# B或C型肝炎性肝硬化的治療方針

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## 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
- 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

## 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**

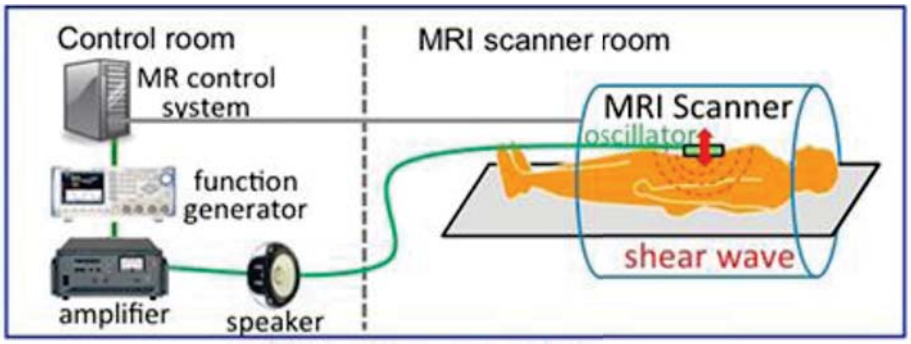
## Vibration Controlled Transient Elastography (VCTE, Fibroscan)

## Acoustic Radiation Force Impulse (ARFI)



**健保 F3 之定義為：ARFI ≧ 1.81m/sec**

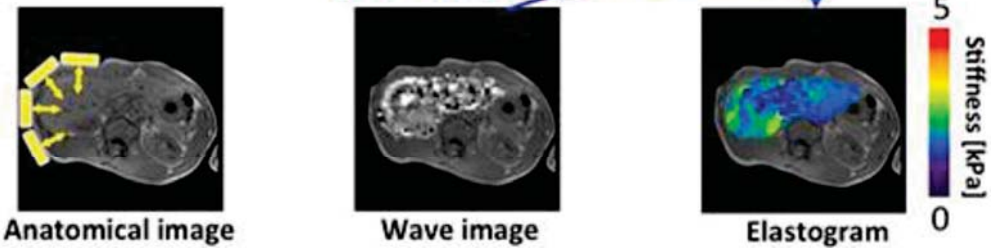
## MR Elastography




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:

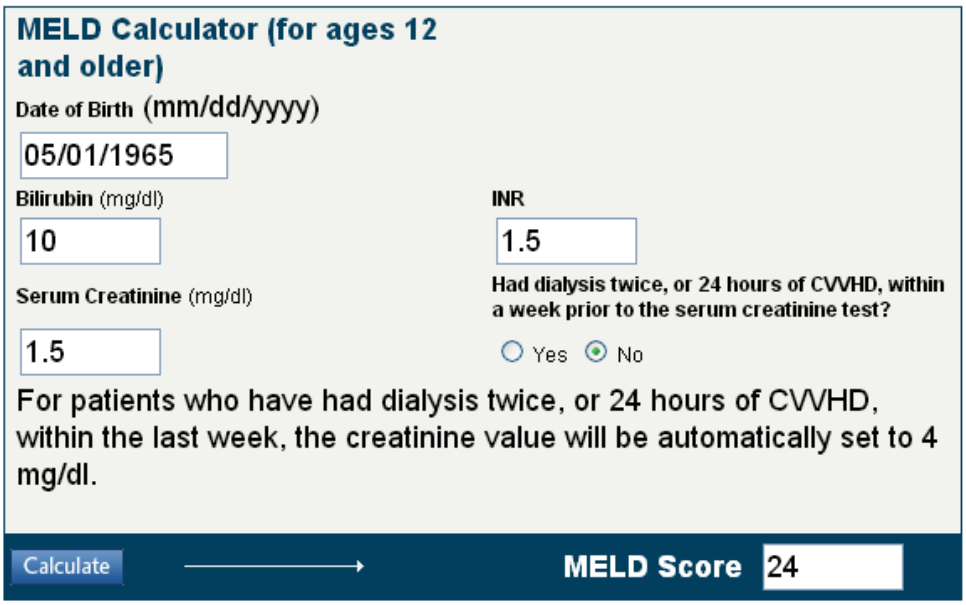
MELD Score = 0.957 x $\text{Log}_e$(creatinine mg/dL)
+ 0.378 x $\text{Log}_e$(bilirubin mg/dL)
+ 1.120 x $\text{Log}_e$(INR)
+ 0.643*

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



## Baveno IV staging of liver cirrhosis

**Compensated**

Stage 1: no varices, no ascites

Stage 2: varices, no ascites

**Decompensated**

Stage 3: ascites ± varices

Stage 4: variceal bleeding ± ascites

Franchis R. JH 2005;43:167–176

In Baveno IV, a session was devoted to predictive models in portal hypertension, during which classification stages of cirrhosis were proposed. Prospective validation of this classification is under way.
JH 2010;53:762–768

# 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)

## 治療C型肝炎的藥物

- 干擾素
- 口服抗病毒藥物
  (direct antirviral agent, DAA)

## 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)

# 健保對於病毒性肝硬化的治療規定

## 全民健康保險加強慢性B、C型肝炎治療試辦計畫

**HBsAg(+)**

↓

肝硬化病患

(1) HBsAg (+)且血清HBV DNA≧2,000IU/mL

+

(2) 肝組織切片（Metavir F4或Ishak F5以上)

or

超音波/電腦斷層/核磁共振診斷為肝硬化併食道或胃靜脈曲張

or

超音波/電腦斷層/核磁共振診斷為肝硬化併脾腫大

**可長期使用**

## 治療C型肝炎的口服抗病毒藥物

**HCV RNA 測得到就可以使用健保藥物治療**

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

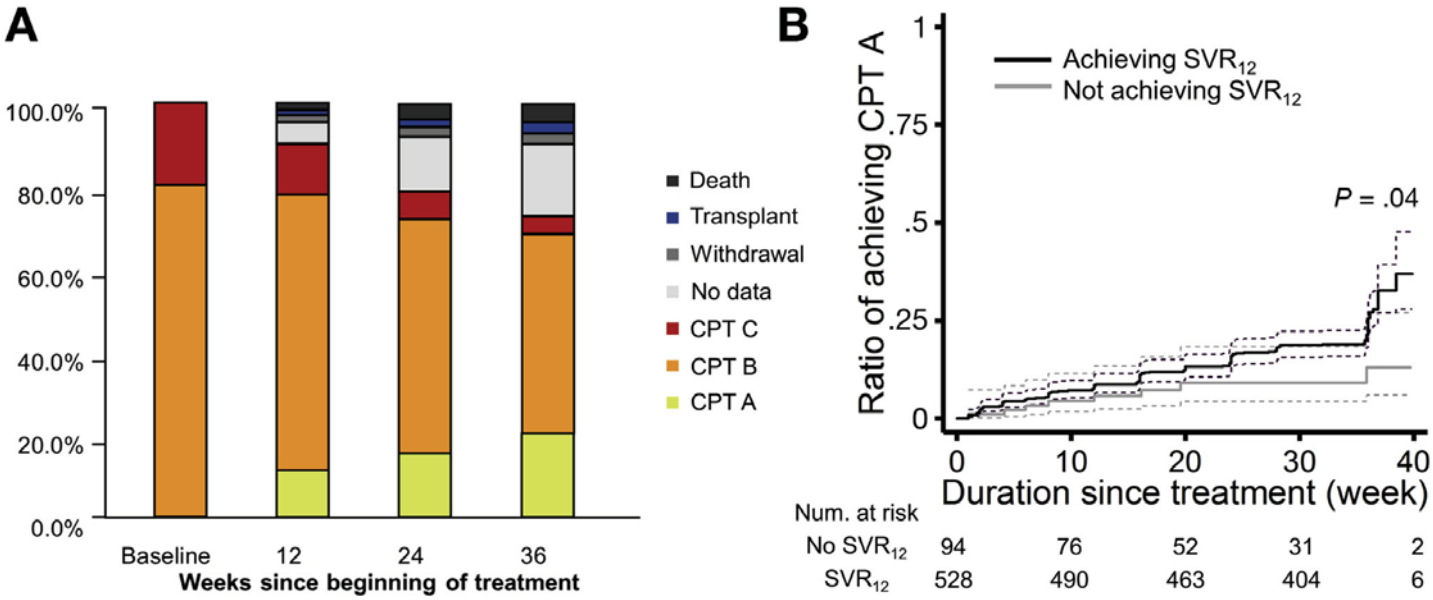
## ETV-048: Improvement in MELD/CTP Scores

| 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.

