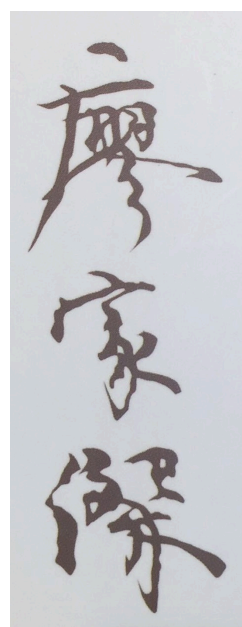




PARIS
HEPATOLOGY
CONFERENCE

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

Role of DAAs therapy in HCC



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Outline

Background

Risk of HCC after SVR by DAAs

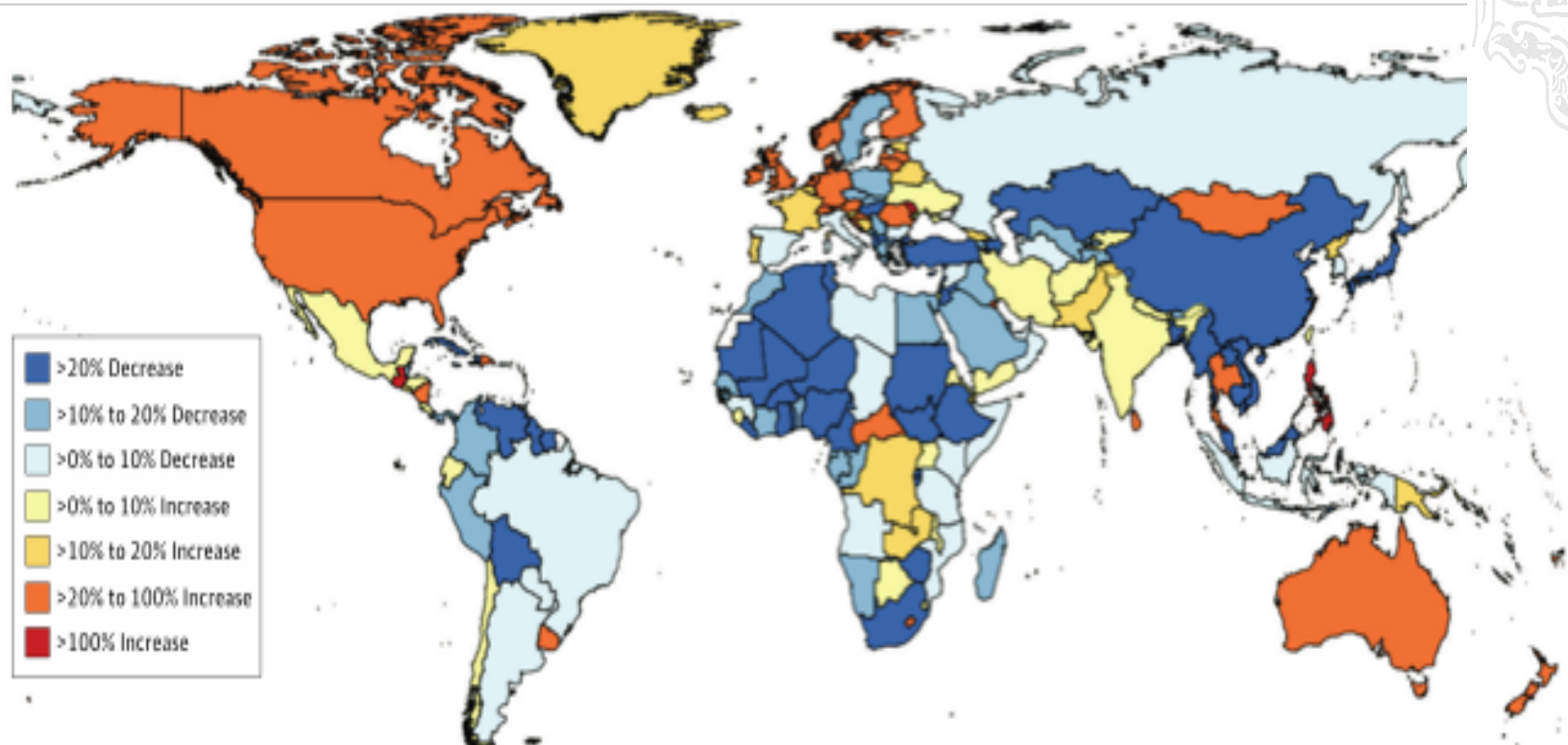
Predictors of HCC after SVR by DAAs

Future Directions

Background



Increase in Age-Standardized Liver Cancer Mortality Between 1990 and 2015 for Both Sexes in 195 Countries/Territories



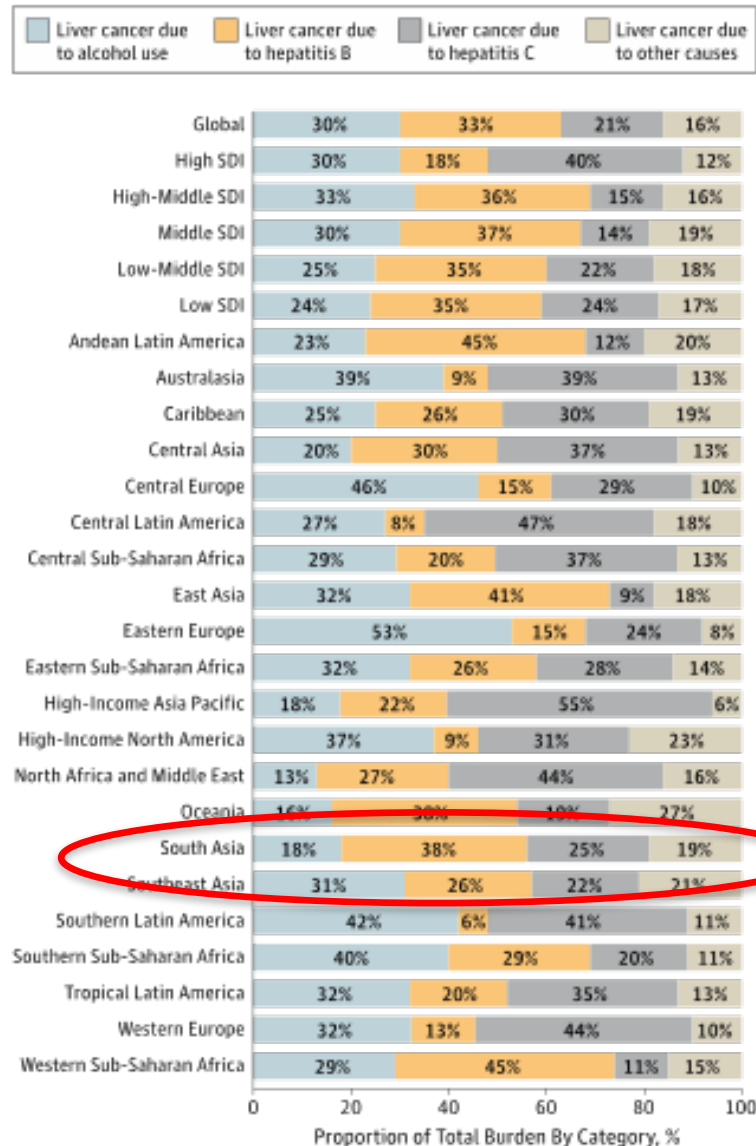
Cases of incident liver cancer increased by 75% between 1990 and 2015

47% -changing population age structures

35%- population growth

88% to changing age-specific incidence rates

Substantial variation between countries in the underlying causes on Absolute Liver Cancer Deaths

