肝硬化與肝癌的抗病毒藥物治療

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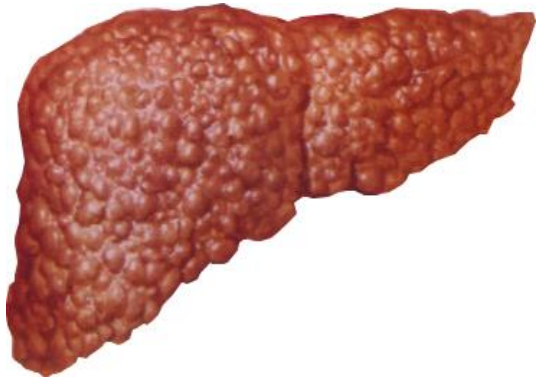
2023-01-05

現在已經可以逆轉肝硬化

如花變志玲

Mission impossible



逆轉肝硬化

Mission possible

肝細胞癌：一個病人，兩種疾病

每個肝癌病人的治療，
都要考慮到兩個病

(1) 肝癌本身

(2) 肝炎或肝硬化

60-85% 的肝癌病人有肝硬化

Outlines

- 如何診斷肝硬化
- 如何評估肝硬化的嚴重度
- 治療病毒性肝硬化的藥物
- 健保對於病毒性肝硬化的治療規定
- 治療病毒性肝硬化能改善Child-Pugh scores
- 治療病毒性肝硬化可以逆轉纖維化
- 治療病毒性肝硬化可以延長病人的存活
- 門靜脈高壓可能繼續存在
- 治療病毒性肝硬化可以降低肝癌的發生率
- 治療病毒性肝硬化可以降低肝癌的復發率

如何診斷肝硬化

肝硬化與纖維化有什麼不同

肝纖維化分期: F0, F1, F2, F3, F4

F0: 完全沒有纖維化
F1: 輕度纖維化
F2: 中度纖維化
F3: 重度纖維化
F4: 肝硬化

如何診斷肝硬化

- 超音波/CT/MRI
- 腹腔鏡
- 肝穿刺(切片)
- 抽血
- Fibroscan / ARFI

Fibrosis-4 (FIB-4)

Fibrosis-4 (FIB-4) Calculator

Share

The Fibrosis-4 score helps to estimate the amount of scarring in the liver. Enter the required values to calculate the FIB-4 value. It will appear in the oval on the far right (highlighted in yellow).

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count } (10^9/L) \times \sqrt{\text{ALT (U/L)}}} = 5.52$$

Age (years): 55

AST Level (U/L): 70

Platelet Count (10^9/L): 90

ALT (U/L): 60

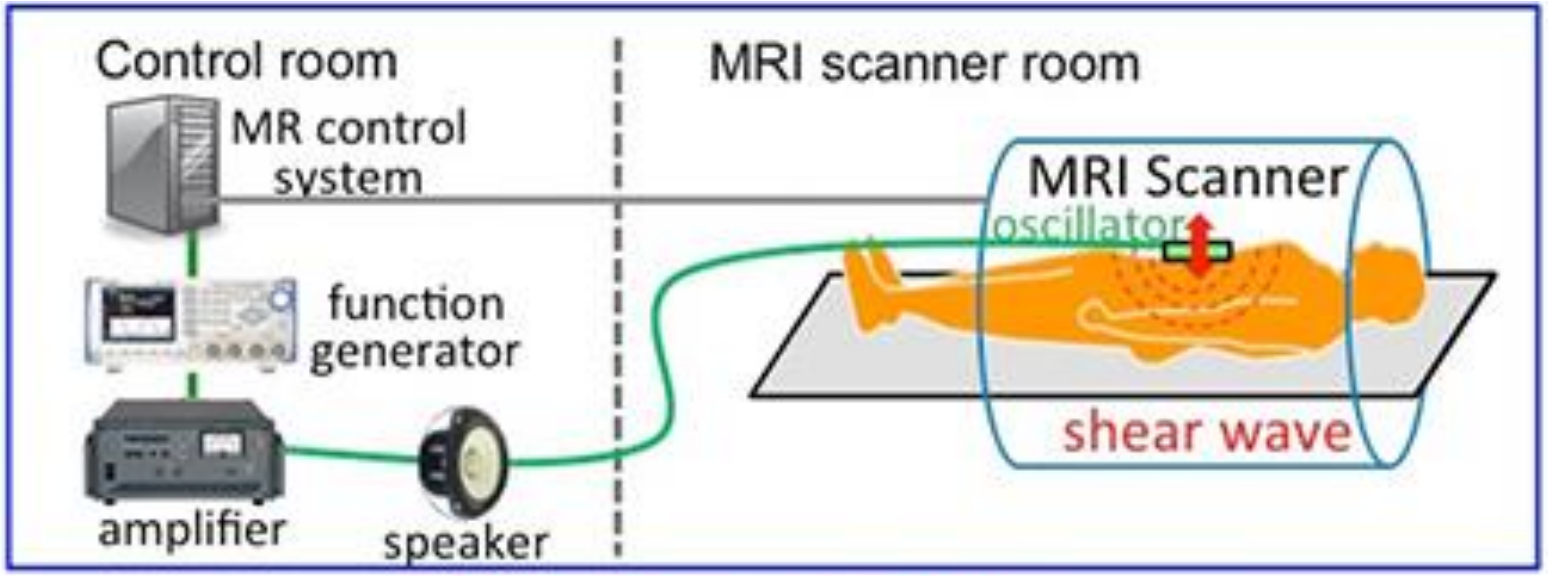
Interpretation:

Using a lower cutoff value of 1.45, a FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4-6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. In the patient cohort in which this formula was first validated, at least 70% patients had values <1.45 or >3.25. Authors argued that these individuals could potentially have avoided liver biopsy with an overall accuracy of 86%.

健保 F3 之定義為：FIB-4 >= 3.25

Vibration Controlled Transient Elastography (VCTE, Fibroscan)

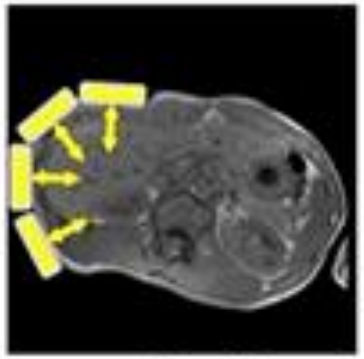
MR Elastography



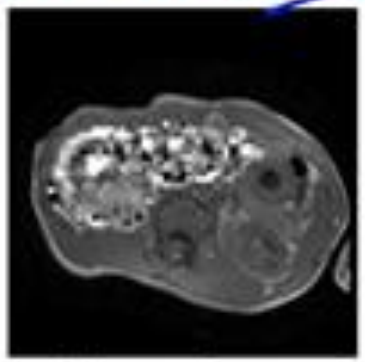
① External Driver (Oscillator)

② Pulse sequence with motion-sensitizing gradients (MSG)

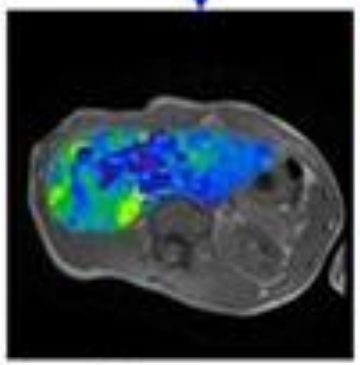
③ Inversion algorithm



Anatomical image



Wave image



Elastogram

評估肝硬化的嚴重度

Child-Pugh classification

	1	2	3
Albumin (g/dL)	＞3.5	2.8-3.5	<2.8
Bilirubin (mg/dL)	<2	2-3	>3
Prothrombin time (seconds increased)	1-3	4-6	>6
Ascites	Nil	Mild	≧moderate
Encephalopathy	Nil	mild	≧moderate

A: 5-6, B: 7-9, C: 10-15

MELD score

3.8 X $\log_e$(膽紅素[mg/dL])

✚ 11.2 X $\log_e$(INR,凝血酶原時間)

✚ 9.6 X $\log_e$(creatinine [mg/dL],肌酸酐,腎功能)

✚ 6.4 X (肝硬化的原因: 0 酒精性, 1 其他)

MELD Formula

The MELD score is calculated using the following formula:

$$\begin{aligned}\text{MELD Score} = \; & 0.957 \times \text{Log}_e(\text{creatinine mg/dL}) \\ & + 0.378 \times \text{Log}_e(\text{bilirubin mg/dL}) \\ & + 1.120 \times \text{Log}_e(\text{INR}) \\ & + 0.643^{*}\end{aligned}$$

Multiply the score by 10 and round to the nearest whole number

HEPATOLOGY 2001;33:464-470

MELD Calculator

http://optn.transplant.hrsa.gov/resources/professionalResources.asp?index=9

MELD Calculator (for ages 12 and older)

Date of Birth (mm/dd/yyyy)

05/01/1965

Bilirubin (mg/dl)

10

INR

1.5

Serum Creatinine (mg/dl)

1.5

Had dialysis twice, or 24 hours of CVVHD, within a week prior to the serum creatinine test?

○ Yes ◉ No

For patients who have had dialysis twice, or 24 hours of CVVHD, within the last week, the creatinine value will be automatically set to 4 mg/dl.

Calculate →

MELD Score 24

. 2021 Aug 5;3(5):100347
Review

ALBI grade

JHEP|Reports

JHEP Rep 2021;3(5):100347

ALBI grade: Evidence for an improved model for liver functional estimation in patients with hepatocellular carcinoma

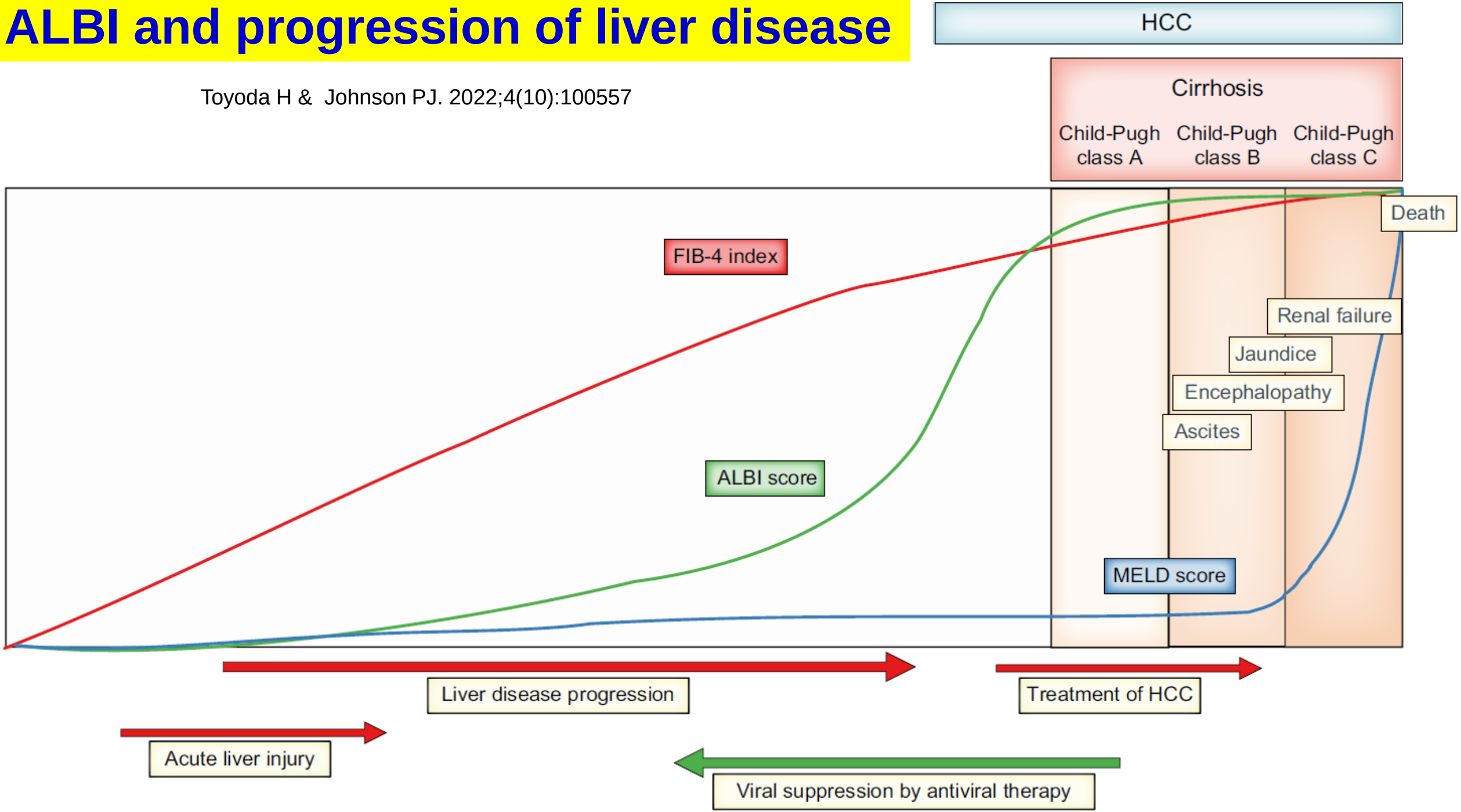
Coskun O. Demirtas,[1,†] Antonio D'Alessio,[2,3,†] Lorenza Rimassa,[3,4] Rohini Sharma,[2] David J. Pinato[2,5,*]

ALBI grade
([log10 bilirubin (in lmol/L) × 0.66] + [albumin (in g/L) × –0.085])

grades 1 = <− –2.60,
grades 2 >–2.60 to <−–1.39
grades 3 > –1.39

ALBI and progression of liver disease

Toyoda H & Johnson PJ. 2022;4(10):100557



治療病毒性
肝硬化的藥物

治療B型肝炎的藥物

- ✓ 長效型干擾素
- ✓ 干安能 (lamivudine, Zeffix)
- ✓ 干適能 (adefovir, Hepsera)
- ✓ 貝樂克 (entecavir, Baraclude)
- ✓ 喜必福 (telbivudine, Sebivo)
- ✓ 惠立妥 (tenofovir, Viread)
- ✓ 韋立得 (tenofovir alafenamide, Vemlidy)

在台灣已經上市的C型肝炎口服藥

- 坦克干(Daklinza)+速威干(Sunvepra)
- 維建樂(Viekirax) +易奇瑞(Exviera)
- 夏奉寧(Harvoni)
- 索華迪(Sovaldi)
- 賀肝樂(Zepatier)
- 艾百樂(Maviret)
- 宜譜莎(Epclusa)

治療病毒性肝硬化能改善Child-Pugh scores
MELD scores

ETV-048: Improvement in MELD/CTP Scores

Parameter	Wk 24		Wk 48	
	ETV	ADV	ETV	ADV
Mean **MELD** score change from BL (SE)	-2.0 (0.45)	-0.9 (0.46)	**-2.6** (0.62)	-1.7 (0.50)
CTP score improvement or no worsening,* n/N (%)	66/100 (66)	65/91 (71)	61/100 (61)	61/91 (67)
CTP score ≥ 2 point reduction,* n/N (%)	32/100 (32)	22/91 (24)	35/100 (**35**)	25/91 (27)
CTP class improvement,† n/N (%)	25/93 (27)	22/81 (27)	35/93 (38)	29/81 (36)

*Noncompleter = failure.
†CTP class C/B to A only.

Liaw YF, et al. Hepatology. 2011;54:91-100.