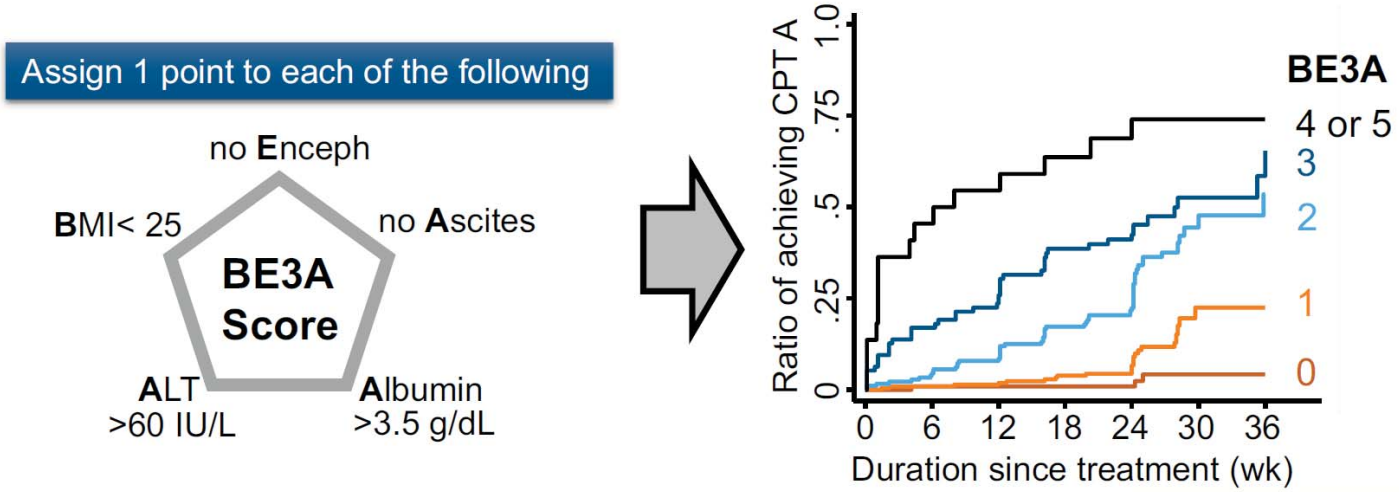
Liaw YF, et al. Hepatology. 2011;54:91-100.

# DAA Improves Child Score in Decompensated Liver Cirrhosis




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

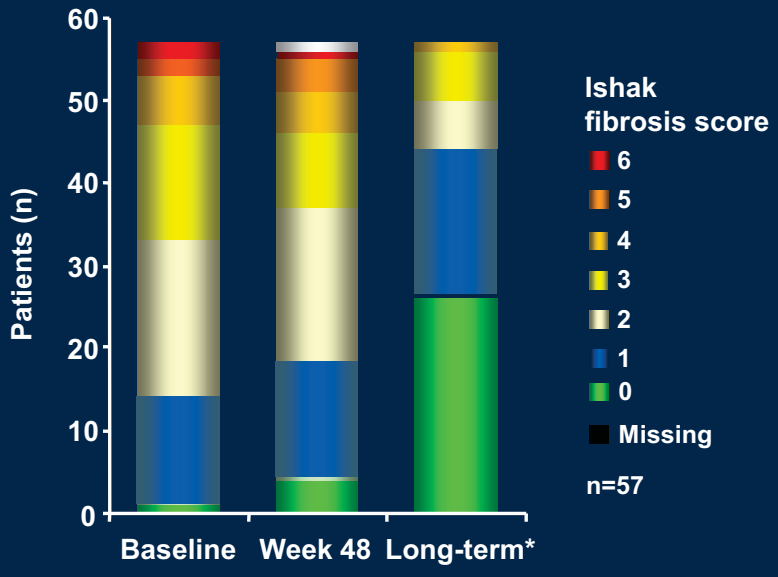
# DAA Improves Child Score in Decompensated Liver Cirrhosis




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

# 治療病毒性肝硬化
# 可以逆轉纖維化

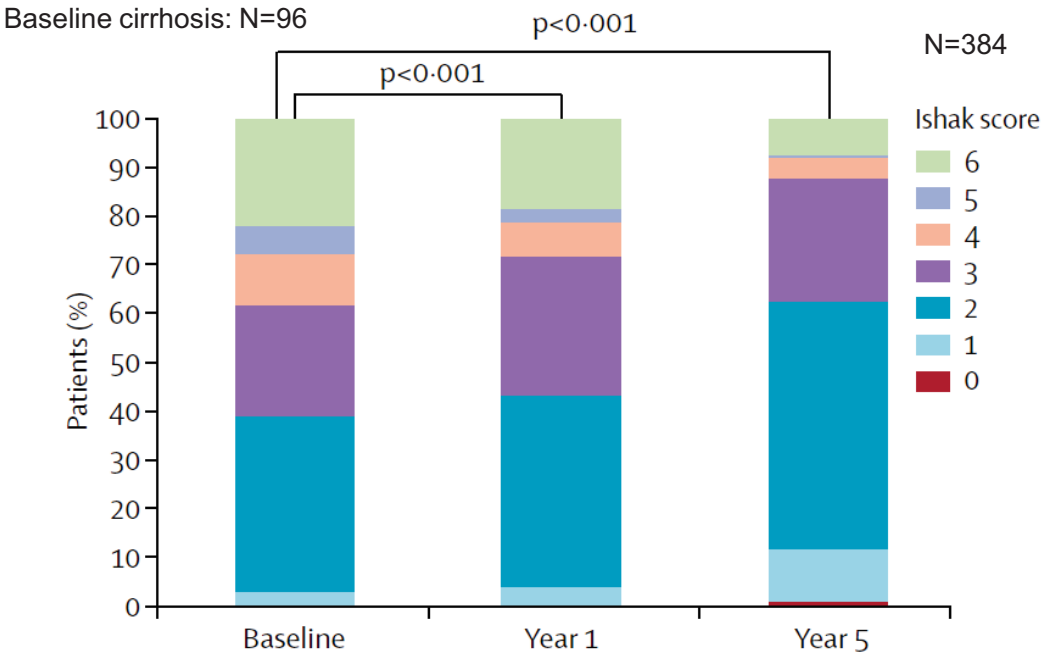
## ETV Long term treatment Distribution of Ishak fibrosis scores at baseline, Year 1 and Years 3–7




* 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




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%**

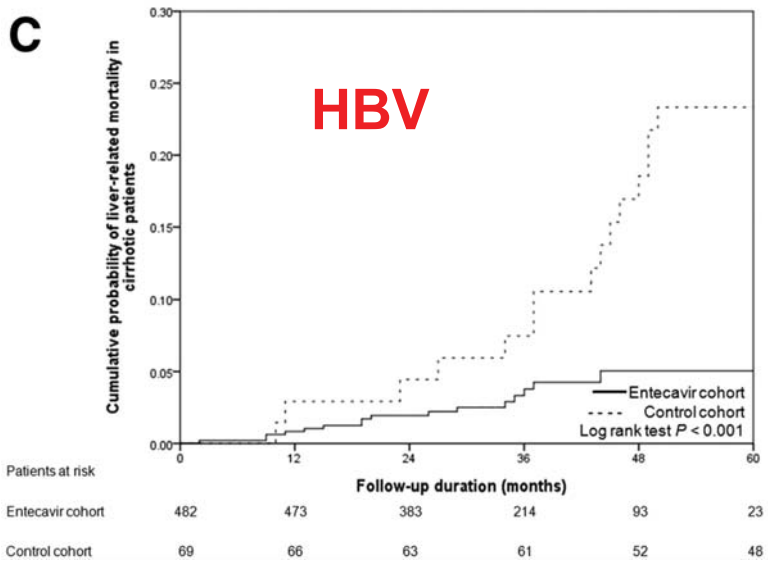
**Regression of cirrhosis in 9/14 patients**

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

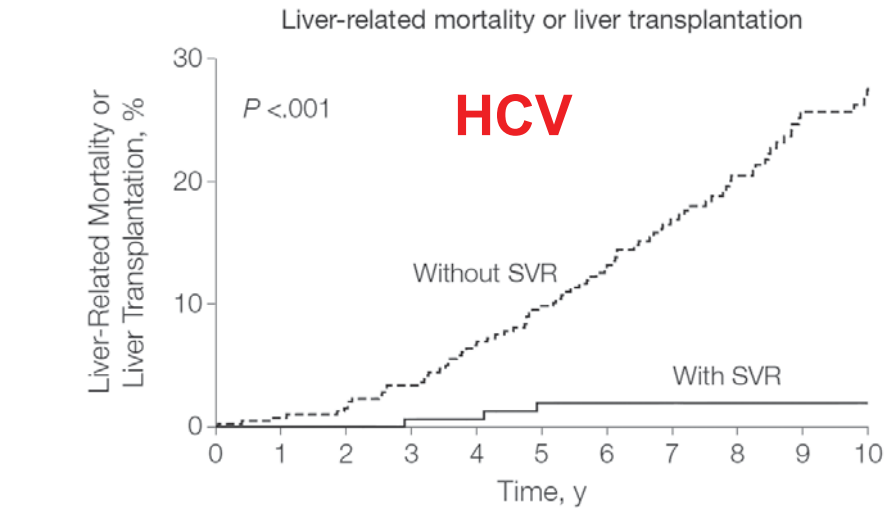
## Cumulative probability of liver-related mortality in cirrhotic patients

