

NAFLD/NASH: PHYSIOPATHOLOGY, DIAGNOSIS AND OUTCOME

Natural history of NASH and HCC



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The poster for the 14th Paris Hepatology Conference (PHC 2021) features a dark blue background with a golden Eiffel Tower on the left. The text is in white and gold. The top left corner has the Eiffel Tower logo and '2021 14th PARIS HEPATOLOGY CONFERENCE'. The top right corner says 'PHC 2021 8 - 9 - 10 March 2021 The Digital Paris Hepatology Conference'. The middle right section says 'International Conference on the Management of Liver Diseases'. The bottom right section says 'Organised by Pr Patrick Marcellin' and 'Association for the Promotion of Hepatologic Care (APHC)'.

2021
14th PARIS
HEPATOLOGY
CONFERENCE

PHC 2021
8 - 9 - 10 March 2021
The Digital Paris Hepatology Conference

**International Conference
on the Management of
Liver Diseases**

Organised by
Pr Patrick Marcellin

Association for the Promotion
of Hepatologic Care (APHC)

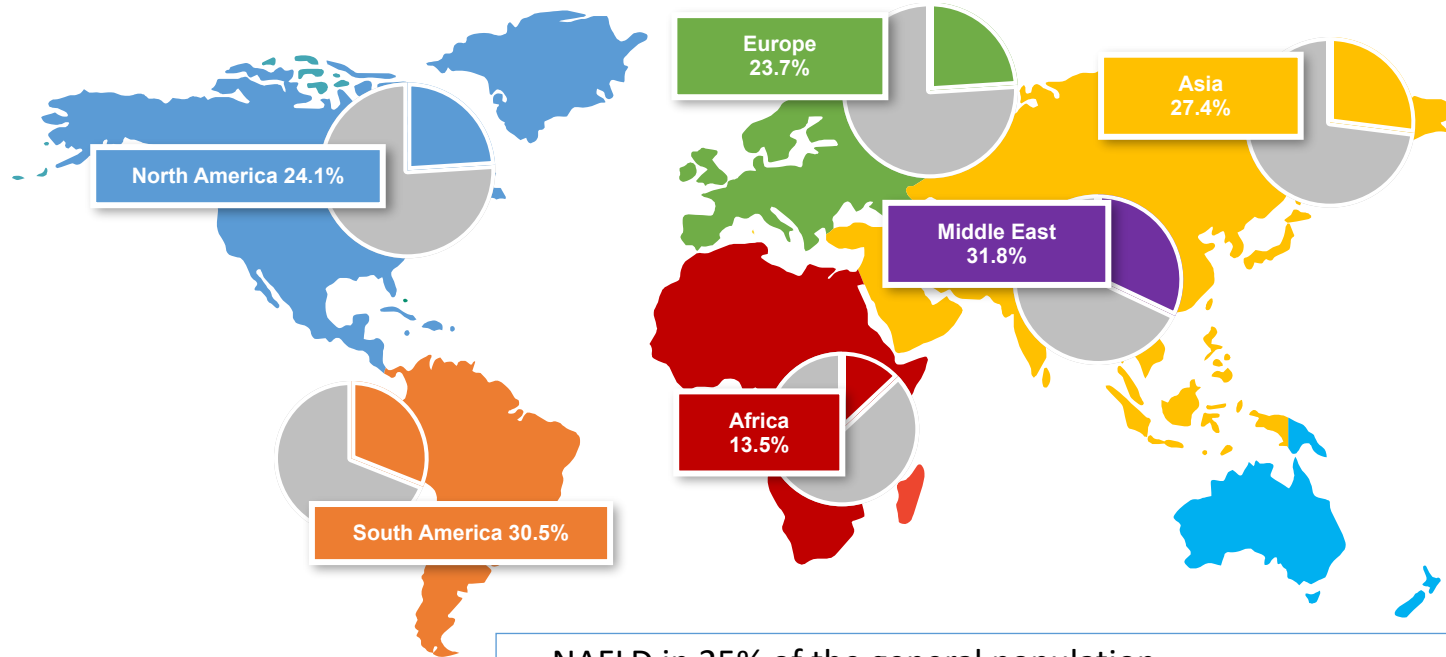
Disclosure of Conflicts of Interest

I herewith declare the following paid or unpaid consultancies, business interests or sources of honoraria payments for the past three years, and anything else which could potentially be viewed as a conflict of interest:

Consultant:

