



## INHSU 2018



# 7<sup>th</sup> International Symposium on Hepatitis Care in Substance Users

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### Management of advanced liver disease and risk of HCC

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### Financial Disclosures

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Advisory committees: Merck, Roche, Novartis, Bayer, BMS, Gilead Science,  
Tibotec, Vertex, Janssen, Achillion, Lundbeck,  
GSK, GenSpera, AbbVie, Alfa Wasserman, Intercept.

Speaking and teaching: Tibotec, Roche, Novartis, Bayer, BMS, Gilead  
Science, Vertex, Merck, Janssen, AbbVie

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## Management of Advanced Liver Disease and Risk of HCC

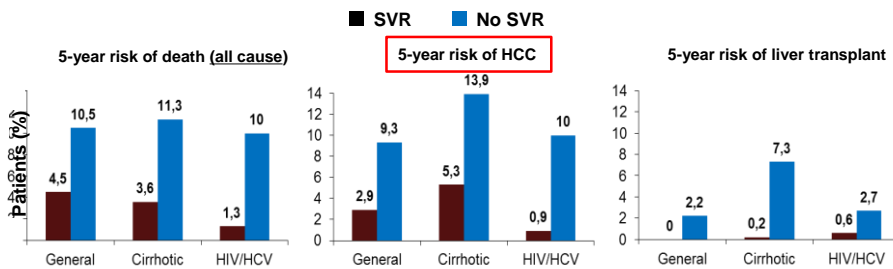
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1. The lesson from Interferon : HCC and mortality reduced.
  2. Is HCC risk further attenuated by DAA therapy?
  3. Is HCC recurrence attenuated by DAA therapy?
  4. Is HCC more aggressive after DAA therapy?
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### SVR is Associated with a Reduced Mortality HCC and Liver Transplant

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Systematic review of 129 studies of IFN-based therapy in 34,563 HCV patients



Achieving SVR was associated with:

- 62–84% reduction in all-cause mortality
- 68–79% reduction in risk of HCC**
- 90% reduction in risk of liver transplant

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Saleem J, et al. Hepatology 2014

## Determinants of Residual HCC Risk in HCV Patients The Veterans Affairs (n = 22,028)

HCC x 1000 PY : 3.27 SVR vs 13.2 non SVR (HR: 0.358)

Predictor of HCC after an SVR*	HR (95% CI)	P-value
➤ <b>Cirrhosis at SVR</b>	4.45 (2.53-7.82)	< .0001
➤ <b>Age at SVR</b> , yrs (vs < 55 yrs)		
▪ 55-64	2.40 (1.53-3.77)	.0002
▪ 65 or older	4.69 (2.04-10.78)	.0003
➤ <b>Diabetes</b>	2.07 (1.35-3.20)	.0010
➤ <b>HCV GT</b> (vs GT1)		
▪ HCV-2	0.56 (0.32-1.01)	.0522
▪ HCV-3	1.91 (1.14-3.18)	.0131

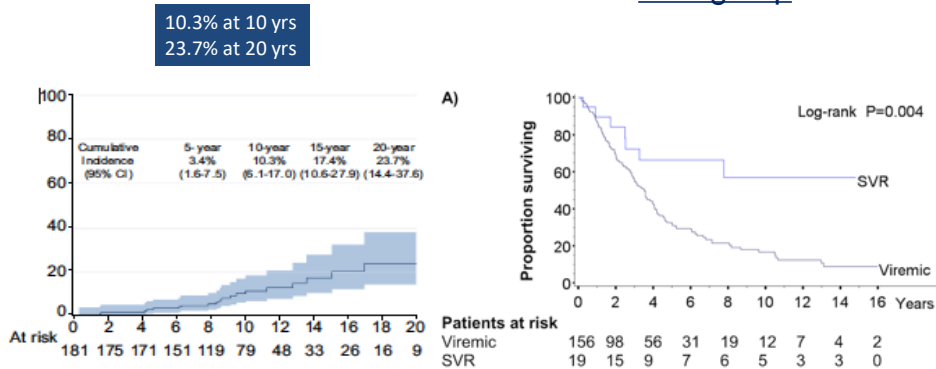
\*Cox proportional hazards model adjusted for competing risk of death.

