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Organised by Pr Patrick Marcellin

A Sad Story…

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Abbvie, BMS, Gilead, MSD

UFC
UNIVERSITÉ DE FRANCHE-COMTÉ

Case report (1)

- Mr T. Philippe 55 yrs old
- Past IV drug user (1985)
- Morbid obesity (149kgs/1.90m; BMI=41.3kg) . Gastric band in 2006: Mascoscopic aspect of liver cirrhosis during surgery. Hep C genotype 4 subsequently diagnosed.
- Good efficacy of gastric band: losses 41 Kgs within 10 months. Persistent Diabetes.
- Peg-IFN+RBV (2007): Null responder. Stop at 3 months. Maintenance therapy during one year. Poor tolerance.

Case report (2)

- In August, 2013 jaundice revealing angiocholitis. Undergoes ERCP+ cholecystectomy. First episode of ascitis after surgery. Child-Pugh B9. Favorable outcome on diuretics: B9->B8.
- In December, 2013, listed for liver transplantation
- In January, 2014, receives Sofosbuvir + RBV 3 months then sofosbuvir + daclatasvir 3 months.
- SVR achieved. Child-Pugh A6 on Sept, 2014.

How SVR could be beneficial for this patient?

- Improvement of survival
- Decreased risk of hepatocellular carcinoma
- No longer need for liver transplantation
- Improvement of diabetes
- Decreased risk of stroke and coronary disease
- All the above

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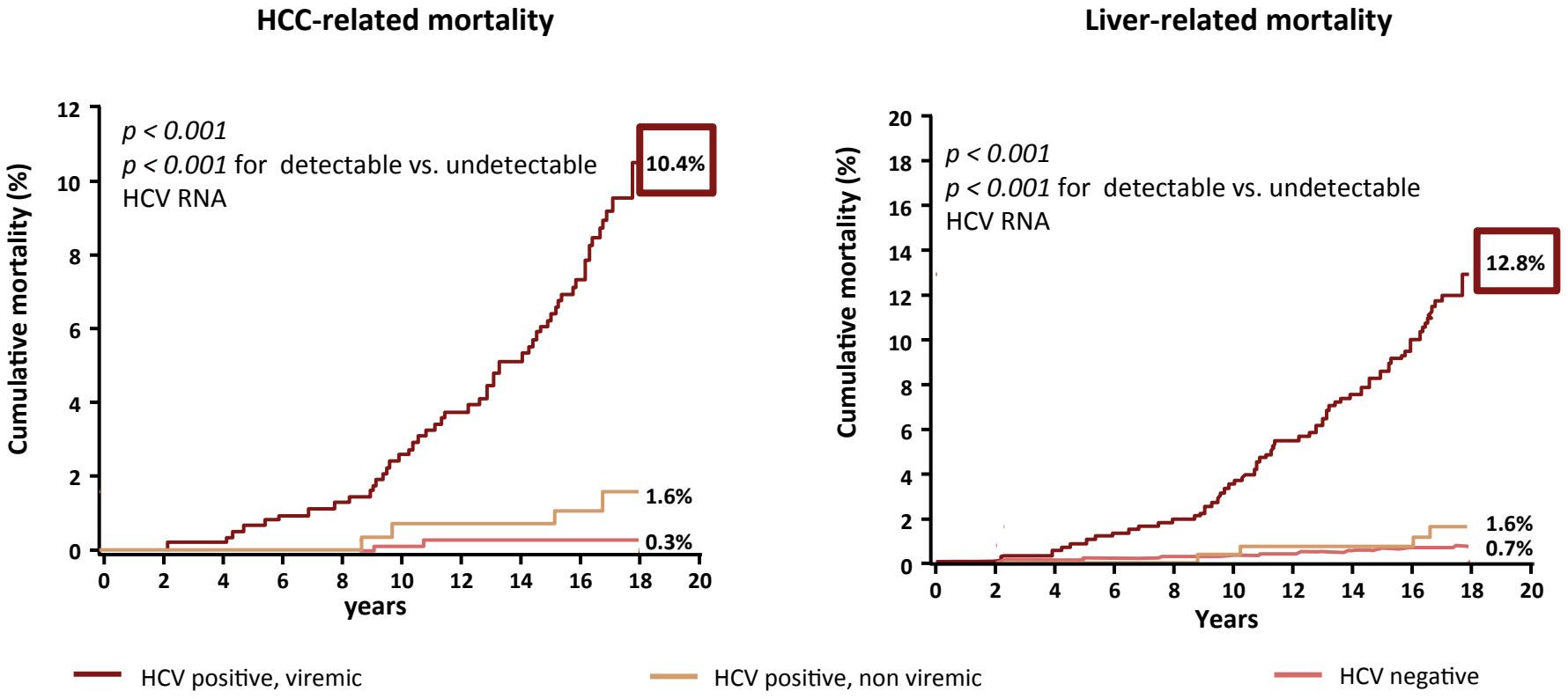
Persistent HCV viremia is associated with liver-related mortality

REVEAL-HCV Cohort study on 23 820 patients including 1095 patients HCV positive

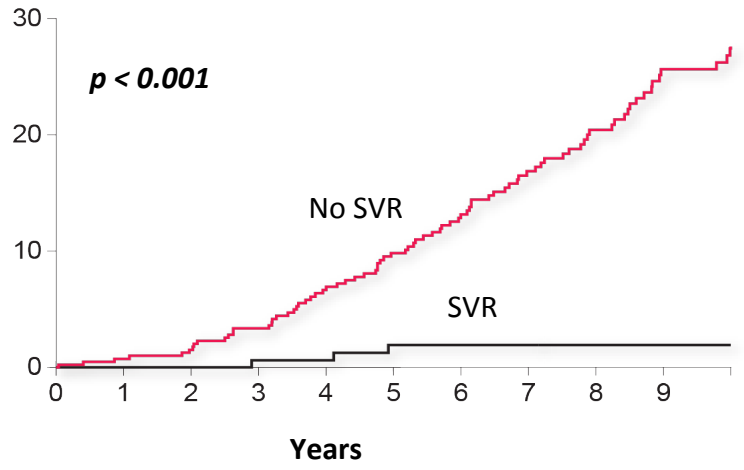


Lee *et al*. *J Infect Dis*. 2012; 206(4): 469-77.

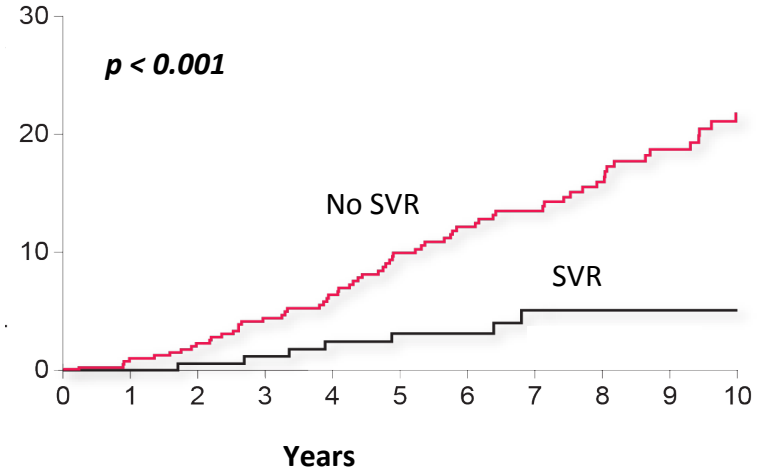
Impact of SVR on liver related mortality and HCC

Muticentric cohort study in 530 patients who received IFN based therapy between 1990 and 2003.

