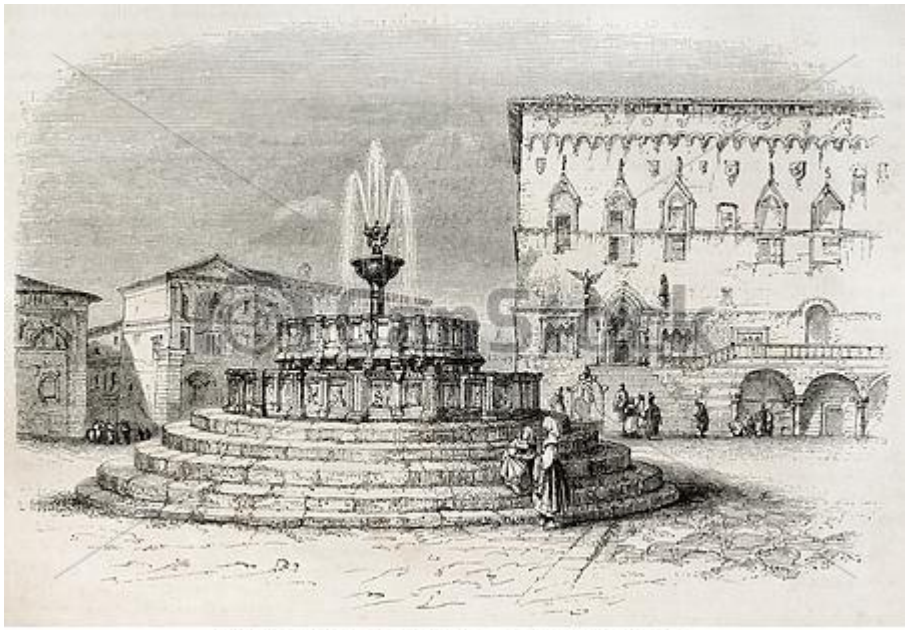
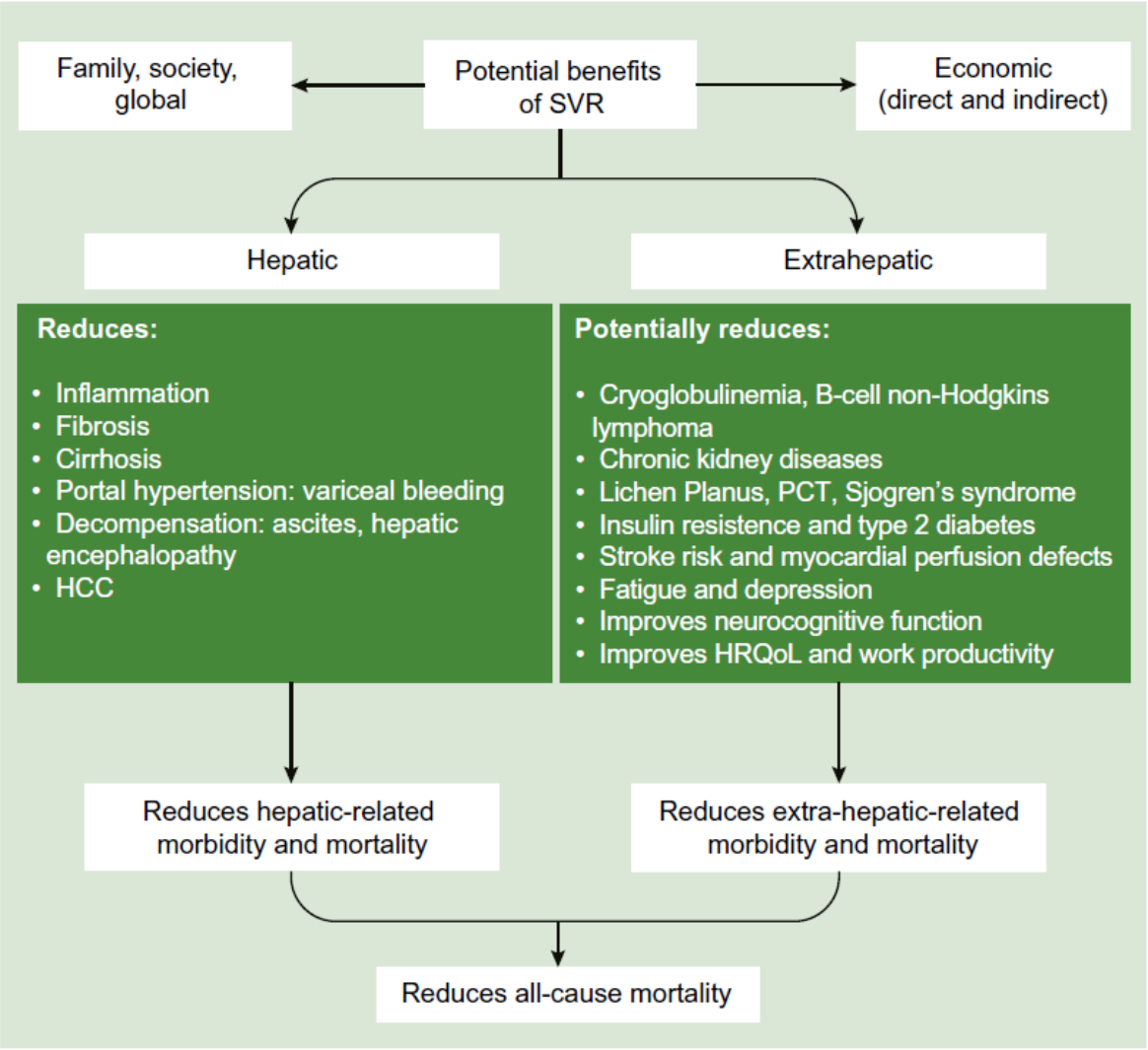
Quale monitoraggio clinico dopo il trattamento nel paziente cirrotico e non



8° WORKSHOP NAZIONALE CISAI
PERUGIA, 30 - 31 MARZO 2017
Prevenzione e gestione delle co-morbidità associate all'infezione da HIV

Barbara Menzaghi



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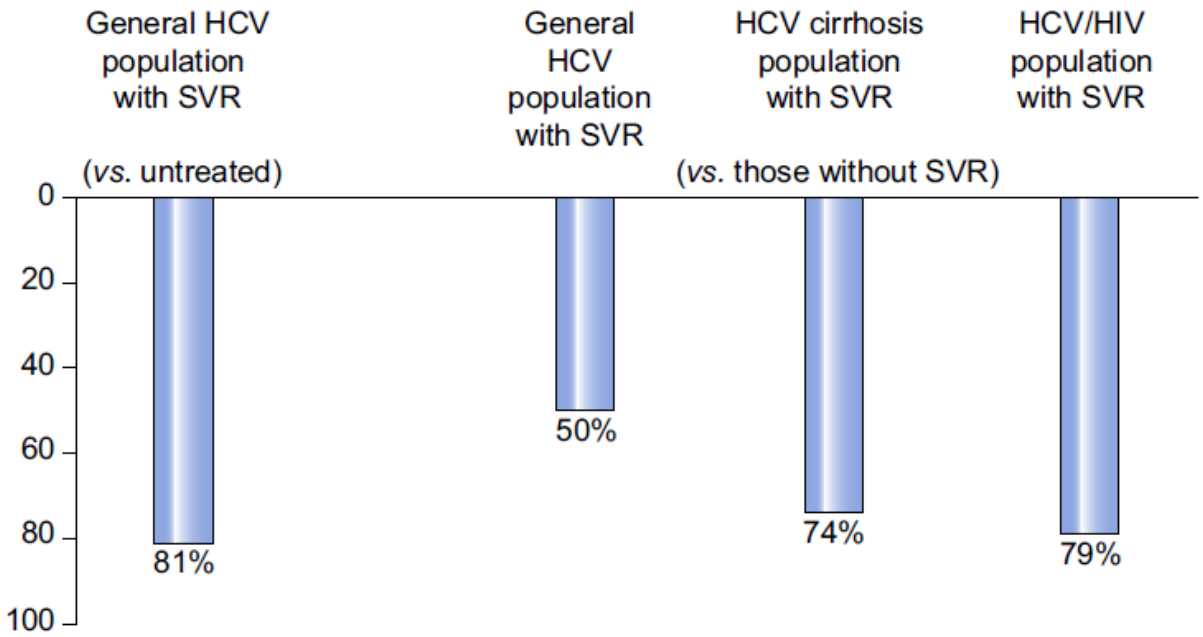
Received 23 July 2016; received in revised form 1 August 2016; accepted 2 August 2016

Fig. 1. Potential benefits of achieving SVR. Multiple benefits of SVR are achievable, including improved quality of life, reduced risk of hepatic and extrahepatic complications and decrease in all-cause mortality. Benefits have been demonstrated for patients with all stages of fibrosis.



EASL JOURNAL OF HEPATOLOGY

Fig. 2. Percent reduction in all-cause mortality in patients with SVR. Achievement of SVR results in significant reductions in all-cause mortality. This is seen in the general population of HCV-infected patients, as well as subgroups with cirrhosis and with HCV-HIV coinfection [14].

