

Optimal management of HCC

Issues associated with early detection and surveillance

**Alessandra Mangia
San Giovanni Rotondo, ITALY**

BG Male Born on 22/07/1953

Active clinical problems at the time of first observation (2009)

- Obesity
- BPH
- Nephrolithiasis

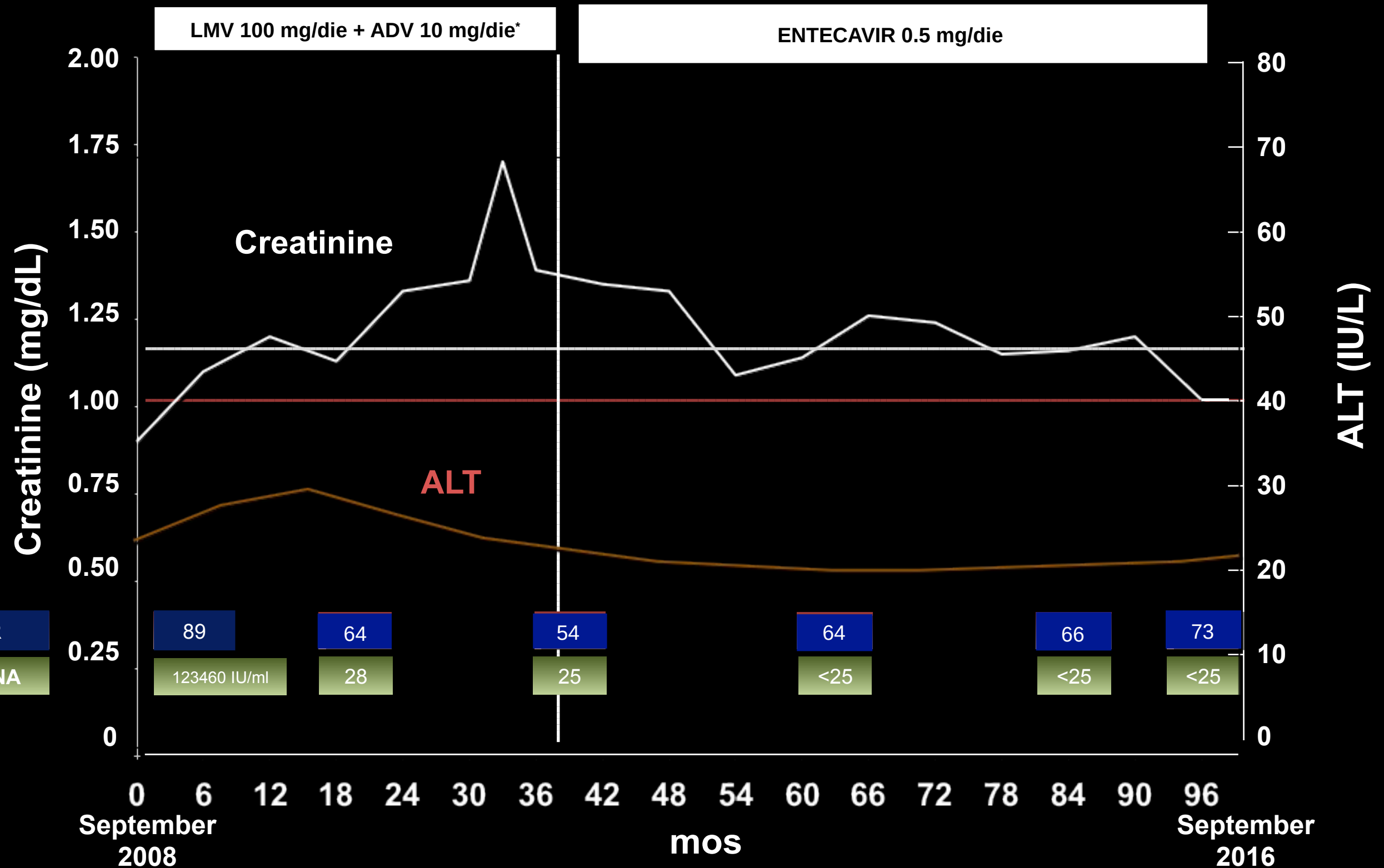
Medical History

HBsAg positivity discovered in 2004. No positive familial history.

Liver Biopsy performed in 2006: Mild chronic hepatitis. Metavir score: grade 2 activity and stage 2 fibrosis. Focal positivity of HBsAg, negative HBcAg.

Treatment with LMV and ADV started in 2008: HBV DNA >20.000 IU/ml.

