Diagnóstico e Tratamento do Fígado Gorduroso no Diabetes Tipo 2

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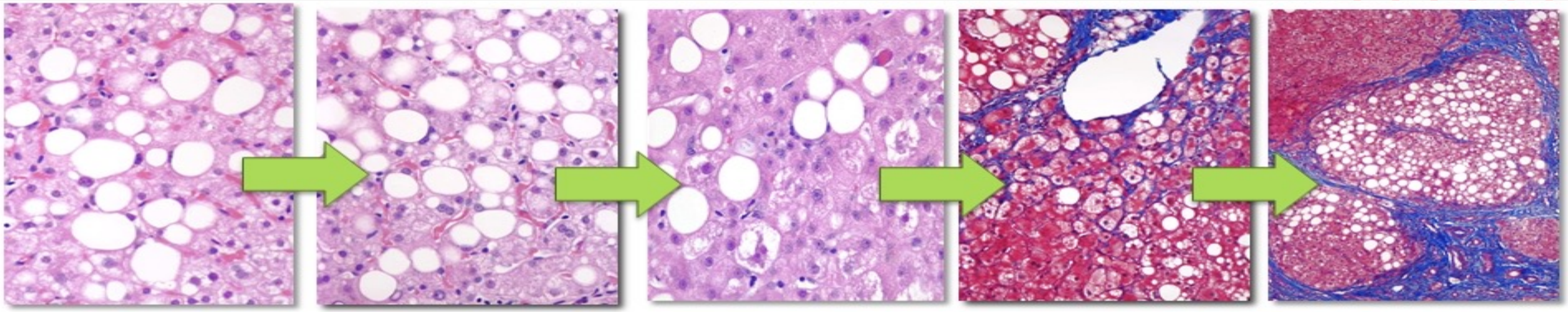
Doença Hepática Gordurosa Não-Alcoólica (DHGNA / NAFLD)

NAFLD



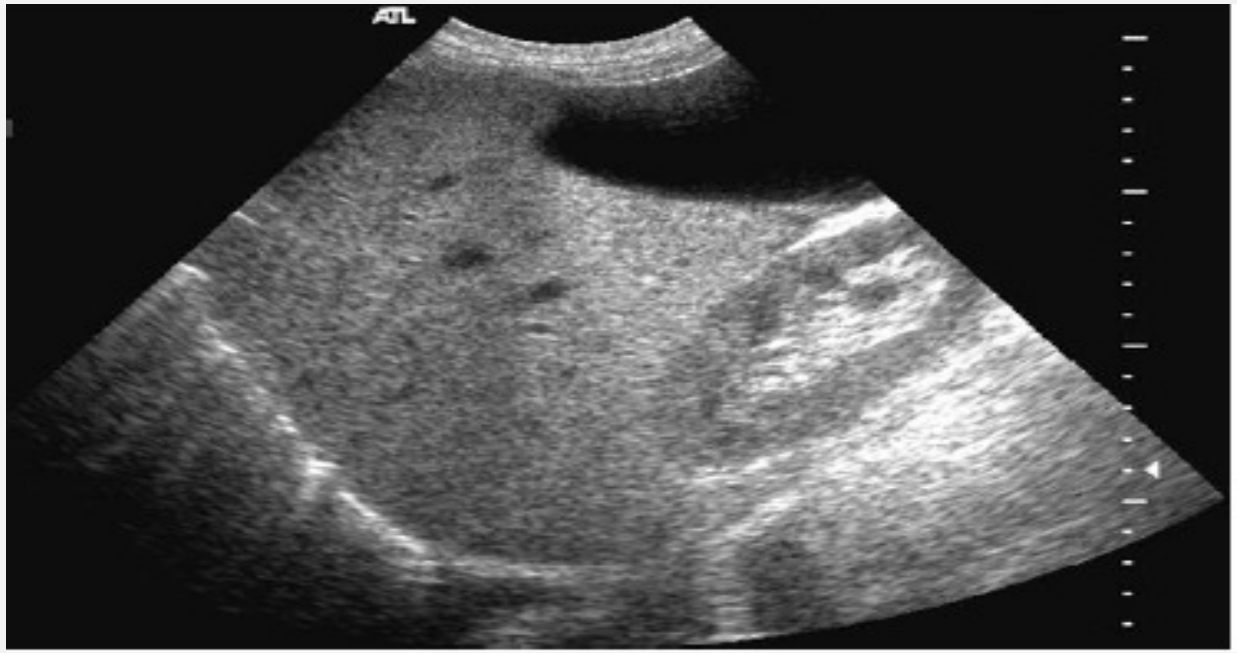
Esteatose Simples | Esteatose + Inflamação | Baronização + Inflamação | Fibrose | Cirrose

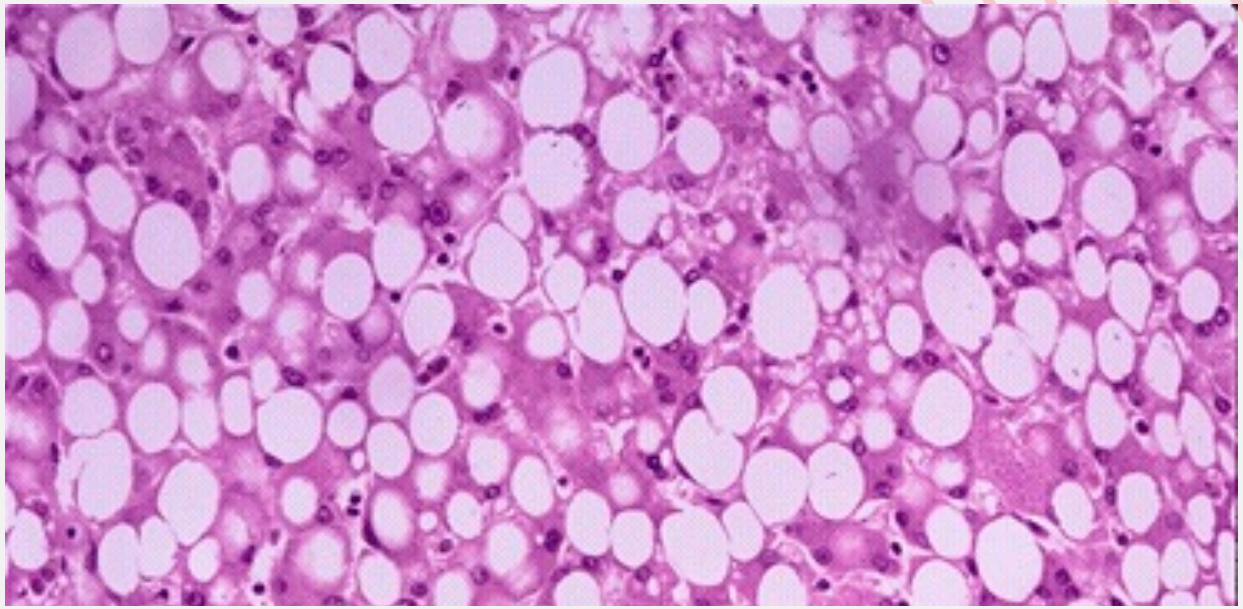
NAFL | **NASH**

Doença Hepática Gordurosa Não-Alcoólica (DHGNA / NAFLD)

Esteatose Hepática

- Achado de gotículas de gordura macrovesicular > 5% dos hepatócitos
- Achado indireto de maior conteúdo hepático de gordura por bioiagem (US/RM/CAP)

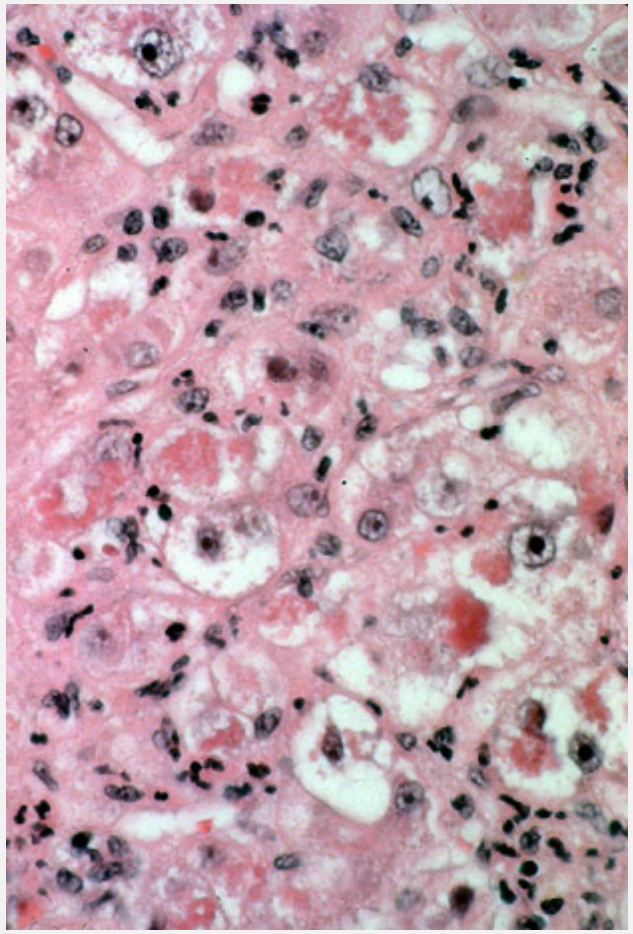




AASLD, AGA, 2012

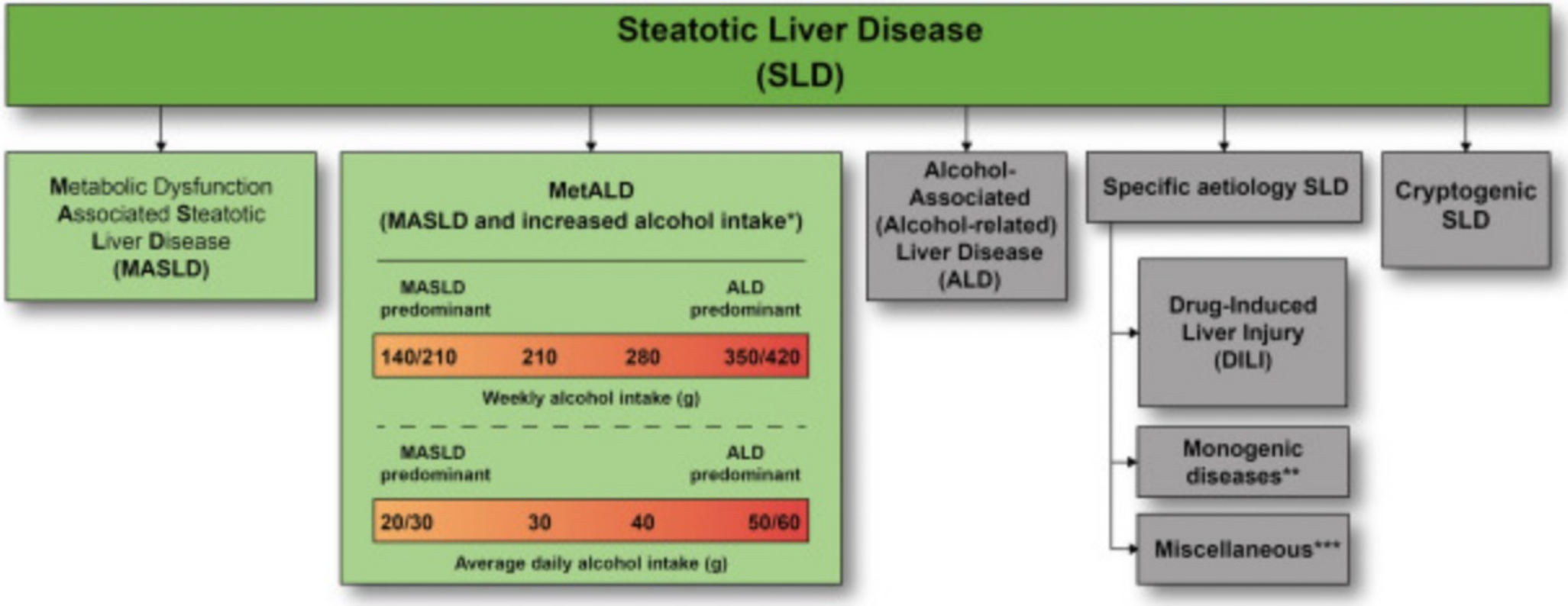
Esteatohepatite Não-Alcoólica

- Esteatose Hepática
- Sinais histológicos de Inflamação, associados a sinais de injúria hepatocelular (balonização dos hepatócitos) com ou sem fibrose.
- Ausência de consumo significativo de álcool e de causas secundárias de esteatose hepática (uso de corticosteróides, amiodarona, tamoxifeno, exposição a agentes petroquímicos, etc)



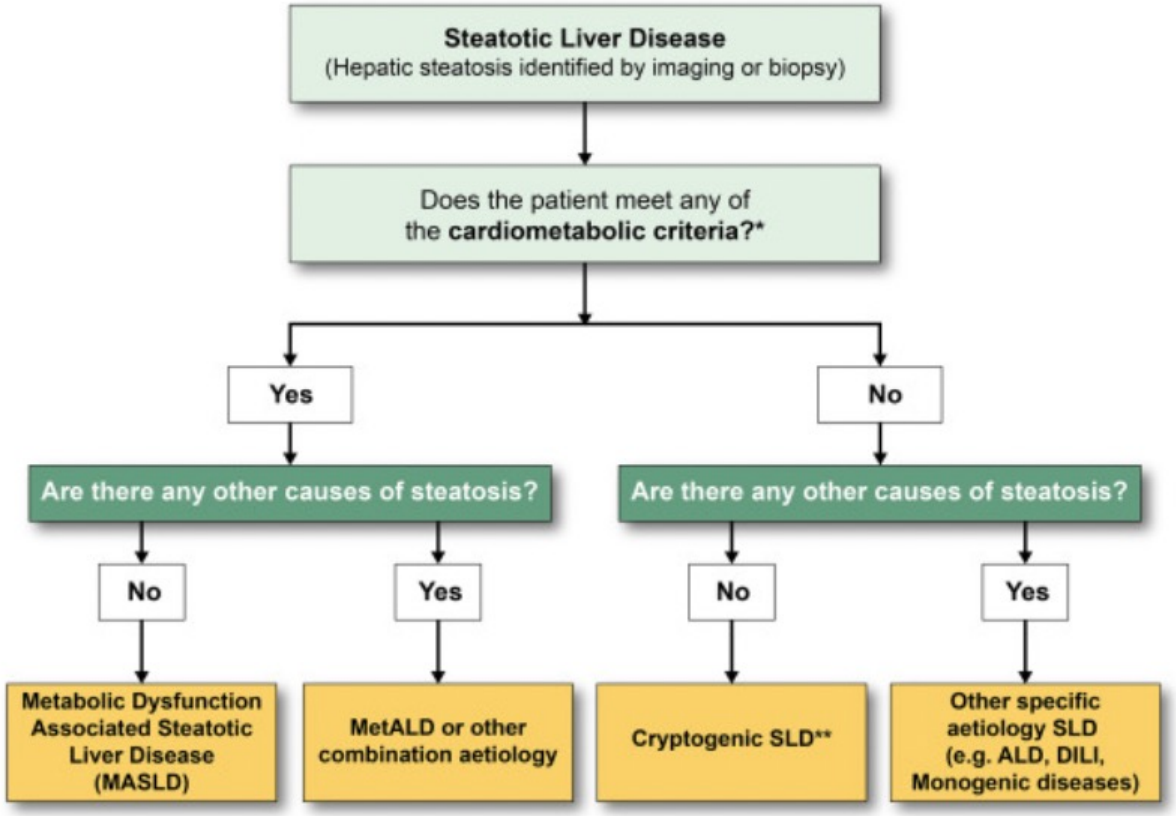
EASL-EASD-EASO CPG for the management of NAFLD

Novas Definições: Doença Esteatótica Metabólica



*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease

Rinella M et al, Hepatology 2023



***Cardiometabolic criteria**

Adult Criteria	Pediatric Criteria
At least 1 out of 5:	**At least 1 out of 5:**
☐ BMI ≥ 25 kg/m² [23 Asia] **OR** WC > 94 cm (M) 80 cm (F) **OR** ethnicity adjusted	☐ BMI ≥ 85th percentile for age/sex [BMI z score ≥ +1] **OR** WC > 95th percentile **OR** ethnicity adjusted
☐ Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** type 2 diabetes **OR** treatment for type 2 diabetes	☐ Fasting serum glucose ≥ 5.6 mmol/L [≥ 100 mg/dL] **OR** serum glucose ≥ 11.1 mmol/L [≥ 200 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol [140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** already diagnosed/treated type 2 diabetes **OR** treatment for type 2 diabetes
☐ Blood pressure ≥ 130/85 mmHg **OR** specific antihypertensive drug treatment	☐ Blood pressure age < 13y, BP ≥ 95th percentile **OR** ≥ 130/80 mmHg (whichever is lower); age ≥ 13y, 130/85 mmHg **OR** specific antihypertensive drug treatment
☐ Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] **OR** lipid lowering treatment	☐ Plasma triglycerides < 10y, ≥ 1.15 mmol/L [≥ 100 mg/dL]; age ≥ 10y, ≥ 1.70 mmol/L [≥ 150 mg/dL] **OR** lipid lowering treatment
☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) **OR** lipid lowering treatment	☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [≤ 40 mg/dL] **OR** lipid lowering treatment

