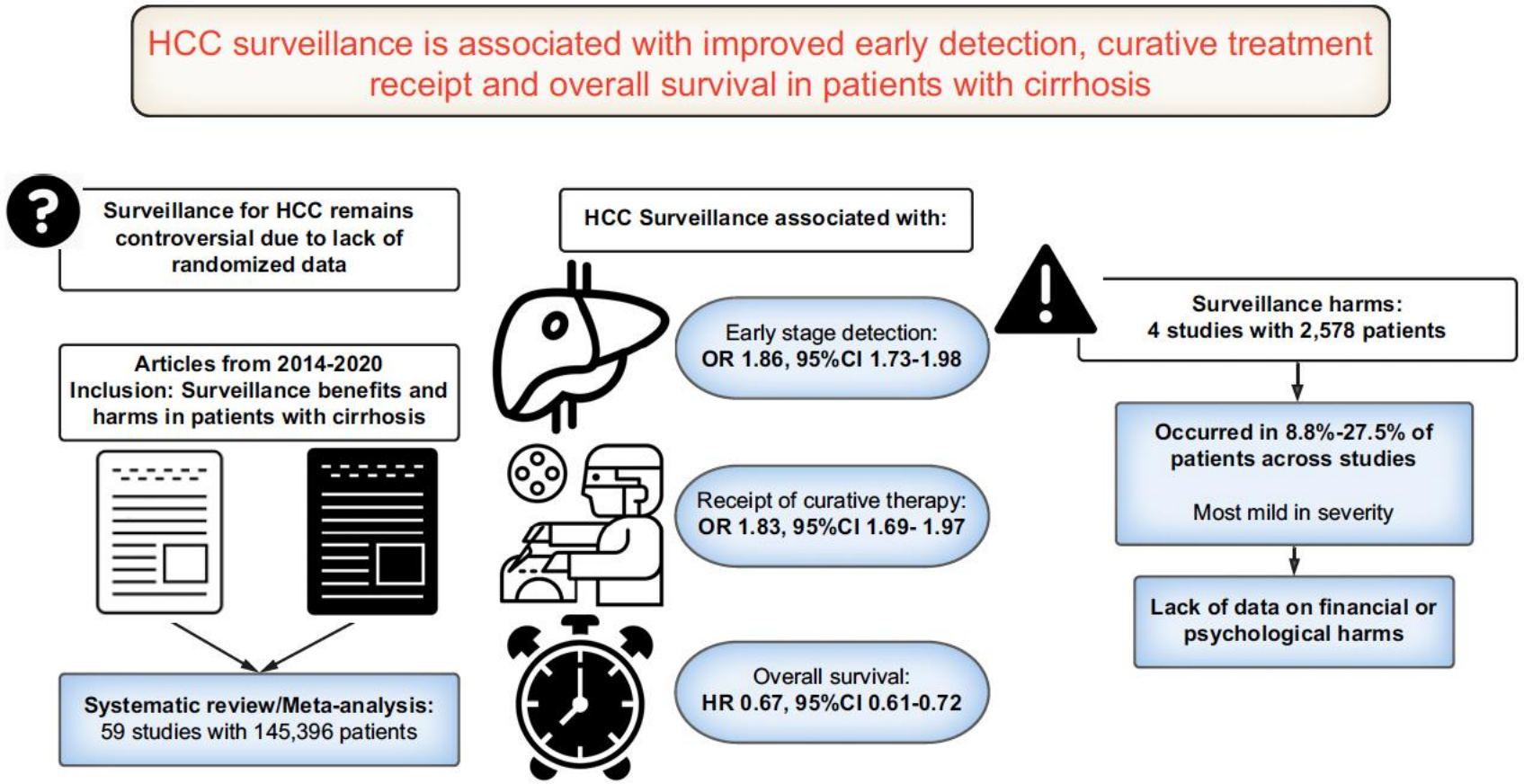
Optimal diagnostic means

hEtG: AUC 0.927
+ uEtG: AUC 0.754
+ AUDIT-C: AUC 0.733

Staufer et al

Staufer K, et al. Ethyl glucuronide in hair detects a high rate of harmful alcohol consumption in presumed non-alcoholic fatty liver disease. J Hepatol. 2022 May 20:S0168-8278(22)00316-6. doi: 10.1016/j.jhep.2022.04.040. Epub ahead of print. PMID: 35605744.

Estratificar el riesgo de hepatocarcinoma



- Esta revisión sistemática de estudios de cohortes contemporáneos, demostró que la detección de CHC se asocia con una mejor detección temprana, posibilidad de tratamiento curativo y supervivencia en pacientes con cirrosis
- Pocos datos acerca de los efectos secundarios.
- Este trabajo sugiere que la detección de HCC es de gran valor en pacientes con cirrosis, aunque aún se necesitan estudios de riesgo/beneficio.

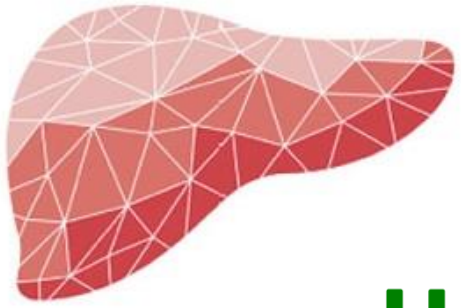
Singal AG, Zhang E, Narasimman M, Rich NE, Waljee AK, Hoshida Y, Yang JD, Reig M, Cabibbo G, Nahon P, Parikh ND, Marrero JA. HCC surveillance improves early detection, curative treatment receipt, and survival in patients with cirrhosis: A meta-analysis. J Hepatol. 2022 Jul;77(1):128-139

NAFLD approach

Identify metabolic risk factors	Disease activity			Identify contributing factors	Evaluation of cardiovascular risk	Nutritional assessment	Assessment of potential therapies
Insulin resistance/Type 2 diabetes Hypertension Dyslipidemia Central obesity	**Diagnose steatosis** **Serum biomarkers:** Fatty Liver Index Hepatic Steatosis Index **Imaging techniques:** Ultrasound scan CAP	**Diagnose liver inflammation** **Serum biomarkers:** OWL Liver Test **Imaging techniques:** NASHMRI **Liver biopsy**	**Diagnose liver fibrosis** **Serum biomarkers:** NAFLD Fibrosis Score FIB-4 **Imaging techniques:** Transient elastography FibroMRI **Liver biopsy**	Drugs Alcohol Vitamin D déficit OSAS/ Psoriasis / POS/ Hypothyroidism PNPLA3 (I148M) / TMGSF2 (E167K)	Electrocardiogram Ankle-brachial index Carotid ultrasound	Lifestyle Dietary habits Physical activity	Weight-los agents Insulin sensitizers Anti-diabetic drugs Hepatoprotectans Antifibrotic drugs

Iruzubieta P et al. Liver Research and Clinical Management, 2018

MÁSTER EN HEPATOLOGÍA



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Universidad de Alcalá