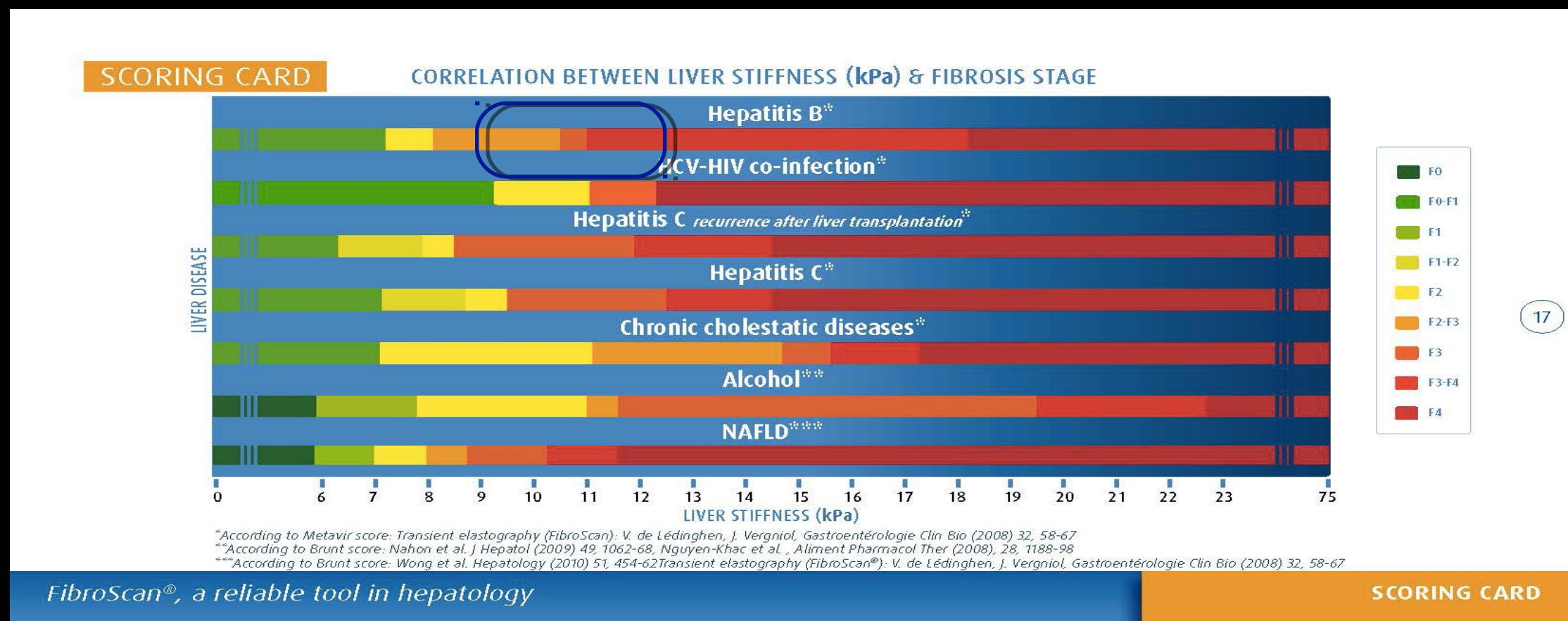
September 2008 – September 2016



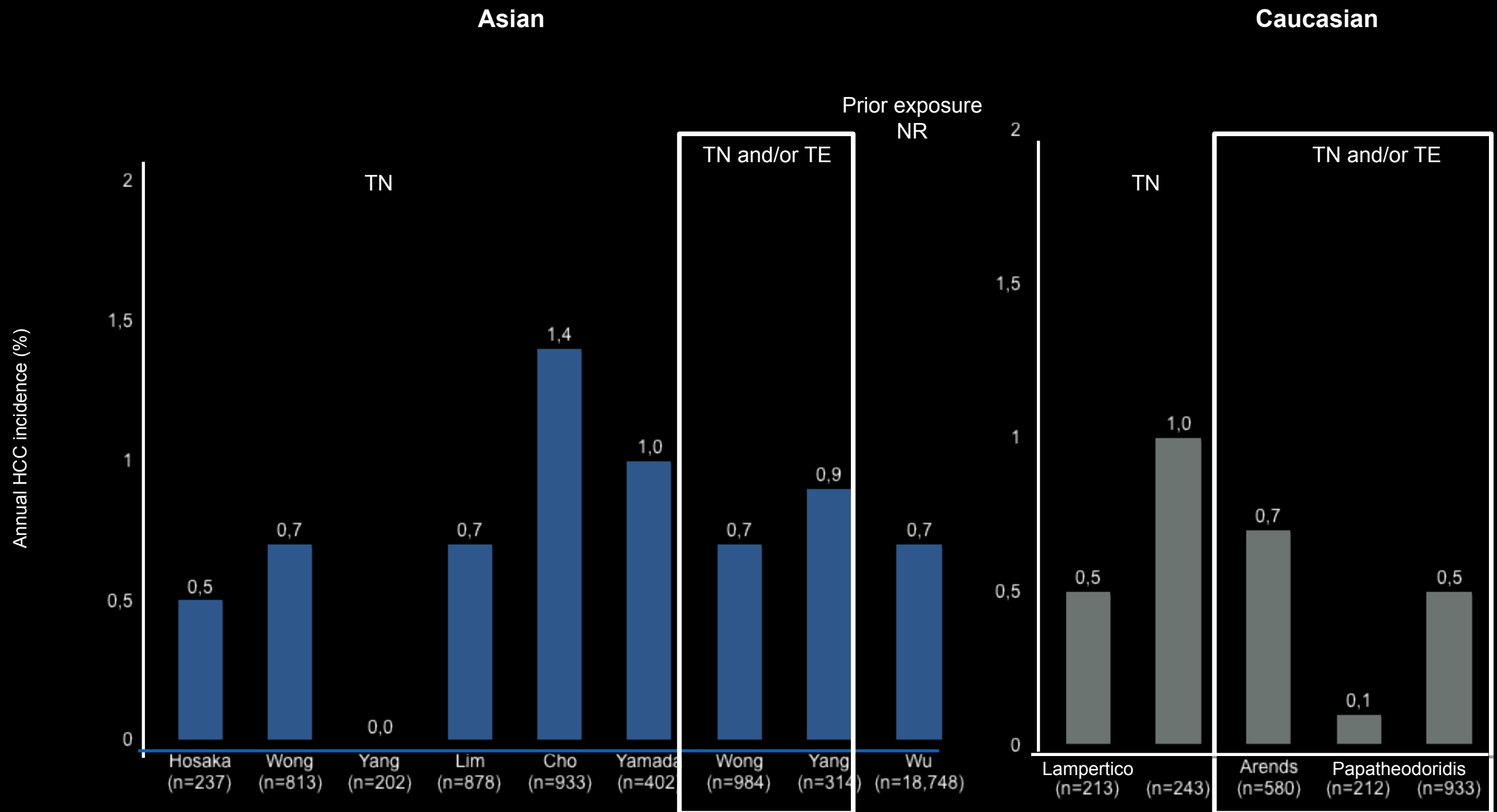
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He was followed by GP and sent to Gastroenterology/Hepatology Unit annually for NAs prescription