Patogênese da DHGNA

Dieta Hipercalórica

Ricas em Frutose

Ricas em Lipídios

DMT2

Obesidade

Síndrome Metabólica

Resistência a Insulina

Ácidos Graxos Livres

Acúmulo Intrahepático de de Lipídios

Esteatose

Oxidação de Ácidos Graxos

Stress Oxidativo

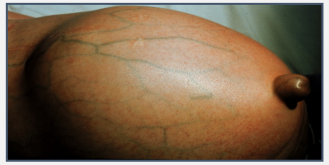
Radicais Livres / Antioxidantes

Citocinas Pró-Inflamatórias

Resposta Inflamatória

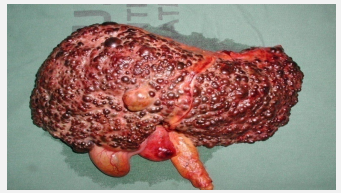
Peroxidação Lipídica

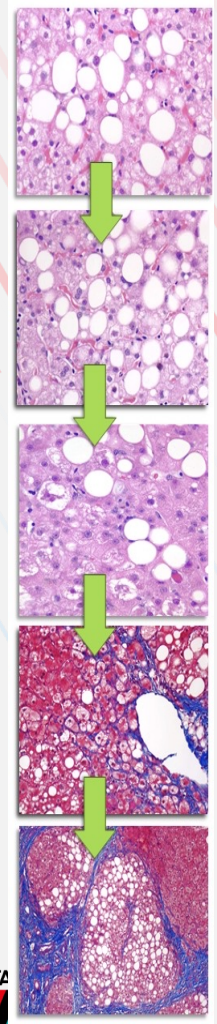
Apoptose



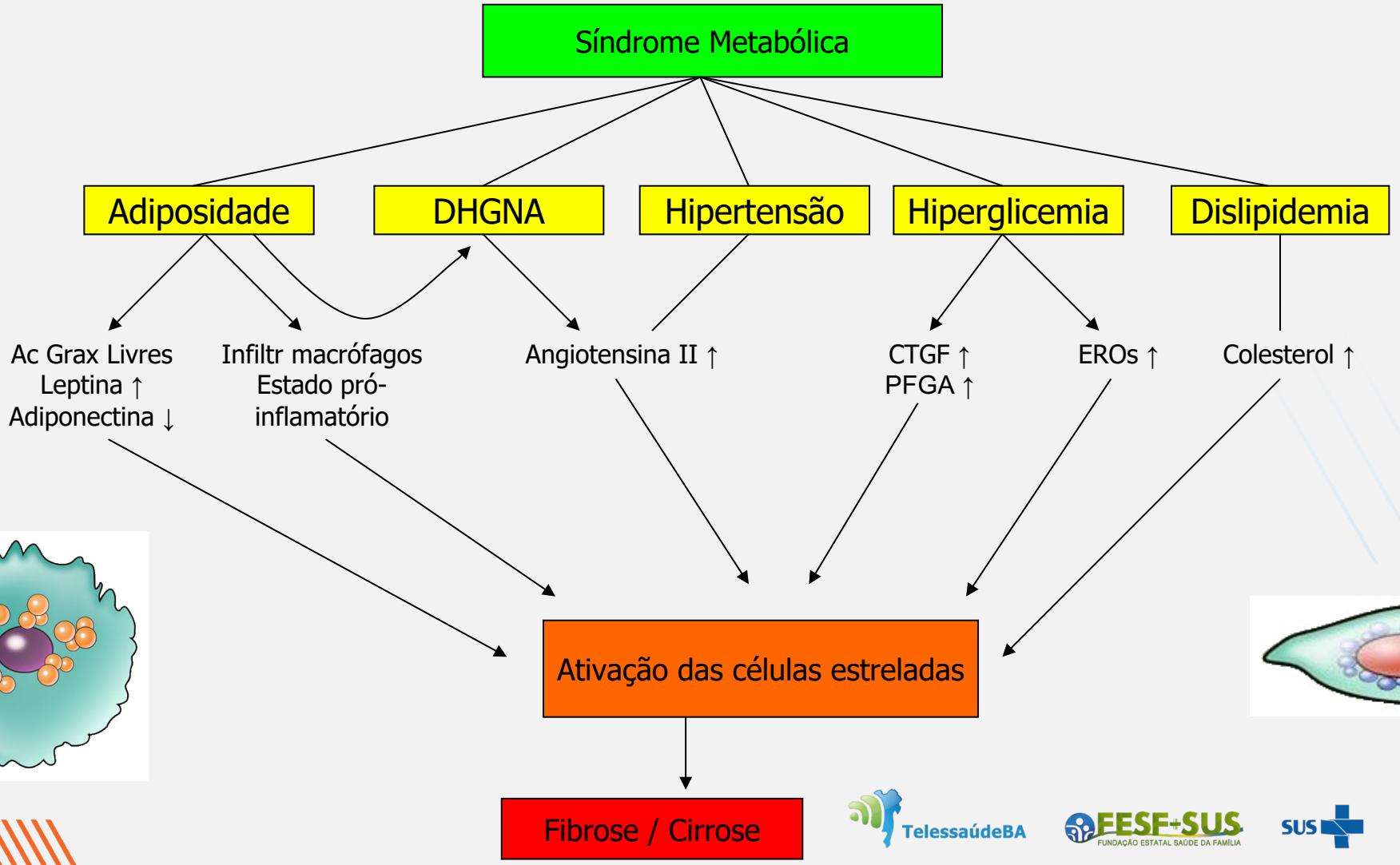
Esteatohepatite

Fibrose / Cirrose



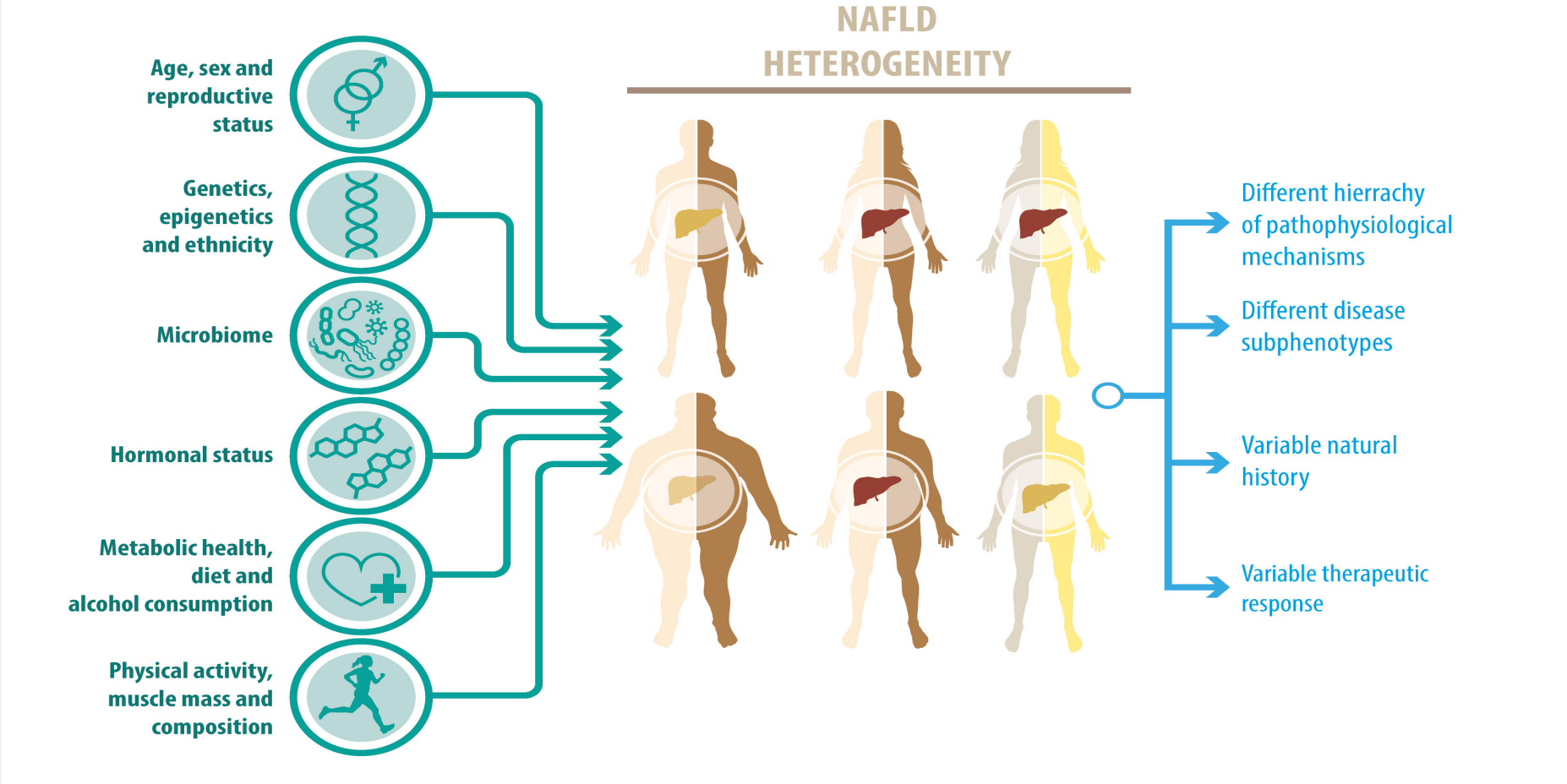


Patogênese da DHGNA



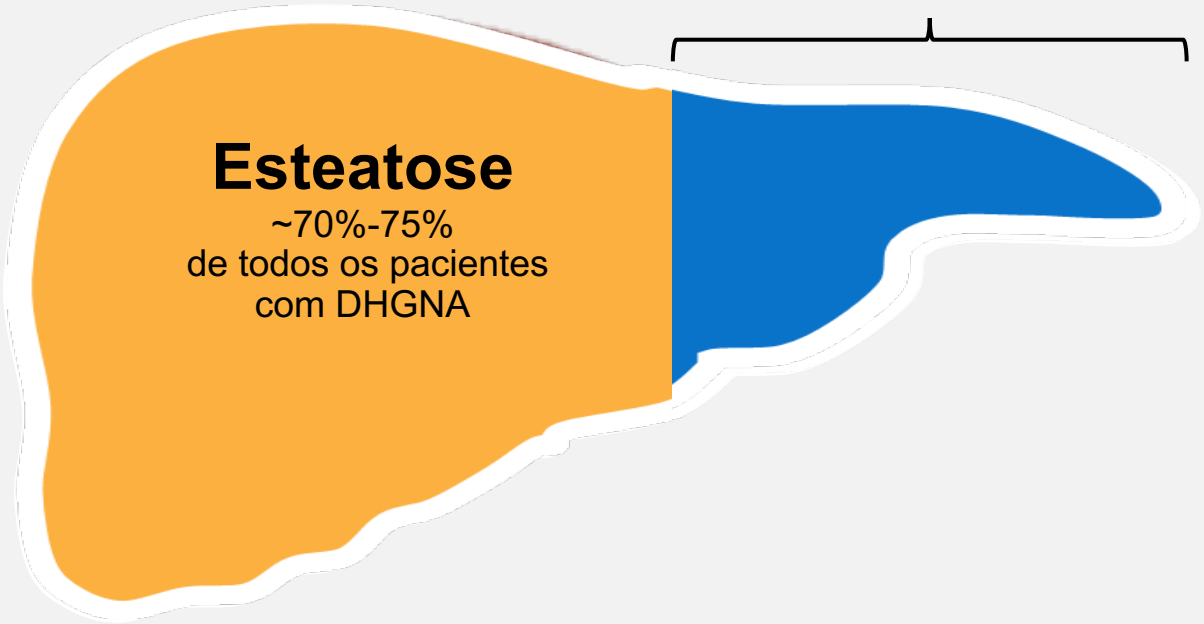
Adaptado de Friedman SL. Physiol Rev 2008;88:125–172,
Lanthier N, et al. Curr Opin Clin Nutr Metab Care 2009;12:404–411

Patogênese da DHGNA



Arrese et al 2021 Seminars in Liver Disease 2021

História Natural da DHGNA

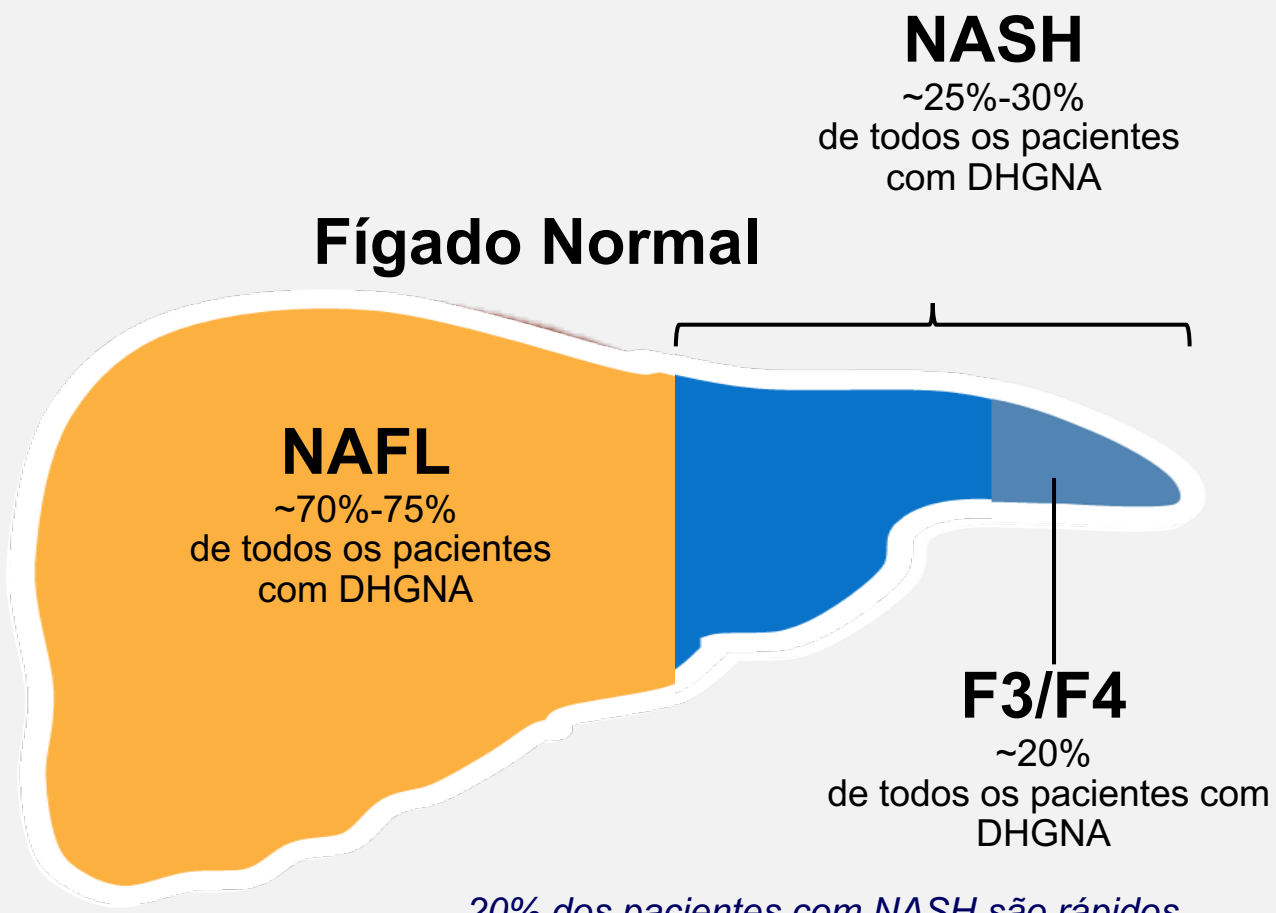


Esteatohepatite Não Alcoólica (NASH)

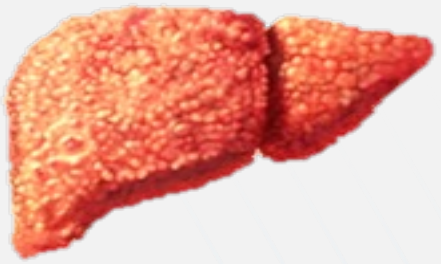
- Lesão hepatocellular com balonização hepatocellular e morte cellular
- Infiltrado inflamatório
- Deposição de colágeno (fibrose)

Rinella ME, et al. *JAMA*. 2015;313(22):2263-227.

História Natural da DHGNA: Cirrose



20% dos pacientes com NASH são rápidos progressores para cirrose em 10 anos



Fibrose Avançada (F3/F4)

- Fibrogênese
- Ativação das células estreladas e produção de colágeno levando a fibrose
- Cirrose que pode progredir para CHC , Falência Hepatica, Transplante hepático e Morte

Rinella ME, et al. *JAMA*. 2015;313(22):2263-227.

Preditores fenotípicos de NASH nos pacientes com DHGNA

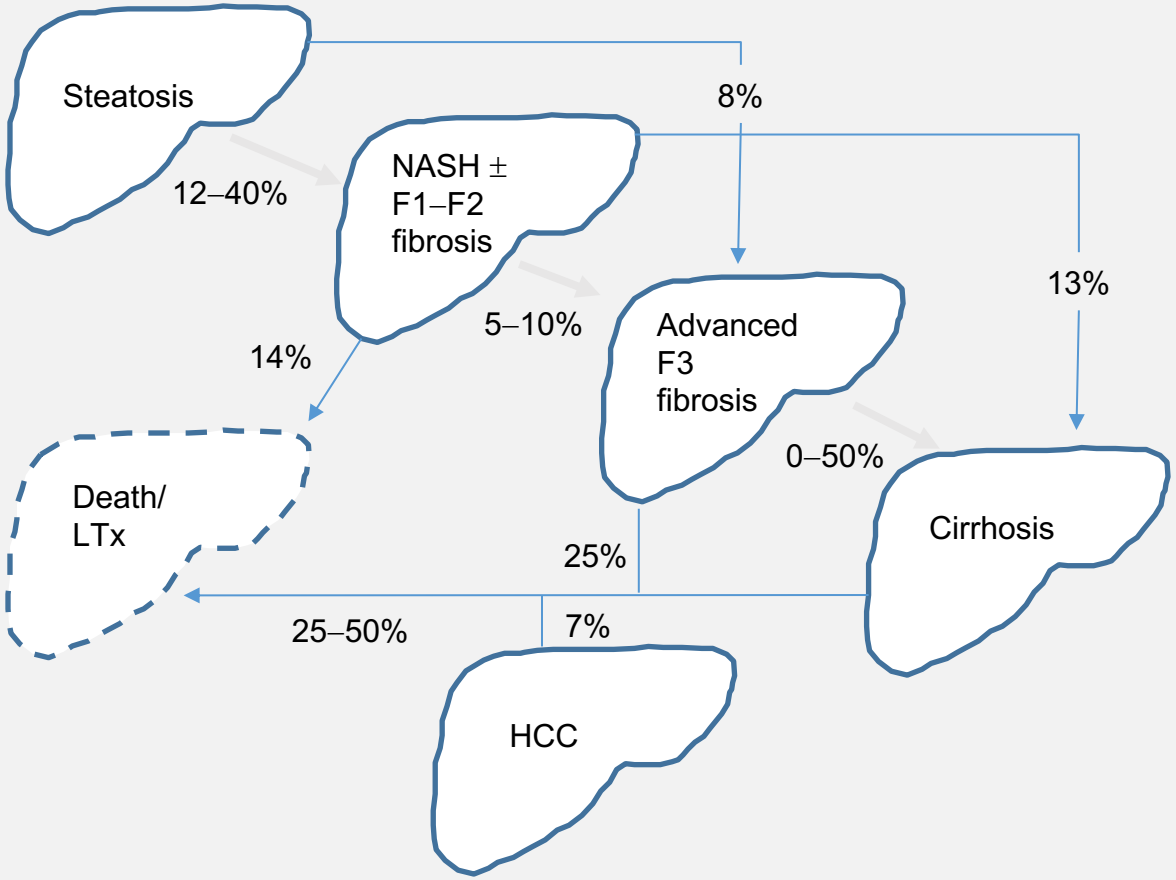
Características	Desfecho
Idade avançada*[1]	Maior duração da doença
Sexo[2]	Mulheres na pós-menopausa apresentam doença mais acelerada
Raça[3]	↑ Prevalência, gravidade em Hispânicos e Asiáticos ; ↓ Prevalência e gravidade reduzida e, pacientes afrodescendentes.
HAS,* obesidade central, dislipidemia (↑ TG, ↓ HDL), resistência à insulina /diabetes*[4]	Síndrome Metabólica aumenta o risco para fibrose avançada (F3) em 66%† se o paciente tiver mais que 50 anos, gor obeso e diabético[5,6]
Razão AST/ALT > 1,[7] plaquetas baixas[8]	Indicadores de cirrose por NASH
ALT persistentemente elevada [9]	Pode estar associada a maior risco de progressão para fibrose avançada.

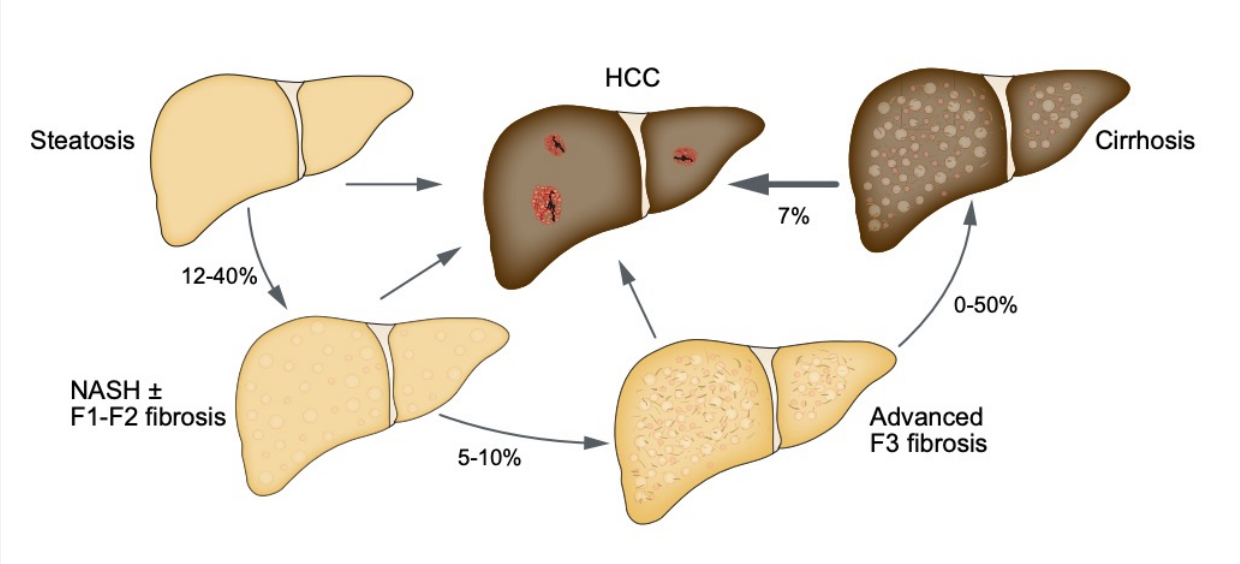
NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis
Adapted from: Anstee & Day, Oxford Textbook of Medicine, 2017
Satapathy SK and Sanyal AJ. *Semin Liver Dis* 2015;35:221–235

*Strongest predictors of advanced disease, regardless of liver enzyme elevation; †Based on ATP III criteria.

1. McPherson S, et al. *Am J Gastroenterol*. 2016;[Epub ahead of print]; 2. Yang JD, et al. *Hepatology*. 2014;59:1406-1414; 3. Pan JJ, Fallon MB. *World J Hepatol*. 2014;6:274-283; 4. Younossi, Z M, et al. *Hepatology*. 2016;64:73–84; 5. Ratziu V, et al. *Gastroenterology*. 2000;118:1117-1123; 6. Angulo P, et al. *Hepatology*. 1999;30:1356-1362; 7. Neuschwander-Tetri BA, et al. *Hepatology*. 2010;52:913-924; 8. McPherson S, et al. *Gut*. 2010;59:1265-1269
9. Ekstedt M, et al. *Hepatology*. 2006;44:865-873; 10. Vernon G, et al. *Aliment Pharmacol Ther*. 2011;34:274-285

História Natural da DHGNA: Carcinoma Hepatocelular

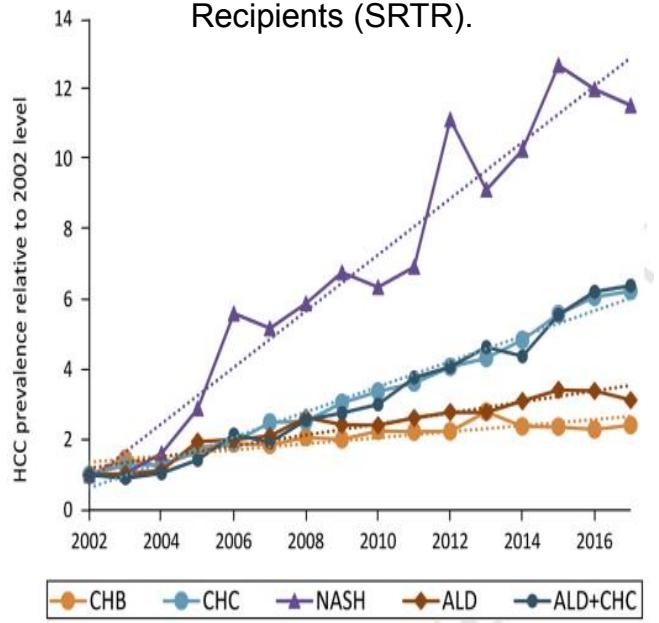




História Natural da DHGNA: Carcinoma Hepatocelular

NAFLD and HCC – the changes in etiology

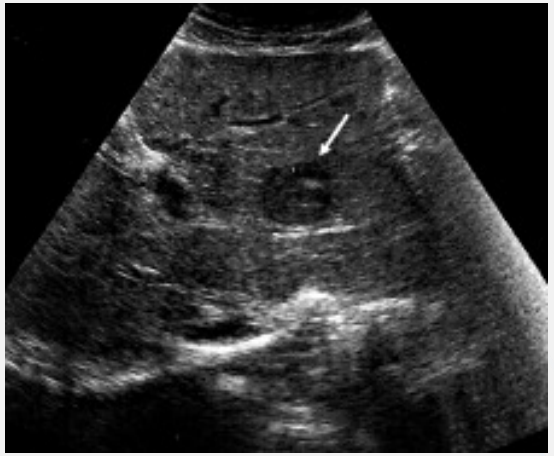
Data from the Scientific Registry of Transplant Recipients (SRTR).