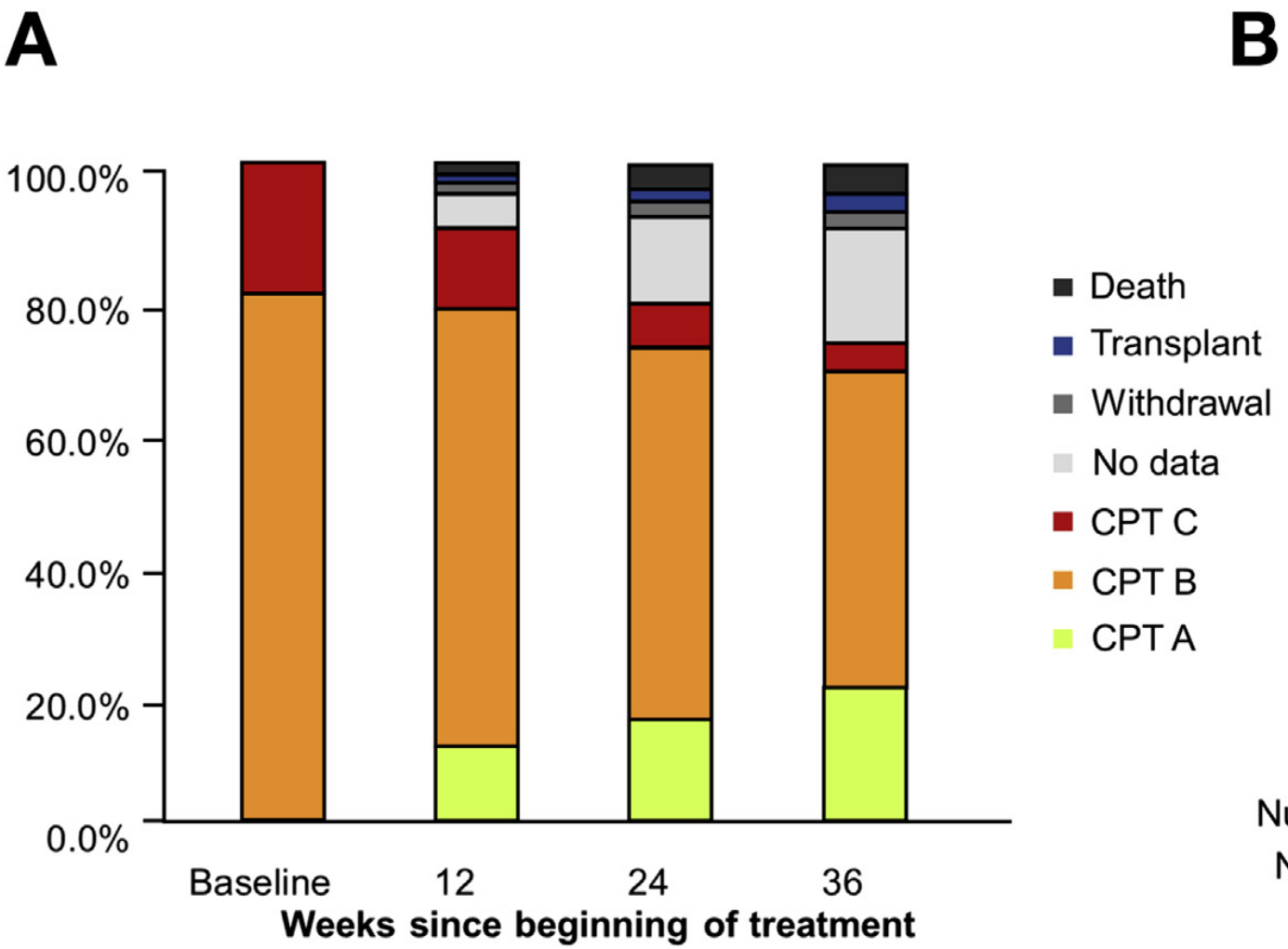
Determinants of re-compensation after antiviral therapy BC2AID score (HBV)

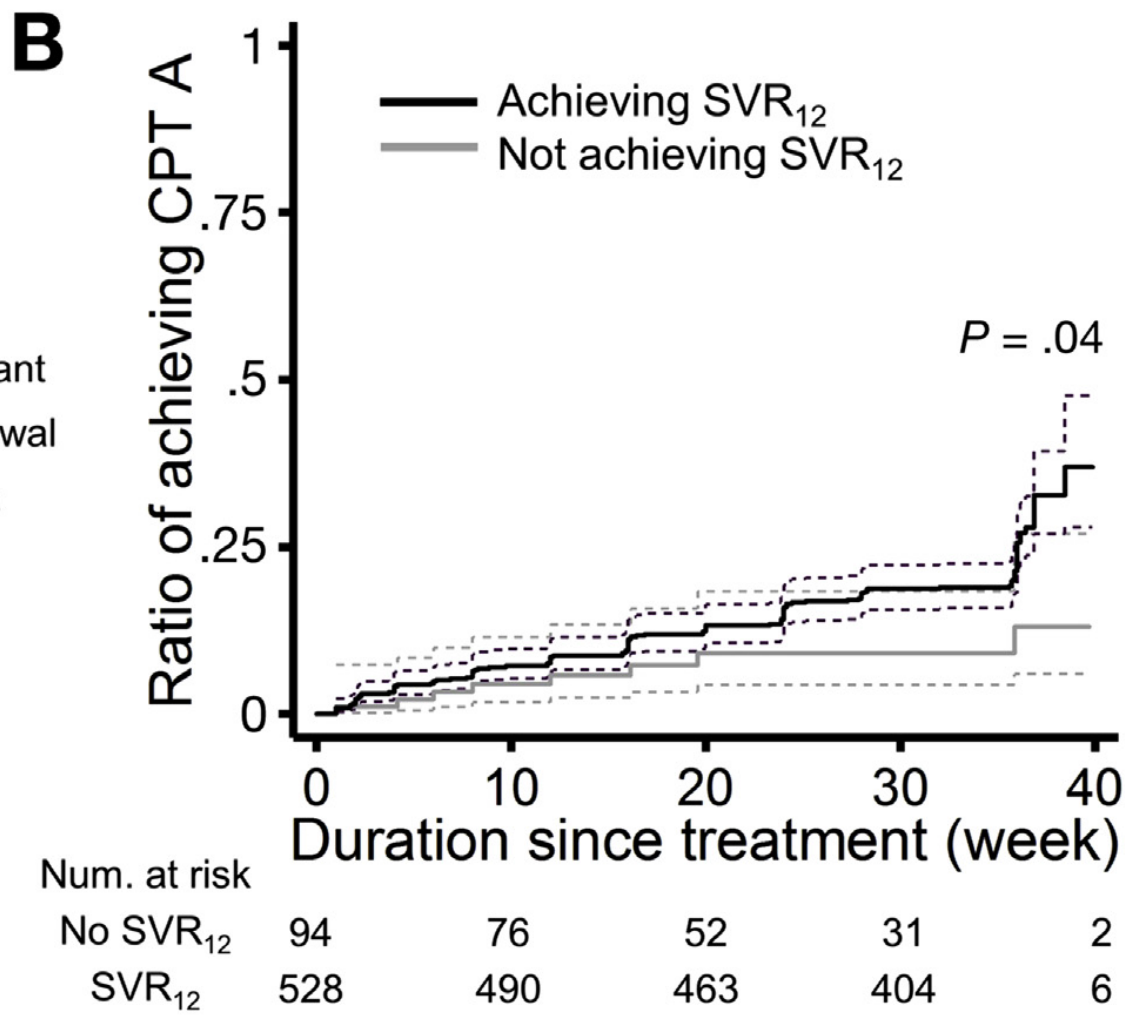
TABLE 3 Construction of BC2AID scoring model and its prognostic performance for predicting re-compensation within 1 year of NUC therapy in comparison with conventional models

Constituents of BC2AID	β-coefficient	Adjusted SHR (95% CI)	*P*-value	Score
Bilirubin ≤5 mg/dL	0.778	2.18 (1.15-4.11)	0.016	1
Lack of severe Complications	1.022	2.78 (1.19-6.48)	0.018	1
AFP ≥ 50 ng/mL	0.933	2.54 (1.68-3.84)	<0.001	1
ALT ≥ 200 IU/L	0.962	2.62 (1.33-5.16)	0.006	1
INR ≤ 1.5	0.861	2.37 (1.55-3.60)	<0.001	1
Duration of decompensation before NUC therapy <6 mo	1.567	4.79 (1.01-22.76)	0.049	2

Kim TH et al., Aliment Pharmacol Ther 2022;55(1):83-9

DAA Improves Child Score in Decompensated Liver Cirrhosis

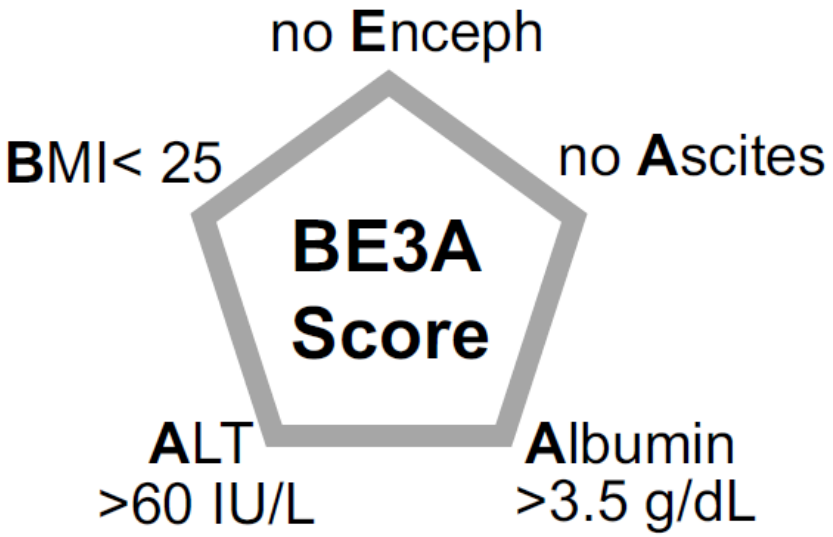


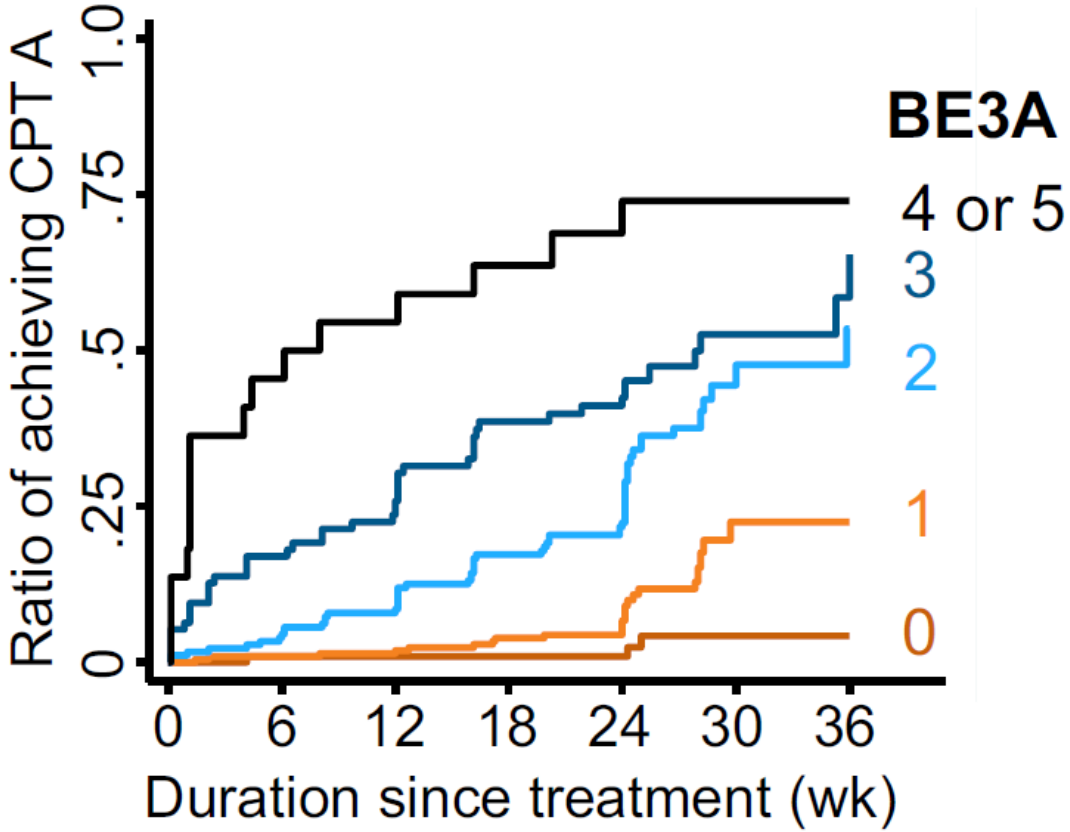


El-Sherif O et al, Gastroenterology 2018;154:2111–2121

DAA Improves Child Score in Decompensated Liver Cirrhosis

Assign 1 point to each of the following





El-Sherif O et al, Gastroenterology 2018;154:2111–2121

失代償的病毒性肝硬化病人，
最好在可以做肝臟移植的中心治療。

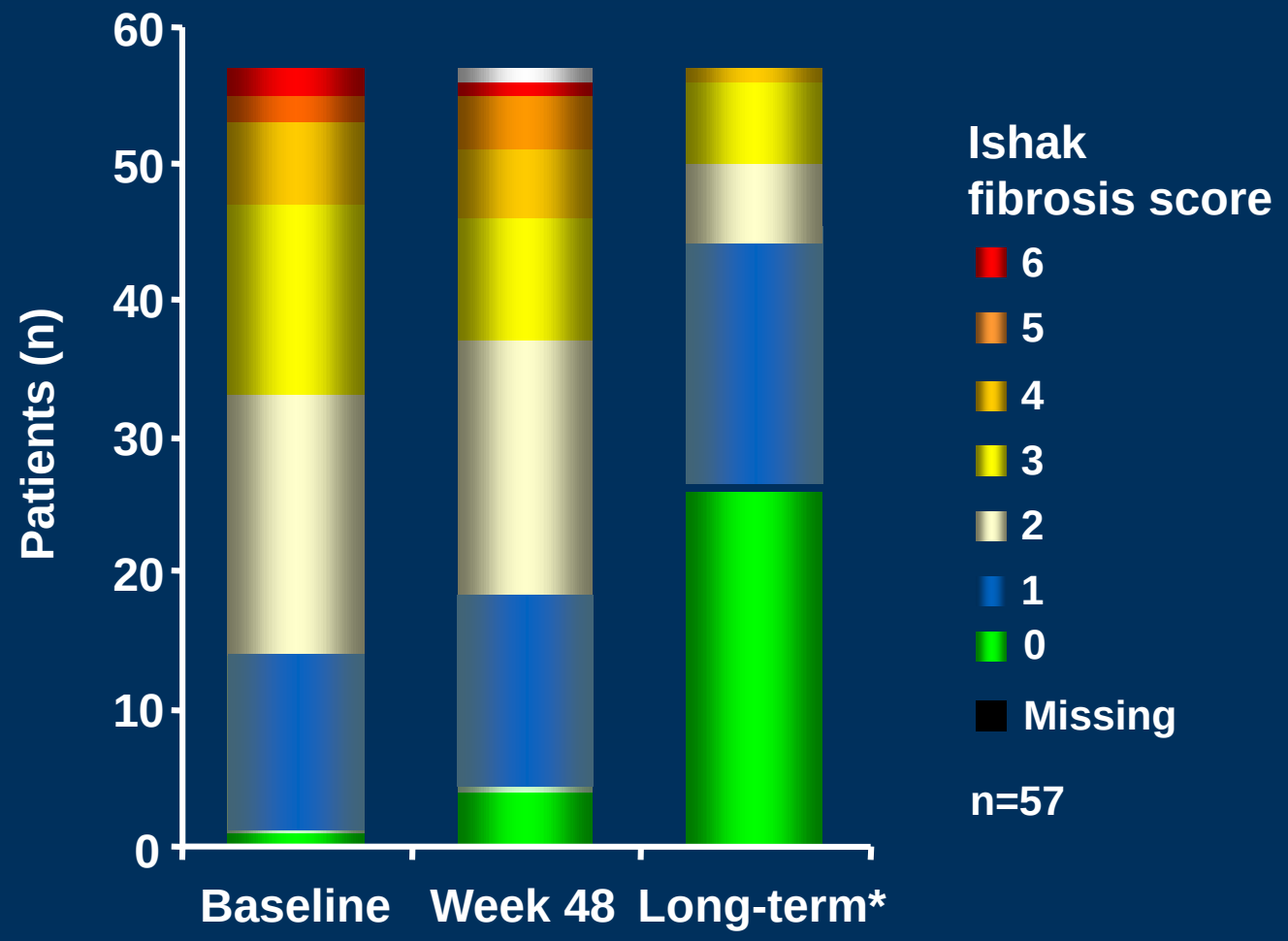
已經開放所有醫師都可以治療C型肝炎

- Decompensated liver cirrhosis
- HCC

以上兩種情況，建議轉醫院，不要留在基層

治療病毒性肝硬化
可以逆轉纖維化

ETV Long term treatment Distribution of Ishak fibrosis scores at baseline, Year 1 and Years 3–7