Liver-related mortality or LT

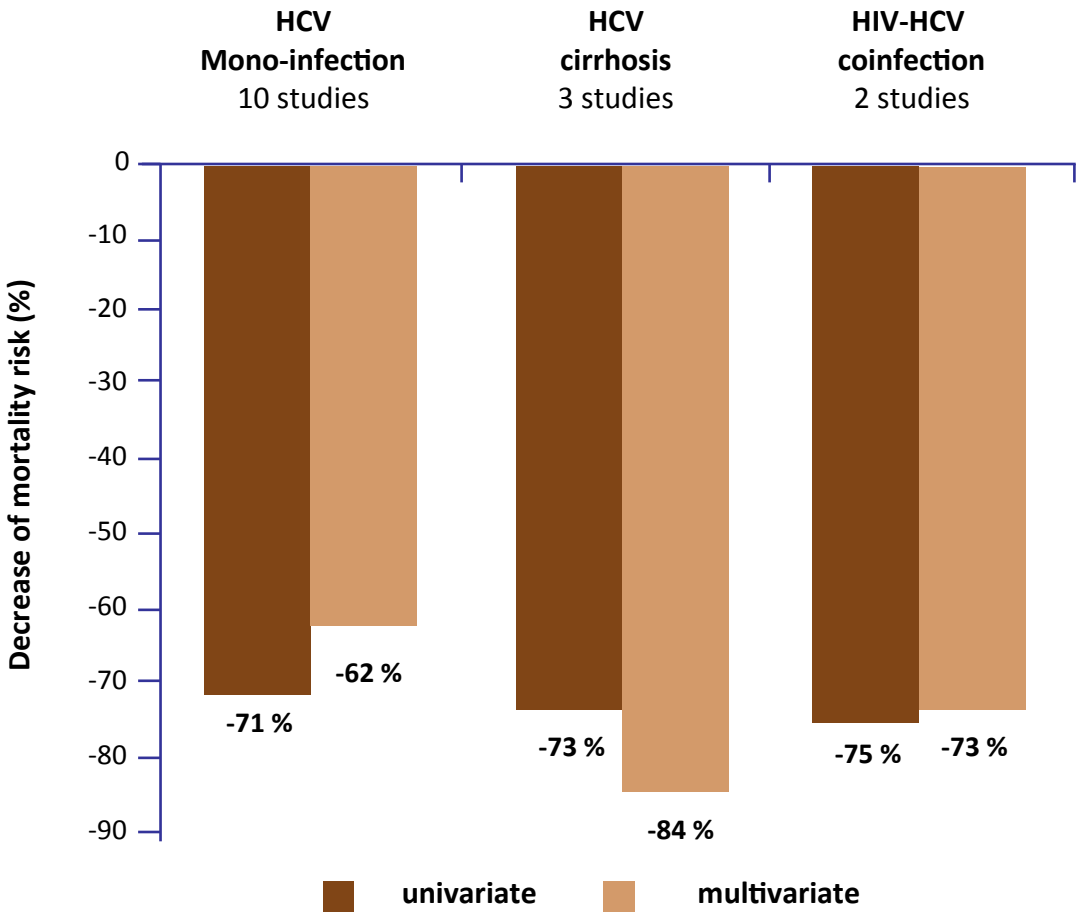


HCC



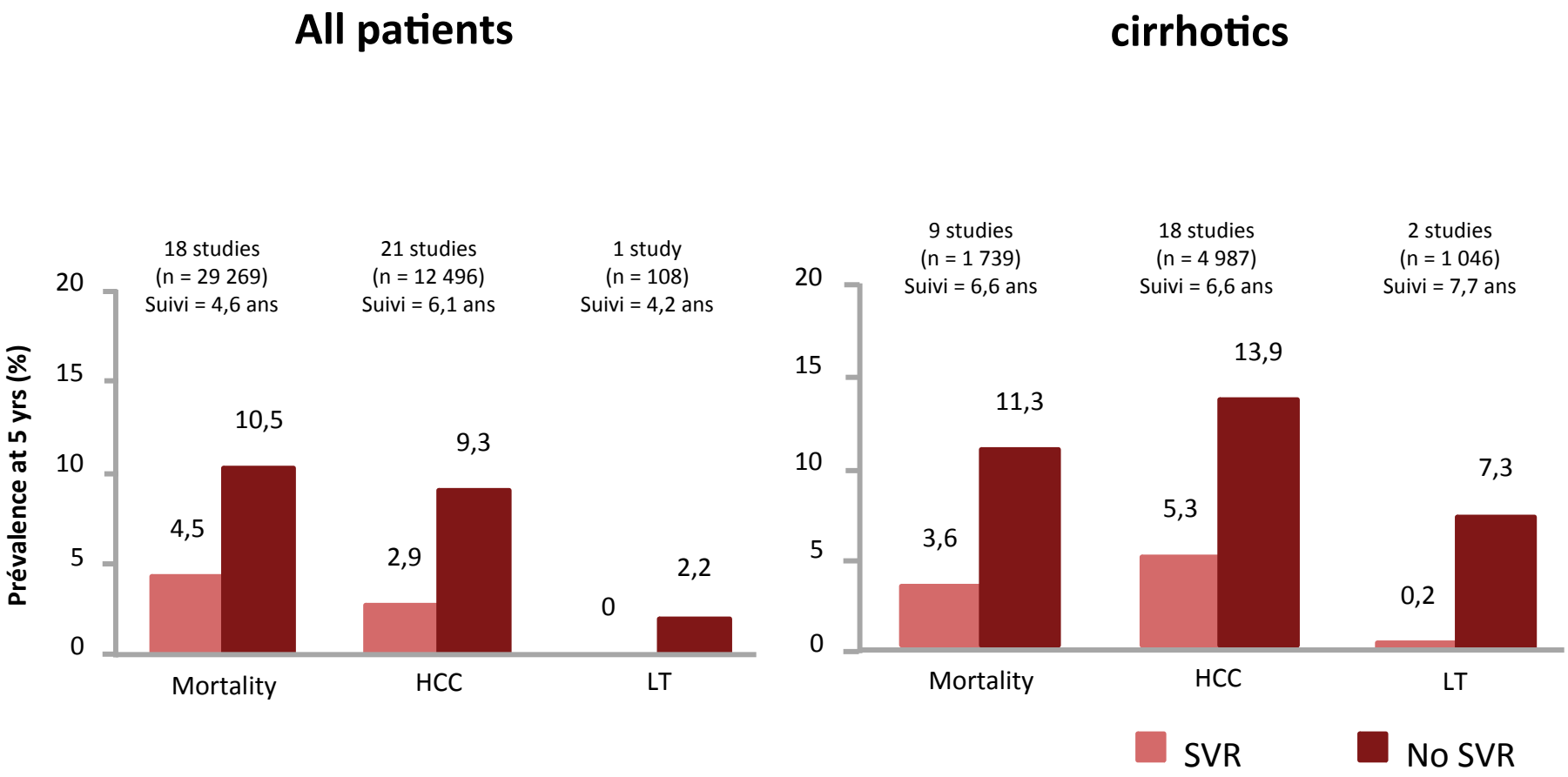
van der Meer *et al*. *JAMA*. 2012; 308(24): 2584-93.

Impact of SVR on of HCV-related mortality: Meta-analysis on 34,563 patients



Hill *et al*. AASLD 2014. Abstract 44.

Impact of SVR on the outcome of HCV-related liver disease: Meta-analysis on 34,563 patients



Hill *et al*. AASLD 2014. Abstract 44.

Regression of HCV cirrhosis: a true event

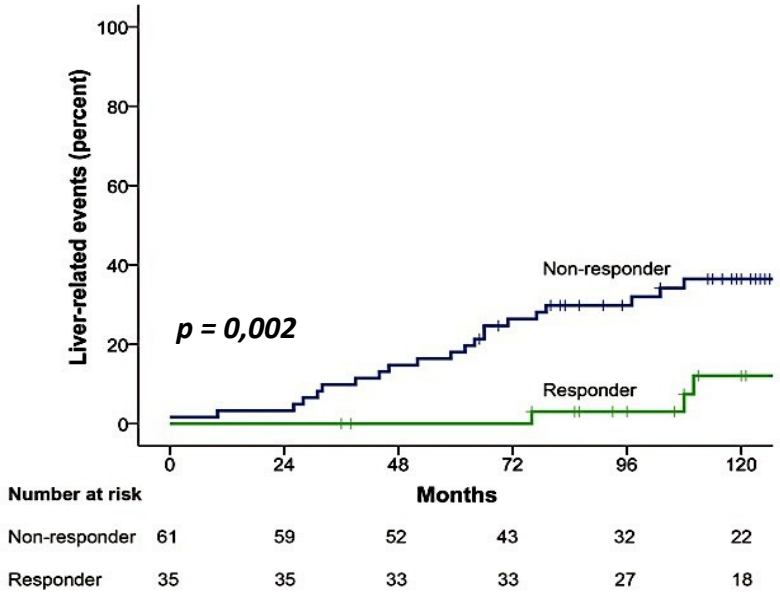
The study	Nr of pre-treatment cirrhotics with SVR	Cirrhosis regression among SVR	Mean/median follow-up time months
Abergel, 2004	18	6 (33%)	6
Maylin, 2008	14	9 (64%)	6 (range 0-14 y)
Mallet, 2008	35	22 (63%) if one stage less, (17/35, 49% if 2 stages less)	11-17
Everson, 2008	40 (F3-F4)	20 (50%)	19.8
Poynard, 2002	37	25 (68%)	21±4
Arif, 2003	6	5 (83%)	27±9
George, 2009	8	6 (75%)	At least 48
Pol, 2004	17	4 (24%)	55.2±26.4
Reichard, 1999	3	3 (100%)	60±22
D'Ambrosio, 2012	38	23 (61%)	61 (range 48-104)

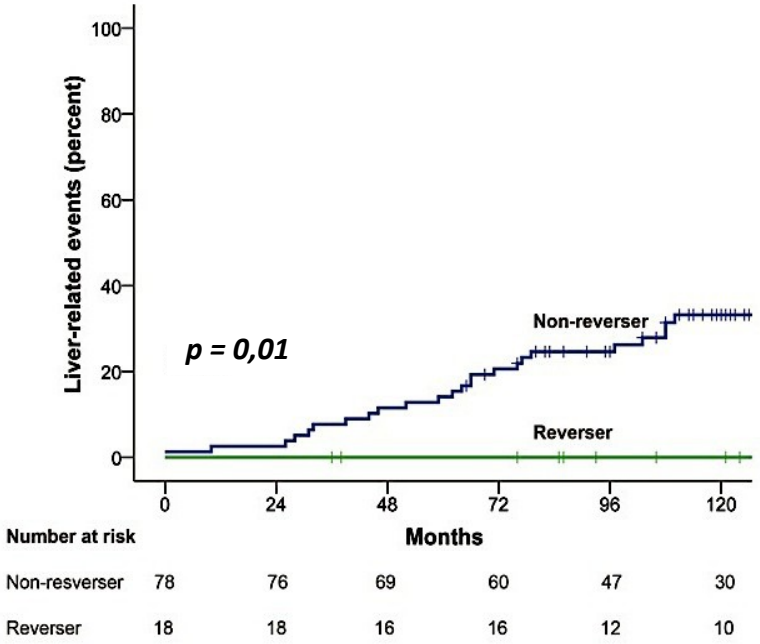
113 pat with pre-tx cirrhosis and liver biopsies after SVR

Akhtar E et al, Liver Int 2015

Impact of SVR on cirrhosis-related complications and mortality

French cohort study conducted between 1988 and 2001, in 96 patients with histologically-proven HCV cirrhosis





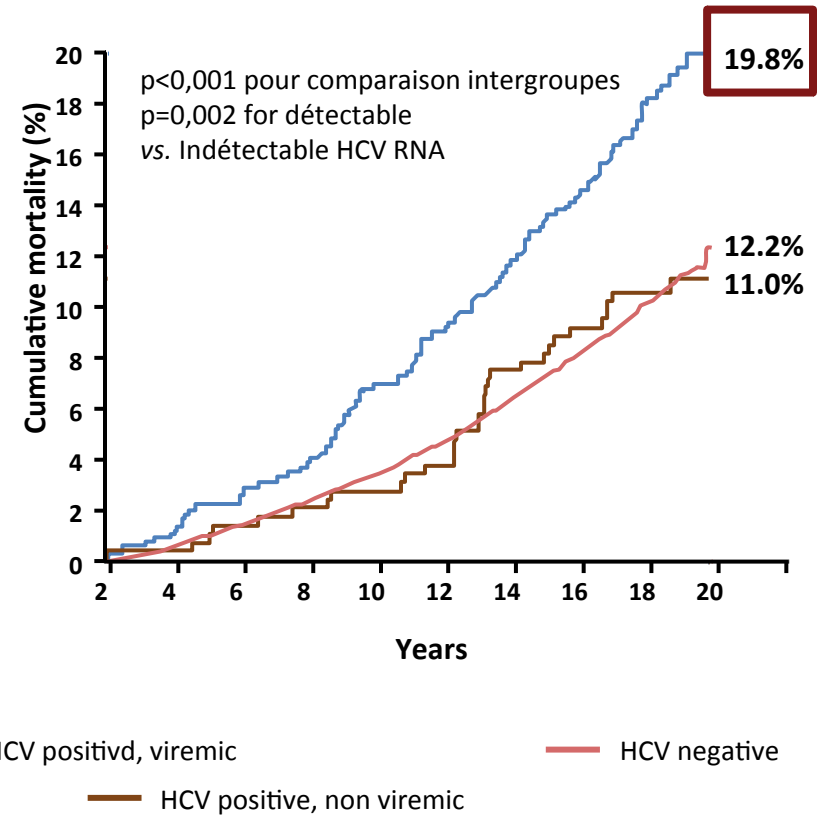
RVS may induce cirrhosis reversion that cancels the risk of cirrhosis-related complications and mortality
The identification of the 'reversers' is challenging

Mallet *et al*. *Ann Intern Med*. 2008 Sep 16;149(6):399-403.