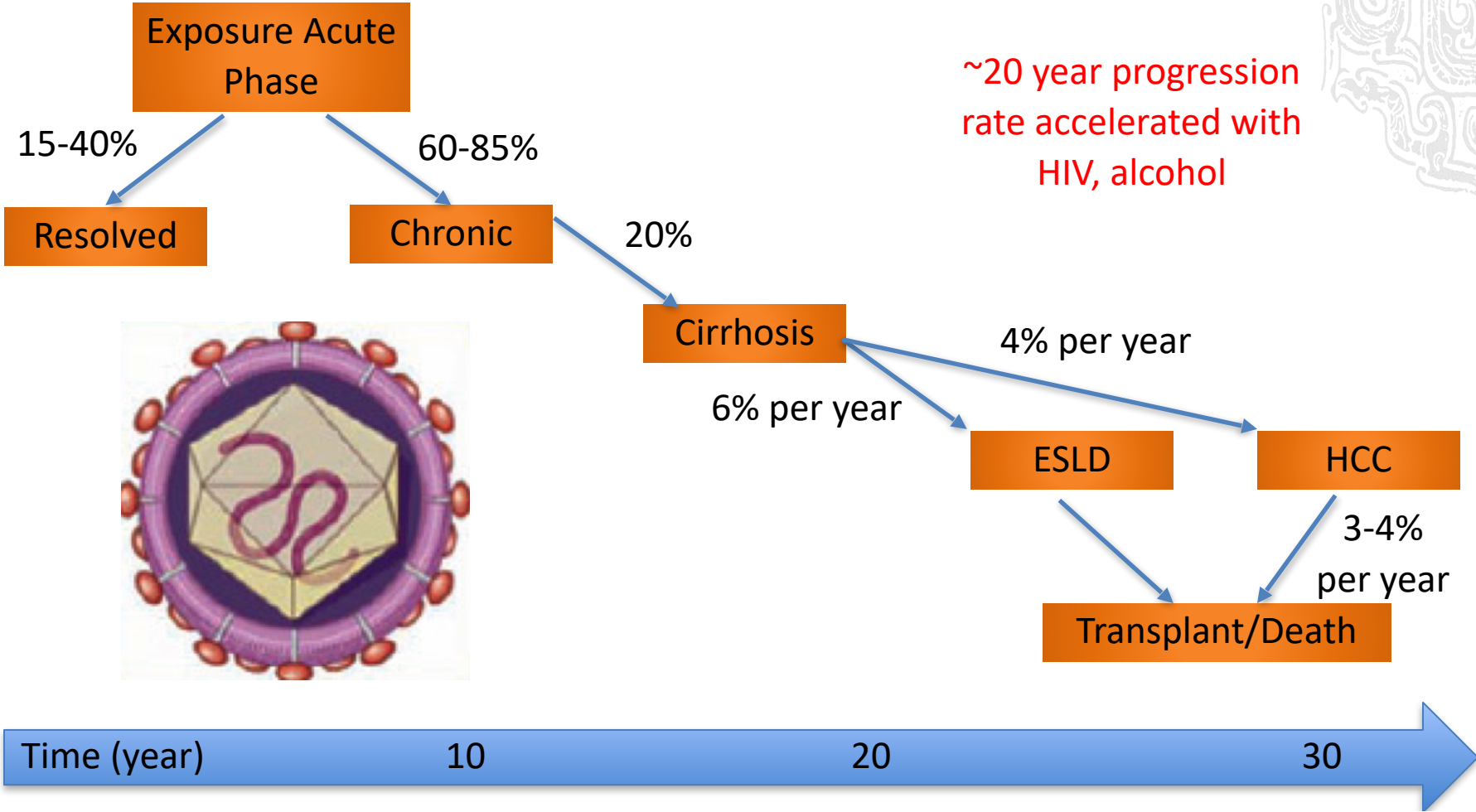


Liver cancer deaths

- HBV - 265 000 (33%)
- Alcohol- 245 000 (30%)
- HCV- 167 000 (21%)
- Other causes- 33 000 (16%)



Natural History of CHC



HCC = Hepatocellular Carcinoma
ESLD = End Stage Liver Disease

HCC in CHC with SVR with IFN-based therapy

- ❖ 30 studies comprised 31528 participants from 17 countries
- ❖ SVR after treatment among HCV-infected persons at any stage of fibrosis is associated with reduced HCC
- ❖ RR for all persons- 0.24 [95% CI, 0.18 to 0.31] moderate-quality evidence
- ❖ RR for advanced liver disease HR 0.23 [CI, 0.16 to 0.35], moderate-quality evidence

Current recommendation for CHC GT1-6

8-24 weeks pan-oral DAAs

All registration study exclude HBV patients

1. Omata M, Kanda T, Wei L, et al. APASL consensus statements and recommendation on management of hepatitis C. Hepatol Int. 2016
2. Hepatitis C Guidance 2018 Update: AASLD-IDSAs Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. CID 2018
3. EASL Recommendations on Treatment of Hepatitis C –Final update of the series. J Hepatol 2020

Risk of HCC after HCV SVR by DAAs

Does DAA therapy really increase the risk of HCC?

Research Article

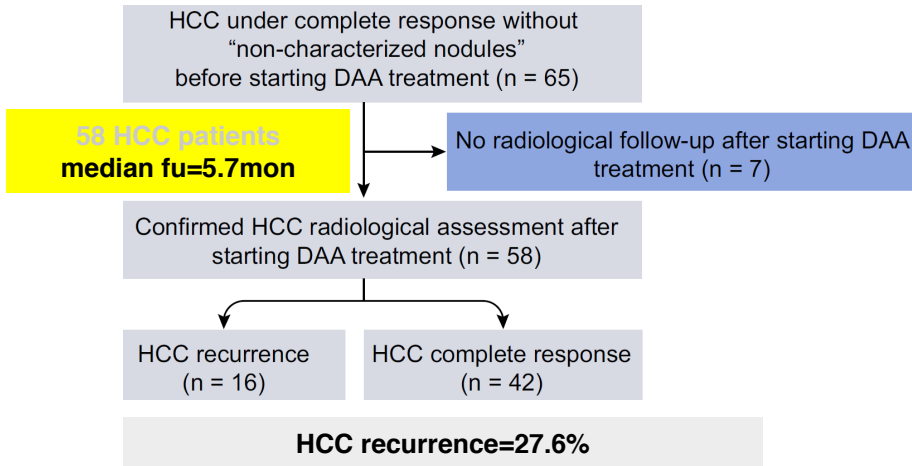


EASL JOURNAL OF HEPATOLOGY

Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy[☆]

María Reig¹*, Zoe Mariño^{2,1}, Christie Perelló³, Mercedes Iñarrairaegui⁴, Andrea Ribeiro¹, Sabela Lens², Alba Díaz⁵, Ramón Vilana⁶, Anna Darnell⁶, María Varela⁷, Bruno Sangro⁴, José Luis Calleja³, Xavier Forns^{2,3}, **Jordi Bruix^{1,*,3}**

[☆]Barcelona Clinic Liver Cancer (BCLC) Group. Liver Unit, Hospital Clinic Barcelona, IDIBAPS, University of Barcelona, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain; ²Liver Unit, Hospital Clinic, IDIBAPS, University of Barcelona, CIBERehd, Barcelona, Spain; ³Liver Unit, Hospital Universitario Puerta de Hierro, CIBERehd, IDIPHIM, Madrid, Spain; ⁴Unidad de



J Hepatol.2016;65(4):719-26.