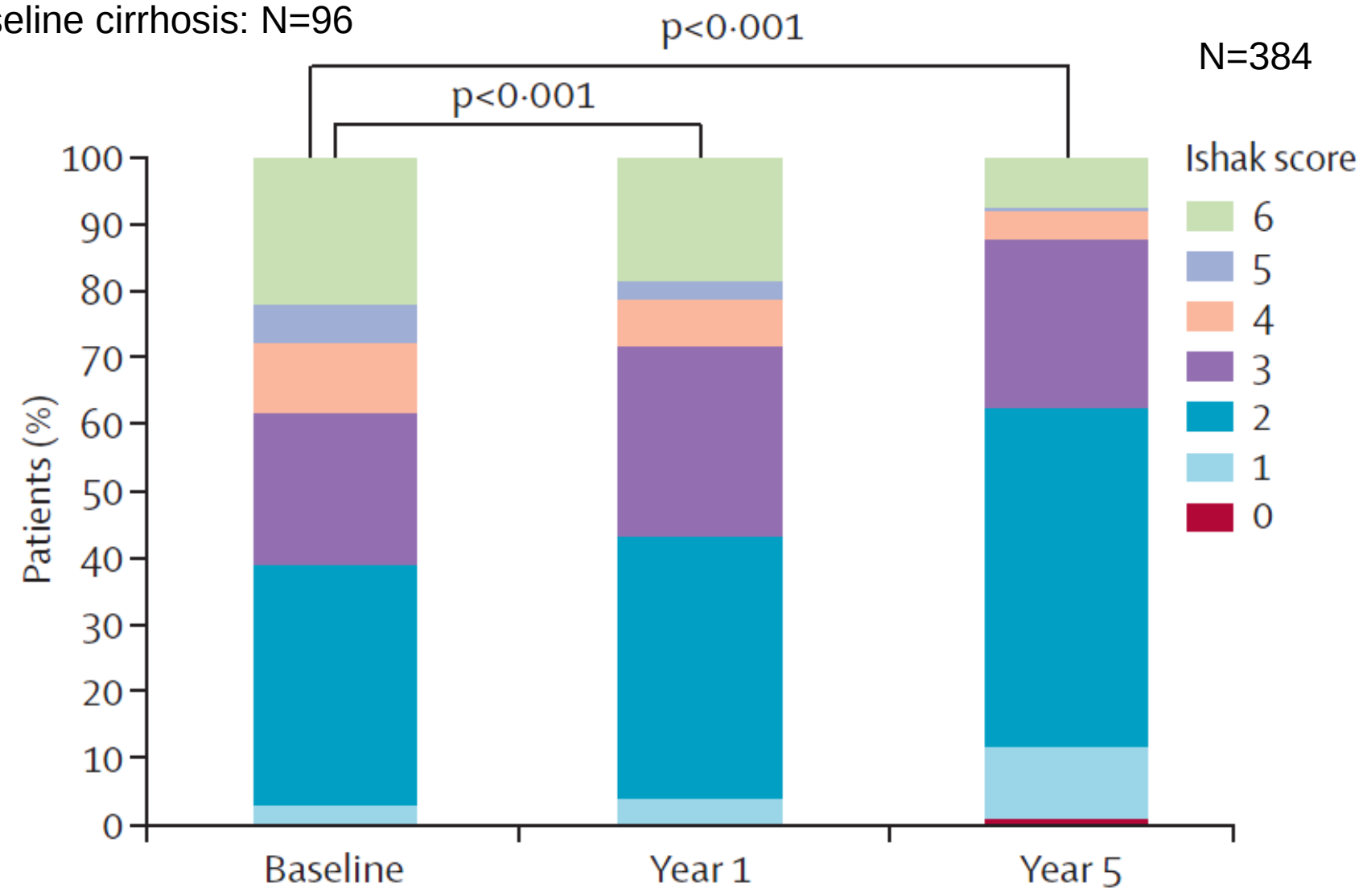


* Median time of long-term biopsy: 280 weeks (range: 144–316 weeks).

Chang TT et al., HEPATOLOGY 2010;52:886-893

Improvement of hepatic fibrosis after 5-year TDF

Baseline cirrhosis: N=96



Marcellin P et al., Lancet 2013; 381: 468–75

Comparison of Liver Fibrosis Stage in patients of CHC reaching SVR

	Fibrosis stage[a]				
	Post-treatment				
Pretreatment	F0	F1	F2	F3	F4
F0	1	2	0	0	0
F1	14	16	7	0	0
F2	7	23	12	2	0
F3	0	5	12	7	4
F4	0	1	2	6	5
Total (n/N) (%) (95% CI)					

Fibrosis improved in 56%, stable in 32%, Deteriorated in 12%

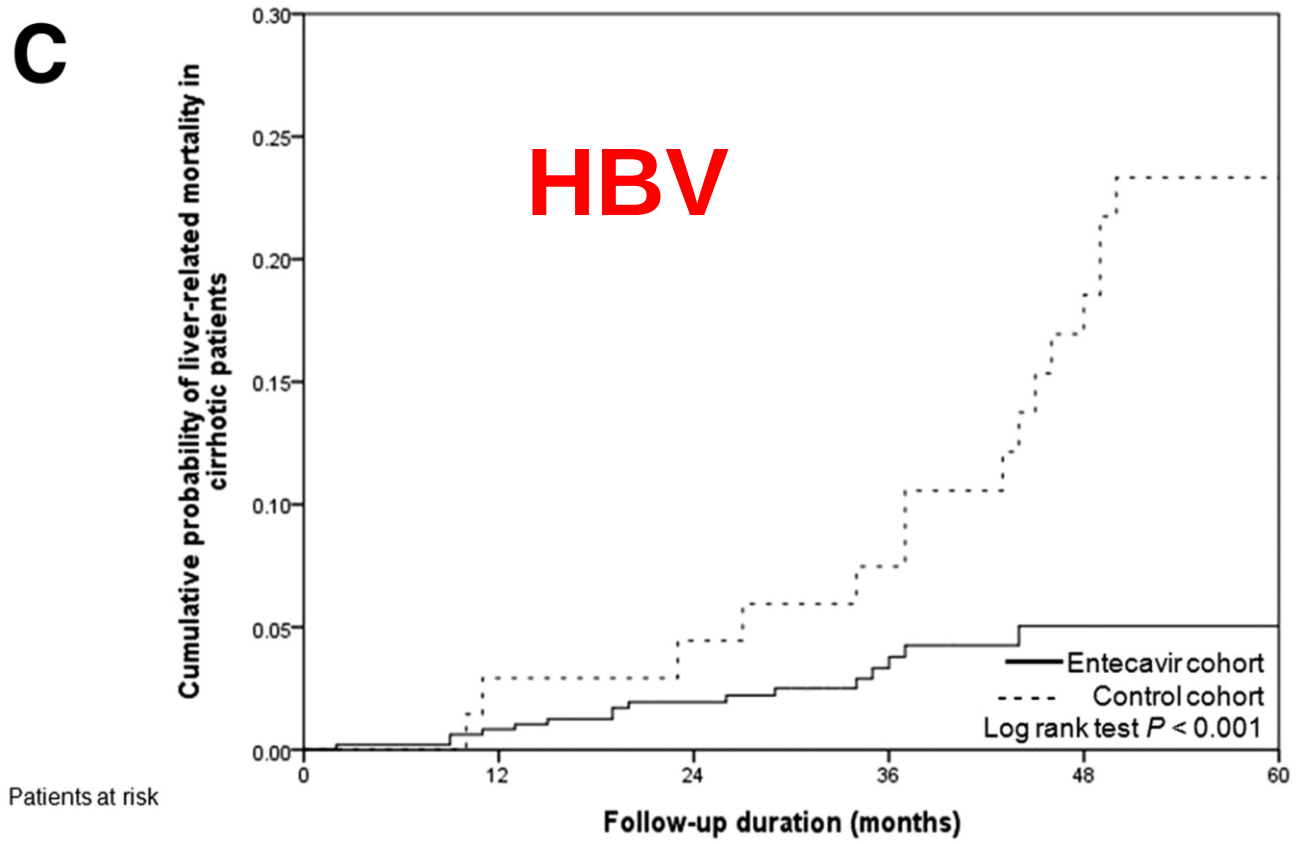
Regression of cirrhosis in 9/14 patients

Maylin S. et al., GASTROENTEROLOGY 2008;135:821–829

治療病毒性肝硬化
可以延長病人的存活

Cumulative probability of liver-related mortality in cirrhotic patients

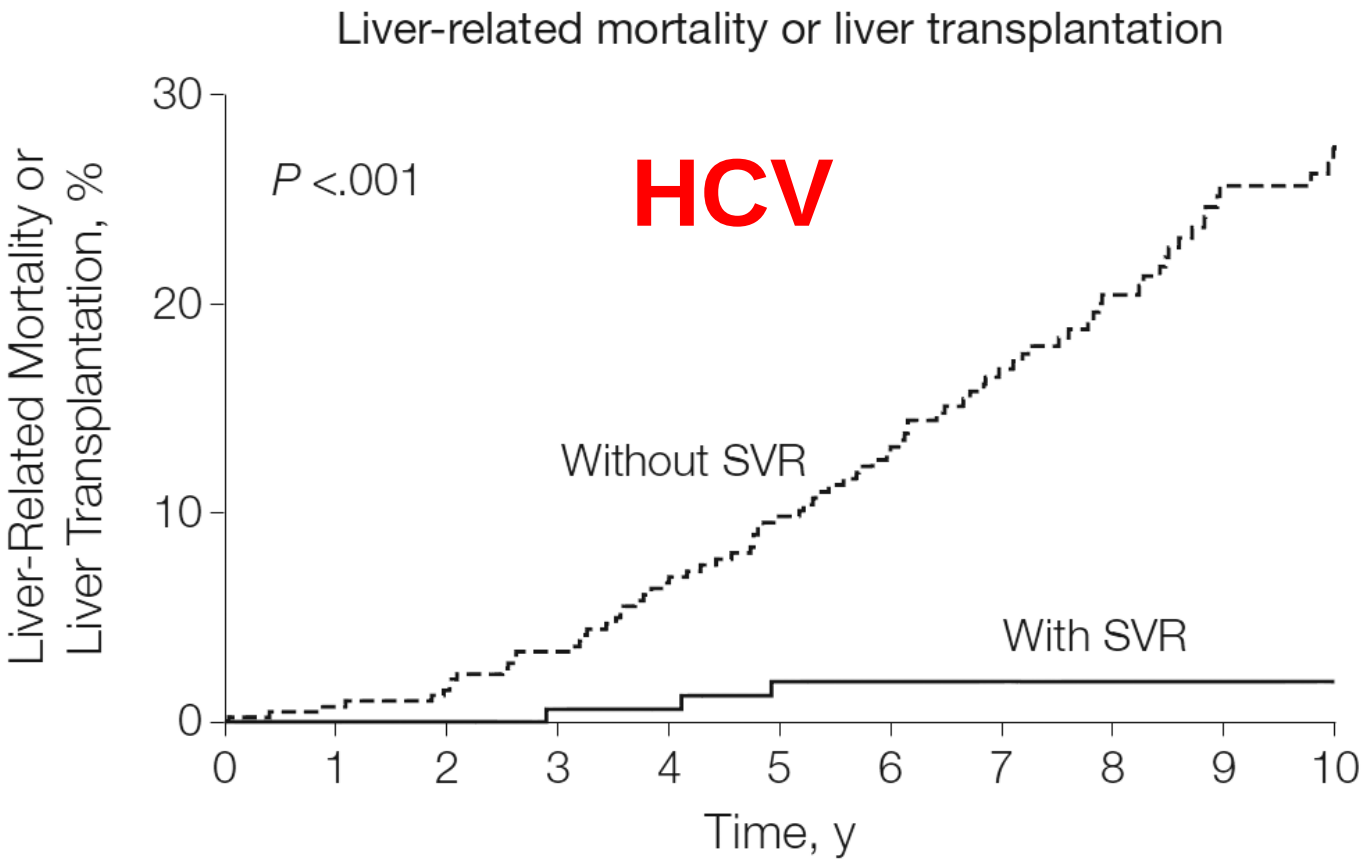
Liver-related mortality: death related to cirrhosis complications and/or HCC



Patients at risk						
Entecavir cohort	482	473	383	214	93	23
Control cohort	69	66	63	61	52	48

Wong GL et al. HEPATOLOGY 2013;58:1537-1547

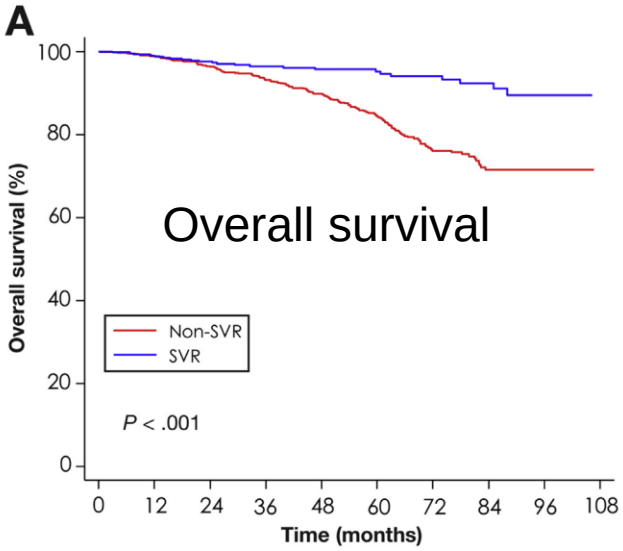
SVR and Liver-related mortality



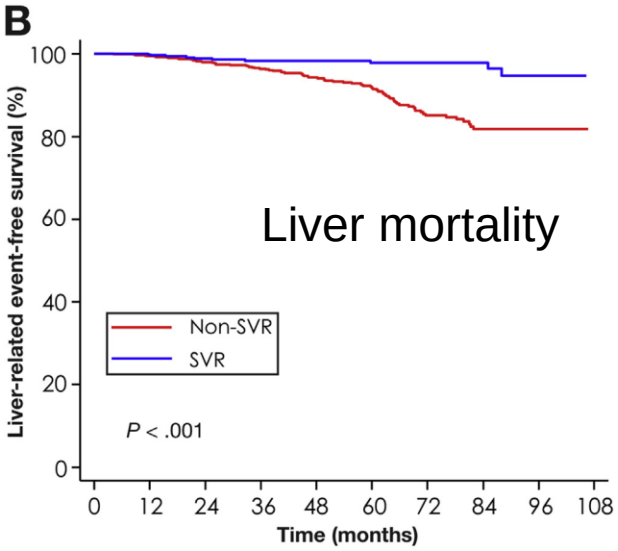
No. at risk											
Without SVR	405	392	380	358	334	305	277	229	187	146	119
With SVR	192	181	168	162	155	144	125	88	56	40	28

Van der Meer AJ et al., JAMA 2012-;308:2584-2593

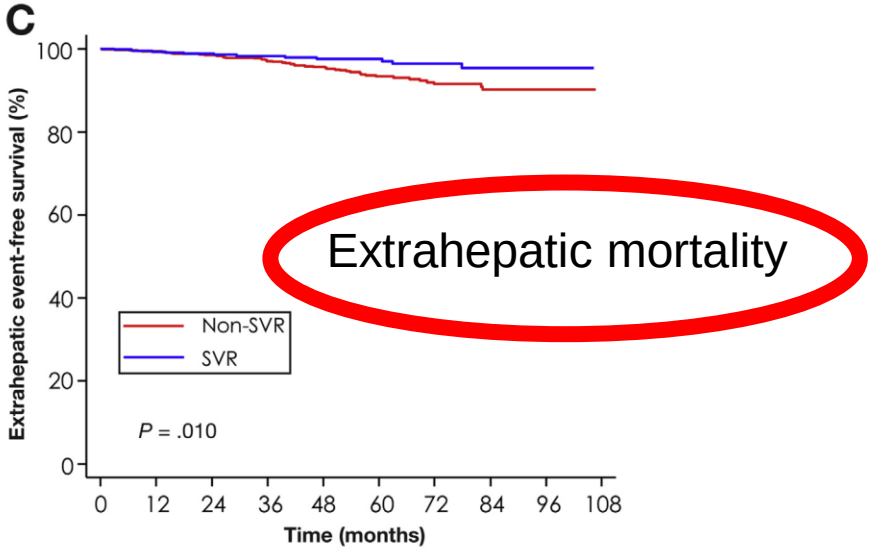
SVR improves survival in HCV-LC



	Number at risk (events)																	
Non-SVR	1029	(11)	877	(20)	765	(24)	622	(20)	496	(26)	349	(29)	220	(9)	122	(0)	33	(0)	3
SVR	667	(6)	492	(6)	389	(4)	303	(2)	230	(1)	180	(2)	129	(2)	78	(2)	32	(0)	3



	Number at risk (events)																	
Non-SVR	1014	(5)	863	(12)	752	(11)	612	(12)	486	(11)	344	(21)	218	(6)	122	(0)	33	(0)	3
SVR	665	(1)	491	(4)	388	(2)	302	(0)	229	(1)	179	(0)	128	(0)	78	(2)	32	(0)	3



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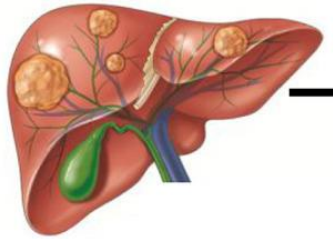
SVR	665	(4)	491	(2)	388	(2)	302	(2)	229	(0)	179	(2)	128	(1)	78	(0)	32	(0)	3

Nahon P et al., Gastroenterology 2017;152:142–156

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

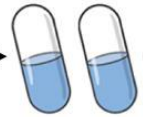
Does DAA therapy improve survival in patients with a history of complete response to HCC treatment?

HCV-associated HCC



Complete response to HCC treatment

DAA Therapy



Impact on survival?