*El-Serag HB, et al Hepatology 2016*

## Persistence of HCC Coupled with Improved Survival after SVR. Milan & Palermo Cohorts

### Hepatocellular Carcinoma

### Patients developing HCC during f-up



*Bruno S, Colombo M, Craxi A et al J Hepatol 2016*

*Bruno S, Colombo M, Craxi A et al Liver Intern 2017*

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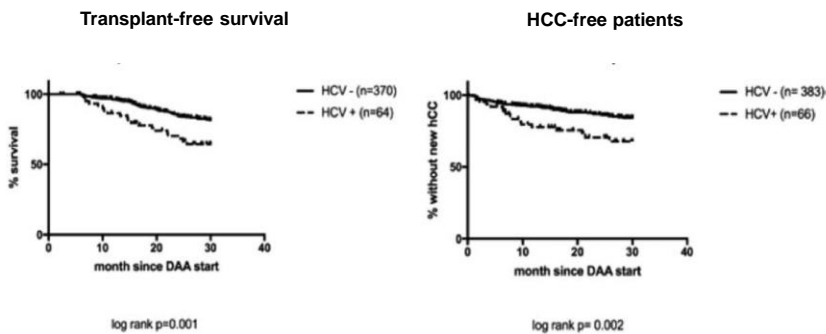
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## Interferon-free DAA Improves the Outcome of Decompensated HCV

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### The Expanded Access Program in U.K



*Cheung M et al EASL ILC Paris 2018 LBP-009*

## All-causes Mortality and HCC Both Reduced by DAA 129 Veterans Affairs Hospitals

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### Veterans Affairs . HCC after DAA

- Adjusted HR of HCC in SVR : 0.28 (0.22-0.36) p < .0001
- 44.8% HCC classified as stage I
- Predictors of persistent HCC risk after SVR : > age  
cirrhosis  
diabetes

Caveats : HCC diagnosed with ICD-9 and 10 codes

*Kanwal et al Gastroenterology 2017*

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*Backus LI et al AASLD Washington 2017 abs # 78 ; Backus LI et al Hepatology 2018*

## A Prospective Observational Study with Planned Surveillance for HCC.NAVIGATOR

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### Second year follow-up

- HCC rates :
 

Metavir stage F3	=	0%
Child-Pugh A	=	0.25%
Child-Pugh B	=	0.69%
- Aggressive tumor : 29% , mostly within 6 mo.of DAA therapy  
non SVR > SVR

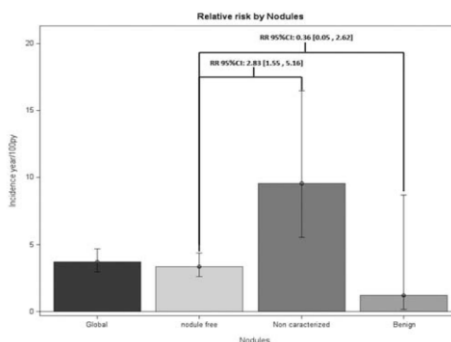
Romano A et al J Hepatol 2018

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*Romano A.et al AASLD 2016 abs #19*

## Increased Risk of HCC in HCV Cirrhotic Patients After DAA. A Multicenter Study Spain

- 1,123 patients, 61% males, 84% Child-Pugh A
- 95% achieved SVR
- 72 developed HCC after 10.3 mo. from DAA start
- **HCC incidence** : 3.73 HCC/100 PY (95% CI 2.96-4.70)