Research Article

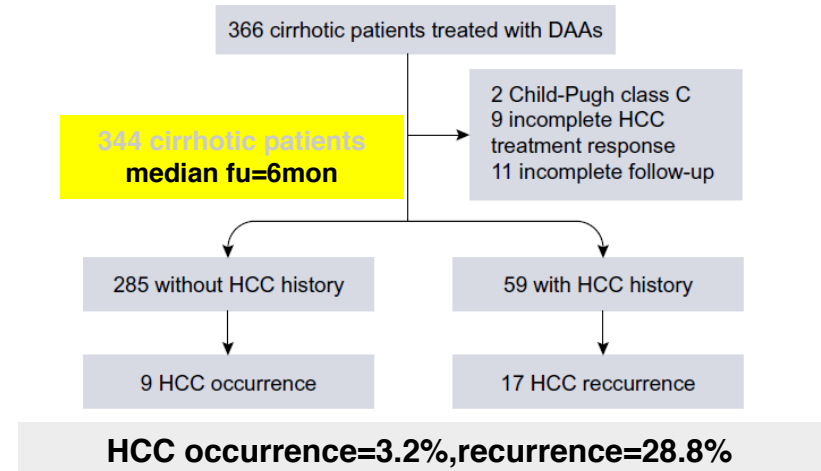


EAS

Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antiviral agents

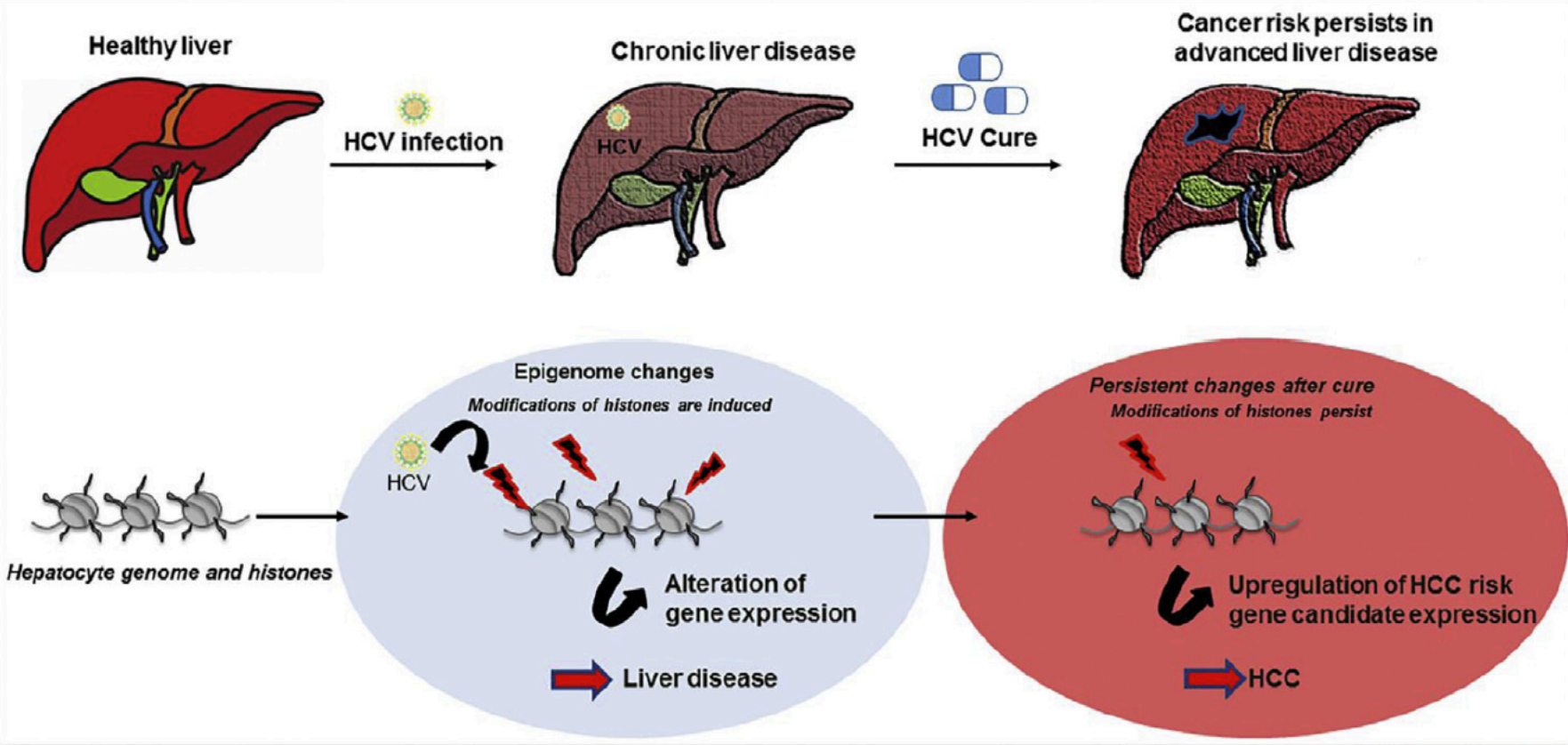
Fabio Conti¹*, Federica Buonfiglioli^{1,4}, Alessandra Scuteri², Cristina Crespi², Lu Paolo Caraceni³, Francesco Giuseppe Foschi⁴, Marco Lenzi¹, Giuseppe Ma Gabriella Verucchi¹, Pietro Andreone^{1,3}, **Stefano Brillanti^{1,*,4}**

¹Research Centre for the Study of Hepatitis, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Italy; ²Department of Digestive Diseases, Policlinico S.Orsola-Malpighi, Bologna, Italy; ³Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Italy; ⁴Division of Internal Medicine, Ospedale di Faenza, Italy



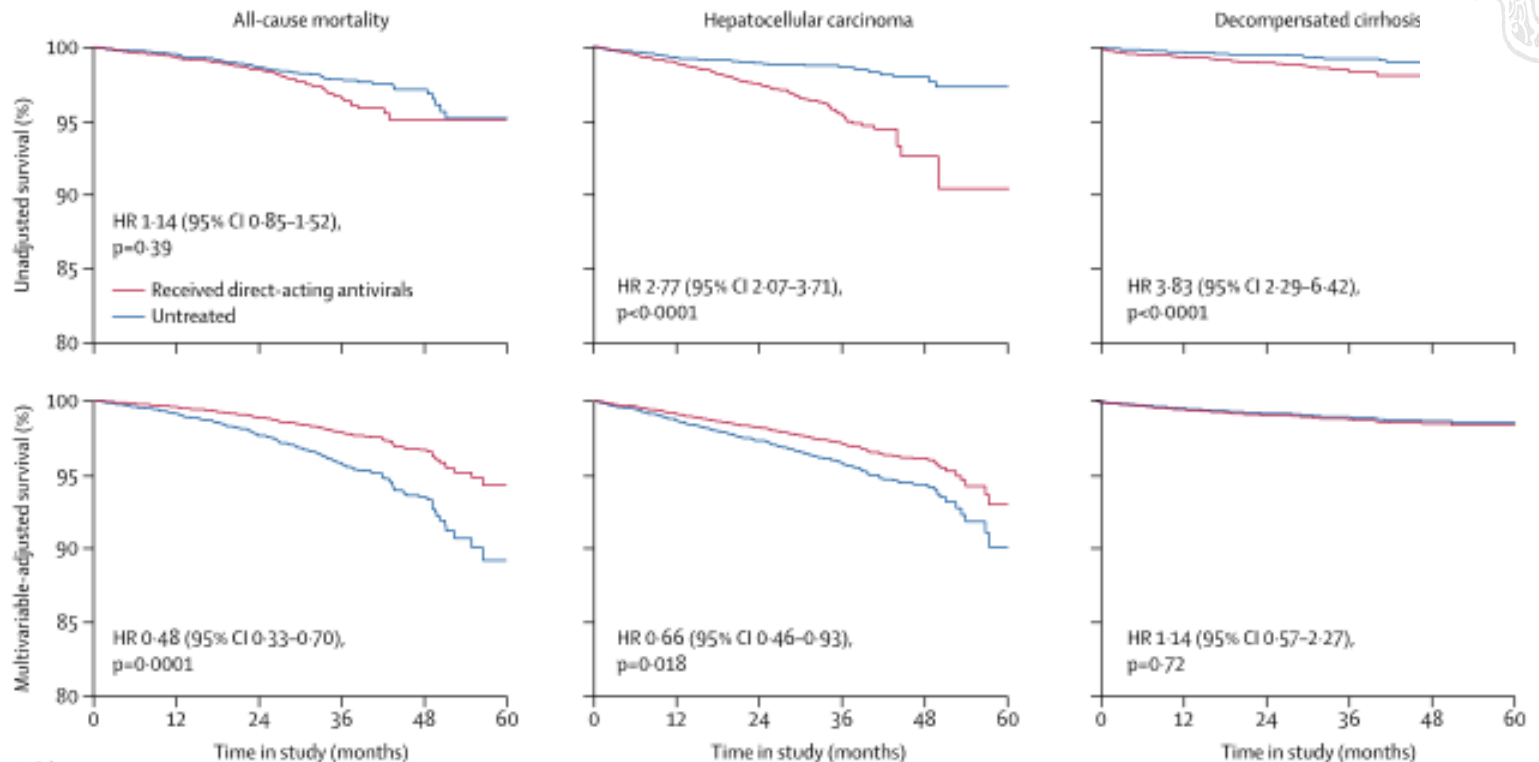
J Hepatol.2016;65(4):727-33.

HCV-Induced Epigenetic Changes Associated With Liver Cancer Risk Persist After Sustained Virologic Response



DAAs is associated with reduced risk for mortality and HCC - French ANRS C022 Hepather cohort

