



FACULTAD DE MEDICINA
PONTIFICIA UNIVERSIDAD
CATÓLICA DE CHILE



HEPATO 2019
XXV CONGRESSO BRASILEIRO
DE HEPATOLOGIA

HCC in NAFLD/NASH: An Overview

Marco Arrese

Departamento de Gastroenterología

Facultad de Medicina

P. Universidad Católica de Chile

marrese@med.puc.cl

www.higadograso.cl

October 3rd, 2019

medicina.uc.cl

Session time: 4:40 p.m. – 5:00 p.m.

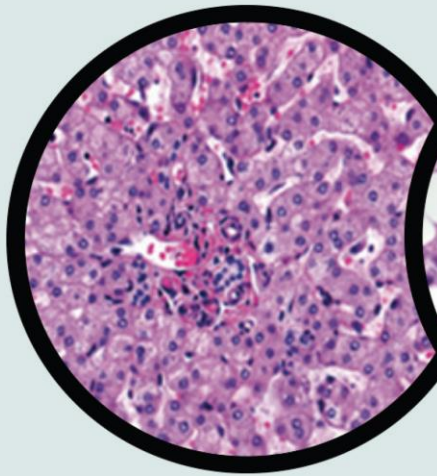
Disclosure

- Presenter's Name: [Marco Arrese](#)
- I have no current or past relationships with commercial entities related to this presentation

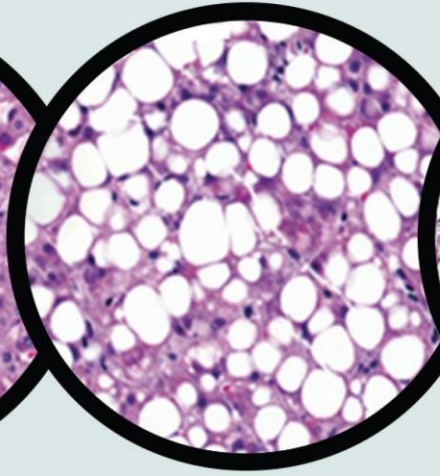
OUTLINE

- ✓ Changing epidemiology of HCC
- ✓ Peculiarities of NASH-related HCC
- ✓ Pathogenic considerations
- ✓ Clinical insights

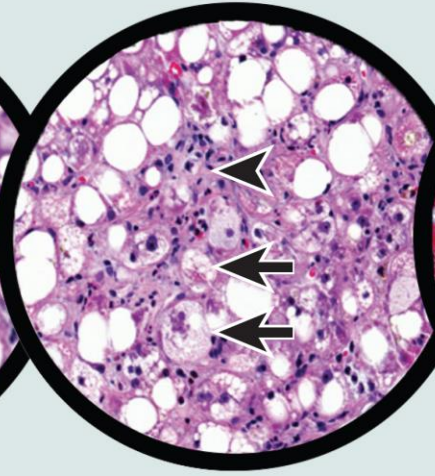
a Normal liver



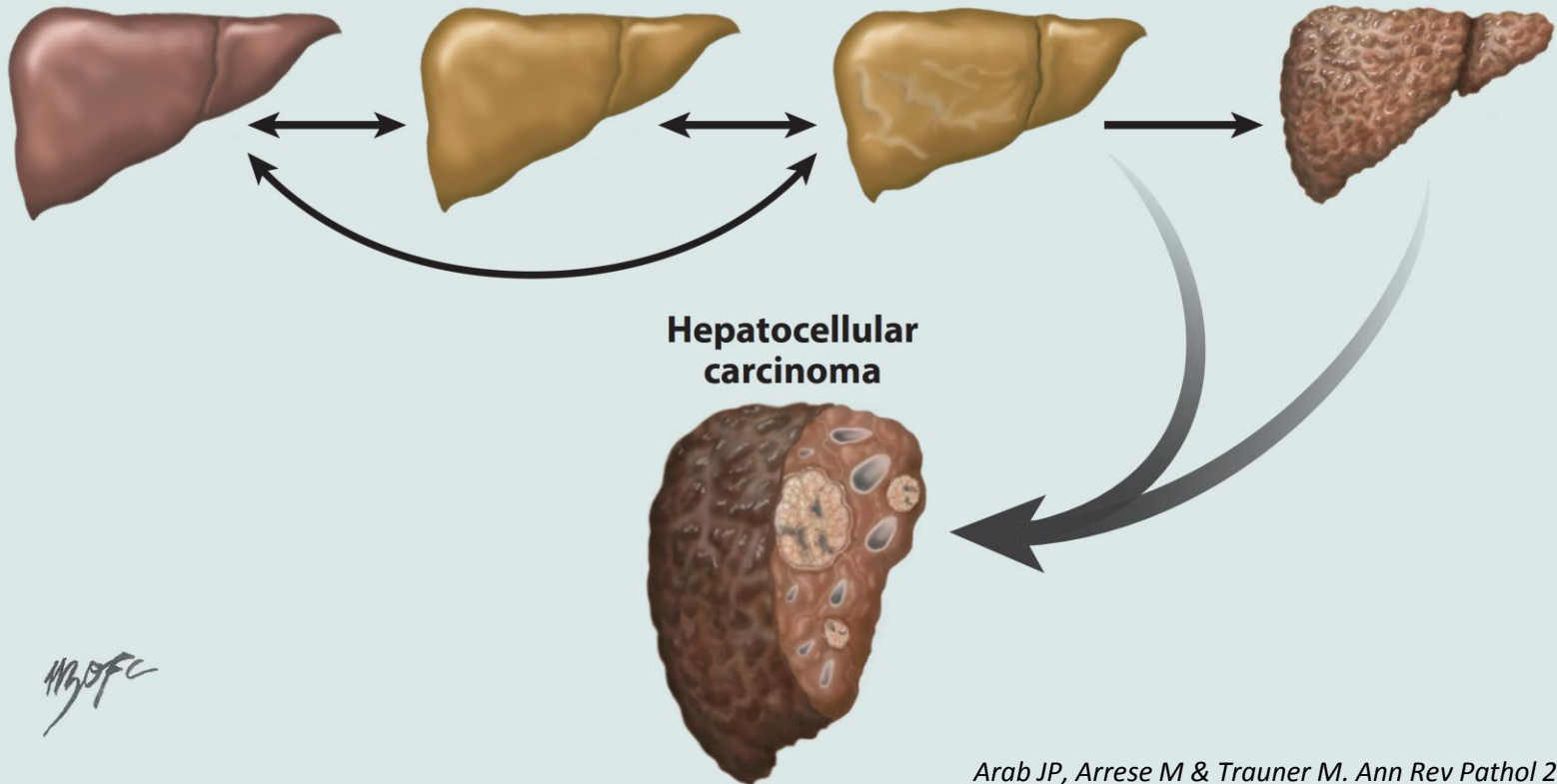
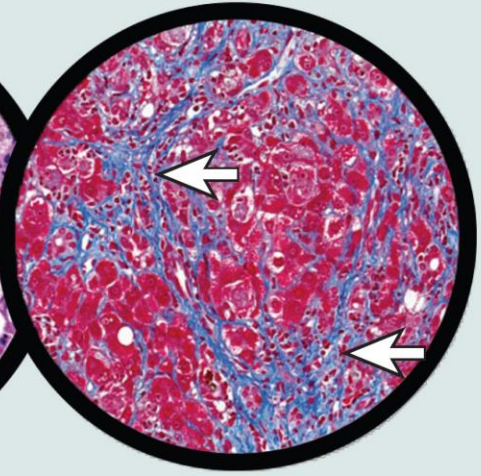
b Isolated steatosis