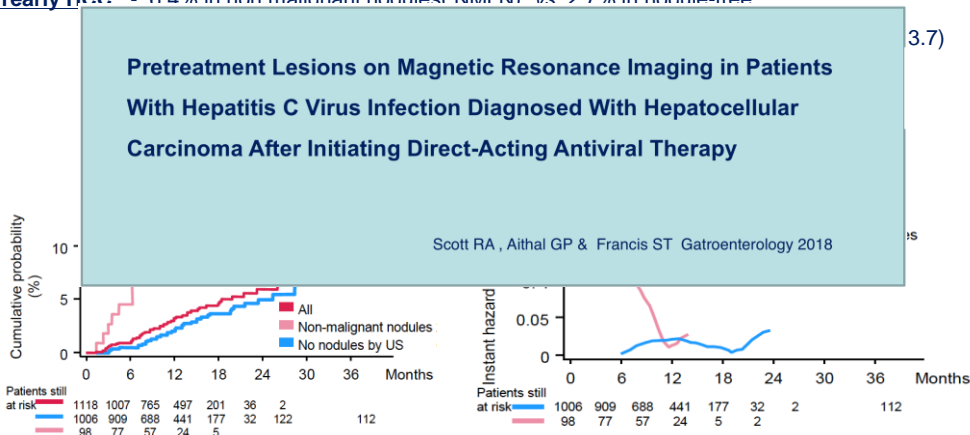


**Increased RR of HCC** : CPT B/C, alcohol, CSPH, non characterized nodules

*Reig M et al EASL ILC Paris 2018 LBP-024*

## Pre-existing Liver Nodules & Early De-novo HCC AISF Multicenter Study, Italy

**Yearly HCC** - 6.4% in non malignant nodules( NMI N) vs. 2.7% in nodule-free



*Sangiovanni A et al EASL ILC Paris 2018 PS-152*

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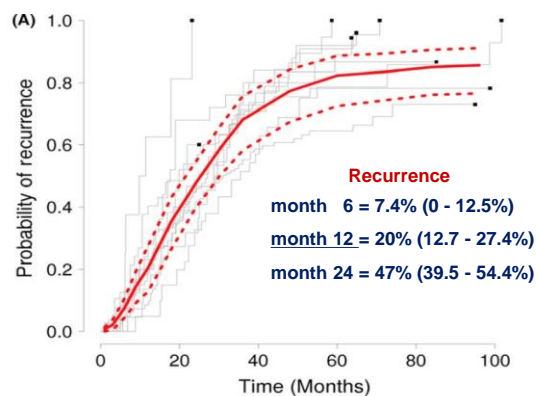
## Recurrence Rates of HCC in HCV Viremic Patients After Curative Resection or Ablation

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### META ANALYSIS

Ikeda 2000  
 Suou 2001  
 Shiratori 2003  
 Hung 2005  
 Nishiguchi 2005  
 Yamanaka 2005  
 Mazzaferro 2006  
 Kudo 2007  
 Jeong 2007  
 Kanogawa 2014  
 Petta 2016

Total of 701 viremic patients



Recurrence risk : albumin, RCT and follow-up

Mortality risk : tumor size and AFP

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## DAA and Increased Risk of HCC Recurrence The Start of the Debate

### CONFIRMATORY STUDIES

- Conti et al, J Hepatol 2016
- Reig et al, Multicenter study in Spain, EASL ILC AMS 2017
- El Kassas et al, JVH 2018 (increased severity not confirmed)

*Reig M et al J Hepatol 2016*

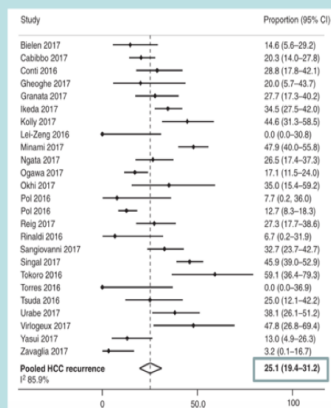
## Studies with Direct Comparisons of Recurrence Rates A Recent Meta-analysis

### Predictors of early recurrence :

- history of prior HCC recurrence
- shorter interval tumor CR – DAA initiation

### Study limitations : heterogeneous cohorts

- potential misclassification
- ascertainment bias for recurrence
- short durations of f-up



*Saraiya N et al Aliment Pharmacol Ther. 2018;48:127-137.*



## Increased Incidence vs Accelerated Recurrence of HCC in DAA Treated Patients?

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### A retrospective study of 191 patients in 10 US centers