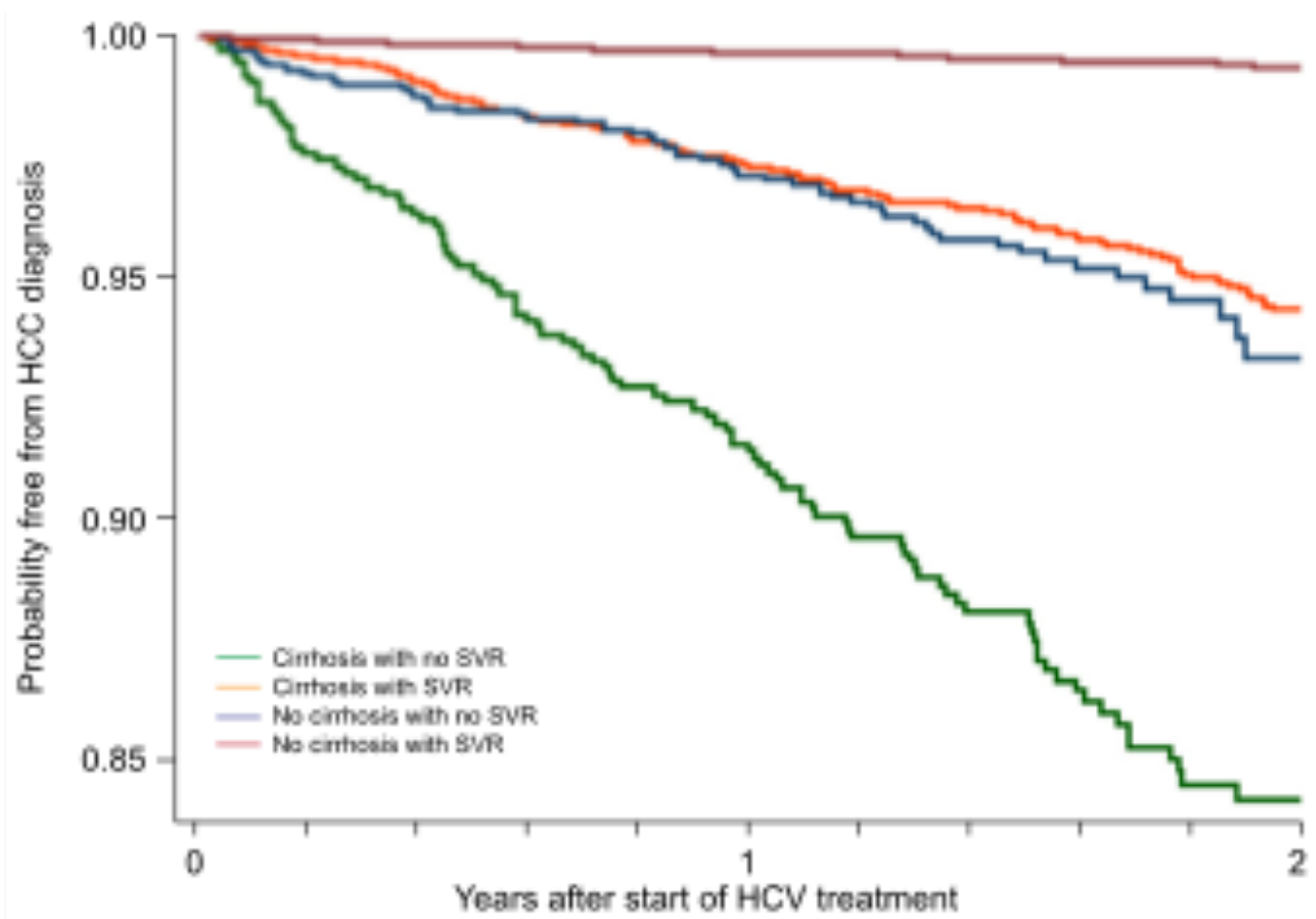
After adjustment for age, sex, body-mass index, geographical origin, infection route, fibro HCV treatment-naive, HCV genotype, alcohol consumption, diabetes, arterial hypertension biological variables, and MELD score in patients with cirrhosis



	0	12	24	36	48	60	0	12	24	36	48	60	0	12	24	36	48	60	
Number at risk (number censored)																			
Received direct-acting antivirals	7344 (0)	5448 (1853)	3469 (3794)	1012 (6211)	59 (7156)	6 (7209)	7308 (0)	5366 (1873)	3368 (3806)	977 (6156)	57 (7065)	6 (7115)	7330 (0)	5408 (1879)	3432 (3837)	996 (6263)	59 (7197)	6 (7330)	
Untreated	9895 (0)	4774 (5094)	2889 (6944)	1344 (8473)	360 (9451)	10 (9796)	9895 (0)	4751 (5100)	2878 (6959)	1337 (8495)	335 (9471)	10 (9814)	9895 (0)	4766 (5110)	2888 (6982)	1342 (8523)	360 (9503)		

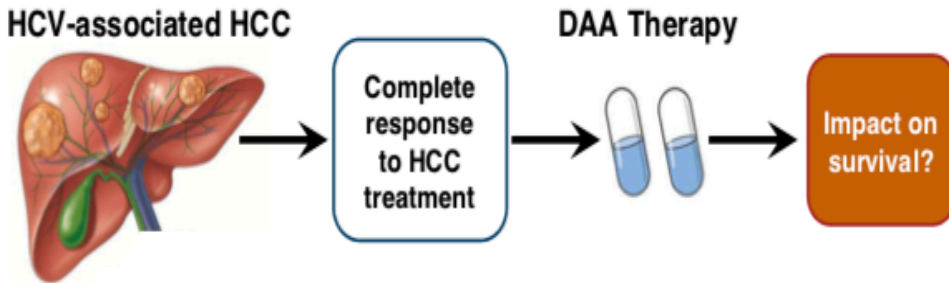


DAA-induced SVR is associated with a **71%** reduction in HCC risk



Direct-Acting Antiviral Therapy is Associated with Improved Survival in Patients with a History of Hepatocellular Carcinoma: A Multicenter North American Cohort Study

Does DAA therapy improve survival in patients with a history of complete response to HCC treatment?



Design:

- 31 centers in North America including 797 patients with HCV-associated HCC with complete radiographic response
- 383 (48.1%) received DAA therapy
- 414 (51.9%) untreated

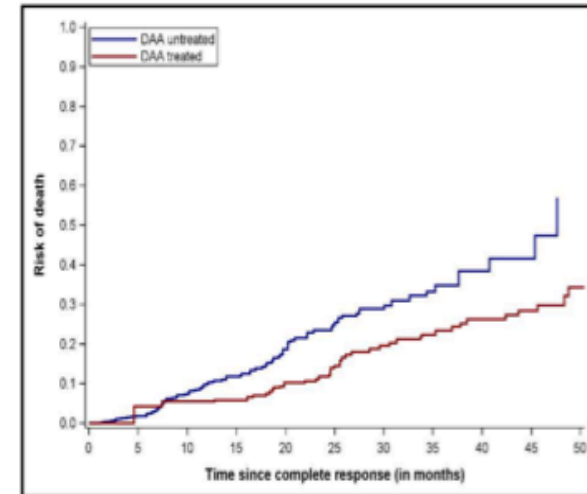
Results:

DAA Treated:
4.6 deaths per 100 person-years follow-up

DAA Untreated:
19.6 deaths per 100 person-years follow-up

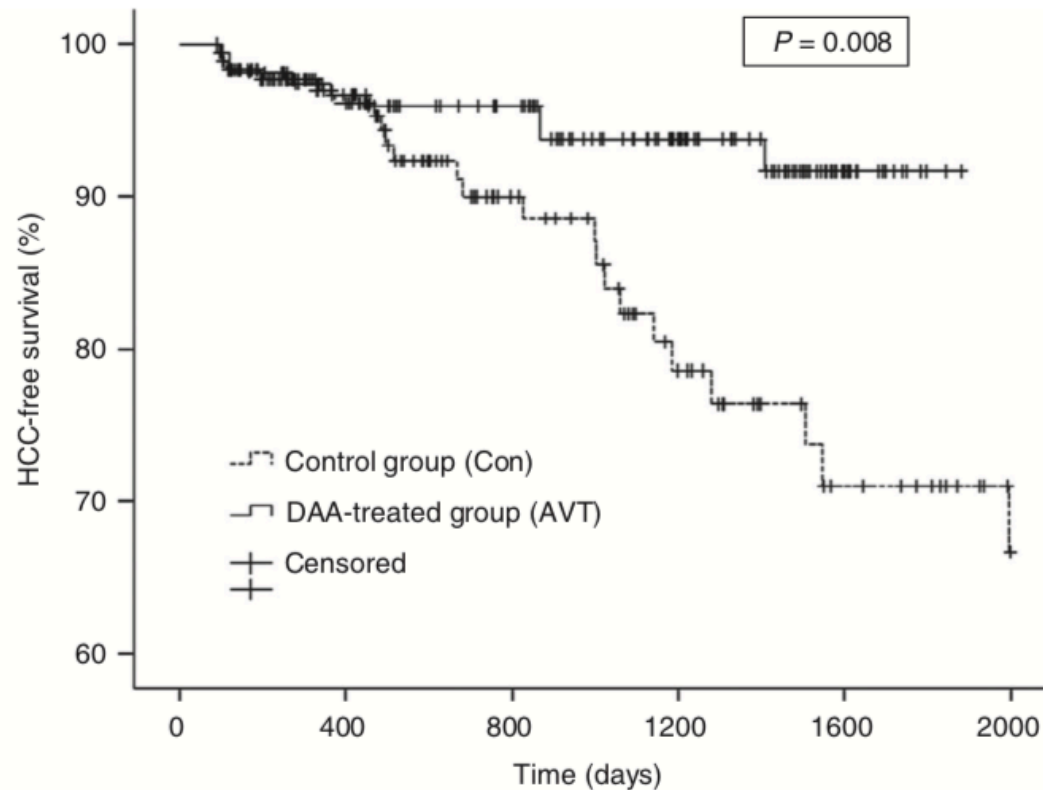
Multivariable analysis

- Adjusted for site, age, sex, Child Pugh score, AFP, tumor burden and HCC treatment modality



DAA therapy associated with lower mortality:
HR: 0.54; 95%CI: 0.33 – 0.90

5-year long-term follow-up study after DAA treatment confirms a reduced HCC risk in a central European cohort of HCV patients with liver cirrhosis