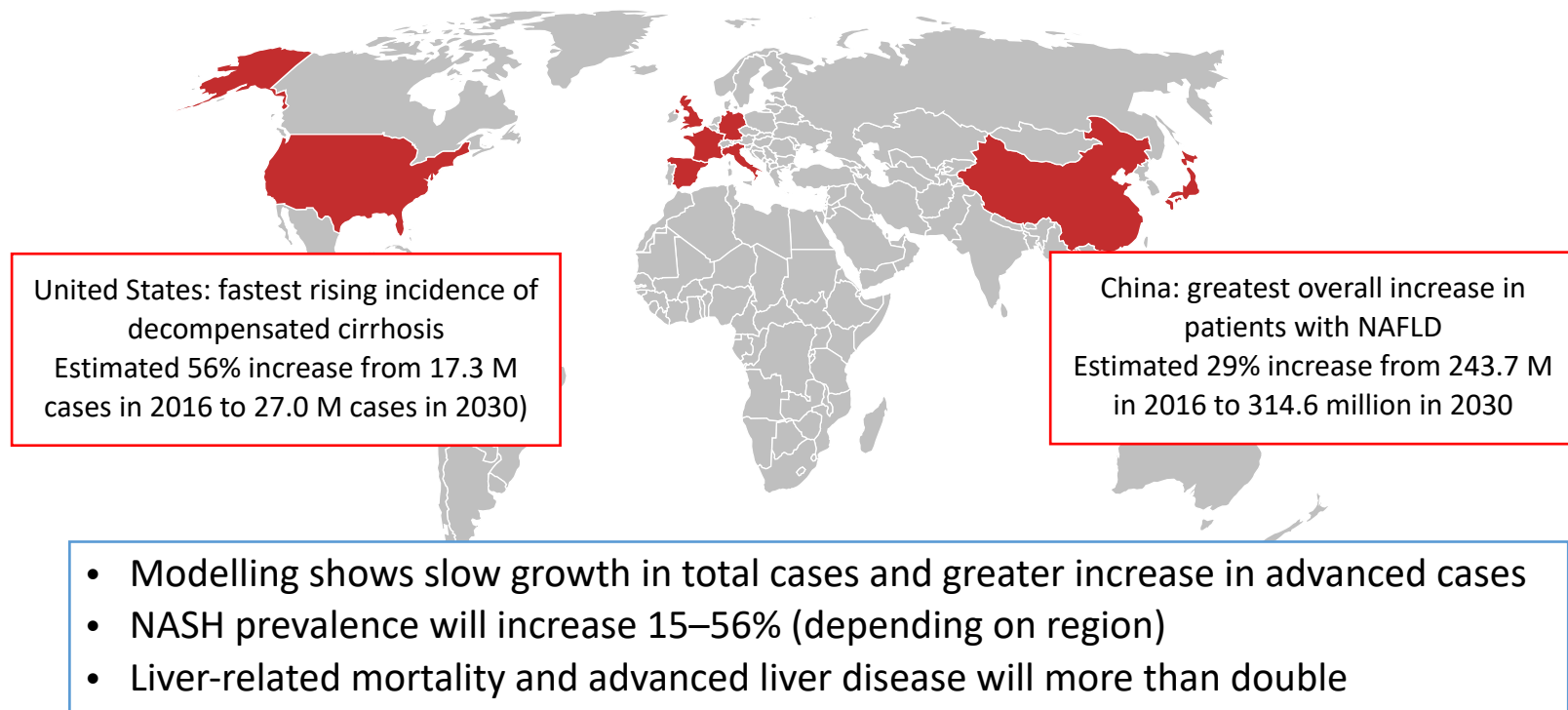
Gilead Sciences, Intercept, BMS, NovoNordisk, Pfizer, Inventiva, Genfit

Global prevalence of NAFLD



- NAFLD in 25% of the general population
- NASH in 10–20% of people with NAFLD (1.5–6.5% general population)
- Advanced fibrosis/cirrhosis in 10–15% of NASH

Modelling the epidemic of NAFLD worldwide by 2030



M, million; NAFLD, non-alcoholic fatty liver disease

*China, France, Germany, Italy, Japan, Spain, UK, and US modelled from 2016 to 2010

1. Estes C et al. J Hepatol 2018;67:896–904; 2. Onis M et al. Am J Clin Nutr 2010;92:1257–64; 3. Hagström H et al. J Hepatol 2016;65:363–8

Global Mortality Burden of NAFLD and NASH

A Meta-Analytic Assessment

Population	Outcome	Incidence Rate Per 1,000 Person-Years*	Number of Studies	95% CI	I ² (%)	Follow-up (Years)
NAFLD	CVD-specific mortality	4.79	6	(3.43-6.7)	91.17	12.96
NAFLD	HCC	0.44	3	(0.29-0.66)	0.00	5.82
NAFLD	Liver-specific mortality	0.77	7	(0.33-1.77)	91.84	13.17
NAFLD	Overall mortality	15.44	7	(11.73-20.34)	97.17	13.17
NASH	Advanced fibrosis	67.95	3	(46.84-98.56)	9.80	4.05
NASH	HCC	5.29	3	(0.75-37.56)	NA	4.50
NASH						4.08
NASH						4.07
NAFLD						4.08
NAFLD						4.08
NASH						4.08
NASH						4.07
NAFLD						4.23
NAFLD						4.23
NASH	Percent fibrosis progression†	40.76	4	(34.69-47.13)	5.70	4.91
NASH	Mean fibrosis annual progression rate†	0.09	2	(0.06-0.12)	0.00	4.01

In NAFLD, the incidence of CV mortality is higher than liver-related mortality

When including studies defining NAFLD by both US and LT, CV mortality is not increased

If NAFLD is diagnosed by US, IRR for CV mortality is increased at 1.37 [95% CI (1.23-1.54)]