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




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

# SVR and Liver-related mortality

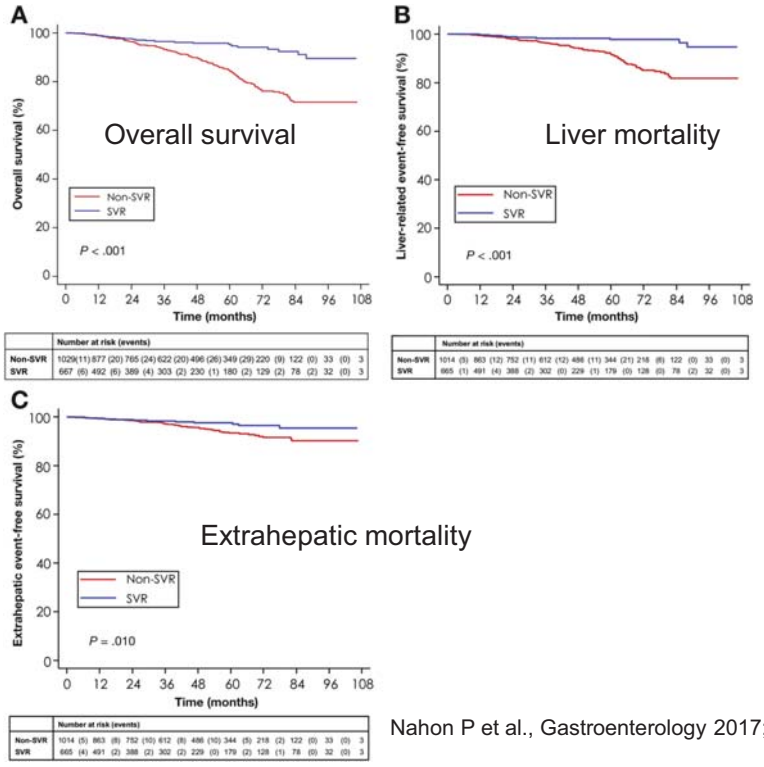



No. at risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 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

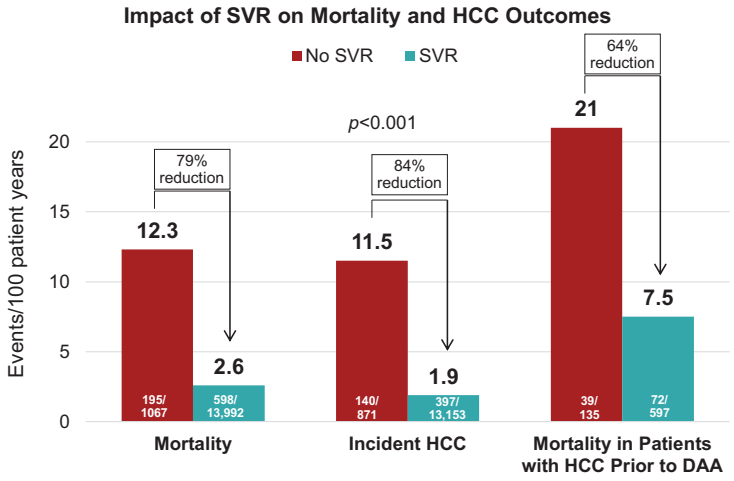



Nahon P et al., Gastroenterology 2017;152:142–156

# Impact of SVR with DAAs On Mortality in Patients With Advanced Liver Disease

Veterans Affairs HCV Clinical Case Registry

All-cause mortality rates and incident HCC rates in 15,059 HCV-infected Veterans with advanced chronic liver disease (FIB-4 >3.25) from the HCV registry through Sept 2016.




**Patients achieving SVR after DAA treatment had significantly lower all-cause mortality and lower incident HCC rates than those who did not achieve SVR.**

Backus, et al. Hepatology. 2018

## 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?

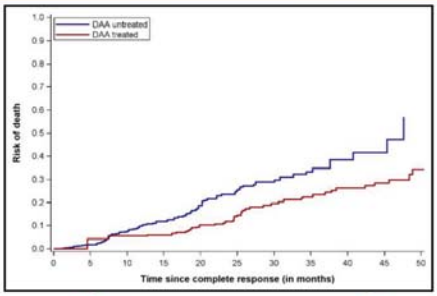
**Design:**

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



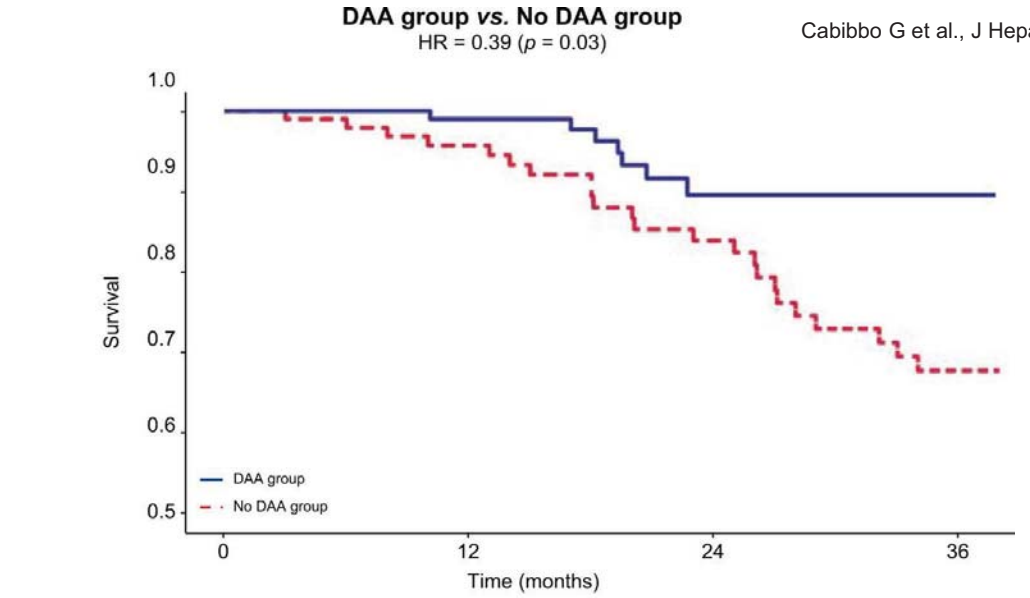

Multivariable analysis
- Adjusted for site, age, sex Child Pugh score, AFP, tumor burden and HCC treatment modality

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

Singal AG et al. *Gastroenterology*. 2019

Gastroenterology

# DAA after successful treatment of early HCC improve survival in HCV-cirrhotic patients

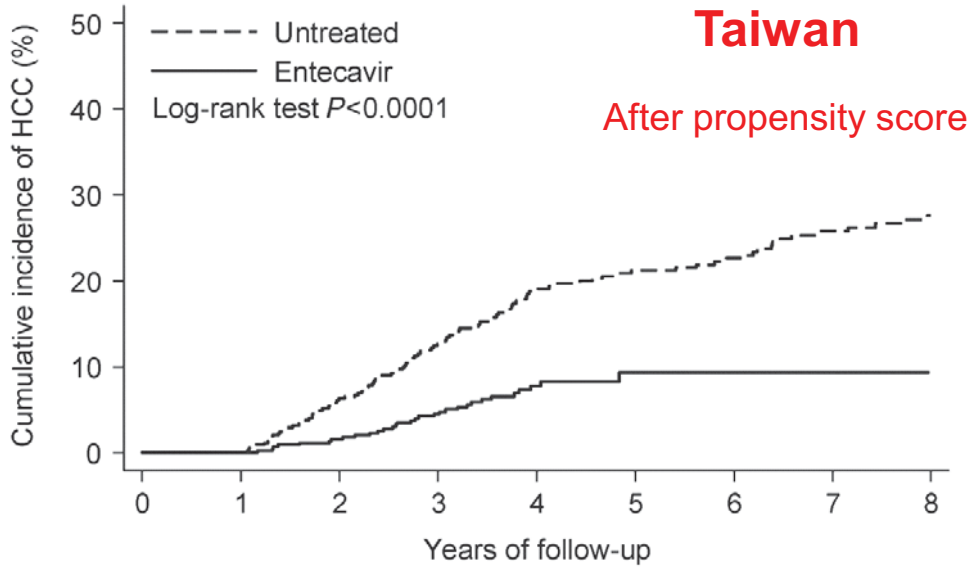



| N° at risk | | | | |
|---|---|---|---|---|
| DAA group | 102 | 88 | 39 | 1 |
| No DAA group | 102 | 81 | 59 | 34 |