Design:

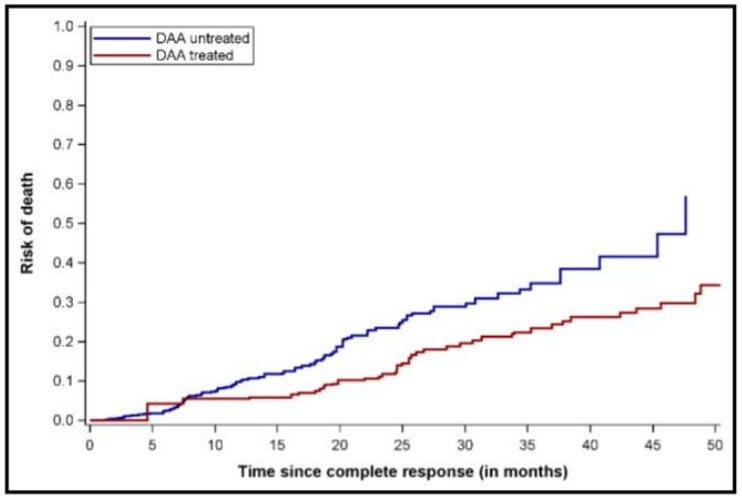
31 centers in North America including 797 patients with HCV-associated HCC with complete radiographic response

- 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

Singal AG et al. *Gastroenterology*. 2019

Gastroenterology

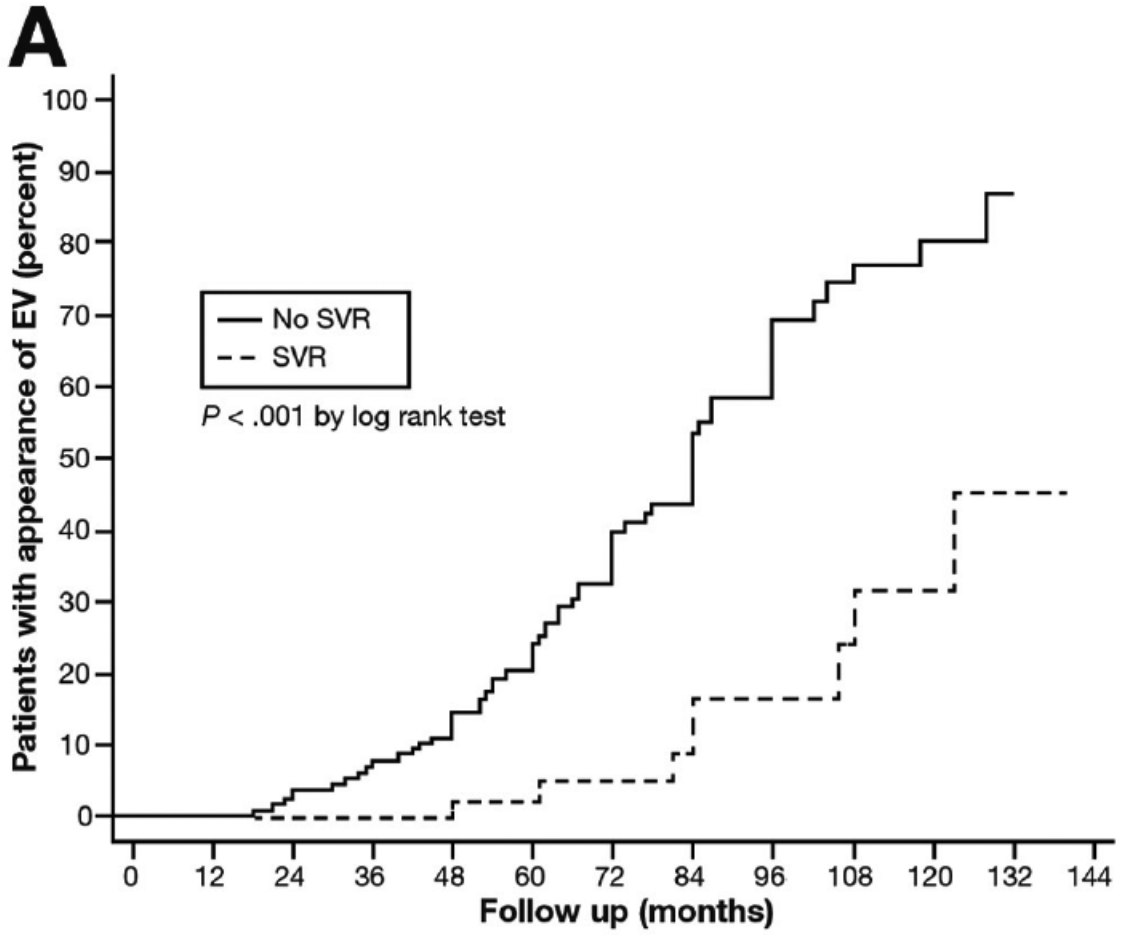
治療病毒性肝硬化後
仍須注意門靜脈高壓

肝硬化

- 纖維化
- 門靜脈高壓

New Esophageal Varices may Still Happen After HCV SVR

Di Marco V et al., Gastroenterology 2016;151:130–139



Number at risk

Group: No SVR	136	136	128	115	94	75	46	29	15	8	3	0	0
Group: SVR	65	64	61	54	42	35	27	18	13	8	5	2	0

	Stages of chronic liver disease				
	No cirrhosis	Compensated cirrhosis			Decompensated cirrhosis
Clinical features (ascites, VH or HE)	No	No			Yes
HVPG (mmHg)	3-5	5-10	>10 higher likelihood of decompensation		>10; >20 worse outcomes in VH
Portal hypertension	None	Mild	Clinically significant (CSPH)		CSPH by definition
Varices/collaterals	No	No	± (if +, CSPH by definition)		± or VH
Liver stiffness (kPa)	<5 to 10	10-20 (grey zone)	>20-25	>25	Not necessary
Platelet count (K/mm^3)	Any	Any	<150	Any	Usually <150

CSPH, clinically significant portal hypertension
HE, hepatic encephalopathy
VH, variceal hemorrhage.

Guadalupe Garcia-Tsao & Juan G Abraldes. Gastroenterology 2021;161(3):770-773

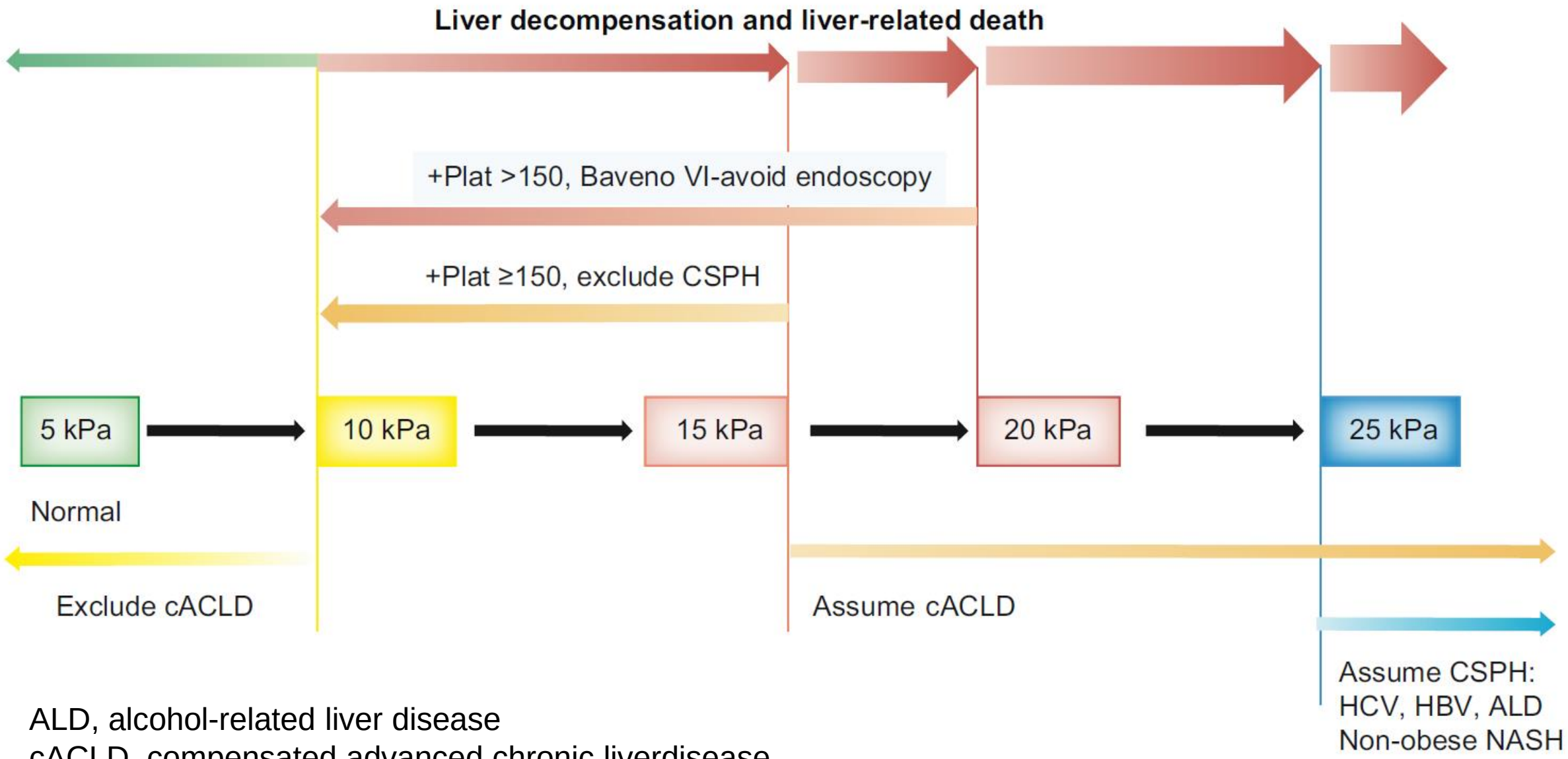
Seminar

JOURNAL
OF HEPATOLOGY

Baveno VII – Renewing consensus in portal hypertension

Roberto de Franchis[1,*], Jaime Bosch[2,3], Guadalupe Garcia-Tsao[4,5], Thomas Reiberger[6,7], Cristina Ripoll[8], on behalf of the Baveno VII Faculty[§]

JH 2022;76:959–974



ALD, alcohol-related liver disease
cACLD, compensated advanced chronic liverdisease
CSPH, clinically significant portal hypertension
NASH, non-alcoholic steatohepatitis.

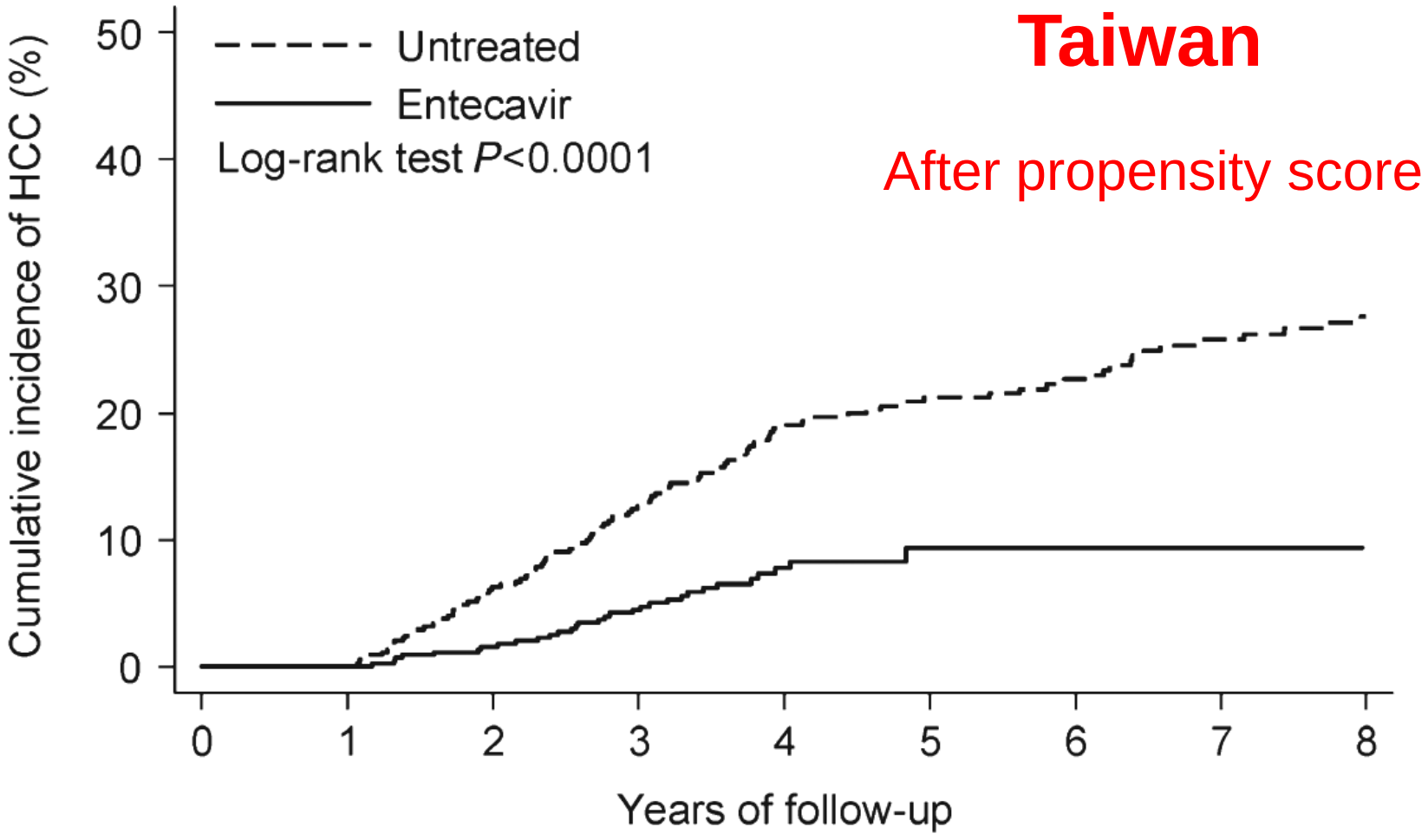
de Franchis R et al., JH 2022;76:959–974

3.7 In the absence of co-factors, patients with HCV-induced cACLD who achieve SVR and show consistent posttreatment improvements with LSM values of <12 kPa and PLT >150x10^9/L can be discharged from portal hypertension surveillance (LSM and endoscopy), as they do not have CSPH and are at negligible risk of hepatic decompensation. In these patients, HCC surveillance should continue until further data is available. (B.1)

de Franchis R et al., JH 2022;76:959–974

治療病毒性肝硬化
可以降低肝癌的發生率

Four-year ETV therapy reduces HCC



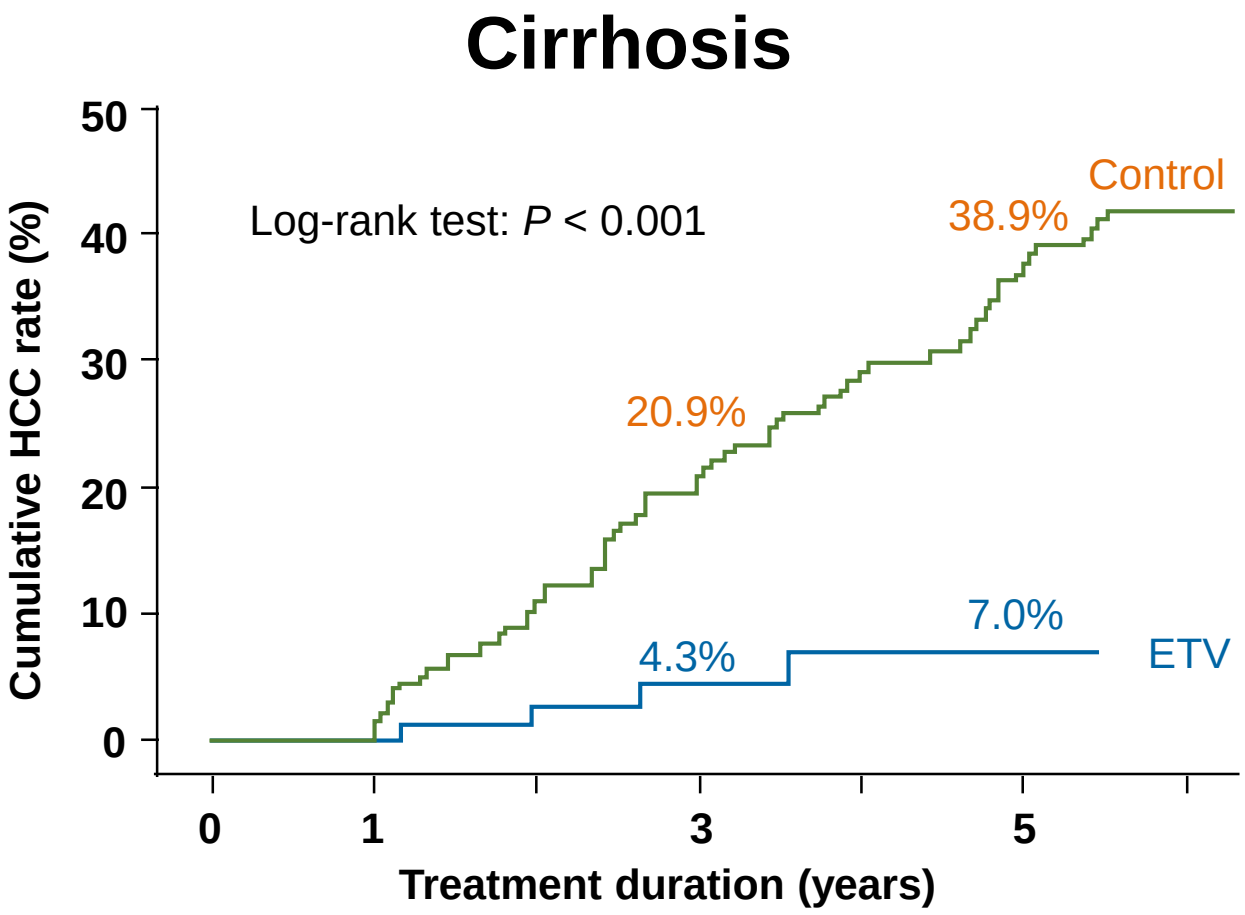
Number at risk

Untreated	450	450	414	351	284	243	211	172	143
Entecavir	450	450	443	363	206	69	37	15	1