Clinical outcomes vary with stage of disease

NASH F3

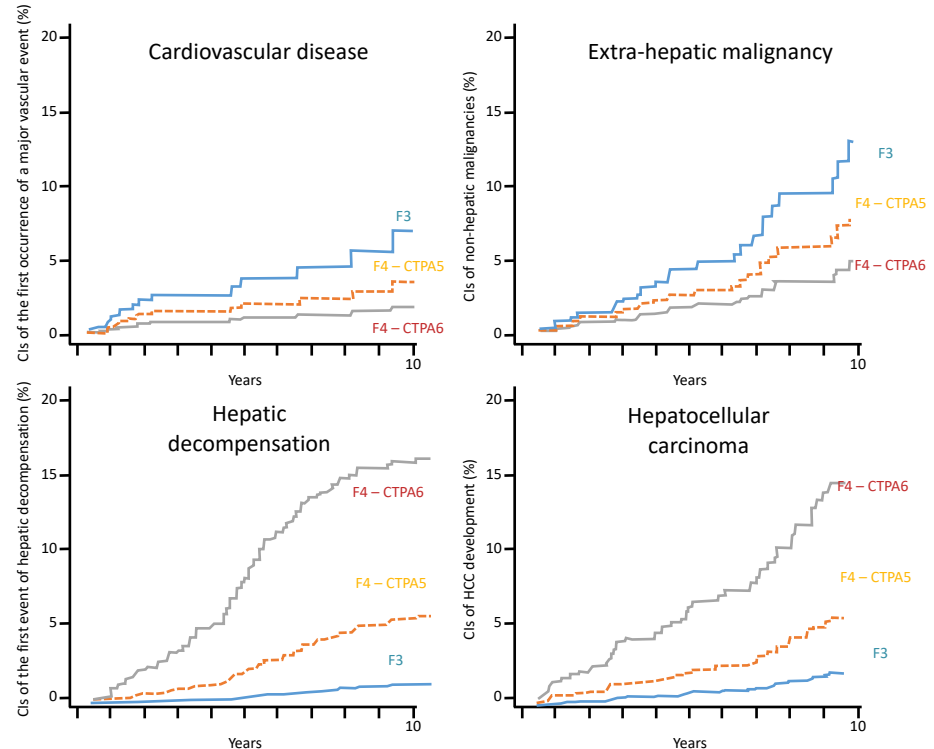
Clinical events

- Cardiovascular disease
- Extra-hepatic malignancy
- HCC

Clinical events

- Liver-related death/OLT
- Hepatic decompensation
- HCC

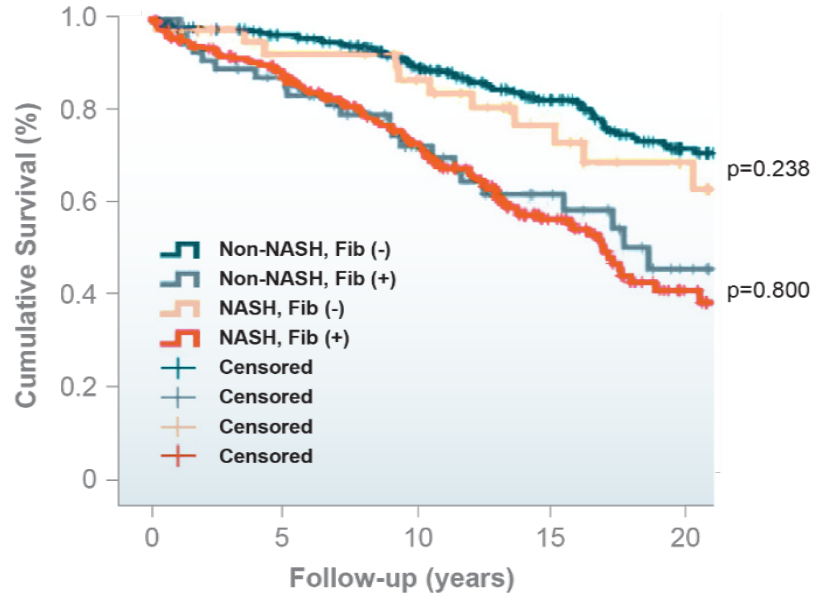
CIRRHOSIS



Fibrosis is a proven predictor of liver-related mortality and liver transplantation-free survival

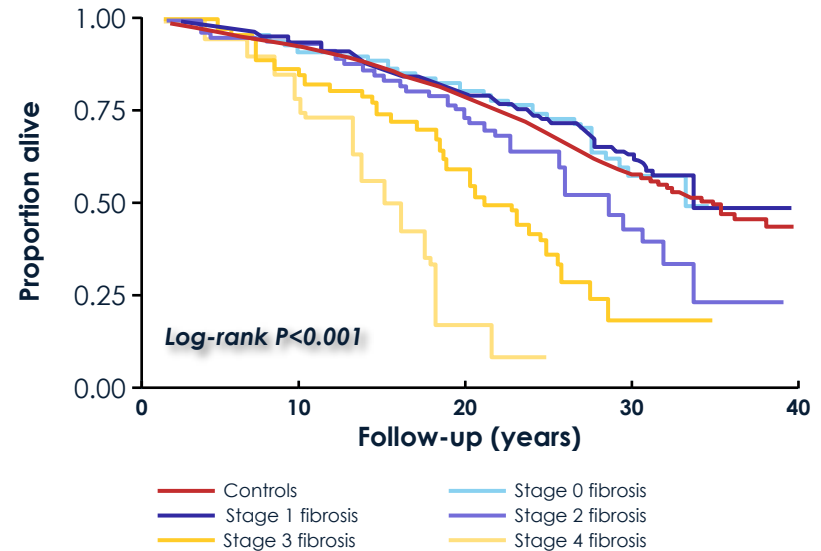
Survival free of liver transplantation³

(Retrospective analysis of patients from USA, Europe and Thailand with NAFLD diagnosis, n=619)