Cabibbo G et al., J Hepatol 2019;71(2):265-273

治療病毒性肝硬化
可以降低肝癌的發生率

# Four-year ETV therapy reduces HCC




**Taiwan**

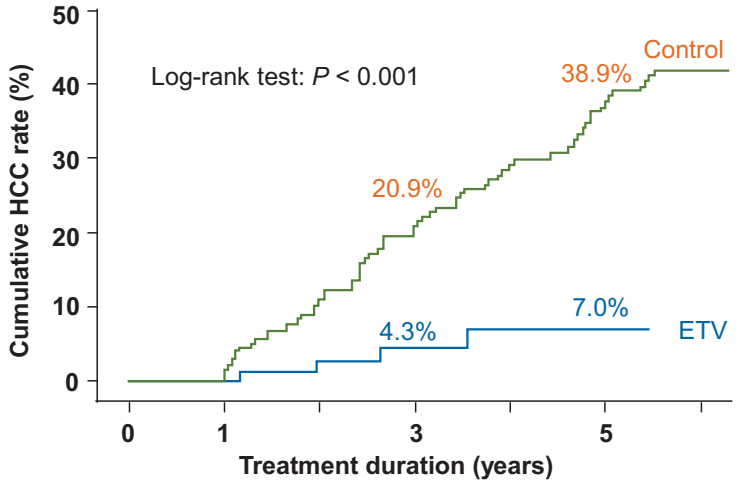
After propensity score

| 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

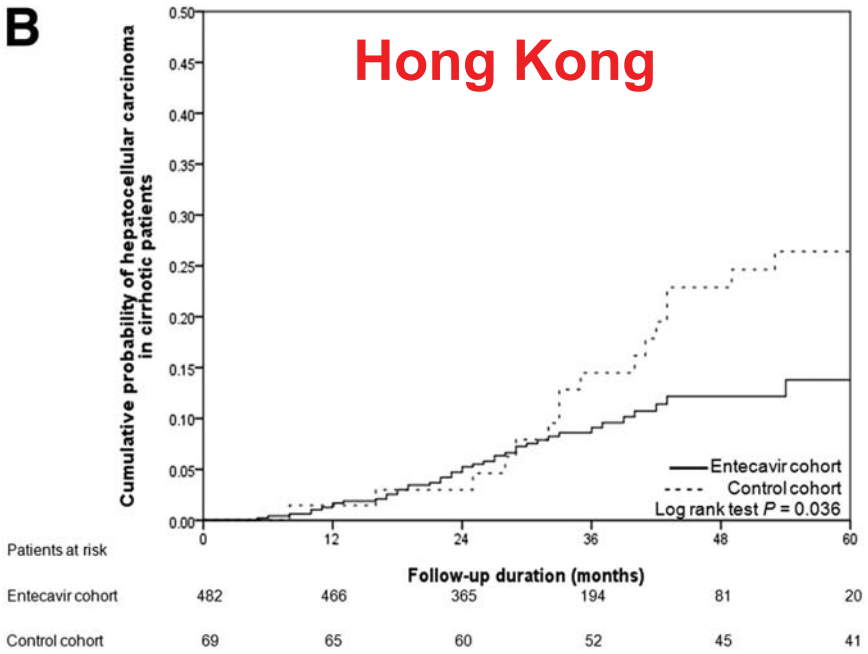
**Japan**




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

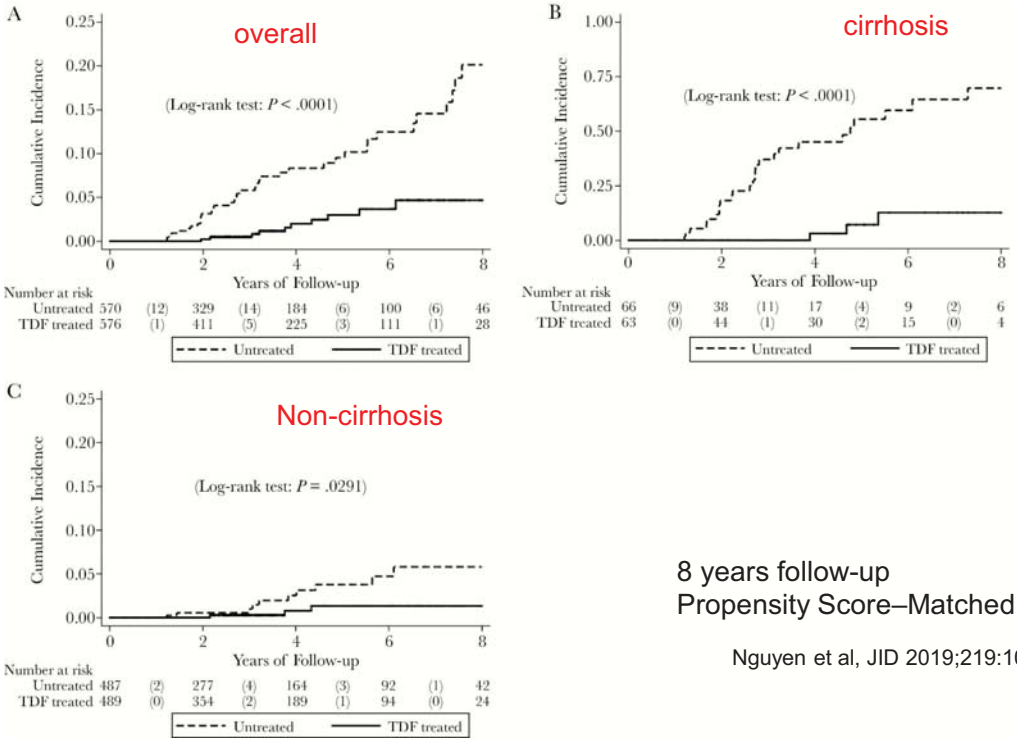
Hosaka T et al. Hepatology 2013;58:98-107