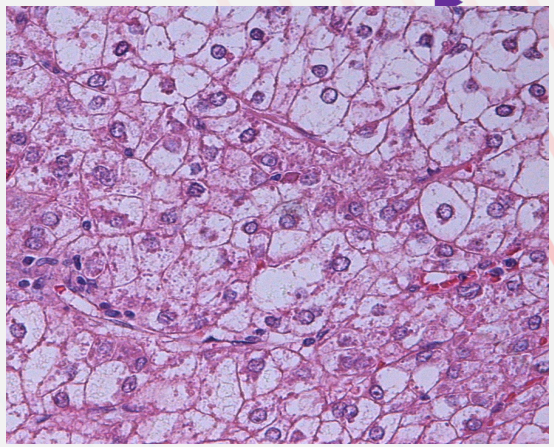


170,540 patients on wait list from 2002 to 2017:

28,935 with HCC (17%)

2690 with NAFLD



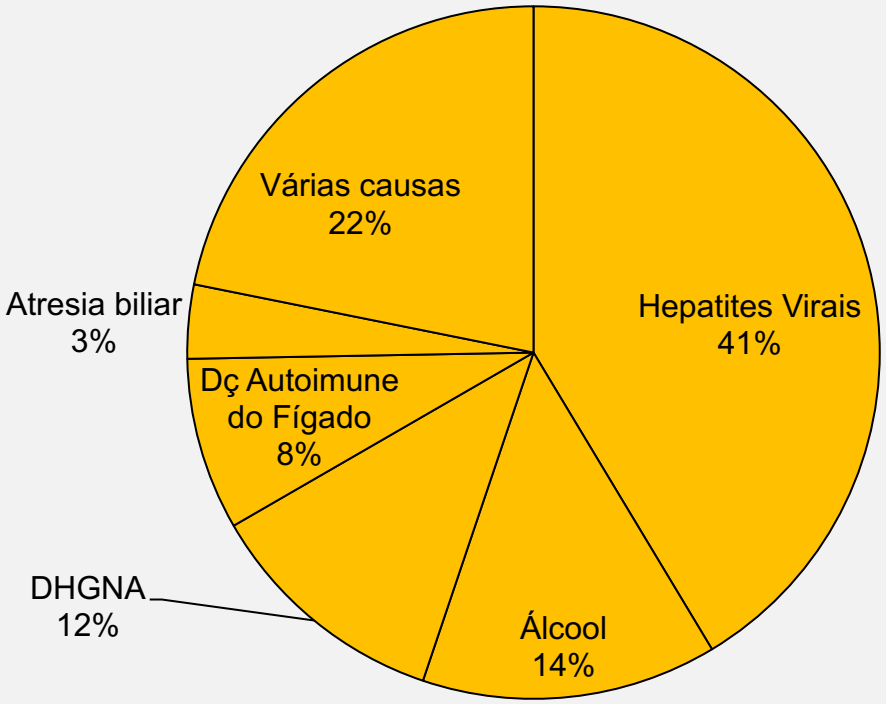


- Aproximadamente 3–8% dos pacientes com DHGNA evolui para cirrose e risco de CHC
- 25%-30% dos pacientes com CHC por DHGNA não tem cirrose

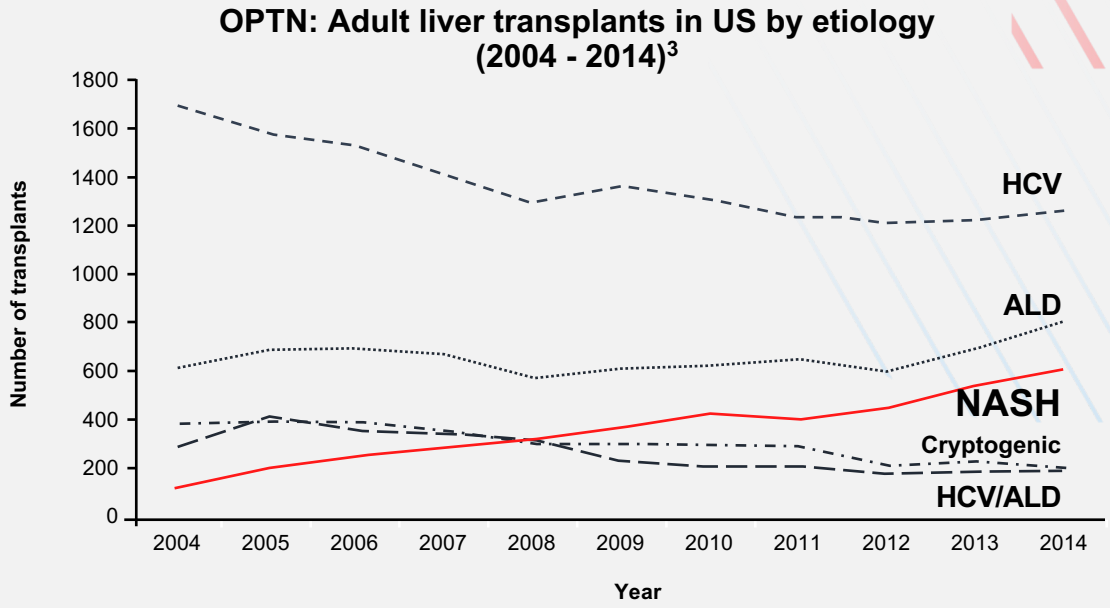
Younoussi et al. 2019

História Natural da DHGNA: Cirrose

Transplante Hepático no Brasil



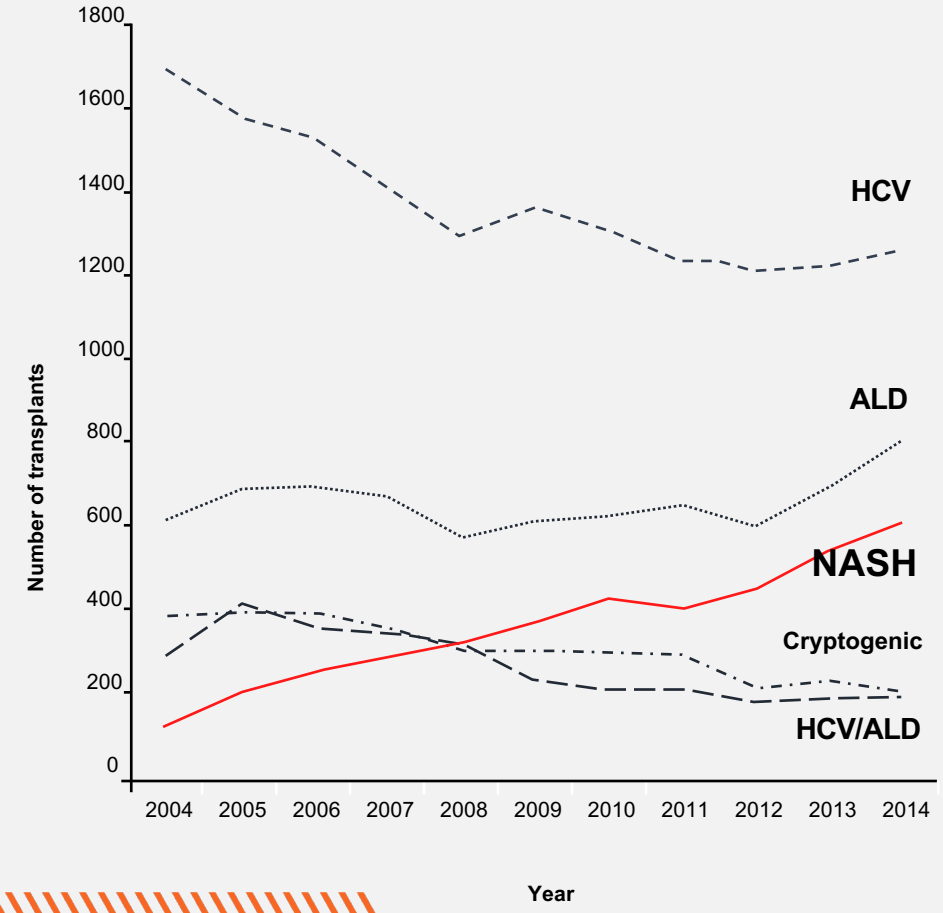
Transplante Hepático nos EUA



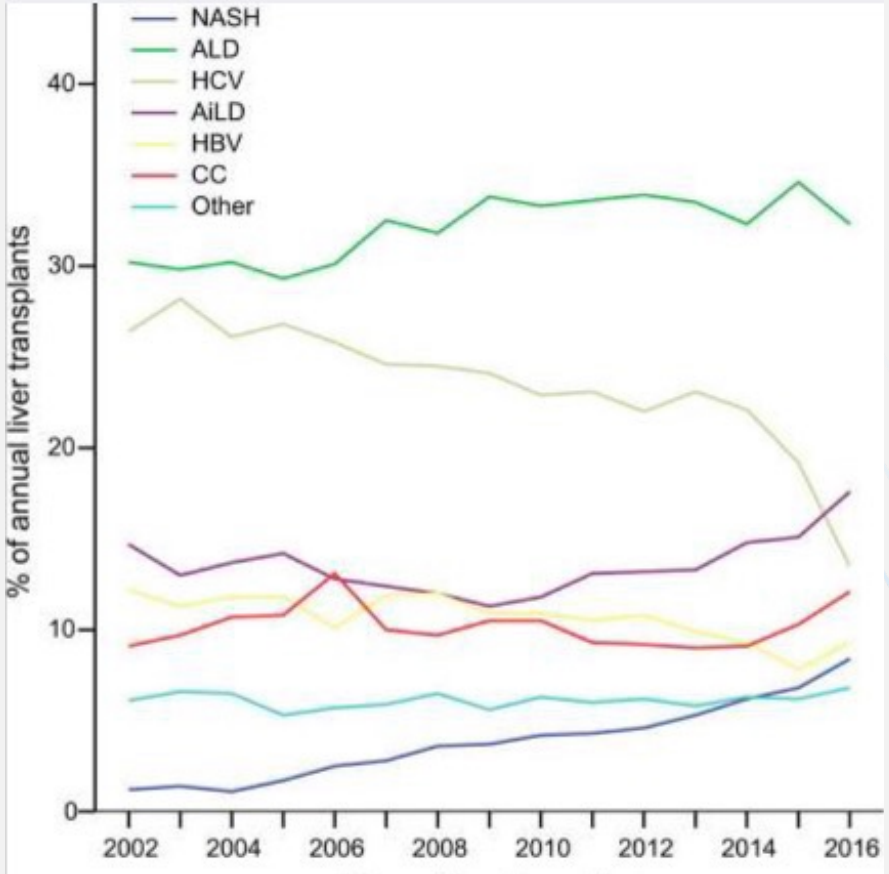
Bittencourt et al. Liver Transplantation 2016

História Natural da DHGNA: Cirrose

Transplante Hepático nos EUA



Transplante Hepático na Europa

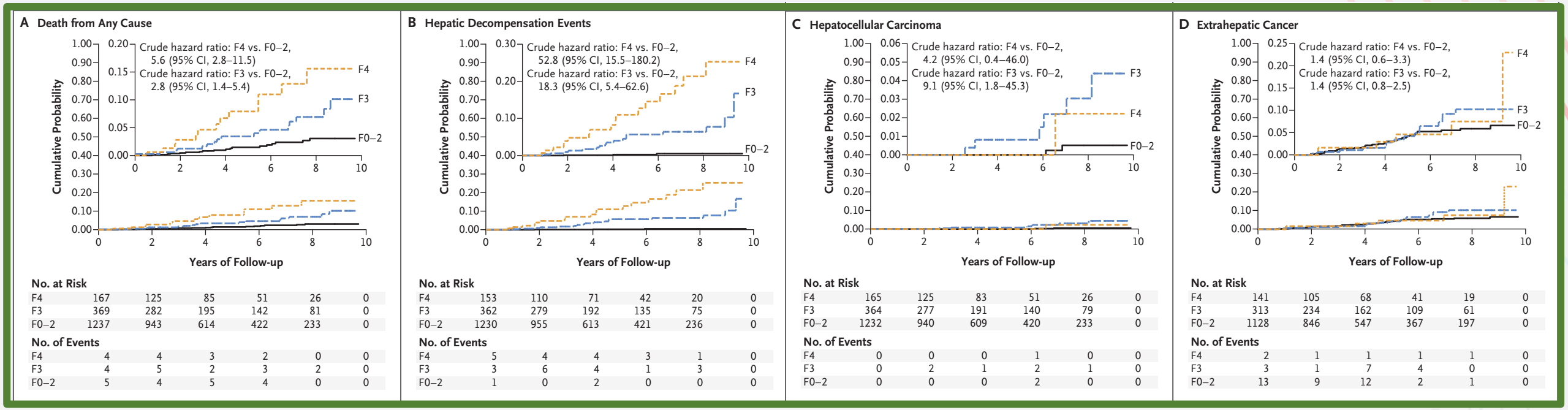


Haldar D et al. J Hepatol 2019;71:313–22

PROGNÓSTICO

Mortalidade por causa não hepática

Doença cardiovascular e câncer são causas comuns



n=1773
Mediana F/U 4 anos

O risco geral de morte aumenta conforme a fibrose hepática

Sanyal et al, NEJM 2021

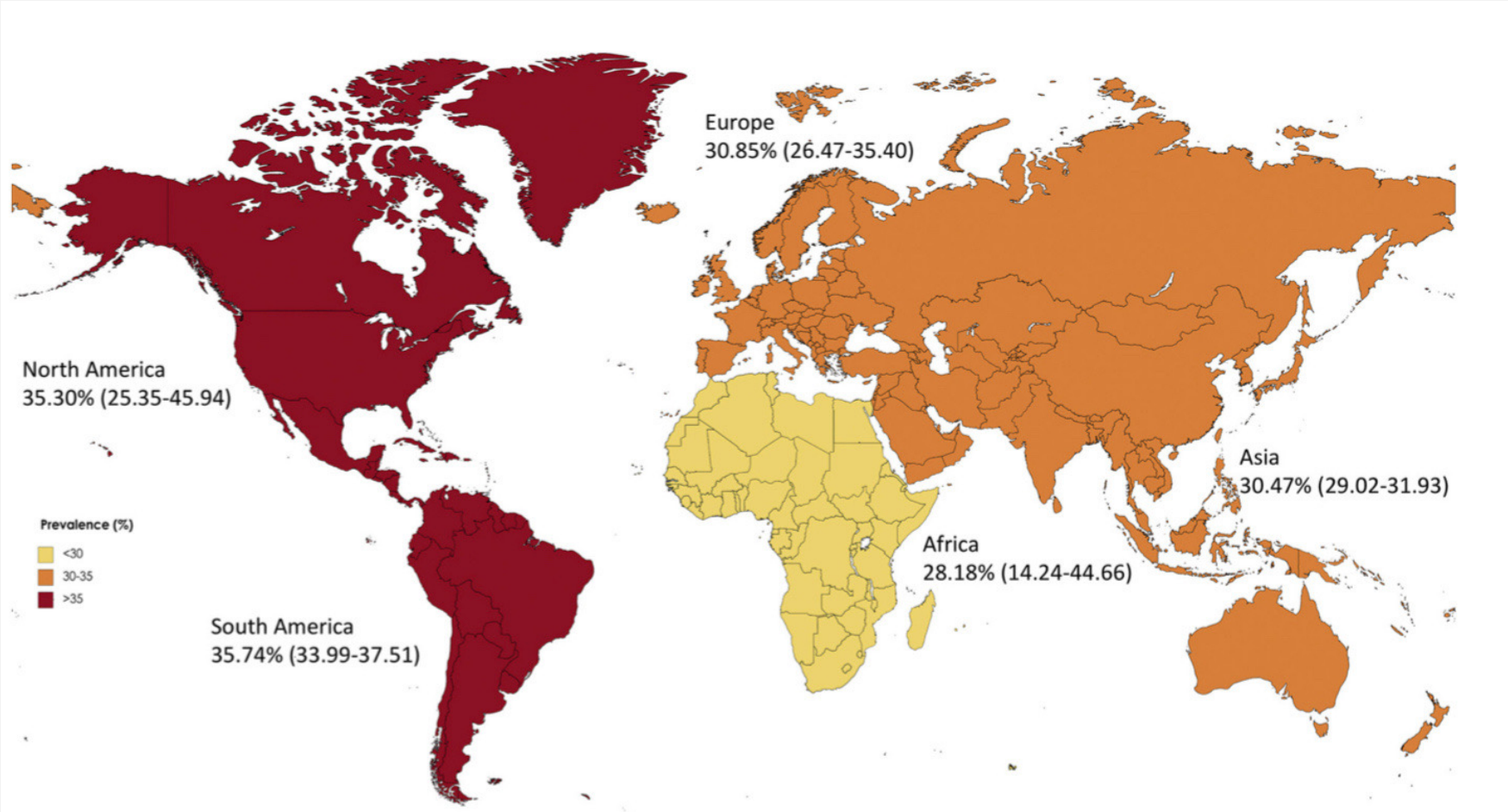
DHGNA/MAFLD/MASLD e Síndrome Metabólica

Table 1. Comorbid Conditions Associated With Nonalcoholic Steatohepatitis

	% Estimated prevalence		
Condition	General US population	Patients with NAFLD	Patients with NASH
Hypertriglyceridemia[7,14]	25.1	40.7	83.3
Obesity[7,15]	39.8	51.3	81.8
Dyslipidemia[7,16]	18.4	69.2	72.1
Metabolic syndrome[7,16]	34.3	42.5	70.7
Hypertension[7,17]	29.0	39.3	68.0
Type 2 diabetes[7,18]	14.0	22.5	43.6

Sheka et al, JAMA 2020

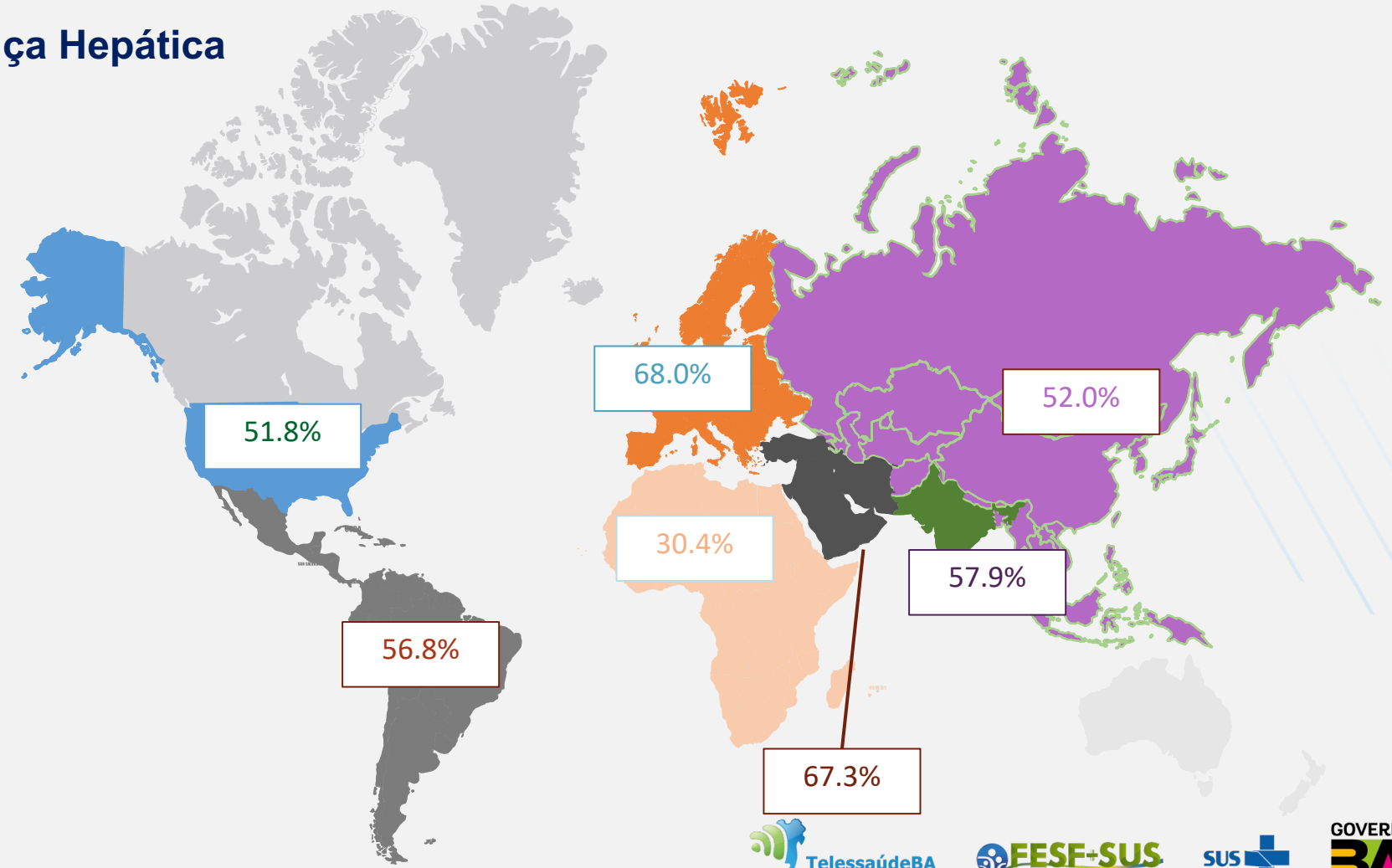
Epidemiologia da DHGNA



Michael et al 2021/Rojas et al 2022/Paik et al 2021/Younossi et al 2016

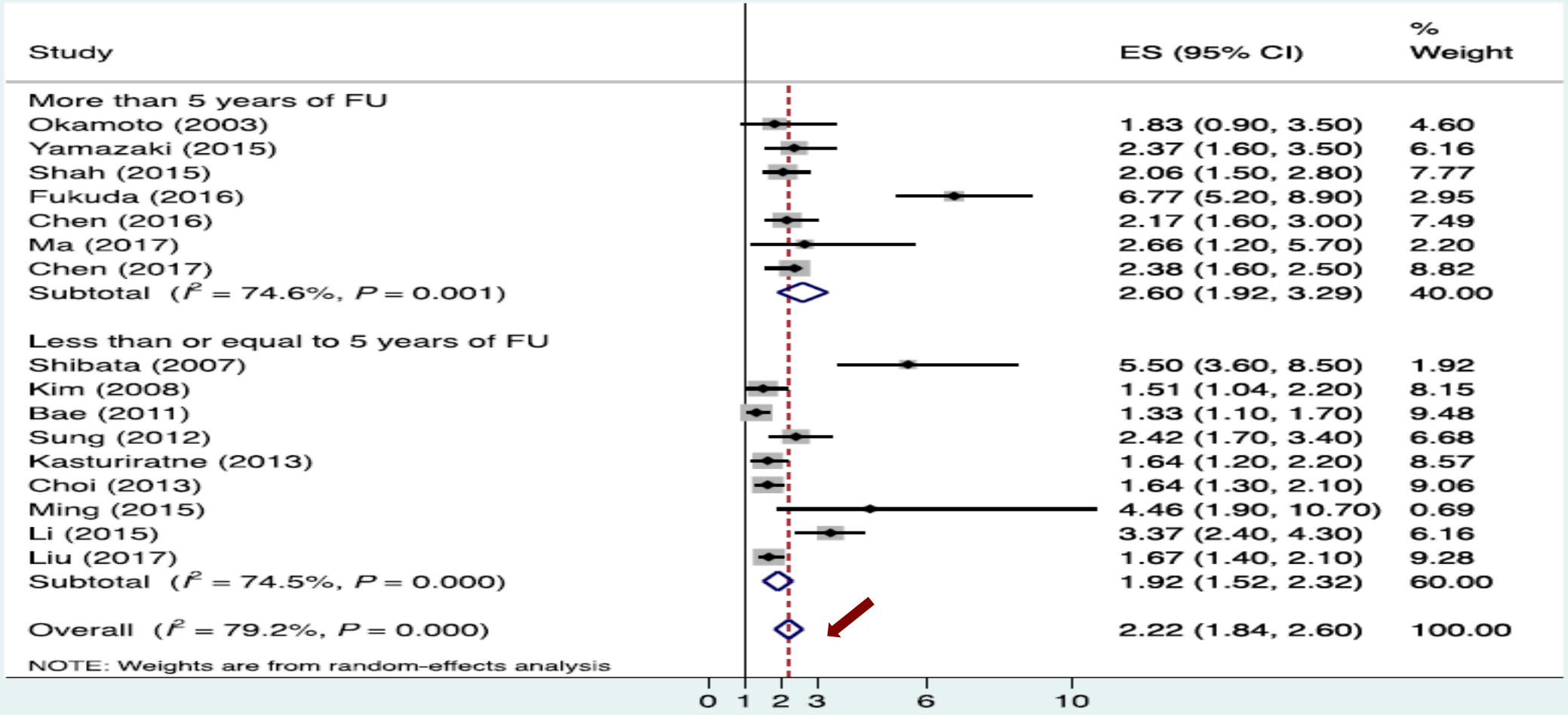
Epidemiologia da DHGNA

Prevalência da Doença Hepática Gordurosa e DMT2



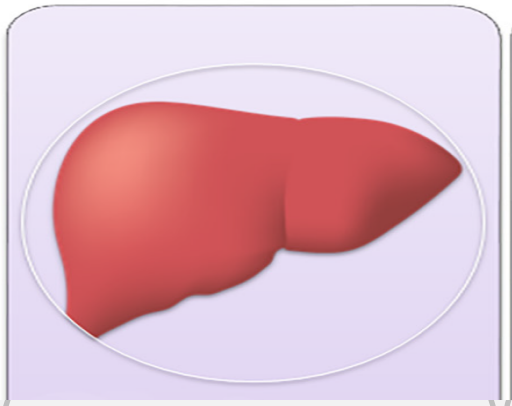
Younossi. J Hepatology. 2019;71:793

Diabetes Mellitus Tipo 2 como fator de risco para DHGNA



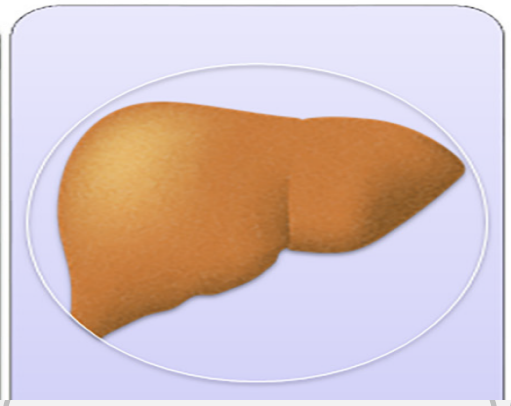
Mantovani et al., Diabetes Care, 2018

Diabetes Melito e DHGNA/MAFLD/MASLD



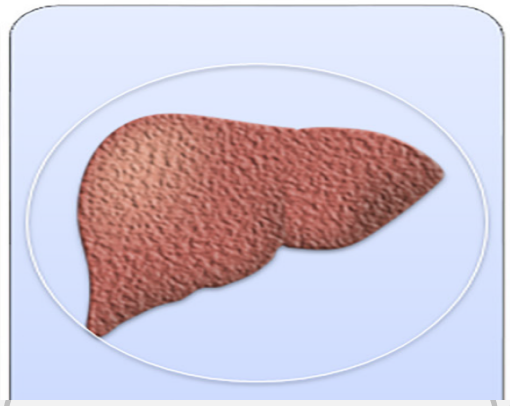
Fígado normal

↑ risco DHGNA em 2 a 5 vezes



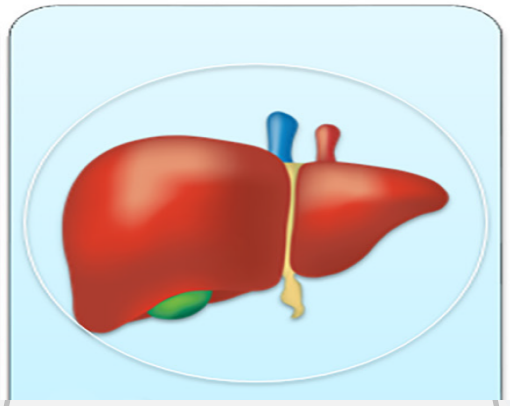
NASH

Acelera a progressão da fibrose
↑ mortalidade geral em 3 vezes
↑ mortalidade hepática em 22 vezes