Su TH et al., Liver International 2016; 36: 1755–1764

Reduction in HCC incidence with ETV in cirrhotic patients

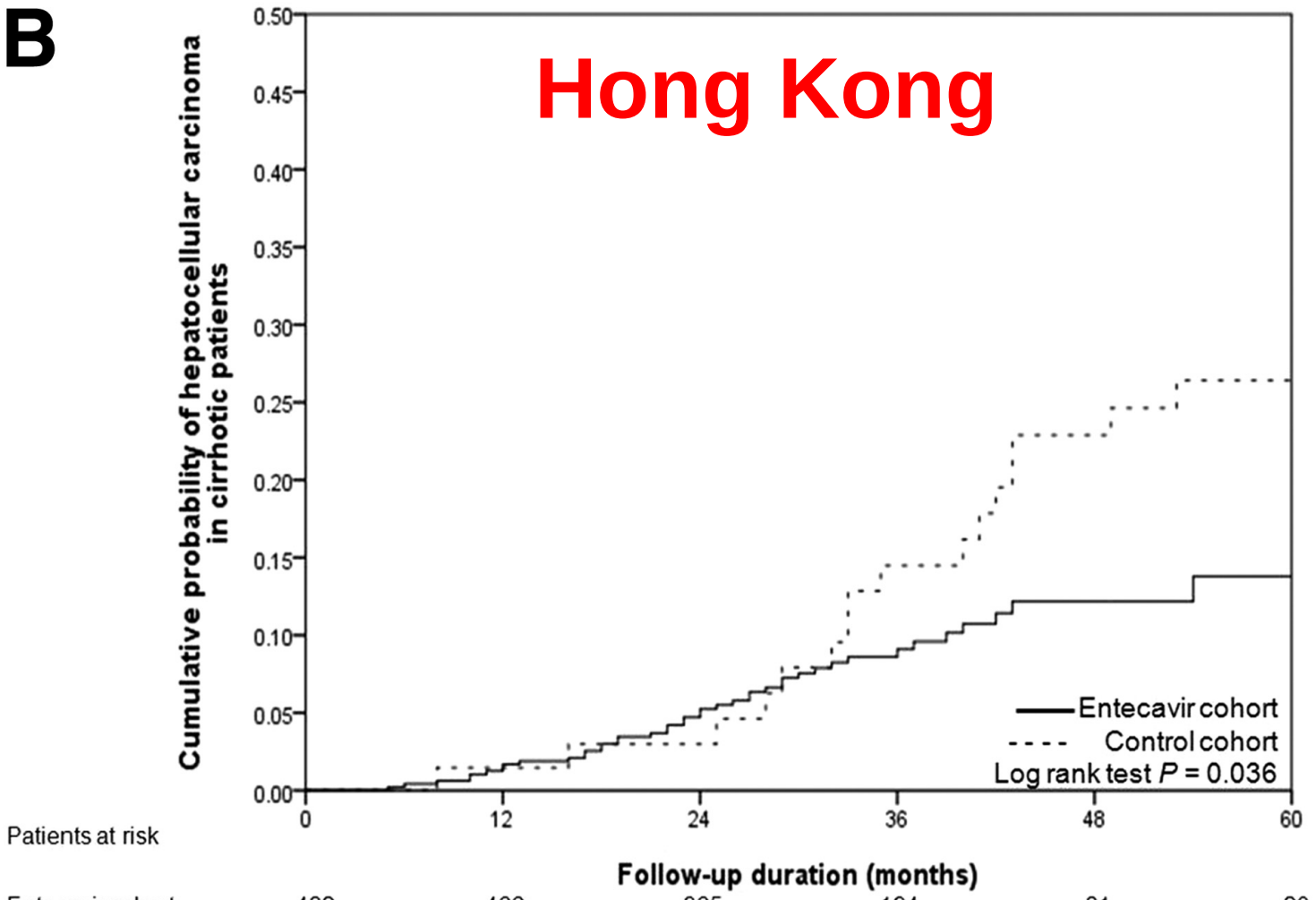
Japan



No. at risk						
ETV	79	79	72	53	35	17
Control	85	85	76	65	54	47

Hosaka T et al. Hepatology 2013;58:98-107

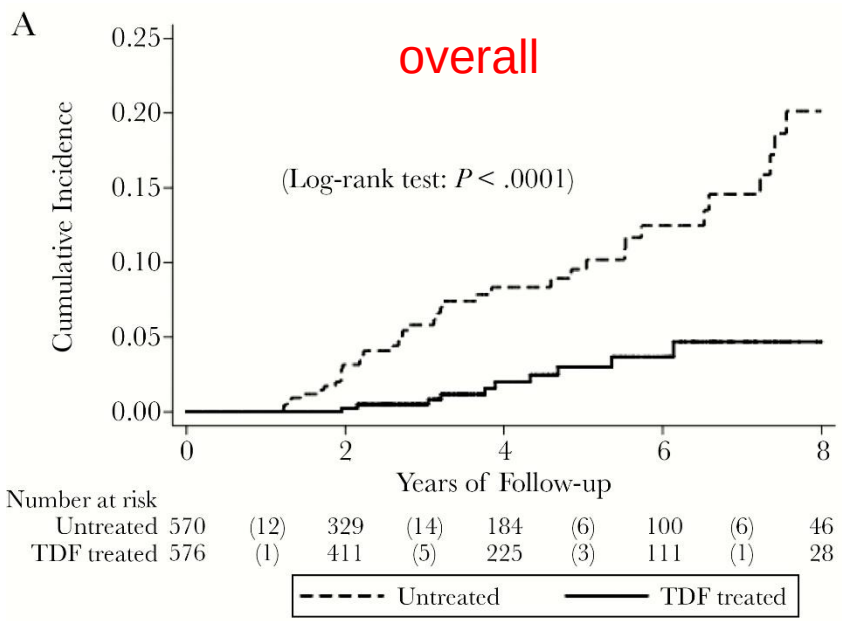
Cumulative probability of HCC in cirrhotic patients

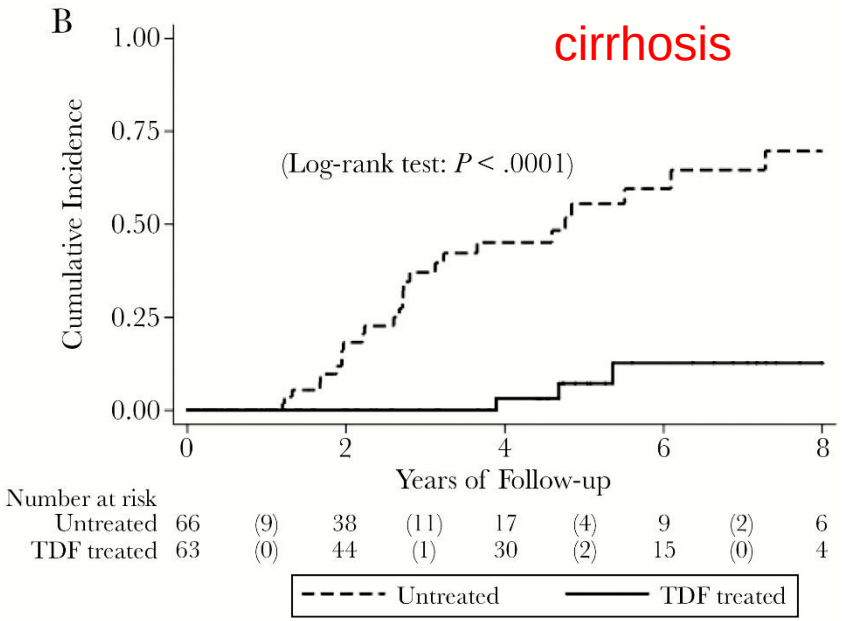


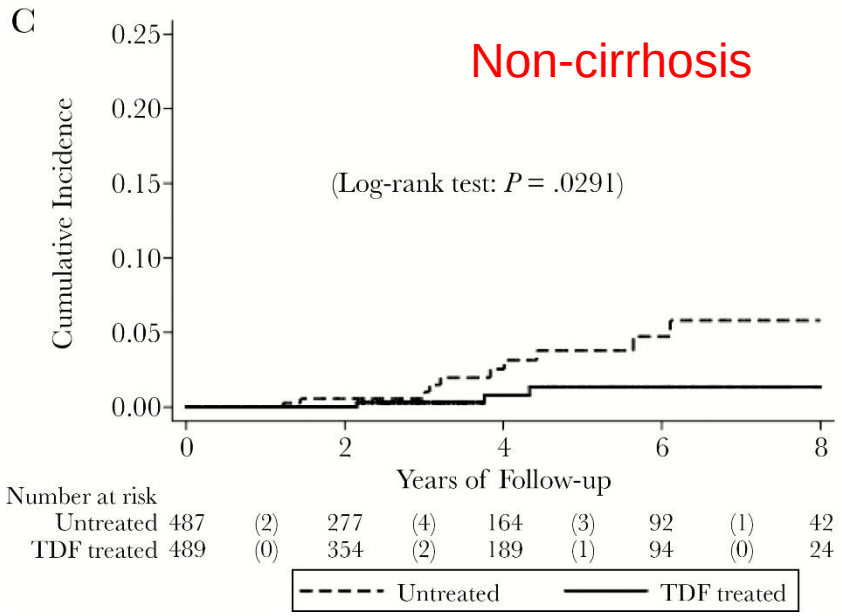
Patients at risk						
Entecavir cohort	482	466	365	194	81	20
Control cohort	69	65	60	52	45	41

Wong GL et al. HEPATOLOGY 2013;58:1537-1547

TDF reduced HCC incidence in HBV-LC



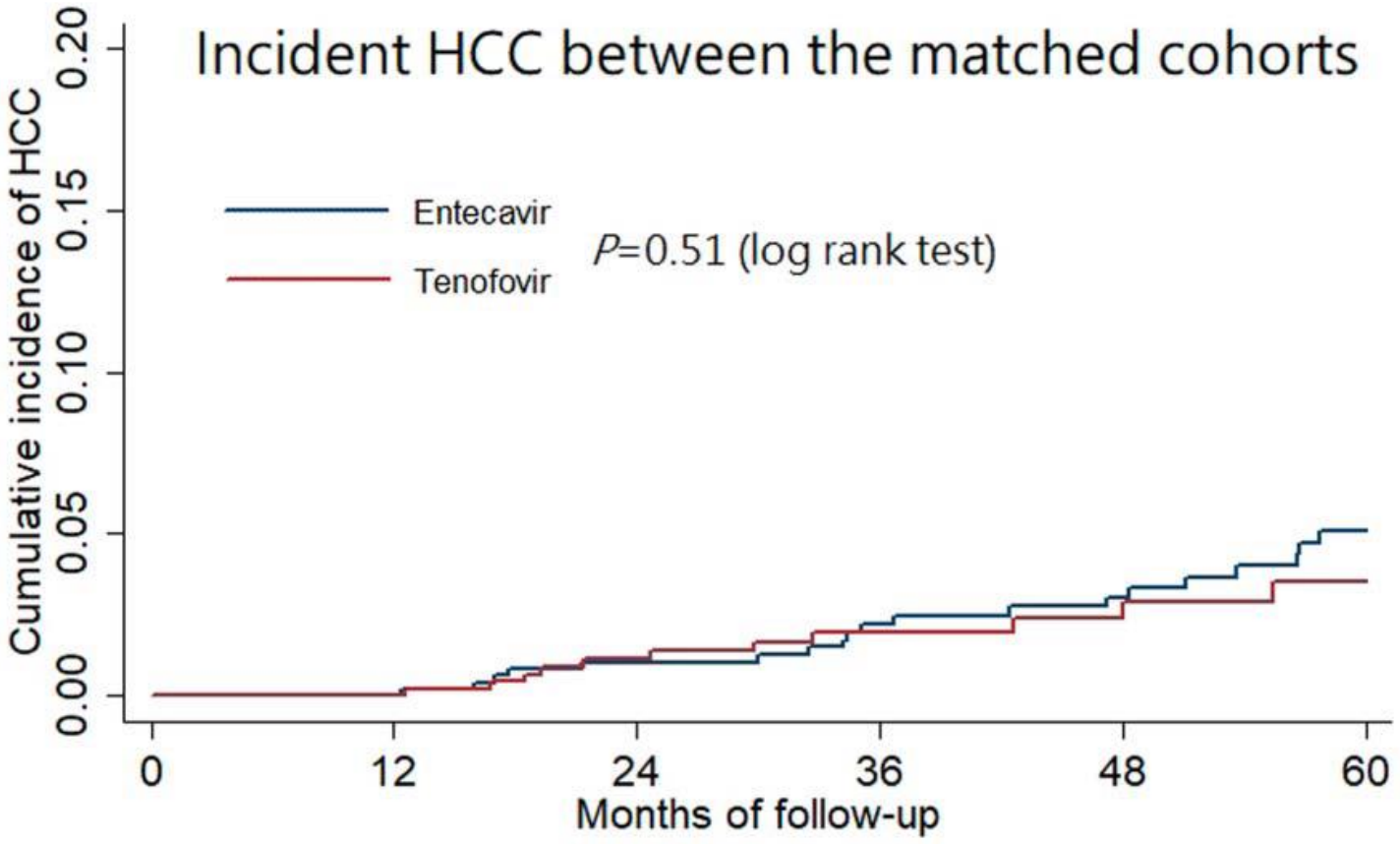




8 years follow-up
Propensity Score–Matched Study

Nguyen et al, JID 2019;219:10–8

No significant difference in the incidences of HCC between ETV and TDF cohorts



Number at risk

Entecavir	520	520	456	401	319	247
Tenofovir	520	520	389	303	191	116

Including LC and non-LC

Yao-Chun Hsu et al. Am J Gastroenterol 2020;115:271–280

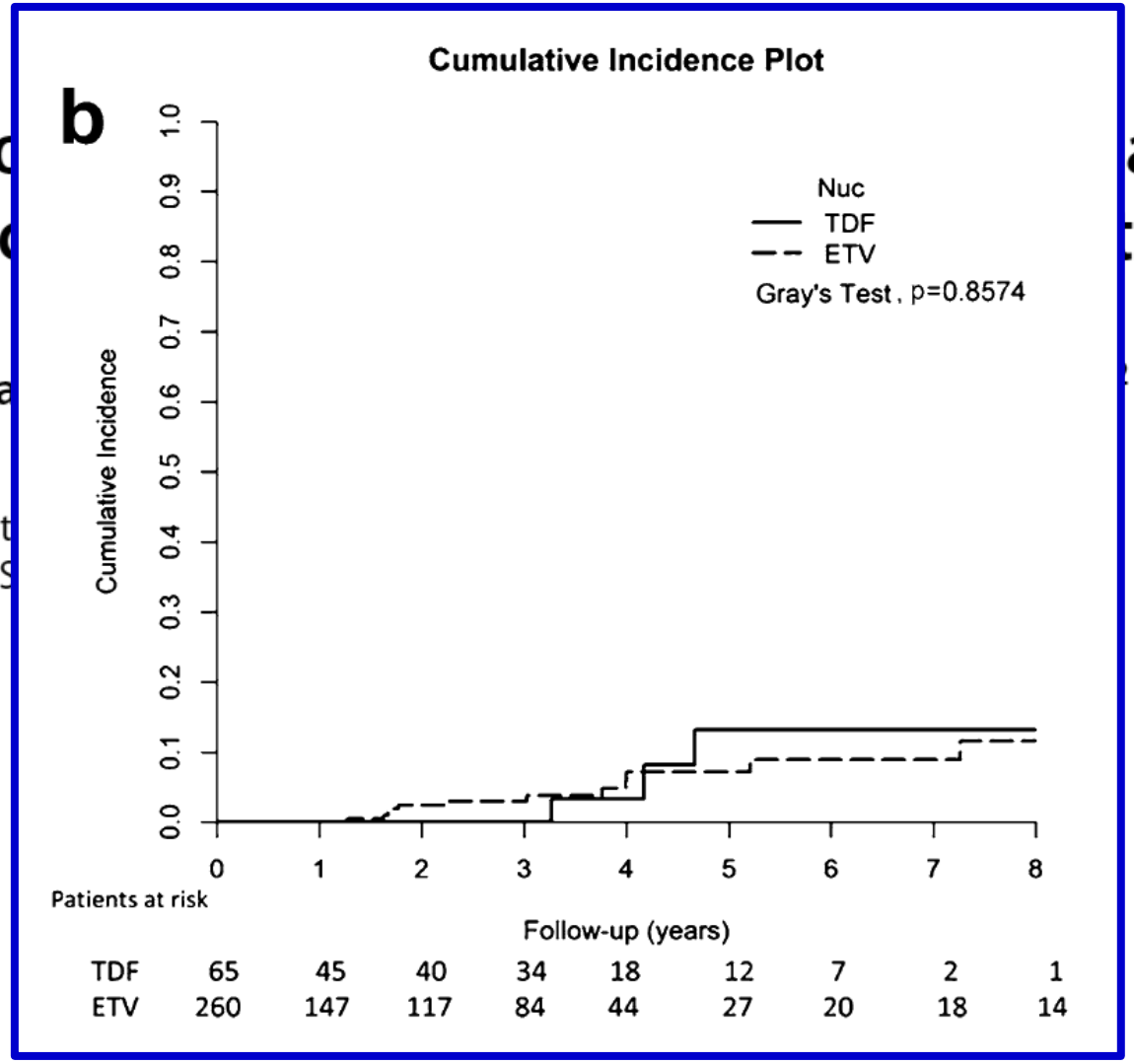
Hepatology International (2022) 16:799–806
https://doi.org/10.1007/s12072-022-10357-0