# Cumulative probability of HCC in cirrhotic patients




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

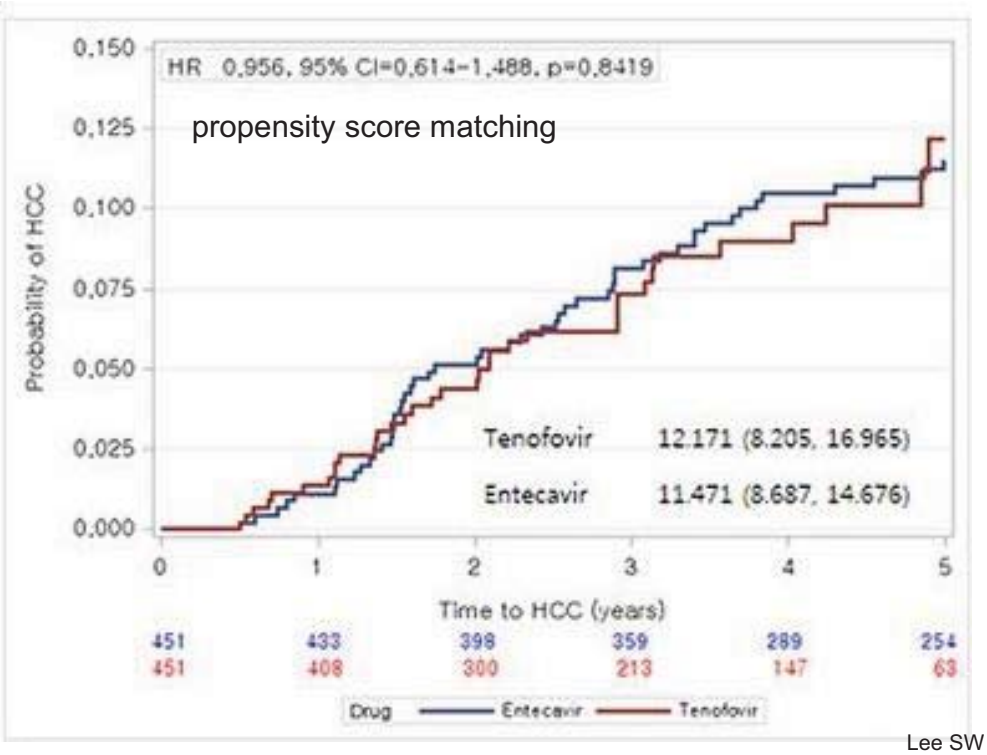
# TDF reduced HCC incidence in HBV-LC




8 years follow-up
Propensity Score–Matched Study

Nguyen et al, JID 2019;219:10–8

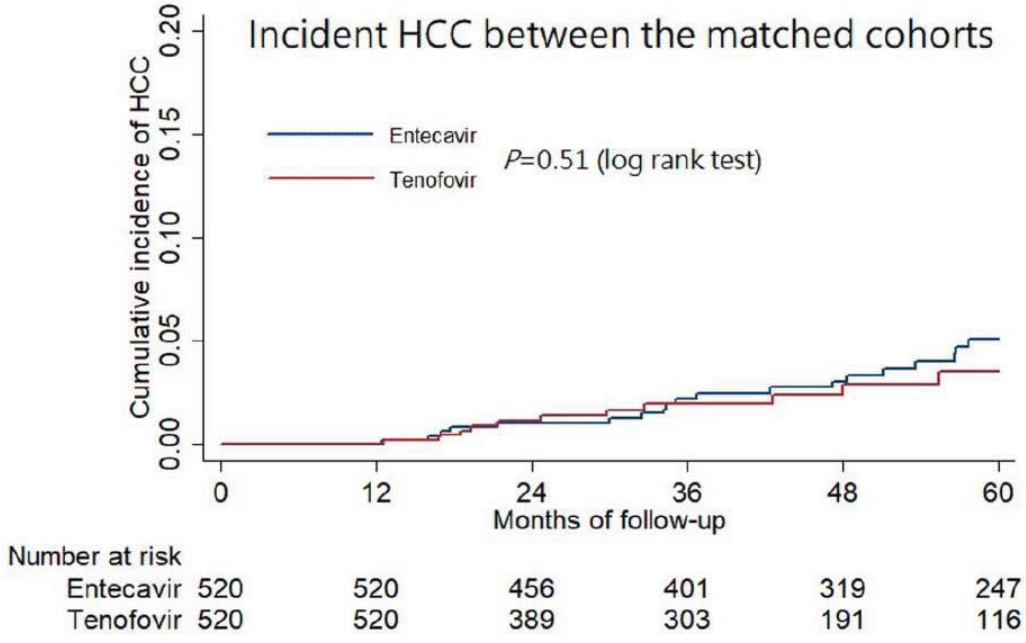
## Cumulative incidences of HCC in HBV-LC under ETV vs. TDF – No difference




Lee SW et al, Gut 2020 in press

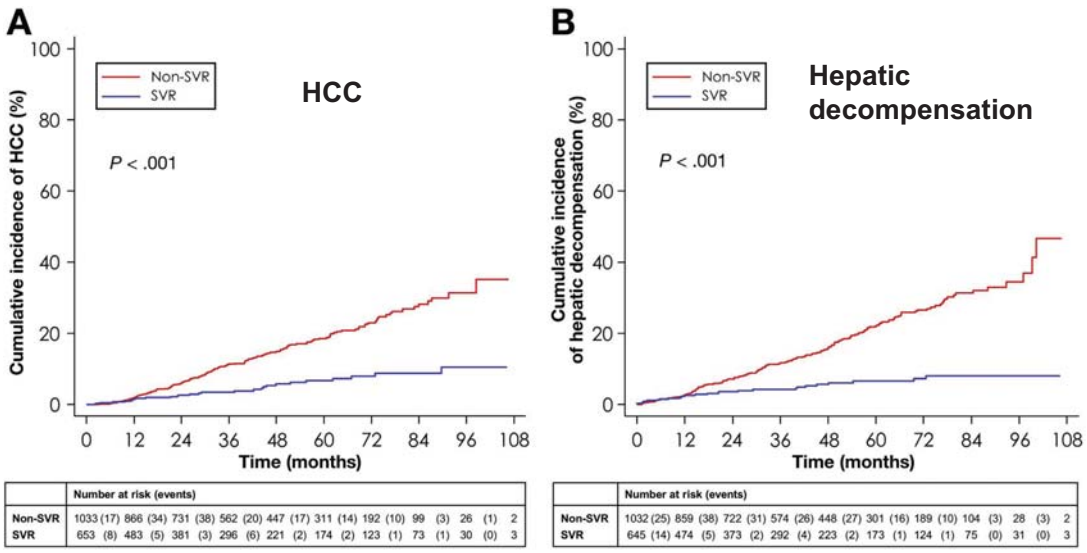
## No significant difference in the incidences of HCC between ETV and TDF cohorts

Hsu YC et al. AJG 2020 in press




Including cirrhosis and non-cirrhosis

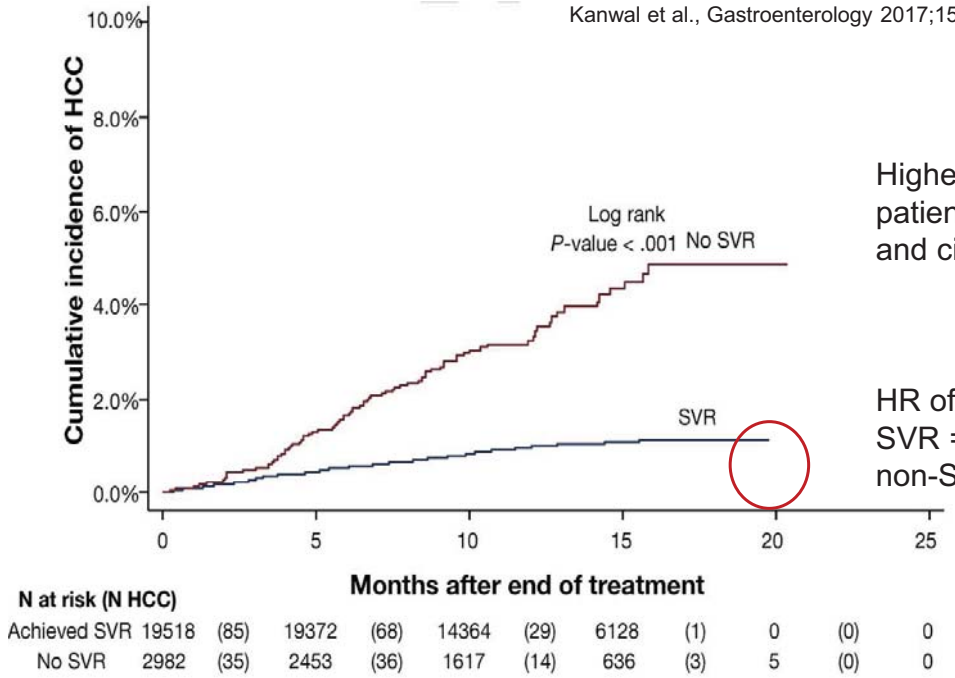
# SVR decreases incidence of HCC and hepatic decompensation in HCV-LC




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

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

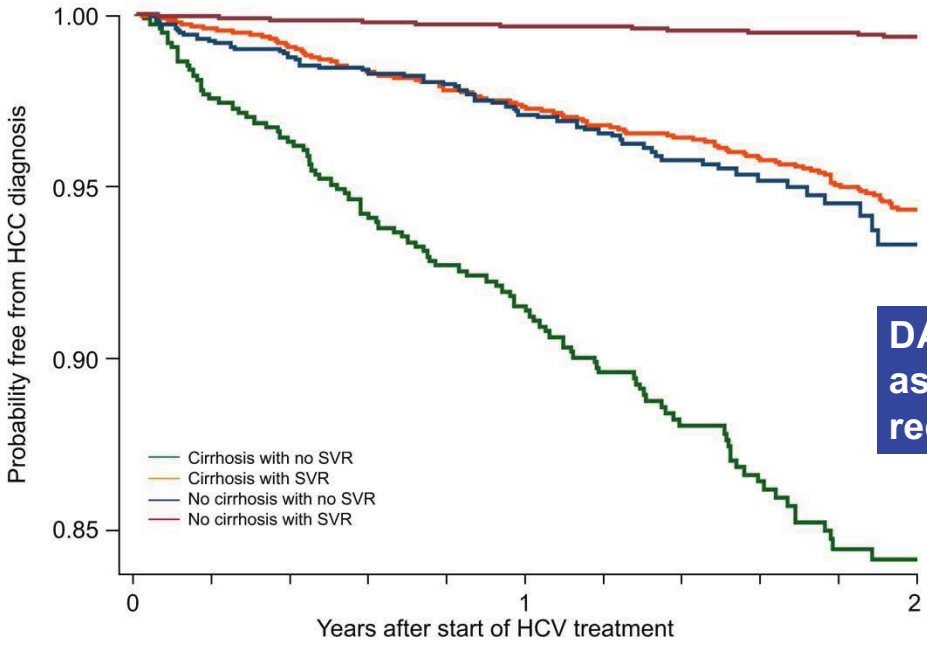
Kanwal et al., Gastroenterology 2017;153:996–1005 Veterans Affairs