c NASH



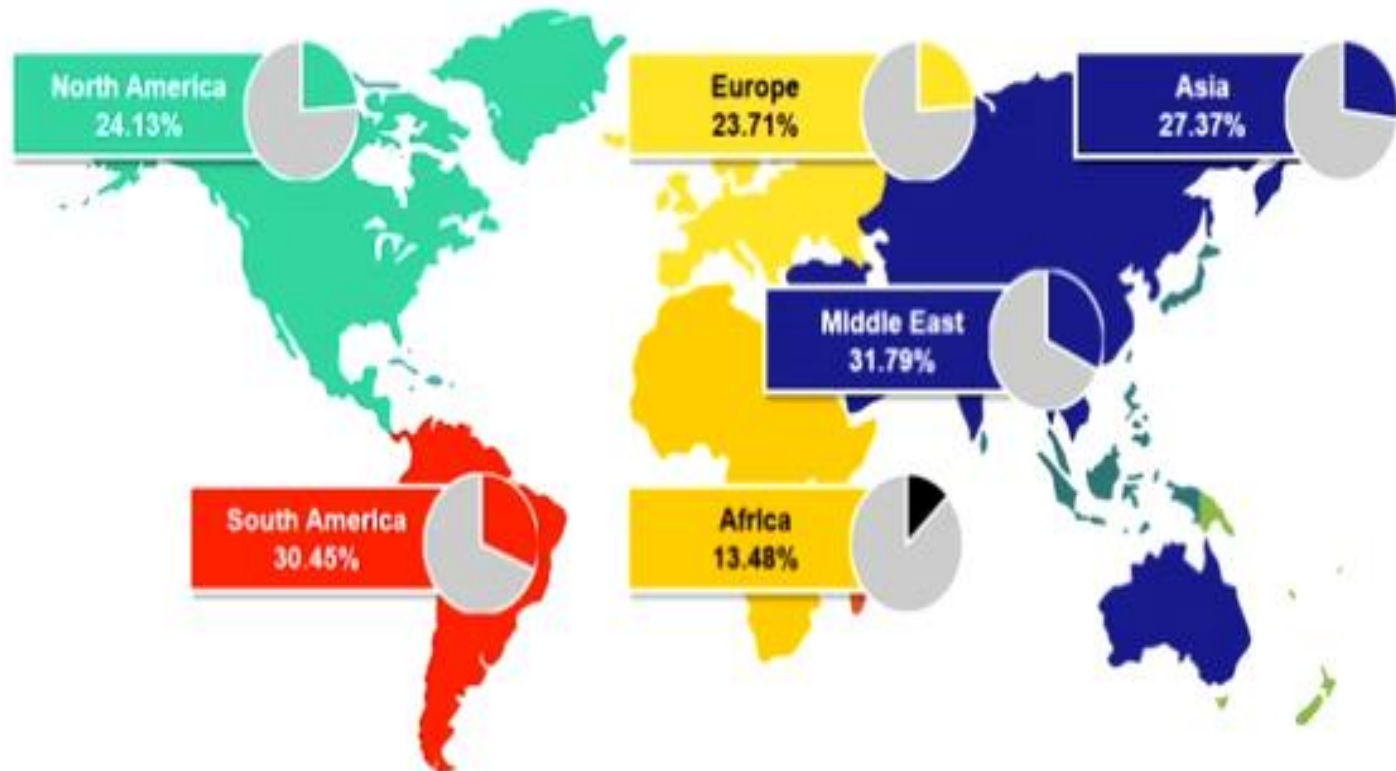
d Cirrhosis



CURRENT SCENARIO

- ✓ Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide
- ✓ NASH can progress to cirrhosis and hepatocellular cancer in 5–15% of patients
- ✓ NAFLD increases the risk of T2DM/CVR and the incidence of several cancers
- ✓ Epidemiological modeling shows alarming figures for the next 15 years

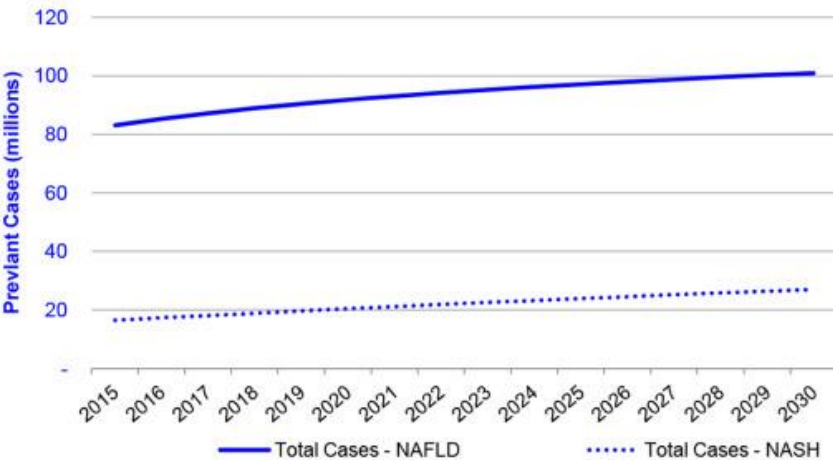
THE NAFLD EPIDEMIC



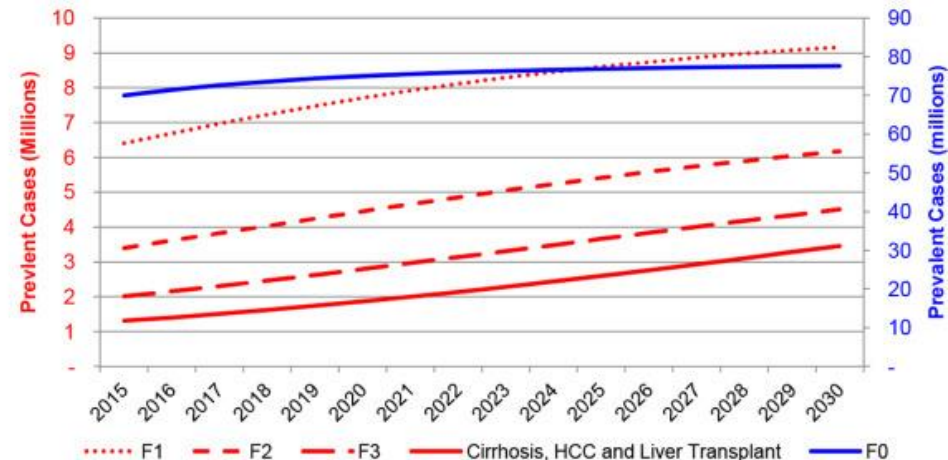
- Global prevalence of NAFLD is 24.13%(19.73-29.15) with highest prevalence in Middle East and South America and lowest in Africa
- Although accurate data is not available, the prevalence of NASH in the general population is estimated between 1.5% and 6.45%

Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease (Estes et al Hepatology 2018)

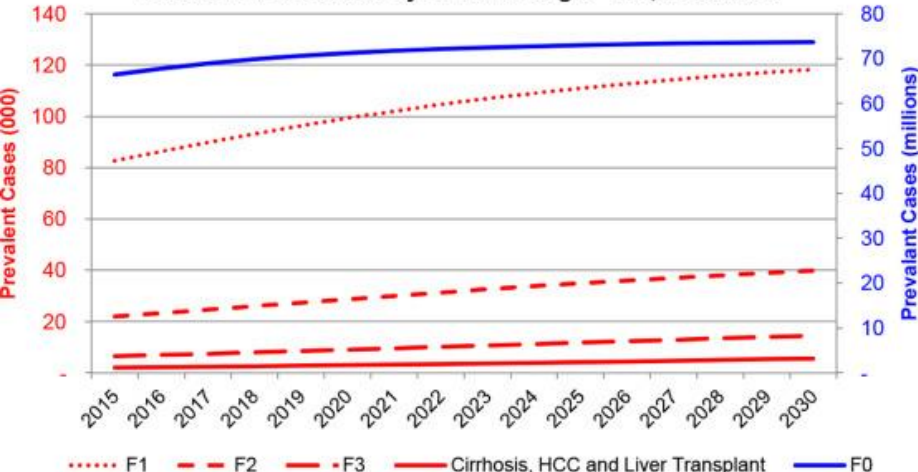
Total Prevalent NAFLD / NASH Cases – US, 2015-2030



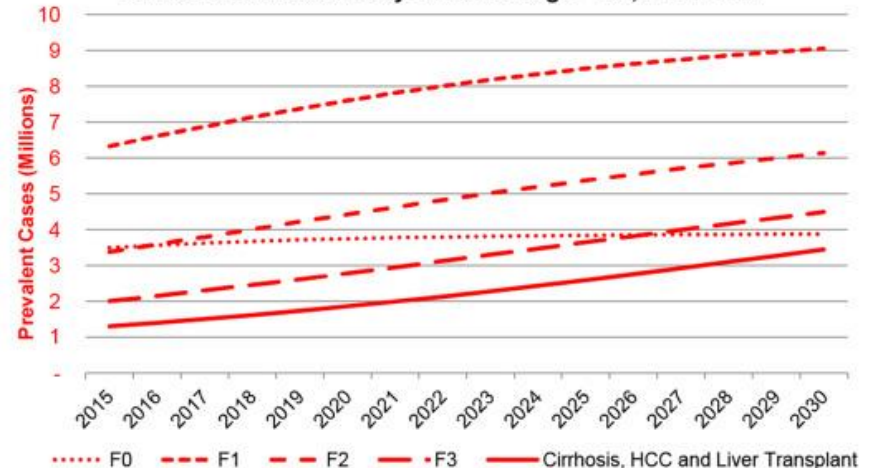
Prevalent NAFLD Cases by Disease Stage – US, 2015-2030