ORIGINAL ARTICLE

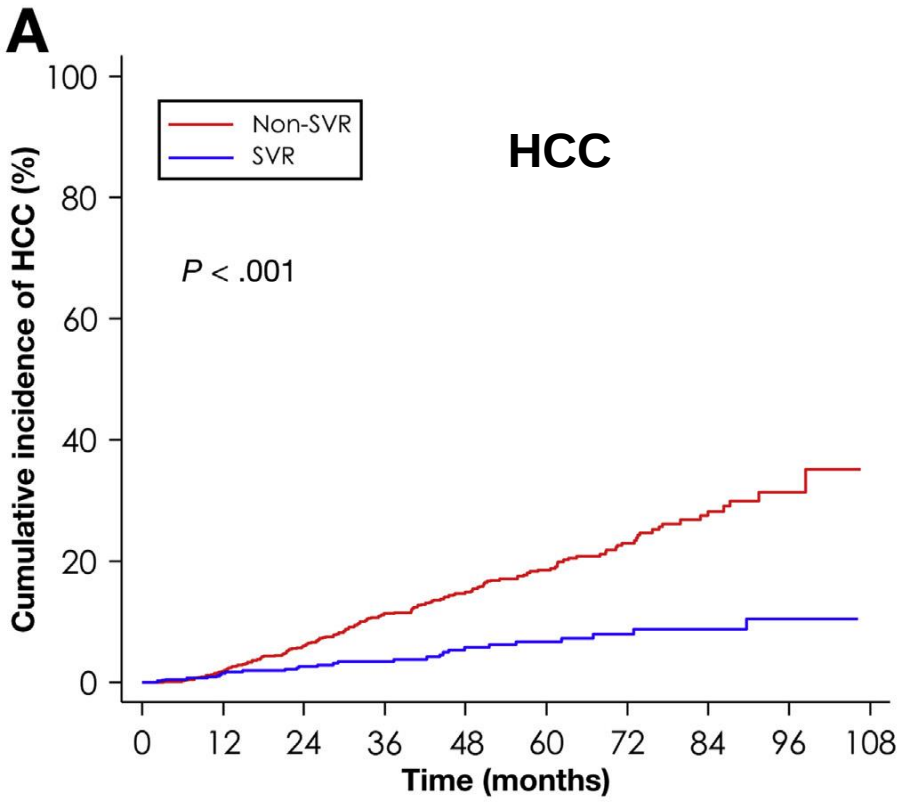
Comparable outco atitis B patients treated with ente tudy

Kuan-Chieh Lee[1,2] · Jur-Sha · Yun-Fan Liaw[1,2]

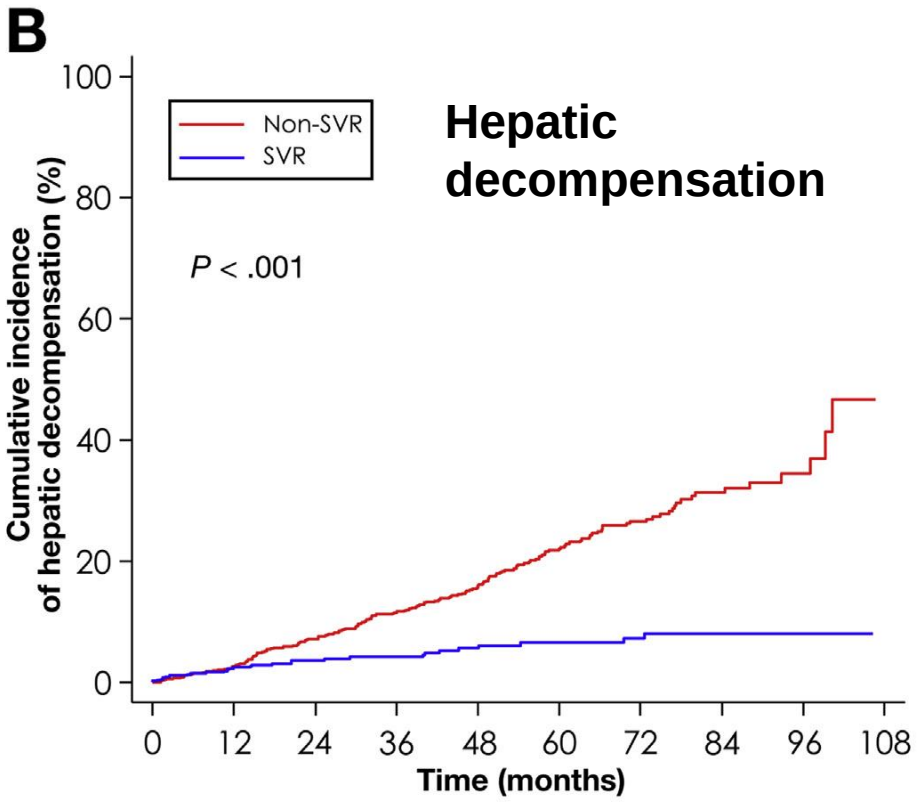
Received: 28 January 2022 / Accept



SVR decreases incidence of HCC and hepatic decompensation in HCV-LC



	Number at risk (events)																	
Non-SVR	1033 (17)	866 (34)	731 (38)	562 (20)	447 (17)	311 (14)	192 (10)	99 (3)	26 (1)	2
SVR	653 (8)	483 (5)	381 (3)	296 (6)	221 (2)	174 (2)	123 (1)	73 (1)	30 (0)	3



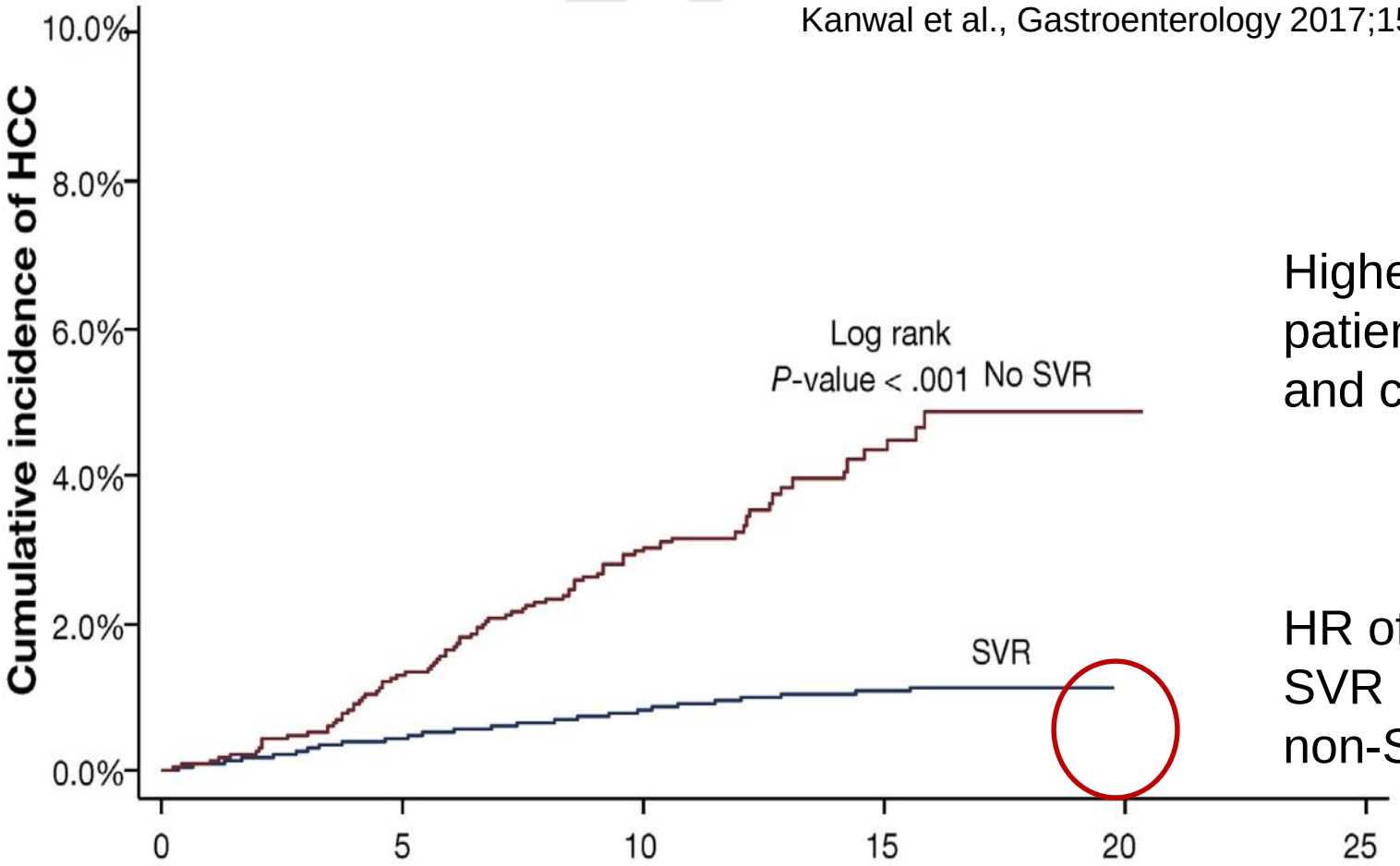
	Number at risk (events)																	
Non-SVR	1032 (25)	859 (38)	722 (31)	574 (26)	448 (27)	301 (16)	189 (10)	104 (3)	28 (3)	2
SVR	645 (14)	474 (5)	373 (2)	292 (4)	223 (2)	173 (1)	124 (1)	75 (0)	31 (0)	3

Nahon P et al., Gastroenterology 2017;152:142–156

The incidence of HCC is Reduced in HCV patients After SVR by DAA

Kanwal et al., Gastroenterology 2017;153:996–1005

Veterans Affairs

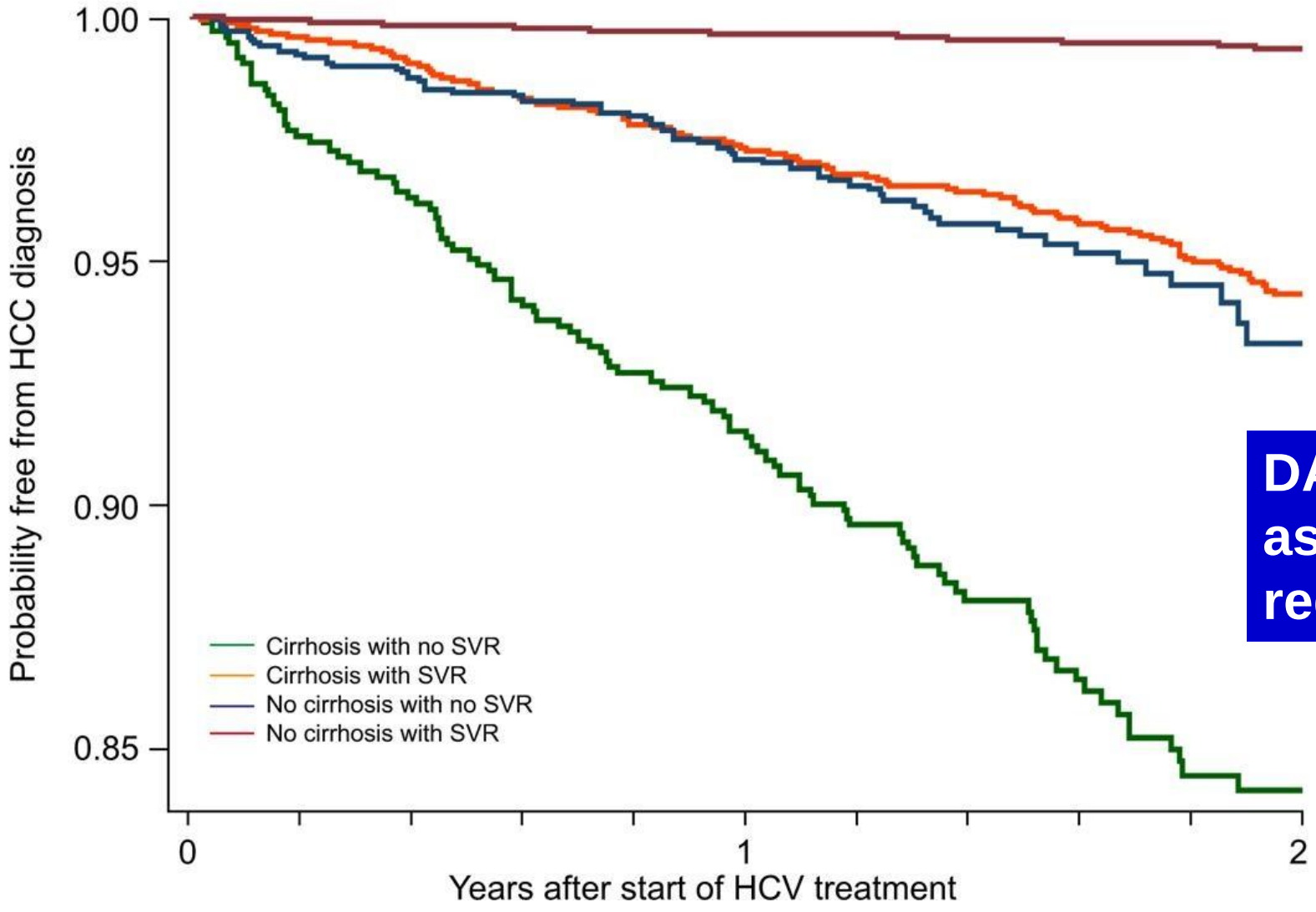


N at risk (N HCC)											
Achieved SVR	19518	(85)	19372	(68)	14364	(29)	6128	(1)	0	(0)	0
No SVR	2982	(35)	2453	(36)	1617	(14)	636	(3)	5	(0)	0

Higher HCC rate in older patients, African Americans, and cirrhotics

HR of developing HCC after SVR = 0.90, versus 3.45 in non-SVR

Kaplan-Meier curves of survival free of HCC by cirrhosis and SVR status after DAA-only antiviral treatment:
SVR is associated with a reduction in HCC risk both among patients with cirrhosis and those without cirrhosis.