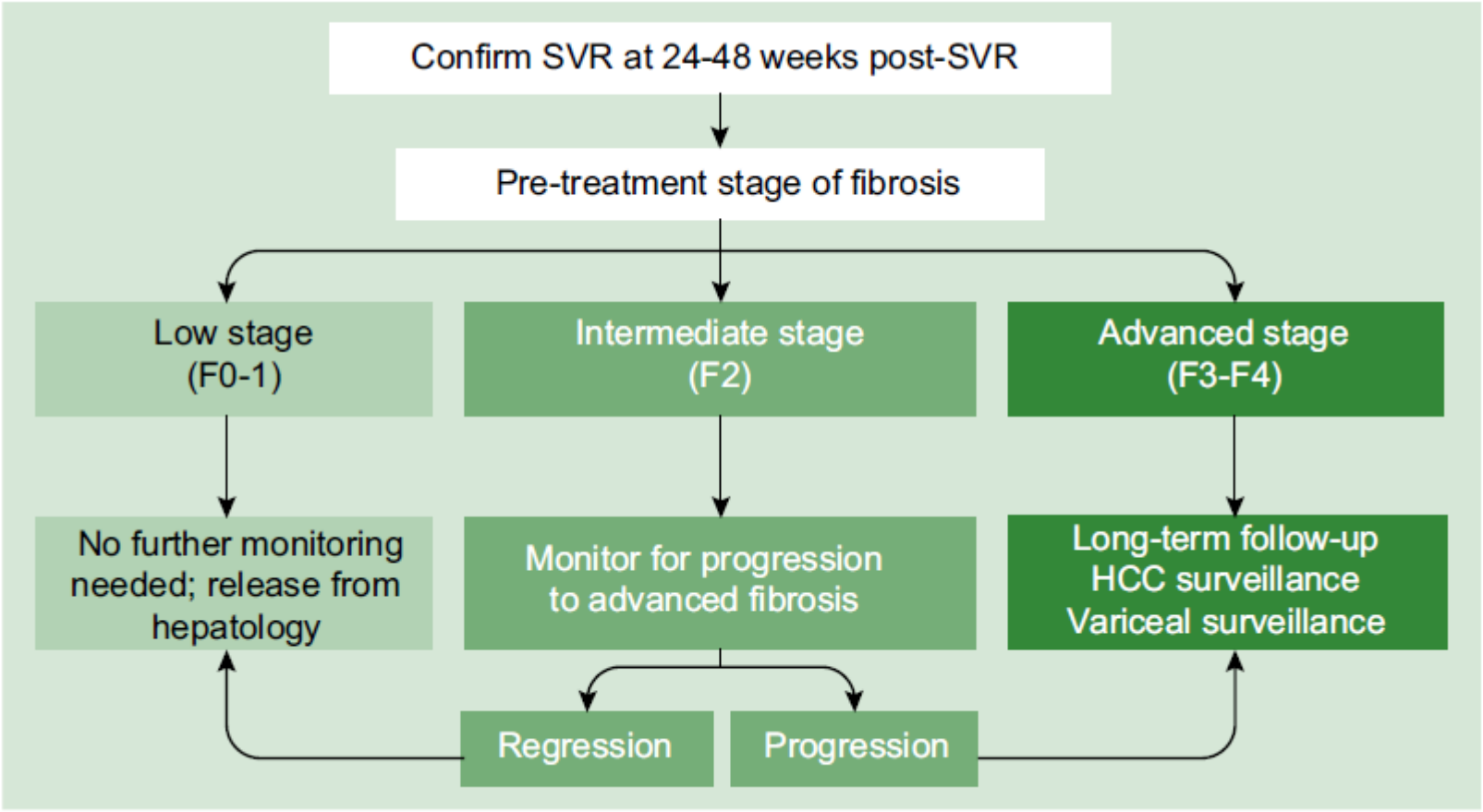


Fig. 3. Suggested algorithm for follow-up of patients with SVR. All patients should undergo confirmatory testing of SVR at or after week 24. The subsequent follow-up is based on the pre-treatment severity of fibrosis. For those with F0-1 fibrosis, continued specialty care is not needed. For those with intermediate stage of fibrosis (F2), follow-up for some years is prudent to insure no progression, especially if the patient has risk factors for progression. Patients with F3 or F4 fibrosis require continued hepatology/specialty care.

F0-F2

Table 1. Guidance for the follow-up and surveillance in patients after SVR.

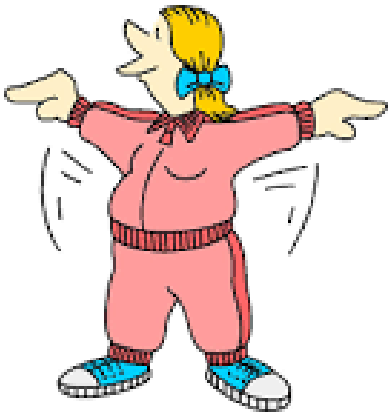
Routine follow-up
F0, F1: no specialized follow-up needed
F2: clinic visits every 1 to 2 years, depending on risk factors for progression
F3 and compensated F4: clinic visits every 6 months
F4 decompensated every 3 months (or more often complications require)
Surveillance
For varices (if F4): every 1-3 years by upper endoscopy depending on the initial grade of varices [70]
For HCC (if F3/F4): every 6 months by ultrasonography with or without alpha-fetoprotein
For fibrosis progression or regression: every 1-2 years by hepatic elastography, serum fibrosis markers; there may be role for selective consideration of liver biopsy
For reinfection: yearly HCV-RNA testing in individuals with high risk behavior

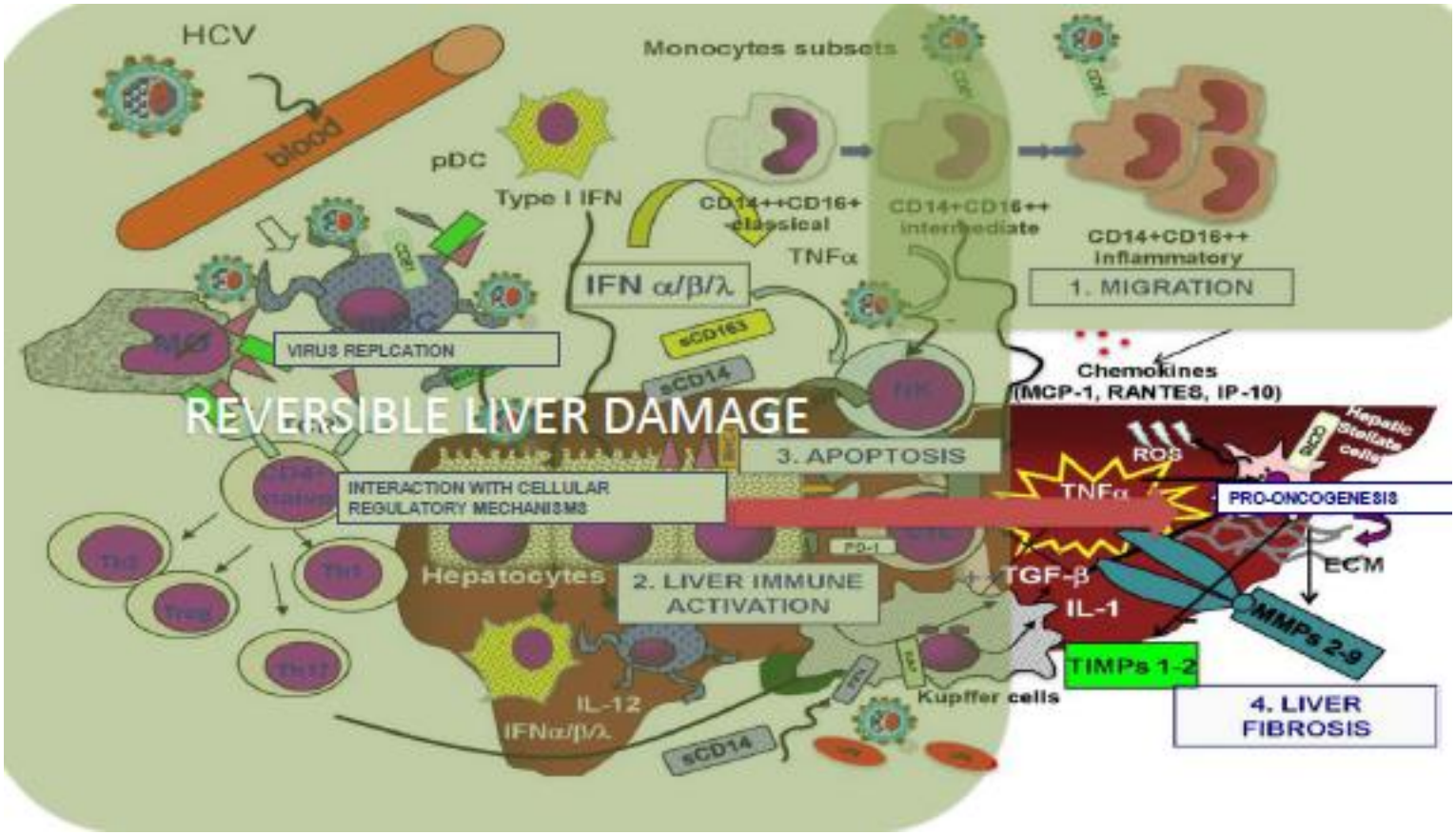
Table 2. Factors influencing future risk of liver-related complications.

Well-established associations
Cirrhosis
Presence of portal hypertension/low platelet count
Likely (frequently reported associations)
Diabetes
Alcohol use
Older age
Possibly important (less consistent associations)
Obesity
Genotype 3
Elevated ALT level
Viral co-pathogens
Male gender

Table 3. Health and liver optimization after SVR.