HCV and extrahepatic mortality

- Significant association between HCV and:
  - diabetes (OR = 1.8) 1*
  - cardiovascular disorders (OR=2.37) 2*
  - stroke (OR= 2.7) 3*
  - Renal disorders (HR if< 59 yrs= 7.8 *vs.* 3.2) 4*
  - Neurocognitive disorders 3
  - Extrahepatic malignancies (breast: OR = 2) 5

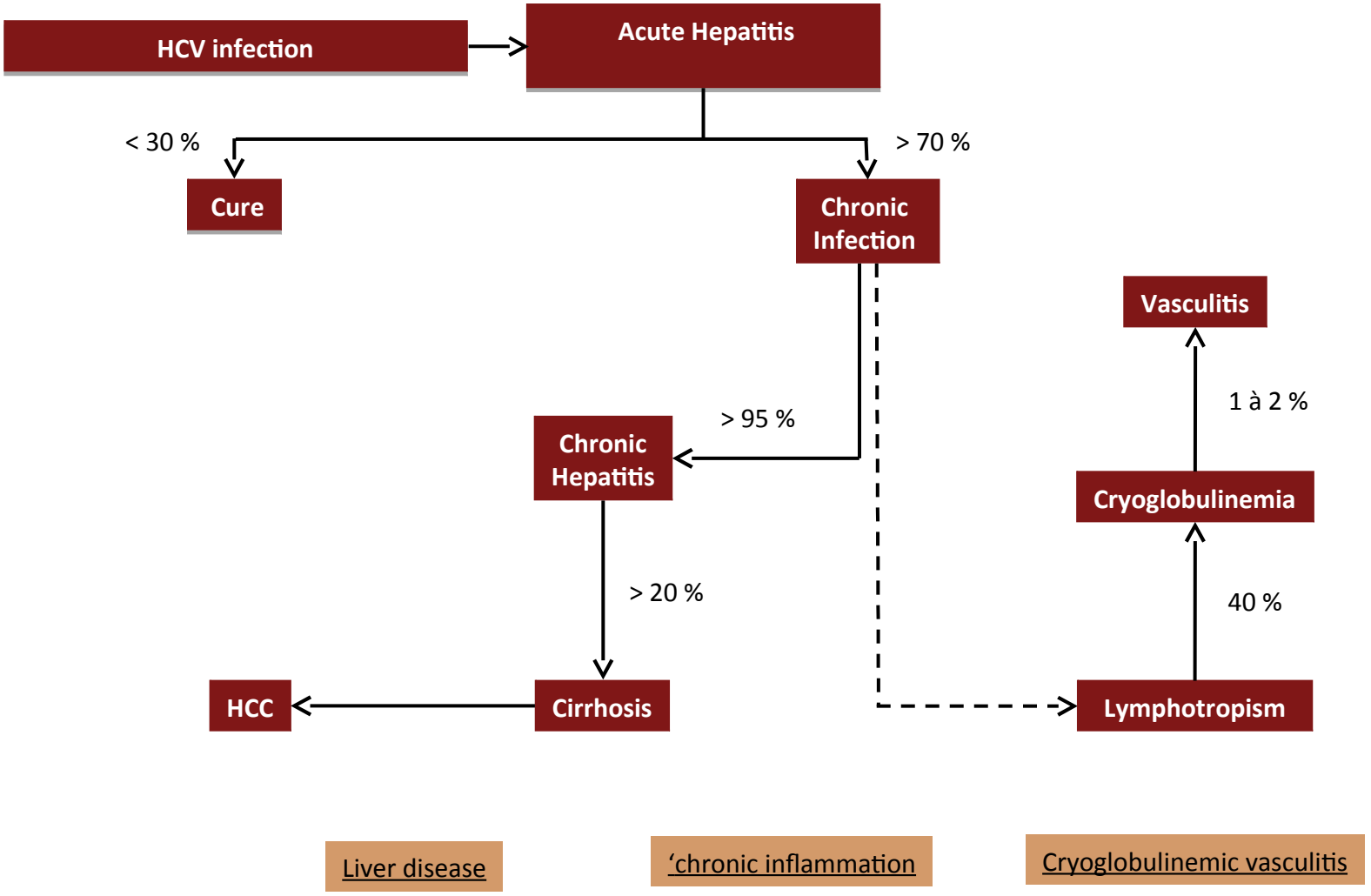
Extrahepatic mortality according to HCV status



* Impact of metabolic syndrome

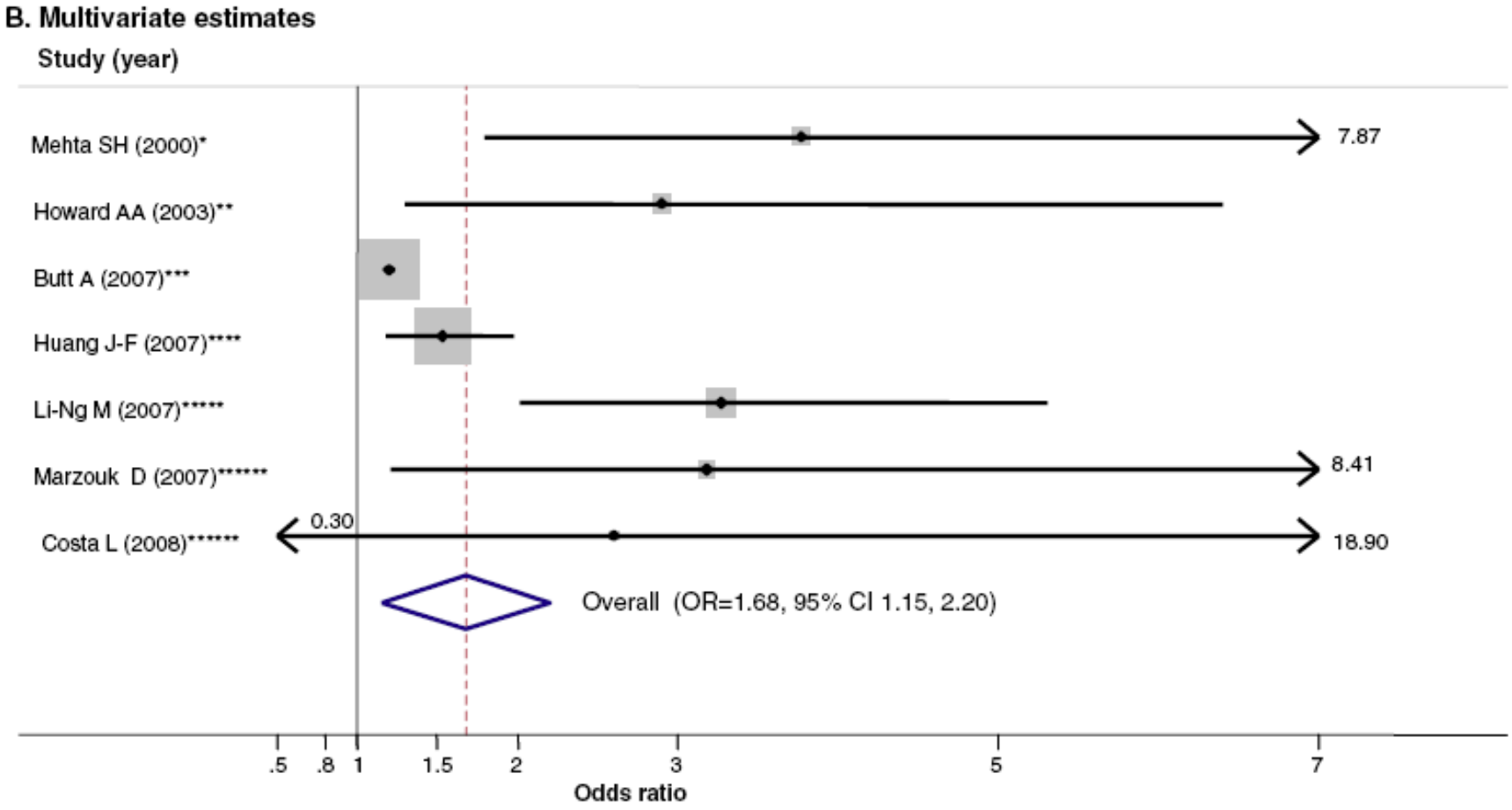
1) White *et al*. *J Hepatol*. 2008; 49(5): 831-44. **2)** Kakinami *et al*. *Int J Clin Pract*. 2013; 67(1): 6-13. **3)** Lee *et al*. *Stroke*. 2010; 41(12): 2894-900. **4)** Su *et al*. *Am J Kidney Dis*. 2012; 60(4): 553-60. **5)** Su *et al*. B*MC Cancer*. 2011; 11: 495. **6)** Lee *et al*. *J Infect Dis*. 2012; 206(4): 469-77.