- Jan 2013 - dec 2016	107 DAA treated
- HCC treatment	32% Res, 35% LAT, 27% TACE
- Recurrence rates	n. 87, 42% DAA <u>vs</u> 53% untreated(p=n.s)
- <u>Days to recurrence</u>	223 DAA <u>vs</u> 554 untreated (p<.006)
- HCC beyond Milan	27%

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*Singal A AASLD Washington 2017 abs 191*

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## Increased Recurrence/Aggressiveness After DAA A Confirmatory Multicenter Study

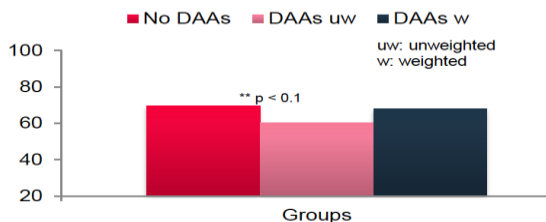
Whole cohort (n=77)		
Median follow-up, months	12.4 (IQR: 8.4-18.7)	
HCC progression	n= 24 (31.2%)	16.7% BSC
Death	n=5 (6.5%)	
HCC recurrence (n=24)		
Median months between start DAA and 1 <sup>st</sup> HCC recurrence	3.5 (IQR: 2-7.6)	
2 <sup>nd</sup> recurrence / progression		n=10
Median months between 1 <sup>st</sup> - 2 <sup>nd</sup> HCC recurrence/progression	6 (IQR:3.2-8.2)	37.5 % Ablation Resection LT
Recurrence/progression within 6 months of 1 <sup>st</sup> recurrence	6/20 (30%)	
Death	n=5 (20.8%)	45.8 % TACE Sorafenib Regorafenib RE Clinical Trials

*Reig M et al EASL ILC Amsterdam 2017; Abstract PS-031*

## Is HCC Developing After DAA More Aggressive ? Multicenter Study in Resected Livers

- 420 consecutive patients with HCC/HCV cirrhosis undergoing liver resection in 18 Italian centers.
- 77 (18.3%) developed either recurrent or de novo HCC after DAA therapy.
- Study group vs controls : tumors 25 mm vs 35 mm
  - severe complications in 3.4% vs. 9.3%
  - early postoperative mortality in 2.0% vs 5.4%.

Rate of HCC-G3 or vascular invasion or satellitosis



*Vitale A et al EASL ILC Paris 2018 PS-023*

## Pattern of HCC Recurrence After DAA Therapy Access to Curative Treatments

Author year	Number with HCC recurrence	Tumour burden at time of recurrence	HCC-directed treatment
Bielen 2017 <sup>16</sup>	6	33% BCLC A, 33% BCLC B, 17% BCLC C, 17% unknown	17% resection, 33% TACE and 50% supportive care
Cabibbo 2017 <sup>17</sup>	29	62% BCLC A, 21% BCLC B, 7% BCLC C, 10% BCLC D	38% resection or ablation, 45% TACE and 7% systemic therapy
Reig 2017 <sup>21</sup>			resection or ablation, systemic therapy
Conti 2016 <sup>23</sup>			ablation
Rinaldi 2016 <sup>25</sup>			
Granata 2017 <sup>30</sup>			
Yasui 2017 <sup>32</sup>			resection or ablation, supportive care
Minami 2017 <sup>33</sup>			
Ohki 2017 <sup>34</sup>			
Sangiovanni 2017 <sup>35</sup>			resection or ablation, systemic therapy
Singal 2017 <sup>37</sup>			resection or ablation, 54% TACE and 7% systemic therapy
Tokoro 2016 <sup>38</sup>	13	Diameter 1.2 cm (0.7-2.0)	Not reported
Tsuda 2016 <sup>39</sup>	9	56% unifocal, 22% 2-3 nodules, 22% >3 nodules	Not reported