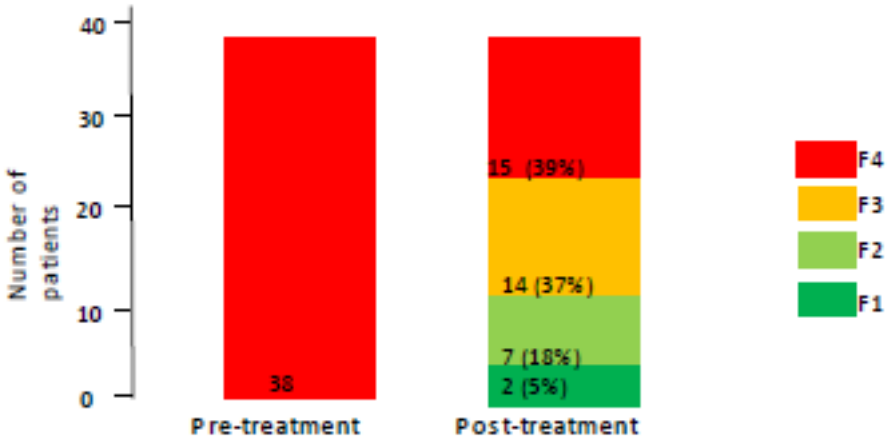
Lifestyle changes:
Weight: Goal to maintain weight as close to normal value as possible using modification of diet and supplemental food [71]
Exercise: Exercise is an important component of weight optimization. Gentle exercise is recommended for cirrhotic patients to maintain musculoskeletal system and avoid sarcopenia and ameliorate osteopenia [72]
Nutrition: Optimizing nutrition requirements is based on metabolic comorbidities, and degree of liver dysfunction to promote liver regeneration and remolding, and to prevent the development of protein and energy malnutrition and to maintain healthy musculoskeletal system [73]
Supplements: Including vitamins, minerals, amino acids and herbs, should be accurately assessed, monitored and supplemented, if needed, under supervision of the treating physician [74]
Social habits:
Alcohol use: Is prohibited for patients with cirrhosis [42]
Cigarette smoking: Is prohibited for patients with cirrhosis [75, 76]
Marijuana use: Daily use if not recommended in patients with fibrosis [77, 78]
Coffee: Is not prohibited for liver patients [79]




HCV
blood
pDC
Type I IFN
Monocytes subsets
CD14++CD16+ classical
CD14+CD16++ intermediate
CD14+CD16++ Inflammatory
TNFα
IFN α/β/λ
1. MIGRATION
VIRUS REPLCATION
sCD163
sCD14
Chemokines (MCP-1, RANTES, IP-10)
REVERSIBLE LIVER DAMAGE
3. APOPTOSIS
INTERACTION WITH CELLULAR REGULATORY MECHANISMS
ROS
TNFα
PRO-ONCOGENESIS
Hepatic Stellate cells
ECM
Hepatocytes
2. LIVER IMMUNE ACTIVATION
TGF-β
IL-1
MMPs 2-9
TIMPs 1-2
IL-12
IFNα/β/λ
Kupffer cells
4. LIVER FIBROSIS

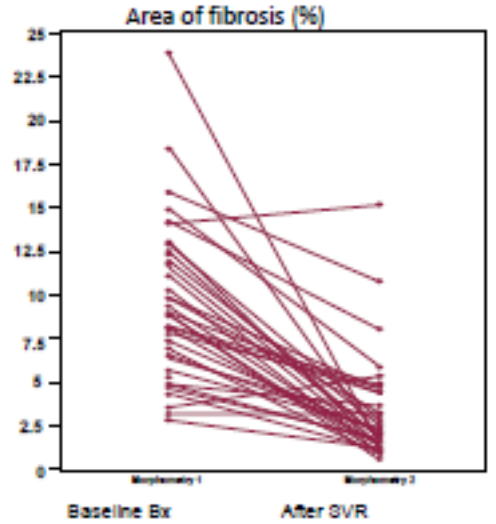
Distribution of Metavir fibrosis stages in pre-treatment and post-treatment liver biopsies

- 38 patients, Hepatitis C cirrhosis, Child-Pugh A
- 24/48 weeks standard bitherapy and SVR
- Paired biopsy, mean interval : 6 years



61% patients with F4 at baseline had cirrhosis regression to lower METAVIR stages

D'Ambrosio *et al Hepatology*. 2012



HCC Risk Among Non-Cirrhotic Patients With SVR

Variables	HR 95% CI	P Value
GGT level (≥75 U/L vs <75)	5.8 (1.9-17.3)	0.002
Age (≥60 yrs vs <60 yrs)	4.1 (1.4-12.0)	0.009
Fibrosis 2-3 vs 0-1	3.7 (1.0-13.5)	0.04

Huang CF, J Hepatol 2014;61:67-74

Cirrhotic patient (n, yr)								
With HCC	1	2	8	11	13	15	15	16
At risk	76	66	51	38	30	21	14	7
Non-cirrhotic patient (n, yr)								
With HCC	2	4	6	8	12	15	16	17
At risk	489	435	383	318	232	169	92	33

N=4 F1
N=8 F2
N=5 F3

Key point

Achievement of SVR does not protect against reinfection so counseling messages to prevent reinfection should be provided to all those who remain at risk for HCV exposures.

RATES OF REINFECTION ARE IN ORDER OF 1-8% PER YEAR

F3-F4

Key point

Patients with advanced fibrosis (F3/4) and SVR have a substantially lower risk of decompensation and hepatocellular carcinoma but remain at risk, so monitoring and surveillance is essential.

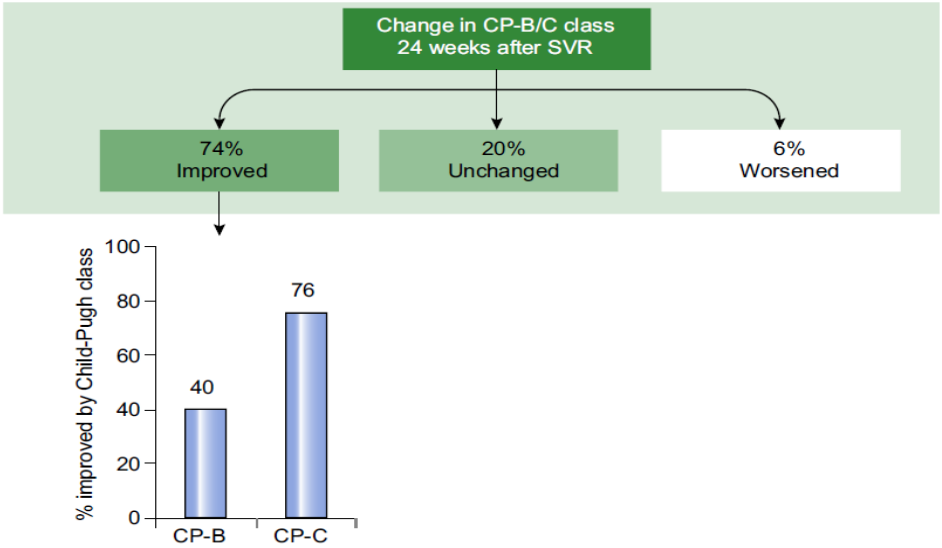


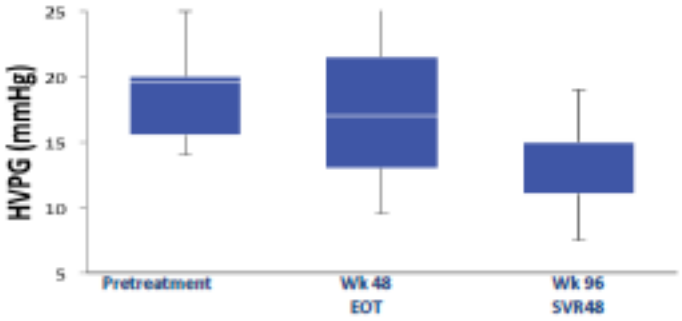
Fig. 4. Improvement in Child-Pugh score among patients with decompensated cirrhosis 24 weeks after SVR. In the combined results of the SOLAR studies (treated with ledipasvir/sofosbuvir plus ribavirin), 74% of patients had a reduction in Child-Pugh class when assessed 24 weeks after achieving SVR. Among those with improved Child-Pugh class, a greater proportion with CP-C improved than CP-B (76% *vs.* 40%).

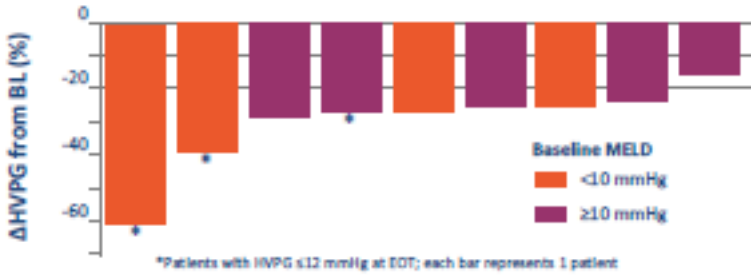
F3 and compensated F4: clinic visits every 6 months
F4 decompensated every 3 months (or more often complications require)
Surveillance
For varices (if F4): every 1-3 years by upper endoscopy depending on the initial grade of varices [70]
For HCC (if F3/F4): every 6 months by ultrasonography with or without alpha-fetoprotein

HCV ERADICATION RESULTS IN REDUCTION OF HEPATIC VENOUS PRESSURE GRADIENT 48 WEEKS AFTER END OF TREATMENT; FINAL RESULTS OF THE STUDY OF SOF + RBV IN PATIENTS WITH CIRRHOSIS AND PORTAL HYPERTENSION

- 46 had paired HVPG at baseline and end-of-treatment
- 9 had follow-up HVPG at 48 weeks post-treatment

HVPG % change at PTW48 in patients with BL HVPG ≥12 mmHg who achieved SVR12 (n=9)