HCV clearance reduces hepatic and extrahepatic mortality: the concept of 'HCV-related chronic inflammation'



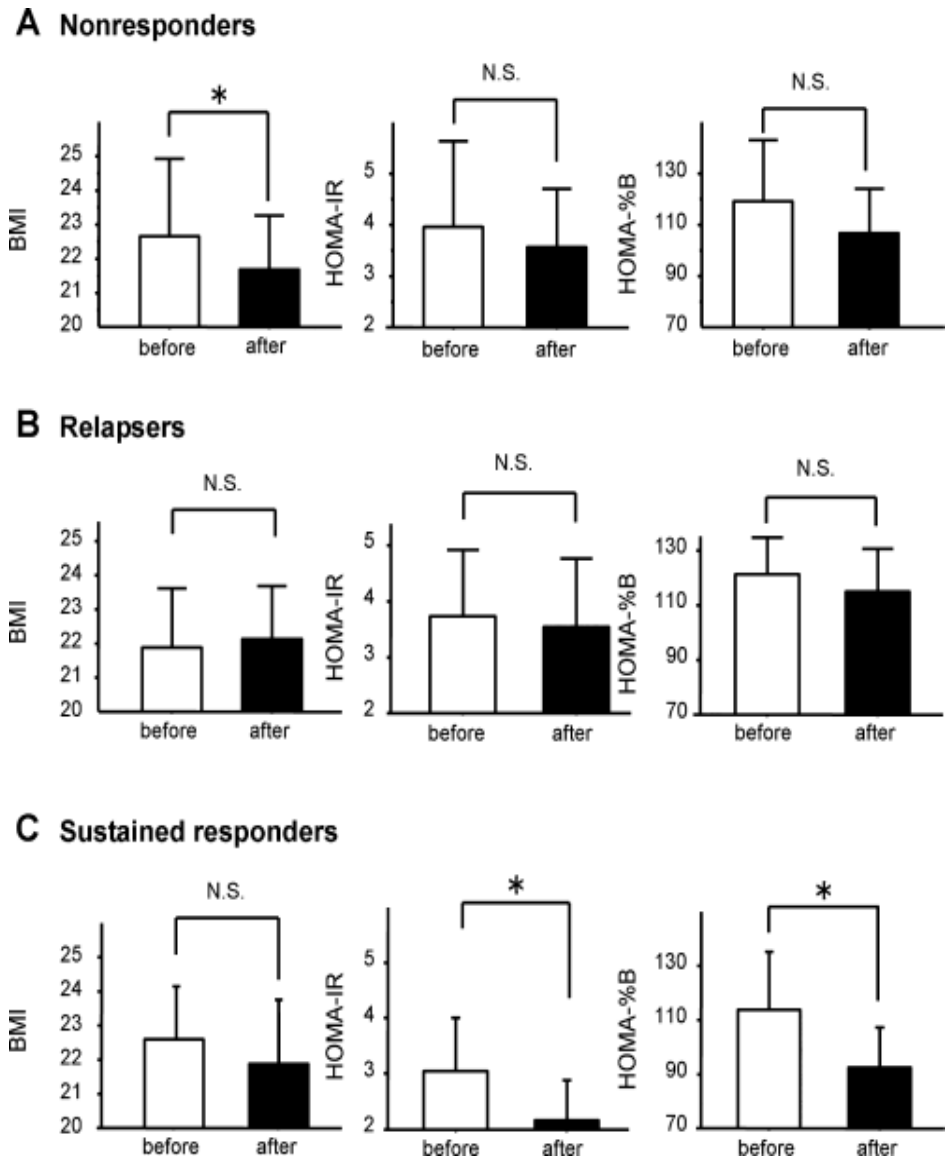
HCV Infection and diabetes

Meta-analysis of 14 retrospective studies



White DL et al, J Hepatol 2008

Clearance of HCV improves insulin resistance

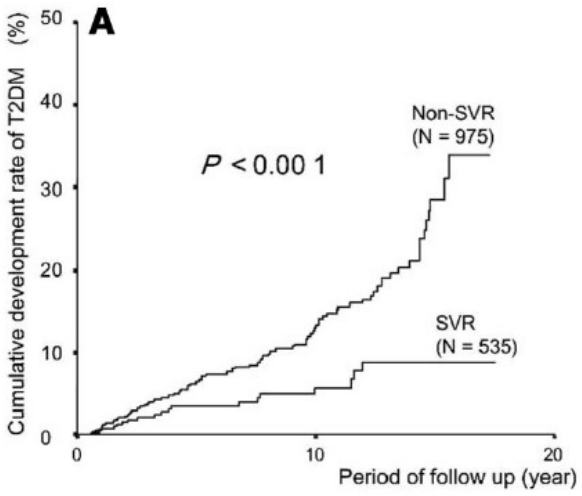


Decreased HOMA-IR and HOMA-B in sustained responders but not in other groups

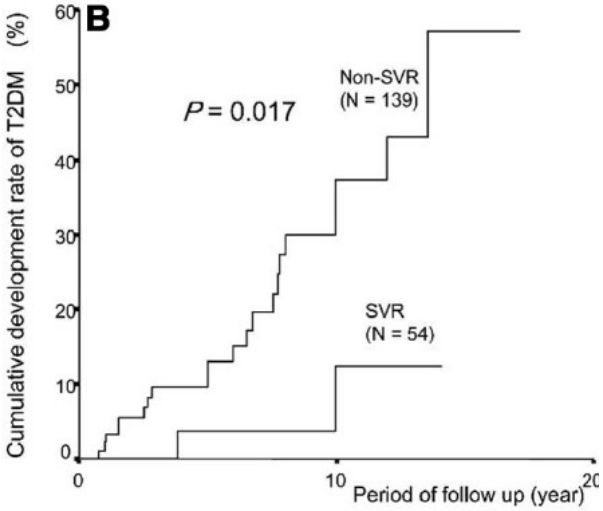
Kawaguchi Am J Gastroenterol 2007

SVR prevents *de novo* diabetes

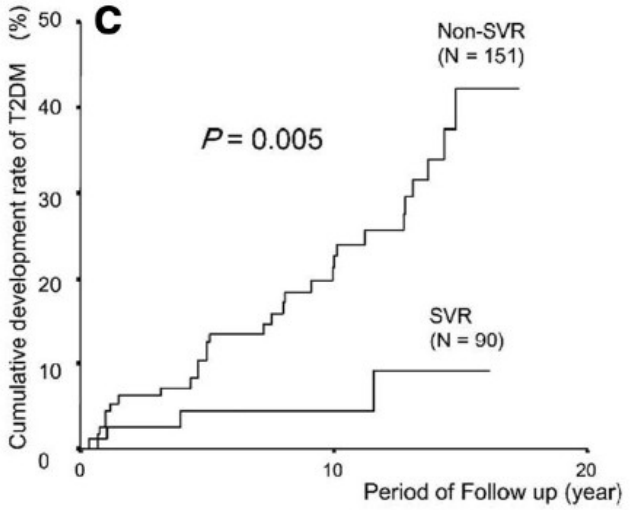
Age 50 yrs



cirrhosis



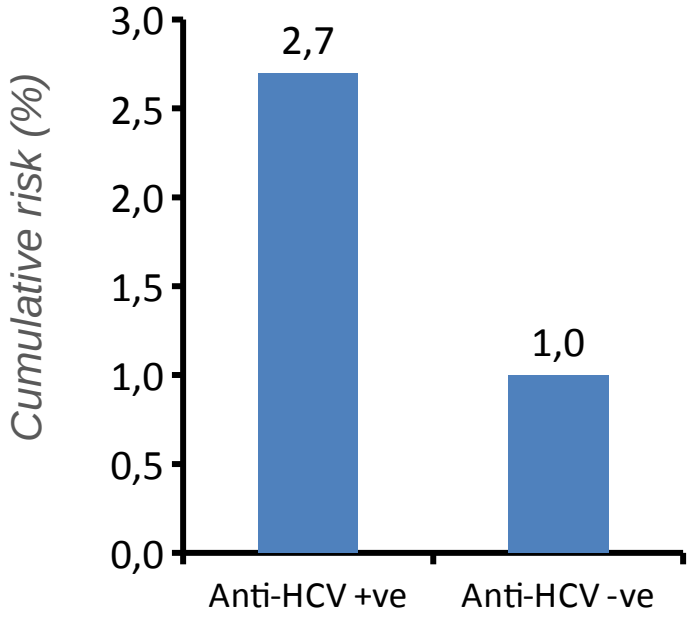
Pré-diabetes

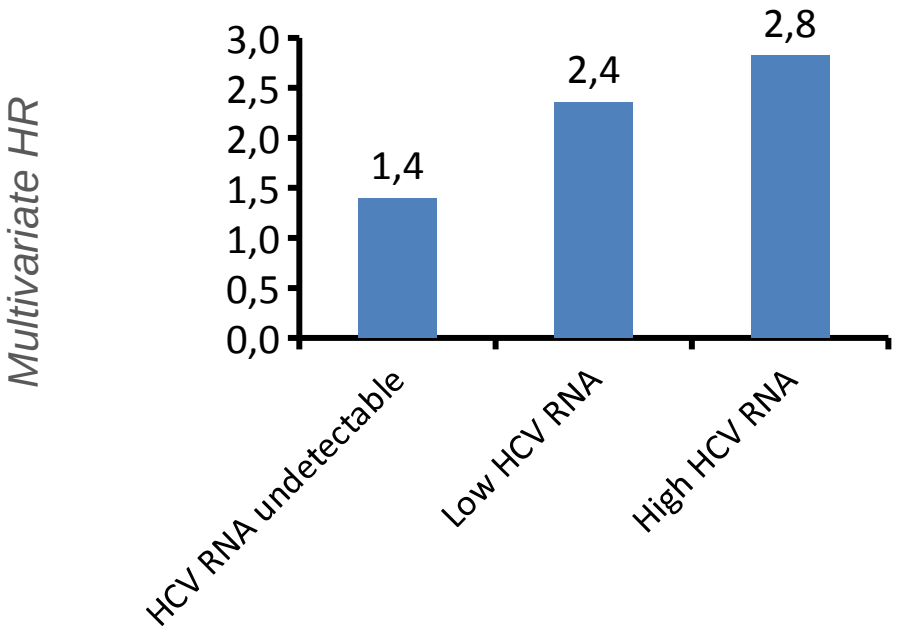


Arase, Hepatology 2009

Cerebrovascular deaths and HCV infection

Community-based prospective cohort study of 23 665 residents in Taiwan
Median follow-up 16.9 years