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

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

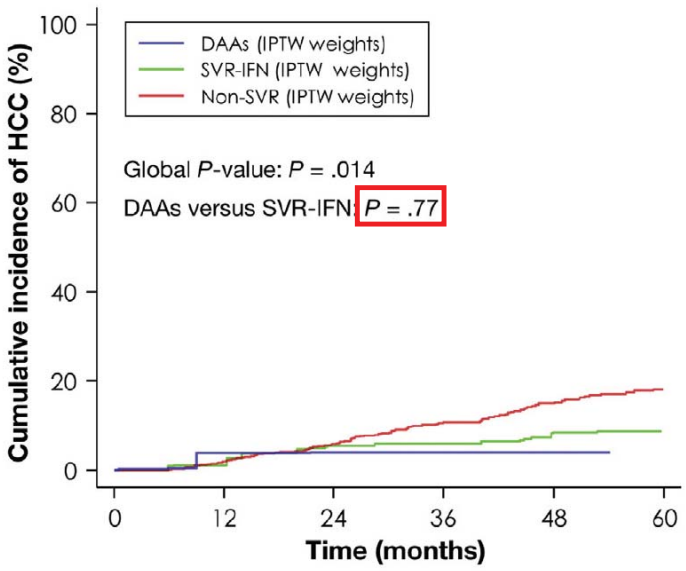
**Kaplan-Meier curves of survival free of HCC by cirrhosis and SVR status after DAA-only antiviral treatment:**
**SVR is associated with a reduction in HCC risk both among patients with cirrhosis and those without cirrhosis.**




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

Ioannou GN et al, JH 2018;68: 25–32

# Incidence of HCC of DAA treatment using IPTCW




| Groups | Number at risk (events) | | | | | |
|---|---|---|---|---|---|---|
| DAAs (IPTW weights) | 956 | 698 | 384 | 92 | 53 | 43 |
| SVR-IFN (IPTW weights) | 1076 | 1043 | 965 | 849 | 771 | 532 |
| Non-SVR (IPTW weights) | 1029 | 892 | 760 | 613 | 478 | 357 |

ANRS CO12 CirVir Group
compensated biopsy-proven HCV-associated cirrhosis recruited from 2006 through 2012 at 35 centers in France

IPTCW: inverse probability of treatment and censoring

Nahon et al, Gastroenterology 2018;155:1436–1450

# Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression

Waziry et al., JH 2017;67:1204–1212

Reem Waziry[1,*], Behzad Hajarizadeh[1], Jason Grebely[1], Janaki Amin[2], Matthew Law[1], Mark Danta[3], Jacob George[4], Gregory J. Dore[1]

[1]*The Kirby Institute, UNSW Sydney, Sydney, Australia;* [2]*Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia;* [3]*St Vincent's Clinical School, UNSW Sydney, Australia;* [4]*Storr Liver Centre, Westmead Millennium Institute and Westmead Hospital, University of Sydney, Sydney, Australia*

**Table 3**. Meta-regression analysis of factors associated with occurrence of hepatocellular carcinoma following HCV cure (Observations = 26).

| Variable | Univariate analysis | | | Multivariate analysis[†] | | |
|---|---|---|---|---|---|---|
| | RR | 95% CI | *p* value | aRR | 95% CI | *p* value |
| Treatment | | | | | | |
| IFN | 1.00 | – | – | 1.00 | – | – |
| DAA | 2.77 | 1.46–5.25 | <0.01 | 0.68 | 0.18–2.55 | 0.56 |
| Average follow-up, years | 0.88 | 0.80–0.97 | 0.01 | 0.75 | 0.56–0.99 | 0.04 |
| Average age | 1.11 | 1.03–1.18 | <0.01 | 1.06 | 0.99–1.14 | 0.12 |
| Genotype 1 | 1.01 | 0.99–1.03 | 0.14 | – | – | – |

All numbers were rounded to two decimal places.
aRR, adjusted rate ratio; CI, confidence interval; DAA, direct-acting antiviral; IFN, interferon; RR, Rate Ratio.
[†] Five studies were excluded from the adjusted analysis due to incomplete data on age.

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。

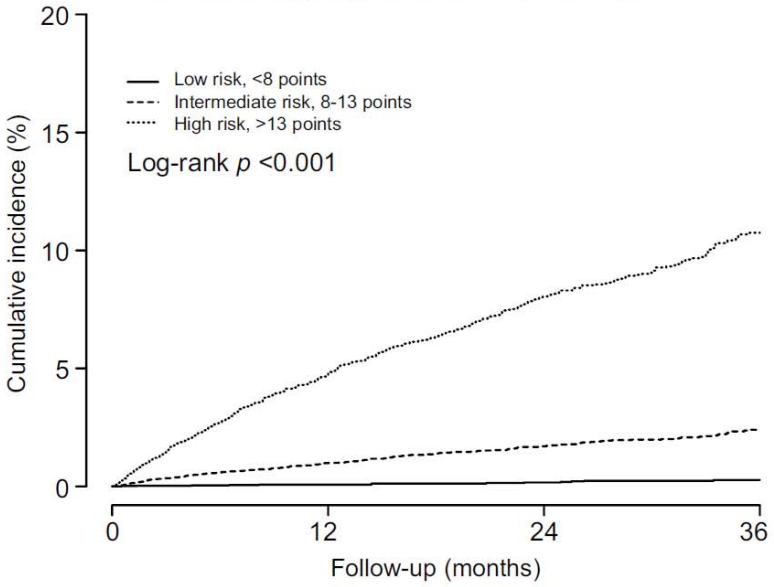
# Antiviral treatment does not completely eliminate the risk of HCC in HBV-LC (CAMD scores)

The simple formula of the CAMD score

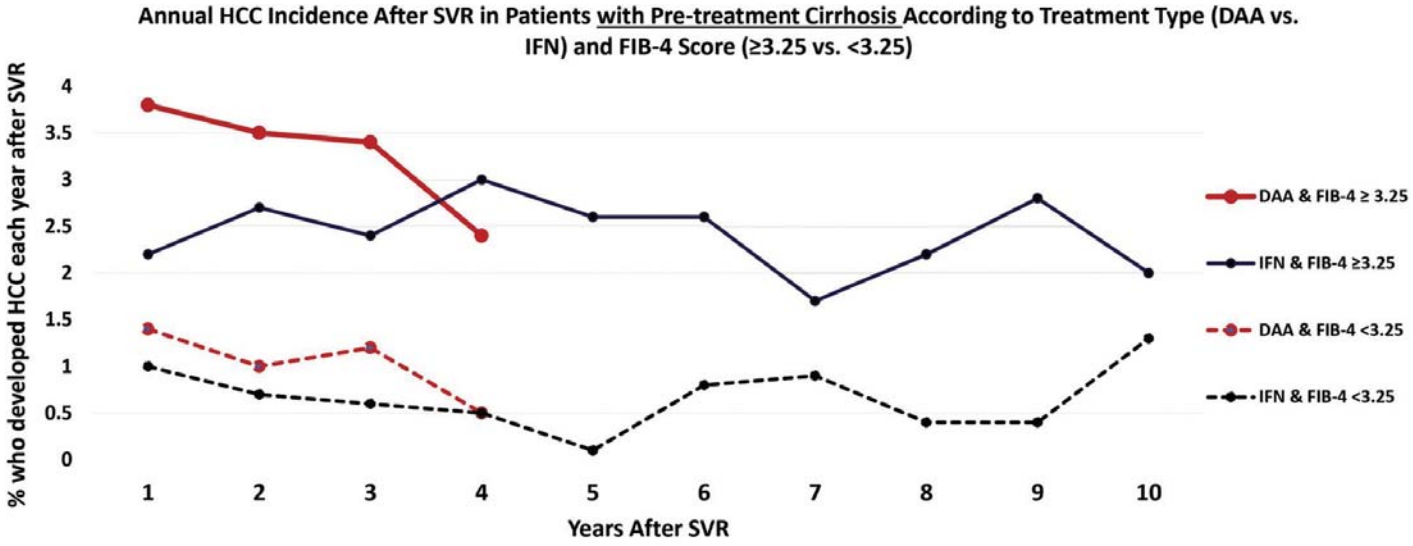
| Variable | Risk score |
|---|---|
| Cirrhosis | |
| No cirrhosis | 0 |
| Cirrhosis with age <40 yr | 10 |
| Cirrhosis with age ≥40 yr | 6 |
| Age | |
| Age <40 yr | 0 |
| Age 40-49 yr | 5 |
| Age 50-59 yr | 8 |
| Age 60 yr or older | 10 |
| Gender | |
| Female sex | 0 |
| Male sex | 2 |
| Diabetes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

