NAFLD and Liver Transplantation

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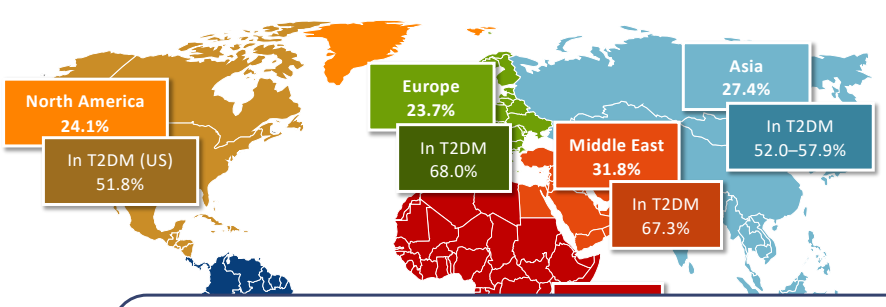
The Global Prevalence of NAFLD and NASH



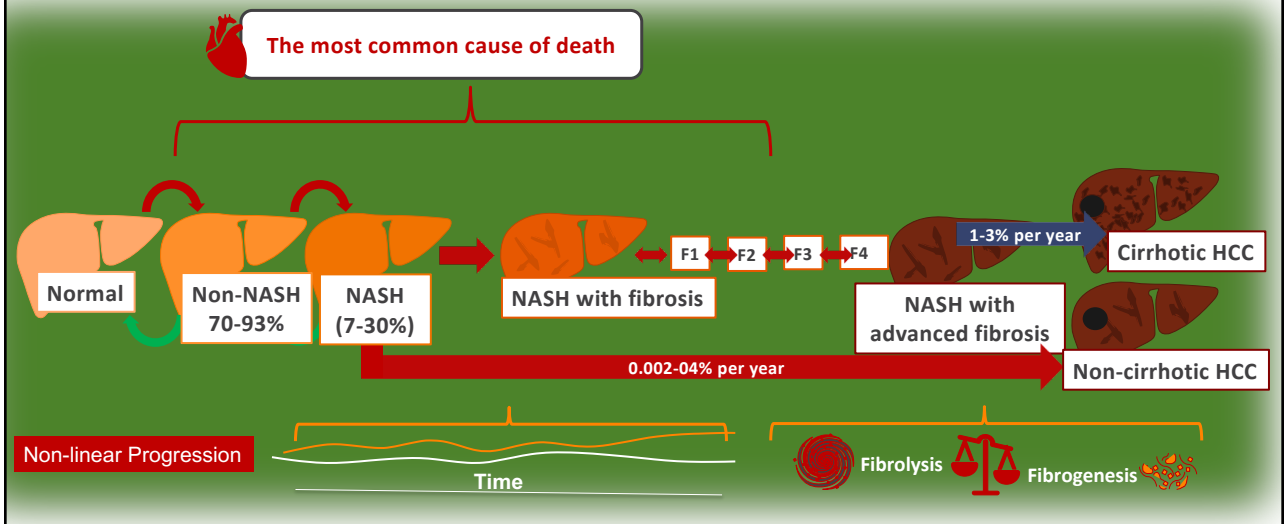
Worldwide prevalence of NAFLD is **25%**

Worldwide prevalence of NAFLD among people

- Prevalence of NASH in general population is between 1.5–6.5%
- Prevalence of NASH among T2DM is 37.3% (24.7-50.0%)
- Prevalence NAFLD in children is 7-10% (highest South America and lowest in Africa)
- Prevalence is higher in Hispanic boys and increases with higher BMI
- The prevalence of NAFLD in the US increased 2.7 fold from the late 1980's to 2010

Younossi ZM et al. *Hepatology.* 2016;64:73–84; Argo CK and Caldwell SH. *Clin Liver Dis.* 2009;13:511–531; Younossi ZM. *J Hepatol.* 2019;70:531–544.

Natural History of NAFLD and NASH

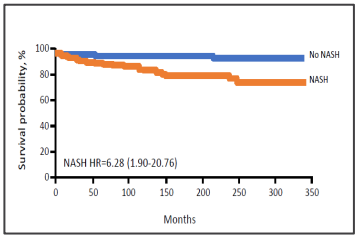


HCC, hepatocellular carcinoma.

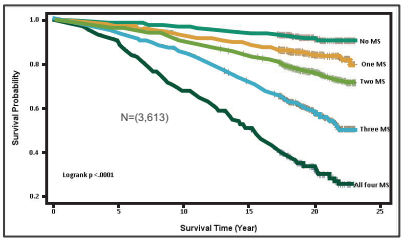
Younossi ZM et al. *Hepatology*. 2018;68:349–360; Younossi ZM et al. *Hepatology*. 2018;68:361–371. Younossi ZM. *J Hepatol*. 2019;70:e17–e32. Jie Li et al. Lancet Gastroenterol Hepatol. May 2019

Clinical Burden of NAFLD and NASH

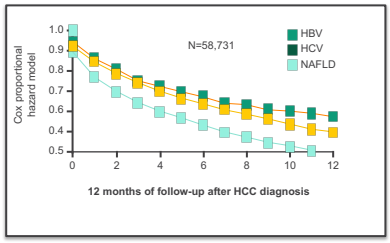
NASH Denotes Progressive Disease



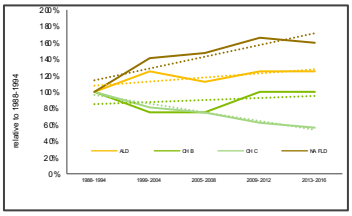
Components of MS Predicts Mortality-NHANES III



HCC and NAFLD- SEER 2004–2009

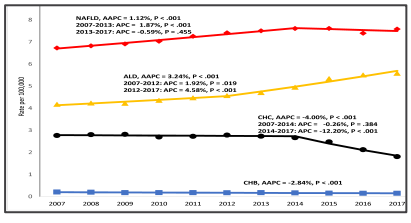


Changes in CLD NHANES 1988-1994 and 1999-2016

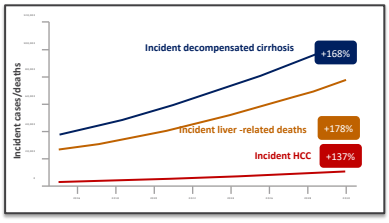


Changes in CLD Mortality

National Center for Health Statistics Mortality data



Future Clinical Burden of NAFLD 2015-2030



Stepanova M, et al. *Dig Dis Sci*. 2013;58(10):3017-3023;, Golabi P, Younossi Z, et al. *Medicine (Baltimore)*. 2018;97(13):e0214; Dulai PS, et al. *Hepatology*. 2017; Younossi ZM, et al. *Hepatology*. 2011., Younossi ZM, et al. *Hepatology*. 2015;62(6):1723-1730, Estes C et al. *Hepatology*. 2018;67:123–133, Younossi ZM, et al. *Clin Gastroenterol Hepatol*. 2018, Younossi Z et al. Clin Gastro and Hep 20111-587, Younossi Z Gut 2020, Paik J, Younossi ZM DDW 2019, Younossi Z AASLD 2019

Global Clinical Burden of NAFLD

AASLD

Trends in Incidence Rates (GBD 2012-2017)