Cirrose

↓ sobrevida geral em 5 anos em 40%
↑ risco de ascite, IRA, infecções bacterianas e encefalopatia
↑ risco e mortalidade de carcinoma hepatocelular



Transplante

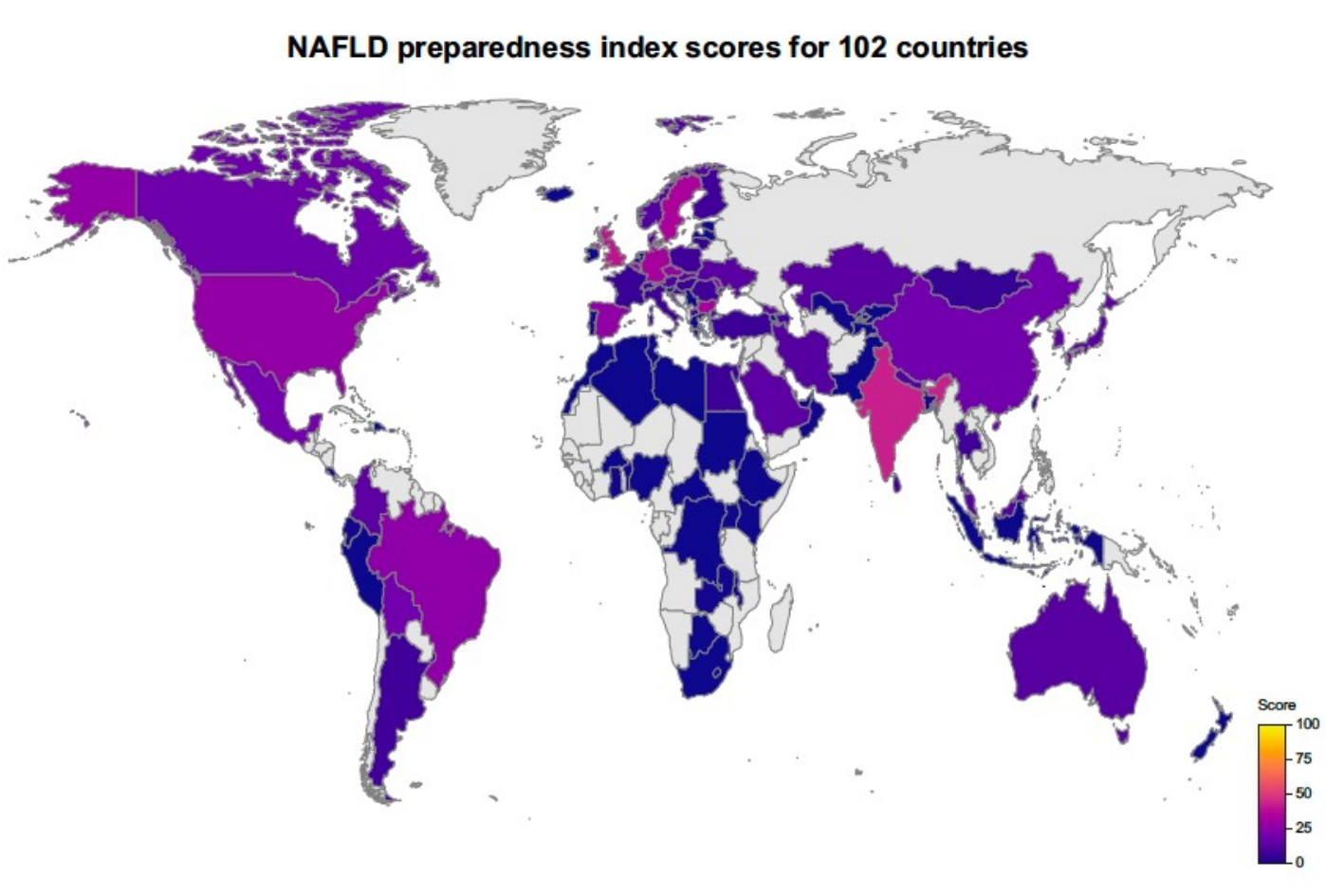
↑ mortalidade pós-TxH
↑ complicações PO
↑ risco de rejeição
↑ risco de SM pós-TXH e de DHGNA de novo

Chung et al, World J Hepatol 2020

Gordura no Fígado como Problema de Saúde Global já está presente nas manchetes dos principais jornais e revistas

TelessaúdeBA FESF-SUS FUNDAÇÃO ESTATAL SAÚDE DA FAMÍLIA SUS GOVERNO DO ESTADO BAHIA SECRETARIA DA SAÚDE

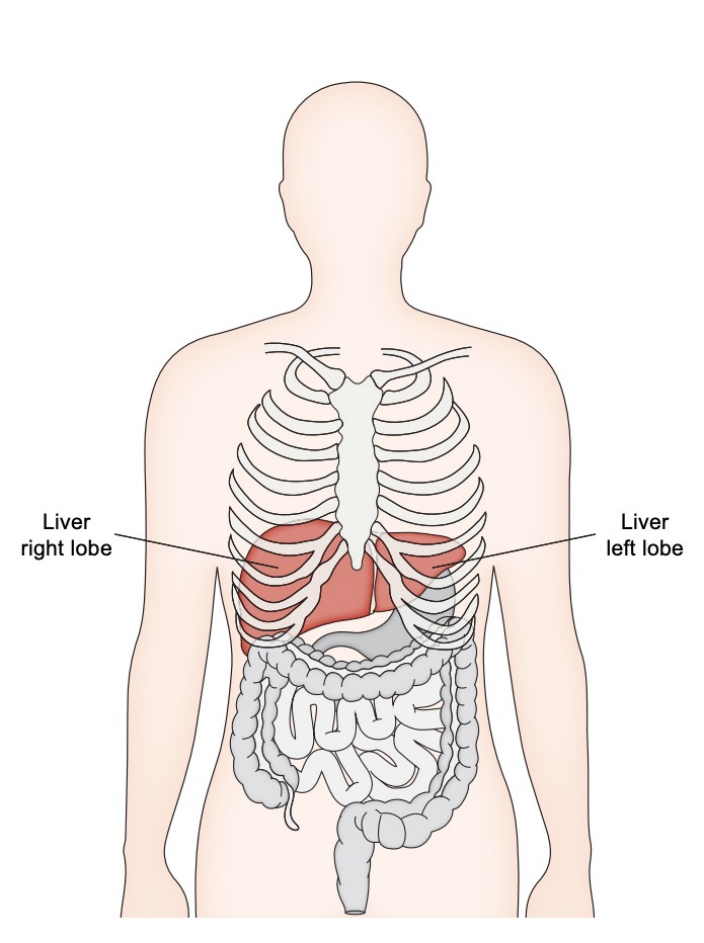
The global NAFLD policy review and preparedness index: Are countries ready to address this silent public health challenge?

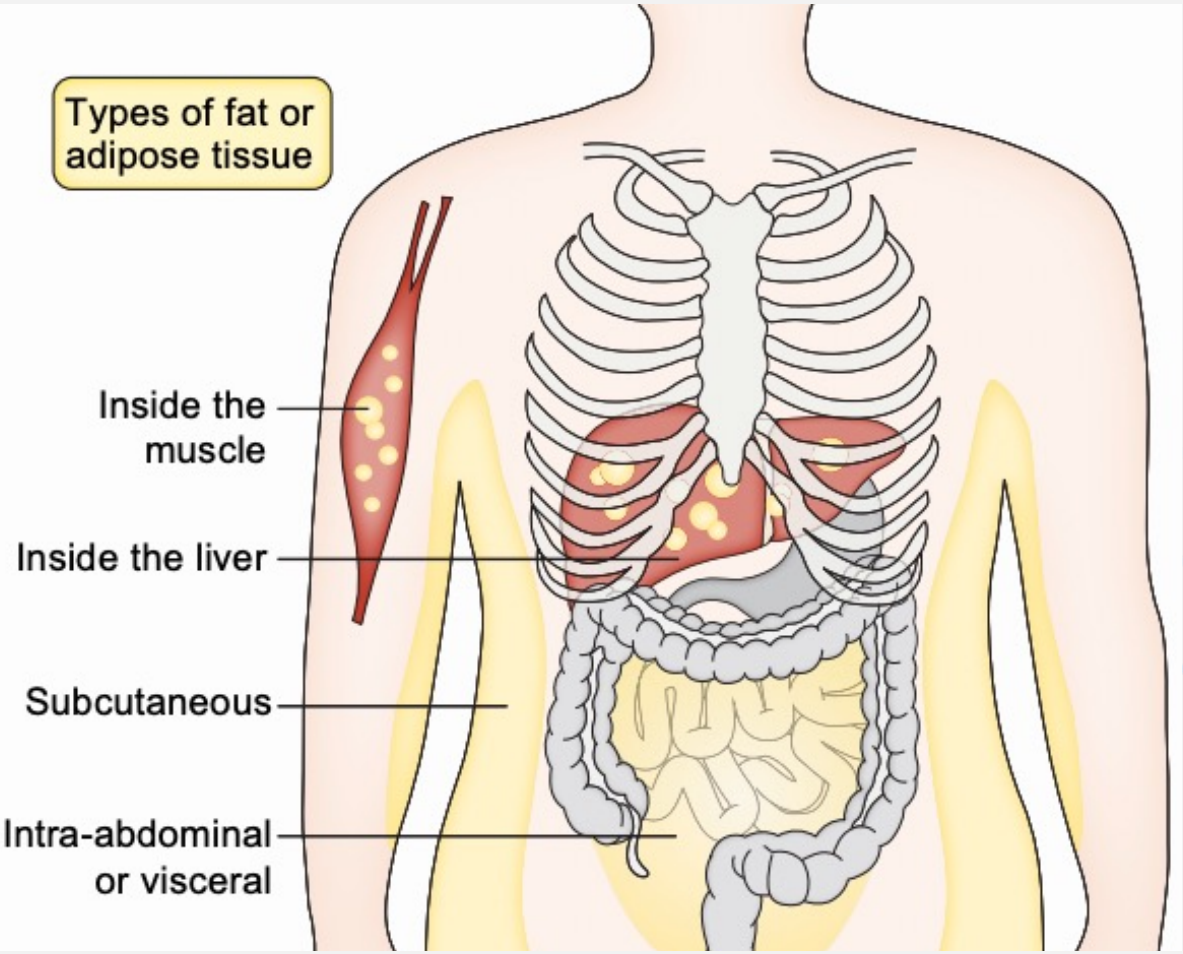


NAFLD preparedness index

- **Policies**
- **Guidelines**
- **Civil awareness**
- **Epidemiology and data**
- **NAFLD detection**
- **NAFLD care management**

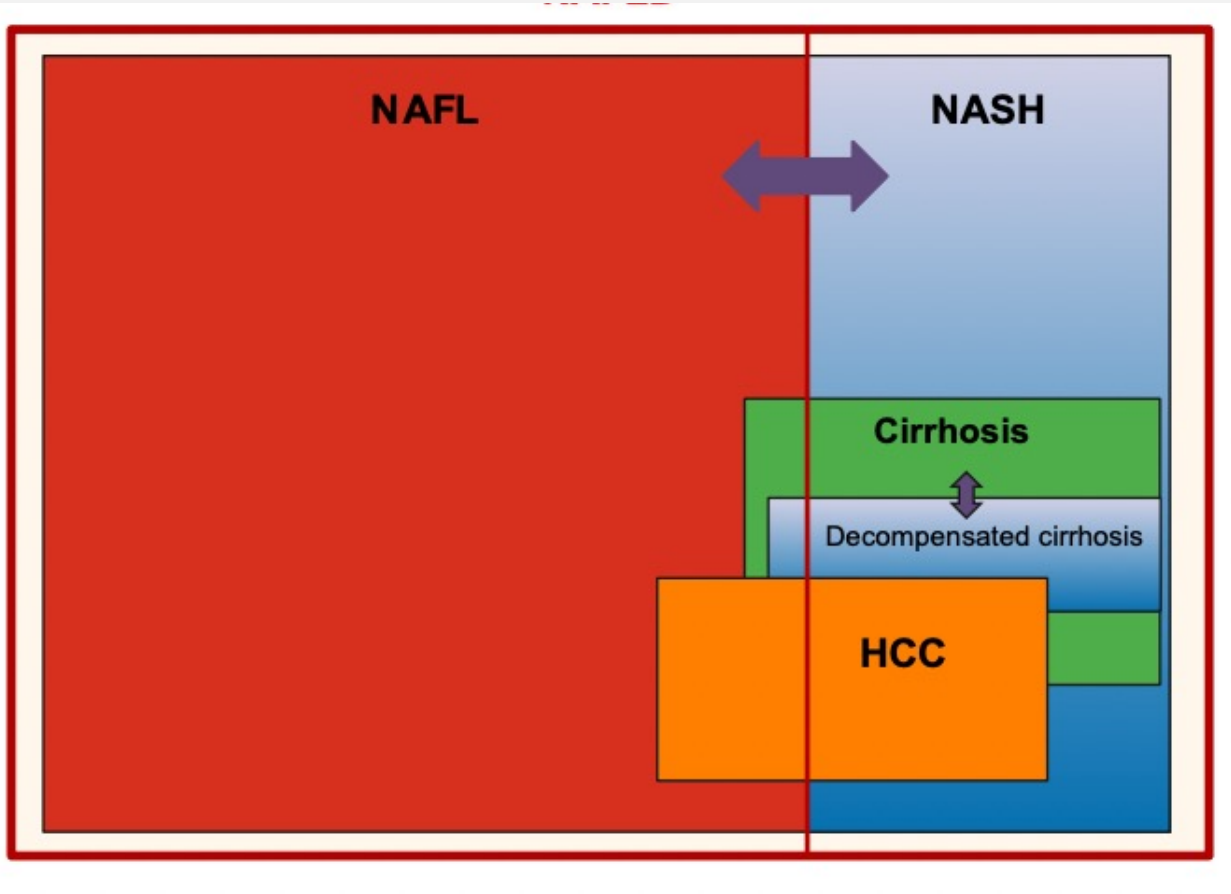
Non-alcoholic fatty liver disease: A patient guideline

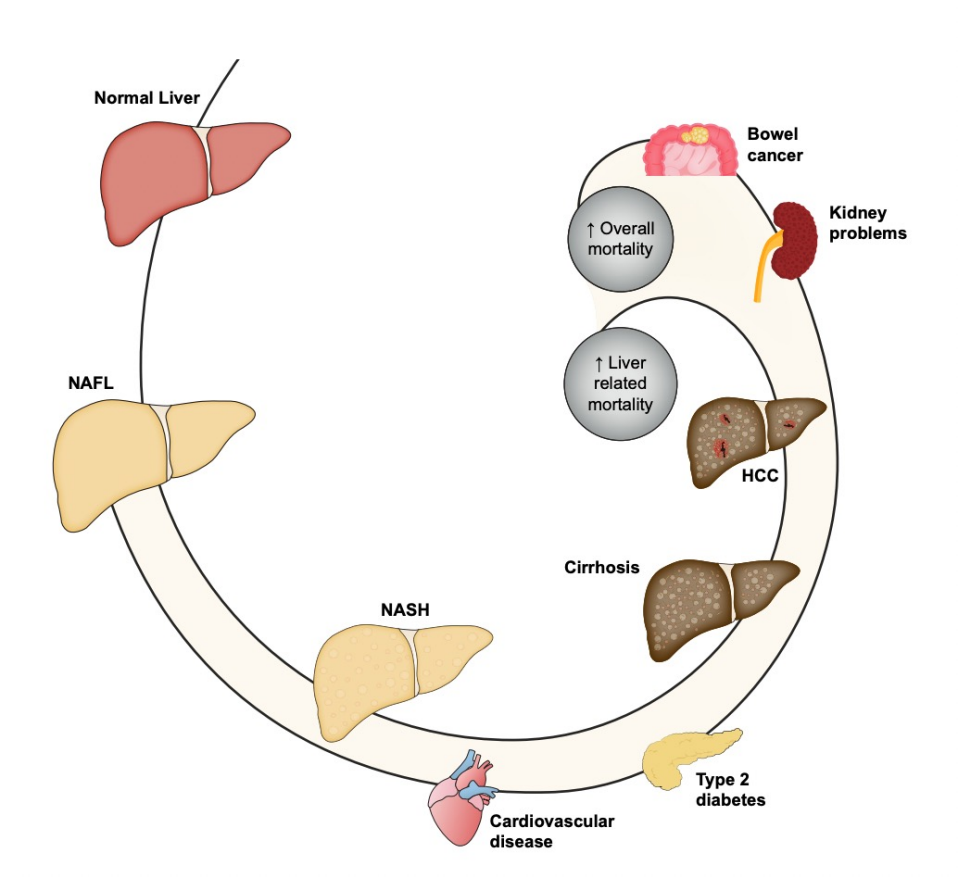




JHEP Reports 2021 vol. 3 j 100322

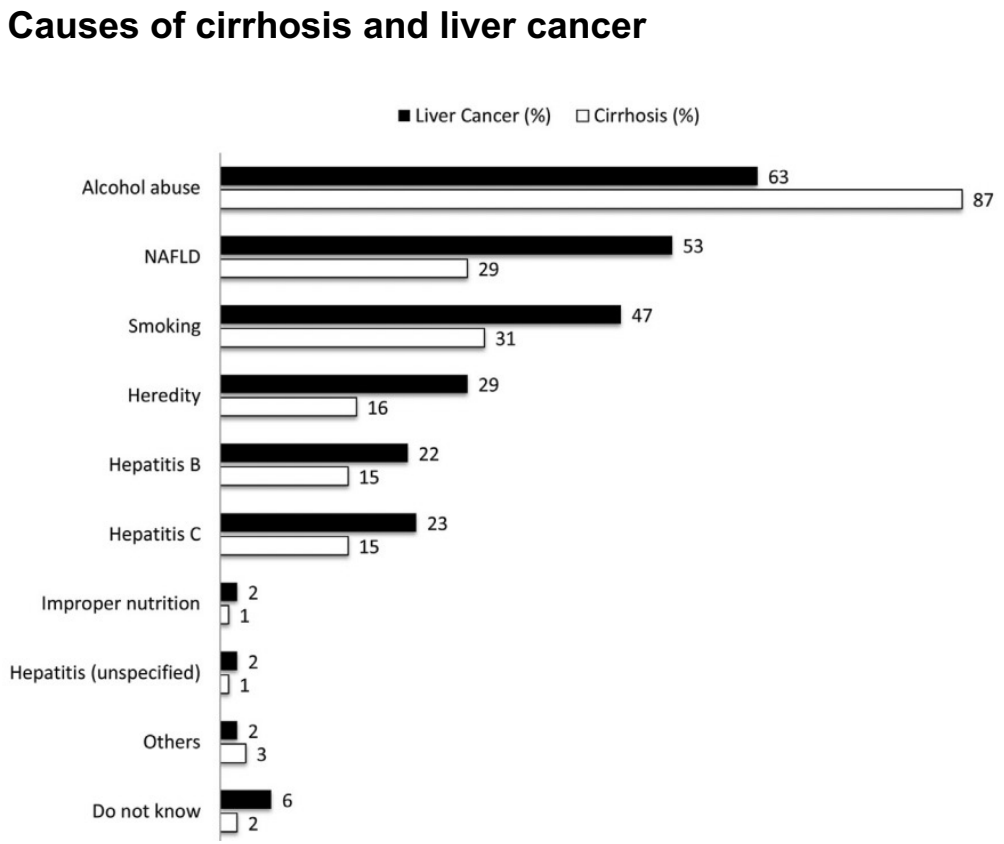
Non-alcoholic fatty liver disease: A patient guideline