Prevalent NAFL Cases by Disease Stage – US, 2015-2030



Prevalent NASH Cases by Disease Stage – US, 2015-2030

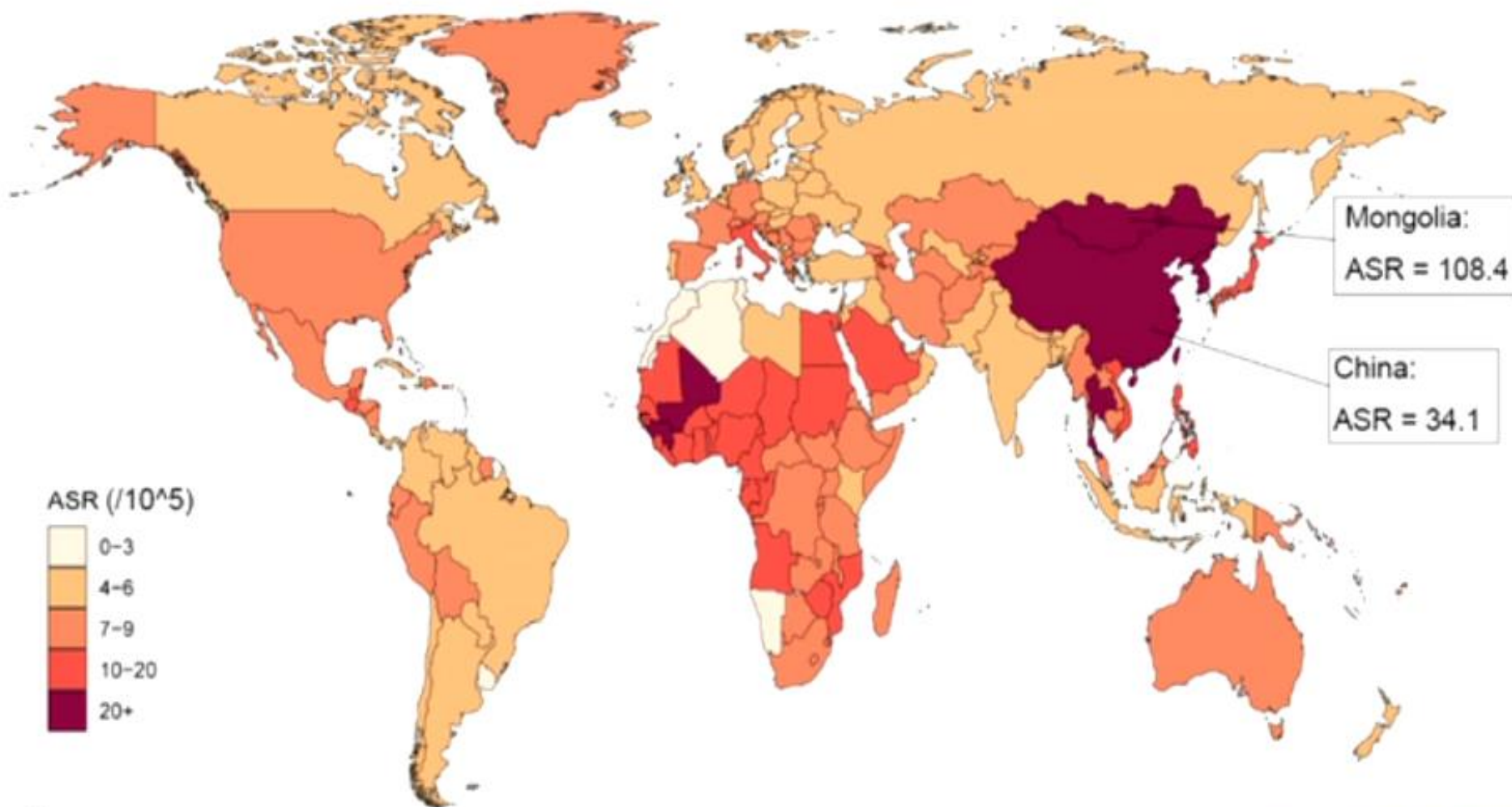


Changing epidemiology of HCC

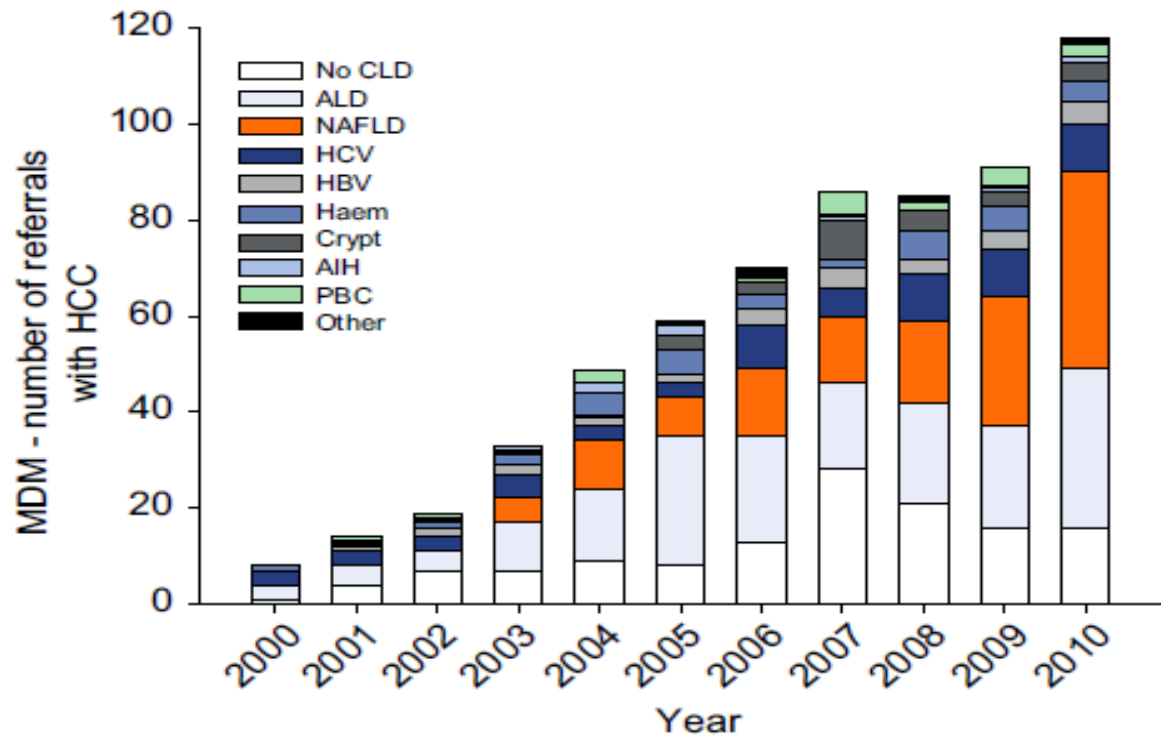
- ✓ Rates of HCC development appears to be increasing worldwide
- ✓ The etiology of HCC is changing in due to successful HBV vaccination programs and effective antiviral treatments for HBV/HCV
- ✓ The increasing prevalence of obesity and T2DM is also influencing HCC epidemiology
- ✓ Epidemiological data suggests that the the increasing prevalence of NAFLD may be contributory (10-20% at present time)

Age-standardized rate [ASR] of liver cancer in 2016: Global Burden of Disease Report

Globally, the incident case of liver cancer increased 114.0% (95% CI 108.4%–119.8%) from 1990 to 2016.

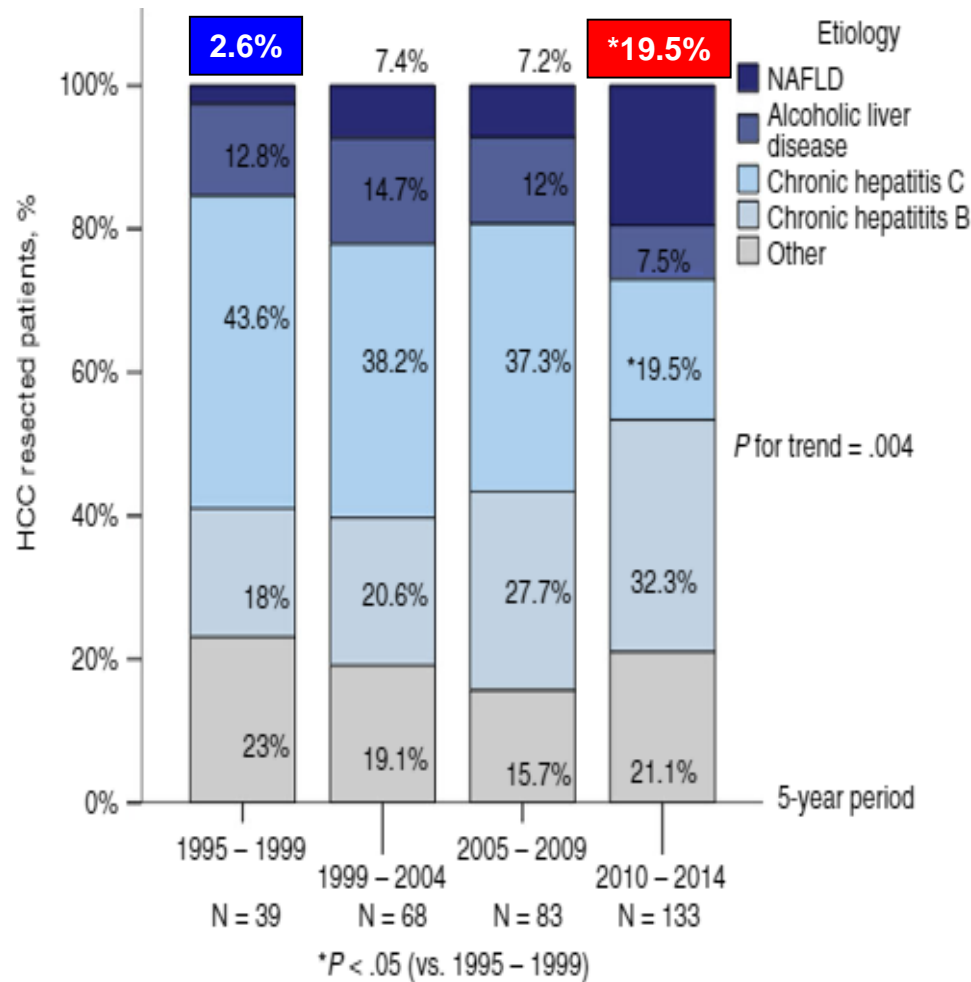


The proportion of HCC attributable to NAFLD is increasing



Ten-fold increase 2000-2010 in Newcastle, UK

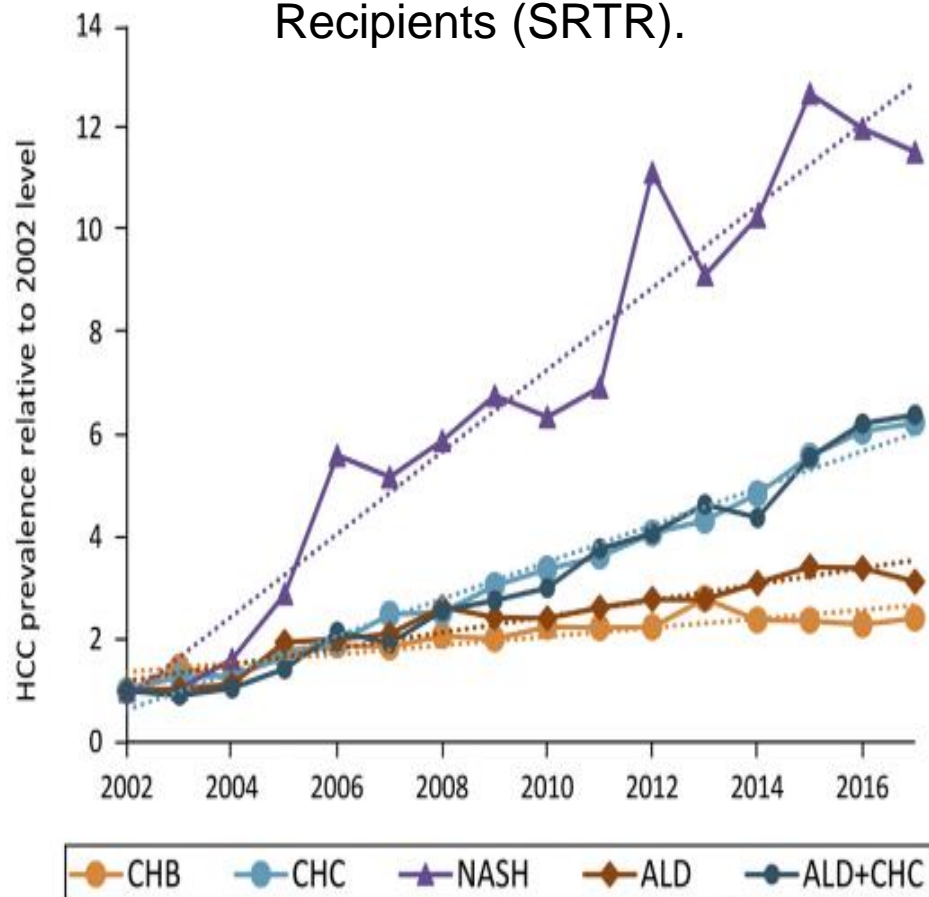
NAFLD and HCC – changes in etiology



323 patients with HCC
(France) who underwent
liver resection over
between 1995-2014
(12% with NAFLD)