	Liver Cancer						Cirrhosis					
	Liver cancer	Liver cancer due to HBV	Liver cancer due to HCV	Liver cancer due to Alcohol use	Liver cancer due to NASH	Liver cancer due to Other causes	Cirrhosis	Cirrhosis due to HBV	Cirrhosis due to HCV	Cirrhosis due to Alcohol use	Cirrhosis due to NASH	Cirrhosis due to Other causes
Global	1.17	1.38	0.75	0.87	1.95	1.61	0.10	-0.90	0.29	0.23	1.27	0.76
Australasia	1.28	1.13	1.49	1.09	1.31	1.09	1.02	1.29	1.13	0.95	1.31	0.61
High-income Asia Pacific	-2.06	-0.75	-2.89	-2.19	-1.57	-1.96	-0.44	-0.53	-0.65	-0.49	-0.13	-0.24
High-income North America	0.60	0.33	0.60	0.56	0.74	0.49	1.30	0.94	1.14	1.33	1.86	1.41
Southern Latin America	0.66	-0.31	0.42	1.36	1.40	0.55	0.48	-0.85	0.55	0.74	1.14	0.71
Western Europe	0.23	0.00	0.10	0.32	0.72	0.46	0.05	-0.39	-0.51	0.00	0.52	0.48
Central Asia	0.26	-0.23	0.23	0.49	0.87	0.11	-1.14	-2.49	-0.96	-0.78	0.00	-1.10
Central Europe	-0.44	-1.01	-0.47	-0.27	-0.19	-0.62	-0.99	-1.80	-1.02	-1.33	-0.59	-0.15
Eastern Europe	0.62	-0.34	0.80	1.02	1.33	0.83	-1.02	-3.20	-0.88	-0.69	0.00	-0.47
South Asia	1.10	0.65	1.13	1.40	1.61	1.00	0.59	0.00	0.81	1.04	1.59	0.56
East Asia	2.09	1.73	2.52	3.08	1.22	2.36	0.28	-0.76	1.58	1.50	2.71	1.15
Southeast Asia	-0.11	-0.30	-0.20	0.00	0.56	-0.59	0.00	0.00	-0.51	0.33	0.67	0.50
Oceania	-0.15	-0.31	-0.08	0.00	0.28	-0.27	0.61	0.35	0.77	0.54	1.00	0.93
Caribbean	1.00	0.85	0.87	1.14	1.41	0.83	1.19	0.80	1.26	1.18	1.58	1.14
Andean Latin America	-1.43	-2.00	-1.04	-1.32	-0.54	-1.55	0.00	-0.89	-0.25	-0.61	0.74	0.65
Central Latin America	0.21	0.00	0.00	0.59	0.74	0.14	0.69	0.26	0.51	0.86	1.01	0.68
Tropical Latin America	1.66	1.61	1.48	1.74	2.55	1.46	-0.21	-0.89	-0.53	-0.43	0.70	0.25
North Africa and Middle East	-0.47	-0.46	-0.84	-0.66	1.07	-0.58	0.27	-0.32	0.19	0.45	1.47	0.46
Central Sub-Saharan Africa	-2.46	-3.15	-2.77	-1.14	-1.85	-2.64	-0.15	-1.39	0.40	0.62	1.03	0.30
Eastern Sub-Saharan Africa	-0.74	-1.34	-0.57	-0.45	-0.29	-0.86	-0.11	-1.55	0.30	-0.03	0.52	0.41
Southern Sub-Saharan Africa	-2.46	-2.73	-2.41	-2.20	-1.99	-2.92	-1.61	-2.56	-1.72	-1.72	-1.12	-1.21
Western Sub-Saharan Africa	-1.58	-2.24	-1.24	-1.22	-0.66	-1.15	-0.28	-0.88	-0.08	-0.20	0.86	0.21
High SDI	-0.26	0.60	-1.00	-0.27	0.36	0.32	-0.23	-0.77	-0.49	-0.20	0.71	0.13
High-middle SDI	2.71	2.61	2.91	2.54	3.69	3.01	0.00	-0.77	0.60	-0.36	1.66	0.27
Middle SDI	1.15	0.89	1.40	1.37	2.06	1.44	0.25	-1.01	0.57	1.04	1.47	0.91
Low-middle SDI	-0.12	-0.88	0.00	0.48	0.93	-0.03	-0.15	-1.27	-0.04	0.39	0.83	0.51
Low SDI	-0.92	-1.50	-0.72	-0.63	-0.31	-0.82	0.44	-0.40	0.64	0.60	1.18	0.90

Trends in Mortality Rates (GBD 2012-2017)

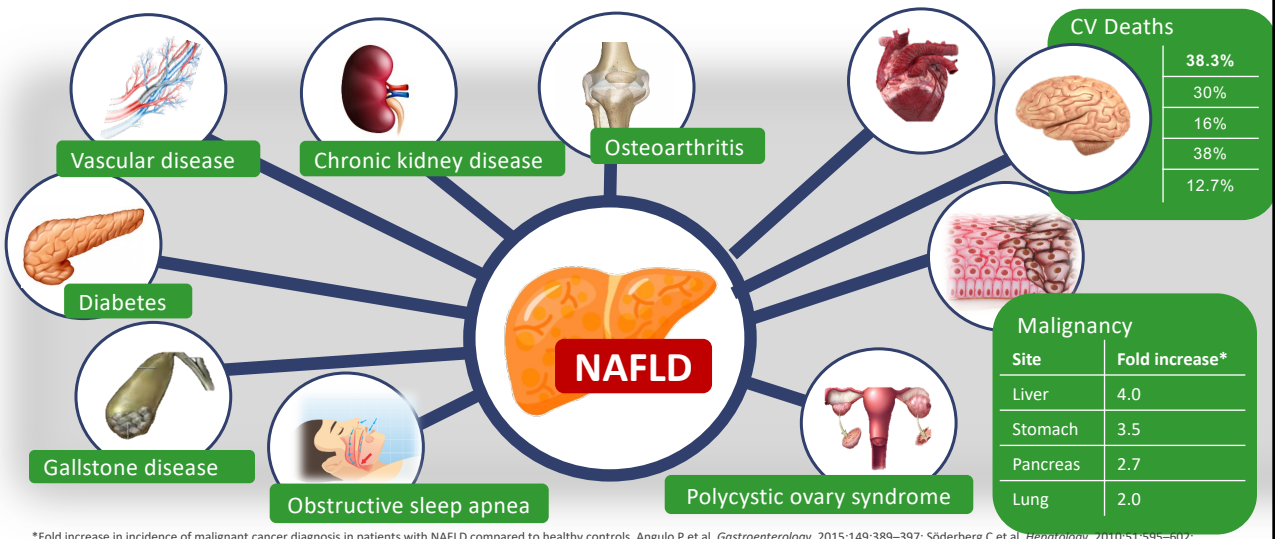
	Liver Cancer					Cirrhosis					
	Liver cancer	Liver cancer due to HBV	Liver cancer due to HCV	Liver cancer due to Alcohol use	Liver cancer due to NASH	Liver cancer due to Other causes	Cirrhosis	Cirrhosis due to HBV	Cirrhosis due to HCV	Cirrhosis due to Alcohol use	Cirrhosis due to NASH	Cirrhosis due to Other causes
Global	0.51	0.00	0.00	0.53	1.41	0.86	-0.70	-1.43	-0.50	-0.44	0.29	-0.52
Australasia	1.55	0.00	1.28	0.00	0.00	0.00	1.63	1.07	1.43	1.22	1.61	0.92
High-income Asia Pacific	-2.88	-1.48	-3.25	-2.54	-2.02	-2.44	-1.51	0.00	-1.87	0.00	0.00	-1.21
High-income North America	0.64	0.46	0.52	0.00	0.51	0.52	0.00	0.00	0.00	0.00	0.00	1.11
Southern Latin America	0.00	-0.82	0.00	0.95	1.01	0.00	-0.18	-1.51	0.00	0.00	0.64	0.00
Western Europe	0.00	-0.66	-0.58	0.00	0.00	0.00	-1.08	-1.39	-1.24	-0.96	0.00	0.00
Central Asia	0.71	0.00	0.75	0.92	1.35	0.56	-0.91	-1.79	-0.65	-0.78	0.21	0.58
Central Europe	0.00	-0.45	0.00	0.00	0.00	0.00	-1.87	-2.15	-1.86	-1.60	-1.12	-1.59
Eastern Europe	2.18	0.00	2.17	2.48	2.46	2.00	0.00	0.00	0.00	0.00	0.00	0.00
South Asia	1.40	0.94	1.44	1.59	1.94	1.46	0.00	-0.95	0.00	0.48	1.29	0.00
East Asia	0.68	0.00	1.21	1.68	1.84	0.94	-1.09	-2.37	0.00	0.00	1.12	0.00
Southeast Asia	0.00	0.00	0.00	0.00	0.71	-0.43	-1.33	-1.68	-1.36	-1.08	-0.46	1.18
Oceania	-0.15	-0.31	-0.09	0.00	0.26	-0.23	-0.60	-0.77	-0.46	-0.58	-0.10	0.60
Caribbean	1.48	1.24	1.38	1.60	1.88	1.33	0.74	0.00	0.63	0.83	1.23	0.46
Andean Latin America	0.00	-1.39	0.00	0.00	0.00	0.00	-1.74	-2.50	-1.91	-1.80	-0.87	1.76
Central Latin America	0.47	0.00	0.00	0.90	0.96	0.45	-0.44	-0.99	-0.57	-0.39	0.00	-0.31
Tropical Latin America	1.44	1.38	1.29	1.54	2.31	1.34	0.00	0.00	0.00	0.00	0.00	0.00
North Africa and Middle East	-0.43	-0.69	-0.62	-0.67	0.95	-0.57	-1.27	-1.62	-1.31	-1.27	0.00	-1.48
Central Sub-Saharan Africa	-2.07	-2.96	-2.21	-1.01	-1.38	-2.10	-0.82	-1.95	-0.49	0.00	0.49	-0.45
Eastern Sub-Saharan Africa	-0.61	-1.30	-0.42	-0.35	-0.15	-0.69	-2.08	-3.10	-1.67	-1.86	-1.30	1.62
Southern Sub-Saharan Africa	-1.24	-1.38	-1.33	-0.95	0.00	-1.63	-1.87	-2.43	-1.70	-1.63	0.00	2.35
Western Sub-Saharan Africa	-1.27	-1.96	-0.98	-0.85	-0.38	-0.86	-2.83	-3.24	-2.32	-2.98	-1.76	1.92
High SDI	-0.81	0.00	-1.28	-0.68	0.00	-0.28	-0.83	-1.14	-0.95	-0.92	-0.44	0.00
High-middle SDI	1.26	0.00	1.67	1.46	2.31	1.35	-1.15	-2.21	-0.75	-0.94	0.00	1.05
Middle SDI	0.00	0.00	0.86	0.95	1.51	0.78	-0.71	-1.49	-0.70	0.00	0.00	-0.59
Low-middle SDI	0.29	-0.42	0.40	0.72	1.26	0.50	-0.84	-1.87	0.00	0.00	0.55	-0.60
Low SDI	-0.59	-1.20	-0.37	-0.30	0.00	-0.49	-0.90	-1.66	-0.66	-0.43	0.00	-0.71