- Mean 29% decrease in HVPG
- HVPG <12 mmHg in 1/3 pts

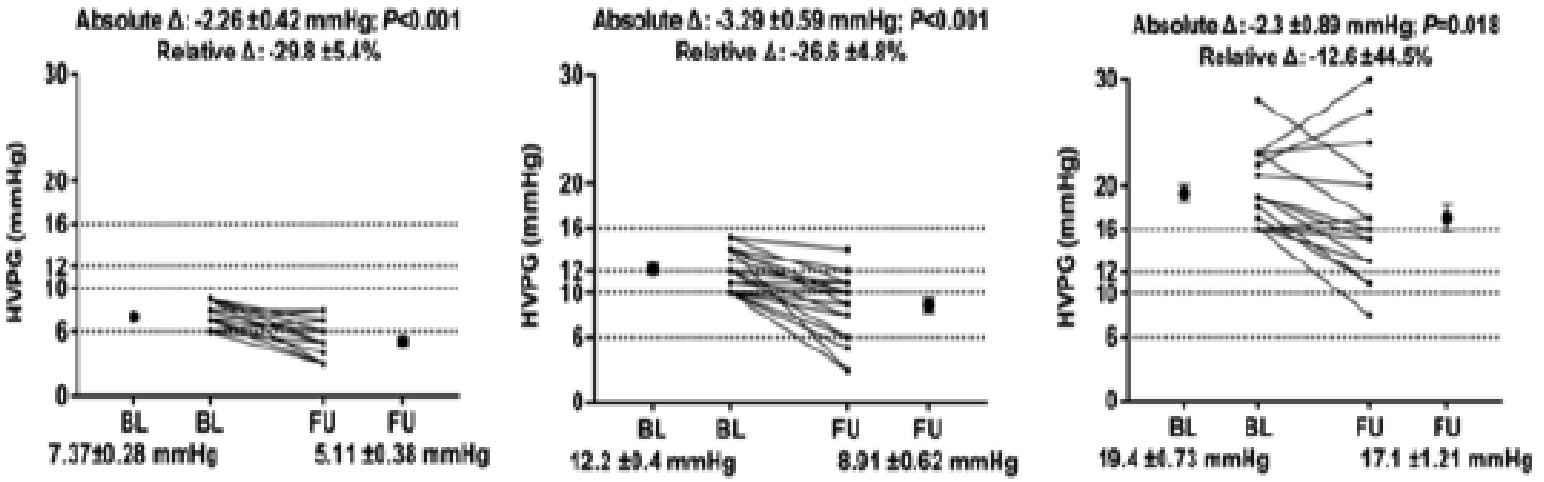
- 8/9 had >20% ↓HVPG

*Patients with HVPG ≤12 mmHg at EOT; each bar represents 1 patient

SOF+RBV for 48 weeks in CTP-A/B + HVPG >6mmHg

Afdhal, et al. EASL 2016; Poster #LBP618

Sustained virologic response to interferon-free therapies ameliorates HCV-induced portal hypertension



Predictors of HVPG decrease

Univariate

- Child-Pugh class
- Relative change in liver stiffness

Multivariate

- Child-Pugh class B vs. A (HR 0.103, 95%CI: 0.002-0.514; P=0.0061)

Mandorfer M,et al., J Hepatol 2016.

Long term monitoring after SVR in HCV: Portal Hypertension

- Pre Tx liver stiffness <20 kPa and PLT >150,000 = low risk esophageal varices → yearly repetition of TE and platelet count
- Pre Tx liver stiffness > 20 Kpa and/or PLT < 150.000 –> EGDS for varices before TX → if SVR
  - No varices at screening pre Tx endoscopy, → EGDS every three years
  - Small Varices at screening pre Tx → EGDS every two years (Non Selective Beta Blockers or Carvedilole optional if no red signs and Child C)
  - Medium- large varices → NSBB or Carvedilol or Band Ligation (NSBB not in ESLD)
  - Isolated gastric varices or large gastroesophageal varices type 2 consider cyanoacrilate

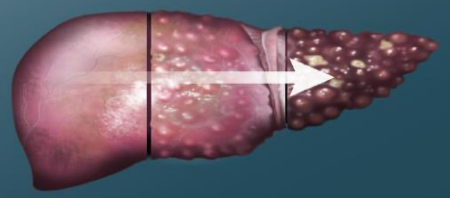
De Franchis R et al Journal of Hepatology 2015 vol. 63 j 743–752

Hepatology Snapshot:

Esophageal varices: Stage-dependent treatment algorithm

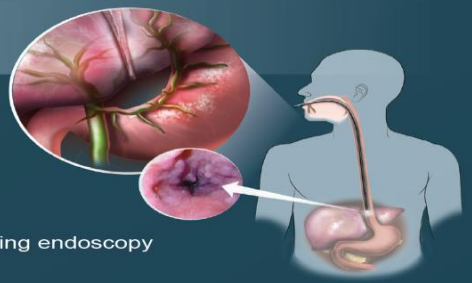
Jaime Bosch[1,2,*], Tilman Sauerbruch[3]

[1]Liver Unit, Hospital Clínic-IDIBAPS, University of Barcelona, Spain; [2]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Spain; [3]Department of Internal Medicine I, University of Bonn, Germany. *Corresponding author. E-mail address: jbosch@clinic.ub.es (J. Bosch)



Chronic liver disease

Assessment of stage
(clinical and laboratory examination, ultrasound, liver stiffness)



Findings inducing endoscopy

Upper GI endoscopy

No varices

Small varices*
no RCS | RCS

Small varices

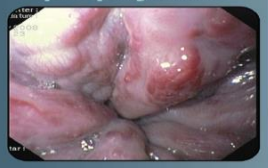
Large varices

Treat etiology/ antifibrotic drugs
Success: endoscopy at 2-3 years
Failure: endoscopy at 1 year
Compensated patient

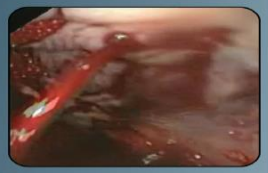
NSBB
No follow-up endoscopy
Decompensated patient

NSBB or EBL
NSBB: no follow-up endoscopy
EBL: follow-up endoscopies at 1, 6 and every 12-months

Primary prophylaxis



Acute bleeding



Bleeding despite NSBB or EBL

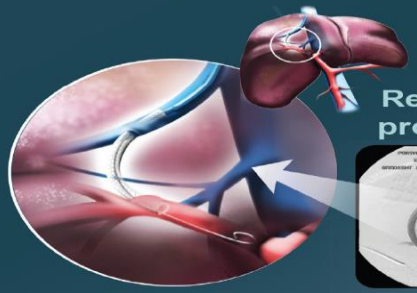
Resuscitation
(volume replacement, **Hb: 7-8 g/dl**), **vasoactive drugs, antibiotics**

Endoscopy within 12 h

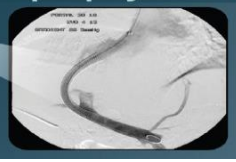
High risk patient

Low risk patient

EBL (glue in GV)



TIPS** Rebleeding prophylaxis



>5 days

Rebleeding prophylaxis: repeat ligation + continue NSBB

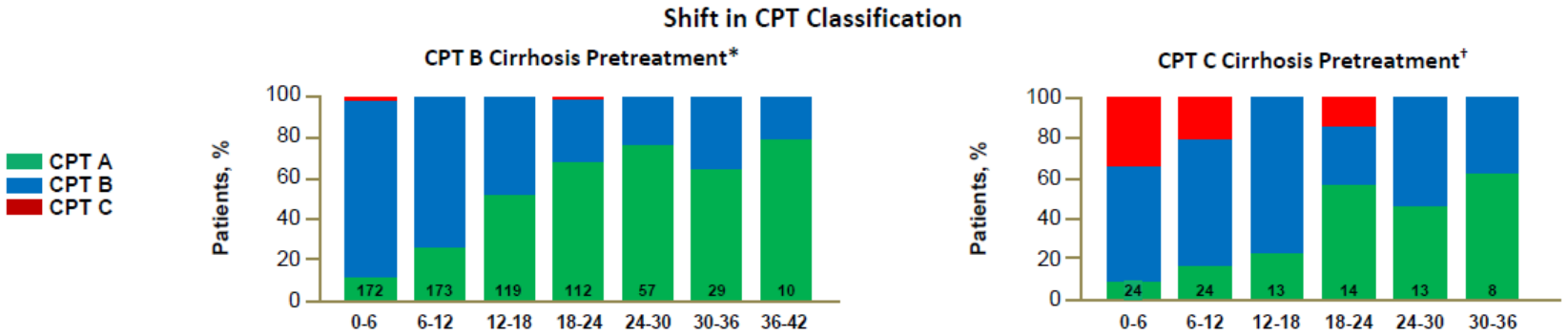
If significant rebleeding or if NSBB are not applicable and no contraindications

DAA Studies in Decompensated Cirrhosis (CTP-B/C)*

	SOLAR-1	SOLAR-2	ASTRAL-4	ALLY-1
	LDV/SOF+ RBV	LDV/SOF+ RBV	SOF/VEL± RBV	DCV+SOF+ RBV
Number with outcomes	93	81	250	39
Last Assessment	SVR4	SVR24	SVR12	SVR12
% CTP score improved	67%	77%	47%	76%
% CTP score worsened	8%	6%	11%	12%
% MELD score improved	67%	73%	54%	40%
% MELD score worsened	17%	16%	25%	40%
% MELD improved in CTP B	64%	65%	54%	43%
% MELD worsened in CTP B	[illegible]	[illegible]	25%	[illegible]
% MELD improved in CTP C	70%	83%	–	67%
% MELD worsened in CTP C	18%	11%	–	0%

*Only SVR patients are included

Long-term Follow-up of >1,000 HCV Patients With Compensated or Decompensated Cirrhosis Who Achieved SVR Following Treatment With Sofosbuvir-Based Regimens