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:

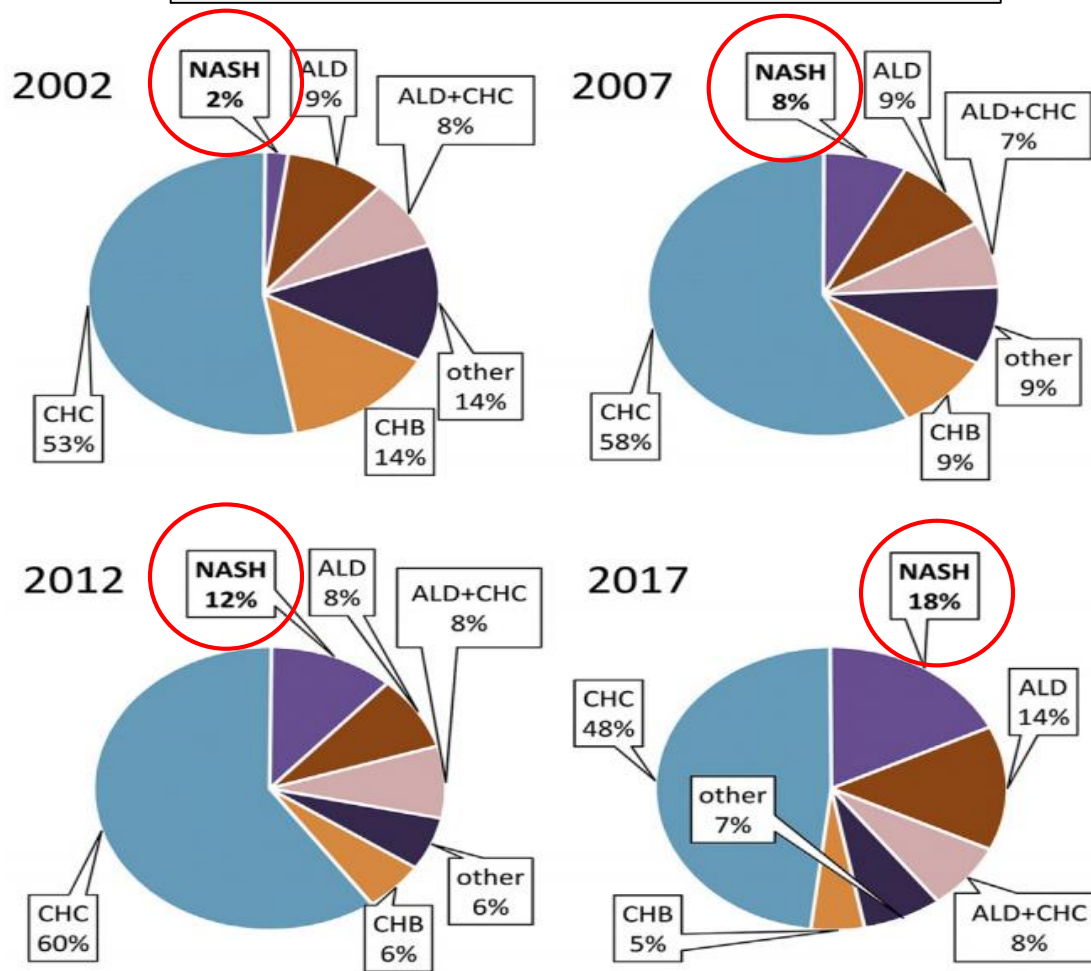
28,935 with HCC (17%)



2690 with NAFLD

NAFLD and HCC – changes in etiology

Etiologies of HCC in waitlisted candidates



NAFLD and HCC in biopsy-proven NAFLD

Cause of Death	Entire Cohort (n = 229)	P	NAS 0-4, F0-2 (n = 76)	P	NAS 5-8, F0-2 (n = 57)	P	NAS 0-8, F3-4 (n = 16)	P
Overall mortality	1.29 (1.04-1.59)	0.020	1.13 (0.79-1.60)	0.511	1.41 (0.97-2.06)	0.072	3.28 (2.27-4.76)	<0.001
Cardiovascular disease	1.55 (1.11-2.15)	0.01	1.19 (0.65-2.20)	0.557	1.38 (0.72-2.65)	0.335	4.36 (2.29-8.29)	<0.001
Hepatocellular carcinoma	6.55 (2.14-20.0)	0.001	No outcome	–	15.7 (4.1-59.9)	<0.001	16.9 (1.95-146)	0.01
Cirrhosis	3.2 (1.05-9.81)	0.041	4.86 (1.08-22.0)	0.04	No outcome	–	10.8 (1.38-83.9)	0.023
Gastrointestinal malignancy	0.60 (0.22-1.64)	0.322	1.26 (0.60-2.65)	0.546	0.54 (0.075-3.96)	0.548	No outcome	–
Nongastrointestinal malignancy	1.18 (0.70-1.98)	0.545	1.24 (0.55-2.76)	0.602	0.85 (0.27-2.65)	0.778	No outcome	–
Infectious disease	2.71 (1.02-7.26)	0.046	3.12 (0.72-13.5)	0.129	2.22 (0.31-16.4)	0.435	13.0 (3.13-54.5)	<0.001
Respiratory disease	1.01 (0.31-3.32)	0.979	No outcome	–	3.95 (1.22-13.0)	0.024	No outcome	–

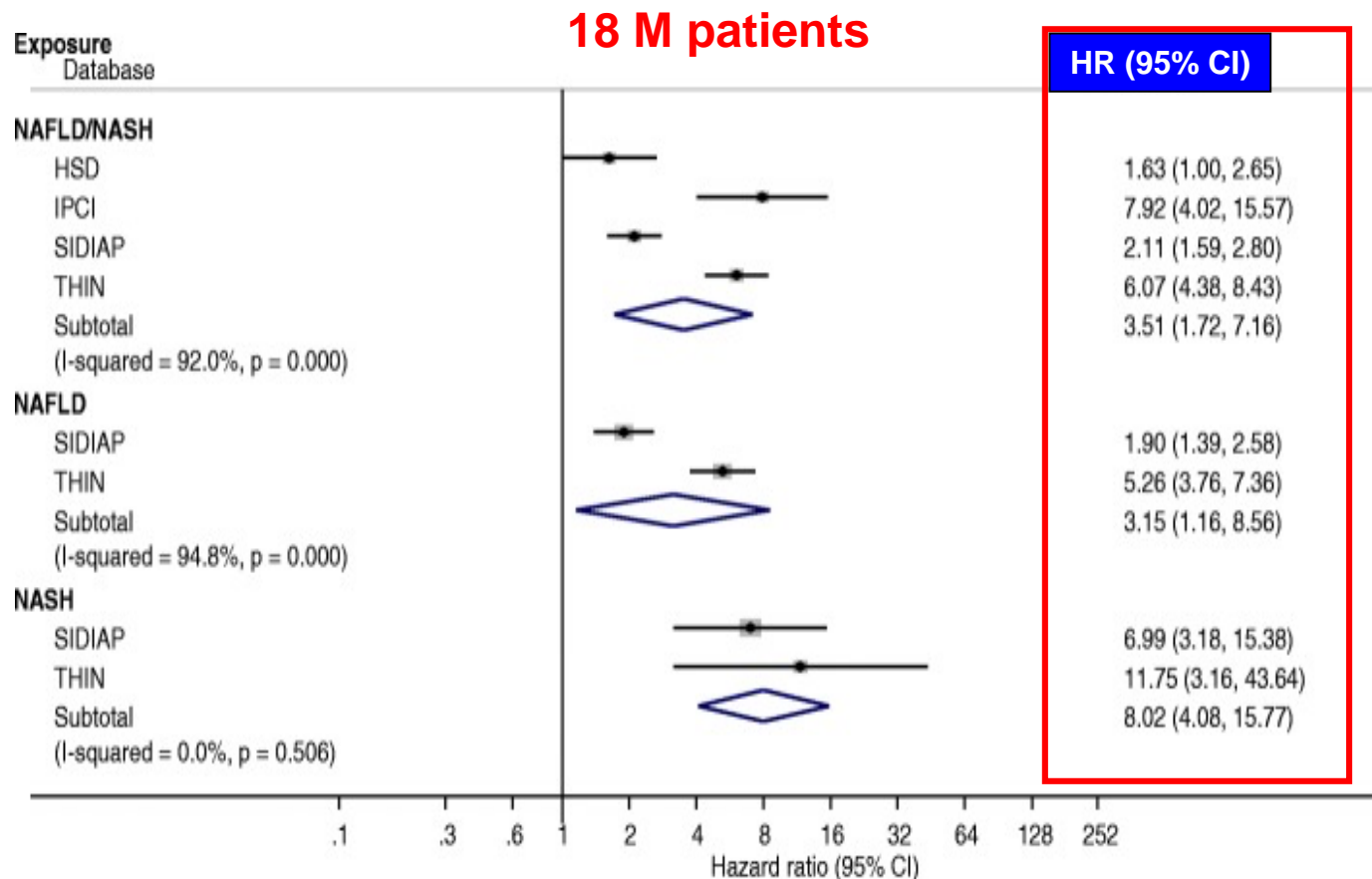
NAS, NAFLD activity score; F, Fibrosis stage; HR, Hazard ratio; CI: confidence interval. NAS is the unweighted sum of the scores for steatosis (0-3), lobular inflammation (0-3), and hepatocellular ballooning (0-2).