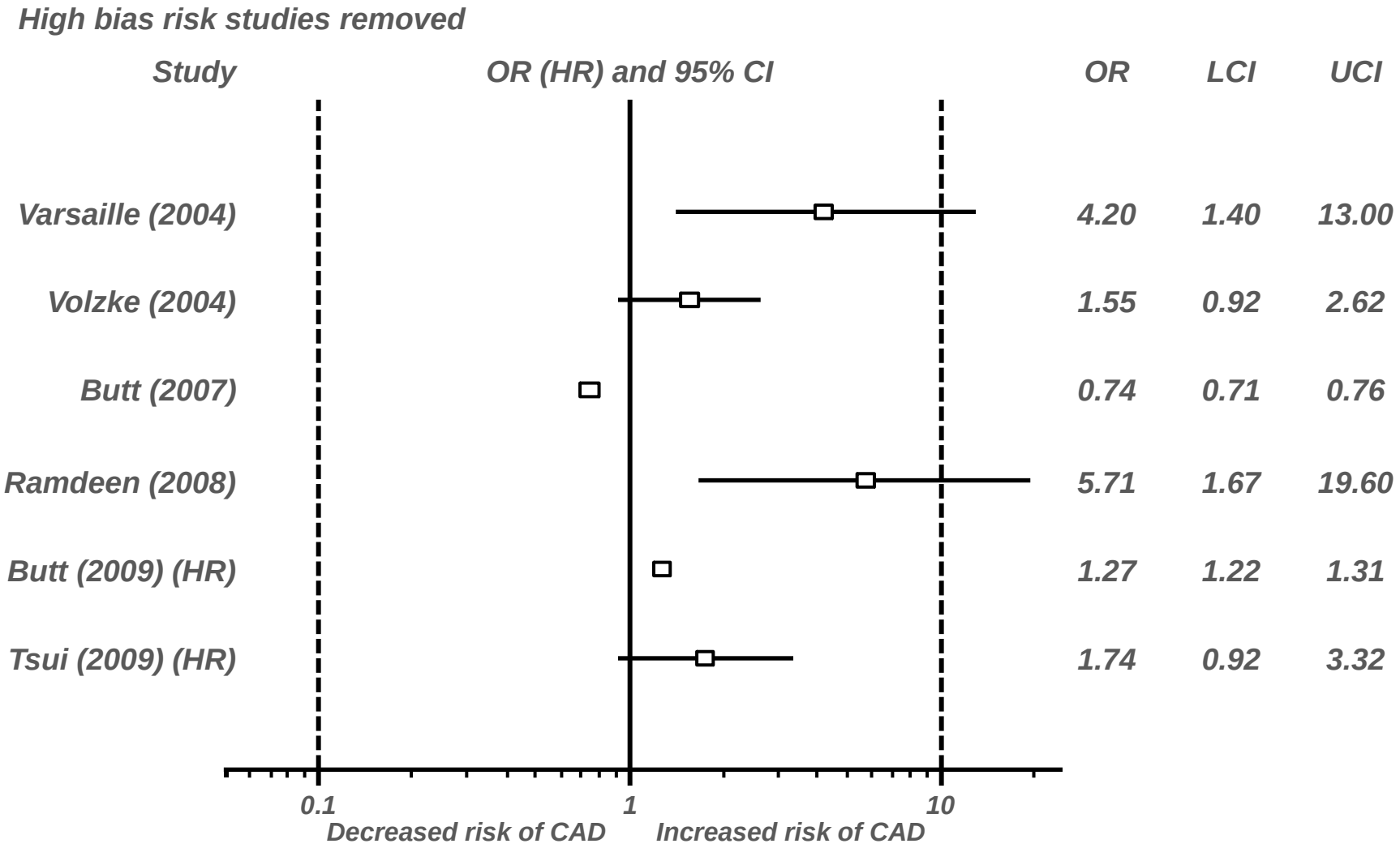




Anti-HCV +ve participants

Lee M-H et al. Stroke 2010;41:2894–2900

Impact of HCV on coronary artery disease



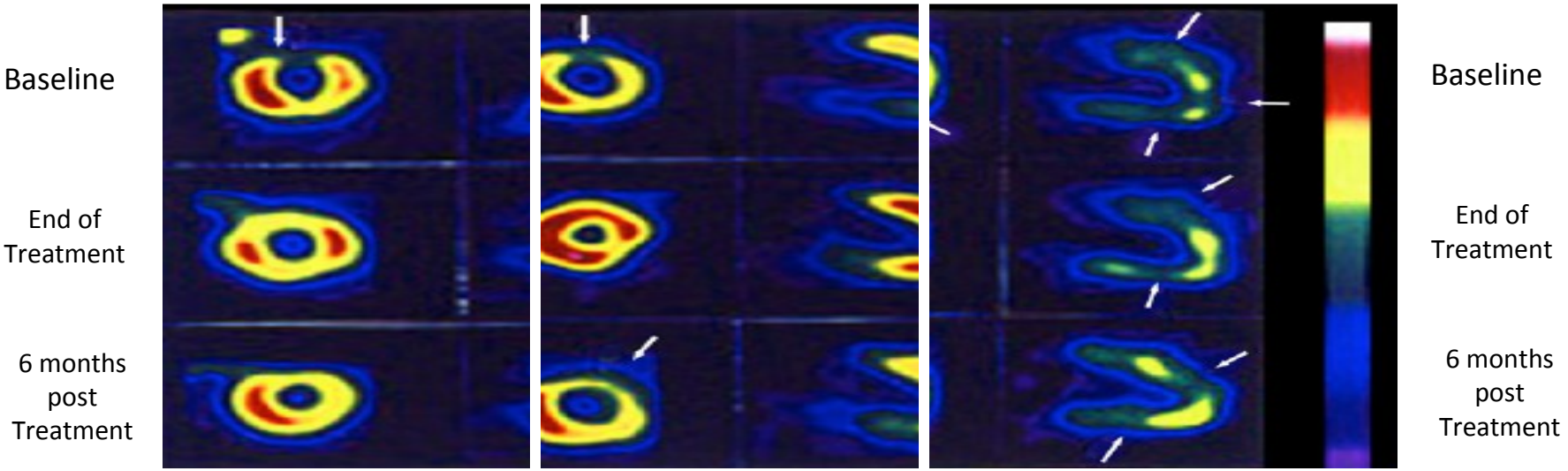
CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; LCI, lower confidence interval; OR, odds ratio; UCI, upper confidence interval

Roed T et al. Clin Physiol Funct Imaging 2012;32:421–430

Impact of SVR on myocardial perfusion

217 HCV infected patients without overt cardiac disorder

Variations of myocardial scintigraphy according to response to tretment



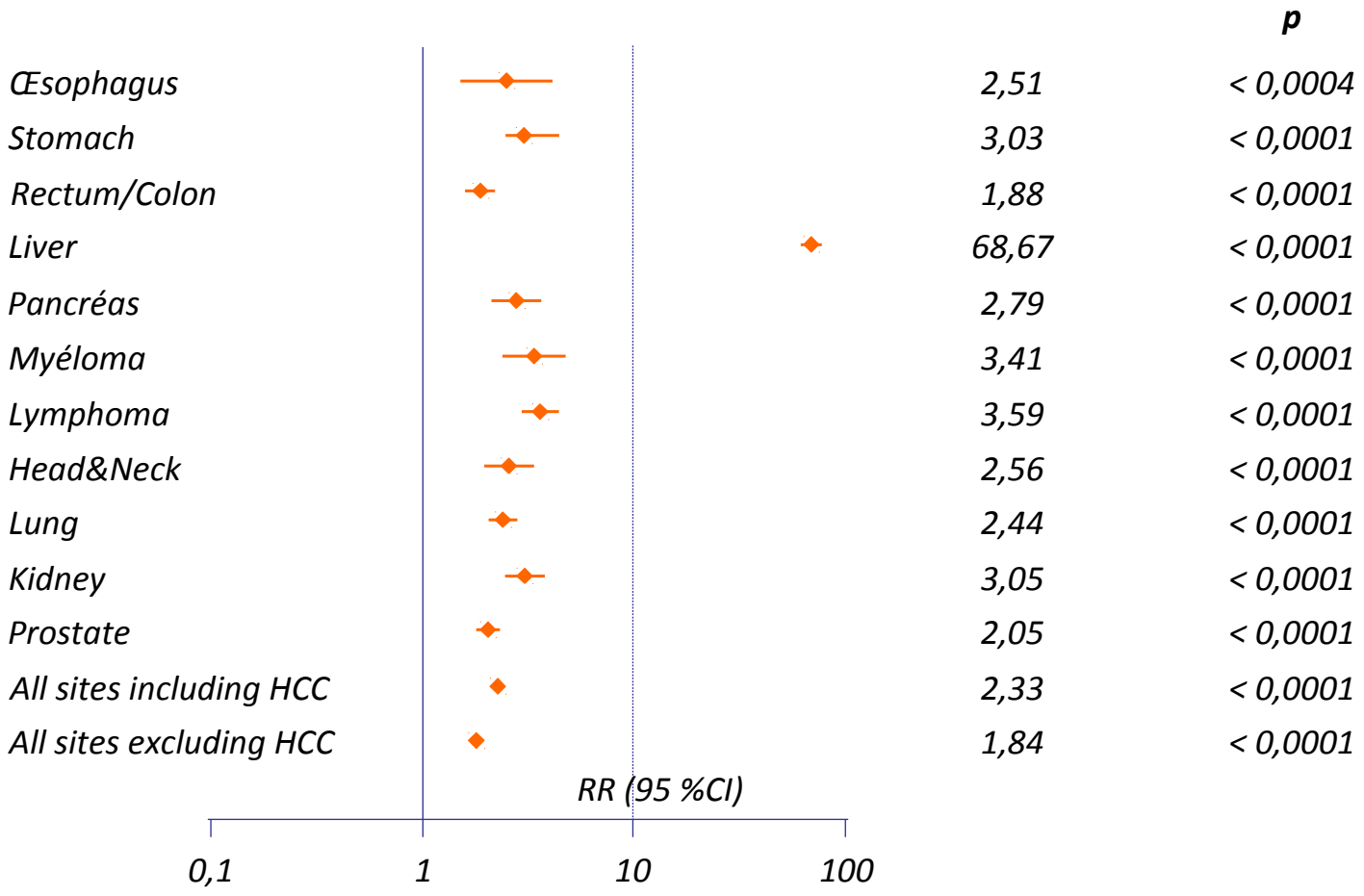
SVR **Relapse** **Non response**

SPECT: single-photon emission computed tomography

Maruyama *et al*. *J Hepatol*. 2013; 58(1): 11-5.