Number of patients at risk

Days	0	400	800	1200	1600	2000
AVT	158	134	105	66	12	
Con	184	124	73	50	34	23



CHC with SVR - Long-term (≥ 2 yrs) FU studies

Country	Cohort	Design of study	DAA's (n)	Median FU (mon)	Risk factors of HCC Occurrence
Japan ¹	Tokyo University	Retrospective	752	46	<ul style="list-style-type: none"> • AFP > 5.4 ng/ml • WFA-H2BP
USA ²	VA patients	Retrospective	21,948	24	<ul style="list-style-type: none"> • DAA's same as IFN
USA ³	VA patients	Retrospective	29,033	48	<ul style="list-style-type: none"> • FIB-4 scores ≥ 3.25
USA ⁴	VA patients	Retrospective	25,232	35.2	<ul style="list-style-type: none"> • Persistently high FIB-4 >3.25/APRI >1.5 • Alcohol • older age • HCV genotype 3
France ⁵	ANRS CO22 HEPATHER	Prospective	9,895	33.4	<ul style="list-style-type: none"> • Age ≥ 50 • Fibrosis scoring (F3,F4) • Hypertension • Albumin < 30 g/L • Platelet count < 100 x 10⁹/L • AFP ≥ 5.5 ng/mL
China ⁶	302(Beijing)-H&H(HK)	Prospective	1,241	48	<ul style="list-style-type: none"> • DAA's • Age ≥ 55 • AFP ≥ 20 ng/mL • NAFLD • Diabetes • LSM > 14.6 kPa or cirrhosis

1. Nagata H, et al. Hepatology 2017
 2. Ioannou GN, et al. J Hepatol 2018
 3. Ioannou GN, et al. Gastroenterology 2019

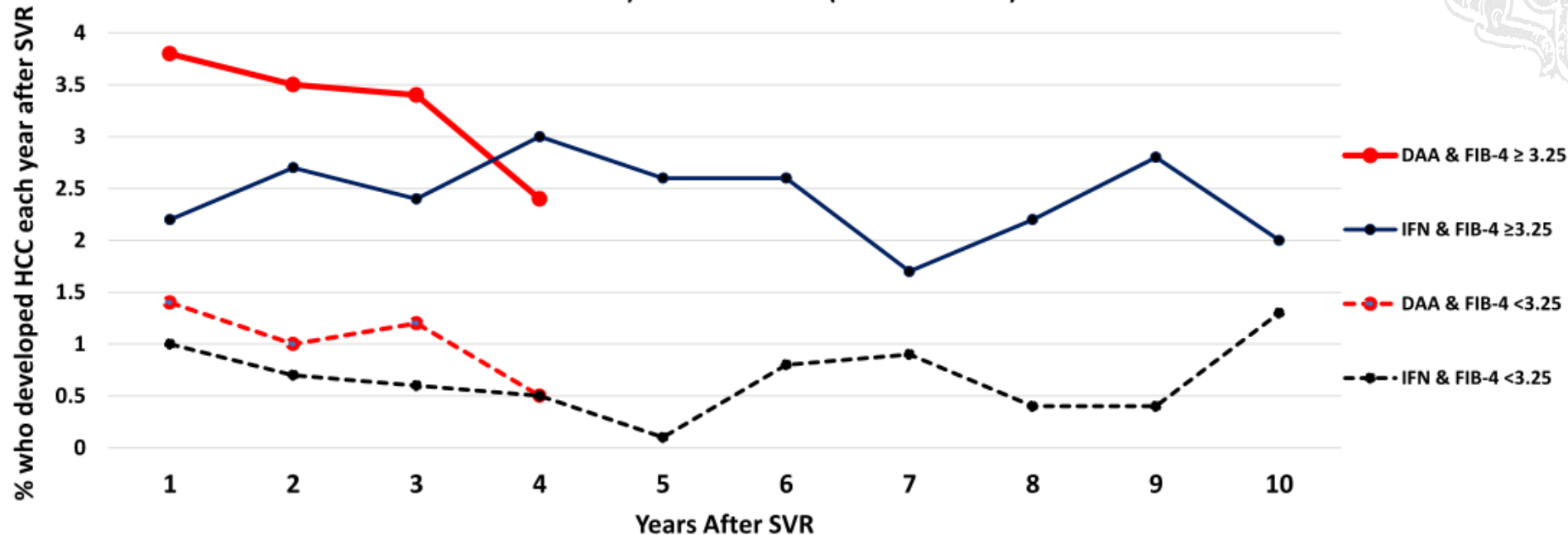
4. Nathwa F, et al. Hepatology 2019
 5. Carrat F, et al. Lancet 2019
 6. D Ji, et al. 2021. (submitted)

Predictors of HCC after HCV SVR by DAAs

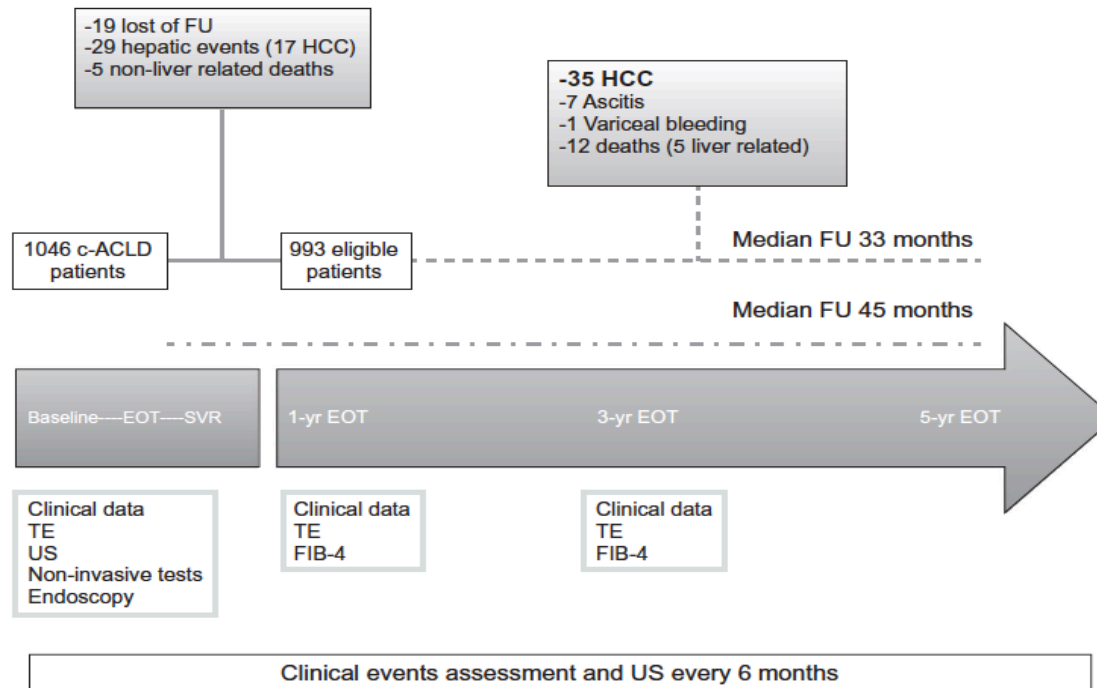


Increased Risk for HCC Persists Up to 10 Years After HCV Eradication in Patients with Baseline Cirrhosis or High FIB-4 Scores

Annual HCC Incidence After SVR in Patients with Pre-treatment Cirrhosis According to Treatment Type (DAA vs. IFN) and FIB-4 Score (≥ 3.25 vs. < 3.25)



A risk models based on baseline and dynamic changes in LSM and noninvasive biomarkers