Paike J and Younossi Z Hepatology 2020

Non-Liver Related Outcomes of NAFLD

NAFLD is Part of A Multisystem Disorder

AASLD

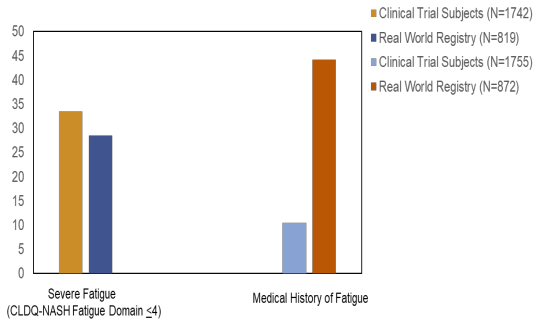


*Fold increase in incidence of malignant cancer diagnosis in patients with NAFLD compared to healthy controls. Angulo P et al. *Gastroenterology*. 2015;149:389–397; Söderberg C et al. *Hepatology*. 2010;51:595–602; Ekstedt M et al. *Hepatology*. 2006;44:865–873; Dam-Larsen S et al. *Scand J Gastroenterol*. 2009;44:1236–1243; Rafiq N et al. *Clin Gastroenterol Hepatol*. 2009;7:234–238; Hicks SB et al. Oral abstract presented at the AASLD Liver Meeting; 31; 11 November 2018; San Francisco, USA.

Symptoms and PROs in NAFLD and NASH

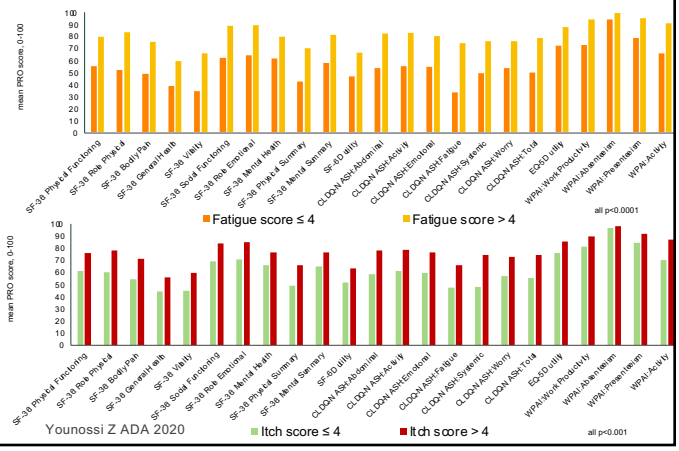
AASLD

- Highest rate of Fatigue in real world setting was observed in NASH/NAFLD



Younossi Z AASLD 2019, Boston MA

- Patients with biopsy-proven NASH (N=1669)
- Prevalence of clinically significant fatigue 31%
- Clinically significant pruritus in 27%
- Pruritus and fatigue had negative impact on PROs



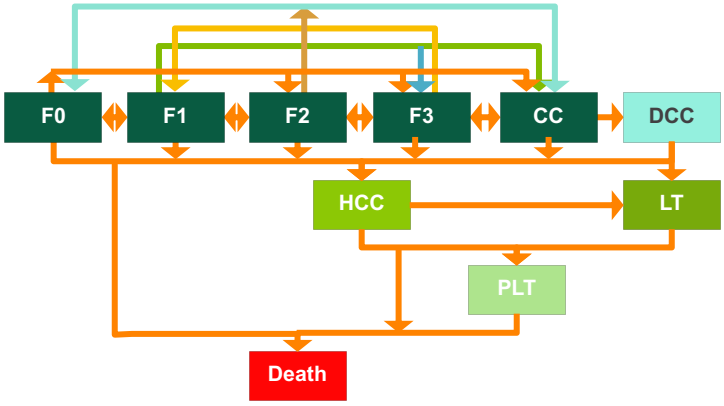
Younossi Z ADA 2020

Economic Burden of NASH

AASLD

- **Economic burden of NASH**
  - Markov models (prevalence and incidence)
  - 6.65 million adults with NASH in the and 232 thousand incident cases in the U.S. (2017).
  - In the U.S., there are 688 thousand cases of advanced NASH
  - Lifetime direct costs of all NASH will be $222.6 billion
  - **Lifetime direct costs of the advanced NASH population will be $95.4 billion.**