HCV infection and cancer

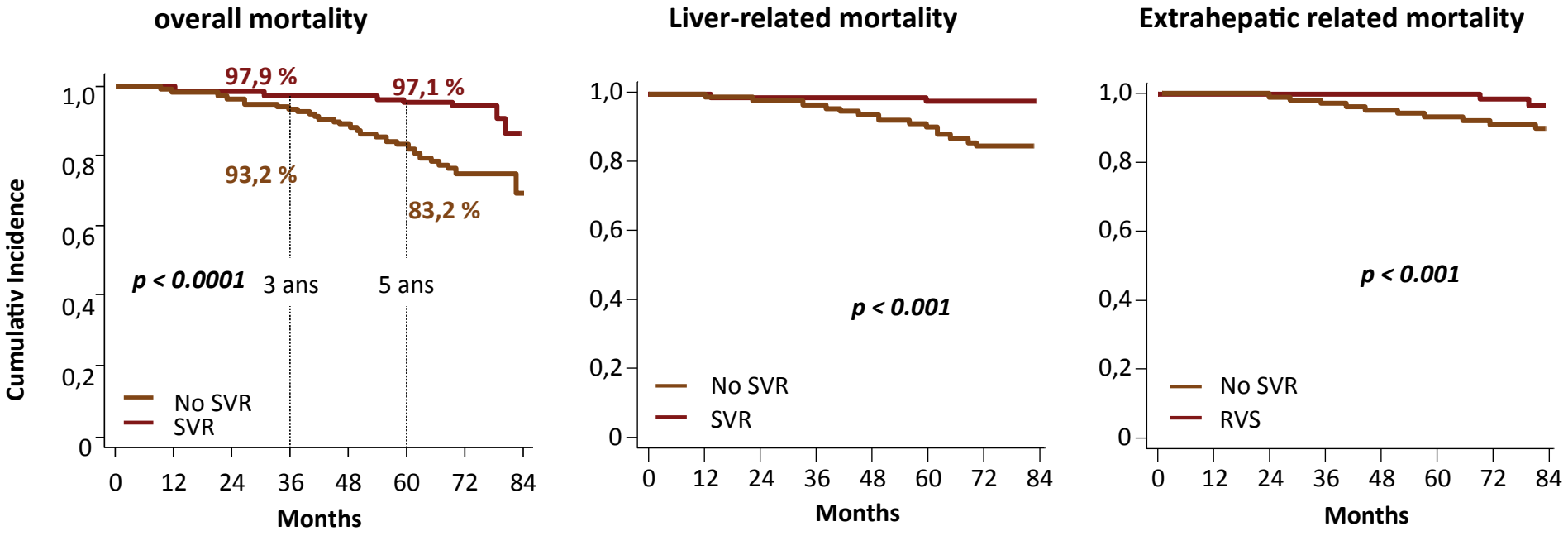
Relative risk of cancers in patients HCV+ vs. HCV



Nyberg AH et al. EASL 2015, Abs. O058

benefits of SVR on extrahepatic mortality is also visible in cirrhotic patients!

CIRVIR : French multicenter prospective cohort study conducted between March, 2006 and June, 2012 in 1323 patients with HCV-related histologically-proven cirrhosis

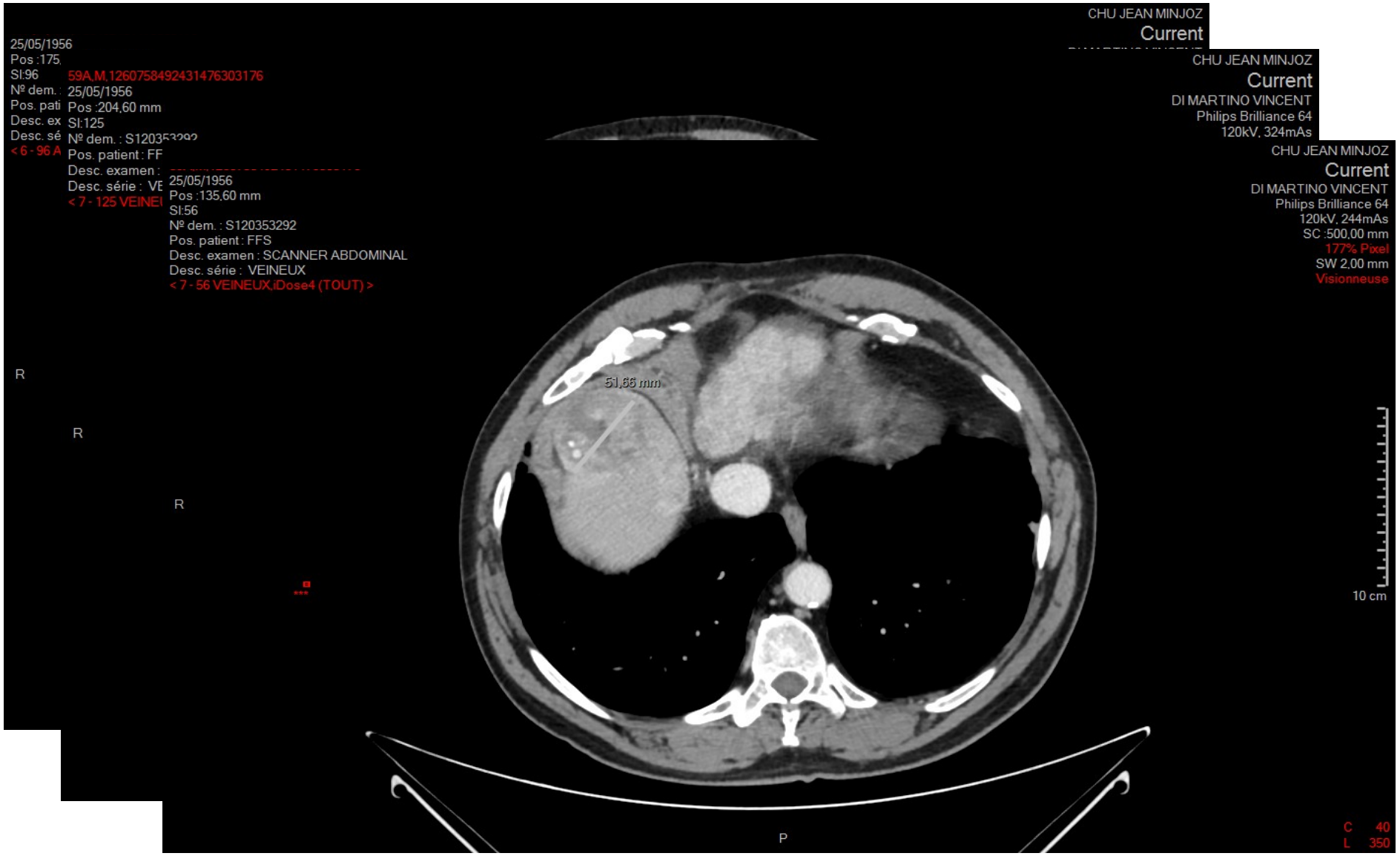


Nahon *et al*. AASLD 2015. Abstract 1808.

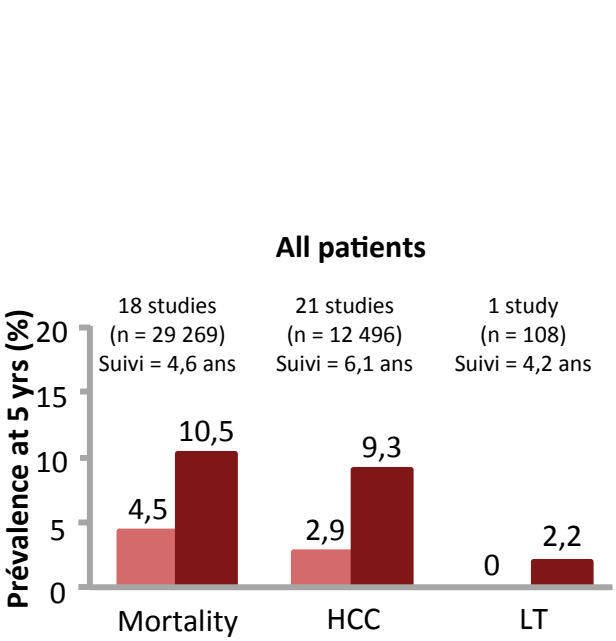
Case report (3)