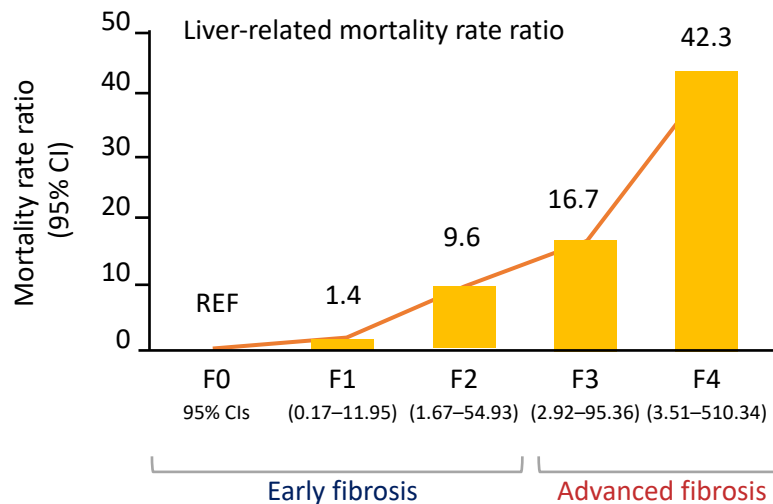
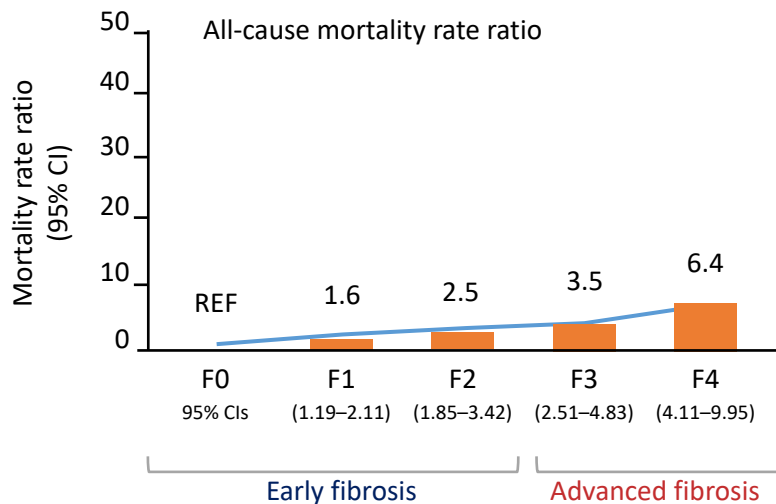
Overall mortality stratified by fibrosis stage scored by Kleiner classification¹

(Swedish retrospective cohort in patients with biopsy-proven NAFLD, n=646)



The risk of liver-related mortality increases with increasing fibrosis stage

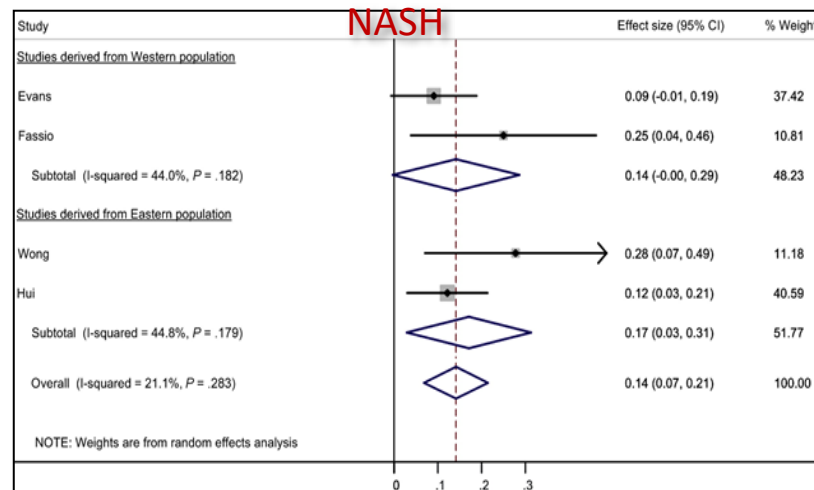
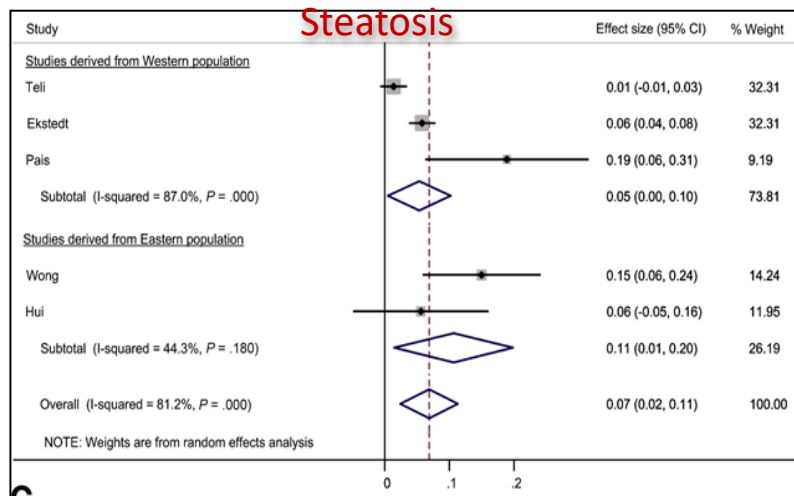
A meta-analysis of five multinational cohorts (17,452 PYF)¹



CI, confidence interval; PYF, patient-years of follow-up
Dulai PS et al. Hepatology 2017;65:1557–65

Fibrosis Progression Rate in patients with NAFL and NASH

Meta-analysis of 11 Paired-Biopsy Studies including 366 patients with NAFLD (2545 person/year)



In 36 % NAFLD patients progression of fibrosis, 46 % stable, 21% improvement in fibrosis.