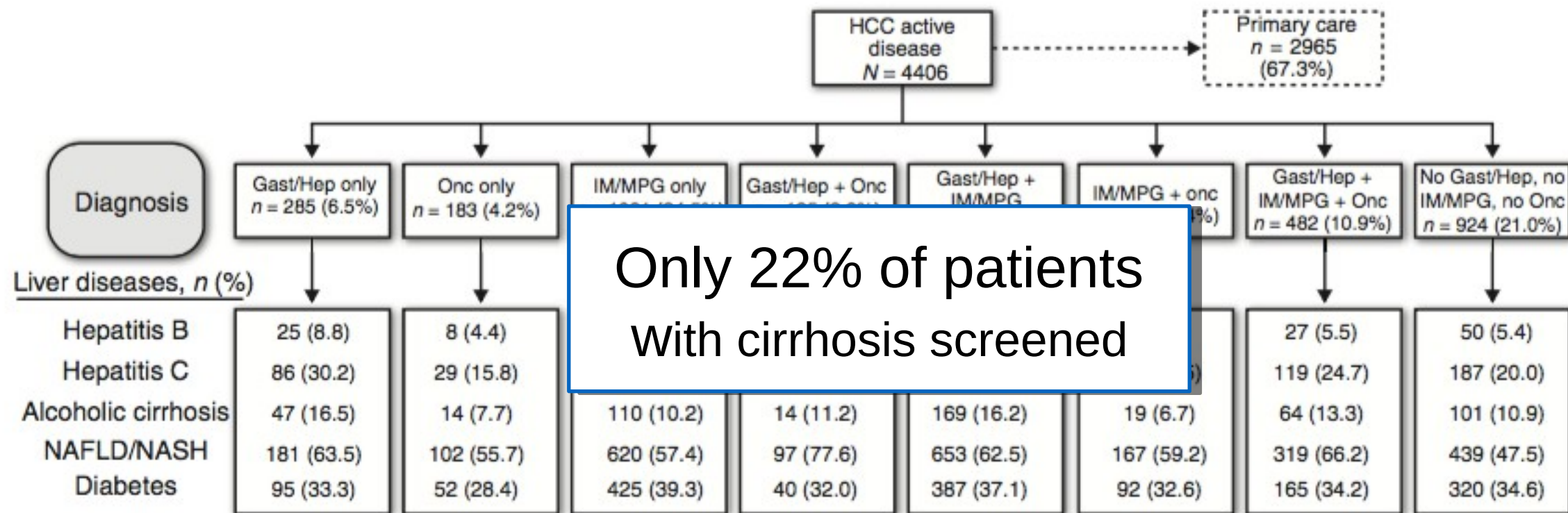
TE in 2009: 10.8 KPa



HCC risk persists in non-cirrhotic pts despite antiviral therapy



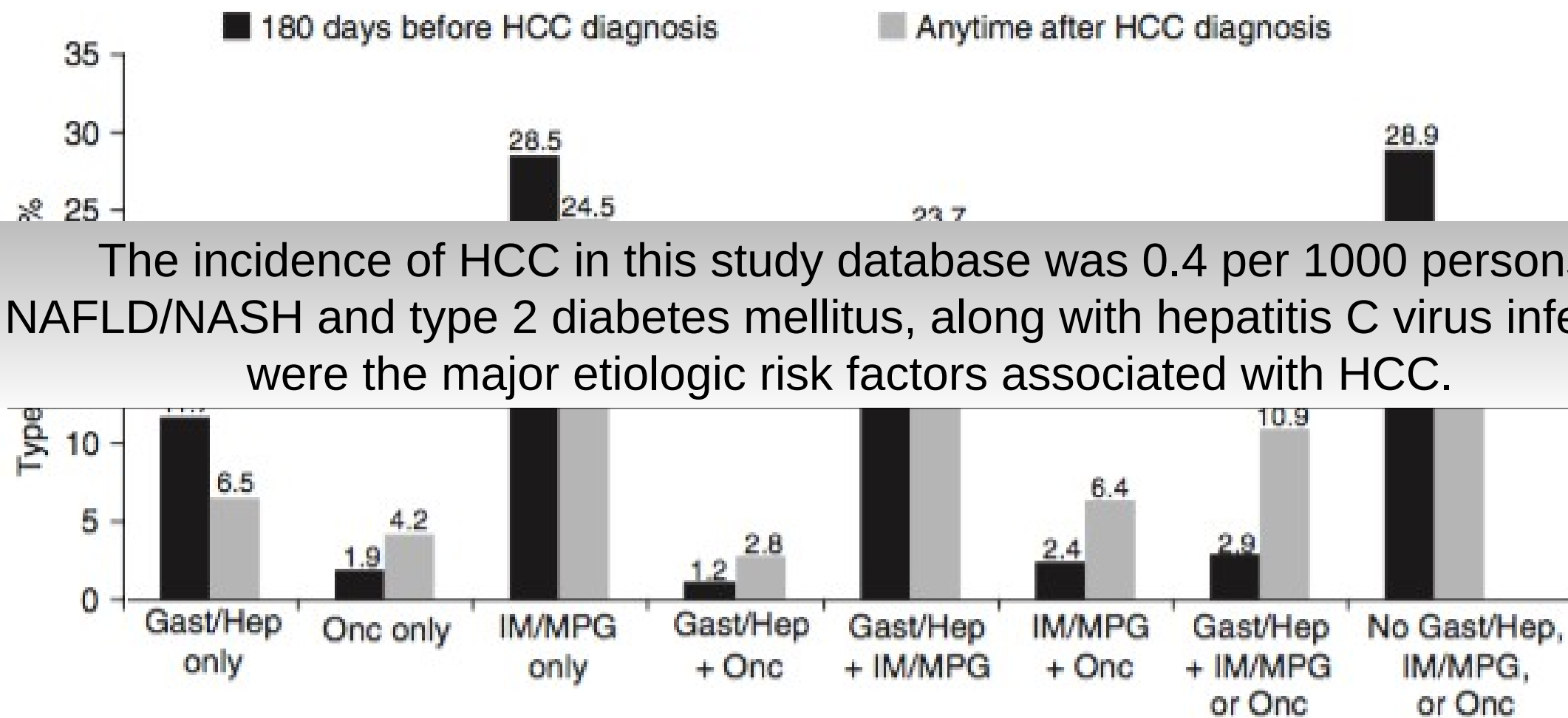
Does the type of provider impact HCC diagnosis?



Types of providers seen by patients with HCC and underlying liver diseases. Gast/Hep, gastroenterologist/hepatologist; IM/MPG, internal medicine/multphysician group; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; Onc, oncologist.

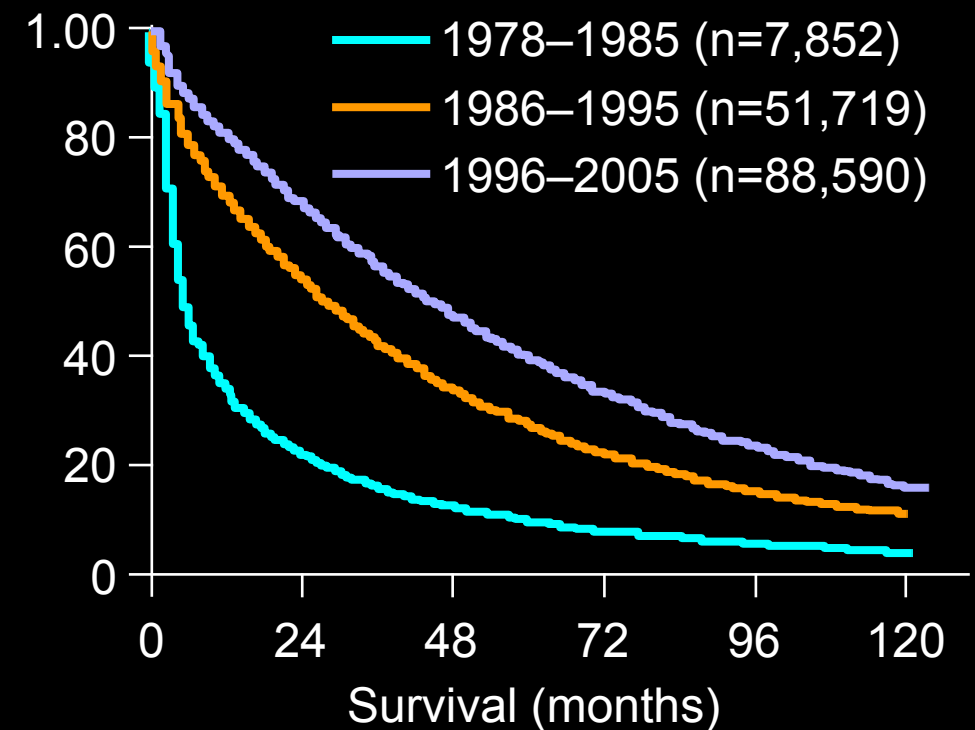
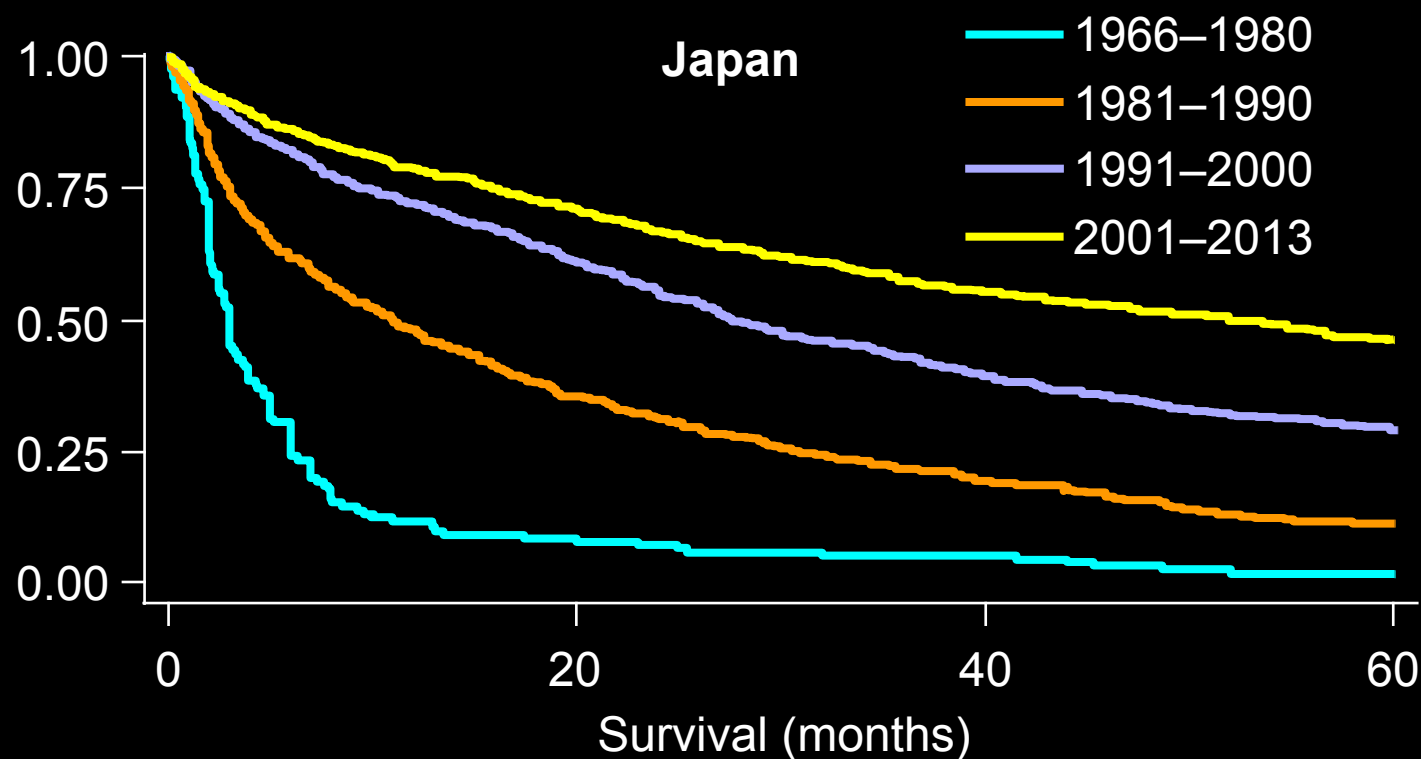
Sanyal A et al CMRO 2010