The highest **increased risk** (hazard ratio) of death was reported for **HCC**.

NAFLD and HCC

Association of NAFLD and NASH with HCC

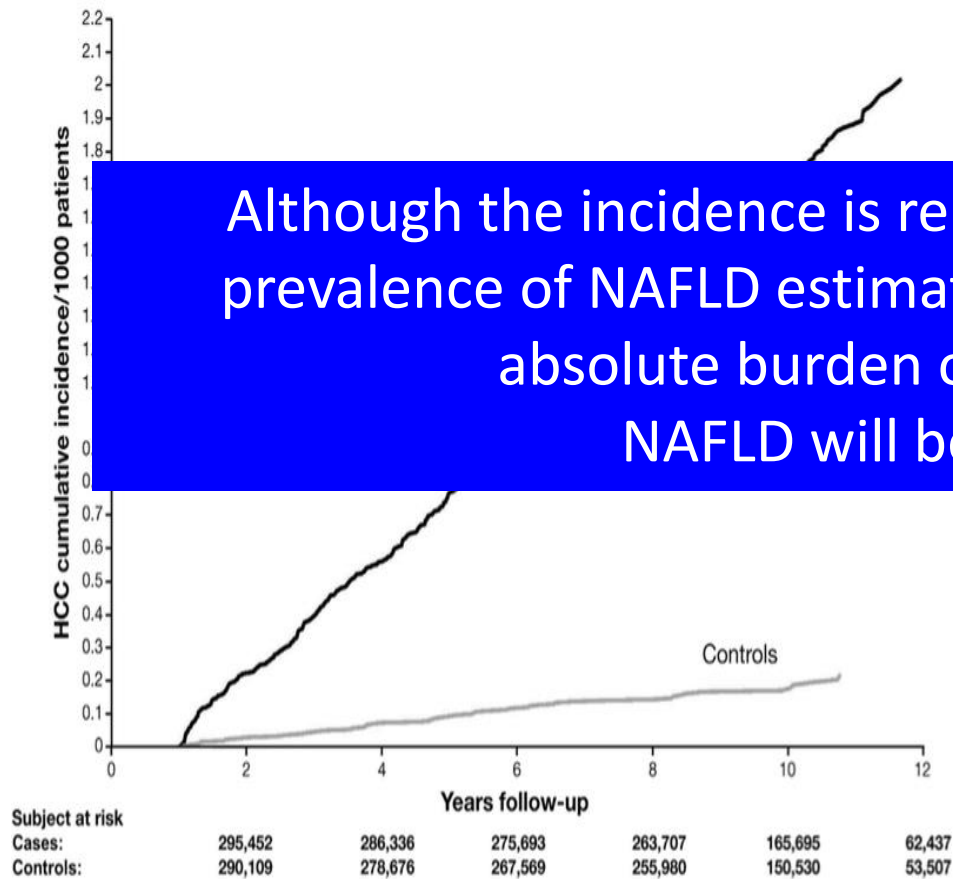
4 different European Cohorts (UK, Netherlands, Italy, Spain)



NAFLD and HCC

296,707 Veterans (USA) with NAFLD followed by a median time of 9 years: **490 developed HCC**

Although the incidence is relatively low, the high global prevalence of NAFLD estimated at 25% suggest that the absolute burden of HCC related to NAFLD will be significant

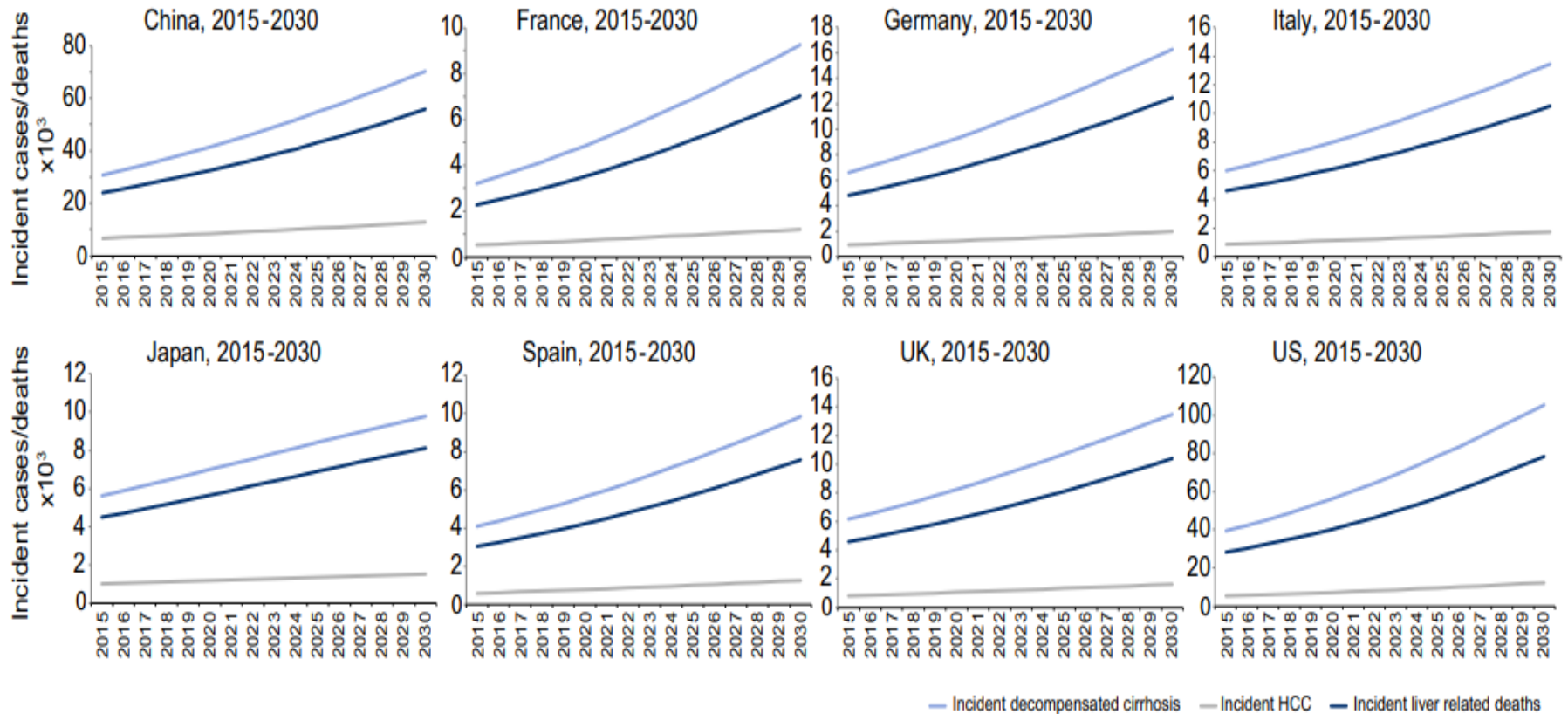


HCC incidence in patients with **non-cirrhotic NAFLD**: 0.08 / 1000 person-year

HCC incidence in patients with **cirrhotic NAFLD**:
10.6 / 1000 person-year

NAFLD and HCC – mortality

Incident decompensated cirrhosis, HCC and liver related deaths in
NAFLD patients



Incident HCC cases related to NAFLD are **estimated to increase**, ranging from
44% in Japan and 122% in US Estes C, et al. *J Hepatol* 2018