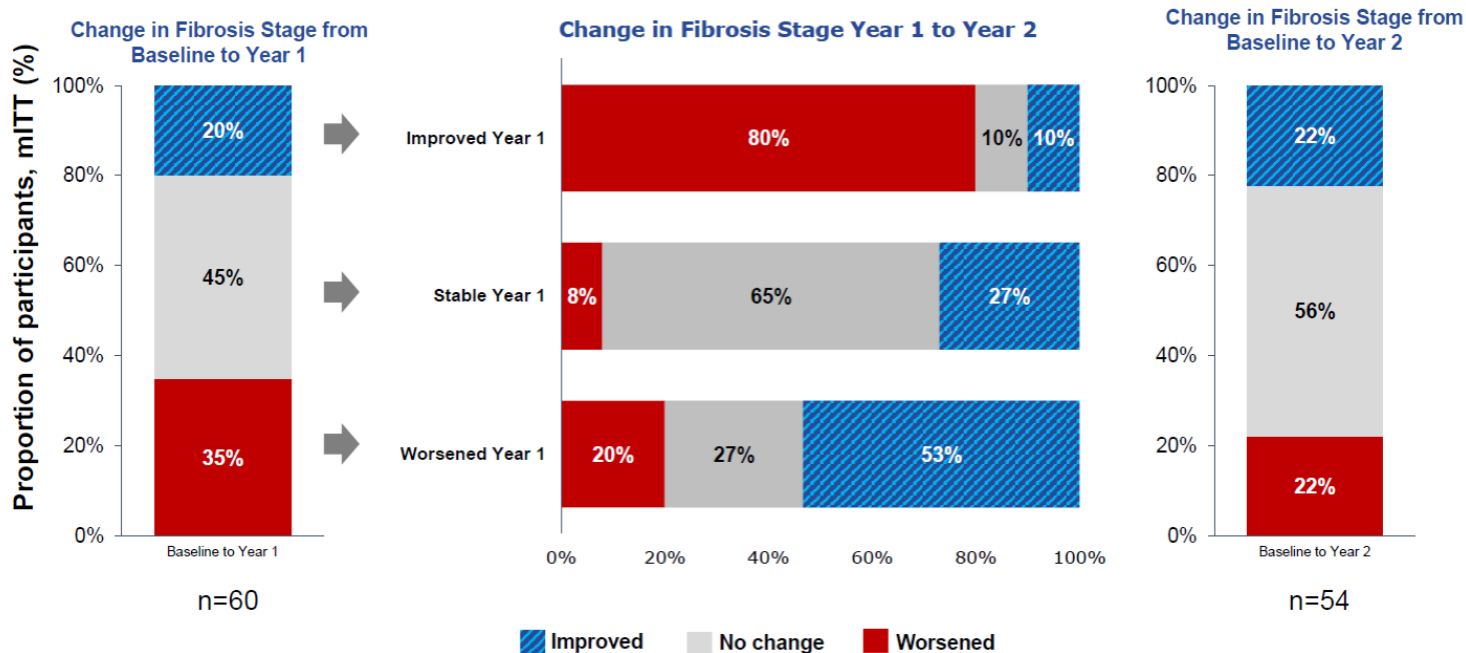
Rates of progression:

In Steatosis 1 stage over 14.3 years (0.07 stages/year)

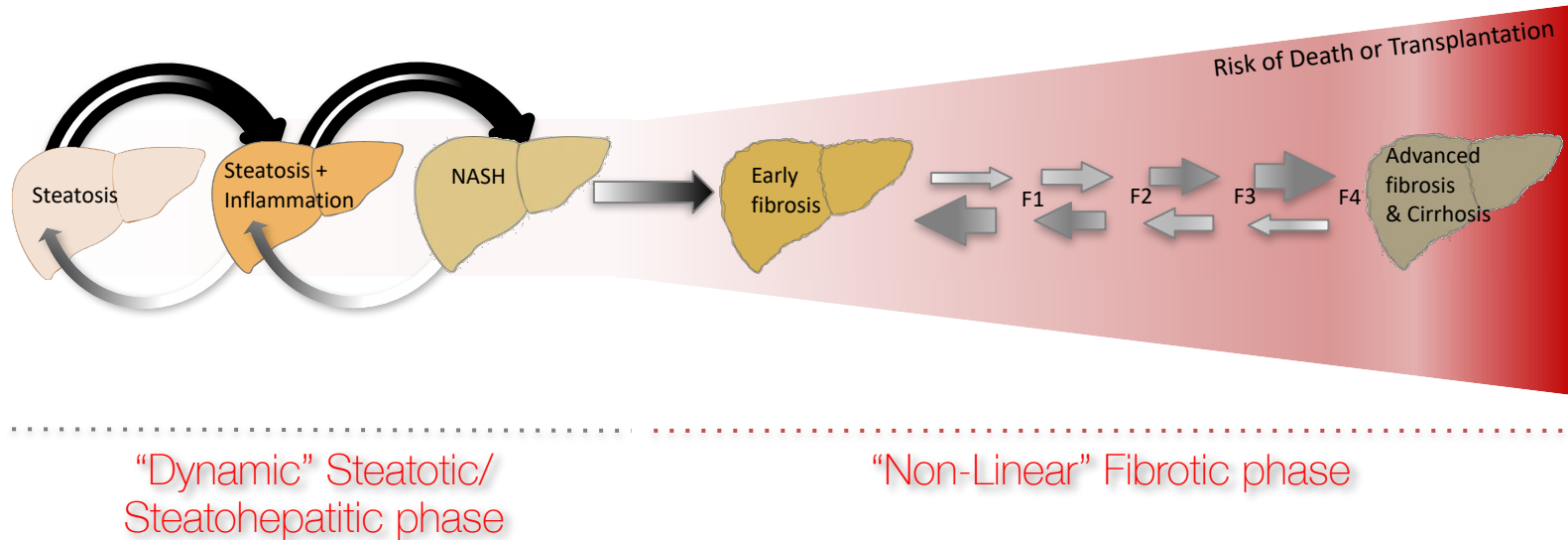
In NASH 1 stage over 7.1 years (0.14 stages/year)

21% patients with baseline stage 0 fibrosis progressed to stage 3 or 4 fibrosis over a mean follow-up period of 6 years