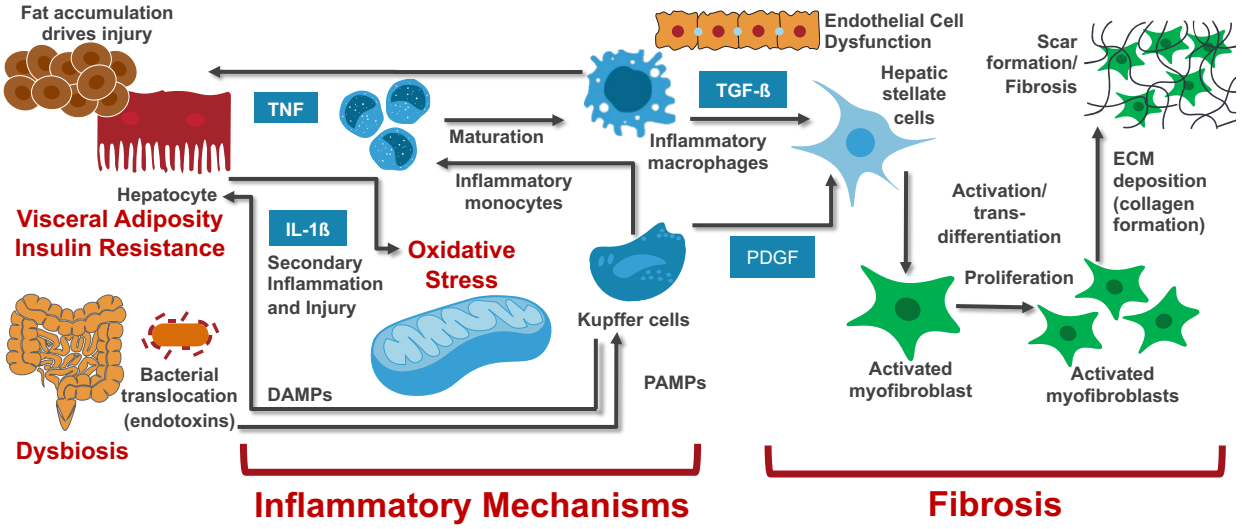
Markov Model Structure



Younossi ZM, et al. *Hepatology.* 2016;64(5):1577-1586; Younossi ZM, et al. Hepatology. 2018 Sep 4. doi: 10.1002/hep.30254. [Epub ahead of print

NAFLD Pathophysiology
Promoters of NASH and Fibrosis Progression

AASLD



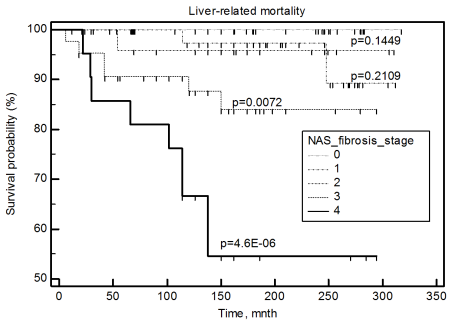
DAMP, danger-associated molecular patterns; ECM, extracellular matrix; IL-1β, interleukin-1beta; PAMP, pathogen-associated molecular patterns; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor beta; TNF, tumor necrosis factor; TNF-β, tumor necrosis factor-beta.

Benedict M, Zhang X. *World J Hepatol.* 2017;9(16):715-732; Bedossa P. *Liver Int.* 2017;37(suppl 1):85-89; Younossi ZM, et al. *Hepatology.* 2011;53(6):1874-1882.

Histologic Features and Outcomes in NASH

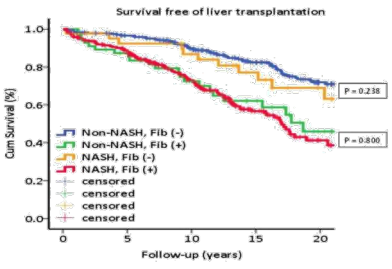
AASLD

- NAFLD liver biopsy (NAS, Brunt, Original NAFLD, and ZG Criteria) and mortality data (N=209)
- During 146 months FU, 31% of patients died with 9% LRM

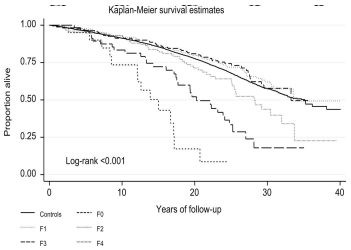


- *Fibrosis stage, but no other histologic features of steatohepatitis, were independently associated with overall mortality and liver-related mortality*

Younossi Z et al, Hepatology 2011, 53(6):1874-82

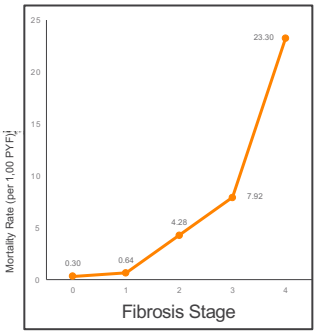


Angulo P et al, Gastroenterology. 2015; 149(2): 389–397



Hagstrom H et al, J Hepatology 2017;67:1265-1273

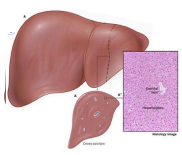
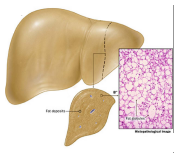
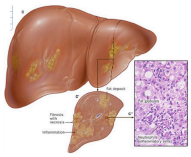
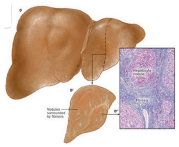
Systematic search of 5 studies of adult NAFLD cohort (N=1495) studies with mortality data and biopsy stage (0–4)



Dulai PS, et al. *Hepatology.* 2017;65(5):1557-1565

Non-Invasive Tests for the Spectrum of NAFLD

AASLD

Normal Liver	Steatosis (NAFL)	Steatohepatitis (NASH)	Fibrosis & Cirrhosis
"Wet" Biomarkers	Fatty Liver Index (FLI)	CK-18 NIS4	"Simple" Scores (FIB4, NFS) Direct Collagen Biomarkers (ELF Test™, PRO-C3™) NIS4
"Dry" (Imaging) Biomarkers	Ultrasound FibroScan™ (CAP) MR-PDFF	MR Liver MultiScan™	FibroScan™ (VCTE) Ultrasound: SSI, ARFI MR Liver MultiScan™ MR Elastography

Non-Invasive Tests for Fibrosis in NAFLD

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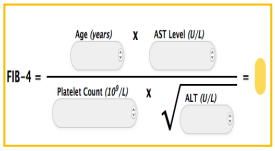
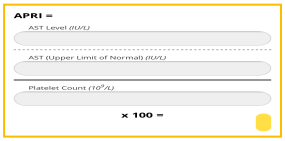
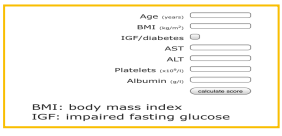
- **FIB-4 Index:**
  - Originally developed to predict advanced fibrosis in HIV/HCV coinfection
  - Subsequently studied in 541 patients with NAFLD (AUROC 0.80)
- **APRI:**
  - Meta-analysis of 40 studies
  - The lower the APRI score (less than 0.5), the greater the negative predictive value (and ability to rule out cirrhosis) and the higher the value (greater than 1.5) the greater the positive predictive value (and ability to rule in cirrhosis).
- **NAFLD Fibrosis Score (NFS):**
  - 733 NAFLD: 480 derivation; 253 validation
  - Multivariate analysis (Age, hyperglycemia, BMI, platelet count, albumin, AST/ALT ratio) are independent predictors of advanced fibrosis



FIB-4 Cutoff Value[2]	Stage
<1.45	F0–F2
>3.25	F3–F4



APRI:
The lower the APRI score (<0.5), the greater the NPV (and ability to rule out cirrhosis) and the higher the value (>1.5) the greater the PPV (and ability to rule in cirrhosis



NFS Cutoff Value[1]	Stage
<-1.455	F0–F2
>0.676	F3–F4

Serum Biomarker for Fibrosis in NAFLD

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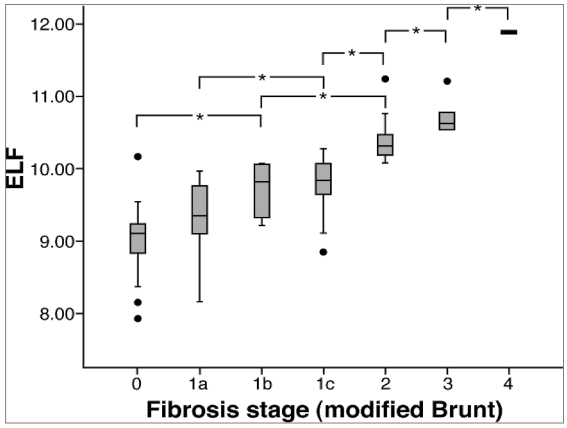
The Enhanced Liver Fibrosis Test (ELF)