Types of providers visited before & after diagnosis of HCC



The incidence of HCC in this study database was 0.4 per 1000 persons. NAFLD/NASH and type 2 diabetes mellitus, along with hepatitis C virus infection, were the major etiologic risk factors associated with HCC.

Changes In Survival In Japan Since Inception of Screening



Such Results are Representative of Japan

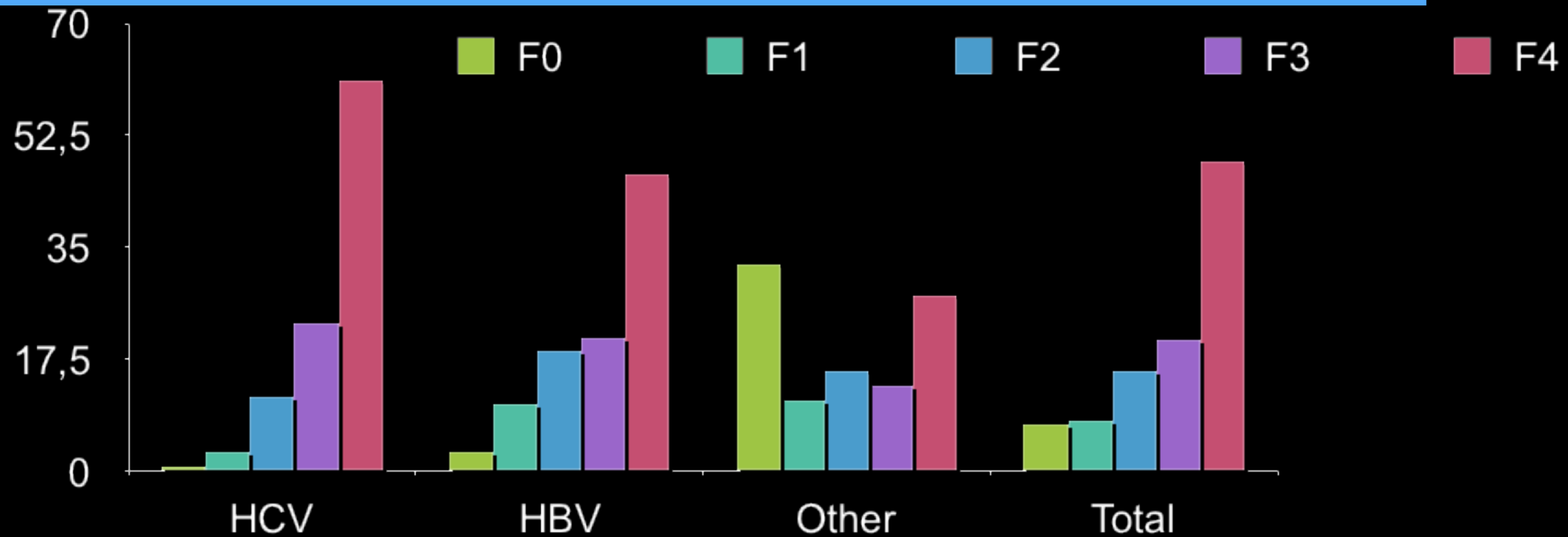
From Ikai I, et al. Hepatol Res 2010;40:1043–59

Pre-screening
→

Period	N	Median survival in months	% screened	Median age (IQR)
1966–1980	178	2.96 (2.4–3.4)	15.23 (n=151)	60 (54–67)
1981–1990	509	10.99 (8.8–13.2)	55.26 (n=418)	61 (55–68)
1991–2000	812	27.5 (25.8–31.1)	72.41 (n=812)	64 (59–70)
2001–2013	1,105	52.2 (44.1–59.7)	76.80 (n=1,103)	70 (63–76)

IQR: interquartile range

A Significant Percentage of Patients With Early HCC Don't Have Cirrhosis: 1,534 Patients Undergoing Resection US/Japan/China



% HCC patients at each fibrosis score according to aetiology						
	<i>F0</i>	<i>F1</i>	<i>F2</i>	<i>F3</i>	<i>F4</i>	Total
HCV	0.74 (n=4)	3.14 (n=17)	11.65 (n=63)	23.29 (n=126)	61.18 (n=331)	100.00 (n=541)
HBV	2.94 (n=21)	10.64 (n=76)	18.91 (n=135)	21.01 (n=150)	46.50 (n=332)	100.00 (n=714)
Other	32.34 (n=87)	11.15 (n=30)	15.61 (n=42)	13.38 (n=36)	27.51 (n=74)	100.00 (n=269)
Total	7.35 (n=112)	8.07 (n=123)	15.75 (n=240)	20.47 (n=312)	48.36 (n=737)	100.00 (n=1,524)

F: fibrosis stage

September 2016

T Bilirubin (Dir.)	0,5 (0,2) mg/dL	Hb	12.6 g/dL
AST	28 UI/L	WBC	6250/mm ³
ALT	29 UI/L	PLT	158.000/mm ³
GGT	100 UI/mL	Creatinine	1,25 mg/dL
PT (INR)	0,99	eGFR (MDRD)	60 mL/min
PCHE	8141 UI/mL	αFP	51 (<7) ng/mL
T Protein (albumin)	7,0 (4,5) g/dL	HBV-DNA	<20 IU/ml

US

disomogeneity of liver structure; well known angiomatous lesions in S5, nodule of **2.7 cm in S6**, no ascites, no splenomegaly.