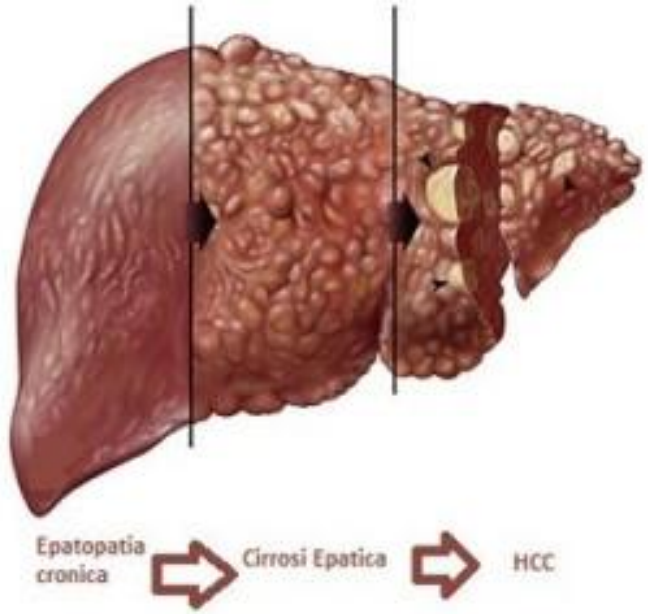


- Monitoraggio seriale CTP score e MELD (ascite, EE, bilirubina, albumina, INR creatinina)
  - The majority of patients maintained or improved their CPT category relative to pretreatment through up to 36 (CPT C) or 42 (CPT B) months relative to treatment start
    - Overall improvements in key laboratory components such as mean bilirubin and mean albumin were observed

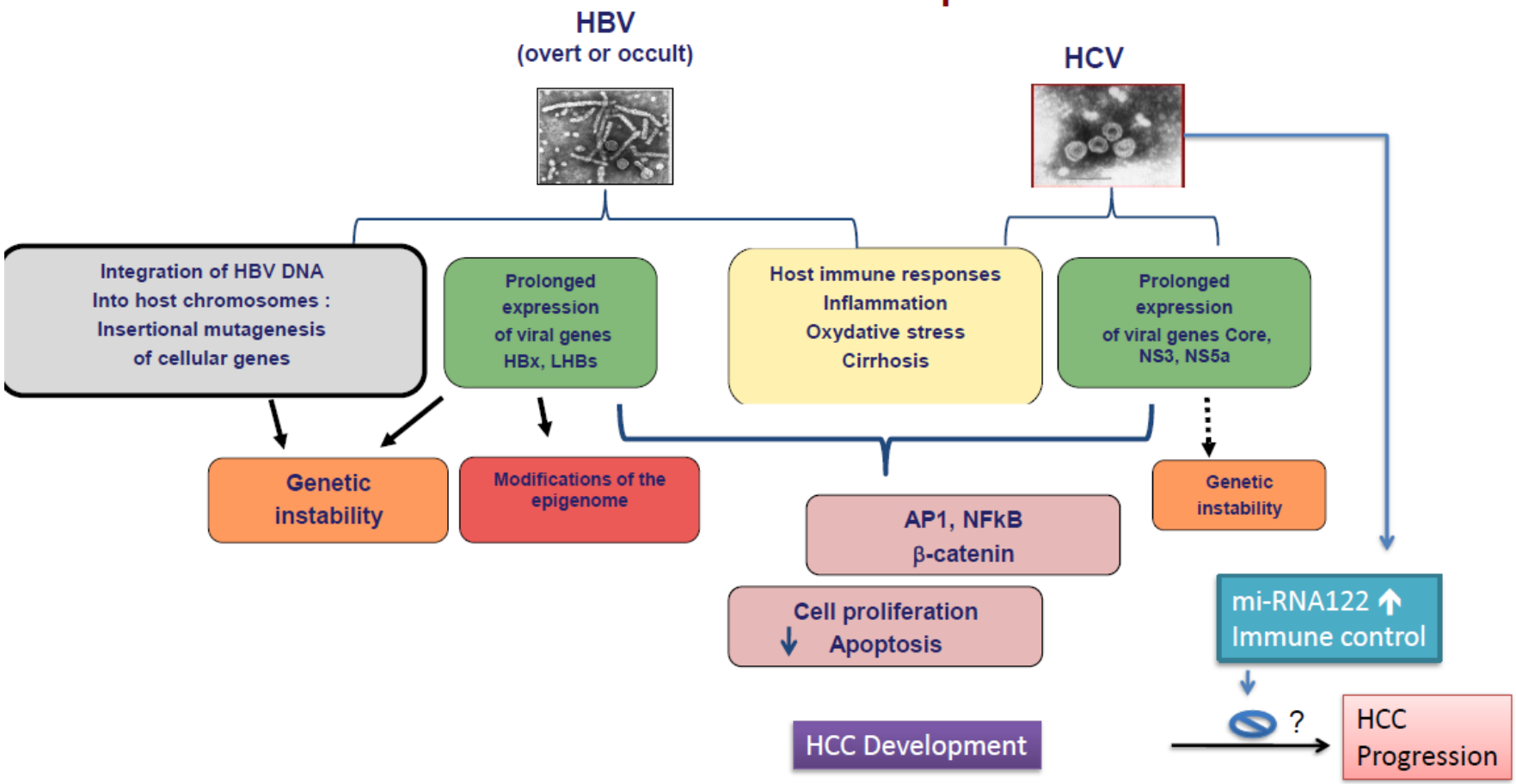
*Only 1 patient with CPT B cirrhosis prior to treatment has reached >42 mo since start of treatment; this patient had CPT A cirrhosis at last assessment.
†Only 1 patient with CPT C cirrhosis prior to treatment has reached >36 mo since start of treatment; this patient had CPT A cirrhosis at last assessment.

Muir A, AASLD, 2016, #880

- Development of HCC in HCV cirrhotic patients treated with DAA



HCC carcinogenesis
Direct and indirect roles of hepatitis viruses



Key Questions

- What is the risk of HCC in patients who achieve SVR?
- Is continued HCC surveillance indicated in this patient?
- If so, what is the optimal HCC surveillance strategy?

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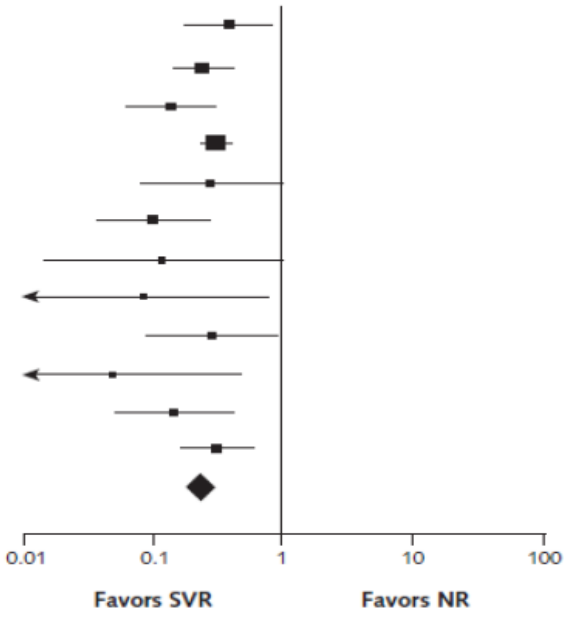
Eradication of HCV and risk of HCC: a meta-analysis of IFN-based studies

Forest Plot Of Adjusted Hazard Effects In Persons At All Stages Of Fibrosis

Study, Year (Reference)	log(Hazard Ratio)	SE	Total SVR	Total NR	Weight, %	Hazard Ratio IV, Random (95% CI)
Asahina et al, 2010 (36)	–0.944	0.388	686	1356	9.2	0.39 (0.18–0.83)
Hung et al, 2011 (46)	–1.423	0.273	1027	443	15.3	0.24 (0.14–0.41)
Kawamura et al, 2010 (50)	–1.985	0.407	1081	977	8.5	0.14 (0.06–0.31)
Kramer et al, 2011 (27)	–1.182	0.126	4292	10 276	31.2	0.31 (0.24–0.39)
Kurokawa et al, 2009 (51)	–1.277	0.631	139	264	4.0	0.28 (0.08–0.96)
Okanoue et al, 2002 (53)	–2.294	0.512	375	586	5.8	0.10 (0.04–0.28)
Osaki et al, 2012 (50)	–2.130	1.053	185	197	1.5	0.12 (0.02–0.94)
Pradat et al, 2007 (17)	–2.481	1.132	87	103	1.3	0.08 (0.01–0.77)
Sinn et al, 2008 (56)	–1.246	0.596	296	194	4.4	0.29 (0.09–0.93)
Takahashi et al, 2011 (57)	–3.022	1.163	89	114	1.3	0.05 (0.00–0.48)
Tateyama et al, 2011 (58)	–1.968	0.537	139	234	5.3	0.14 (0.05–0.40)
Yoshida et al, 1999 (61)	–1.164	0.324	789	1568	12.1	0.31 (0.17–0.59)
Total			9185	16 312	100.0	0.24 (0.18–0.31)