Components

- Procollagen III N-terminal peptide (PIIINP)
- Hyaluronic acid (HA)
- Tissue inhibitor of metalloproteinase 1 (TIMP1)

Fibrosis	ELF	S (%)	Sp (%)	PPV (%)	NPV (%)
	9.93	57	90	88	64
Significant fibrosis ≥2	10.09	100	88	61	100
	10.18	**94**	**93**	**70**	**99**
	10.30	82	100	100	97
Advanced fibrosis ≥3	**10.51**	**100**	**98**	**80**	**100**
	10.78	50	99	80	96
	11.56	25	100	100	95



- Patients with NASH and bridging fibrosis (n=219) or compensated cirrhosis (n=258) enrolled in two Phase 2b SIM studies were used to show that ELF can predict progression to cirrhosis and development of liver-related clinical events
- Optimal threshold of baseline ELF: 9.76 (sensitivity 77%, specificity 66%)

Nobilli V et al. Gastroenterology 2009, Loomba R EASL 2019

Radiologic Tests To Measure Liver Stiffness

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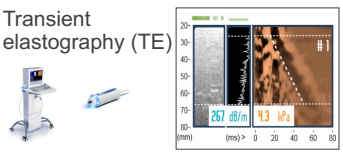
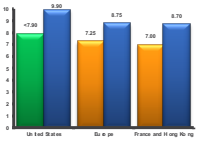
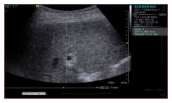
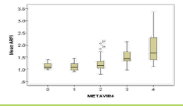
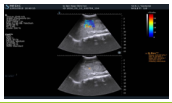
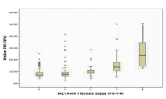
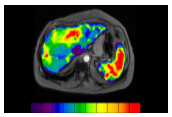
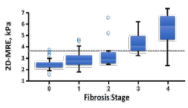
Technique			Visualize liver		
Transient elastography (TE)		US	• Liver stiffness expressed in kPa; correlates with liver fibrosis stage • Controlled Attenuation Parameter (CAP™) expressed in dB/meter • Accurate in detecting advanced fibrosis • Predicts risk of decompensation • Correlates well with portal pressure • Most widely used		Fibrosis Severity / Median LSM (range) Without F3-F4 fibrosis: 6.6 kPa (5.3-8.9) With F3-F4 fibrosis: 14.4 kPa (12.1-24.3)
Acoustic radiation force impulse (ARFI)		US	• Employs high intensity acoustic beam to mechanically excite tissue and monitor tissue displacement response • No need for an external compression • Degree of displacement is interpreted into degree of lightness and darkness		F1 – 1.24 m/s F2 – 1.48 m/s F3 – 1.61 m/s F4 – 1.75 m/s
Shear wave elastography (SWE)		US	• Shear waves are generated from acoustic pulses forced at five different tissue depth levels and SW velocity estimated by ultrafast Doppler-like acquisition of 5,000 frames/sec. • SW is converted to tissue stiffness as kilopascals		**Median Values** F0 6.93 kPa F1 7.7 kPa F2 9.6 kPa F3 13.95 kPa F4 23.73 kPa
Magnetic resonance elastography (MRE)		MR	• Most accurate of the imaging modalities • Costly, no point-of-care access • MRI Methods to Estimate Proton Density Fat Fraction • MRI-PDFF shown to have high correlation to morphometric fat[3]		**Stiffness cutoff: 3.63 kPa** - Sensitivity 0.86 - Specificity 0.91 AUC for advanced fibrosis: 0.924

Sequential Tests for Advanced Fibrosis in NASH

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Meta-Analysis of NITs to Distinguish Simple Steatosis From NASH

- In 122 studies, 219 blood markers (single markers and scoring systems) were evaluated
- In meta-analysis, no test reliably differentiated simple stetaosis from NASH with a high level of pooled sensitivity and specificity

Verhaegh P et al, Clin Gastro Hepatol 2018;16:837-61

- Study of baseline data from STELLAR trials (N = 3202) to diagnose F3/F4 fibrosis
  - **Single tests** (either NFS, FIB-4, ELF, or *FibroScan*) led to up to 50% indeterminate results
  - **Sequential tests** (FIB-4, then ELF or *FibroScan*) led to up to 24% indeterminate results

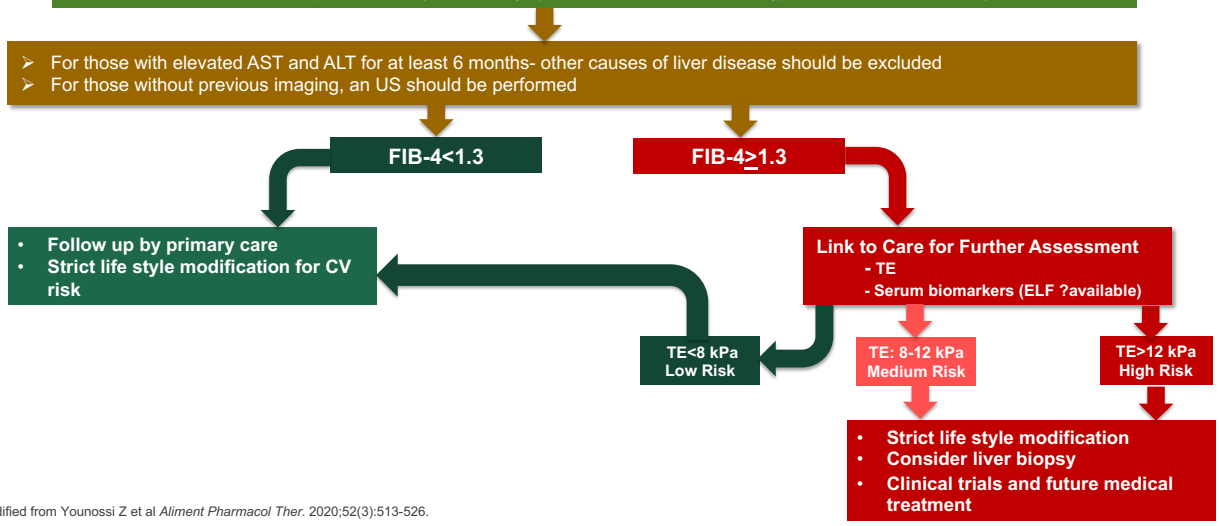
Outcome With Sequential Tests,% (95% CI)*	FIB-4, then ELF (N = 3180)	FIB-4, then FS (N = 3141)
Prevalence of F3/F4	71	71
Sensitivity	69 (67 to 71)	77 (75 to 78)
Specificity	92 (90 to 94)	89 (87 to 91)
PPV	96 (94 to 97)	95 (93 to 96)
NPV	55 (53 to 58)	60 (58 to 63)
Misclassified	24 (23 to 26)	20 (18 to 21)

Anstee. *Hepatology*. 2019;70:1521

An Algorithm for Risk Stratification in NAFLD

AASLD

1. History of chronic elevation of AST or ALT (1.5-times ULN in the past 6 months) or
2. History of fatty liver by any radiologic modality (US, CT, MRI) or liver biopsy (any historical test will be sufficient)
3. T2DM with one additional component of metabolic syndrome (BMI>29.9 or Dyslipidemia treated with meds or Hypertension treated with meds) or
4. Non-diabetics with 3 other components of MS (BMI>29.9, Dyslipidemia treated with meds and Hypertension treated with meds)



Modified from Younossi Z et al *Aliment Pharmacol Ther*. 2020;52(3):513-526.