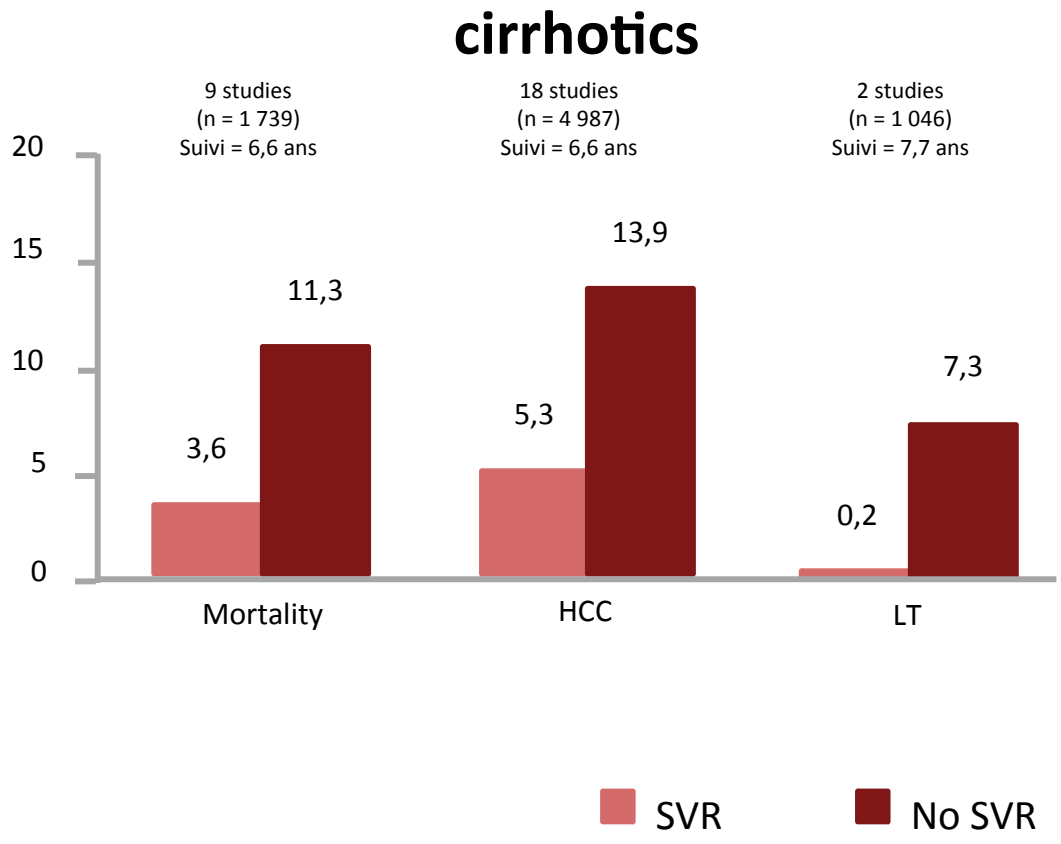
- Patient was not delisted but maintained in ‘temporary contra-indication’
- In September, 2015 abdominal US was ‘normal’. aFP=30 UI/mL
- In October 2015, abdominal pain. -> CT scan

CT scan findings: multinodular HCC with macrovascular invasion



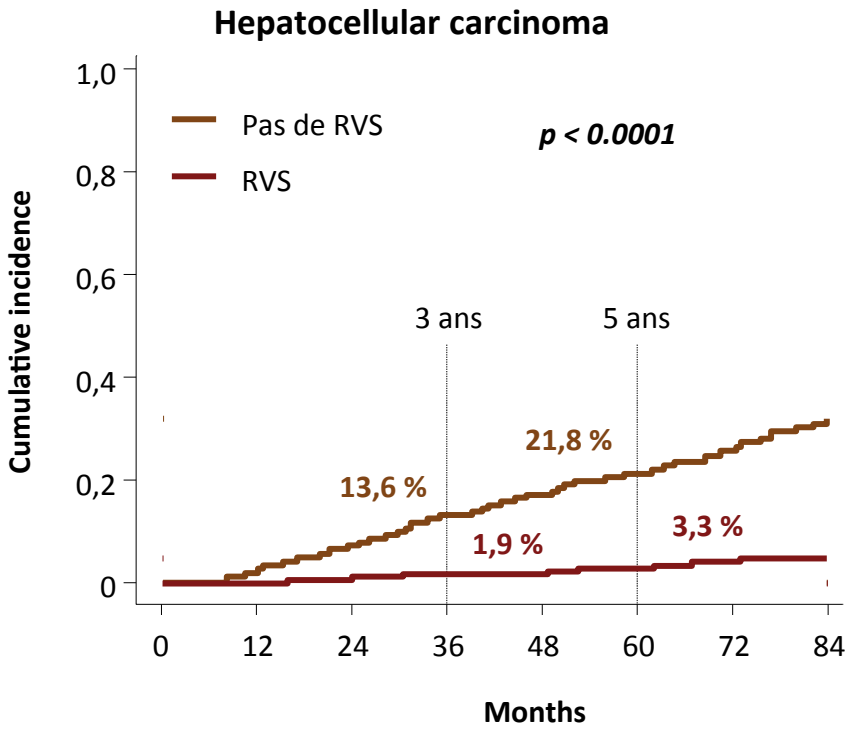
Impact of SVR on the prognosis of HCV-related liver disease: Meta-analysis on 34,563 patients

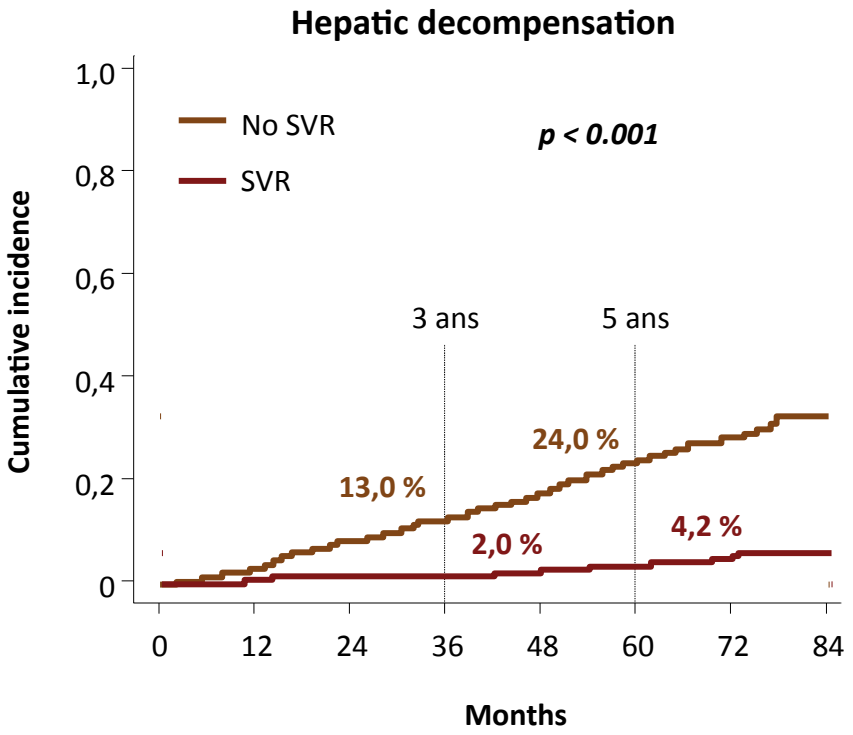




Hill *et al*. AASLD 2014. Abstract 44.

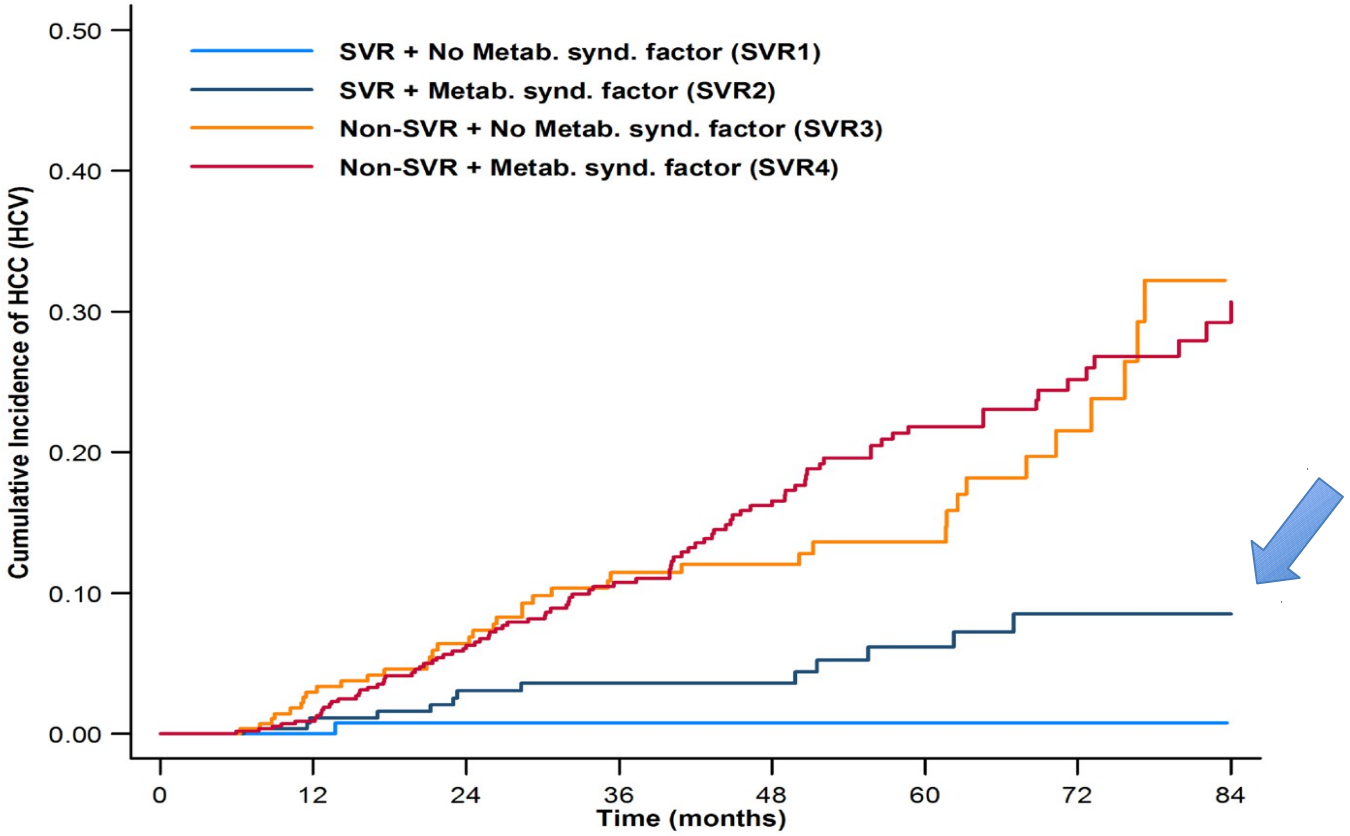
Residual risk of HCC and hepatic decompensation in sustained responders: the CirVir cohort (1323 cirrhotic patients)





Nahon *et al*. AASLD 2015. Abstract 1808.