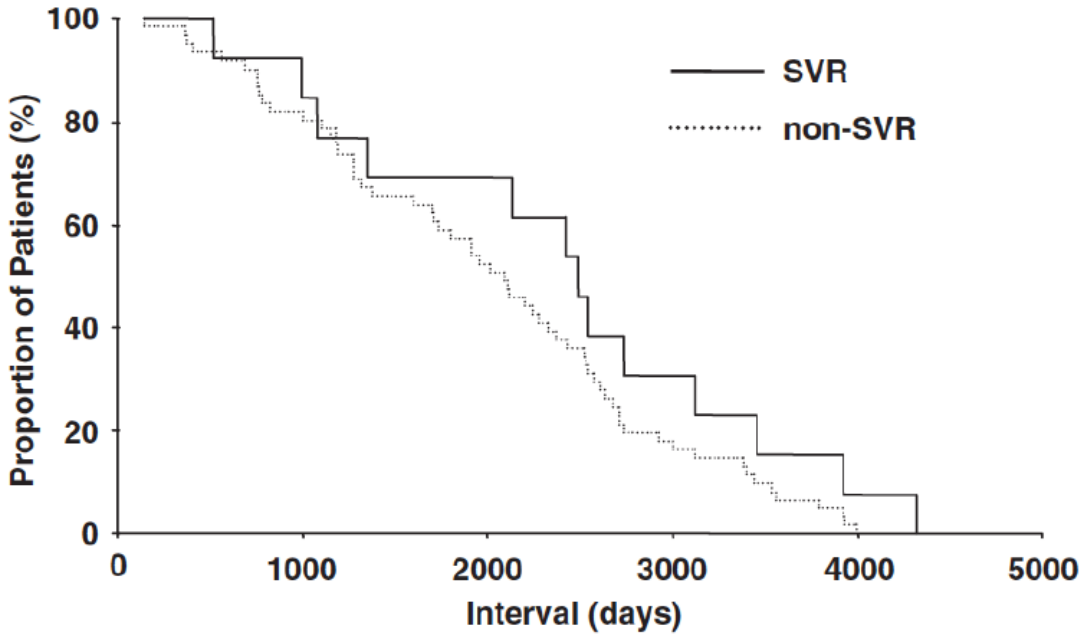
Heterogeneity: tau-square = 0.04; chi-square = 14.05; $P = 0.23$; $I^2 = 22\%$

Test for overall effect: $Z = 10.80$; $P < 0.001$



Morgan et al, Ann Int Med 2013;158:329-337

However, HCC risk persists in patients post SVR



Kobayashi et al. Liver Int 2007

Risk factors for HCC Development among SVR Patients

Study	SVR Patients with Cirrhosis	Median Follow-up	# Incident HCC	Risk Factors
Van der Meer 2012	843 (84%)	6.7 years	50 (5%)	Age
Chang 2012	339 (38.9%)	3.5 years	37 (4.2%)	Age, F3-F4, AFP, thrombocytopenia
Arase 2013	149 (7.8%)	8.1 years	44 (2.3%)	Male, age, alcohol, diabetes
Huang 2014	86 (13.4%)	4.4 years	33 (5.1%)	Age, F4 stage, GGT

HCC in HCV

Known risk Factors for HCC in HCV+ve Cirrhosis

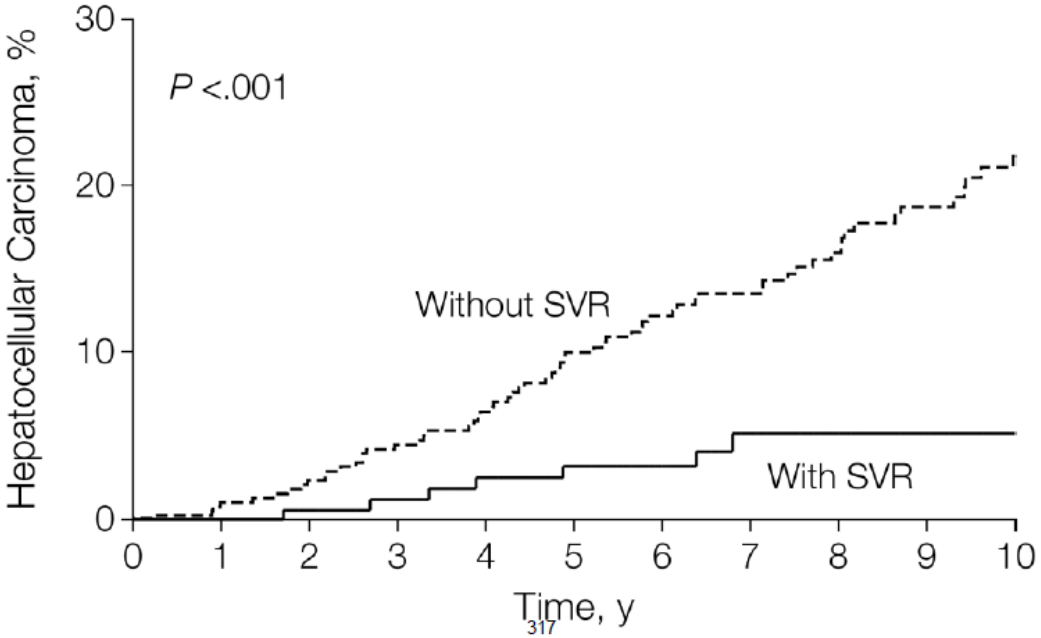
- Older Age
- Older Age at Infection
- Male Gender
- Co-infections (HBV / HIV)
- Heavy Alcohol Consumption
- Diabetes
- Obesity
- HCV genotype

Risk persists for > 10 years after SVR despite potential fibrosis regression

Case No	Years after HCV treatment	Histology
1	18	F2
2	18	F1
3	11	F3
4	15	F3
5	> 10 years	F3

Nojiri et al. Oncol Lett 2010

SVR associated with with reduced risk of HCC but risk may plateau >7 years post SVR



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Van der Meer et al JAMA 2012

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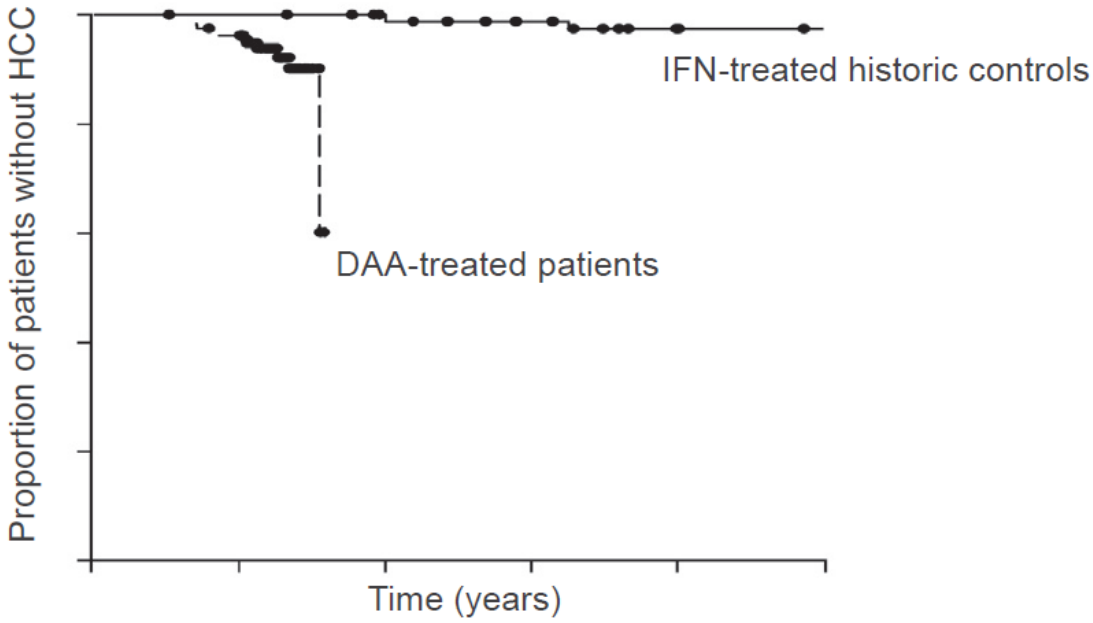
Key Question

- What is the risk of HCC in patients who achieve SVR and is continued HCC surveillance indicated?
  - SVR reduces HCC risk, but patients remain at elevated risk (annual incidence 0.5 – 2%) so surveillance indicated
  - HCC risk prolonged (> 10 years) so surveillance may be be needed indefinitely
    - HCC risk appears to plateau after first 6-7 years but unknown when falls below cost effectiveness threshold

Follow-up Question

- Does this recommendation change with new DAA agents compared to IFN-based treatments?

HCC risk likely persists in patients post SVR with new DAA agents



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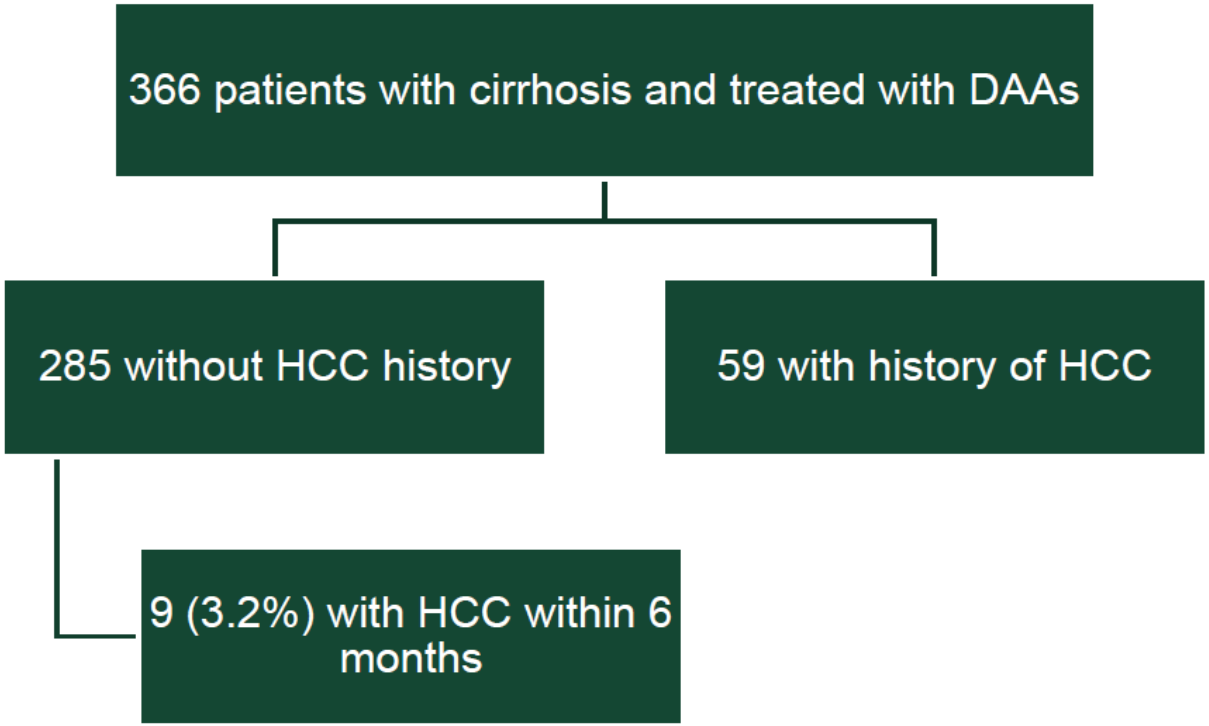
Kozbial et al. J Hepatology 2016