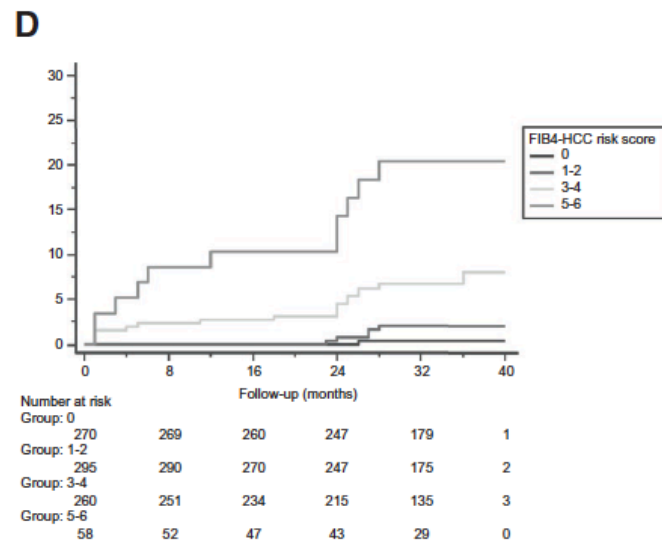
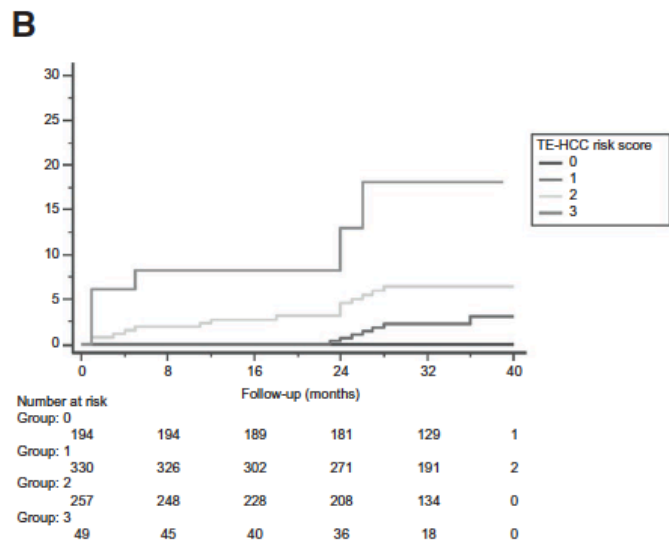
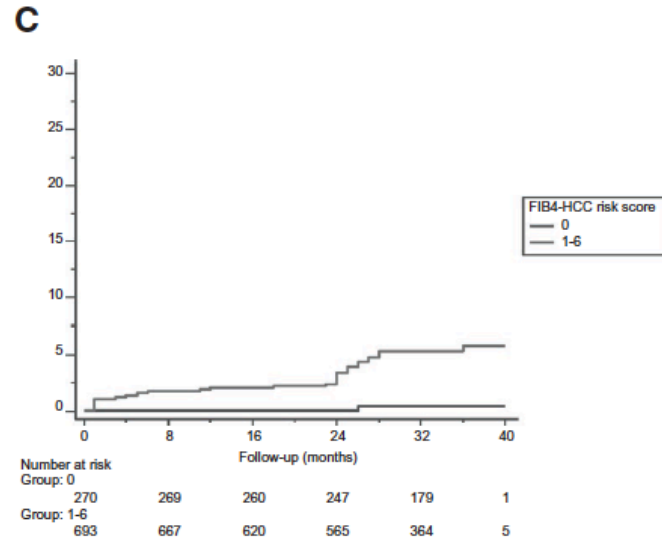
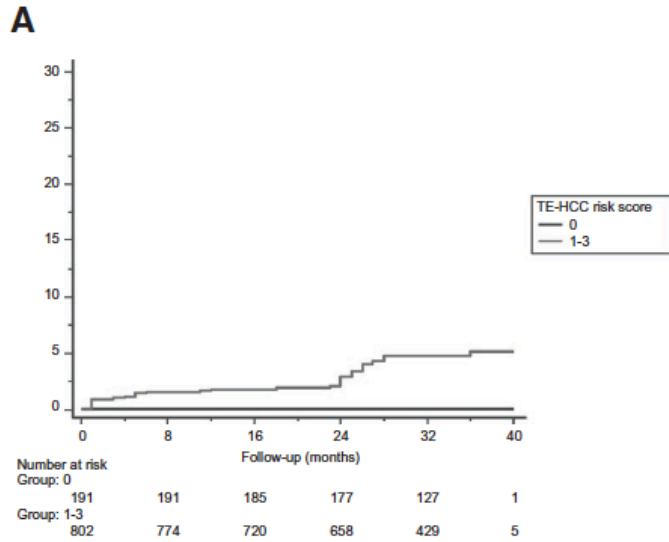
(A)

Baseline LSM (kPa)	1y-DeltaLSM (%)	Baseline Albumin (g/dL)
≤17.3: 0	≥25.5: 0	≥4.2: 0
>17.3: 1	<25.5: 1	<4.2: 1

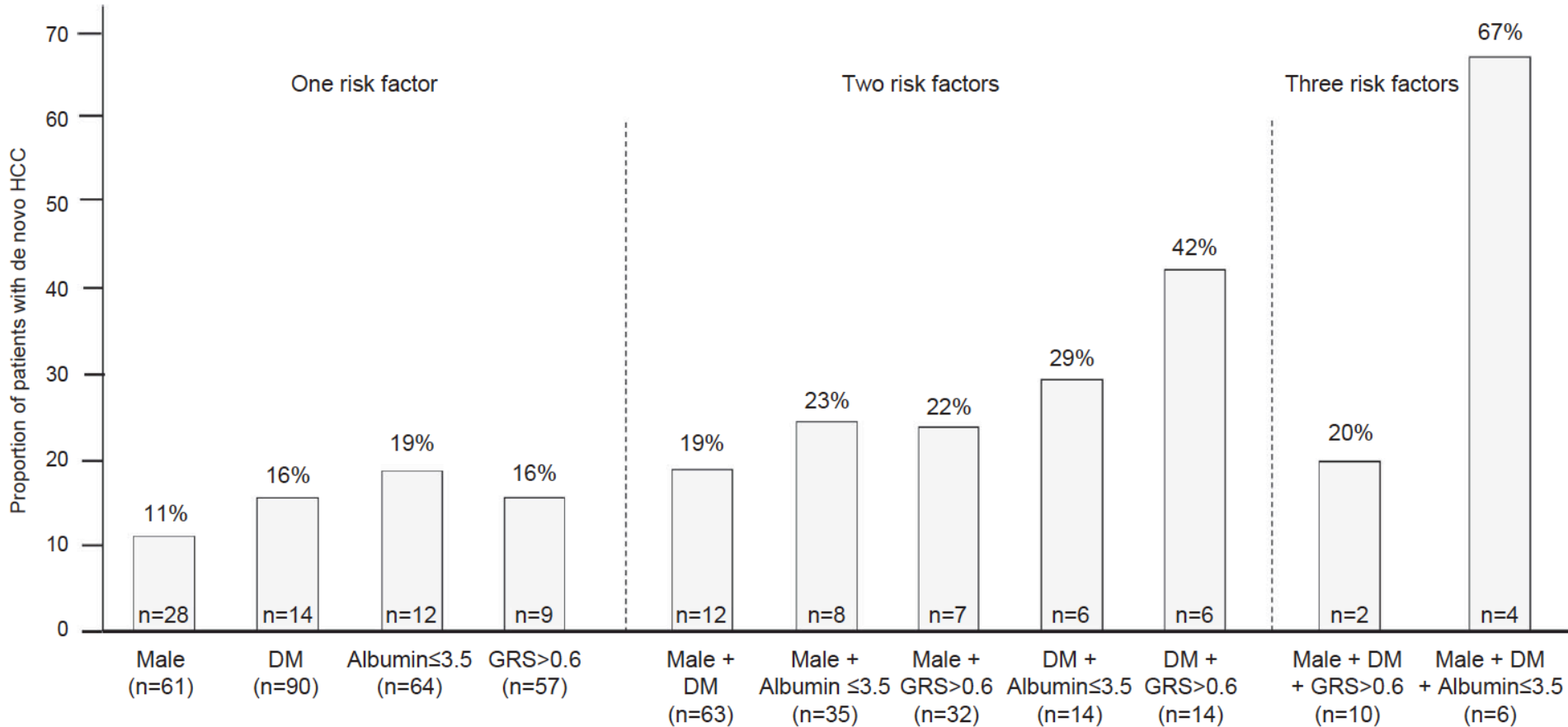
(B)

Baseline FIB-4	1y-FIB-4	Baseline albumin (g/dL)	1y-GGT (UI/L)
≤3.7: 0	≤3.3: 0	≥4.2: 0	≤42: 0
>3.7: 1	>3.3: 1	<4.2: 2	>42: 0

Cumulative risk of HCC at 3 years according to scores of both LSM and noninvasive biomarkers



Hepatic Fat-genetic risk score (GRS) predicts de novo HCC in cirrhotic HCV treated with DAAs



DAAAs in Chinese - 2021



Special HCV Clinic (Beijing 302 Hospital, China)



解放军第302医院-香港天下仁心医疗集团

丙肝诊疗中心

Beijing 302 Hospital of PLA-Hong Kong Humanity&Health Medical Group
Hepatitis C Diagnosis and Treatment Center