Surveillance might also fail because of lack of detection

Over a mean follow up of 6.1 yrs, in 1005 pts followed 68.9% of patients had consistent surveillance

83 patients were discovered to have HCC

Of them 27.7% were within Milan criteria

Of the remaining,

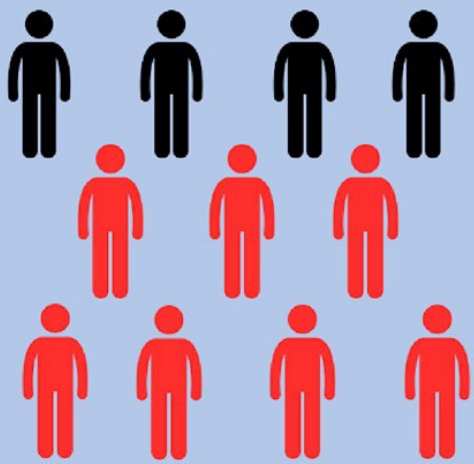
- 13% had late stage HCC due to the absence of screening
- 17% due to the absence of FU

70% due to the absence of detection

Can we improve the current detection rate?

Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Cirrhosis: A Meta Analysis

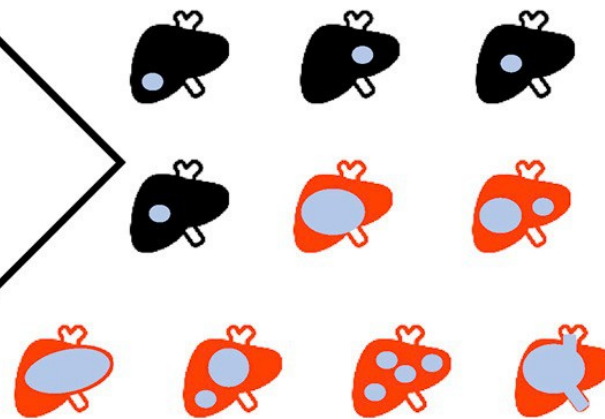
Only 4 in 10 hepatocellular carcinoma are detected at an early stage



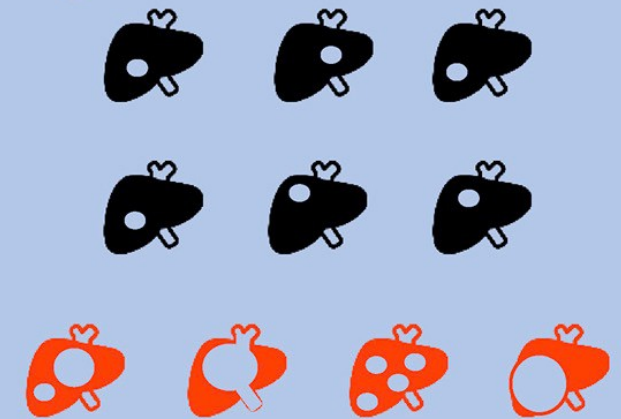
What is the best strategy for early detection?



Sensitivity ultrasound alone: 45%



Sensitivity ultrasound + alpha fetoprotein: 63%



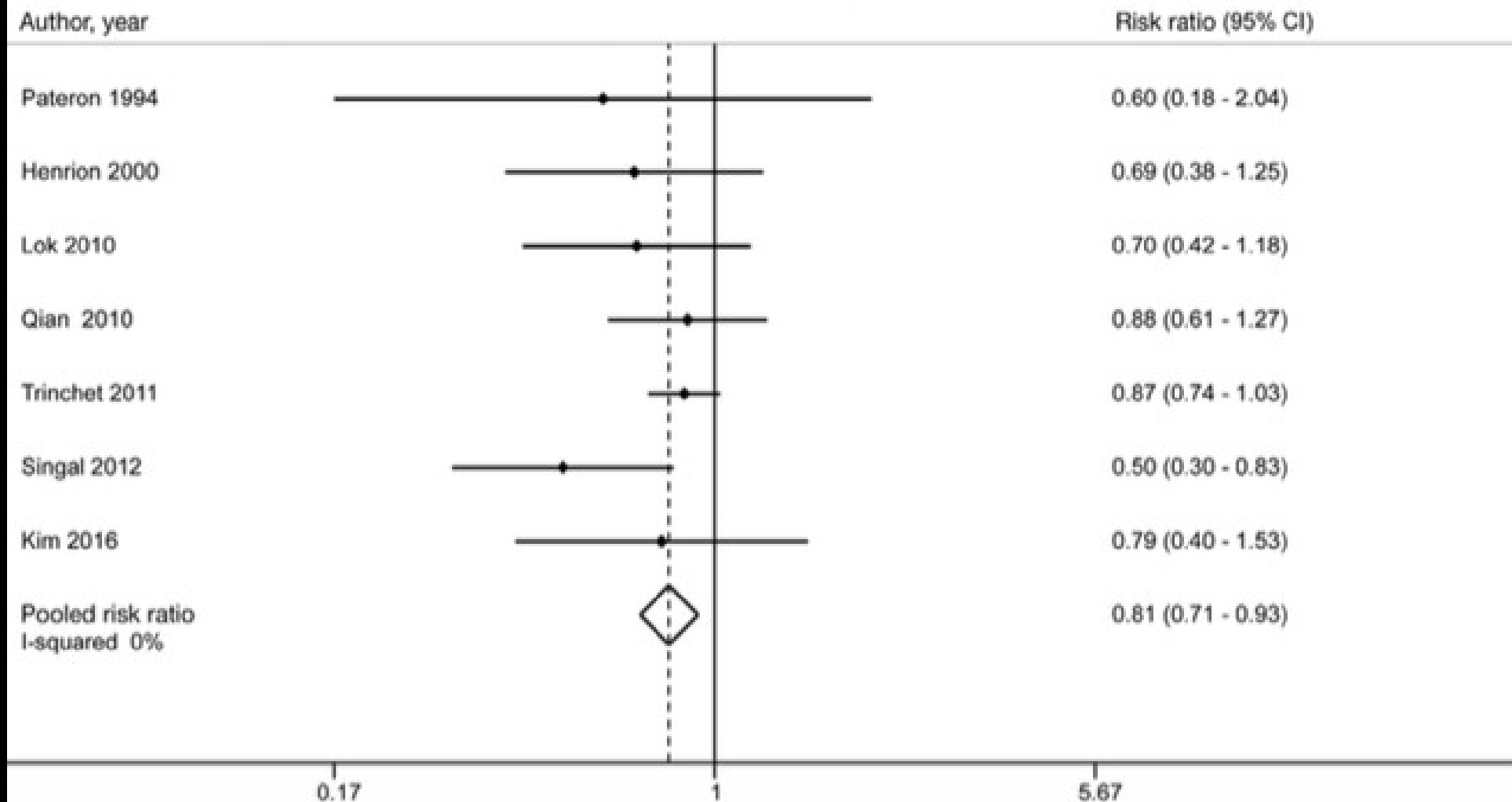
Authors: Tzartzeva, Obi, Rich, Parikh, Marrero, Yopp, Waljee, Singal