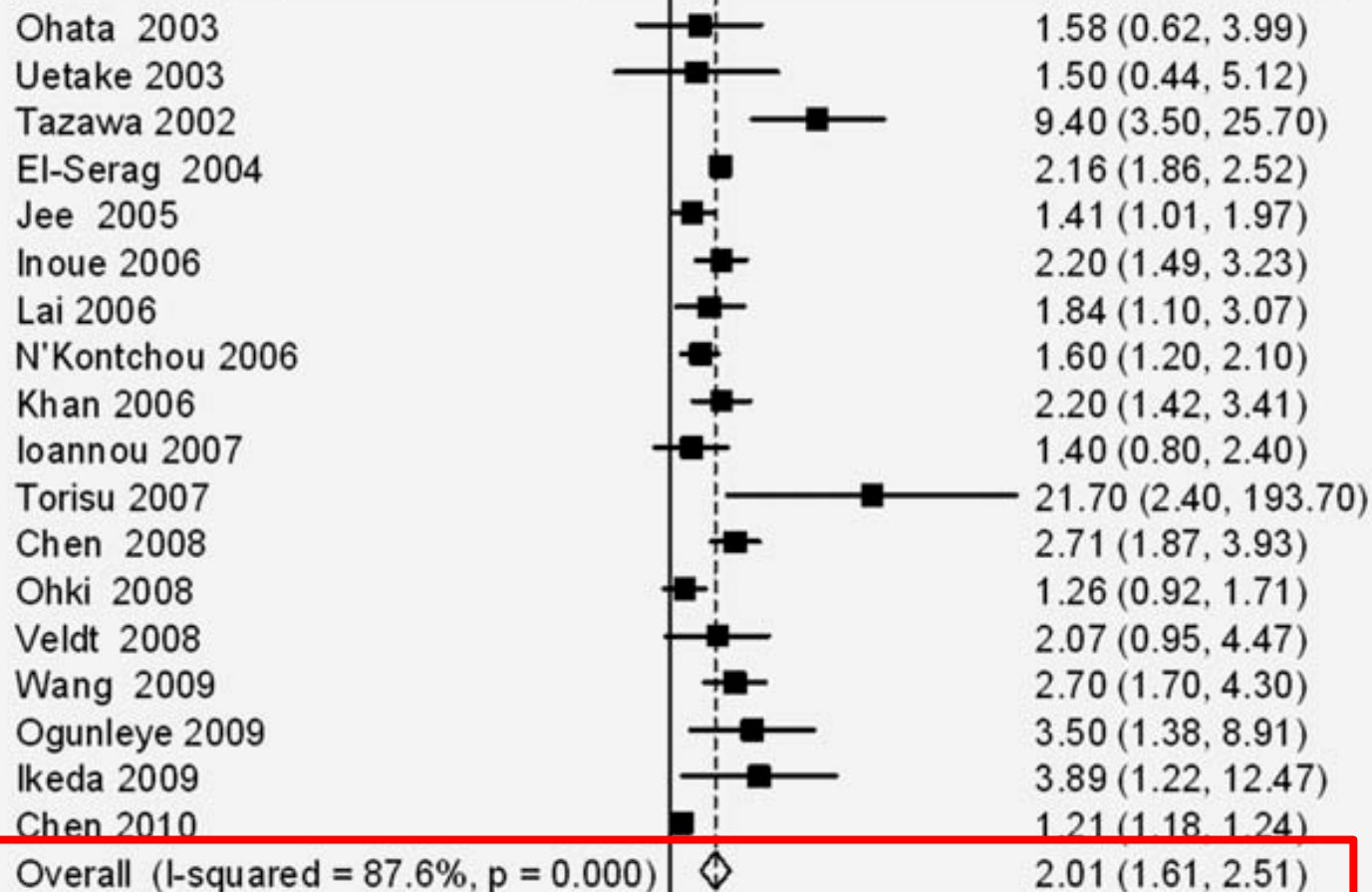
Risk factors for HCC in NAFLD

- ✓ Liver cirrhosis is the strongest risk factor (two-thirds of cases occur in cirrhotic patients)
- ✓ Older age and male gender
- ✓ Type 2 diabetes and obesity
- ✓ Diabetic medications & statins
- ✓ Hispanic ancestry?
- ✓ Other factors (oh/tobacco/iron)

Diabetes as a Risk factors for HCC

Studies (incidence)

RR (95%CI)



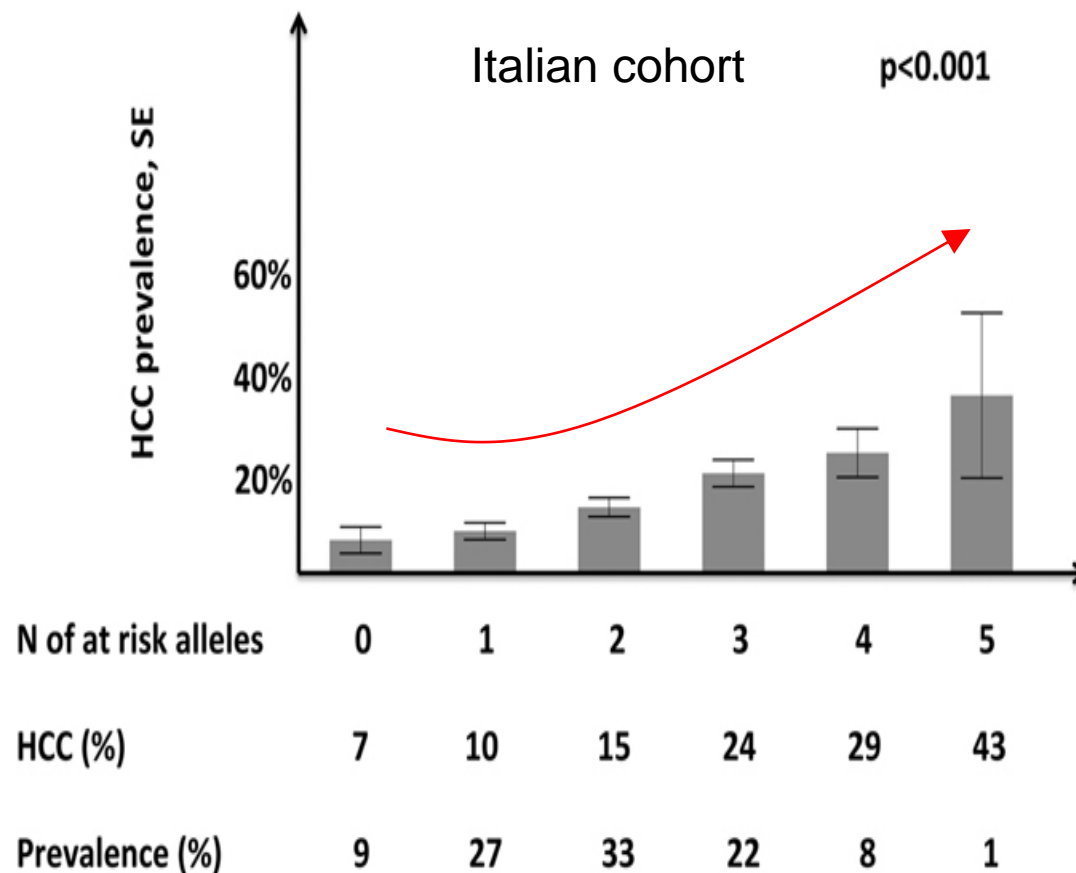
Clinical Patterns of Hepatocellular Carcinoma in Nonalcoholic Fatty Liver Disease: A Multicenter Prospective Study

TABLE 1. Demographic, Clinical, and Liver Function Characteristics of the Study Populations

Variable	HCC on NAFLD (n = 145)	HCC on HCV (n = 611)	P*
Demographic and clinical			
Age in years (mean, SD)	67.8 (9.0)	71.1 (9.5)	<0.0001
Male gender (n and percent of patients)	115 (79.3%)	374 (61.2%)	<0.0001
Body mass index (mean, SD)	29.1 (5.0)	27.6 (4.4)	0.430
Alcohol (n and percent of drinkers)	66 (45.5%)	41 (8.6%)	<0.0001
Tobacco (n and percent of smokers)	84 (60.9%)	108 (23.8%)	<0.0001
Metabolic risk factors [†]			
Diabetes (n and percent of patients)	106 (73.1%)	148 (24.9%)	<0.0001
Hypertension (n and percent of patients)	106 (73.1%)	204 (37.1%)	<0.0001
Hypertriglyceridemia (n and percent of patients)	37 (25.7%)	17 (3.8%)	<0.0001
Hypercholesterolemia (n and percent of patients)	47 (32.9%)	34 (7.3%)	<0.0001
Atherosclerosis (n and percent of patients)	44 (31.0%)	89 (19.1%)	0.004
Ischemic cardiomyopathy (n and percent of patients)	18 (12.4%)	47 (8.5%)	0.151
Blood glucose (mg/dL; mean and SD)	124.3 (61.2)	108.0 (39.6)	<0.0001
LDL cholesterol (mg/dL; mean and SD)	90.1 (44.79)	94.5 (43.0)	0.516
HDL cholesterol (mg/dL; mean and SD)	46.9 (24.9)	43.3 (16.5)	0.204
Triglycerides (mg/dL; mean and SD)	150.3 (163.2)	104.4 (48.5)	<0.0001
Liver function			
Bilirubin (mg/dL; mean and SD)	1.1 (0.7)	1.6 (2.2)	0.013
Albumin (g/dL; mean and SD)	4.8 (6.4)	3.9 (3.6)	0.015
International normalized ratio (mean and SD)	1.2 (0.4)	1.0 (0.5)	<0.0001
Child-Pugh score (median and range) [‡]	5.6 (5-11)	5.8 (5-12)	0.154
MELD score (median and range)	8.3 (3-28)	9.0 (3-24)	0.136
ECOG PS ≥2 (n and percent of patients)	22 (16.9%)	90 (16.8%)	1.000
Clinical hepatic encephalopathy (n and percent of patients)	7 (4.9%)	31 (5.1%)	1.000
Ascites (n and percent of patients)	32 (22.2%)	196 (36.7%)	0.009
CTP 5-6 (n and percent of patients)	107 (82.3%)	366 (68.1%)	0.001
CTP 7-9 (n and percent of patients)	20 (13.8%)	151 (24.7%)	0.002
CTP ≥10 (n and percent of patients)	3 (2.3%)	20 (3.7%)	0.595

Emerging risk factors for HCC – gene variants

Number of **PNPLA3**, **TM6FS2** and **MBOAT7** risk alleles and the risk for **HCC**



Emerging risk factors for HCC – *PNPLA3* variant

Freeman Hospital, Newcastle-upon-Tyne, UK and Inselspital Hospital,
Bern, Switzerland