Risk of HCC according to Metabolic syndrome and SVR: the CirVir cohort

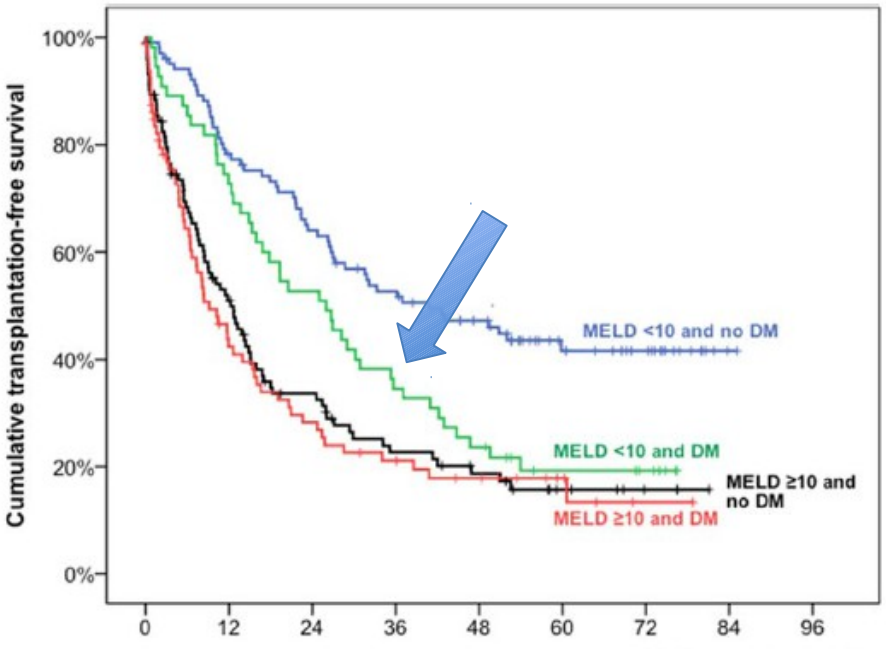


	At-risk patients (events)														
SVR1	147	(0)	129	(1)	99	(0)	68	(0)	42	(0)	31	(0)	20	(0)	9
SVR2	288	(3)	250	(4)	191	(1)	149	(0)	121	(3)	94	(2)	60	(0)	26
SVR3	301	(8)	251	(8)	200	(10)	156	(1)	122	(2)	85	(6)	39	(4)	13
SVR4	591	(5)	505	(25)	425	(19)	310	(18)	234	(13)	159	(5)	96	(5)	47

Nahon *et al*. EASL 2015. Abstract P0328.

Diabetes: risk factor of HCC and mortality in patients with HCV cirrhosis

Fig. 2. Probability of survival in patients with cirrhosis according to MELD score and diabetes status at inclusion (MELD <10 and no DM vs. MELD <10 and DM, $P = 0.005$; MELD <10 and no DM vs. MELD ≥ 10 and no DM, $P < 0.001$; MELD <10 and no DM vs. MELD ≥ 10 and DM, $P < 0.001$; MELD <10 and DM vs. MELD ≥ 10 and no DM, $P = 0.045$; MELD <10 and DM vs. MELD ≥ 10 and DM, $P = 0.019$; MELD ≥ 10 and no DM vs. MELD ≥ 10 and DM, $P = 0.6$; and $P < 0.001$ for the overall comparison by the log-rank test).



Number of patients at risk								
MELD <10 and no DM	102	78	63	49	40	22	14	1
MELD <10 and DM	55	40	29	19	13	7	4	0
MELD ≥10 and no DM	104	48	28	18	12	6	2	0
MELD ≥10 and DM	81	30	20	13	9	5	3	0

ElKrief, Hepatology 2014

Diabetes: risk factor of HCC and mortality in patients with HCV cirrhosis

Table 5. Multivariate Cox Regression Analysis Evaluating Baseline Factors Associated With the Occurrence of Major Complications of Cirrhosis During Follow-up

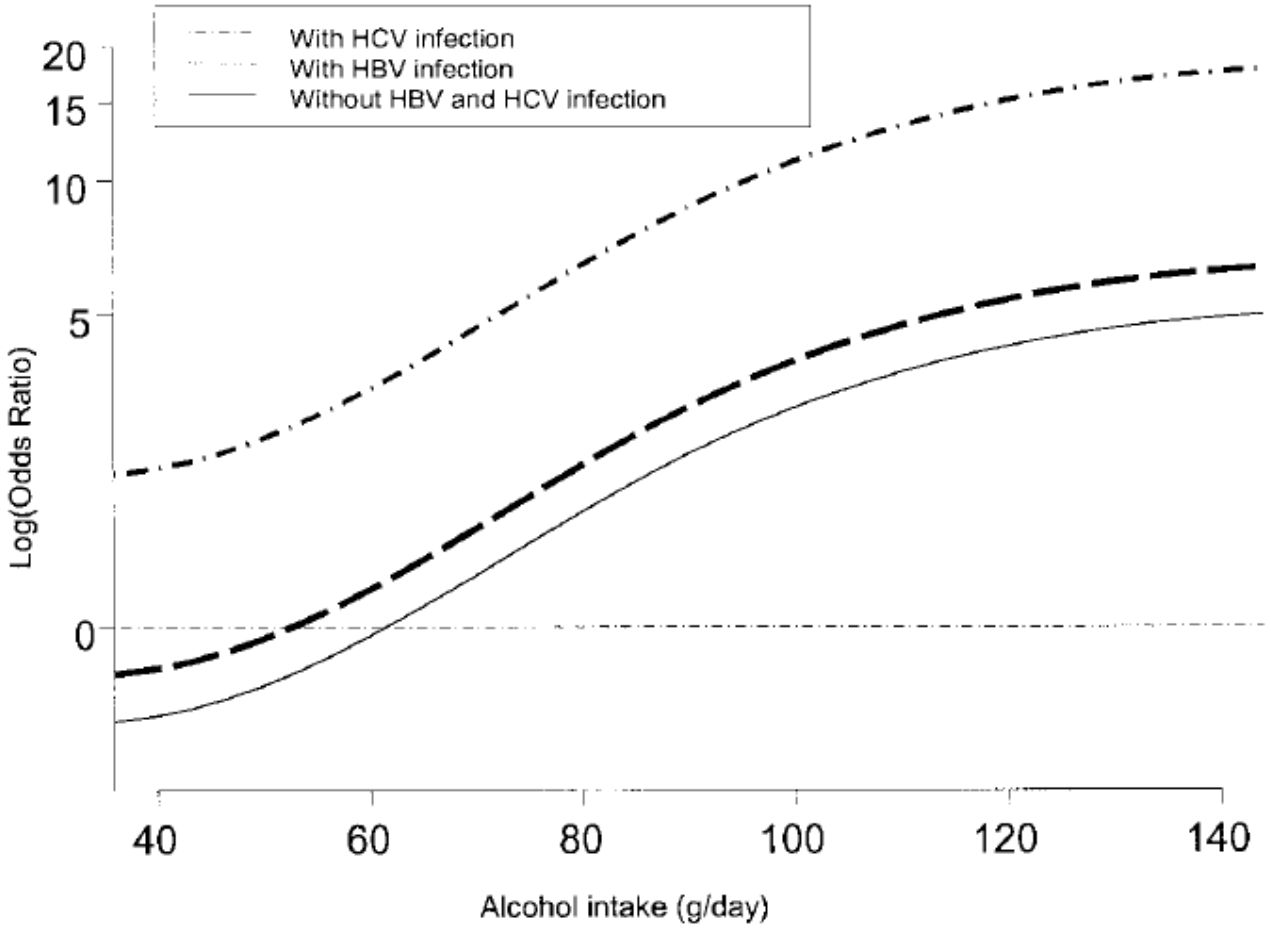
	HR	95% CI		*P* Value
Ascites				
MELD score ≥10	1.904	1.124	3.224	0.017
Diabetes ←	1.631	0.985	2.703	0.057
Alcohol	1.754	1.016	3.023	0.044
Renal Dysfunction				
Male gender	2.471	1.154	5.290	0.020
Diabetes ←	2.352	1.318	4.196	0.004
Bacterial Infection				
MELD score ≥10	2.527	1.452	4.398	0.001
Diabetes ←	2.098	1.227	3.589	0.007
HE				
Age ≥60 years	0.756	0.364	1.568	0.452
MELD score ≥10	6.868	2.927	16.112	<0.001
GI Bleeding				
None of the baseline variables were included in multivariate analysis.				
HCC				
Age ≥60 years	2.017	1.196	3.401	0.009
MELD score ≥10	0.605	0.351	1.041	0.070
Diabetes ←	1.938	1.129	3.328	0.016

Variables with a *P* value ≤0.05 in multivariate Cox's regression analysis were included in Cox's multivariate analysis (Supporting Table 7).

ElKrief, Hepatology 2014

Alcohol increases the risk of hepatocellular carcinoma in patients with HBV and HCV infection

Odds ratio of Hepatocellular carcinoma



Donato F, Am J Epidemiol 2002

The majority of hospitalized HCV infected patients has comorbidities

- French PMSI Database 2008-2012
- 28 953 755 adults admitted at least once

Comparison of HCV positive vs HCV negative patients

	VHC+	VHC-	RR (IC 95 %)
Alcohol related disorders	20.8 %	2.4 %	6.33 (6.23-6.43)
≥ 1 severe comorbidity	56.2 %	28.7 %	2.43 (2.40-2.46)

Schwarzinger M, et al. EASL 2015, Abs. G16

Case report (4)

- Sorafenib started on November, stopped on December for encephalopathy associated with deterioration of liver function.

- Patient still on waiting list… awaiting death

In summary

- The rationale of gains attributed to SVR in terms of extrahepatic morbidity/mortality is strong since numerous studies indicate the impact of HCV viremia on extrahepatic disorders, but
- At an individual level, This gain is inconstant, depending on comorbidities
- At a population level (long-term follow-up cohort studies including untreated patients) the magnitude of the gain also depends on whether patients were selected for receiving HCV treatment (Interferon+++)
- No data available to date with SVR obtained with DAAs.

In summary (2)

- In patients with advanced fibrosis/cirrhosis who develop SVR, HCC can occur, particularly in the event of associated diabetes or metabolic syndrome or alcohol consumption
- Improvement of some hepatic or extrahepatic conditions after SVR doesn't guarantee that everything will improve and that HCC will not occur
- **All F3/F4 patients MUST be followed all life long regardless of additional risk factors for HCC or outcome of liver function after SVR.**