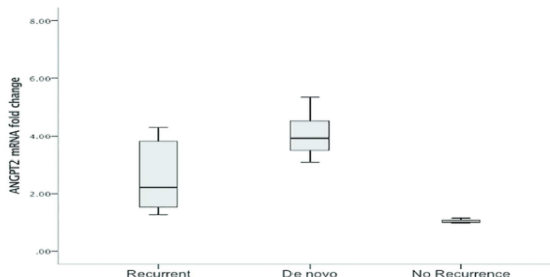
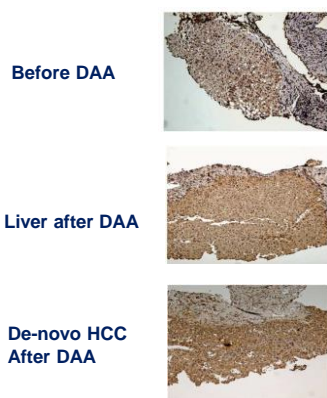
**Pattern of HCC recurrence**

- Early HCC in 77.8 %
- Curative treatments in 64.7%

Saraiya N et al Aliment Pharmacol Ther. 2018;48:127–137.

## Liver Angiopoietin-2 Predicts De Novo and Recurrent HCC after DAA. A Prospective Study

**Predictors of HCC :** high liver fibrosis scores, portal pressure and systemic inflammation



Faillaci F et al Hepatology 2018

## 2018 EASL CPG on HCC

Recommendations	■ Level of evidence	■ Grade of recommendation
Once cirrhosis is established: <ul style="list-style-type: none"> <li>• <b>Antiviral therapy*</b> is beneficial in <b>preventing cirrhosis progression</b> and decompensation</li> <li>• Successful <b>antiviral therapy reduces but does not eliminate</b> the risk of <b>HCC</b> development</li> </ul>	Moderate	
For patients with HCV-associated cirrhosis and treated HCC: <ul style="list-style-type: none"> <li>• <b>HCC recurrence rate is high</b> even after SVR with DAA therapy<sup>†</sup></li> <li>• <b>Close surveillance is advised</b> in these patients</li> <li>• The benefit of viral cure must be weighed against a potentially higher recurrence risk</li> </ul>	Low	Strong

*EASL CPG HCC J Hepatology 2018*

## Management of Advanced Liver Disease and Risk of HCC

- |   |                             |
|---|-----------------------------|
| 1. Is the incidence of de-novo HCC increased?         | No, likely to be reduced    |
| 2. Are de-novo tumors more aggressive?                | No, sparse cases only       |
| 3. Is time to recurrence from a tumor cure shortened? | Yes, significantly          |
| 4. Are rates / pattern of recurrent HCC modified?     | High quality studies needed |

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## Liver Cancer is the Dominant Cause of Death in HCV The REVEAL Study

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Causes of Death	Multivariate-adjusted HR (95%CI)
All causes	1.89 (1.66–2.15)
All liver-related	12.48 (9.34–16.66)
<b><u>Hepatocellular carcinoma (HCC)</u></b>	<b><u>21.63 (14.83–31.54)</u></b>
All extrahepatic diseases	1.35 (1.15–1.57)
All cancer, except HCC	1.32 (1.00–1.74)
Cardiovascular diseases	1.50 (1.10–2.03)
Nephritis/nephrosis	2.77 (1.49–5.15)

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*Lee et al, J Infect Dis 2012;206:469-77*