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

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



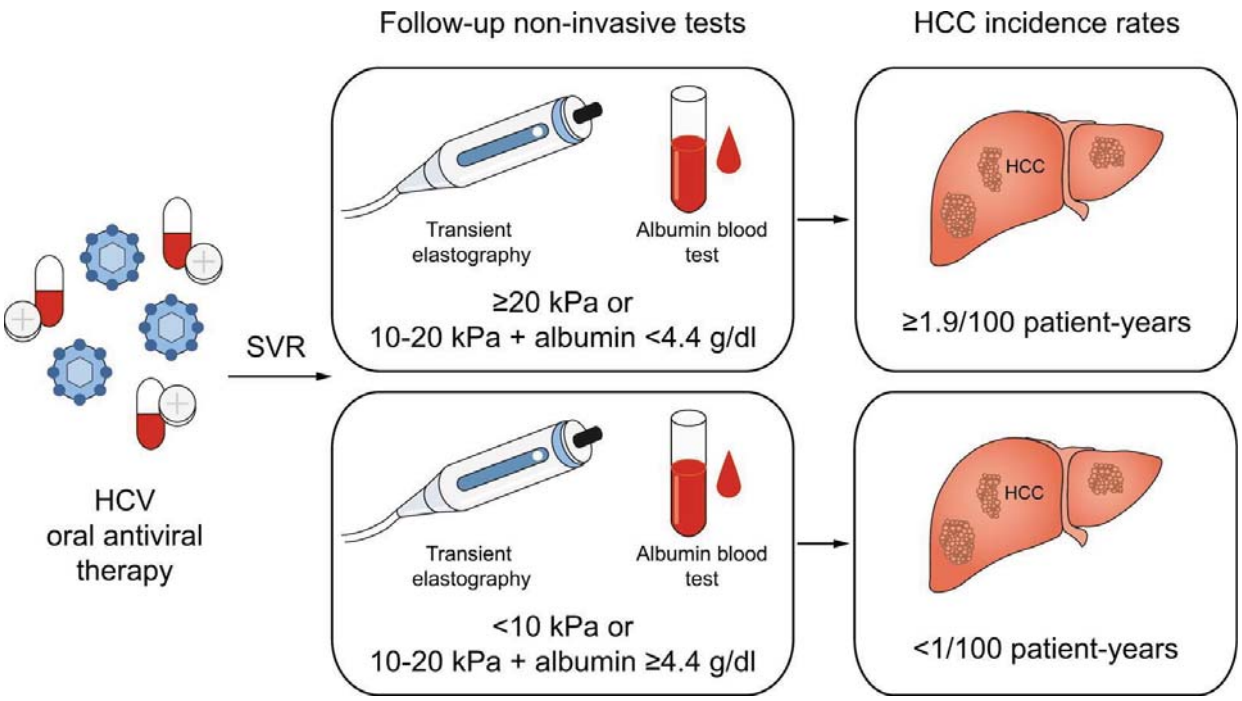

# Increased Risk for HCC Persists Up to 10 Years After HCV Eradication in Patients With Baseline Cirrhosis or High FIB-4 Scores




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

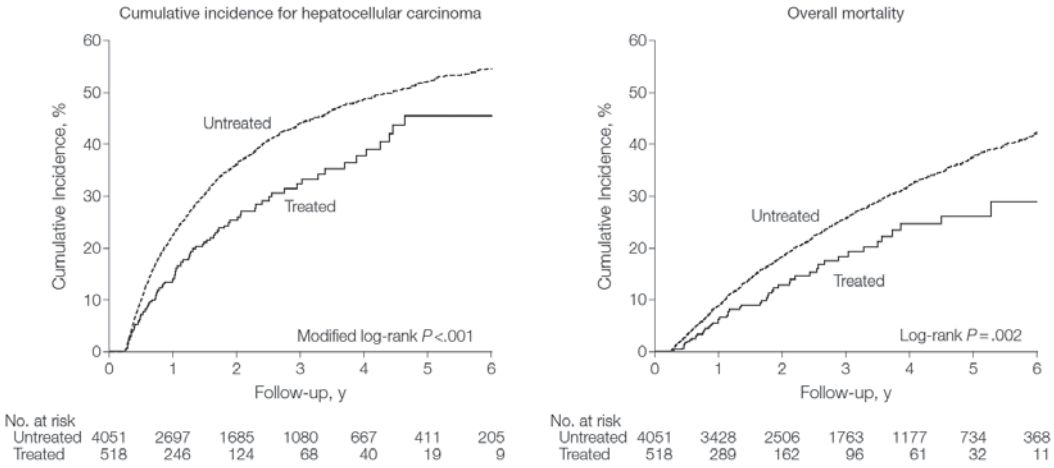
## Non-invasive prediction of liver-related events in patients with HCV-associated compensated advanced chronic liver disease after DAA

Pons M et al., J Hepatol 2020 in press



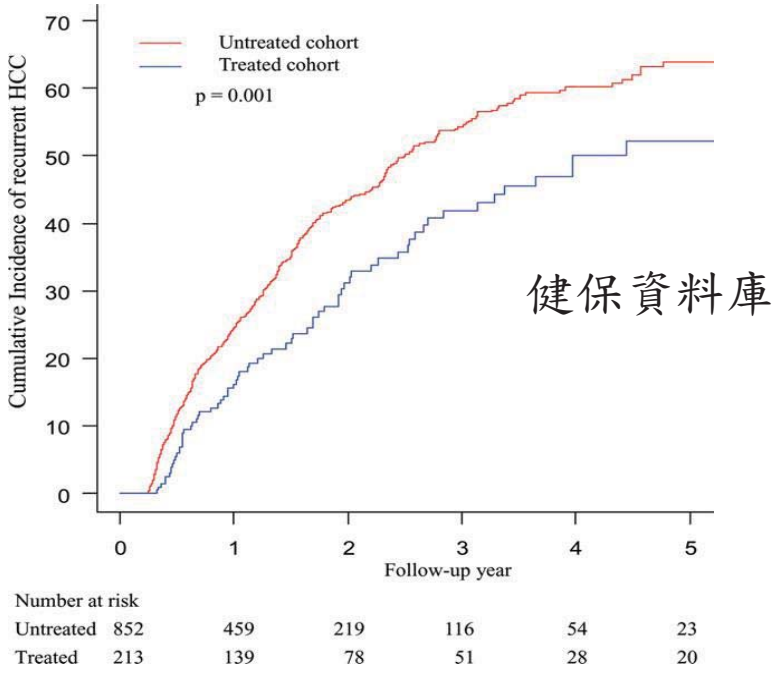

# 治療病毒性肝硬化
# 可以降低肝癌的復發率

# 使用核苷(酸)類似物可以降低術後肝癌的復發




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

# Recurrence of resected HCC in chronic hepatitis C




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

Research Article JH 2016;65:727–733


EASL | JOURNAL OF HEPATOLOGY

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

Fabio Conti[1,†], Federica
Paolo Caraceni[3], F
Gabriel

[1]Research Centre for the Study
[2]Department of Digestive Diseases,
University

ina Crespi[2], Luigi Bolondi[3],
, Giuseppe Mazzella[3],
Brillanti[1,*,‡]

(DIMEC), University of Bologna, Italy;
of Medical and Surgical Sciences (DIMEC),
e di Faenza, Italy