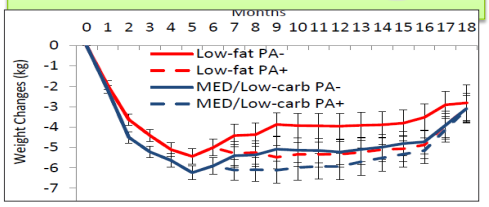
Lifestyle Interventions to Manage NAFLD and NASH

AASLD

Diet and exercise counseling are recommended for patients with NAFLD

- **Decreasing caloric intake** by ≥30% improves IR and hepatic fat
- **Mediterranean diet** improves steatosis
- **Low-carbohydrate diet** improves liver fat metabolism
- **Coffee** (caffeinated, filtered) ≥ 3 cups/day decreases NAFLD mortality
- Reduction or elimination of alcohol consumption

Diet



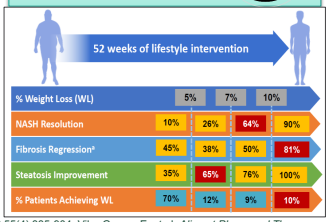
- **Physical activity** ≥150 min/week decreases serum aminotransferases
- **Moderate exercise** ≥5 times/week is associated with greatest benefit for long-term NAFLD prevention and improvement

Exercise

	Low-Fat Diet		Mediterranean/Low-Carbohydrate Diet	
18 Month Change	PA-	PA+	PA+	PA+
Visceral adipose tissue, cm^2	−32.9±33.5	−48.9±43.0	−31.1±32.7	−47.3±36.6
Intrahepatic fat, %, absolute units	−3.72±7.12	−3.88±6.32	−3.67±6.51	−4.74±7.63

- Losing **≥5%** of body weight improves HS
- Losing **≥7%** of body weight improves NAS
- Losing **≥10%** of body weight improves all features of NASH
- >10% weight loss is hard to achieve and hard to maintain

Weight Loss



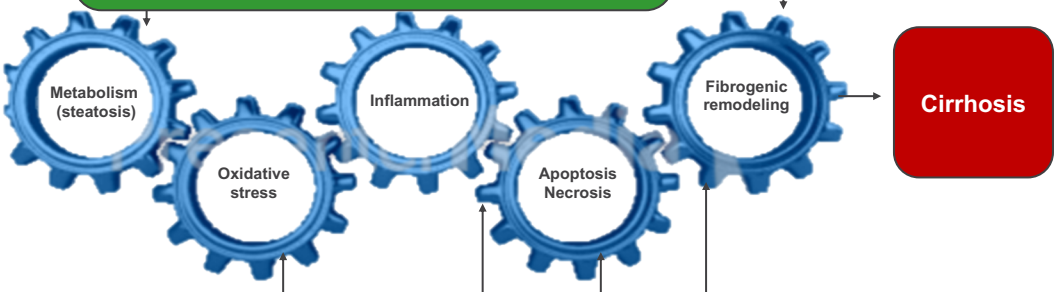
Kirk E, et al. *Gastroenterology*. 2009;136(5):1552-1560; Haufe S, et al. *Hepatology*. 2011;53(5):1504-1514; Sung KC, et al. *J Hepatol* 2016;65:791-797; Musso G, et al. *Diabetologia*. 2012;55(4):885-904; Vilar-Gomez E, et al. *Aliment Pharmacol Ther*. 2017;45(2):332-344; Poole R, et al. *BMJ* 2017;359:j5024; Mardinoglu A, et al. *Cell Metab*. 2018;27(3):559-571.e5.

Current and Future Treatment for NASH

AASLD

- **PPAR-γ (pioglitazone)**
- PPARα/σ agonist
- mTOT
- GLP1RA
  GLP1–GIP–glucagon
- Fatty acid–bile acid conjugates
- FXR agonist
- FGF19
- FGF21
- ACC1 and FASN FGF21
- THRβ agonist

Integrin inhibitors



- **Vitamin E**
- Betaine
- S-Adenosyl methionine

Caspase inhibitors

ASK1 inhibitor

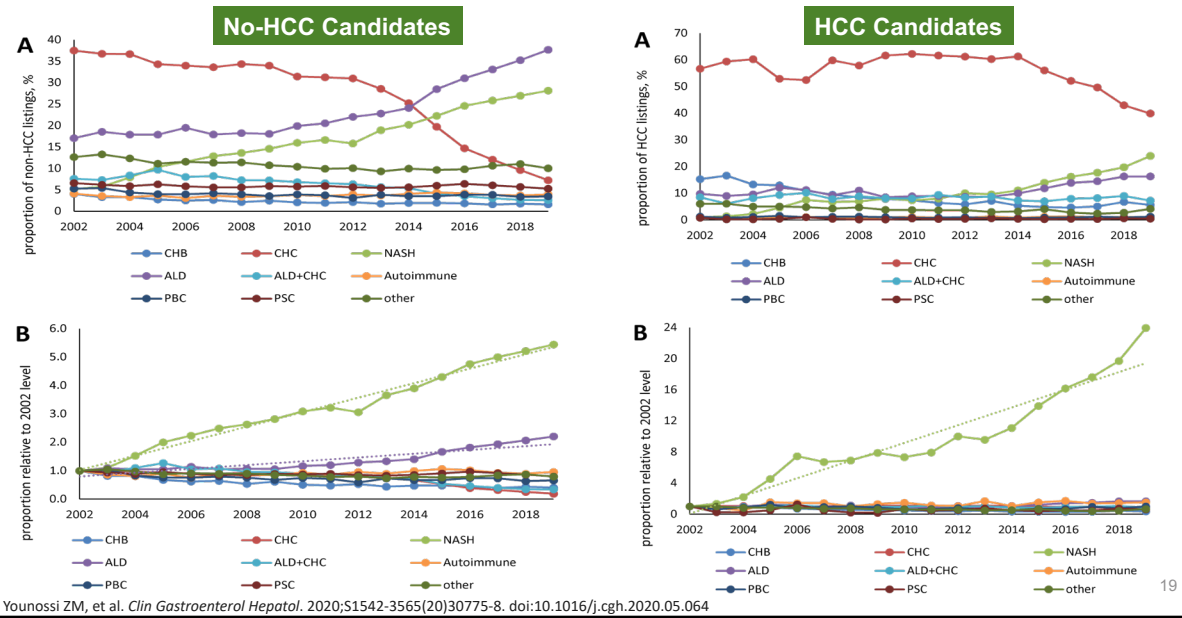
- CCR2–CCR5 antagonist
- VAP1 inhibitor

Modified from Sanyal AJ. *Nat Rev Gastroenterol Hepatol*. 2019;16:377-386.

ACC1, acetyl-CoA carboxylase 1; ASK1, Apoptosis signal-regulating kinase 1; FASN, fatty acid synthase; FGF19, fibroblast growth factor; FXR, farnesoid X receptor; GIP, gastric inhibitory peptide; GLP1, glucagone-like peptide 1 receptor agonist; mTOT, mitochondrial target of thiazolidinedione;THRβ, thyroid receptor beta; VAP-1, vascular adhesion protein 1.