Liver Cirrhosis
Diagnosis and Treatment Center
肝硬化诊疗中心



中国人民解放军第三〇二医院
302 MILITARY HOSPITAL OF CHINA

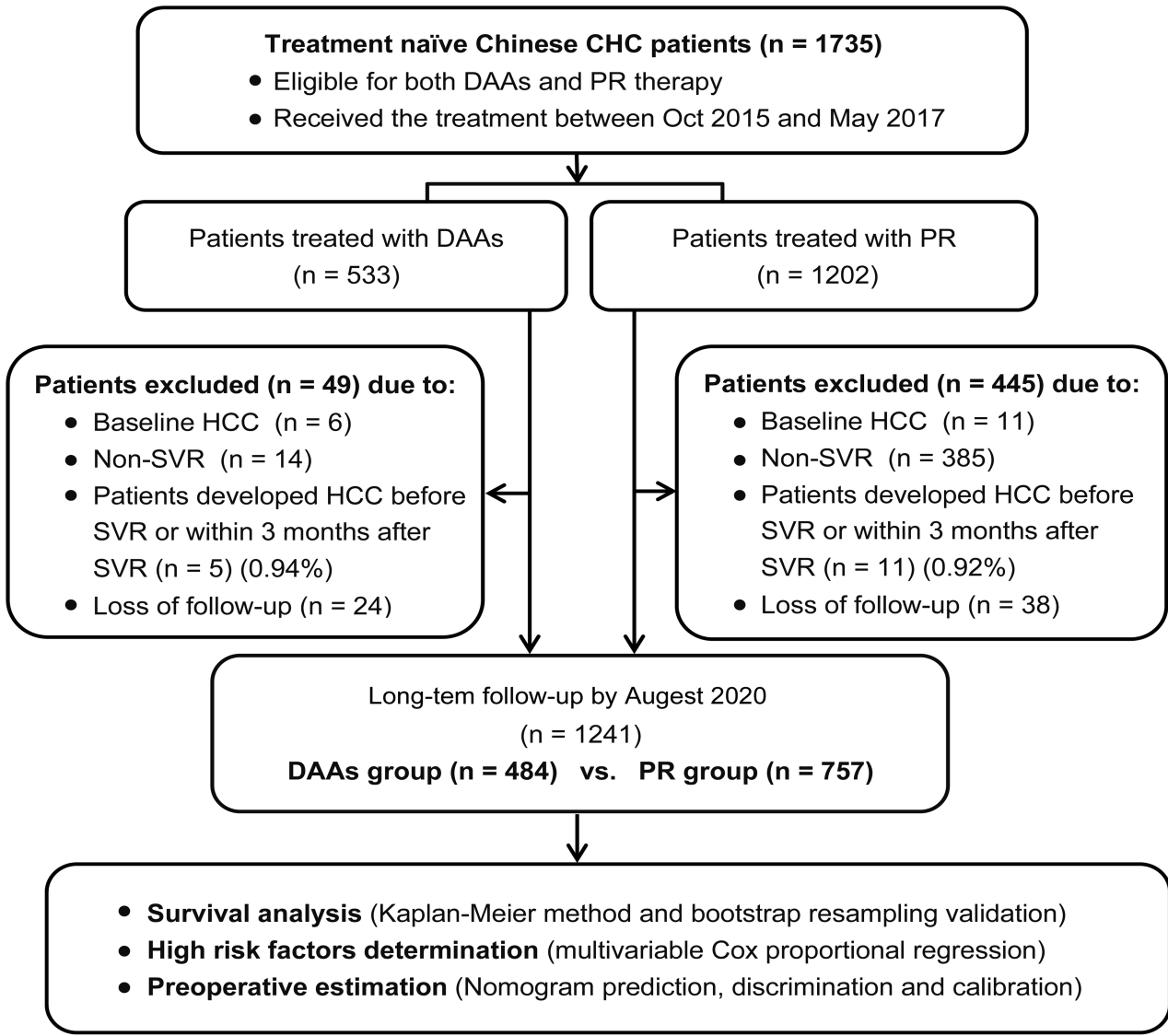


HUMANITY & HEALTH
天下仁心醫療集團

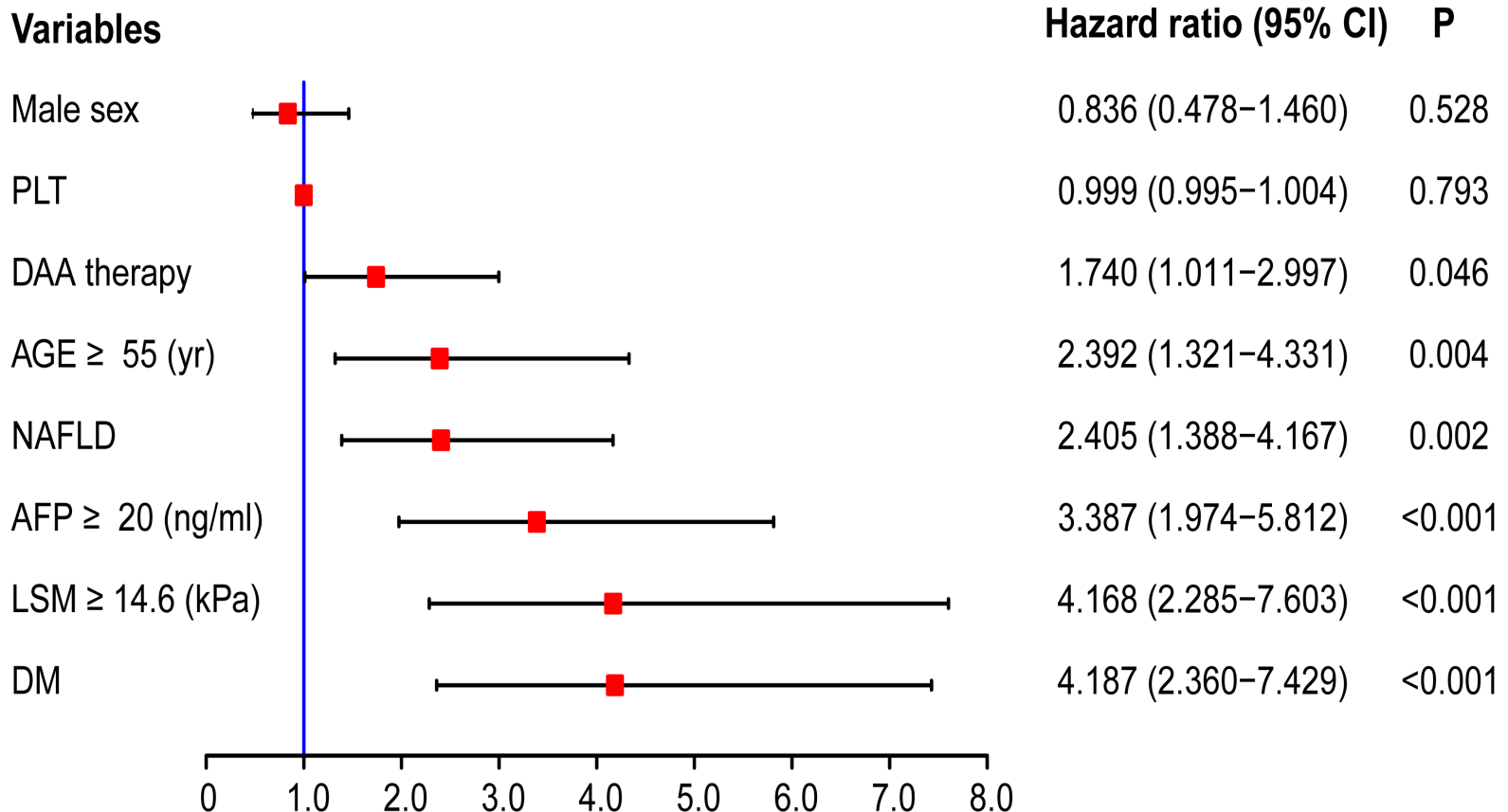




Occurrence of HCC after SVR in CHC patients: a prospective four years follow-up study

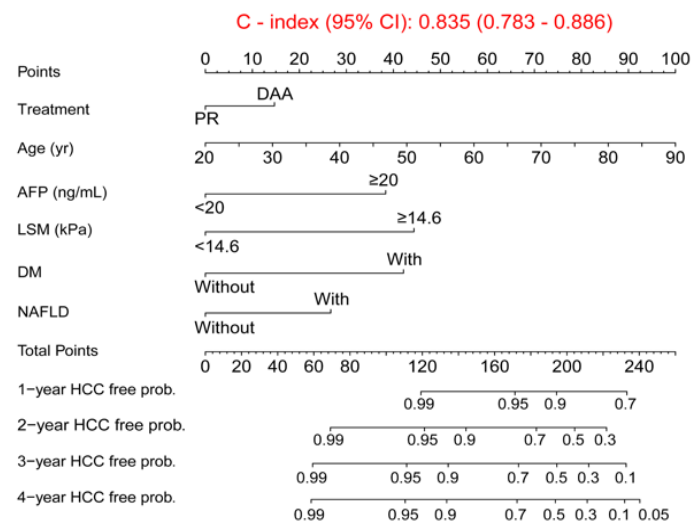


Current Risk factors associated with development of HCC in patients with HCV who achieved SVR

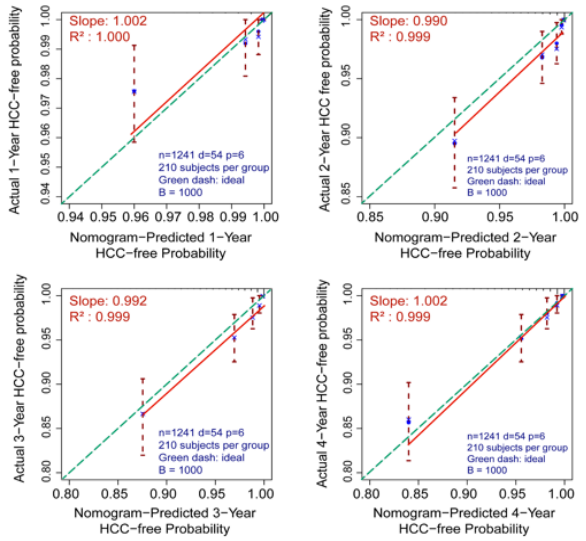


Nomogram to estimate the risk of HCC incidence in patients with HCV who achieved SVR