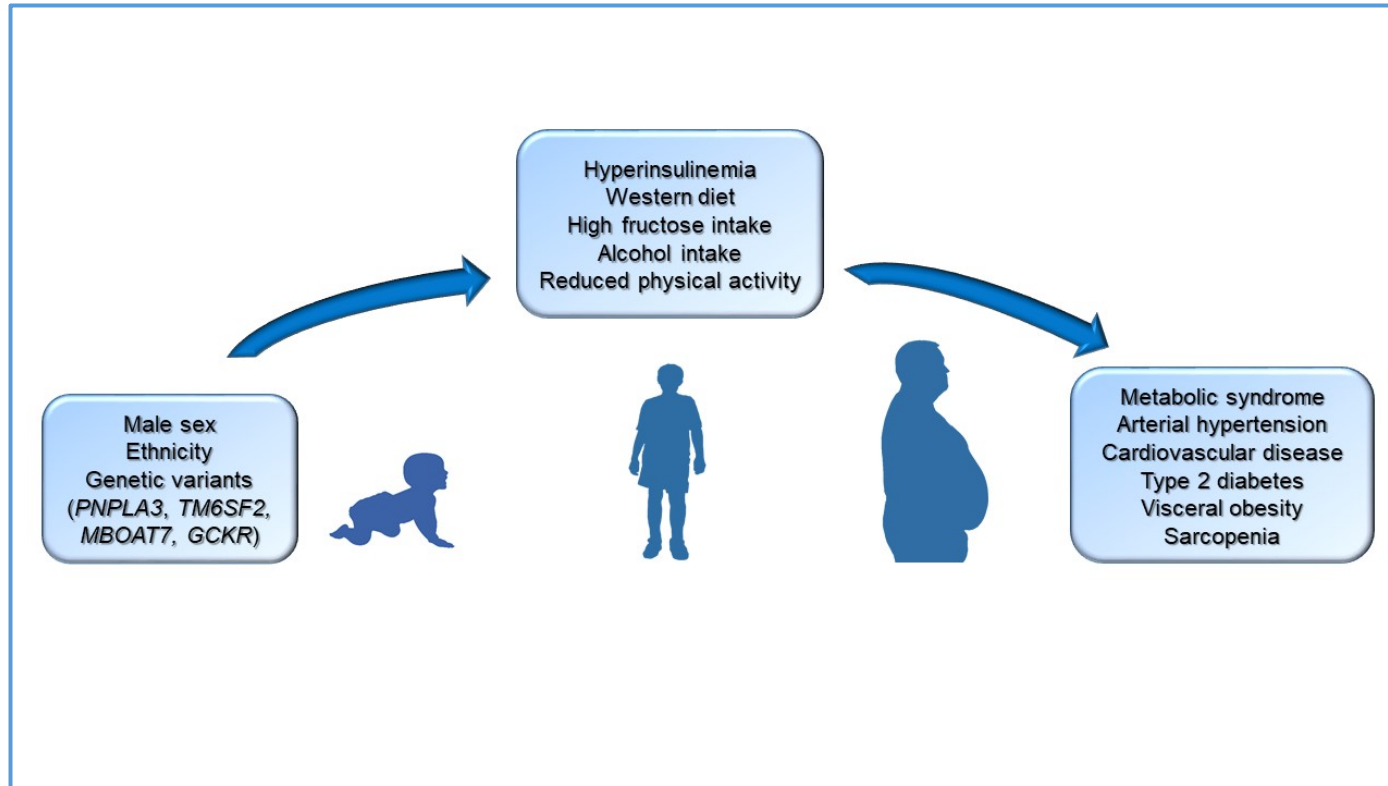
Seesaw effect: substantial variability in fibrosis stage in placebo group of Phase 2b CENTAUR study



Substantial inter-patient variation in disease natural history, rate of disease progression and outcome