100 European Caucasians with NAFLD-related HCC

275 controls with biopsy-proven NAFLD

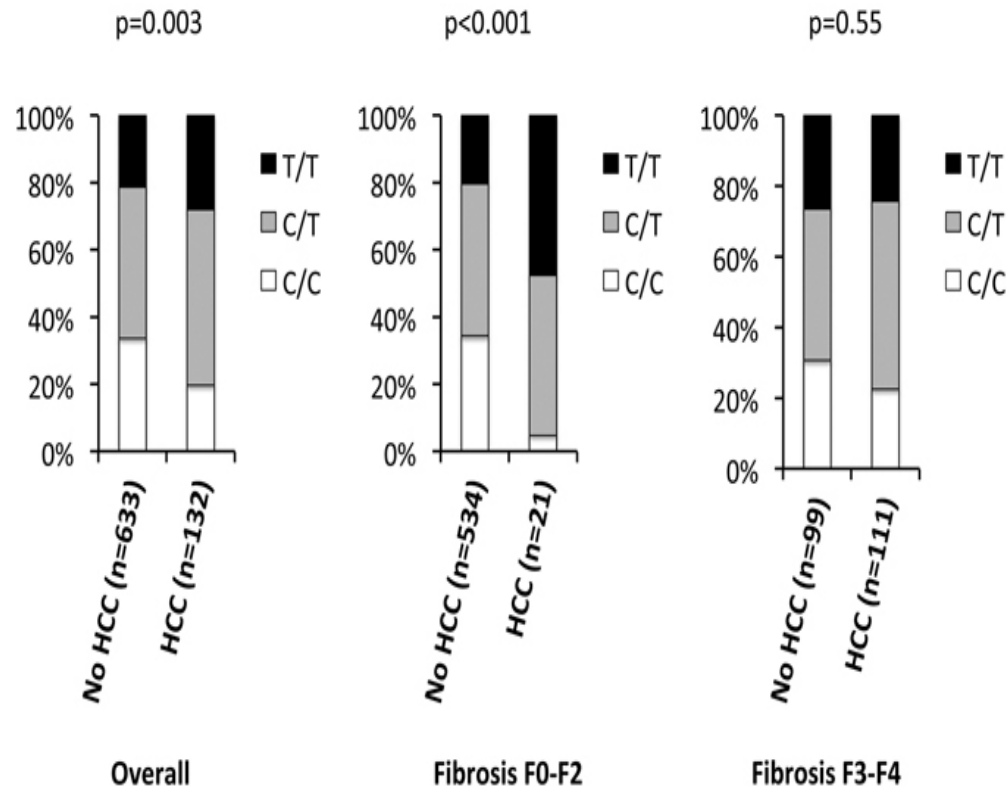
Table 1. Details of NAFLD-HCC and NAFLD cohorts.

Phenotype	NAFLD-HCC cohort n = 100	NAFLD cohort n = 275	p value
<i>PNPLA3</i> rs738409 G-allele frequency	0.505	0.333	<0.0001
Age (Mean ± SD)	70.3 ± 8.0	50.9 ± 12.4	<0.0001
Sex, male (%)	82 (0.82)	161 (0.59)	<0.0001
BMI (Mean ± SD)	32.0 ± 6.6	34.4 ± 5.2	0.0003
Diabetes (%)	68 (0.68)	117 (0.43)	<0.0001
Cirrhosis (%)	67 (0.67)	26 (0.09)*	<0.0001

Variables	OR (95% CI)	p value
<i>PNPLA3</i> rs738409 genotype	2.26 (1.23-4.14)	0.0082
Age	1.24 (1.17-1.32)	<0.0001
Sex (Male)	11.11 (4.17-33.33)	<0.0001
BMI	0.94 (0.87-1.02)	0.148
Diabetes	2.33 (0.93-5.81)	0.070
Cirrhosis	9.37 (3.82-23.00)	<0.0001

Additive model including age, gender, BMI, diabetes, and cirrhosis as covariates.

Emerging risk factors for HCC - *MBOAT7* variant



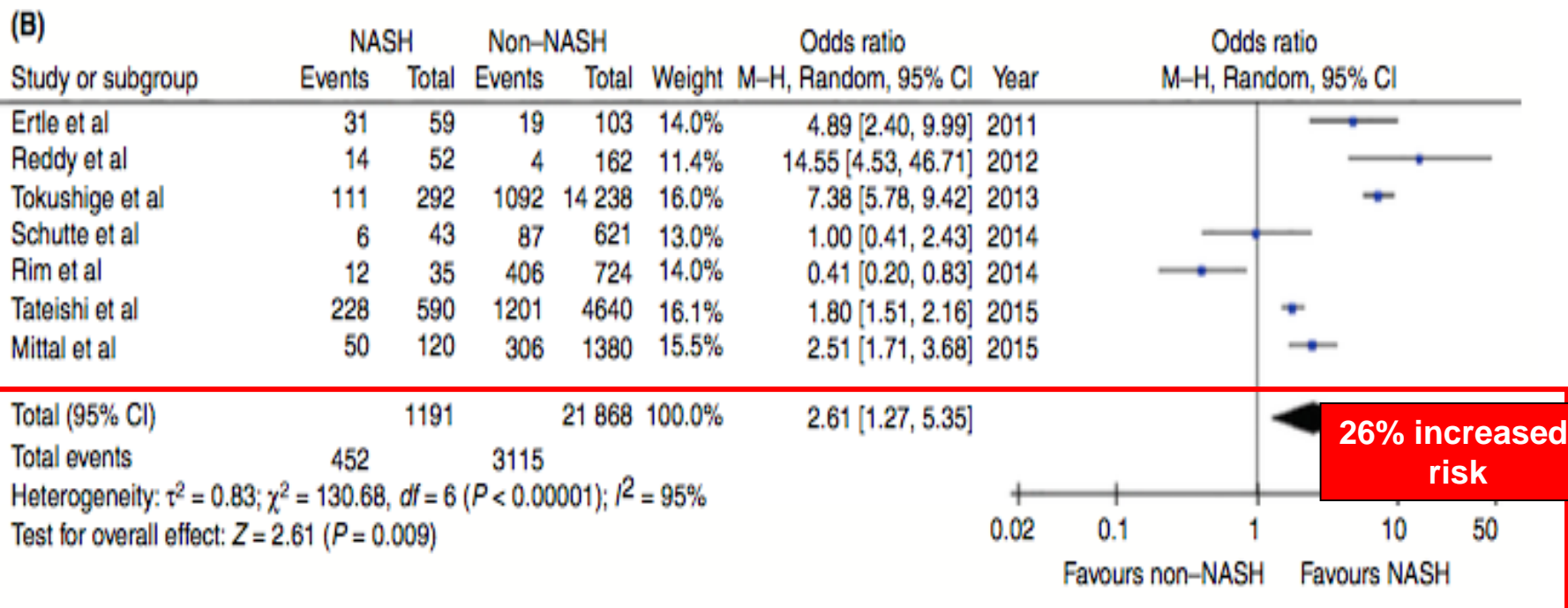
In italian NAFLD patients, the rs641738 T allele was **associated with NAFLD-HCC (OR 1.65)**, particularly in those **without advanced fibrosis**.

Peculiarities of NASH-related HCC

- ✓ Pre- cirrhotic NAFLD might confer an increased risk of HCC
- ✓ Updated classification distinguish an histological subtype (Steatohepatitic variant) with some differential molecular patterns
- ✓ Some studies have reported that survival in patients with NAFLD-related HCC is lower (25.5 months) than that of patients with HCV- associated HCC (33.7 months)