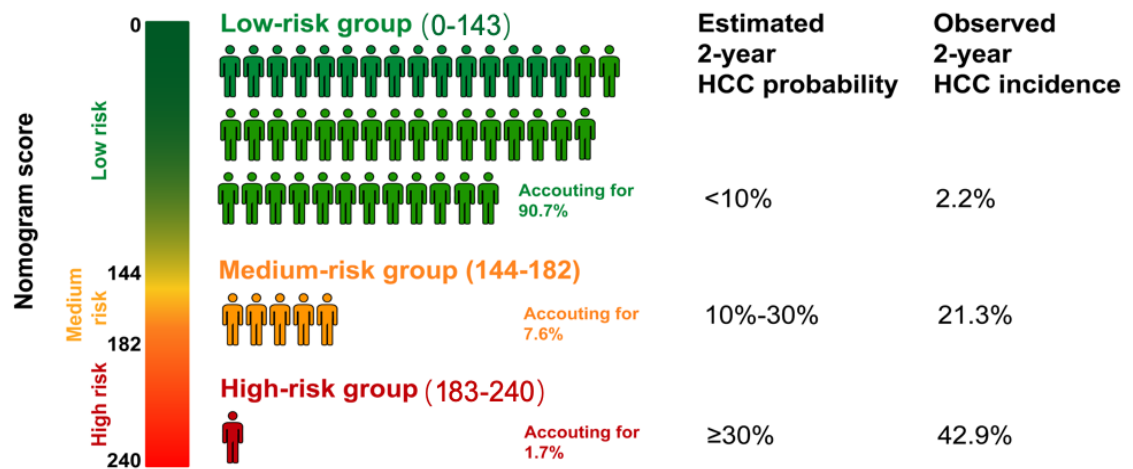
A. Nomogram



B. Calibration curve



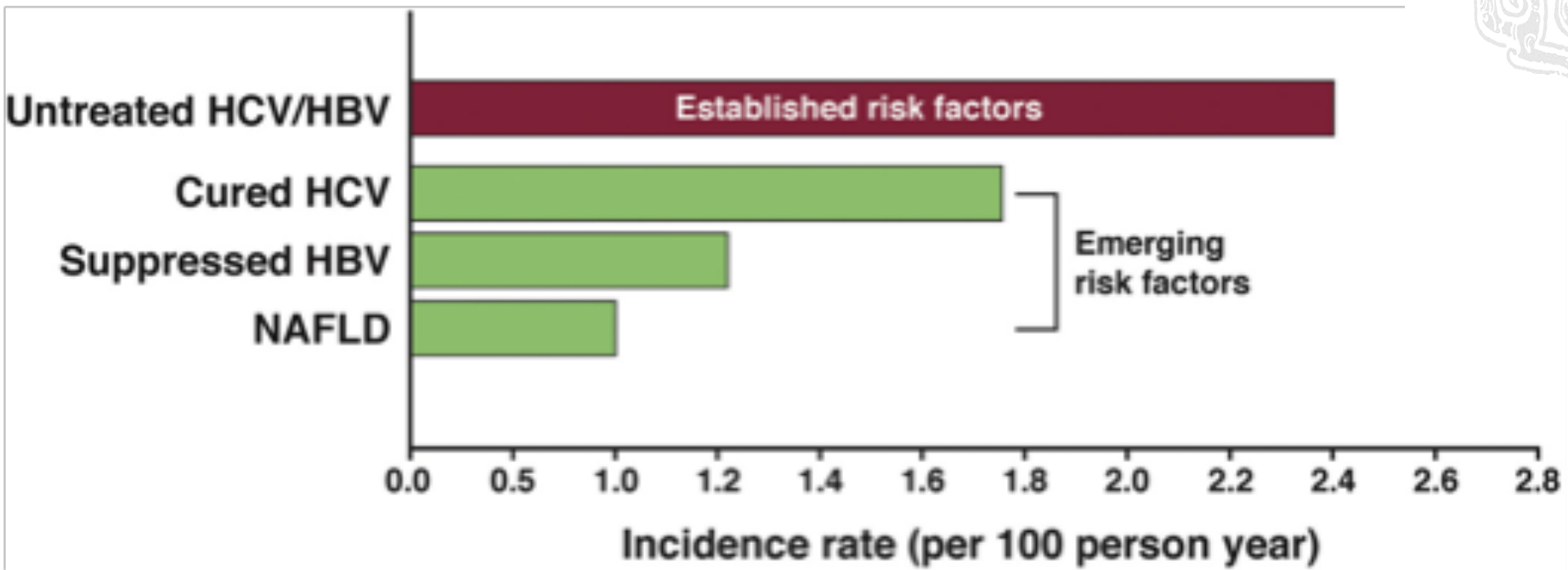
C. Prediction for 2-year HCC probability



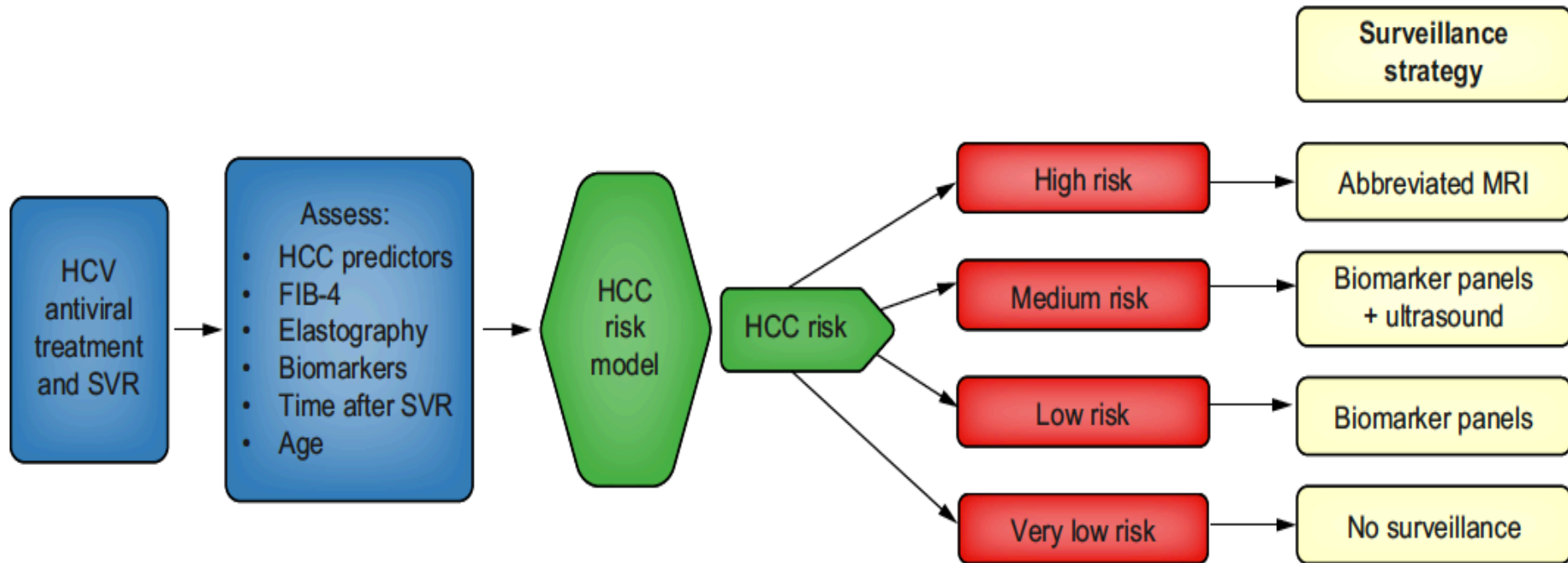
Future Directions



Annual risk of HCC in cirrhosis patients



HCC risk stratification and risk-based surveillance in patients who achieve SVR



Questions to be answered

- ❖ Not all HCC after SVR has advanced liver fibrosis or cirrhosis
- ❖ End-points used
 - HCC occurrence or recurrence
 - HCC staging
 - Survival
- ❖ Other more sensitive imaging or molecular testing
- ❖ Asian Vs Caucasian

OUR TEAMS



- Liver Cirrhosis Diagnosis and Treatment Center, The Fifth Medical Centre of Chinese PLA General Hospital
- Liver Diseases and Transplant Centre, The Fifth Medical Centre of Chinese PLA General Hospital, Beijing - Humanity & Health Medical Group)



Institute of Translational Hepatology (Beijing)

H & H Medical Group (Hong Kong)