Gastroenterology

Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis

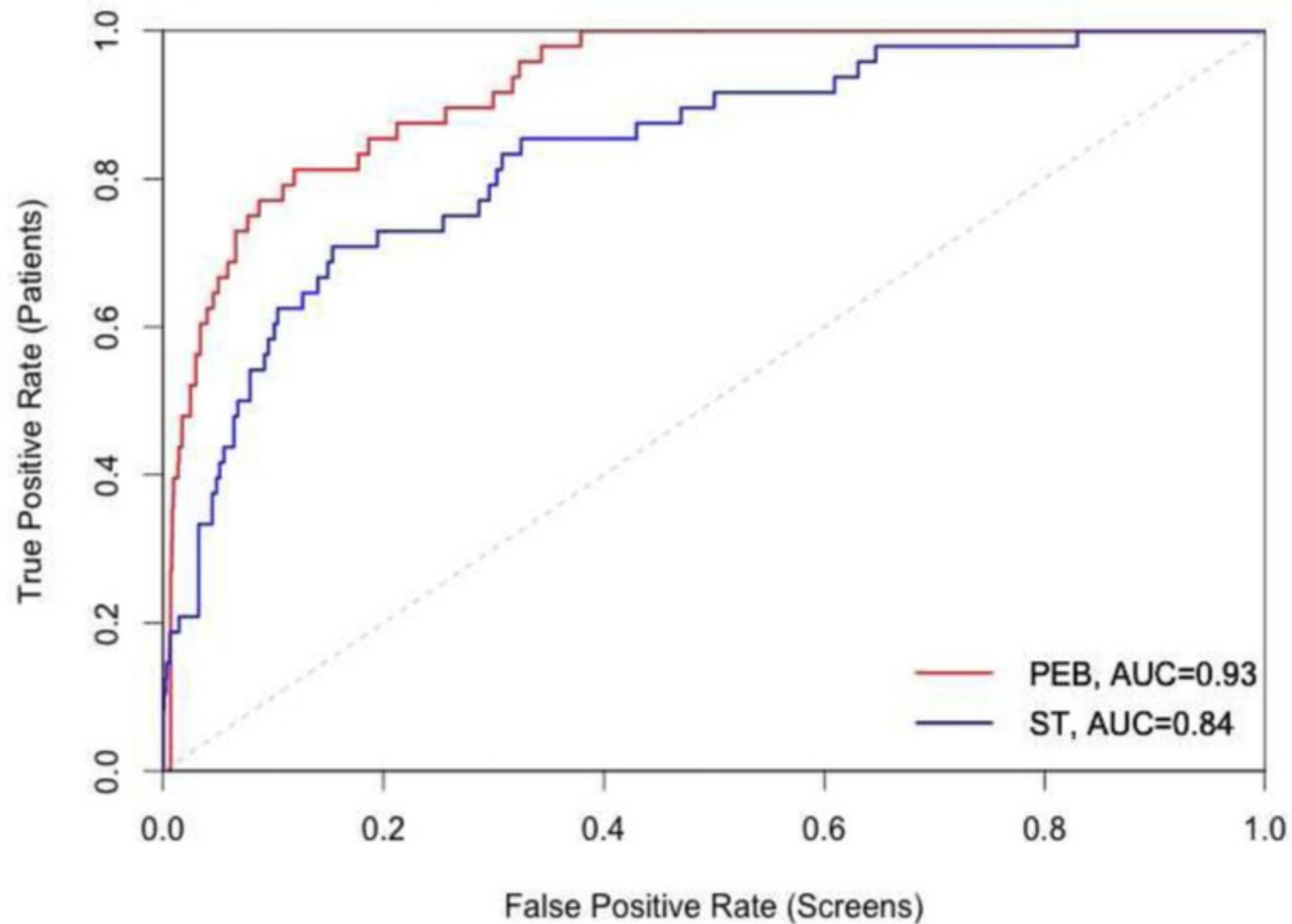


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Reintroduction of AFP as an adjunct to ultrasound due to better real life performance and potential to detect infiltrative disease

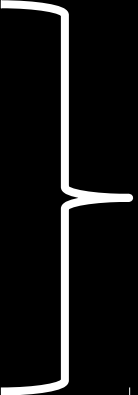
Does longitudinal alphafetoprotein evaluation improve early HCC diagnosis?



Are combined biomarkers able to increase the
number of early diagnosis?
The GALAD model

The GALAD Model Combines The Markers

G – Gender
A – Age
L – AFP- **L**3
A – Alpha-fetoprotein
D – Des-carboxy prothrombin