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

Ioannou GN et al, JH 2018;68: 25–32

雖然藥物治療可以降低肝癌的發生率，

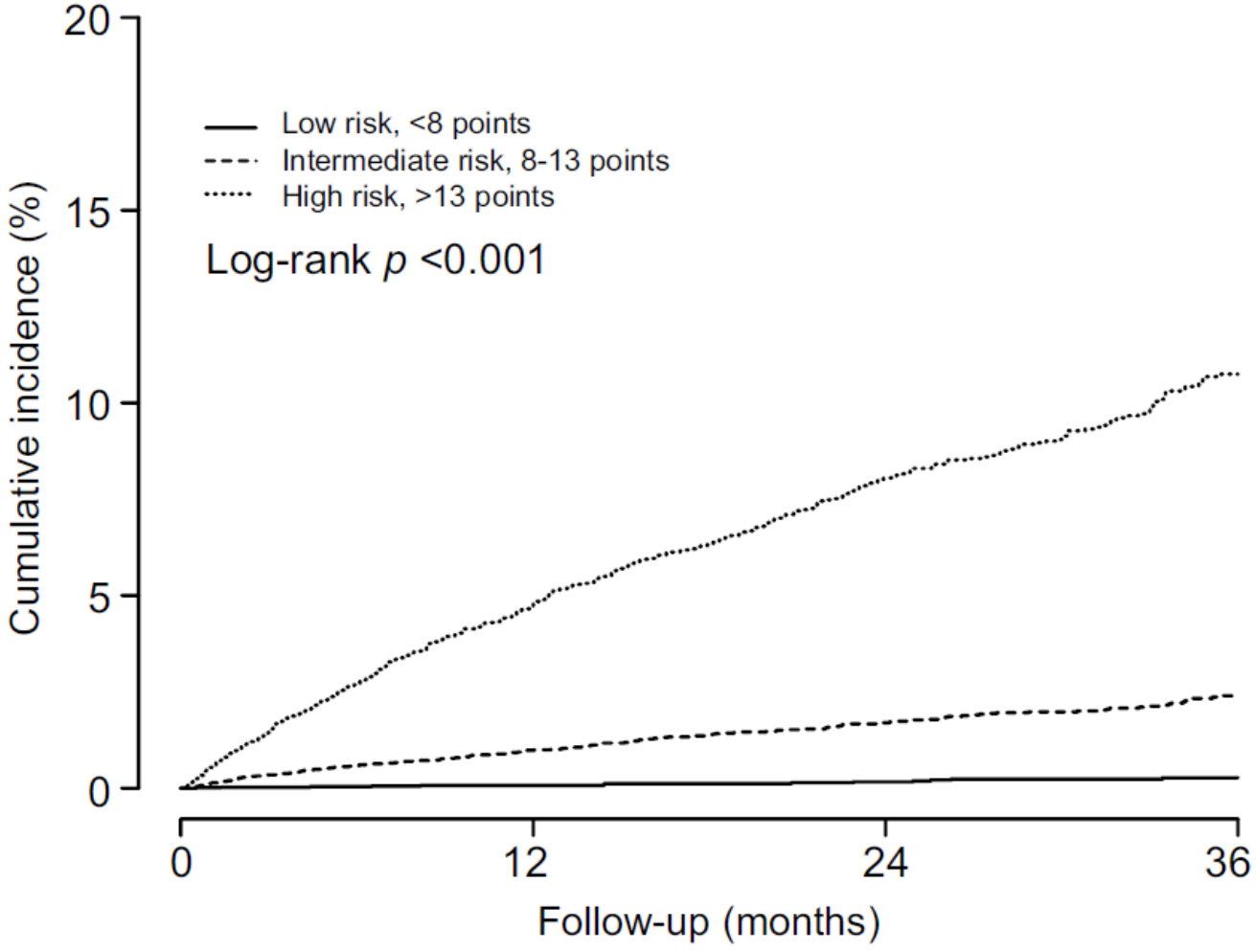
但是無法降到零發生率。

Antiviral treatment does not completely eliminate the risk of HCC in HBV-LC (CAMD scores)

The simple formula of the CAMD score

Variable	Risk score
Cirrhosis	
No cirrhosis	0
Cirrhosis with age <40 yr	10
Cirrhosis with age ≥40 yr	6
Age	
Age <40 yr	0
Age 40-49 yr	5
Age 50-59 yr	8
Age 60 yr or older	10
Gender	
Female sex	0
Male sex	2
Diabetes mellitus	
Not diabetic	0
Diabetic	1

The CAMD score stratifies the risks of HCC during continuous antiviral therapy in patients with chronic hepatitis B



Yao-Chun Hsu et al, JH 2018;69:278–285

LIVER

Comparative Performance of 14 HCC Prediction Models in CHB: A Dynamic Validation at Serial On-Treatment Timepoints

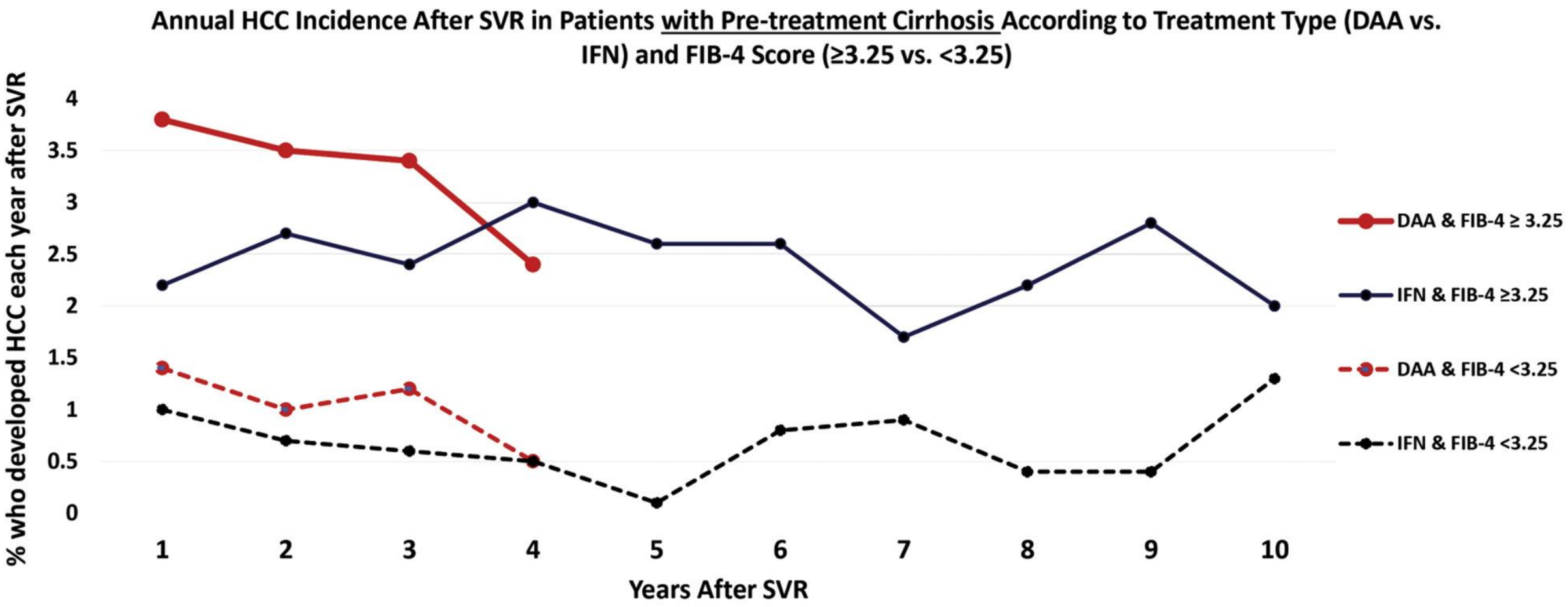
Am J Gastroenterol 2022;117:1444–1453

Shanshan Wu, PhD[1], Jialing Zhou, MS[2], Xiaoning Wu, PhD[2], Yameng Sun, PhD[2], Bingqiong Wang, PhD[2], Yuanyuan Kong, PhD[1], Siyan Zhan, PhD[3], Jidong Jia, PhD[1,2], Hwai-I Yang, PhD[4,5,6,7] and Hong You, PhD[1,2]

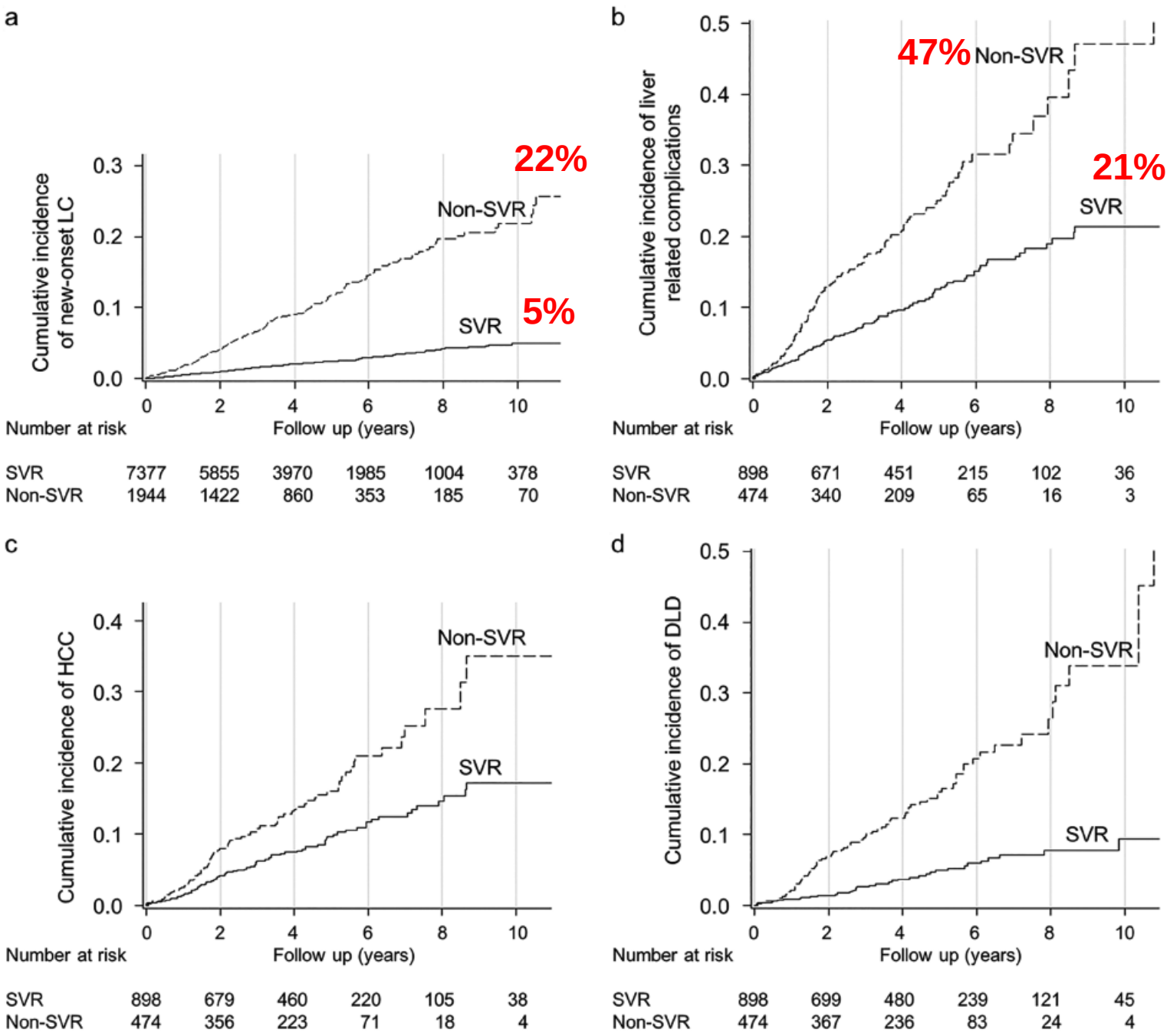
14 models
untreated patients: GAG-HCC, NGM1-HCC, NGM2-HCC, REACH-B
treated patients: mREACH-BI, mREACH-BII, PAGE-B, mPAGE-B, AASLHCC, CAMD, and REAL-B
mixed treatment status: CU-HCC, LSM-HCC, RWS-HCC

In this undergoing antiviral treatment CHB cohort, most HCC prediction models performed well even using on-treatment values during first 2 years, particularly REAL-B, AASL-HCC, CAMD, and mPAGE-B model.

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



Ioannou GN et al, Gastroenterology 2019;157:1264–1278

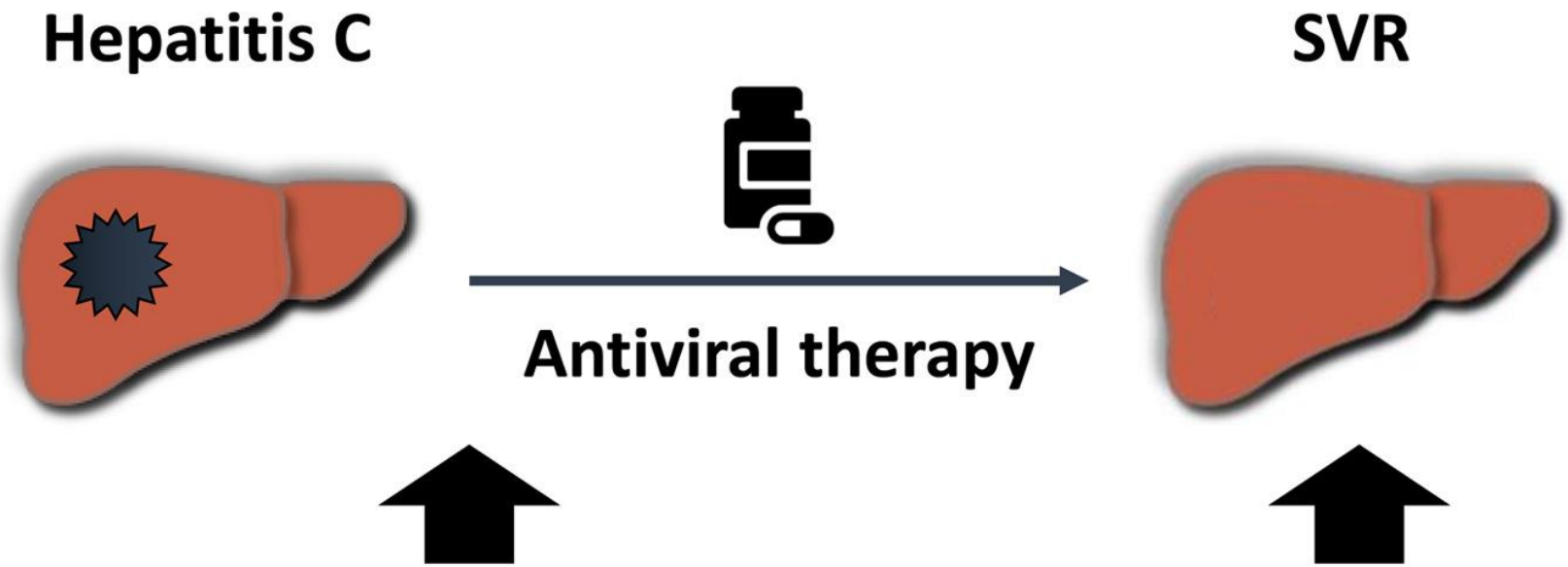


HCV SVR後，還是有可能會有liver-related events (decompensation, HCC)

Taiwan multi-center study

JGH 2021;36:2884–2892

Liver-related Events after HCV SVR



Post-SVR surveillance is recommended if:

Comorbidities (steatosis, diabetes, excess alcohol consumption)
Male gender
Age >64
F4, portal hypertension
Elevated FIB-4, APRI, AFP
History of decompensation
History of IFNα therapy (?)
HCV genotypes 1, 3 (?)

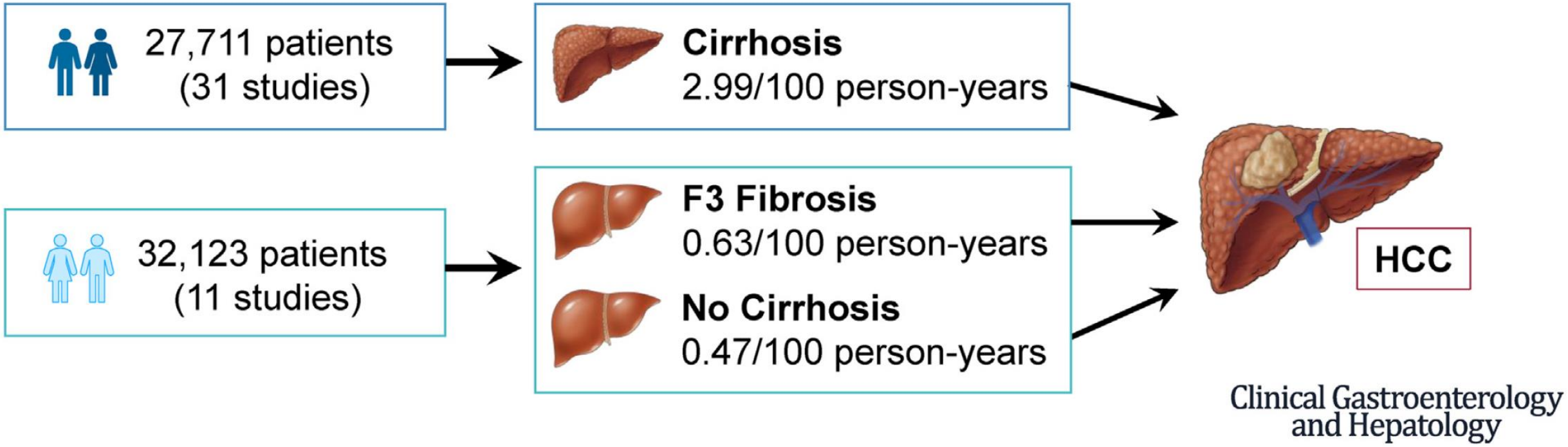
In addition to baseline features, continue surveillance after SVR if:

Persistently elevated ALT, AST, GGT, AFP, liver stiffness, FIB-4, APRI, or VITRO
Hypoalbuminemia
Increasing body weight (?)