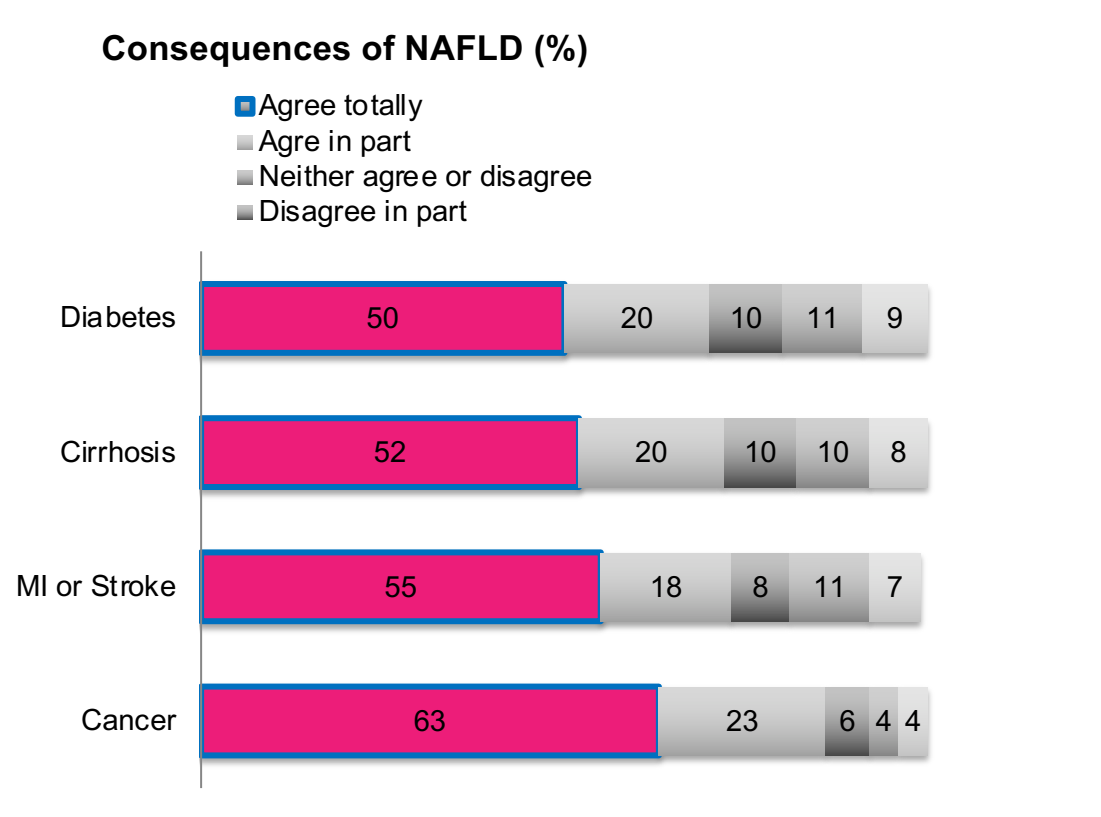




JHEP Reports 2021 vol. 3 j 100322

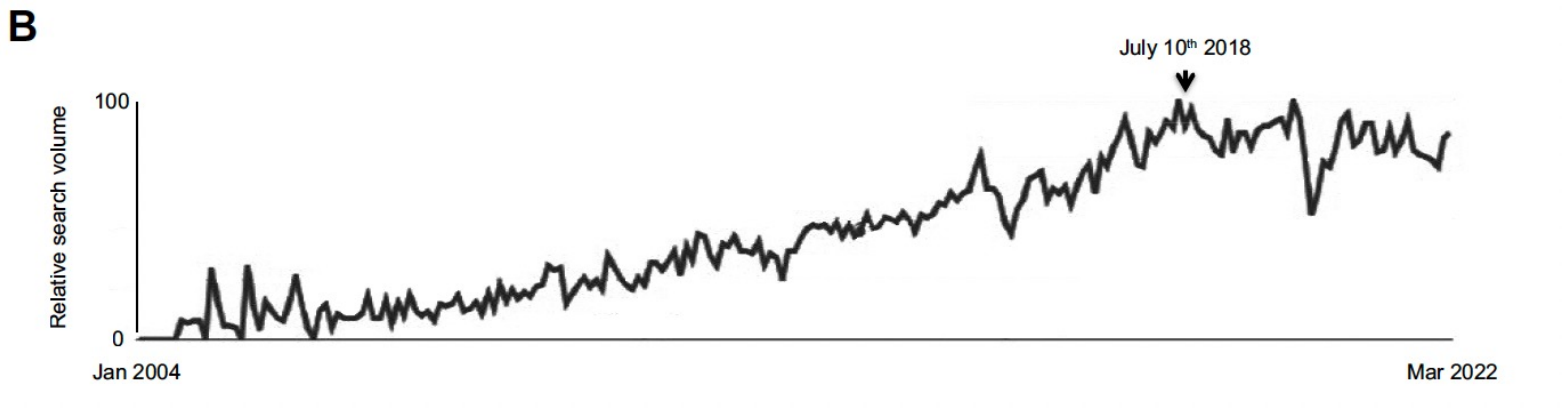
Public knowledge and attitudes toward liver diseases and liver cancer in the Brazilian population: a cross sectional study

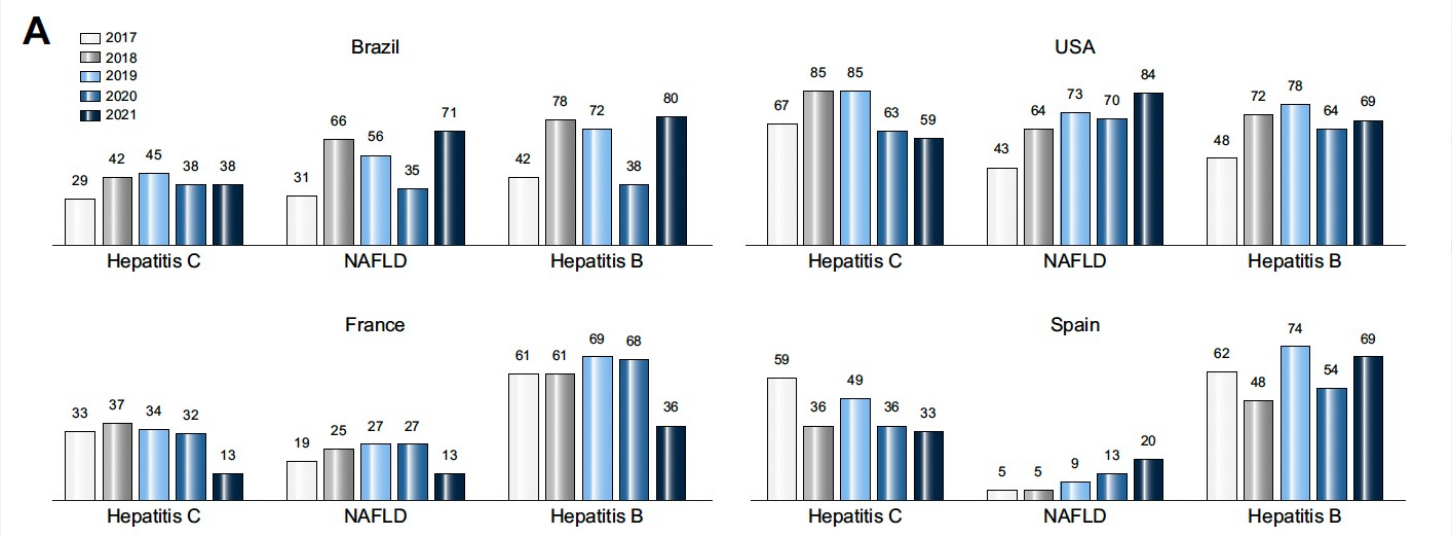




Bittencourt PL et al. The Lancet Regional Health - Americas 2023;23: 100531

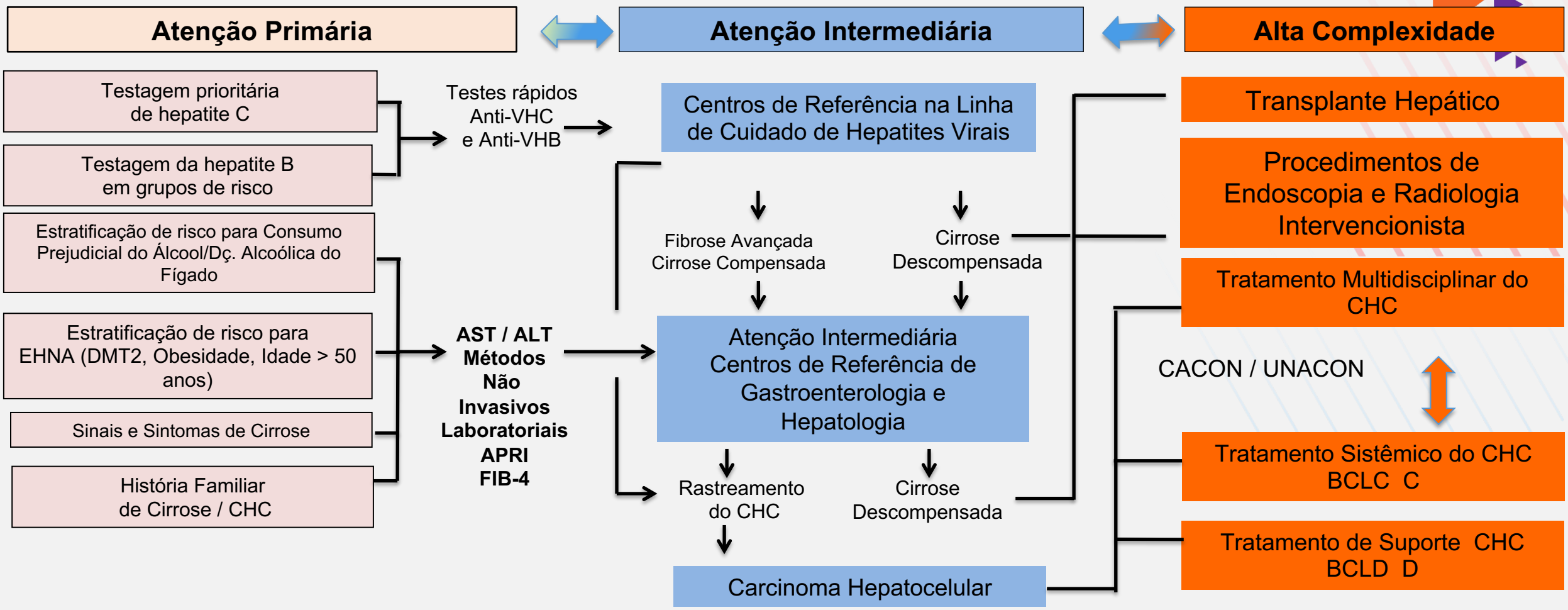
Internet search engines and social media are improving awareness on non-alcoholic fatty liver disease in Brazil





Bittencourt PL et al. J Hepatol 2022, 77:1207–1230

LINHA DE CUIDADO DA CIRROSE (DHGNA) NO SUS



Adaptado de Bittencourt et al. 2019. Linha de Cuidado de Cirrose no SUS

IDENTIFICANDO O PACIENTE DE RISCO

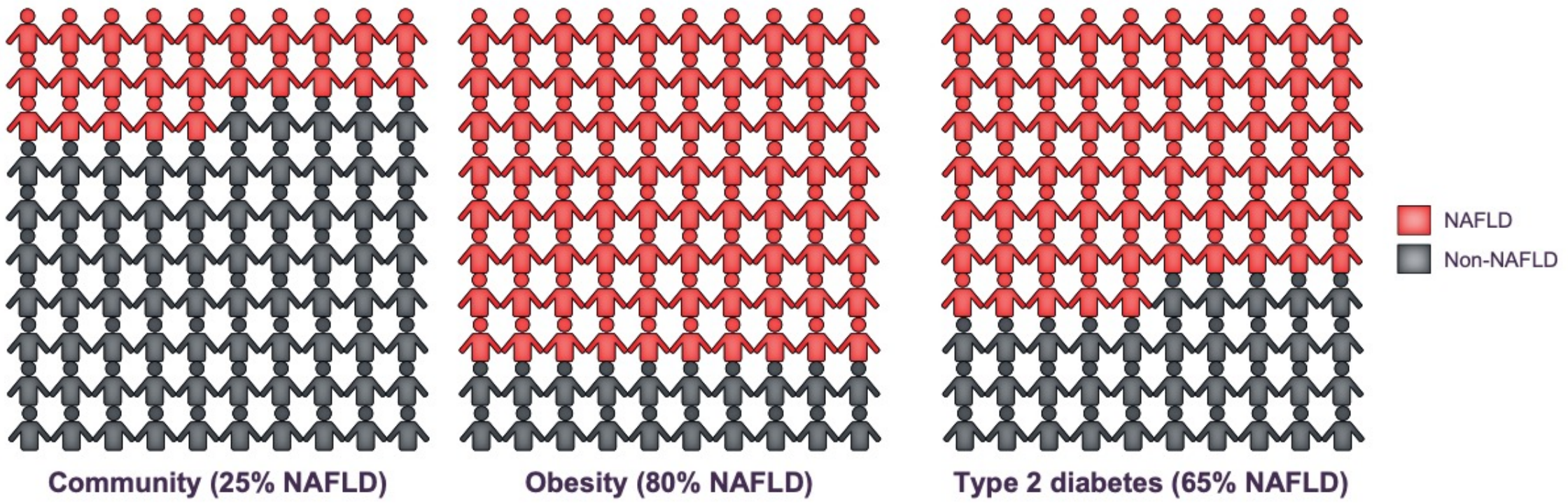
TelessaúdeBA

FESF+SUS FUNDAÇÃO ESTATAL SAÚDE DA FAMÍLIA

SUS

GOVERNO DO ESTADO BAHIA SECRETARIA DA SAÚDE

IDENTIFICANDO O PACIENTE DE RISCO



Enzimas Hepáticas : Inadequadas para identificar DHGNA/*NASH*

- Na DHGNA, ALT não é indicativa nem preditiva de NASH ou estágio de fibrose:
  - ALT normal não exclui NASH/doença progressiva
  - ALT elevada não pode prever NASH ou fibrose
  - ALT ou AST não sensível para NAFLD/NASH
  - ALT ou AST normais e doença progressiva são frequentes no DMT2

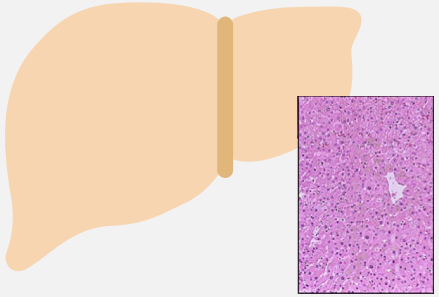
ALT anormal pode justificar a investigação para DHGNA, mas não é sensível para confirmar, descartar ou caracterizar DHGNA

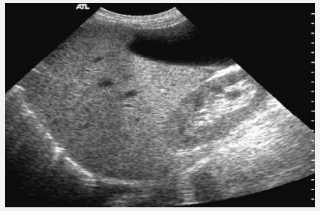
Mofrad. Hepatology. 2003;37:1286. 2. Younossi. Am J Gastroenterol. 2020;00:1.

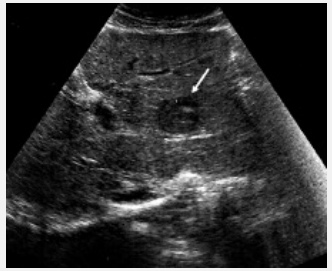
Identificando DHGNA: Ultrassonografia

A ultrassonografia pode identificar fígado gorduroso (esteatose), mas não pode distinguir esteatose vs. NASH vs. fibrose/cirrose precoce

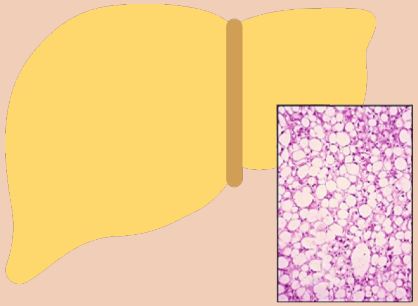
Fígado Normal





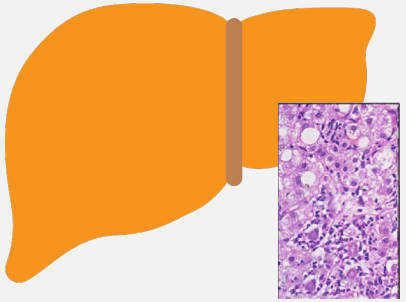


Esteatose "NAFL"



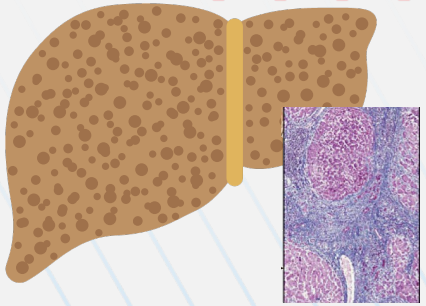
Esteatose com inflamação ausente ou minima sem balonizacao

Esteatohepatite "NASH"



Esteatose com inflamação significativa e balonização

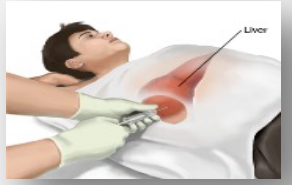
Cirrose

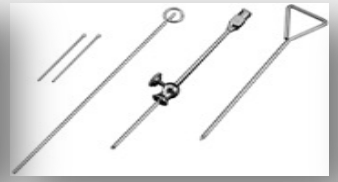


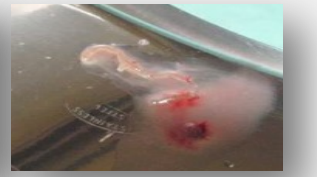
Fibrose progressiva, cirrose e CHC

Younossi. J Hepatol. 2019;70:351. Kabbany. Am J Hepatol. 2017;112:581.

Biópsia hepatica permanece sendo padrao-ouro para diferenciar Esteatose de NASH e estadiar DHGNA