Liver Transplantation for NASH: Transplant Candidates 2002 to 2019 SRTR data (N=168,441)

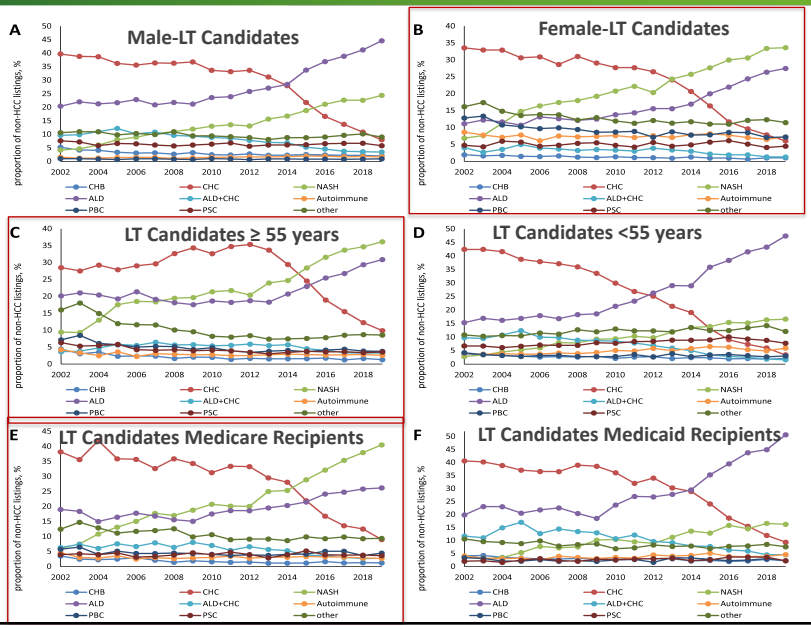
AASLD



Younossi ZM, et al. *Clin Gastroenterol Hepatol*. 2020;S1542-3565(20)30775-8. doi:10.1016/j.cgh.2020.05.064

Liver Transplantation for NASH: Transplant Candidates 2002 to 2019 SRTR data (N=168,441)

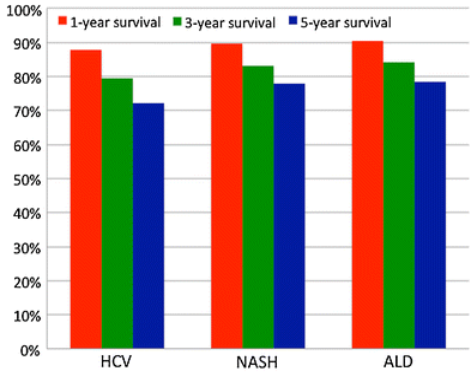
AASLD



Younossi ZM, et al. *Clin Gastroenterol Hepatol*. 2020;S1542-3565(20)30775-8. doi:10.1016/j.cgh.2020.05.064

Liver Transplantation for NASH: Survival of Liver Transplant Recipients

- United Network for Organ Sharing and Organ Procurement and Transplantation (UNOS/OPTN) 2003–2014 database
- On MVA, **NASH had significantly higher post-transplant survival compared to patients with HCV (HR 0.75; 95% CI 0.71–0.79; P=.001)**
- ALD also had significantly better post-transplant survival compared to HCV patients (HR 0.80; 95% CI 0.76–0.84; P=.001).
- Patients with underlying **diabetes had significantly lower post-transplant survival** (diabetes = HR 1.30; 95% CI 1.25–1.36; P=.001).
- Concurrent diagnosis of HCC was also associated with significantly lower posttransplant outcomes (HR 1.25; 95% CI 1.19–1.32; P=.001)

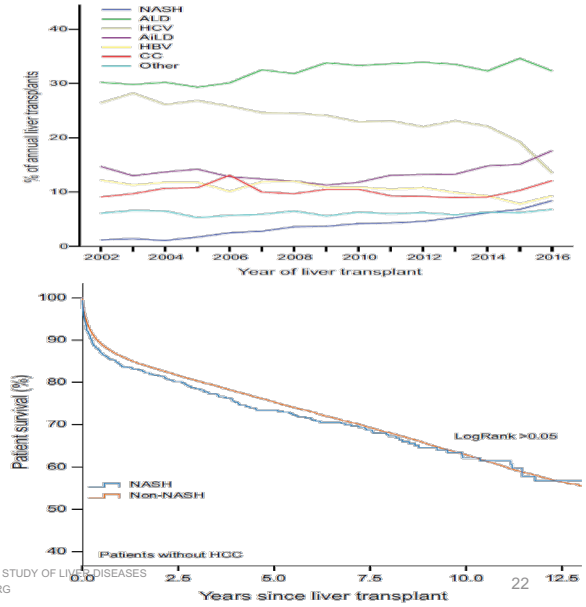


Note: HCV – hepatitis C virus; NASH – nonalcoholic steatohepatitis; ALD – alcoholic liver disease

Cholankeril, G., Wong, R.J., Hu, M. *et al. Dig Dis Sci* **62,** 2915–2922

Liver Transplantation for NASH: Transplant Candidates and Recipients (European Data)

- European Liver Transplant Registry database (January 2002 and December 2016) (N= 68,950)
- Overall, **4.0% were transplanted for NASH** – an increase from **1.2% in 2002 to 8.4%** in 2016.
- A greater proportion of patients transplanted for NASH (39.1%) had hepatocellular carcinoma (HCC) than non-NASH patients (28.9%, p<0.001).
- NASH was **not significantly associated with survival** of patients (hazard ratio [HR] 1.02, p=0.713) or grafts (HR 0.99; p=0.815) after accounting for available recipient and donor variables.
- Increasing recipient age (61–65 years: HR 2.07, p<0.001; >65: HR 1.72, p=0.017), elevated model for end-stage liver dis-ease score (>23: HR 1.48, p = 0.048) and low (<18.5 kg/m2:HR 4.29, p = 0.048) or high (>40 kg/m2: HR 1.96, p = 0.012) recipient body mass index independently predicted death in patients transplanted for NASH without HCC.



Haldar D, Kern B, Hodson J, et al. *J Hepatol*. 2019;71(2):313-322. doi:10.1016/j.jhep.2019.04.011

Long-term outcomes after LT for NASH

Author, year	Country, Period	Population, sample size	MELD score	Patient survival, %			Leading cause of death
				1 yr	3 yr	5 yr	
Malik, 2009	US single center 1997–2008	NASH = 98	17	79%	74%	72%	Infections: 57% CV: 21%
Yalamanchilli 2010	US single center 1986–2004	NASH = 18, CC = 239	-	85%	-	71%	CV: 21%, Malignancies,18%, Infections: 15%
Bhagat 2009	US single center 1997–2007	NASH = 71	-	82%	79%	75%	Infections: 53% CV: 26%
Barritt, 2011	US single center 2004–2007	NASH = 21	23	76%	76%	-	Infections: 20% CV: 20%
Houlihan, 2011	Israel, single center 2000–2008	NASH = 48	15	88%	-	82%	CV events, sepsis
Park, 2011	US single center 1998–2008	NASH = 9	13	78%	-	-	n.r.
Charlton, 2011	US, SRTR registry 2001–2009	NASH = 1840	-	84%	78%		No accurate information on causes of death or graft loss
Agopian, 2012	US single center 2002–2011	NASH = 144	33	84%	75%	70%	n.r.
Reddy, 2012	US single center 2000–2010	NASH-HCC (LT) = 20	9	-	83%	-	Liver failure. Similar overall survival in patients with NASH and HCV/ALD-related HCC
Wagner, 2012	US single center 1993–2010	NASH = 115	24	81%	73%	60%	Infections: 11% CV events: 9%
Kennedy 2012	US single center 1999–2009	NASH = 129	23	90%	88%	85%	Infections: 38% CV events: 19%
Afzali, 2012	US, UNOS 1997–2010	NASH = 1810; CC = 3843.	21	87%	81%	75%	Primary cause of deathunknown in 25% of the cases. CV events: 19%

Pais R, Barritt AS 4th, Calmus Y, et al. *J Hepatol*. 2016;65(6):1245-1257. doi:10.1016/j.jhep.2016.07.033