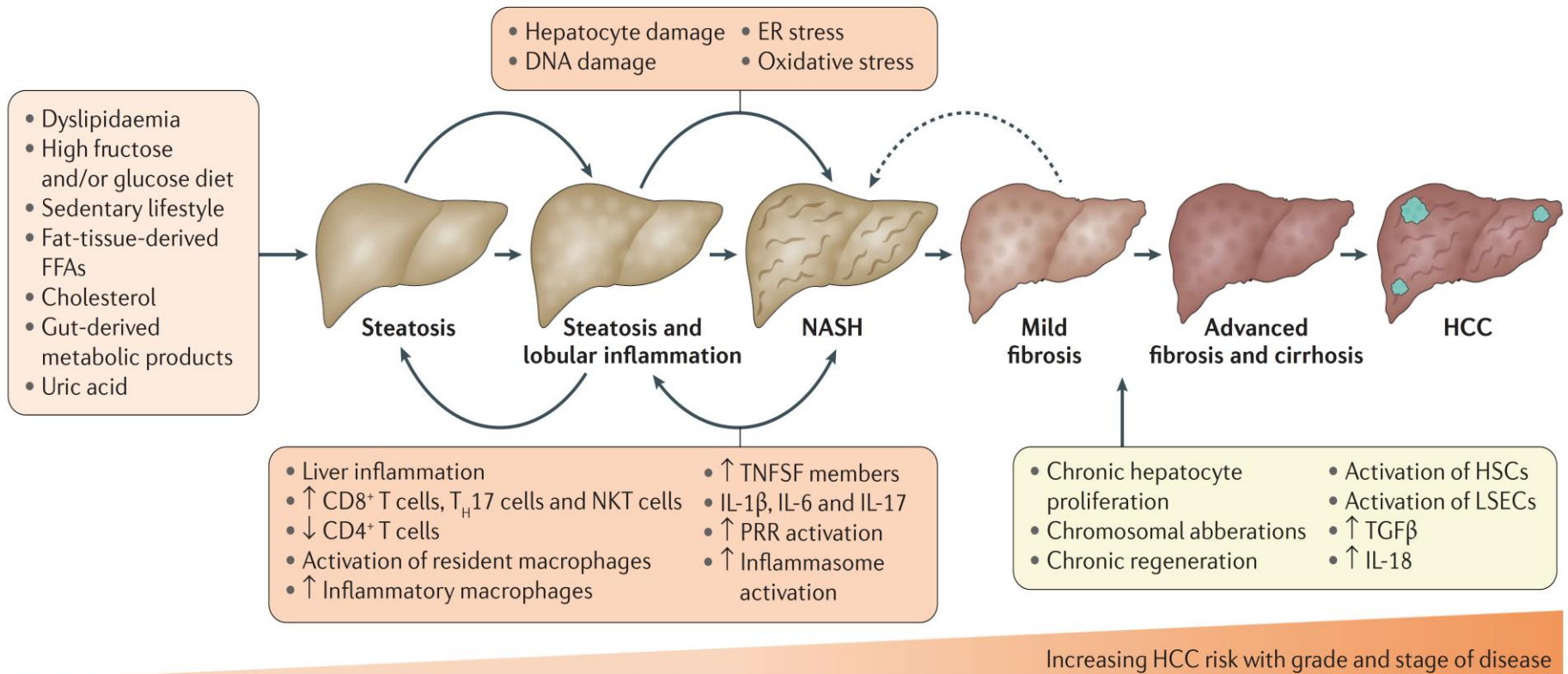
HCC in non-cirrhotic NAFLD

Meta-analysis including 7 studies: 5 cohort and 2 cross-sectional

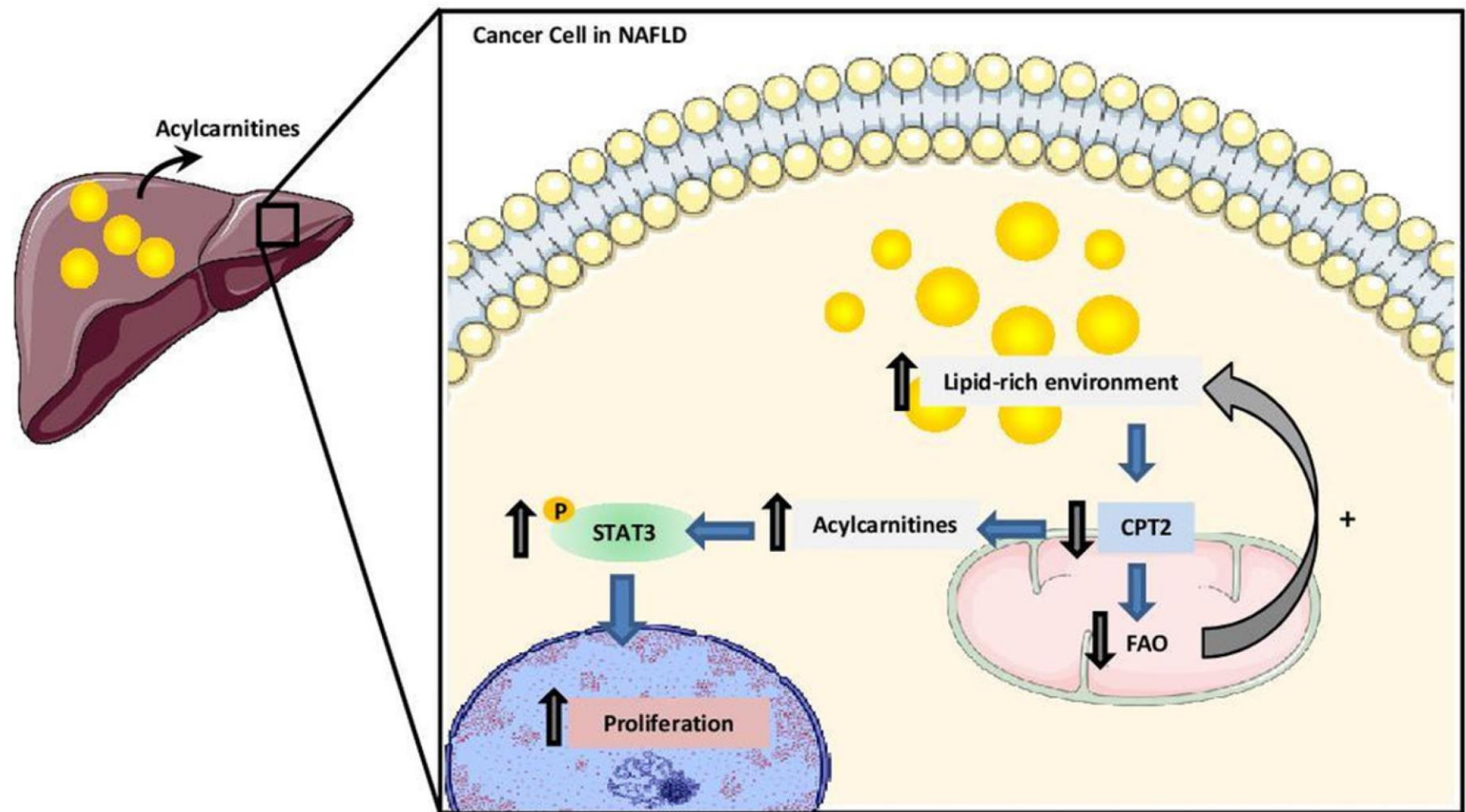


In absence of cirrhosis, patients with **NASH** have
a **26.1% increased risk of HCC** compared to
other etiologies of liver disease

NASH-RELATED HCC pathogenesis: environmental and gut- derived factors



NASH-RELATED HCC pathogenesis: lipid microenvironment??



NASH-RELATED HCC pathogenesis: microbiota

- ✓ Intestinal microbiota impacts NAFLD/NASH through multiple mechanisms
- ✓ Microbiota contribute to the development of cirrhosis and HCC in NAFLD

Chronic inflammation

Altered BA metabolism

TLR4/TLR9 activation

Clinical insights

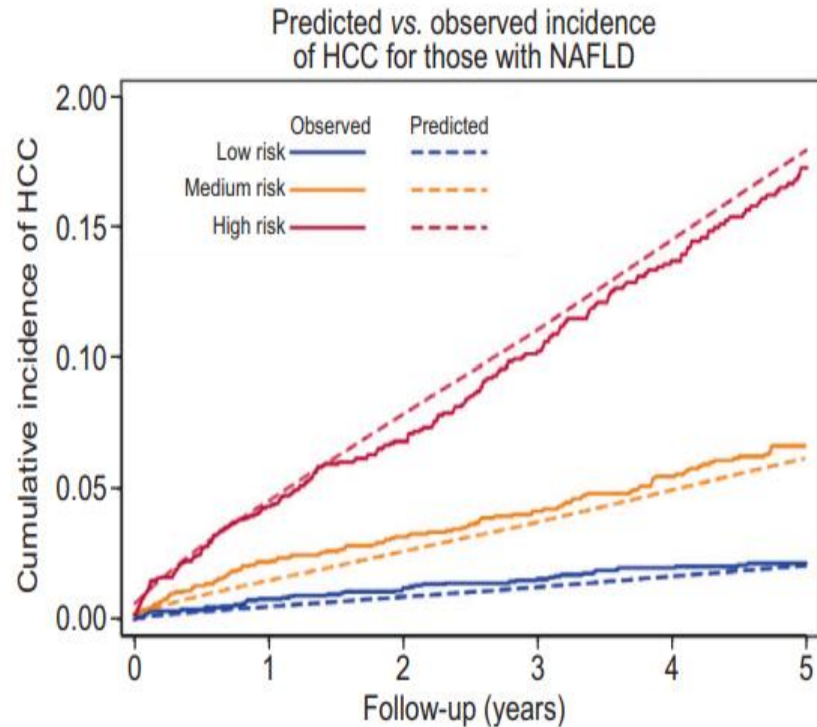
- ✓ Screening of HCC in NAFLD/NASH
- ✓ How can we better stratify patients with NASH that are at high risk to develop HCC?

HCC risk calculator in NAFLD

HCC risk calculator

HCV	ALD - Cirrhosis	NAFLD - Cirrhosis
Age <input type="text"/> Years		
Gender <input type="text"/> Select		
BMI <input type="text"/> kg/m ²		
Diabetes <input type="text"/> Select		
Platelet Count <input type="text"/> × 10 ⁹ per liter		
AST <input type="text"/> u/L		
ALT <input type="text"/> u/L		
Albumin <input type="text"/> g/dL		
3-year HCC risk <input type="text"/>		
5-year HCC risk <input type="text"/>		
<input type="button" value="Calculate"/>		<input type="button" value="Reset"/>

Development of an **HCC predictive model** based On 7 parameters



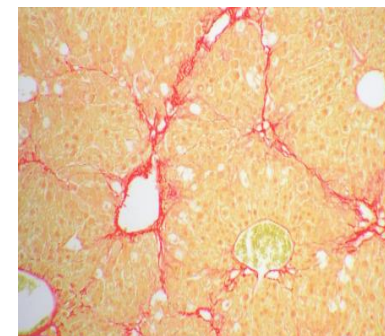
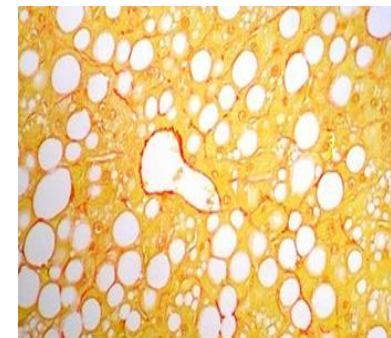
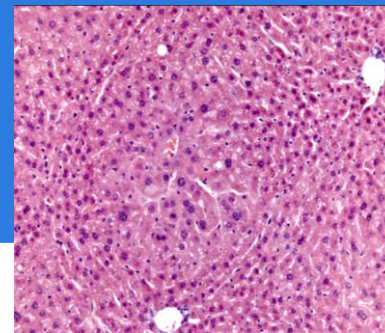
Excellent overlap between observed and predicted cumulative incidence

SUMMARY & CONCLUSIONS

- ✓ The epidemiology of HCC is changing likely driven by the increasing NAFLD prevalence
- ✓ Cirrhosis, metabolic and genetic modifiable risk factors have been identified
- ✓ NAFLD-HCC may occur in the absence of cirrhosis
- ✓ Pathophysiology is complex and contributes to HCC heterogeneity
- ✓ Additional studies are needed to define the best HCC screening and treatment strategies in patients with NAFLD



Experimental Hepatology



FONDECYT

Fondo Nacional de Desarrollo
Científico y Tecnológico



Departamento de Gastroenterología
Facultad de Medicina
Pontificia Universidad Católica de Chile
Diagonal Paraguay #362
8330077
Santiago
CHILE

Phone/Fax: 56-2-3543822
e-mail: marrese@med.puc.cl