Esteatose vs. NASH

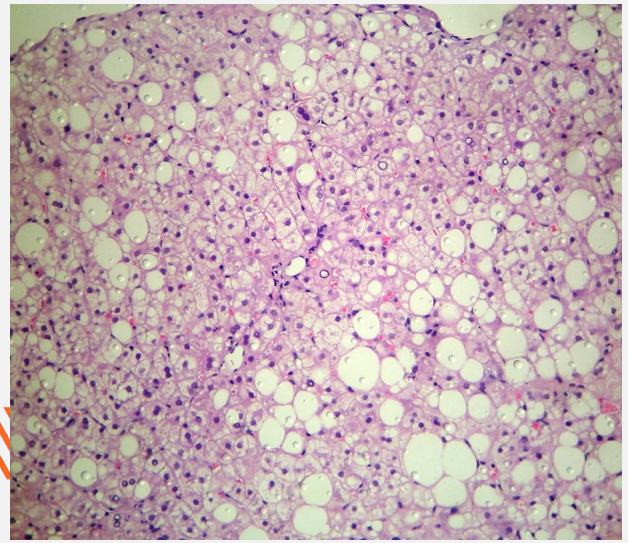
diagnóstico

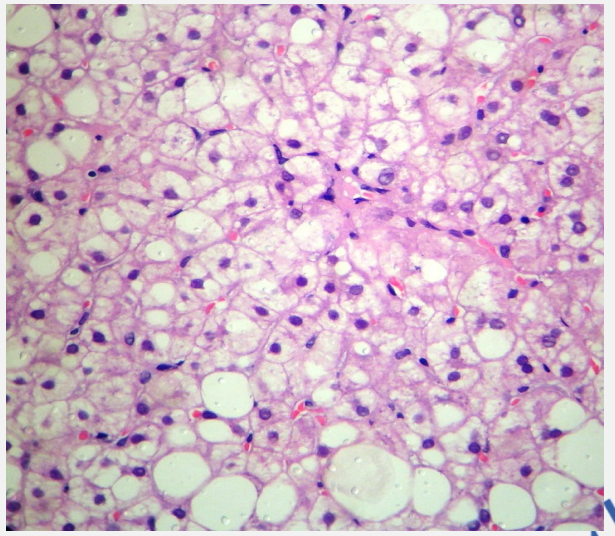
NASH Grau/Estadiamento

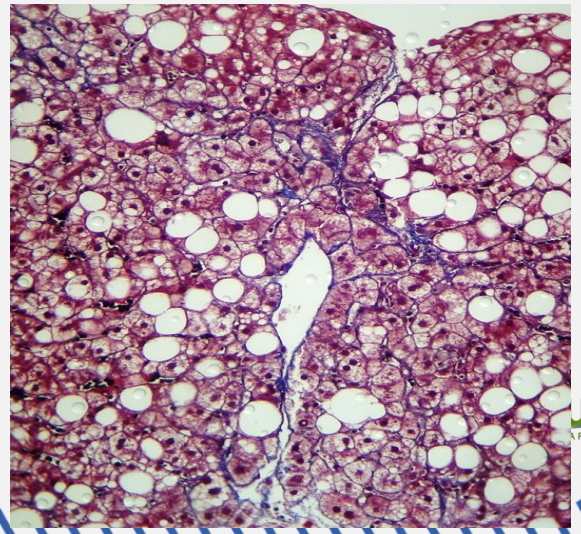
prognóstico

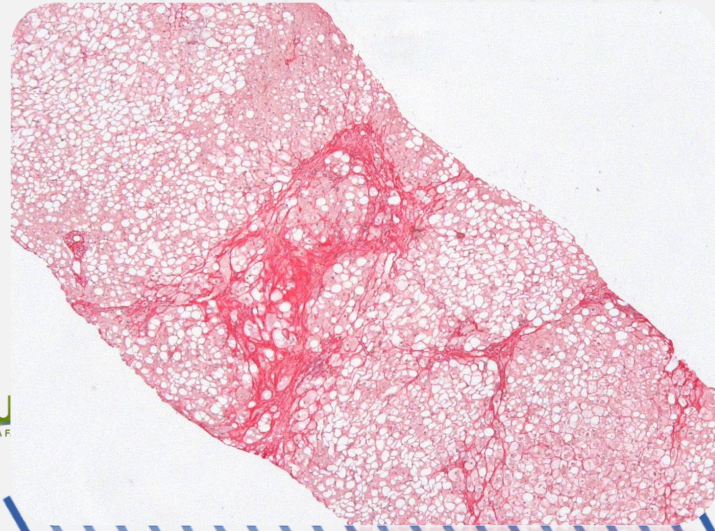
USO DE SISTEMAS DE ESTADIAMENTO

- GRAU DE ESTEATOSE
- INFLAMACAO LOBULAR
- BALONIZACAO
- FIBROSE



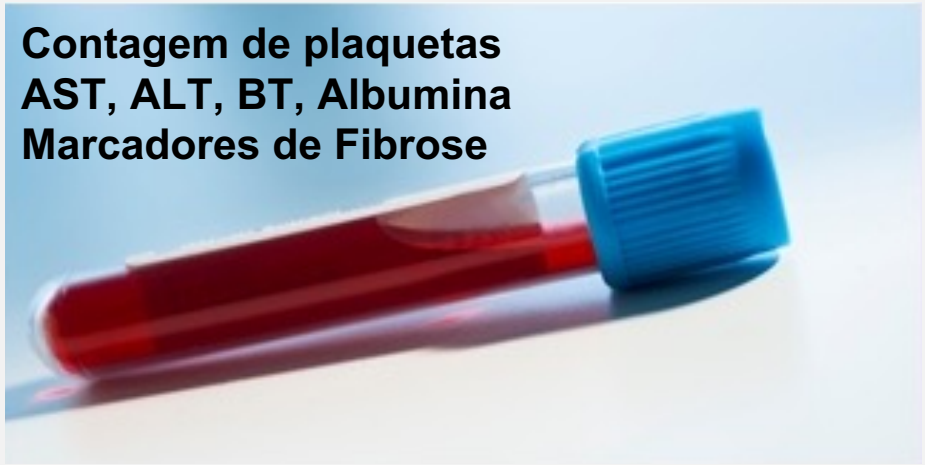


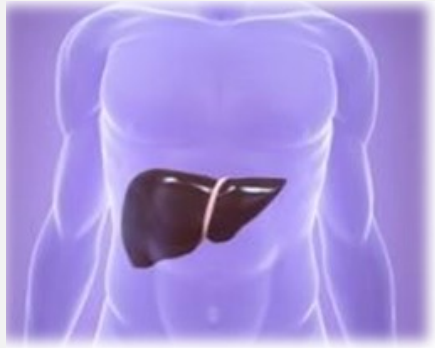


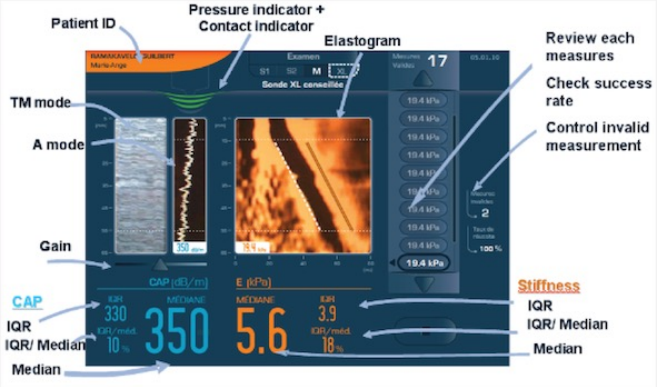


IDENTIFICANDO O PACIENTE DE RISCO

Métodos Não Invasivos Laboratoriais

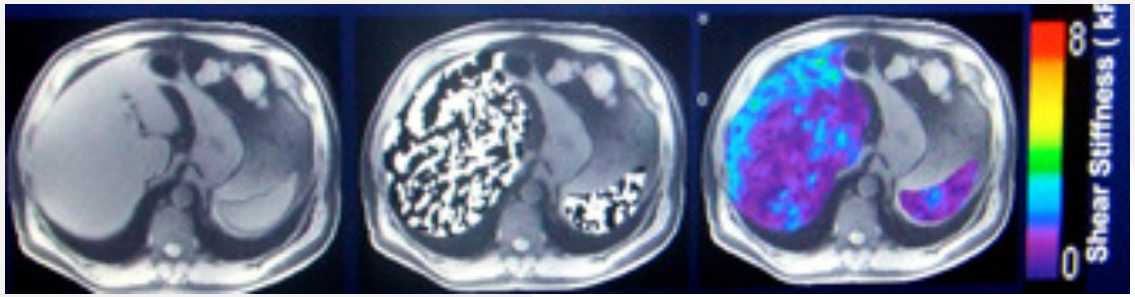






Métodos Não Invasivos de Imagem: Ultrassonografia/TC/RM

Elastografia hepática
- Ultrassônica:
- Ressonância magnética



Cardoso AC, Villela-Nogueira CA, de Figueiredo-Mendes C, Leão Filho H, Silva RA, Tovo CV, Perazzo H, Matteoni AC, de Carvalho-Filho RJ & Bittencourt PL. Ann Hepatol 2021

Métodos Não Invasivos

Escores Clínicos e Laboratoriais

Simples

- Fibrosis-4 (FIB-4)[1,2]
- NAFLD fibrosis score[1,2]
- AST/platelet ratio index[1]

Patenteados

- Enhanced Liver Fibrosis Test[1] (not available in US)
- NIS4
- ADAPT/Pro-C3[3] (not available in US)
- *FibroSure*[1]
- Hepascore

Imagem

Elastografia

- Transient elastography (eg, *FibroScan*)[1,2]
- 2D shear wave elastography[4]
- Magnetic resonance elastography[1]
- Corrected T1 (*Liver MultiScan*)[5,6]
- MRI-PDFF[7]
- FAST score[8]

1. EASL. J Hepatol. 2015;63:237. 2. Alkhouri. Gastroenterol Hepatol (N Y). 2012:8:661. 3. Daniels. Hepatology. 2019;69:1075.
4. Sigrist. Theranostics 2017;7:1303. 5. Jayaswal. AASLD 2018. Abstr. 1042. 6. Jayaswal. Liver Int. 2020;40:3071.
7. Idilman. Radiology. 2013;267:767. 8. Newsome. Lancet Gastroenterol Hepatol. 2019;[Epub].

Métodos Não Invasivos Laboratoriais estão disponíveis no SUS

› Para calcular o FIB4:

$$FIB4 = \frac{\text{Idade (anos)} \times \text{AST (UI/L)}}{\text{Contagem de Plaquetas } (10^9) \times \sqrt{\text{ALT (UI/L)}}}$$

Como calcular o Índice FIB-4?

FIB-4: índice de fibrose 4 (índice de fibrose hepática)

Dados necessários: **idade**, **TGO**, **TGP** e **plaquetas**.

CALCULE AQUI:

Aponte seu celular para esse **QR Code** e descubra o **FIB-4** de maneira **simples e rápida.***

*Disponível apenas para iOS.

NAFLD fibrosis score
Online calculator

Angulo P, Hui JM, Marchesini G et al. **The NAFLD fibrosis score** *A noninvasive system that identifies liver fibrosis in patients with NAFLD* Hepatology 2007;45(4):846-854 doi:10.1002/hep.21496

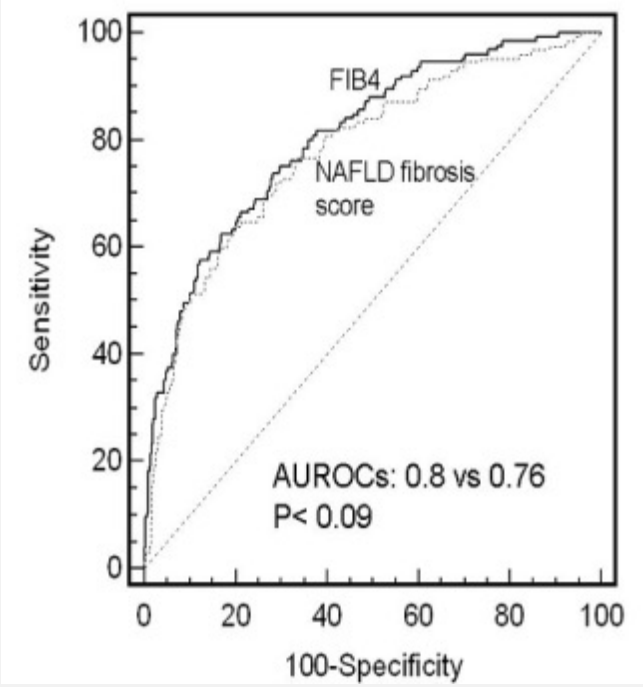
Age (years)
BMI (kg/m²)
IGF/diabetes
AST
ALT
Platelets (x10⁹/l)
Albumin (g/l)
calculate score

http://nafldscore.com/

TelessaúdeBA · FESF-SUS Fundação Estatal Saúde da Família · SUS · Governo do Estado Bahia Secretaria da Saúde

Métodos Não Invasivos: FIB-4

$$(\text{Age[years]} \times \text{AST[U/L]})/(\text{platelet } [10^9] \times \sqrt{\text{ALT[U/L]}})$$

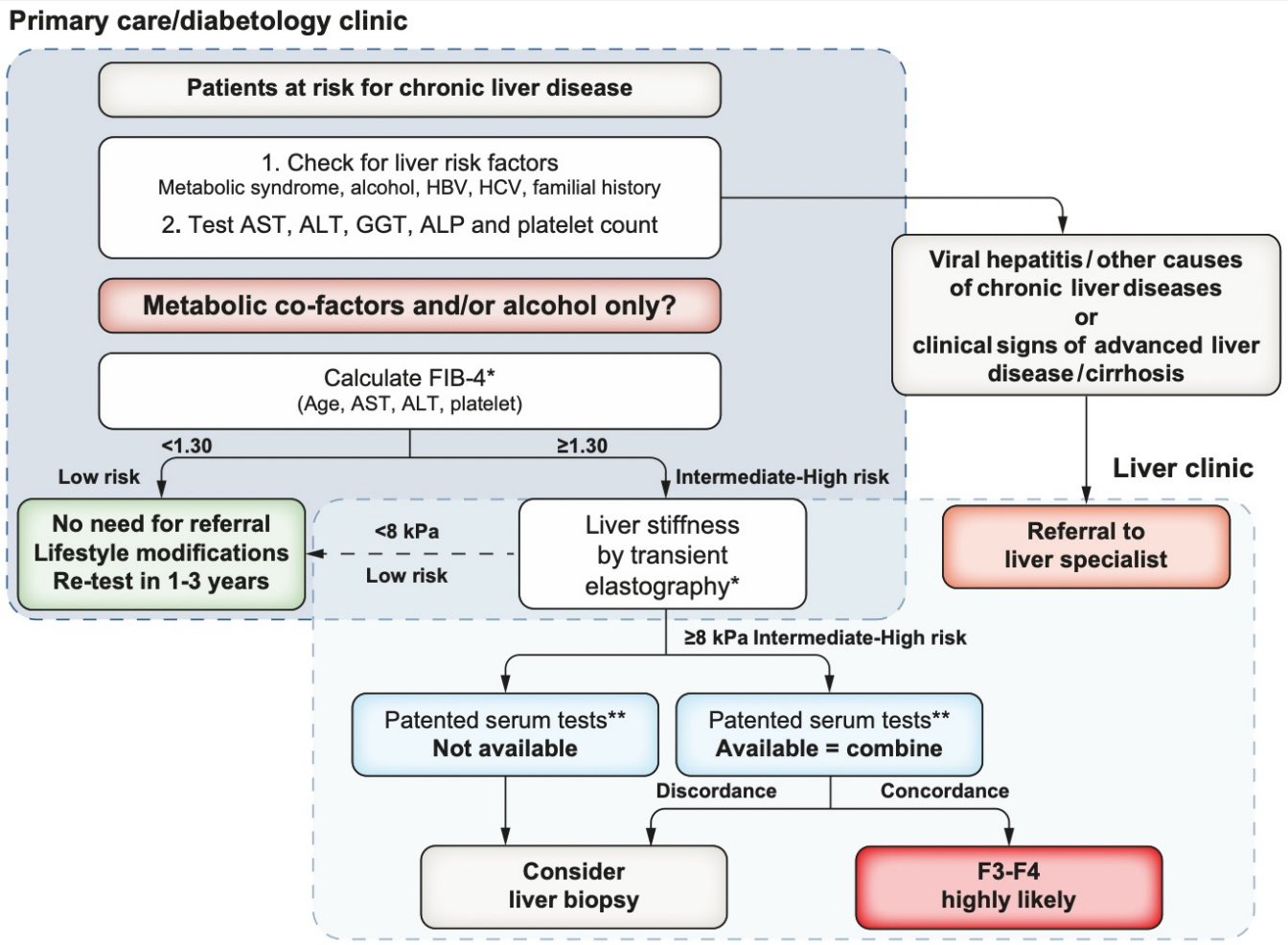


Predictive Values of FIB-4 Index Scores for Advanced Fibrosis (stage 3–4)*

	Low cutoff point (<1.30)	Indeterminate (1.30–2.67)	High cutoff point (>2.67)	Total
Total	327	163	51	541
No advanced fibrosis	294	112	10	416
Advanced fibrosis	33	51	41	125
Sensitivity	74%		33%	
Specificity	71%		98%	
Positive predictive value	43%		80%	
Negative predictive value	90%		83%	
Interpretation	Absence of advanced fibrosis		Presence of advanced fibrosis	

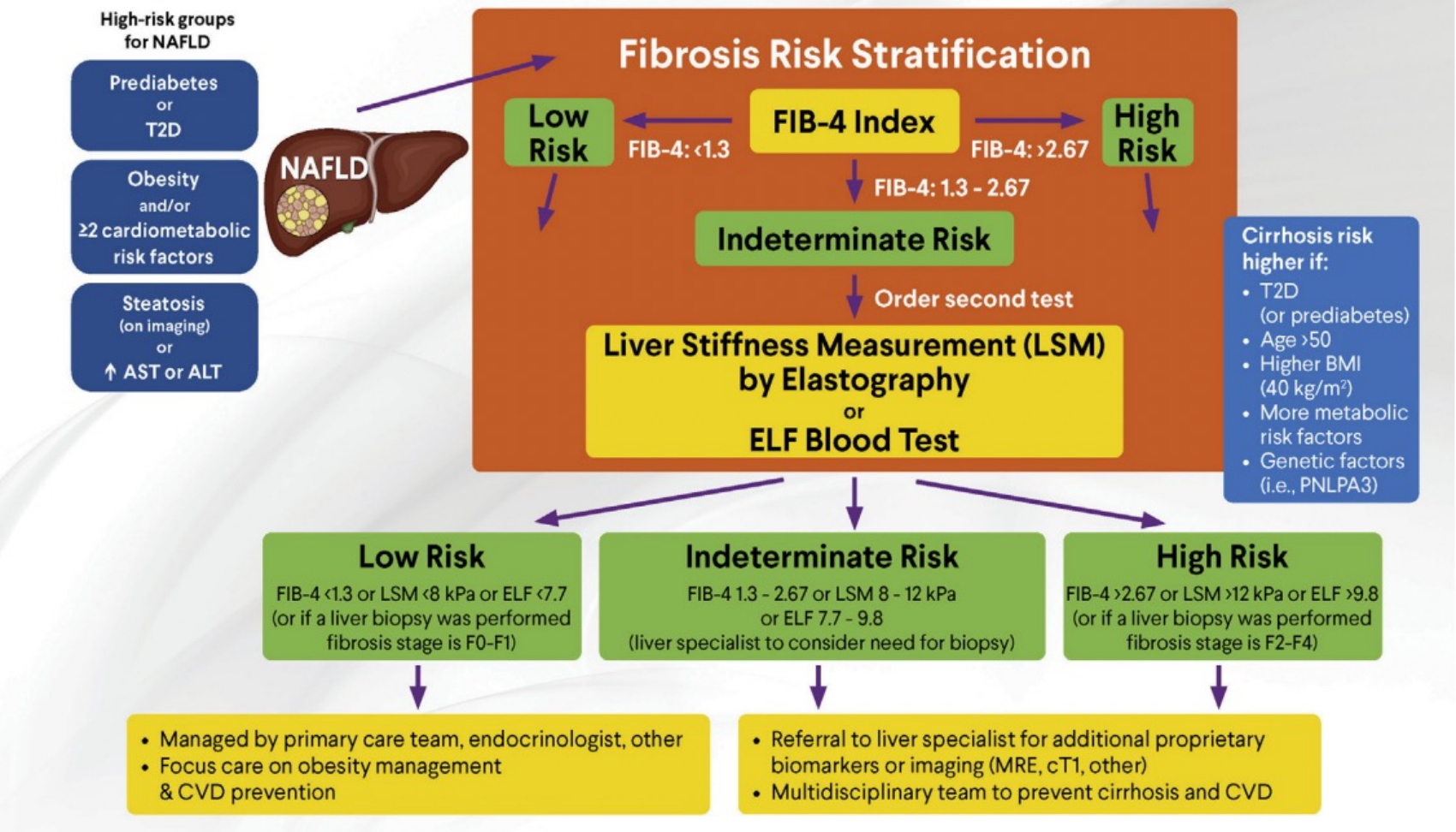
Shah et al. Clin Gastroenterol Hepatol 2009

INVESTIGAÇÃO DE PACIENTES COM SUSPEITA DE DHGNA/MAFLD/MASLD



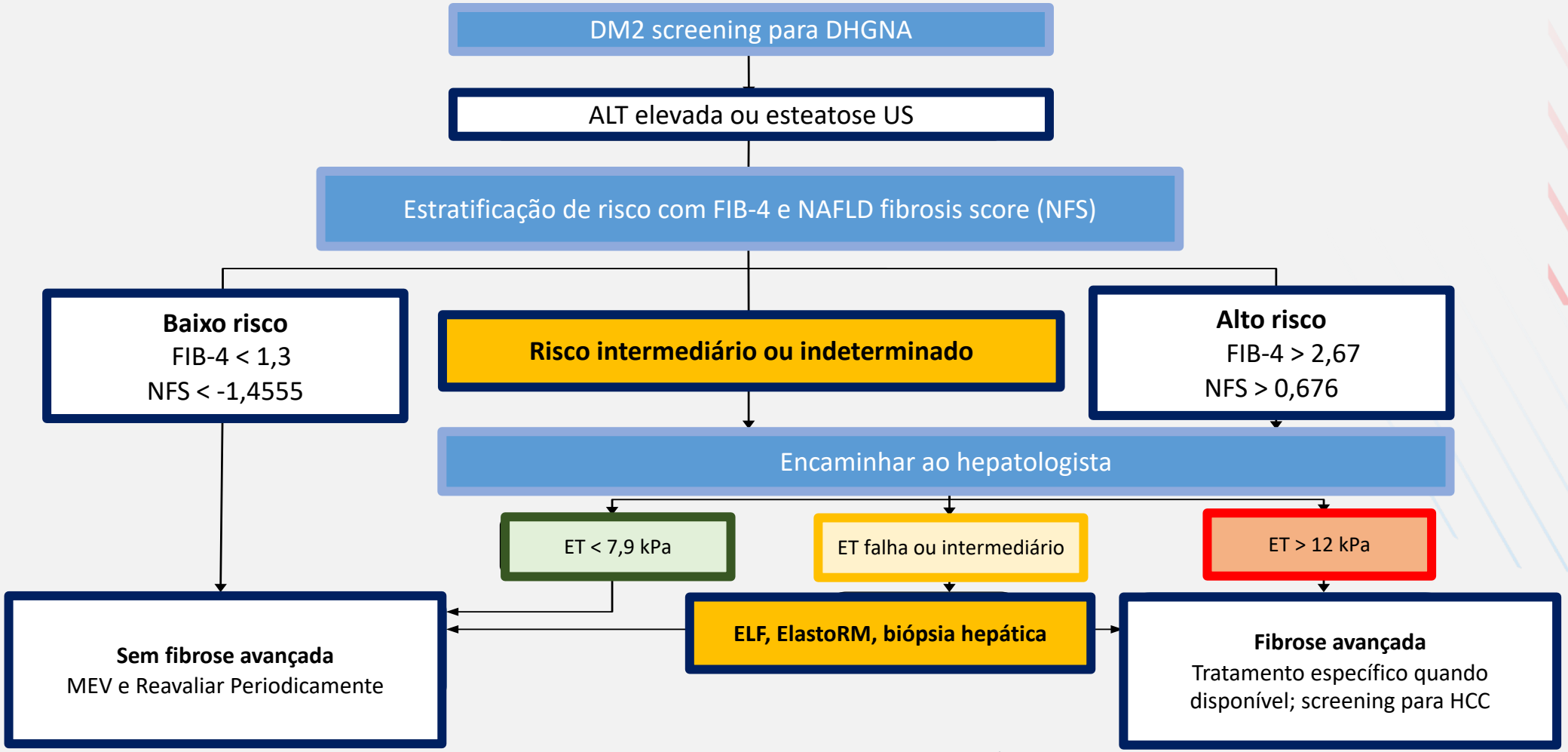
Journal of Hepatology 2021 vol. 75 | 659–689

ESTRATITIFACAO DE RISCO DE DHGNA NA DMT2



Cusi K, et al .AACE CPG for the Diagnosis and Management of NAFLD in Primary Care and Endocrinology Clinical Settings. Endocr Pract. 2022 May;28(5):528-562.