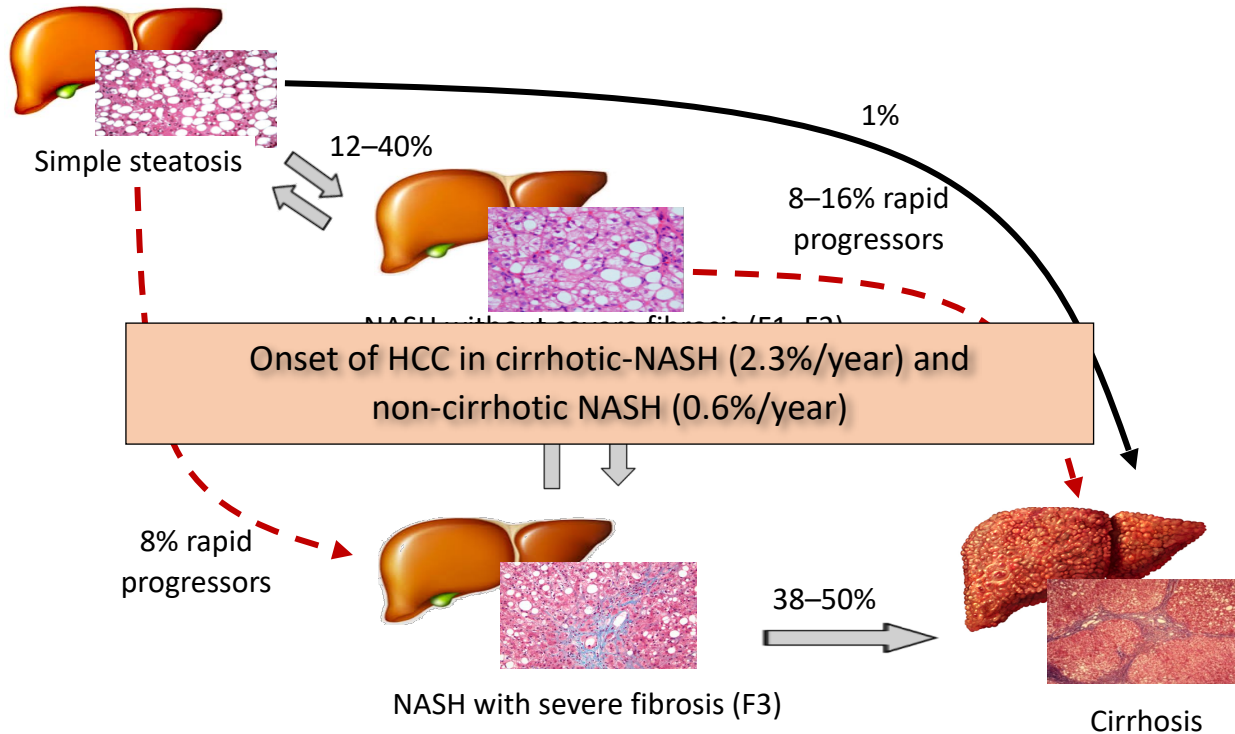


Environmental and genetic factors influencing the progression of NAFLD



Natural history of NAFLD

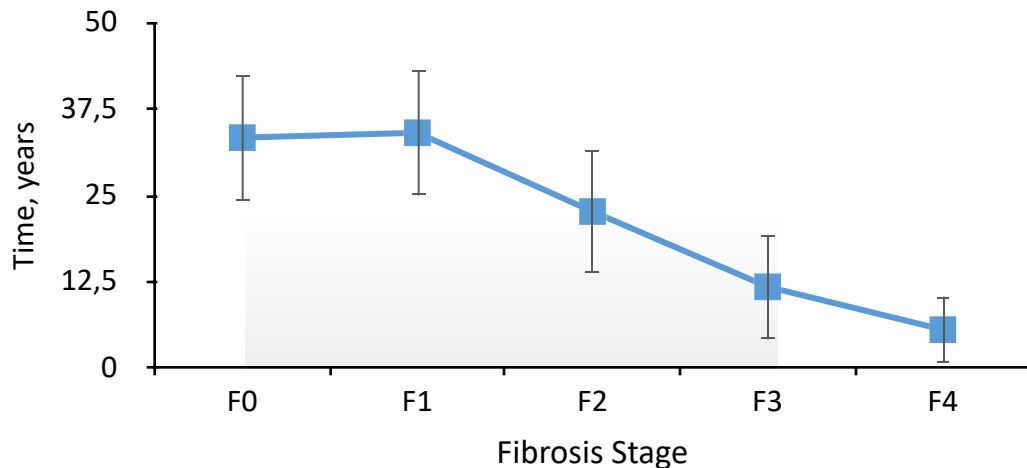
Ratziu 2002
 Fassio 2004
 Sanyal 2006
 Ekstedt 2006, & 2015
 Bhala 2011
 Younossi 2011
 Pais 2013
 McPherson 2015
 Singh 2015



Patients with NASH and Bridging Fibrosis May Progress Faster to Liver Decompensation

Laplace regression used to calculate time to clinical outcomes in a Swedish retrospective cohort of patients with biopsy-proven NAFLD (n= 646)

Time for first 10% of patients to develop liver decompensation by fibrosis stage



Patients with NASH who have bridging fibrosis or cirrhosis may progress to liver decompensation in as little as 4.3 years and 1 year, respectively

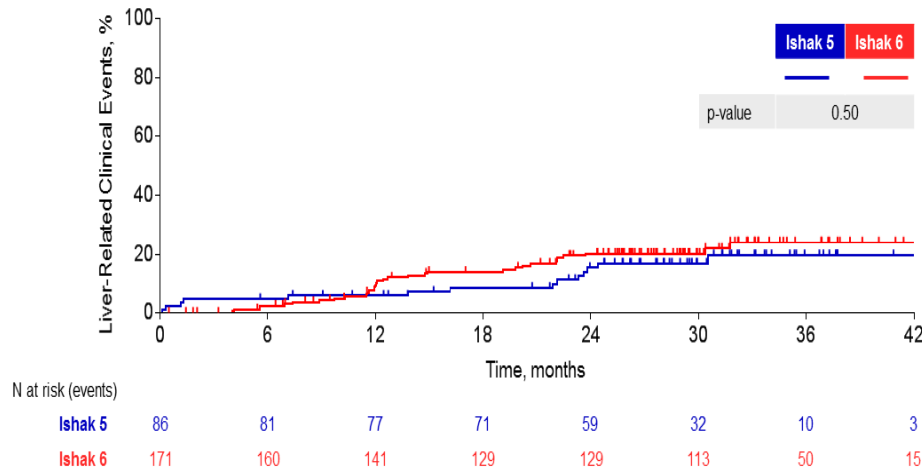
The Natural History of Advanced Fibrosis Due to Nonalcoholic Steatohepatitis: Data From the Simtuzumab Trials

Arun J. Sanyal,¹ Stephen A. Harrison,² Vlad Ratziu,³ Manal F. Abdelmalek,⁴ Anna Mae Diehl,⁴ Stephen Caldwell,⁵