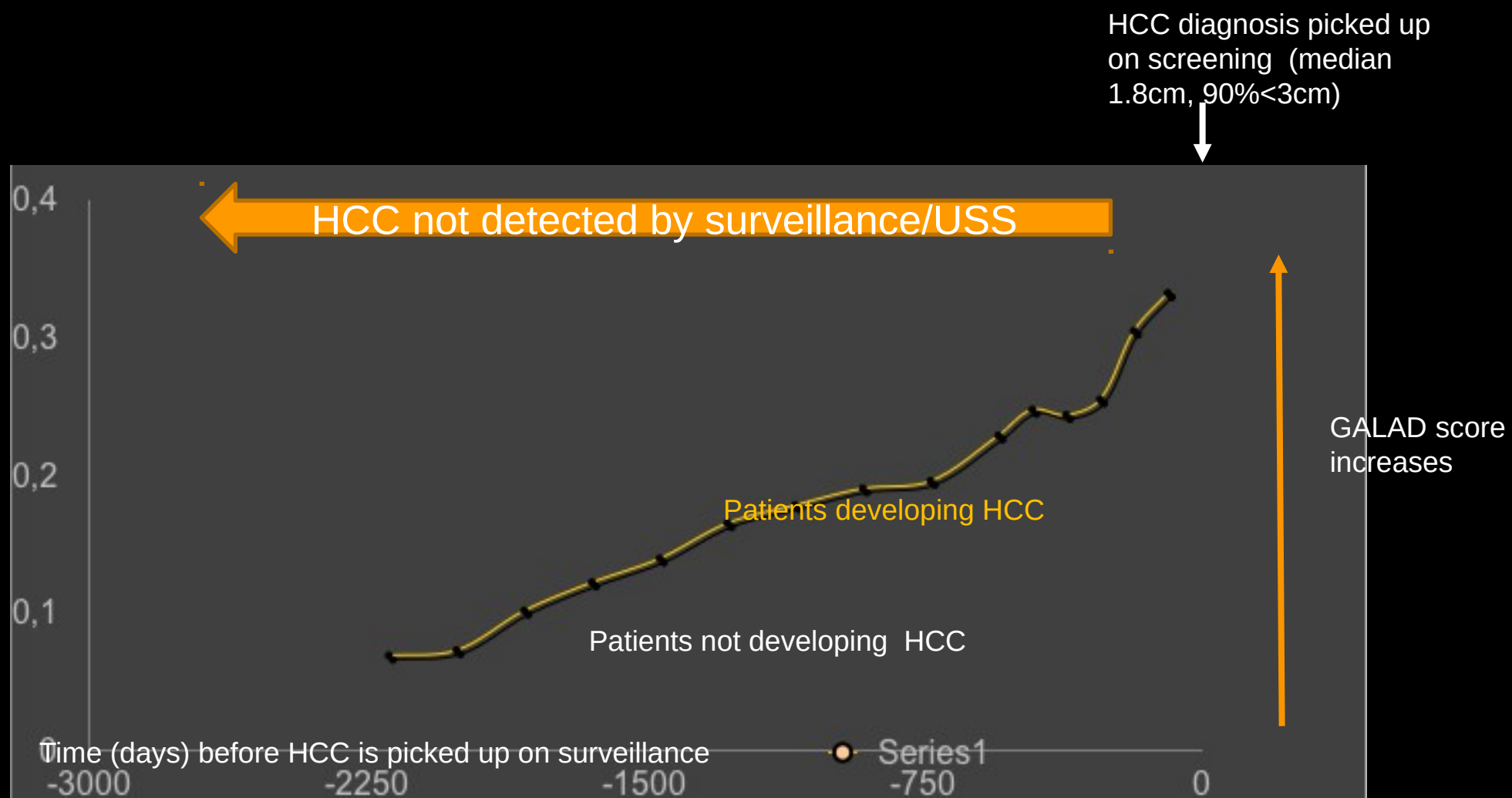


‘GALAD’

GALAD SCORE Z = -10.32 + 0.10 x [Age] + 1.39 x [Gender] + 2.43 x log[AFP] + 0.040 x [AFP-L3] + 1.45 x log[DCP]

- Rigorous statistical methodology
- Treats variables in their continuous form - no dichotomisation
- Then extensive validation, internally and externally

Change in GALAD Score Before Clinical Diagnosis of HCC



Data analysis courtesy of Emily and Oliver de Groot

BG Male Born on 22/07/1953

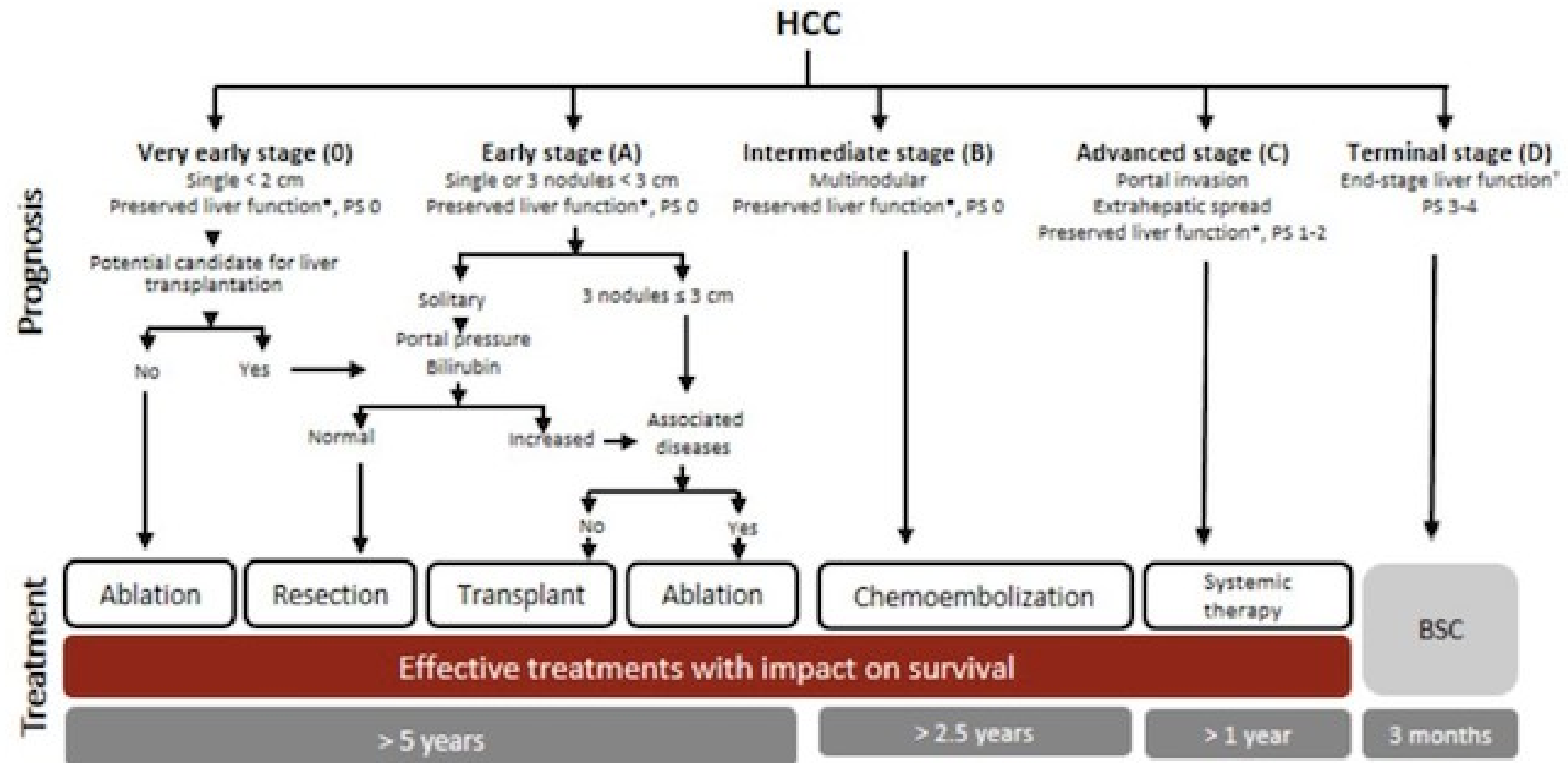
TC addome sup c/s mdc (01/2016)

In S5/S6 focal nodular lesion, 2.5 x 3.0 x 2.8 cm with hypervascularity in arterial phase and washout of contrast on portal venous and equilibrium phase. Normal spleen diameter, patent portal vein of normal diameter, no evidence of venous shunts

OGD (01/2016): no evidence of oesophageal varices

Liver biopsy (02/2016): Moderate chronic hepatitis with fibrosis stage 3 according to Metavir. Micro and macrovesicular steatosis