Negro F. JH 2021

Fibrosis-stage Specific Incidence of Hepatocellular Cancer after Hepatitis C Cure with Direct-Acting Antivirals:

A Systematic Review & Meta-Analysis

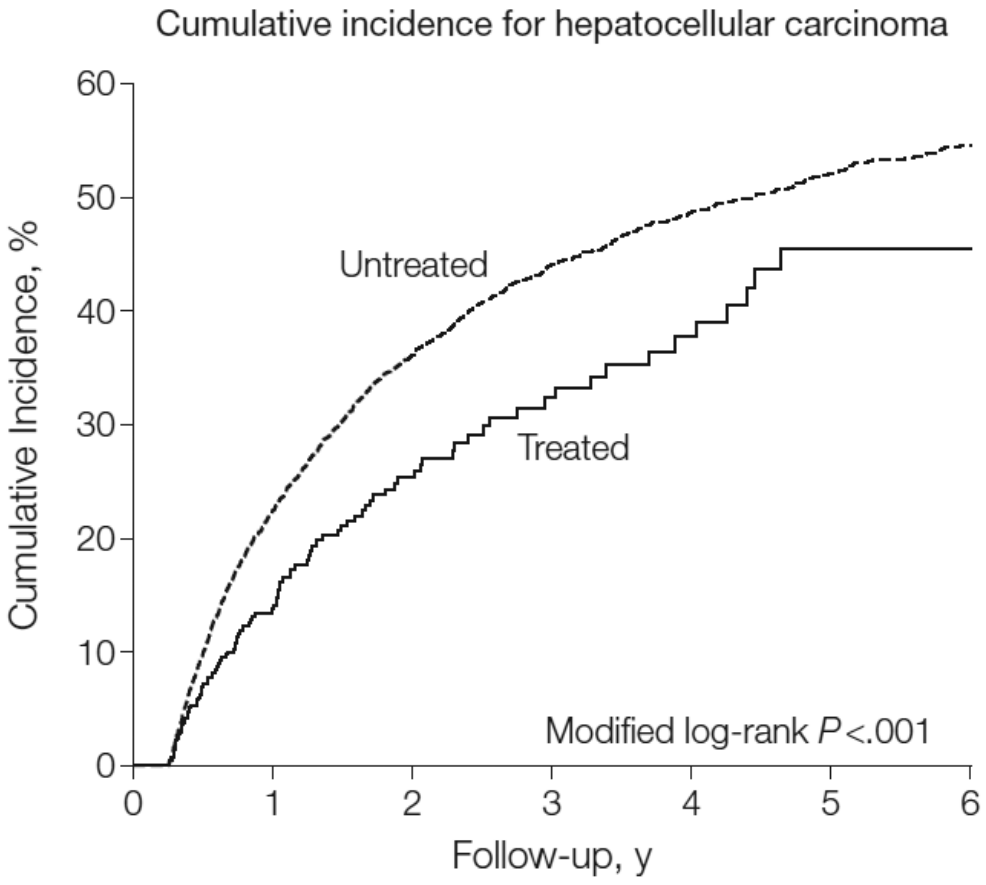


Kim NJ et al., CGH 2022 in press

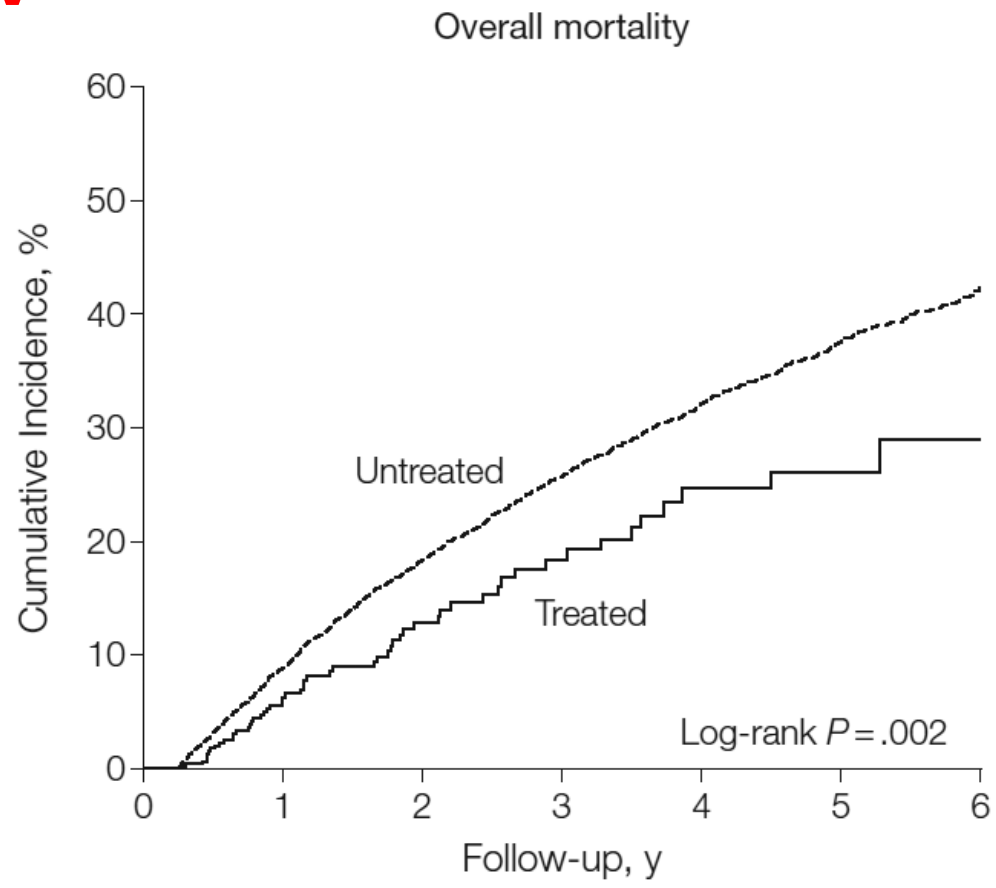
治療病毒性肝硬化
可以降低肝癌的復發率

使用核苷(酸)類似物可以降低術後肝癌的復發

HBV



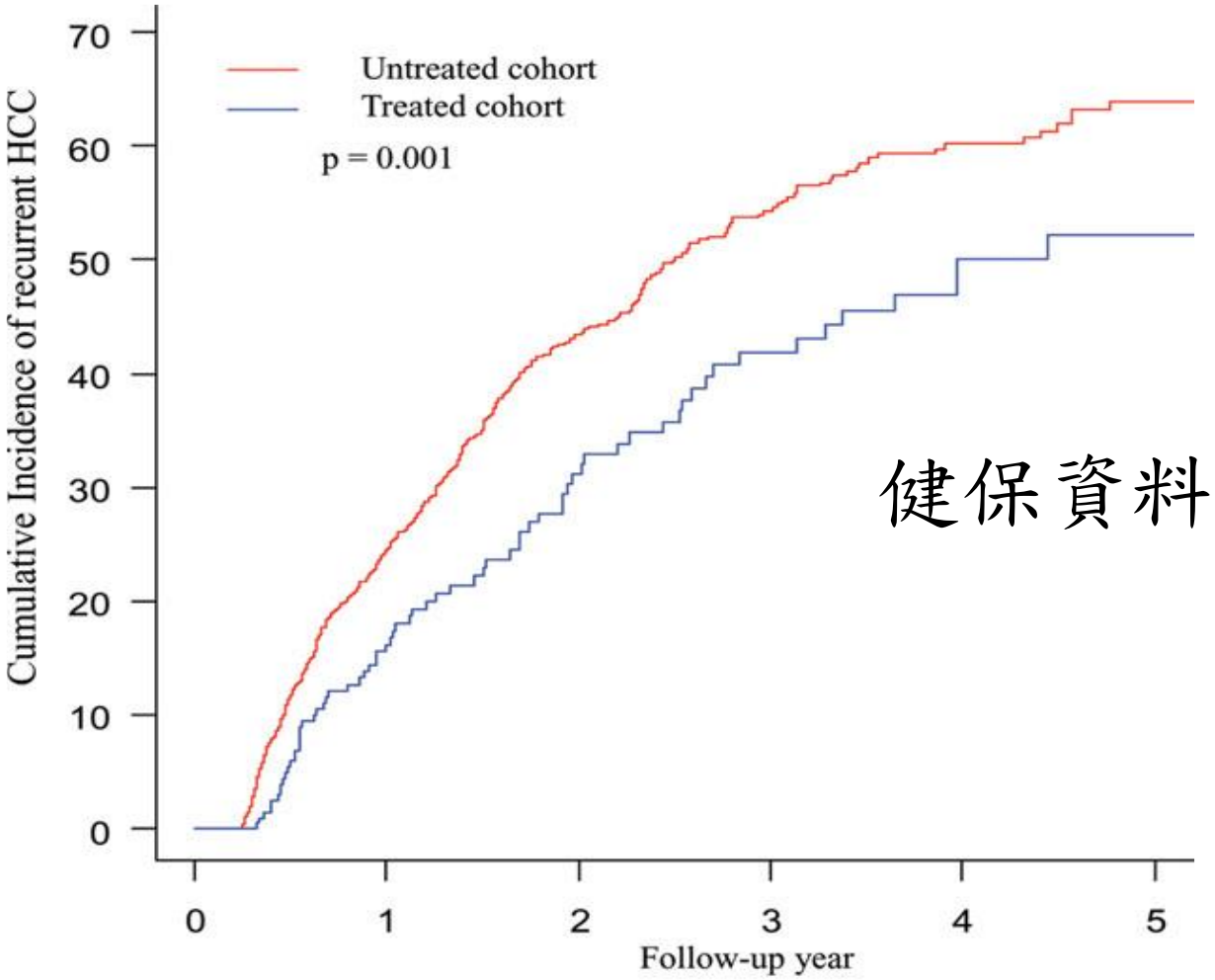
No. at risk							
Untreated	4051	2697	1685	1080	667	411	205
Treated	518	246	124	68	40	19	9



No. at risk							
Untreated	4051	3428	2506	1763	1177	734	368
Treated	518	289	162	96	61	32	11

Wu CY et al. JAMA 2012;308(18):1906-1913

Recurrence of resected HCC in chronic hepatitis C

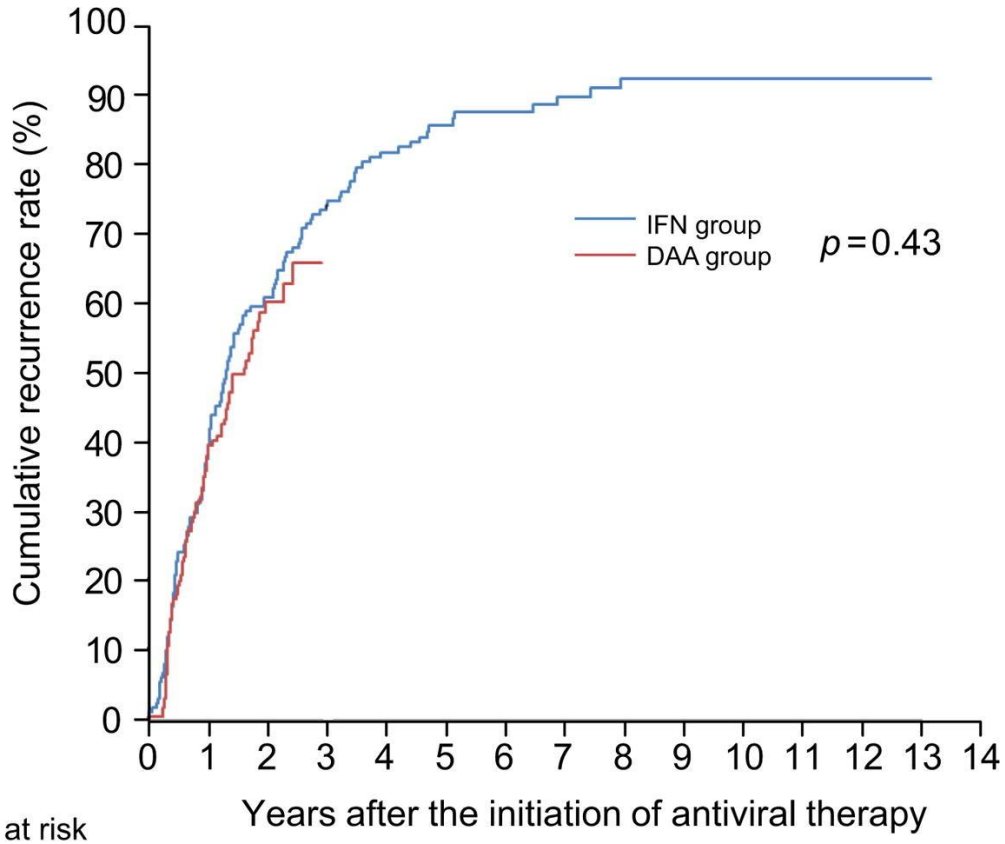


健保資料庫

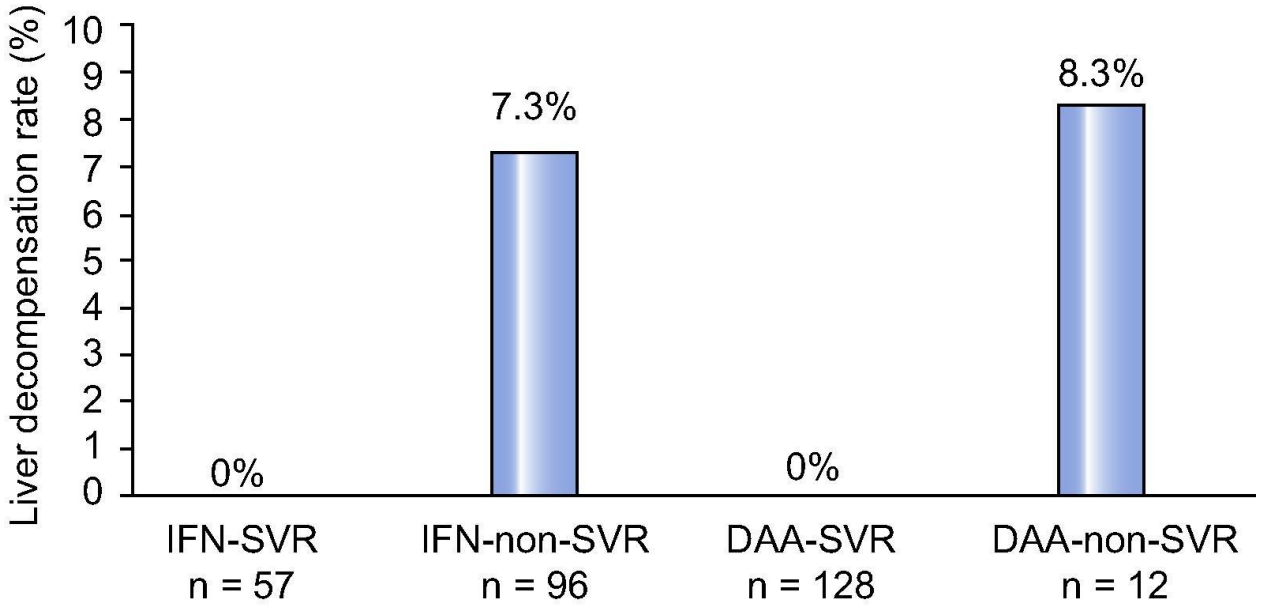
Number at risk						
Untreated	852	459	219	116	54	23
Treated	213	139	78	51	28	20

Yao-Chun Hsu et al. HEPATOLOGY 2013;58:150-157

HCC recurrence rates did not differ between patients who received IFN-based therapy and DAA therapy



Number at risk														
IFN group	156	94	60	38	25	14	12	9	5	4	4	4	3	1
DAA group	147	82	23											



Nishibatake Kinoshita M et al, J Hepatol 2019;70:78-86

結論

- 病毒性肝硬化是可逆的
- 治療病毒性肝硬化可延長病人的存活
- 治療病毒性肝硬化可降低肝癌的發生率
- 治療病毒性肝硬化可降低肝癌的復發率
- 需要積極治療
- 與移植中心合作

您與您的病人，可以雙贏

結論

- 病毒性
- 治療病 人的存活
- 治療病 癌的發生率
- 治療病 癌的復發率
- 需要積
- 與移植

您與您的病人一可以雙贏

Thanks