Results: Liver-Related Clinical Events

Cirrhosis

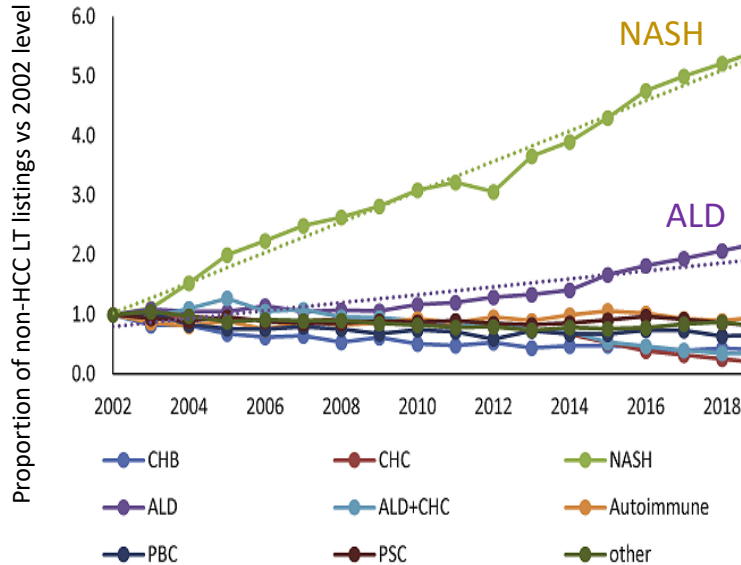
Sanyal GS-004



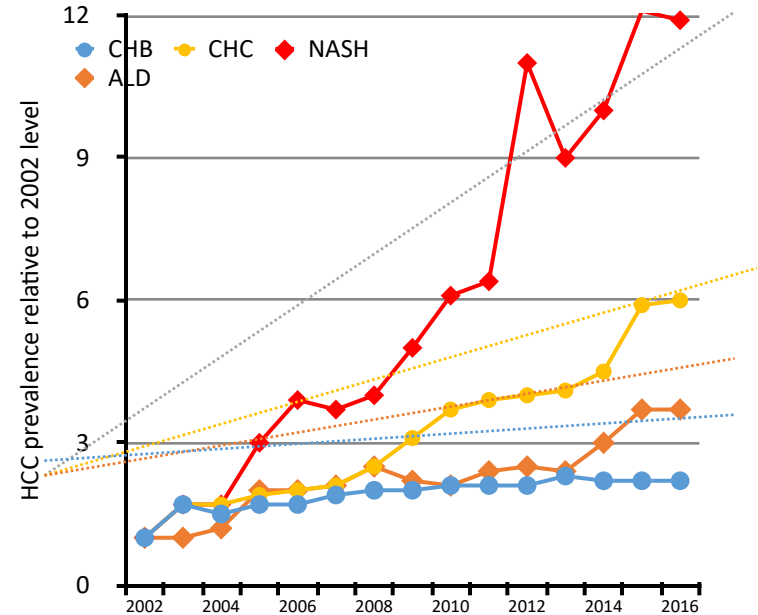
- Over 2 years, ~25% of patients with NASH and bridging fibrosis progress to cirrhosis, and ~20% of cirrhotic patients have liver-related events in the clinical trial setting
- Increased risk of clinical events with worsening of fibrosis (by Ishak stage, collagen content, ELF)

Liver transplant due to NASH

Listing for LT in the US

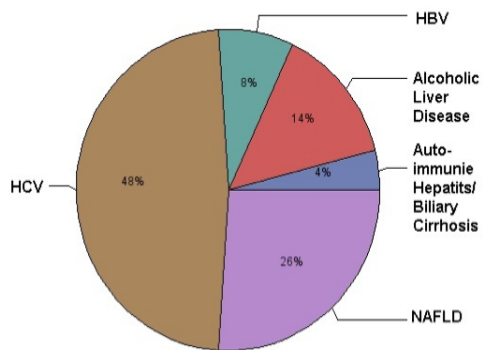


Listing for LT with HCC in the US



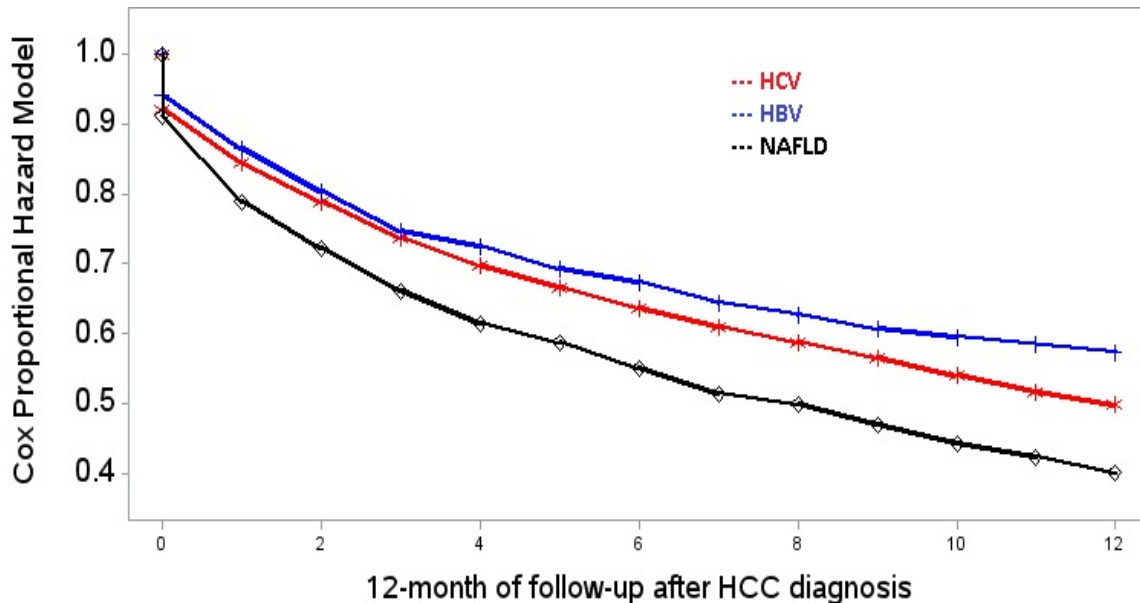
Survival Curves of pts with HCC by Liver Disease

5,748 HCC cases



Factors associated with one-year mortality:

- ✓ Older age (HR: 1.02)
- ✓ Un-staged tumor (1.24)
- ✓ NAFLD (HR: 1.21)



Source: SEER-Medicare, 2004-2009

* Adjusted for age (years) at HCC diagnosis, tumor stage

Take home message

- NAFLD is a complex disease with pathogenesis and progression determined by combinations of genetic and environmental factors.
- The Natural History of NAFLD/NASH progression is much more dynamic than has previously been appreciated.
- Factors leading to the progression of NAFLD are only partially understood, a limitation that is particularly serious when considering that up to 40% of HCC cases occur in non-cirrhotic livers.
- Genetic factors may be one component of these processes
- Large cohorts and detailed multi omics datasets have the potential to provide insights into these processes and help us to identify robust stratifiers.

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Thank you for your attention!