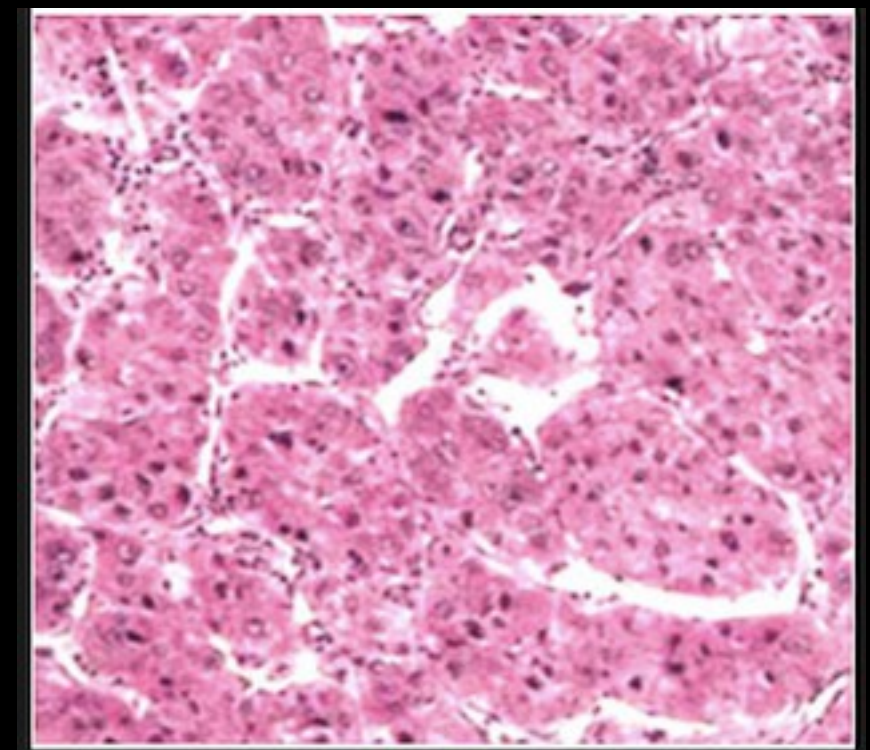
BCLC Prognostic and Treatment strategy



In non cirrhotic patients surgical resection is the preferred treatment

cal resection is the accepted treatment of choice for noncirrhotic patients and offers the best curative rate

Histology of the explanted nodule: intermediate grade of differentiation HCC of trabecular pseudo-glandular type(Edmondson grade III), no capsule, irregular infiltration growth type with multifocal sclerosis
Absence of vascular invasion. absence of satellites nodes.Tumor free margins. T1G2Nx.



HCC recurrence after resection/ablation in cirrhotics

Recurrence of HCC (50% to 70% at 5 yrs)

Predictors

Microscopic vascular invasion
Satellites/additional nodules
Increased AFP

True recurrence

50% to 70%
Early follow-up

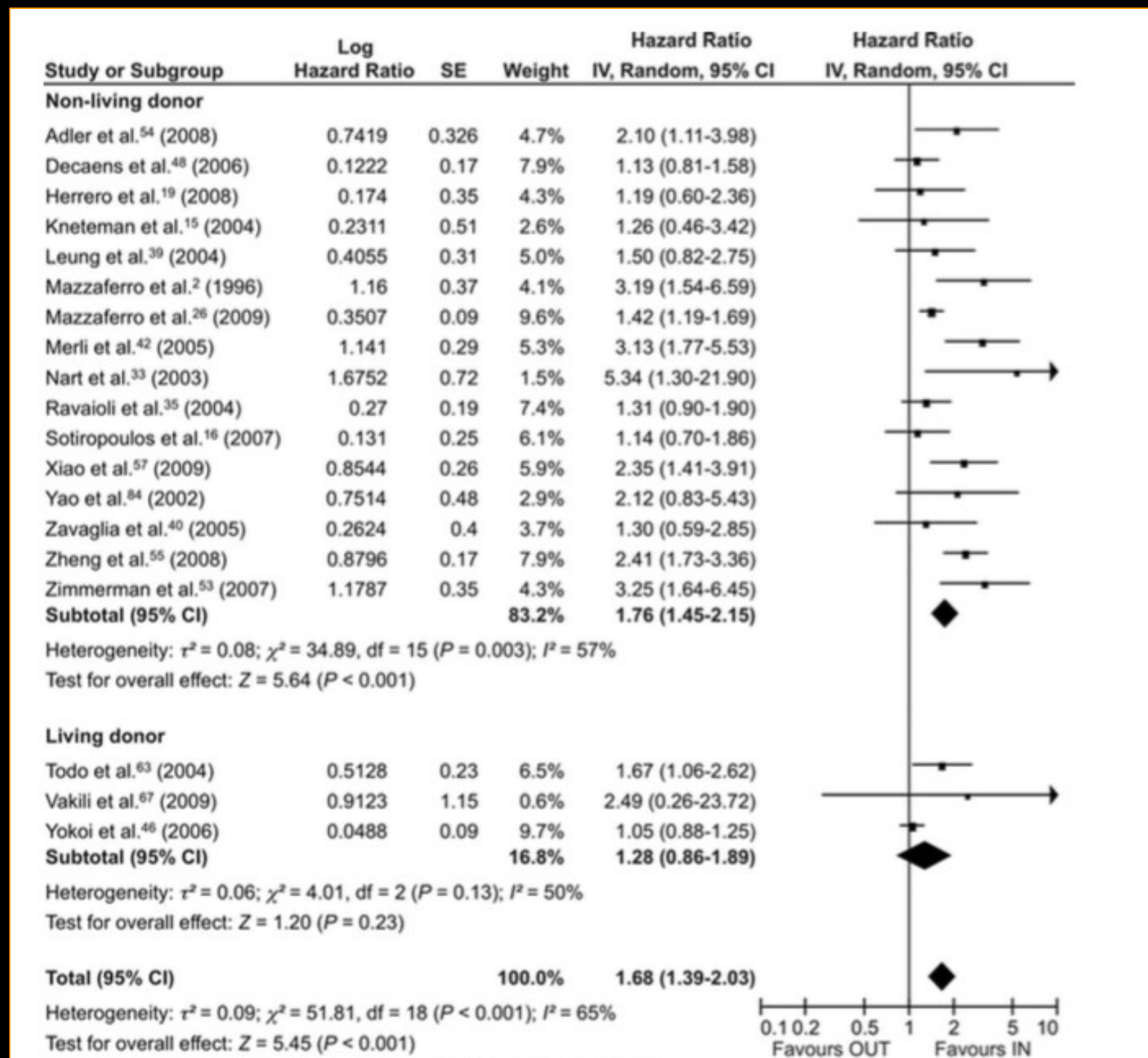
De novo HCC

30% to 50%
Late follow-up

If he was cirrhotic how do we determine the best treatment?

- Patients with underlying cirrhosis have high rates of recurrence after surgery or ablation; typically 20% at 2 yrs; up to 50% at 3 years and up to 70% at 5 years
- Liver transplantation replaces the diseased cirrhotic liver and is associated with low rates of recurrence, typically 15% at 5 years, and 70-75% 5 year survival

Milan Criteria in Liver Transplantation for Hepatocellular Carcinoma: An Evidence-Based Analysis of 15 Years of Experience



Will tumor biology become more and more important?

The introduction of a protocol for a biopsy to exclude patients with poorly differentiated tumors and use of aggressive bridging therapy improved overall survival in the M+ group ($P = 0.034$)

Serum alpha-fetoprotein more than 400 at LTx was associated with poorer disease-free survival (hazard ratio: 2.3; $P = 0.031$)

DuBay et al 2011

Tumor biology is associated with early recurrence after surgical resection

Robert L AASLD 2018

Take home messages

- Surveillance of at risk persons for HCC is key to improving outcomes
- Continue surveillance for HCC on HBV tx & in pts with co-morbidities
- Combined biomarkers may be better than surveillance in increasing the number of early diagnoses
- While OLT remains the only curative surgical procedure, the shortage of available organs precludes this therapy for many patients with HCC