Research Article JH 20

CrossMark

EASL | JOURNAL OF HEPATOLOGY

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

María Reig[1,†], Zoe Mari
Sabela Lens[2], Alba Díaz
Jos

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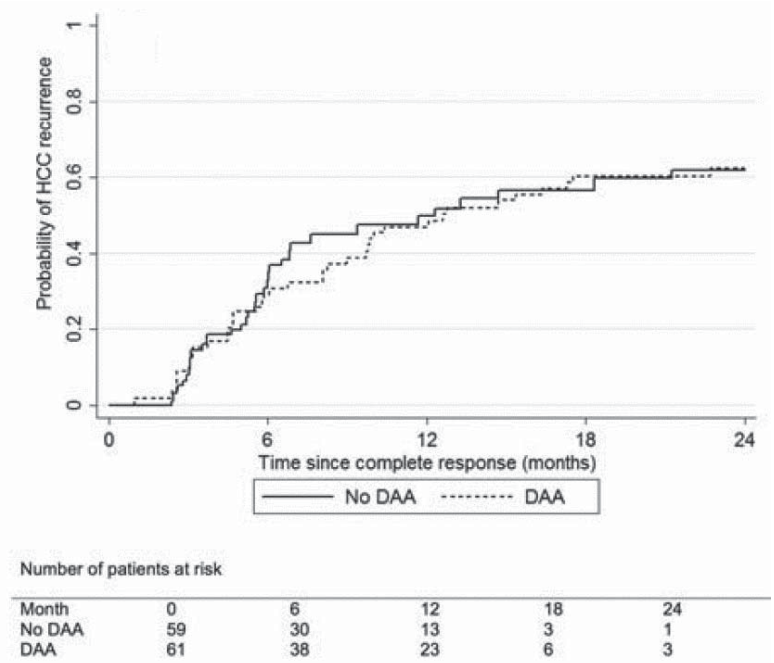
Biomédica en Red de Enfermedades He
Barcelona, CIBERehd, Barcelona, Spain;
Hepatología, Clínica Universidad de Na
Barcelona, IDIBAPS, Universi
University of Barcel

airaegui[4], Andrea Ribeiro[1],
ía Varela[7], Bruno Sangro[4],
uix[1,*,‡]

iversity of Barcelona, Centro de Investigación
r Unit, Hospital Clinic, IDIBAPS, University of
BERehd, IDIPHIM, Madrid, Spain; [4]Unidad de
nt of Pathology, BCLC Group, Hospital Clínic
Group, Hospital Clinic Barcelona,
le Asturias, Oviedo, Spain

# DAAs Do Not Increase the Risk of HCC Recurrence After Local-Regional Therapy




- Retrospective study
- 149 LT candidates
- inverse probability of treatment weights (IPTW)

Huang AC et al, HEPATOLOGY 2018; 68:449-461

# Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression

Waziry et al., JH 2017;67:1204–1212

Reem Waziry[1,*], Behzad Hajarizadeh[1], Jason Grebely[1], Janaki Amin[2], Matthew Law[1], Mark Danta[3], Jacob George[4], Gregory J. Dore[1]

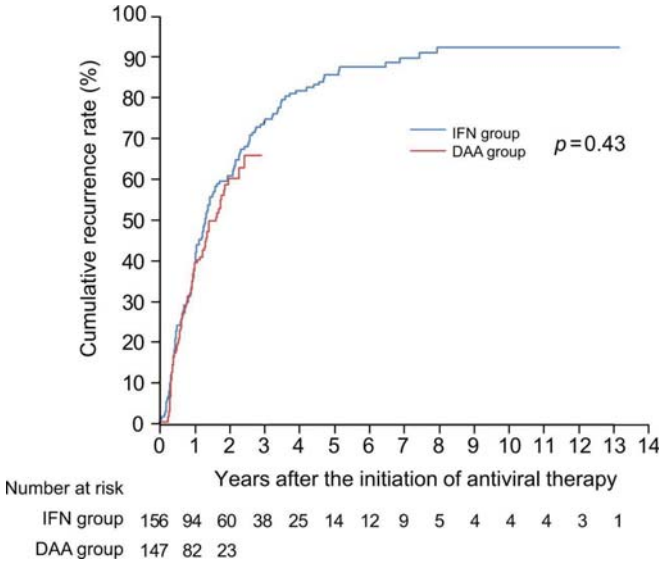
[1]*The Kirby Institute, UNSW Sydney, Sydney, Australia;* [2]*Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia;* [3]*St Vincent's Clinical School, UNSW Sydney, Australia;* [4]*Storr Liver Centre, Westmead Millennium Institute and Westmead Hospital, University of Sydney, Sydney, Australia*

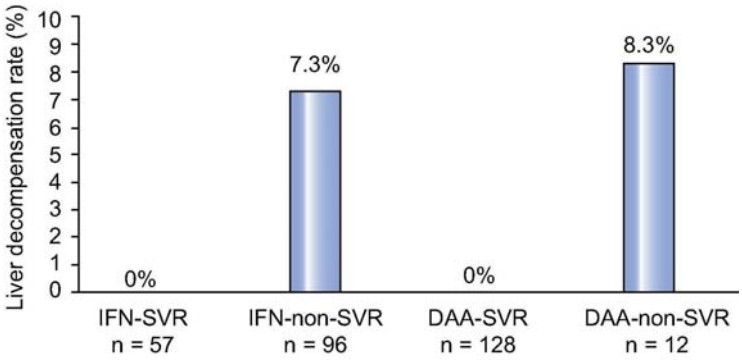
**Table 4**. Meta-regression analysis of factors associated with recurrence of hepatocellular carcinoma following HCV cure (Observations = 17).

| Variable | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | RR | 95% CI | *p* value | aRR | 95% CI | *p* value |
| Treatment | | | | | | |
| IFN | 1.00 | – | – | 1.00 | – | – |
| DAA | 1.36 | 0.49–3.76 | 0.53 | 0.62 | 0.11–3.45 | 0.56 |
| Average follow-up, years | 0.86 | 0.70–1.05 | 0.15 | 0.79 | 0.55–1.15 | 0.19 |
| Average age | 1.11 | 0.96–1.28 | 0.12 | 1.11 | 0.96–1.27 | 0.14 |
| Genotype 1 | 1.01 | 0.97–1.05 | 0.49 | – | – | – |

All numbers were rounded to two decimal places.
aRR, adjusted rate ratio; CI, confidence interval; DAA, direct-acting antiviral; IFN, interferon; RR, Rate Ratio.

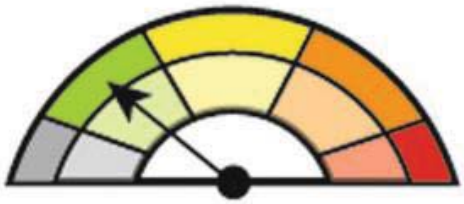
## HCC recurrence rates did not differ between patients who received IFN-based therapy and DAA therapy



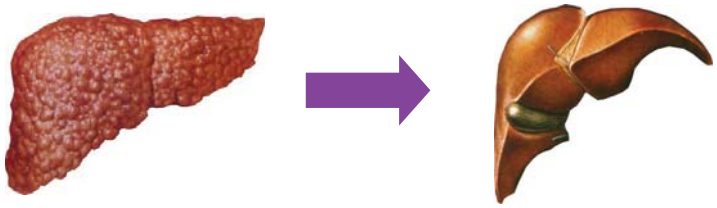

Nishibatake Kinoshita M et al, J Hepatol 2019;70:78-86

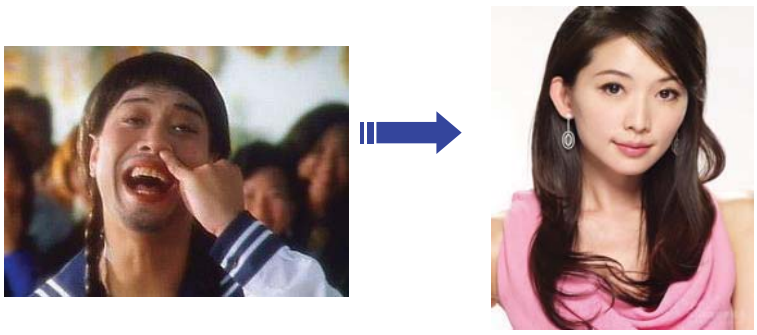
# Benefit of DAA

| LEVEL OF EVIDENCE | DAA BENEFITS |
| --- | --- |
| Low-Inconclusive Level  | HCC recurrence |

Ioannou GN & Feld JJ. Gastroenterology 2019

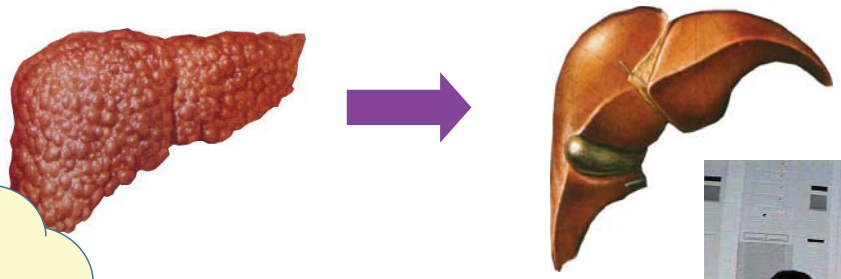
# 逆轉肝硬化 (in the past)





**Mission impossible**

# 逆轉肝硬化 (now)



肝硬化是可逆的

**Mission impossible?**

Tom Cruise都完成了耶!

**Mission possible**

# 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
- 需要積極治療
- 與移植中心合作


來治療B、C肝

**您與您的病人，可以雙贏**

# Thanks