HCC risk persists in patients post SVR



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Conti et al. J Hepatology 2016

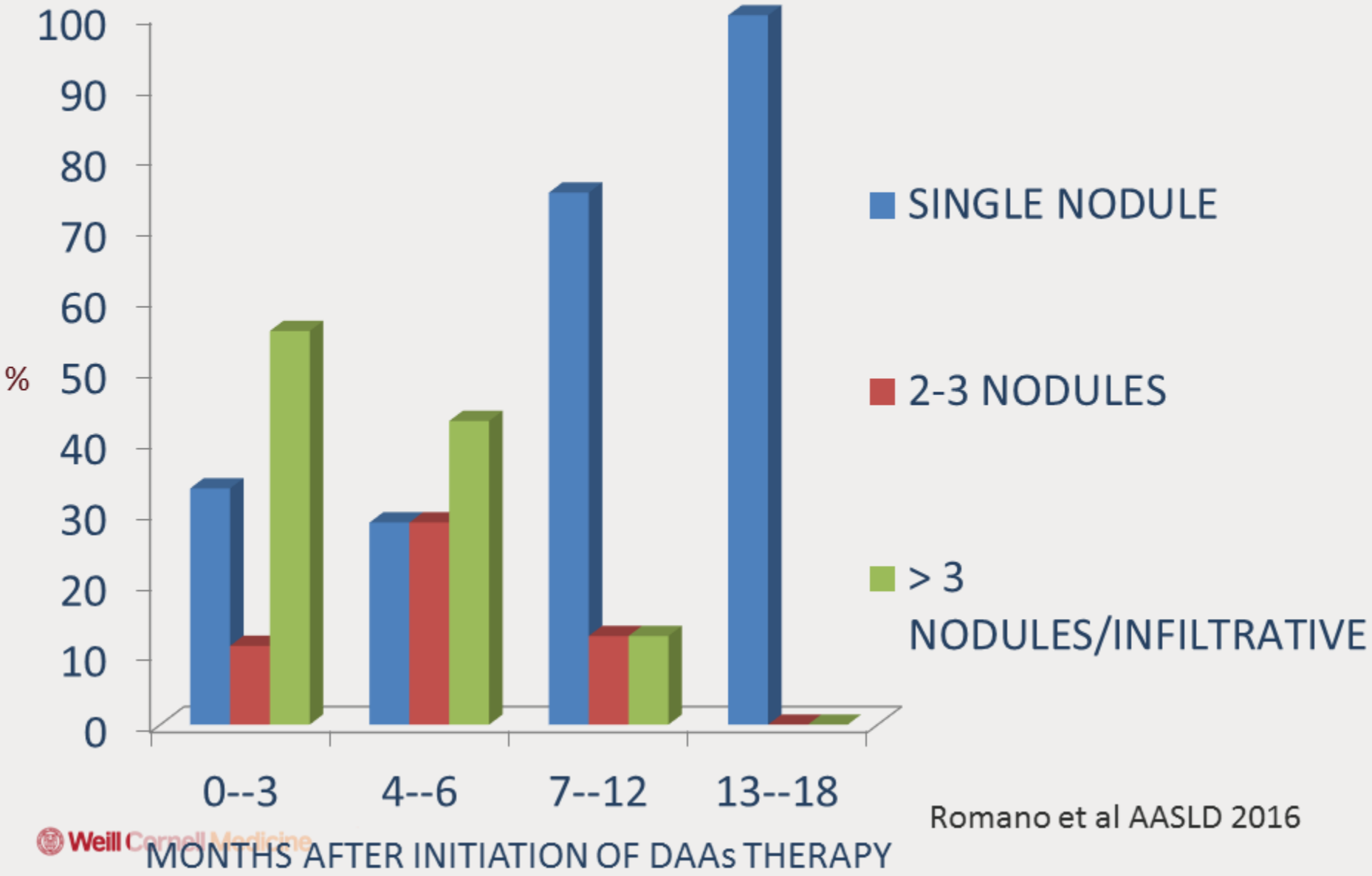
HCC PATTERNS IN RELATION TO SVR

27/2279 patients developed HCC (SVR 20/27)

overall calculated incidence x100 patient-years : 2.1 (95% CI : 1.40-3.10).

Romano et al AASLD 2016

PATTERNS OF HCC DEVELOPMENT IN RELATION TO TIMING OF DAA TREATMENT

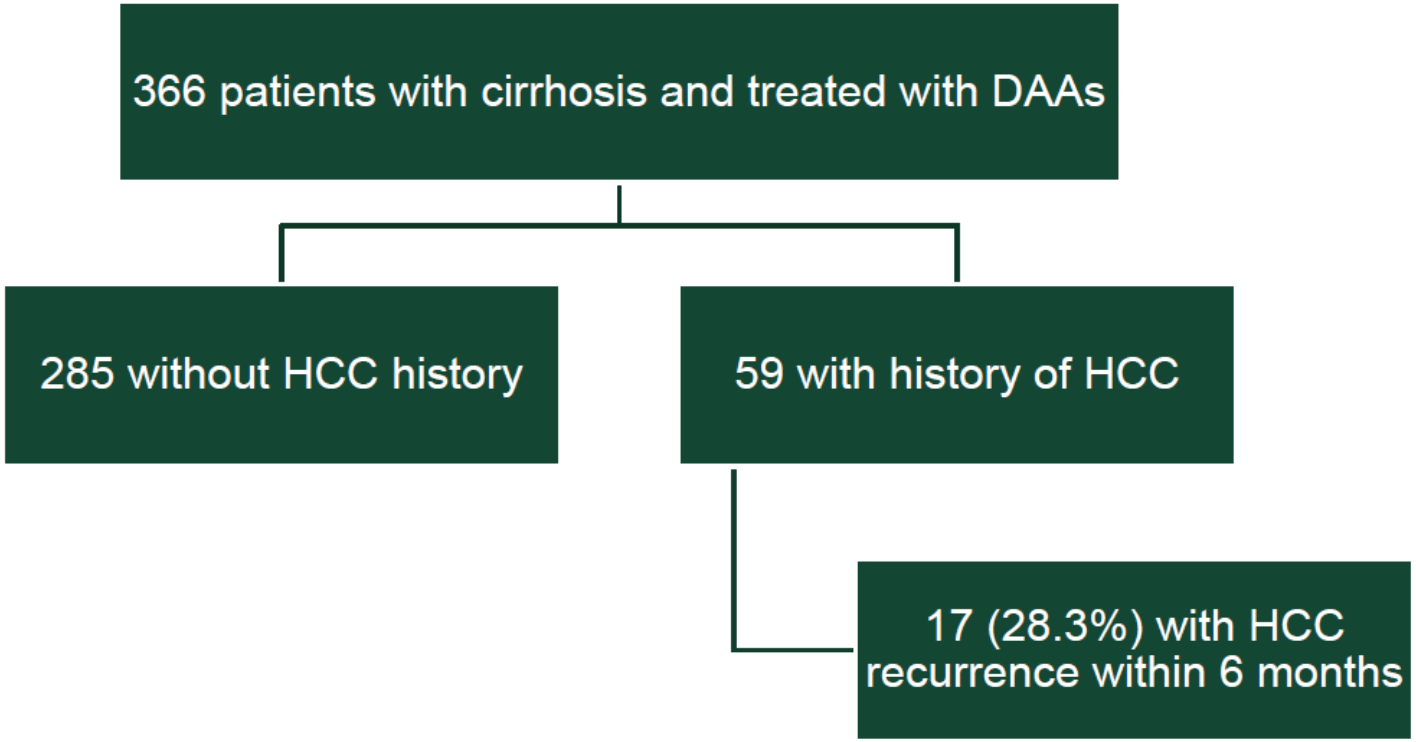


Romano et al AASLD 2016

Romano et al AASD 2016

- The best baseline predictor of the HCC risk was **APRI**
- HCC risk increased linearly by 10% at each 1 point increase in APRI value.
- These results indicate that in cirrhotic patients the incidence of HCC during the first 6-9 months following initiation of DAAs therapy **is not different** from that expected in untreated patients according to historical controls.
- However, the **atypical HCC pattern** seen in about half of the cases deserves better understanding.