INVESTIGAÇÃO DE PACIENTES COM SUSPEITA DE DHGNA/MAFLD/MASLD



Tomah et al, Clin Endocrinol Metabol 2020

INVESTIGAÇÃO DE PACIENTES COM SUSPEITA DE DHGNA/MAFLD/MAFLD

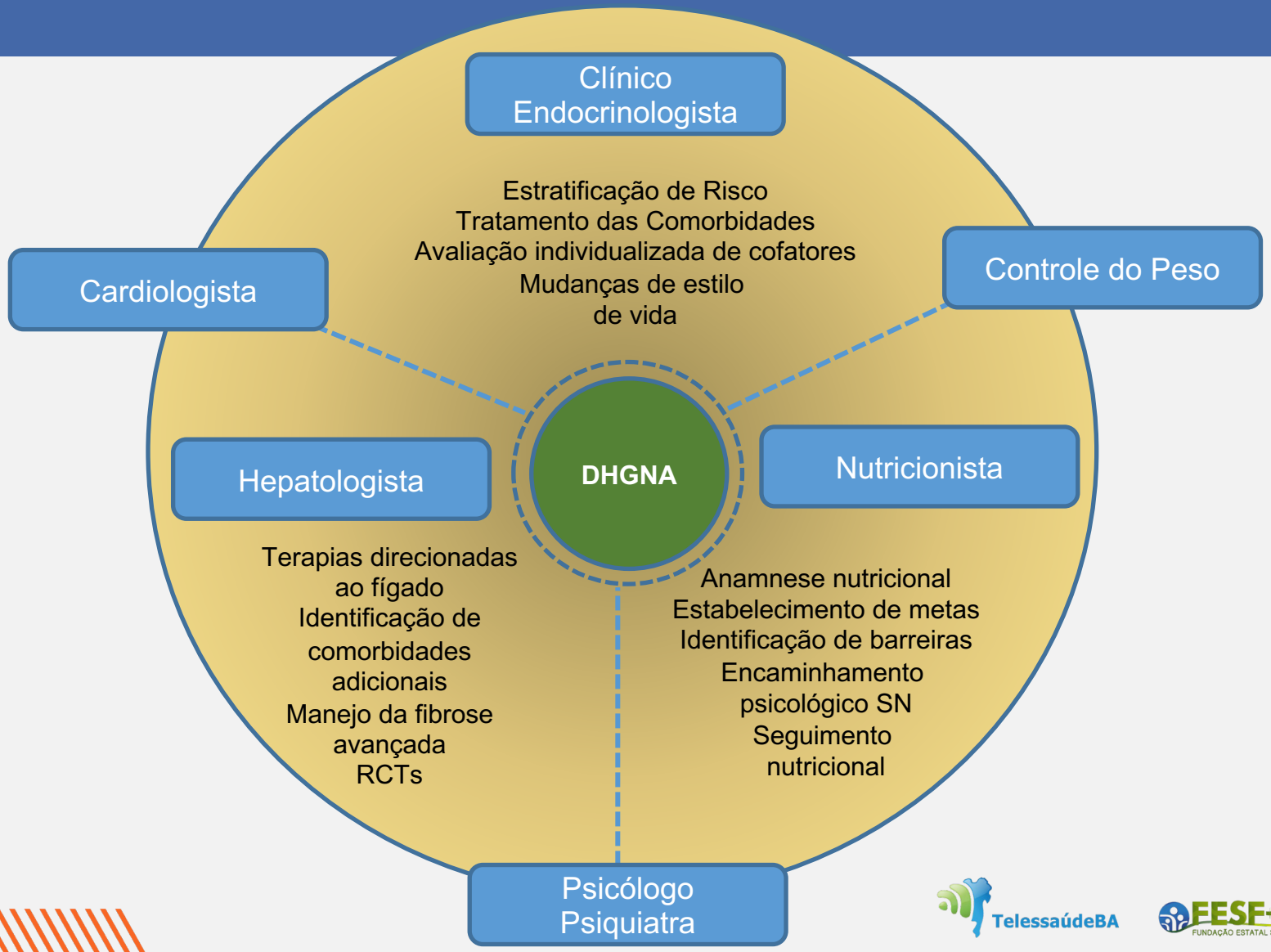
Esteatose Simples	Reavaliação a cada 2-5 anos ou anual na presença de DMT2 ou DCV
NASH sem fibrose ou F1	Reavaliação a cada ano ou na presença de DMT2 ou DCV
NASH COM F2-F3	Reavaliação a cada 6-12 meses eventualmente com maior na presença de DMT2 ou doenca cardiovascular Considerar rastreamento semestral de CHC (mandatório em pacientes com cirrose)
NASH com cirrose	Reavaliação a cada 6 meses com rastreamento de CHC

Atenção Primaria

Intermediária

Terciária

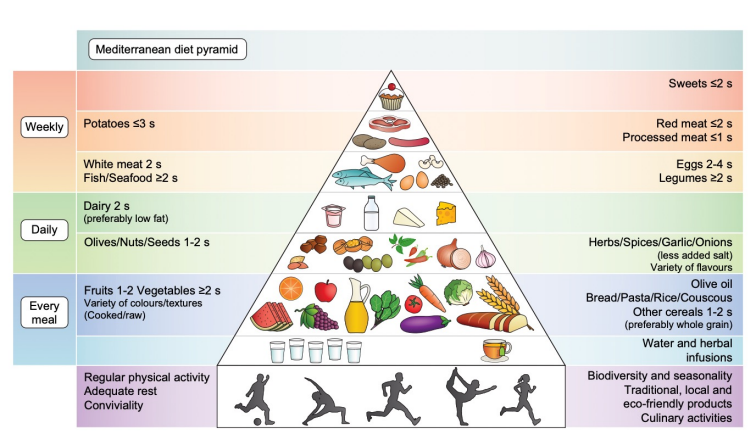
Abordagem da DHGNA: Muldidisciplinar



AASLD Practice Guidance 2023

Abordagem da DHGNA: Orientações Nutricionais

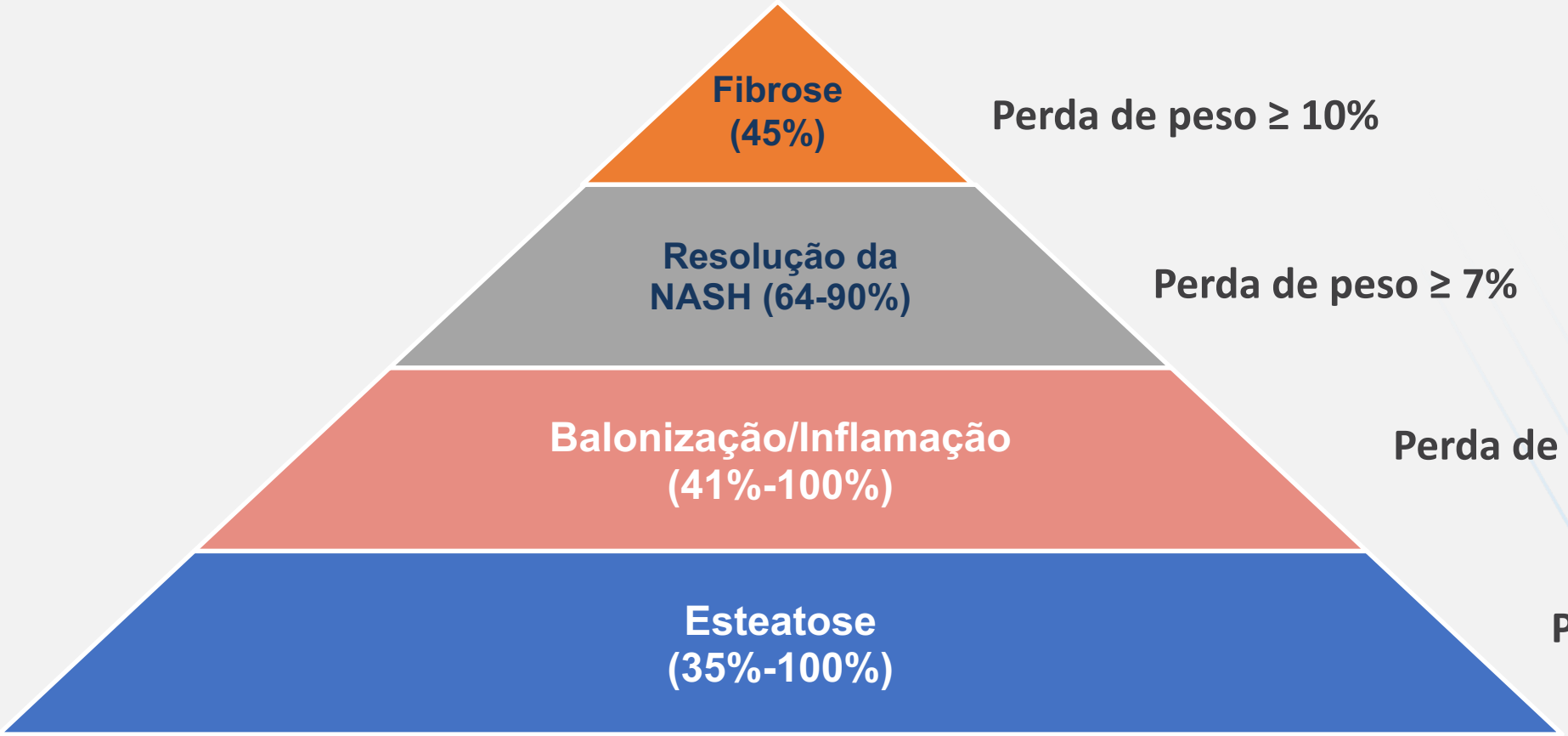
- Restrição de calorias para 1.200-1.800 kcal/dia ou com deficit de 500-750 kcal/dia (obesidade e sobrepeso)
- Dieta sugerida: padrão mediterrâneo pobre em gorduras e carbohidratos de acordo com status sócio-econômico e preferências do paciente
- Composição de dieta rica em fibras e vegetais, com redução no consumo de alimentos/bebidas com sucrose e frutose e moderação no consumo de carbohidratos complexos (40% das calorias)



- Limitação no consumo de gordura saturada e trans e alimentos ricos em colesterol
- Estimular consumo de alimentos ricos em ácidos graxos poli-insaturados e omega-3
- Desestimular consumo de álcool
- Desestimular consumo de alimentos processados
- Na ausência de contraindicações, estimular uso de café

Rinella ME. Nat Rev Gastroenterol Hepatol, 2016

Perda Ponderal: Qualquer perda é melhor que nenhuma



Perda de peso ≥ 10%

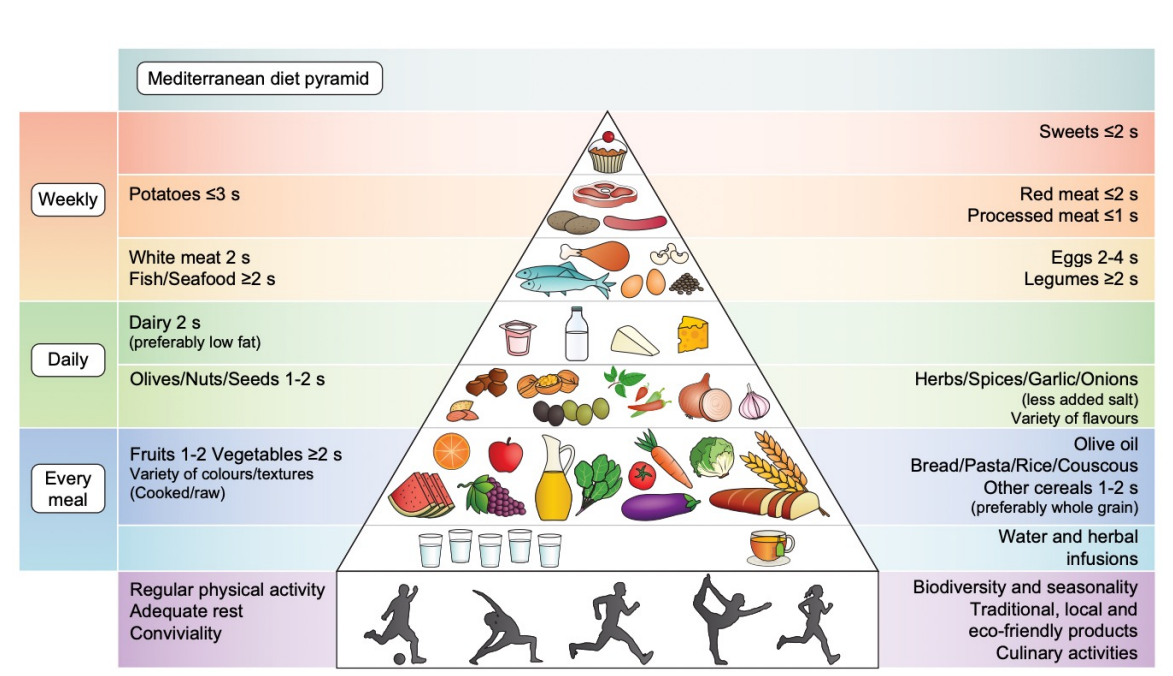
Perda de peso ≥ 7%

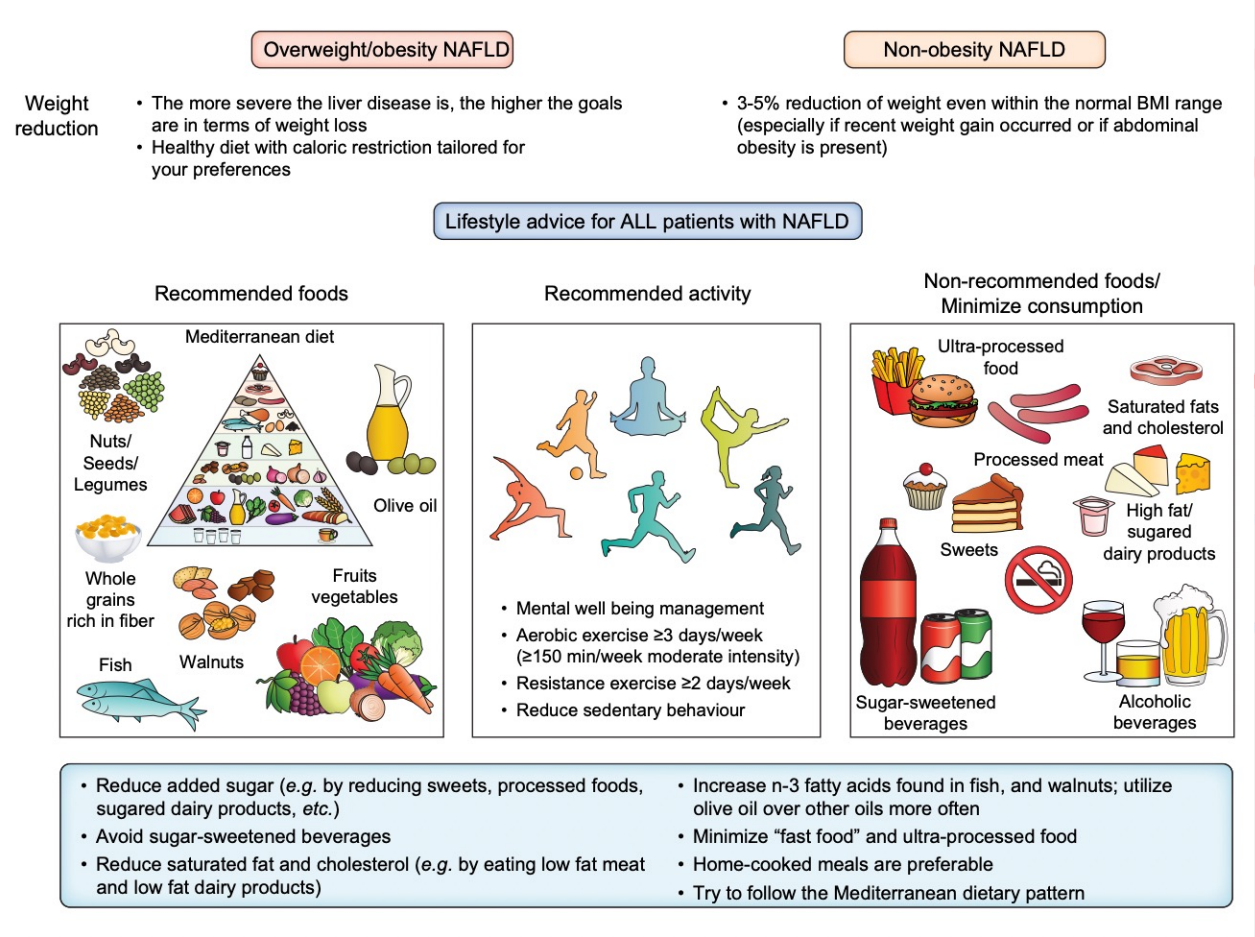
Perda de peso ≥ 5%

Perda de peso ≥ 3%

Hannah Jr WN. Clin Liver Dis, 2016

Abordagem da DHGNA: Orientações Nutricionais





Atividade Física: Qualquer exercício é melhor que o sedentarismo

- Preferência por exercícios aeróbicos
- Aumentar frequência e intensidade de acordo com a tolerância e condições clínicas
- Programa ideal:
  - Treinamento cardiovascular 5x/semana
  - Treinamento de resistência ≥2x/semana
  - 150 -300 minutos/semana com intensidade moderada
  - 75-150 minutos/semana com atividade intensa

Rinella ME. Nat Rev Gastroenterol Hepatol, 2016

Abordagem da DHGNA

Tratamento farmacológico deve ser indicado em pacientes não respondedores a MEV com:

- - Progressão de esteatohepatite (F2-F4)
- - Esteatohepatite em estágios iniciais (F0-F1) com alto risco de progressão (idade > 50 anos, DMT2, SM, ALT elevada)
- - Esteatohepatite com atividade necroinflamatória acentuada

Cirurgia bariátrica e uma opção terapêutica para pacientes não respondedores a MEV e tratamento farmacológico, sendo contraindicada na presença de cirrose descompensada

EFEITO DAS MEDICACOES DISPONIVEIS PARA TRATAMENTO DA DHGNA EM DESFECHOS CLINICOS RELEVANTES

Drogas	Desfechos Clínicos	EC	Benefícios CV
Vitamina E	⬇ NAFL/ NASH?	AVCH	-
	Sem efeito na fibrose	Neo de próstata	
Pioglitazona[1]	⬇ NAFL/NASH	⬆ Peso/ICC	+
	Fibrose ?	⬇ DMO	
Liraglutida[1,2]	⬇ NAFL/ Fibrose ?	GI / PA	+
Semaglutida[1,2]	⬇ NAFL/NASH / Fibrose ?	GI / PA	+
Tirzepatida[1,2]	⬇ NAFL	GI / PA	?
SGLT2i[1]	⬇ NAFL	ITU / ⬇ DMO	+
		Desidratação	+

AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver Disease. Hepatology 2023

RECOMENDAÇÕES PARA TRATAMENTO FARMACOLÓGICO DA DHGNA

1 - Não existe tratamento farmacológico recomendado pela FDA para DHGNA, mas drogas aprovadas para tratamento das comorbidades associadas podem exibir benefícios potenciais para tratamento da doença

2 - Pioglitazona pode ser considerada no contexto DMT2 por se associar a melhora da DHGNA. Vitamina E pode ser alternativamente empregada em pacientes sem DMT2

3 - Semaglutida pode ser considerada no contexto da DMT2 e obesidade em pacientes com DHGNA pelos seus efeitos cardiovasculares benéficos e melhora da EHNA

4 - Pioglitazona, Vitamina E e semaglutida não tem efeito demonstrado sobre fibrose e nenhuma das drogas foi adequadamente investigada em pacientes com cirrose

5 - Metformina, AUDC, Inibidores da DDP-4, Estatinas e Silimarina não devem ser usadas para tratamento da DHGNA por não se associarem a melhora histológica

AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver Disease. Hepatology 2023

MANEJO DA DMT2 NA DHGNA

	Low Risk FIB-4: <1.3 LSM <8 kPa ELF <7.7	Indeterminate Risk FIB-4: 1.3 - 2.67 LSM 8 - 12 kPa ELF 7.7 - 9.8	High Risk[1] FIB-4: >2.67 LSM >12 kPa ELF >9.8
General goal	Optimize glycemic control using preferred agents that reverse steatohepatitis, whenever possible. Prefer GLP-1 RA and SGLT2i in CVD. Prefer SGLT2i in CKD and HF.		
Dietary recommendations	Glycemic load reduction via emphasis on whole food carbohydrates (vegetables, legumes, fruit) versus sugar/processed carbohydrates.		
Individualize A1c target	≤6.5% for persons without concurrent serious illness and at low hypoglycemic risk (>6.5% otherwise).		In advanced cirrhosis[1], caution with risk of hypoglycemia and avoid oral agents[2]
Preferred diabetes pharmacotherapy	Consider agents that reduce liver fat (pioglitazone, GLP-1 RA, SGLT2i).	Strongly consider agents with efficacy in NASH: Pioglitazone and/or GLP-1 RA[3]. No evidence that SGLT2i improve steatohepatitis.	Strongly consider agents with efficacy in NASH: Pioglitazone and/or GLP-1 RA[3]. No efficacy data in cirrhosis.
Metformin, sulfonylurea, DPP-4i, acarbose and insulin	May continue but limited benefit on liver histology in NAFLD.	May continue but limited benefit on liver histology in NAFLD.	May continue (F2-F3) but avoid oral agents if advanced cirrhosis present. Cannot avoid insulin in patients with advanced liver cirrhosis – often only option

Cusi K, et al .AACE CPG for the Diagnosis and Management of NAFLD in Primary Care and Endocrinology Clinical Settings. Endocr Pract. 2022 May;28(5):528-562.

MANEJO DA DISLIPIDEMIA NA DHGNA

Lipid risk levels are similar in the presence of NAFLD or NASH

General goal	Early intensive management of dyslipidemia needed to reduce cardiovascular risk. Intensify therapy until lipid goal is reached.		
Dietary recommendations	Increase fiber intake (>25 g/d), prioritize vegetables, fruits whole grains, nuts, reduce saturated fat & added sugars (e.g., Mediterranean diet).		
Lipid risk levels	**High CV Risk**[1] ≥2 risk factors and 10-year risk 10-20% Diabetes or CKD ≥3 with no other risk factors	**Very high CV Risk**[1] Established CVD or 10-year risk >20% Diabetes with >1 risk factor, CKD ≥3, HeFH	**Extreme CV Risk**[1] Progressive CVD CVD + diabetes or CKD ≥3 or HeFH FHx premature CVD (<55 yrs male <65 yrs female)
LDL-C goal (mg/dL)	<100	<70	<55
Non-HDL-C goal (mg/dL)	<130	<100	<80
Triglycerides goal (mg/dL)	<150	<150	<150
Apo B goal (mg/dL)	<90	<80	<70
First line pharmacotherapy: Statins	Use a moderate-to-high intensity statin[2], unless contraindicated. Statins are safe in NAFLD or NASH but do not use in decompensated cirrhosis (Child C).		
If LDL-C not at goal[3]: Intensify statin therapy	Use higher dose or higher potency statin.		
If LDL-C not at goal (or statin intolerant)[4]: add 2nd agent, then add 3rd agent	Ezetemibe, PCSK9 inhibitor, bempedoic acid, colesevelam, inclisiran.		
If triglycerides > 500 mg/dL	Fibrates, Rx grade omega 3 FA, icosapent ethyl (if diabetes, optimize glycemic control and consider pioglitazone).[5]		
If TG 135-499 mg/dL on max statin dose	Emphasize diet (as above).	Add icosapent ethyl.[6]	Add icosapent ethyl.[6]

Cusi K, et al .AACE CPG for the Diagnosis and Management of NAFLD in Primary Care and Endocrinology Clinical Settings. Endocr Pract. 2022 May;28(5):528-562.

MANEJO DO PESO NA DMT2

	Low Risk FIB-4: <1.3 LSM <8 kPa ELF <7.7	Indeterminate Risk FIB-4: 1.3 - 2.67 LSM 8 - 12 kPa ELF 7.7 - 9.8	High Risk FIB-4: >2.67 LSM >12 kPa ELF >9.8
General lifestyle changes	Decrease sedentary time and increase daily movement. Stress reduction through exercise and other methods.		
Dietary recommendations	Creating an energy deficit is the priority with reduction of saturated fat, starch, & added sugars. Persons with cirrhosis need an individualized nutritional assessment and treatment plan.		
Exercise	To improve cardiometabolic health, support weight loss and mitigate sarcopenia. Aerobic exercise for 30-60 min (3-5 days/week) + resistance training 20-30 min (2-3 times/week).		
Alcohol intake	Minimize	Minimize	Avoid if F3 or cirrhosis (F4)[1]
Weight loss goal to treat NAFLD (if overweight or obesity)[2]	Greater weight loss associated with greater liver and cardiometabolic benefit.		
Weight loss tools	Behavioral modification counseling. In person or remote programs.	Greater intensity of weight loss to reverse steatohepatitis and fibrosis.	Specialized obesity management, with a structured program, anti-obesity medications, bariatric surgery.
Medical therapy to treat obesity	Phentermine, phentermine/topiramate ER, naltrexone/bupropion, orlistat, liragluitde 3 mg/d, semaglutide 2.4 mg/wk	GLP-1 RA preferred for NASH.[3,4]	GLP-1 RA preferred for NASH.[3,4]
Bariatric surgery	Consider to treat obesity and comorbidities.	Strong consideration to treat steatohepatitis and fibrosis.	Stronger consideration to treat steatohepatitis and fibrosis. Avoid in decompensated cirrhosis.

Cusi K, et al .AACE CPG for the Diagnosis and Management of NAFLD in Primary Care and Endocrinology Clinical Settings. Endocr Pract. 2022 May;28(5):528-562.