NAFLD Post Liver Transplantation:
Recurrent, de novo NAFLD and advanced fibrosis

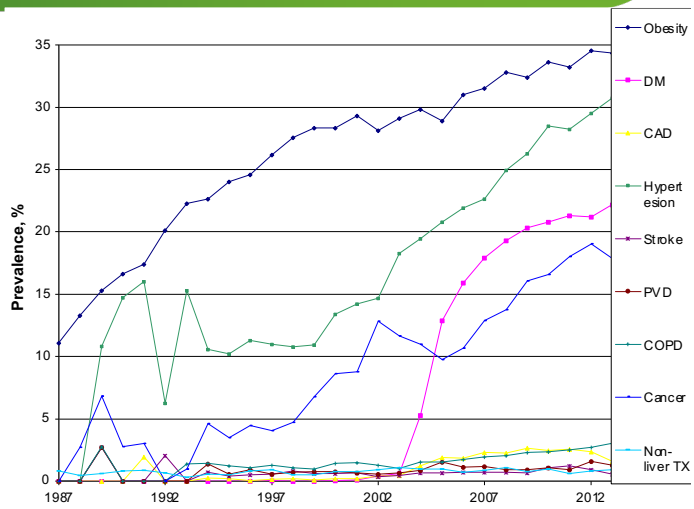
Study	Population, N	Time after LT	NAFLD	NASH	Fibrosis	Comments
Contos 2001	NASH&CC N = 27	1 year	52%	11%	≥F3: 4%	Risk of allograft steatosis: at 5 years 100% Recurrent NASH developed later than fatty liver alone. Cumulative dose of steroids correlated with time to NAFLD development.
Charlton 2001	NASH N = 15	1 year	60%	33%	≥F2: 33%	Cirrhosis developed in 12.5% of patients. 1 patient required re-transplantation for graft failure after 27 months.
Ong 2001	CC N = 51	2 years	25.4%	16%	≥F3:4%	Bridging fibrosis occurred in patients with post LT NASH.
Se0 2007	Non-NAFLD CLD N = 68	2 years	18%	9%	-	Increase of BMI of >10% was associated with post LT NAFLD
Bhagat 2009	NASH N = 64	>6 months	-	33%	-	No cirrhosis or re-transplantation because of recurrent disease. 24% of patients developed graft failure over follow-up.
Malik 2009	NASH N = 98	5 years	-	25%	-	Recurrent NASH did not adversely affect survival. 6 patients in NASH group were re-transplanted within 60 days after LT.
Yalamanchili 2010	NASH & CC N= 257	5 years	31%	4%	≥F3: 5%/5 yrs 10% at 10 yrs	Advanced fibrosis was more frequent amount those with post LT NASH (31%) than simple steatosis (6%)
Dumortier 2010	Non-NAFLD CLD N = 421	>6 months	31%	5.3%	≥F3: 2.25%	Most of the patients (52%) had grade 1 steatosis. The evolution of NAFLD during follow-up was: regression (48%), stability (22%), progression (30%). PTMS and liver graft steatosis were independent predictors of de novo NAFLD.
Duseja 2011	NASH or CC N = 88	1 year	39%	28%	≥F2: 9%	Only 9% of recurrent NAFLD had NAS ≥5. NAFLD recurrence was associated with increased risk for CV disease and correlated with post-transplant BMI, post LT TG levels and corticosteroids dose at 6 month.
El Attrache 2012*	NASH7CC N = 83	1.5 years	-	24%	≥F3: 3.6%	The recurrence rate was significantly higher amoung patients with PTMS (34% vs. 13% in patients without MS). 3 patients were re-transplanted secondary to graft failure from NASH recurrence.
Kim 2014	Non-NAFLD CLD N = 156	>1 year	27.1%	6.7%	F2: 4.4%	Obesity and donor graft steatosis were independent predictors for post LT NAFLD.

Over 1-2 years:
- 20-60% recurrence of NAFLD Post-LT
- 5-33% recurrence of NASH
- 4% of advanced fibrosis

Pais R, Barritt AS 4th, Calmus Y, et al. *J Hepatol*. 2016;65(6):1245-1257. doi:10.1016/j.jhep.2016.07.033

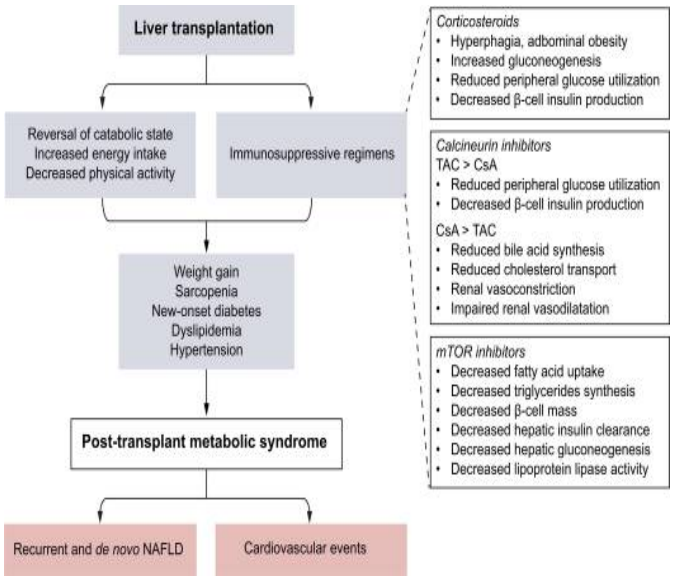
The prevalence of comorbidities in adult liver transplant recipients (SRTR 1987 to June 2013)

- Consistent with the changes in US population, LT recipients are becoming older, more commonly male and sicker
- Average MELD score increased slightly.
- Rates of nearly all chronic conditions increased
- **What contributes to post-LT metabolic profile?**
- Given the epidemic of obesity and T2DM, these rates are also higher in LT recipients
- **How about meds?**



Stepanova M, Wai H, Saab S, Mishra A, Venkatesan C, Younossi ZM. The portrait of an adult liver transplant recipient in the United States from 1987 to 2013. *JAMA Intern Med*. 2014;174(8):1407-1409. doi:10.1001/jamainternmed.2014.2903

Factors Contributing to Post LT Metabolic Profile



	CST	Calcineurin inhibitors		mTOR inhibitors (sirolimus, everolimus)
		TAC	CSA	
Abdominal obesity	+	–	–	–
New Onset DM	+++	++	+	-
Dyslipidemia	+	+	+	+++
HTN	+	++	++	+

Pais R, Barritt AS 4th, Calmus Y, et al. *J Hepatol*. 2016;65(6):1245-1257. doi:10.1016/j.jhep.2016.07.033

Clinical Issues in Patients with NASH and LT

- **CV and CKD Risks:**
  - Liver transplant candidates with NASH are at high risk of developing CV events before and after LT
  - Accumulation of CV risk factors should be carefully assessed by transplant team (cardiologists and anesthesiologists)
  - Patients with Child A/B NASH cirrhosis and CV comorbidities can be considered for management of dyslipidemia and CV risk
  - NASH is an independent risk factor for pre and post-LT renal dysfunction; appropriate screening and management of kidney disease is highly recommended in this patient population
- **Management of Metabolic Comorbidities:**
  - A multidisciplinary approach is recommended to establish a risk minimization plan
  - Appropriate screening for hypertension, diabetes, and dyslipidemia is recommended in NASH-patients considered for LT and medical optimization is strongly recommended
  - Post-LT moderate exercise is recommended with the dual objective of losing weight and improving muscle mass

Modified from Tsochatzis E et al. Transplantation 2019;103: 45–56)

NAFLD and Liver Transplantation

Summary

- NASH is becoming the most common cause of liver disease in the United and possibly the world
- NASH has significant clinical, economic and quality of life burden
- NASH is the second common indication for LT in the US and the top indication among women
- NASH can recur post LT
- Post LT outcomes for NASH are similar to other etiologies
- Given close associations with metabolic risk factors, CV risk, CKD risk and other metabolic abnormalities, there is a need for assessment and aggressive management both pre-LT and post-LT