## Competing Risks of Death in Compensated Cirrhosis A Multicenter Study in France

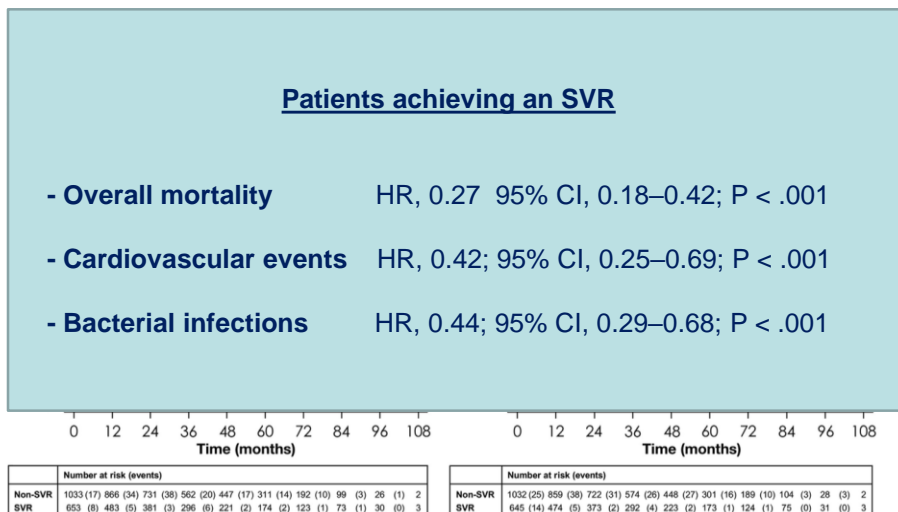
35 Centers : follow-up 34 months from 2006 to 2012

	HCV (n=1308)	HBV (n=315)	HCV and HBV (n=31)	Whole cohort (n=1654)
<b>Death</b>	<b>93 (7.1%)</b>	<b>6 (1.9%)</b>	<b>3 (10%)</b>	<b>102 (6.2%)</b>
<b><u>HCC-related</u></b>	<b>17 (19.5%)</b>	1 (16.6%)	0	18 (18.7%)
<i>Non-HCC liver-related</i>	27 (30.7%)	2 (33.3%)	1 (50%)	30 (31.2%)
<i>Bacterial infection</i>	13 (14.7%)	0	0	13 (13.5%)
<i>Extrahepatic cancer</i>	7 (7.9%)	3 (50%)	0	10 (10.4%)
<i>Cardiovascular disease</i>	5 (5.7%)	0	0	5 (5.2%)
<i>Other extrahepatic dis.</i>	19 (21.5%)	0	1 (50%)	20 (20.8%)
<i>Missing data</i>	5 (5.4%)	0	1 (33.3%)	6 (5.8%)

-49.8%

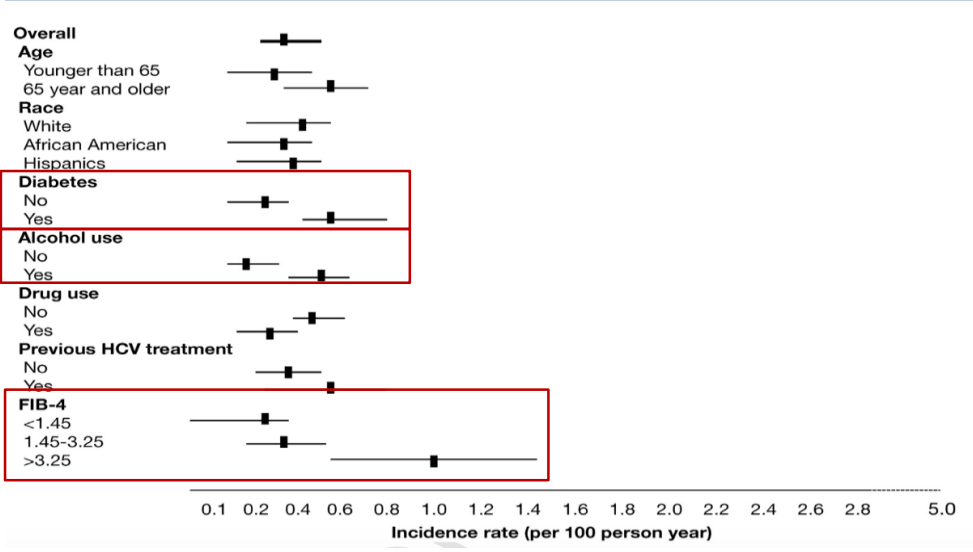
*Trinchet et al, Hepatology. 2015;62:737-50*

## IFN Eradication of HCV in Cirrhosis Reduces Risk of Liver and Non-Liver Complications



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

### Annual Incidence of HCC Among Non-cirrhotic Patients with SVR



Kanwal et al Gastroenterology 2017