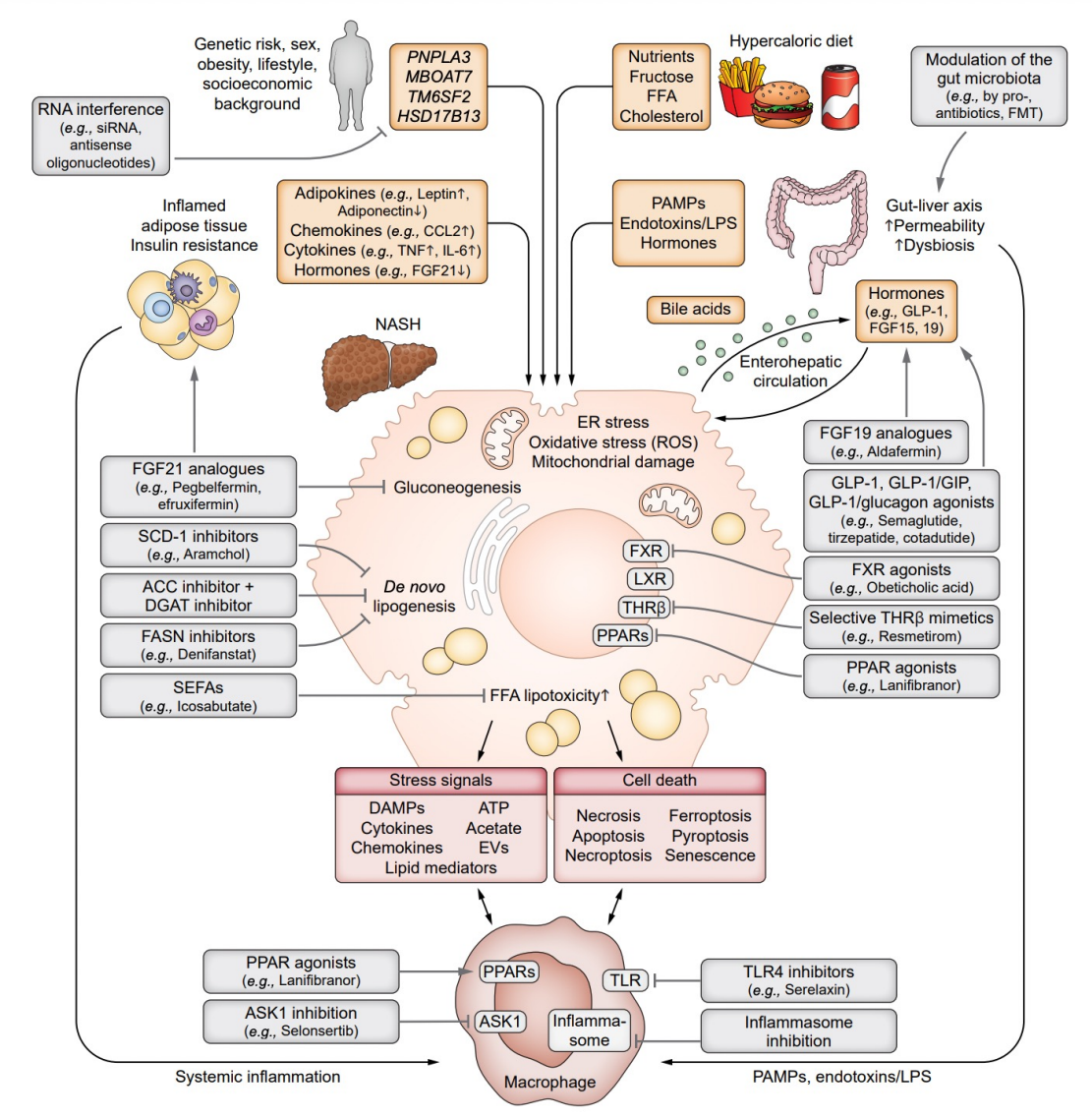
MANEJO DA HIPERTENSAO ARTERIAL NA DHGNA

	Low Risk FIB-4: <1.3 LSM <8 kPa ELF <7.7	Indeterminate Risk FIB-4: 1.3 - 2.67 LSM 8 - 12 kPa ELF 7.7 - 9.8	High Risk[1] FIB-4: >2.67 LSM >12 kPa ELF >9.8
General goal	Optimize BP control and improve cardiovascular health using preferred agents, whenever possible. Assess every 3 months and intensify therapy until goal achieved.		
Goal (individualize) [2,3,4]	Systolic < 130 mm Hg / Diastolic < 80 mm Hg	Systolic < 130 mm Hg / Diastolic < 80 mm Hg	Systolic < 130 mm Hg / Diastolic < 80 mm Hg; individualize if decompensated cirrhosis
Dietary recommendations	In addition to general dietary recommendations, reduce sodium & increase high potassium foods (e.g., DASH diet).		
Pharmacotherapy for hypertension[5]	First-line therapy: ACEIs and ARBs.	First-line therapy: ACEIs and ARBs.	Same but avoid ACEI or ARB if decompensated cirrhosis.
Intensification of therapy	Second agent: CCB, BB[6] or thiazide diuretic (as additional agents as needed).		Same but individualize if decompensated cirrhosis. Use diuretics with caution (risk of excessive diuresis).
Additional options	Additional BP medication choices: alpha blockers, central agents, vasodilators, aldosterone antagonist.		Same but individualize if decompensated cirrhosis.

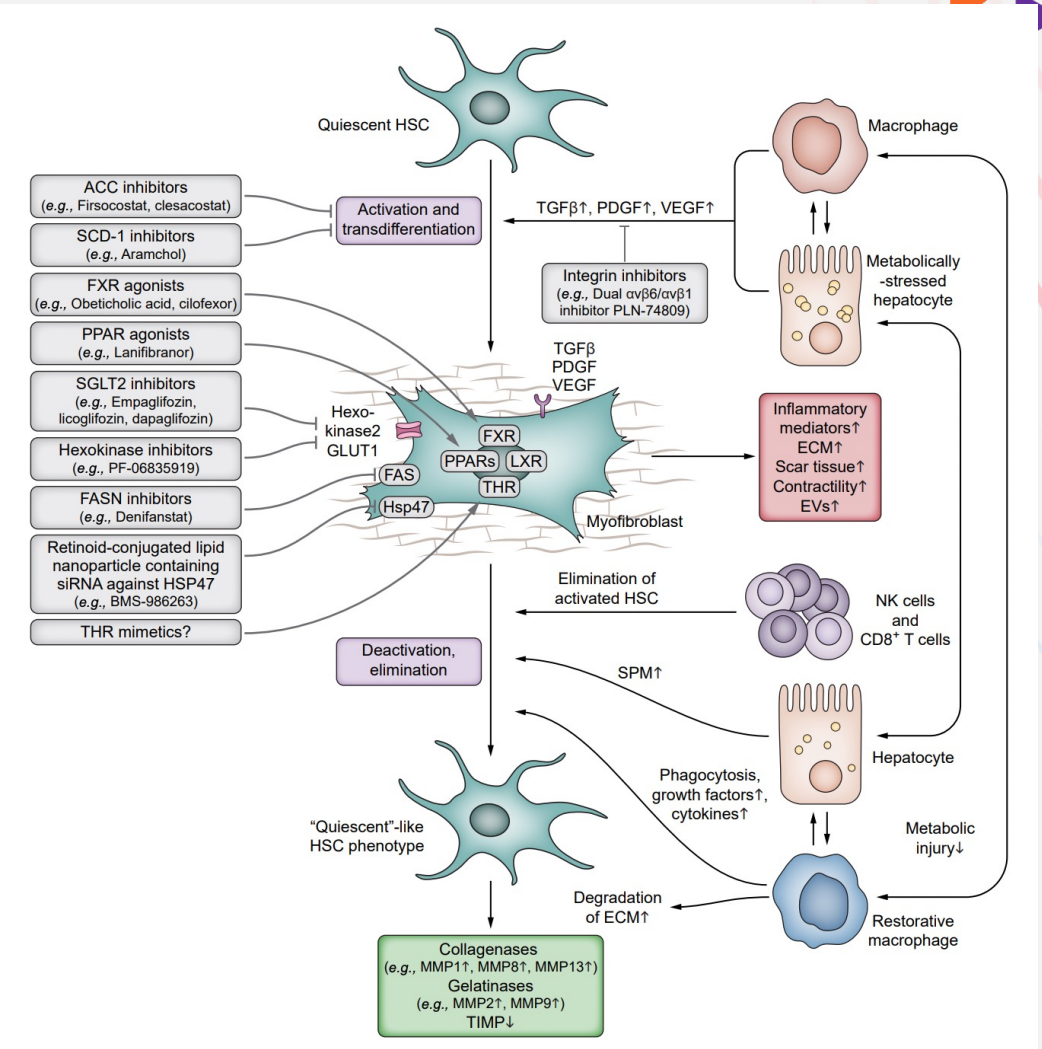
Cusi K, et al .AACE CPG for the Diagnosis and Management of NAFLD in Primary Care and Endocrinology Clinical Settings. Endocr Pract. 2022 May;28(5):528-562.

DROGAS EMERGENTES PARA O TRATAMENTO DA DHGNA

Targeting the activation of inflammatory cascades



Targeting fibrosis



Journal of Hepatology, August 2023. vol. 79 j 552–566

DROGAS EMERGENTES PARA O TRATAMENTO DA DHGNA

web PALESTRA

Estudos em andamento de Fase III para DHGNA

REGENERATE NCT02548351	Obeticholic acid	FXR agonist
REVERSE NCT03439254	Obeticholic acid	FXR agonist
MAESTRO-NASH NCT03900429	Resmetirom	THR-β agonist
MAESTRO-NAFLD1 NCT04197479	Resmetirom	THR-β agonist
NATiV3 NCT04849728	Lanifibranor	Pan-PPAR agonist
ARMOR NCT04104321	Aramchol	SCD1 inhibitor
ESSENCE NCT04822181	Semaglutide	GLP1 agonist
NAVIGATE NCT04365868	Belpectin	Galectin 3 inhibitor
DEAN NCT03723252	Dapagliflozin	SGLT2 inhibitor

Estudos Combo em andamento para DHGNA

CONTROL NCT02633956	Phase II	Obeticholic acid	Atorvastatin
TANDEM NCT03517540	Phase II	Tropifexor	Cenicriviroc
ELIVATE NCT04065841	Phase II	Tropifexor	Licogliflozin
ATLAS NCT03449446	Phase II	Cilofexor	Firsocostat Selonsertib
NCT03987074	Phase II	Cilofexor	Semaglutide Firsocostat
NCT03776175	Phase IIa	PF-05221304 ACC inhibitor	PF-06865571, DGAT2 inhibitor

TelessaúdeBA FESF-SUS FUNDAÇÃO ESTATAL SAÚDE DA FAMÍLIA SUS GOVERNO DO ESTADO BAHIA SECRETARIA DA SAÚDE

Sodium-glucose cotransporter 2 inhibitor versus sulfonylurea in patients with type 2 diabetes and nonalcoholic fatty liver disease

Histologic features	Tofogliflozin (n=20)			Glimepiride (n=20)			P value (Tofogliflozin vs. Glimepiride)‡
	Before	After	P Value†	Before	After	P Value†	
Steatosis							
Score-no. of subjects							
0 (<5%)	0	5		0	0		
1 (5-33%)	8	11		6	11		
2 (33-66%)	8	3		9	5		
3 (>66%)	4	1		5	4		
Improvement-%		**65**	**0.001**		30	0.058	0.141
Hepatocellular ballooning							
Score-no. of subjects							
0 (None)	3	10		1	5		
1 (Few balloon cells)	10	9		14	11		
2 (Many balloon cells)	7	1		5	4		
Improvement-%		**55**	**0.002**		**25**	**0.025**	0.098
Lobular inflammation							
Score-no. of subjects							
0 (0 focus)	1	4		0	0		
1 (<2 foci per 200*field)	11	16		13	14		
2 (2-4 foci per 200*field)	7	0		7	6		
3 (>4 foci per 200*field)	1	0		0	0		
Improvement-%		**50**	**0.003**		15	0.655	0.064
Fibrosis							
Sore-no. of subjects							
0 (None)	3	10		2	6		
1 (Perisinusoidal or periportal)	7	7		11	7		
2 (Perisinusoidal and portal or periportal)	8	1		3	3		
3 (Bridging fibrosis)	2	2		3	4		
4 (Cirrhosis)	0	0		1	0		
Improvement-%		**60**	**0.001**		35	0.096	0.172

† The P values were calculated with the Wilcoxon signed-rank test
‡ The between-group comparison for the effect of treatment (change from baseline) was performed with the chi-square test

Histologic variables	Tofogliflozin (n=20)	Glimepiride (n=20)	P value
NAS			
Baseline	4.40 (1.76)	4.50 (1.19)	0.834
Week 52	**2.35 (2.57)***	**3.90 (1.51)***	**0.003†**
AST (IU/L)			
Baseline	42.4 (28.5)	39.7 (35.4)	0.602
Week 48	**25.5 (17.0)***	38.5 (30.6)	0.142
ALT (IU/L)			
Baseline	59.4 (46.7)	61.3 (56.2)	0.398
Week 48	**30.8 (23.6)***	56.9 (54.9)	0.096
γ-GTP (IU/L)			
Baseline	56.7 (27.0)	57.6 (64.3)	0.221
Week 48	**33.7 (20.5)***	57.4 (68.6)	0.121
FIB-4			
Baseline	1.34 (0.82)	1.26 (1.08)	0.277
Week 48	**1.14 (0.69)***	1.38 (1.12)	0.779
FPG (mg/dl)			
Baseline	142.8 (23.6)	144.9 (36.0)	0.947
Week 48	**112.4 (20.2)***	**124.1 (22.6)***	0.092
HbA1c (%)			
Baseline	8.1 (1.1)	8.3 (1.3)	0.565
Week 48	**6.9 (0.9)***	**7.4 (0.9)***	0.040
Body weight (kg)			
Baseline	79.3 (18.2)	84.7 (25.4)	0.449
Week 48	**75.2 (17.6)***	85.5 (26.1)	0.154
BMI			
Baseline	31.0 (6.7)	32.0 (8.8)	0.968
Week 48	**29.0 (6.2)***	32.3 (9.1)	0.383

Data at baseline and week 48 are mean (SD)

† Intergroup comparison performed with Mann-Whitney's U test in nonparametric parameters or with the two-sample t-test in normal distribution

* Internal group comparison between baseline and 48 weeks performed with the Wilcoxon signed-rank test

CONCLUSION

- Tofogliflozin administration was associated with a significant liver histology improvement compared with glimepiride under similar glucose level reduction
- SGLT2 inhibitors may have a hepatoprotective effect and could be promising agents in the treatment of type 2 diabetes with NAFLD

Takeshita Y, et al. NAFLD Summit 2022; P01-03

Primary results from MAESTRO-NASH: a pivotal phase 3 52-week serial liver biopsy study in 966 patients with NASH and fibrosis

web PALES TRA

RESULTS

Baseline characteristics	N=966
Age, years, mean (SD)	57 (11)
Sex, female, %	56
Ethnicity, white, %	90
BMI	36 (7)
Type 2 diabetes, %	67
Hypertension, %	78
Dyslipidemia, %	71
FibroScan VCTE, kPa	13 (7)
CAP	348 (38)
MRI-PDFF, % fat fraction	18 (7)
LB, NAS ≥ 5, %	84
Fibrosis stage, %	
F3	62
F2	33
F1B	5

- Both primary endpoints and the key secondary endpoint were met with both resmetirom doses
- Similar results for both endpoints were obtained by both central pathologists
- Results were independent of diabetes status and baseline fibrosis stage
- Other LB endpoints were

Endpoints	Resmetirom 80 mg (n=316)	P value	Resmetirom 100 mg (n=321)	P value	Placebo (n=318)
NASH resolution* with ≥2-point reduction in NAS and no worsening of fibrosis	26%	<0.0001	30%	<0.0001	10%
≥1-stage improvement in fibrosis with no worsening of NAS	24%	0.0002	26%	<0.0001	14%
LDL-C lowering (24 weeks)	-12%	<0.0001	-16%	<0.0001	1%

- Multiple biomarker endpoints were met†
- Resmetirom had a good safely safety profile and was well-tolerated, with similar numbers of SAEs across groups
  - An increase in incidence of diarrhea and nausea in the resmetirom groups occurred at the beginning of therapy

CONCLUSION

- NASH resolution and fibrosis reduction endpoints were achieved with both doses of resmetirom
- Resmetirom appeared safe and was generally well-tolerated
- These data support the potential for resmetirom treatment to be beneficial for patients with NASH and liver fibrosis

Harrison S, et al. EASL 2023; GS-001

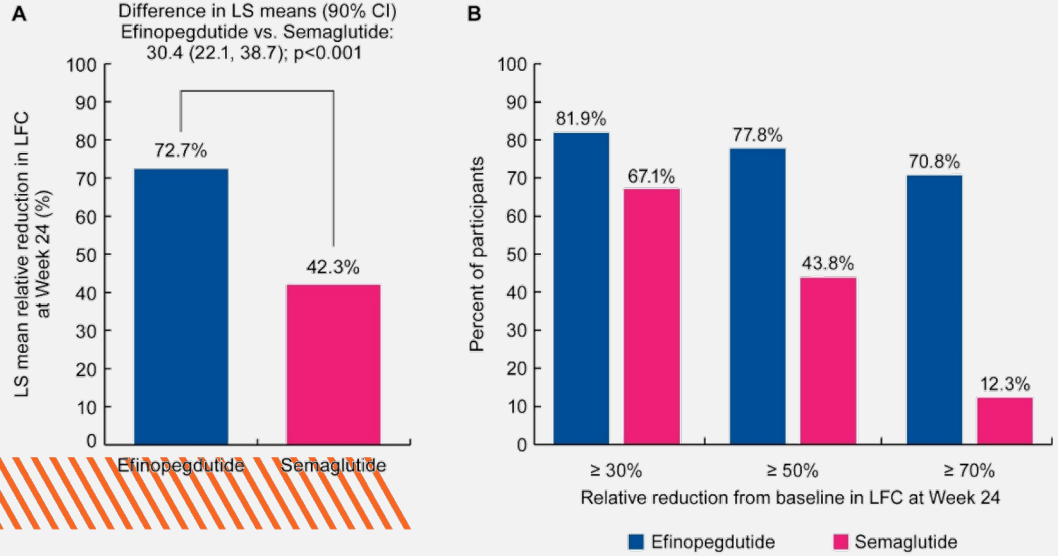
A Phase 2a, randomized, active-comparator-controlled, open-label study to evaluate the efficacy and safety of efinopegdutide in individuals with NAFLD

RESULTS

Baseline characteristics and demographics

Characteristic	N=145
Sex, male, %	55.2
Hispanic, %	35.2
T2D present, %	33.1
BMI, kg/m^2, mean	34.3
LFC, %, mean	20.3

Relative reduction in LFC from baseline to week 24



- The LS mean reduction in LFC from baseline was significantly greater with efinopegdutide (72.7%; 90% CI: 66.8–78.7) vs. semaglutide (42.3%; 90% CI: 36.5–48.1; p<0.001)
  - Median reductions: efinopegdutide 83.8%, semaglutide 44.4%
- A greater proportion of patients achieved normal LFC (<5%) with efinopegdutide (66.7%) vs. semaglutide (17.8%)
- Greater proportions of patients had LFC reductions of ≥30%, ≥50%, and ≥70% with efinopegdutide vs. semaglutide
- Weight loss was similar (efinopegdutide, 8.5%; semaglutide, 7.1%; p=0.085)
- LFC reduction by weight loss category (≤5%, 5–10%, >10%) was greater with efinopegdutide (52.4%, 76.6%, 86.2%) vs. semaglutide (13.4%, 39.6%, 64.2%)
- There were no meaningful differences in the incidence of AEs (overall, serious, drug-related, leading to discontinuation)

CONCLUSION

- Efinopegdutide 10 mg treatment led to a significantly greater reduction in LFC than semaglutide 1 mg
- Efinopegdutide may be an effective treatment option for patients with NASH

Romero Gomez M, et al. EASL 2023; OS-060

Pemvidutide significantly reduces LFC, fibro-inflammation, and body weight in patients with NAFLD: A 24-week multicenter, randomized, double-blind, placebo-controlled trial

RESULTS

- Pemvidutide met its primary endpoint at both 12 and 24 weeks in all groups
  - Over 90% of subjects achieved ≥30% LFC reduction and ~50% achieved LFC normalization* in the 1.8 mg and 2.4 mg groups
- Across all pemvidutide treatment groups, 84.6% achieved a cT1 reduction of ≥80 ms at week 24 vs. 0% with placebo
- Pemvidutide significantly reduced ALT in a dose-dependent manner, particularly in those with baseline ALT ≥30 IU/L
  - All pemvidutide groups achieved mean reductions ≥17 IU/L
- Patients with and without T2D administered pemvidutide 1.8 mg experienced a weight loss of 7.2% and 5.3%, respectively, at 24 weeks
- Pemvidutide was well-tolerated, with no serious or severe AEs related to study drug, and low rates of AEs leading to treatment discontinuation

	Week 12				Week 24			
	PBO	Pemvidutide, mg			PBO	Pemvidutide, mg		
		1.2	1.8	2.4		1.2	1.8	2.4
Change in LFC								
Absolute reduction, %	0.2	8.9	14.7	11.3	1.6	11.2	17.0	15.6
Relative reduction, %	4.4	46.6	68.5	57.1	14.0	56.3	75.2	76.4
30% reduction, %	4.2	65.0	94.4	85.0	5.6	76.9	92.3	100
50% reduction, %	0.0	40.0	72.2	70.0	0.0	61.5	84.6	72.7
Normalization*, %	0.0	20.0	55.6	50.0	0.0	30.8	53.8	45.5
Change in ALT								
All participants, IU/L	-6.2	-11.2	-13.8	-13.6	-2.2	-13.3	-13.7	-15.2
Baseline ALT ≥30 IU/L	-12.6	-17.8	-20.8	-27.0	-3.1	-17.0	-17.7	-20.6
Change in cT1								
Participants with 80 ms cT1 reduction, %	0.0	87.5	83.3	85.7	0.0	85.7	75.0	100.0
Weight loss								
Without T2D, %	0.2	3.4	4.9	3.5	1.2	5.2	7.2	5.8
With T2D, %	0.5	3.3	3.8	4.4	3.4	4.3	5.3	3.5

Baseline characteristics	N=94
BMI, kg/m^2, mean	36
LFC, %, mean	22
cT1, ms, mean	920
ALT, IU/L, mean	37
T2D, n (%)	27 (29.0)
Hispanic, n (%)	71 (75.5)

CONCLUSION

- Pemvidutide led to rapid and potent reductions in LFC, serum ALT, cT1, and body weight and was well-tolerated with low rates of AEs leading to treatment discontinuation

Harrison S, et al. EASL 2023; OS-063

Obrigado

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NÚCLEO TELESSAUDE BAHIA

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