Recurrence of HCC may increase post SVR



Conti et al. J Hepatology 2016

Recurrence of HCC may increase post SVR

- 58 HCC patients from 4 centers in Spain who had complete response after resection, ablation, or TACE
  - All underwent DAA therapy after complete response
- Recurrence occurred in 16 (27.6%)
  - Median time from HCC treatment to DAA treatment was 11.2 (3.6 – 23.2) months
  - Median time from DAA treatment to HCC recurrence was 3.5 (1.1 – 8) months
- Subgroup analysis: 41.2% recurrence if started DAA < 4 months of complete response vs. 21.9% if started > 4 months after complete response

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

María Reig[1,†], Zoe Mariño[2,†], Christie Perelló[3], Mercedes Iñarrairaegui[4], Andrea Ribeiro[1], Sabela Lens[2], Alba Díaz[5], Ramón Vilana[6], Anna Darnell[6], María Varela[7], Bruno Sangro[4], José Luis Calleja[3], Xavier Forns[2,‡], Jordi Bruix[1,*,‡]

HCC DURANTE E DOPO TRATTAMENTO CON DAA: L'ESPERIENZA DELLA COORTE SCOLTA

Poster No :E42LB

B. Menzaghi[1], C. Magni[2], L. Nicolini[3], G. Cenderello[4], V. Fiore[5], M. Gussio[6], R. Gulminetti[7], F. Vichi[8], P. Bonfanti[9]

1 Unit of Infectious Diseases, ASST Valle Olona - Busto Arsizio 2 Department of Infectious Diseases, ASST Fatebenefratelli-Sacco 3 Infectious Diseases, San Martino Hospital Genoa, University of Genoa 4 Unit of Infectious Diseases, Galliera Hospital,Genoa 5 Unit of Infectious Diseases, Department of Clinical and Experimental Medicine, University of Sassari, Sassari, Italy 6 Unit of Infectious Diseases, Garibaldi Hospital, Catania, Italy 7 Department of Infectious Diseases, IRCCS Policlinico San Matteo Foundation university of Pavia, Pavia 8 Unit of Infectious Diseases, Santa Maria Annunziata Hospital, Firenze 9 Unit of Infectious Diseases, A. Manzoni Hospital, Lecco

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ABSTRACT

Background

Interferon (IFN)-free direct antiviral agents (DAAs) effectively eradicate hepatitis C virus (HCV) and rapidly improve liver residual functions.

Recent data have suggested that hepatocellular carcinoma (HCC) risk increases during and after DAAs treatment, in HCV-infected patients with advanced liver disease, but no strong evidence exists.

Methods

The SCOLTA (Surveillance Cohort Long-Term Toxicity of Antiretrovirals/Antivirals)-HCV project is an observational, prospective, multicenter cohort study enrolling patients, either HCV mono- or HIV/HCV co-infected, who started DAA treatment. For HCV treatment and HCC surveillance, patients were followed according to Italian guidelines.

Results

Overall 1,154 pts were included in this study. Males were 69.2%; median age was 56.2 years. HIV/HCV co-infected were 392 (34.0%). Twenty-nine (2.5%) patients had a history of HCC (24, 3.2%, with HCV and 5, 1.3%, with HCV/HIV).

At the time of this analysis, median follow-up from initiation of DAA therapy was 16.7 months (IQR 12.7-19.4). Twenty-seven patients developed HCC, as a first diagnosis in 21 cases and recurrence in 6; the incidence rate/100 patient-years was 1.44 (95% CI 0.92-2.16) and 16.61 (95% CI 6.73-34.55) respectively. HCC was diagnosed during DAA treatment in 10 patients (8 new diagnoses and 2 recurrences). All recurrences occurred in HCV mono-infected patients (5 with SVR 12 and 1 with relapse).

Among 21 subjects with first HCC diagnosis, 4 were co-infected with HIV: the rate ratio in comparison with HCV mono-infected patients was 0.43 (95% CI 0.13-1.22, p=0.12). In a multivariate Cox model including age, sex, Metavir, HIV co-infection, HCV genotype, and outcome at 12 weeks, age (HR 1.06, 95% CI 1.01-1.12, by 1 year) and Metavir F4 (HR 4.70, 95% CI 1.08-20.44 as compared to F0-F3) were significantly associated to HCC.

Conclusions

In untreated historical controls, HCC incidence rate ranged between 1 and 3/100 patient-years. Our findings indicate that, in cirrhotic patients, the incidence rate of HCC during the first 16 months following initiation of DAA therapy is not different from that expected in untreated patients.

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Table 1.
Characteristics of 1155 patients on DAA treatment in the SCOLTA Cohort.

Variable	N (%)
Mean age (SD)	56.2 (10.8)
Males	799 (69.2)
Genotype	
1a	288 (25.0)
1b	402 (34.8)
2	89 (7.7)
3	213 (18.5)
4	162 (14.0)
Metavir	
F0-F3	428 (37.1)
F4	726 (62.9)
Previous diagnosis of HCC	29 (2.5)
HIV positive	392 (34.0)
DAA	
SOF+SFM	277 (24.1)
SOF+LED	227 (19.7)
3D	210 (18.3)
SOF+RBV	183 (15.9)
SOF+DAC	171 (14.9)
3D	56 (4.9)
SFM+PEG	22 (1.9)
SFM+DAC	4 (0.4)
Outcome at 12 wks	
SVR 12	999 (93.7)
Failure	13 (1.2)
Relapse	44 (4.1)
Interruption	10 (0.9)
HCC diagnosis	27 (2.4)
-during DAA treatment	10 (0.9)
-after DAA treatment	17 (1.5)
-recurrence (n=29)	6 (20.7)
-new diagnosis (n=1126)	21 (1.9)

Results

Overall 1,154 pts were included in this study (table 1) Males were 69.2%; median age was 56.2 years. HIV/HCV co-infected were 392 (34.0%).
Twenty-nine (2.5%) patients had a history of HCC (24, 3.2%, with HCV and 5, 1.3%, with HCV/HIV).

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Figure 1

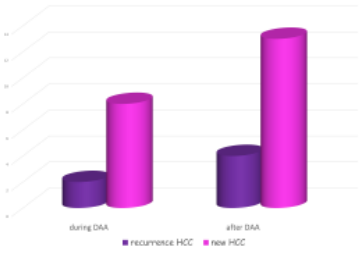


Figure 2

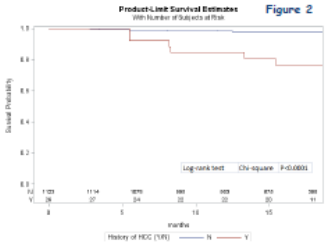
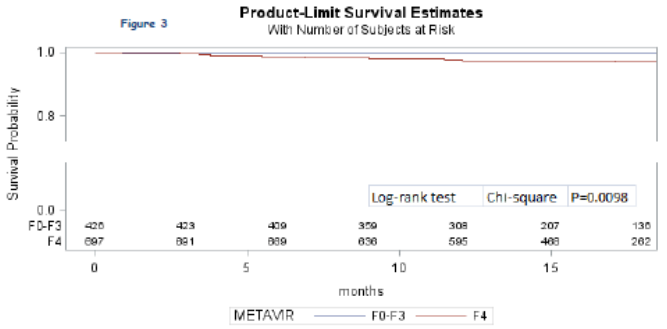


Figure 3



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In untreated historical controls, HCC incidence rate ranged between 1 and 3/100 patient-years. Our findings indicate that, in cirrhotic patients, the incidence rate of HCC during the first 16 months following initiation of DAA therapy is not different from that expected in untreated patients.

References

1 M. Reig et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. Journal of Hepatology

2 C. Cabibbi et al. Direct-acting antiviral agents and risk for HCC early recurrence: Much ado about nothing. Journal of Hepatology

3 The ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CirVir and CO23 CirrH Cohorts. Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: data from three ANRS cohorts

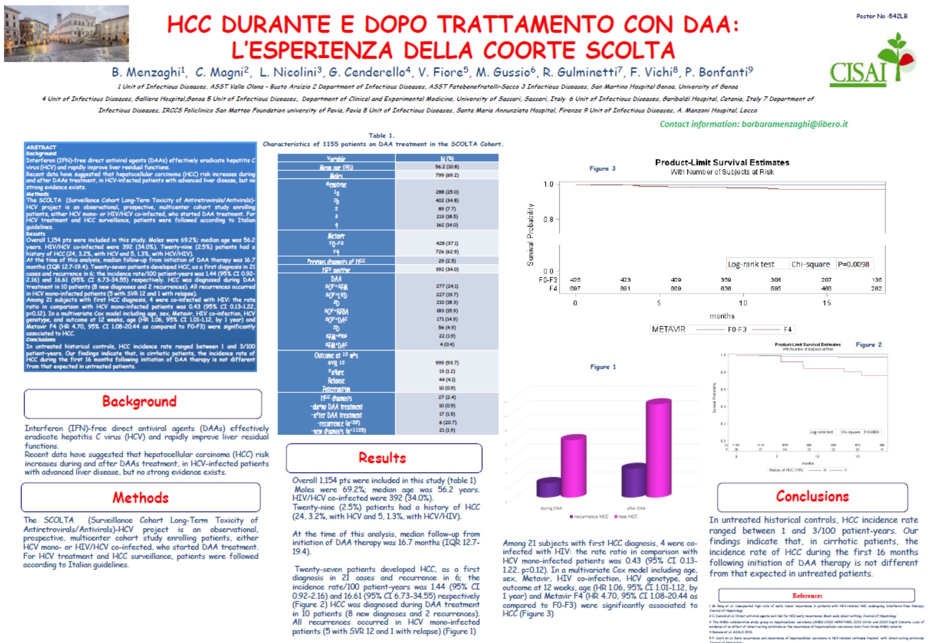
4 Banerjee et al. ASCO 2016

5 F. Conti et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. Journal of Hepatology

8° WORKSHOP NAZIONALE CISAI

PERUGIA, 30 - 31 MARZO 2017

Prevenzione e gestione delle co-morbidità associate all'infezione da HIV



HCC DURANTE E DOPO TRATTAMENTO CON DAA:
L'ESPERIENZA DELLA COORTE SCOLTA
Poster No :642LB
B. Menzaghi[1], C. Magni[2], L. Nicolini[3], G. Cenderello[4], V. Fiore[5], M. Gussio[6], R. Gulminetti[7], F. Vichi[8], P. Bonfanti[9]
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CISAI
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Figure 3
Product-Limit Survival Estimates
With Number of Subjects at Risk
Figure 1
Figure 2
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Key Question

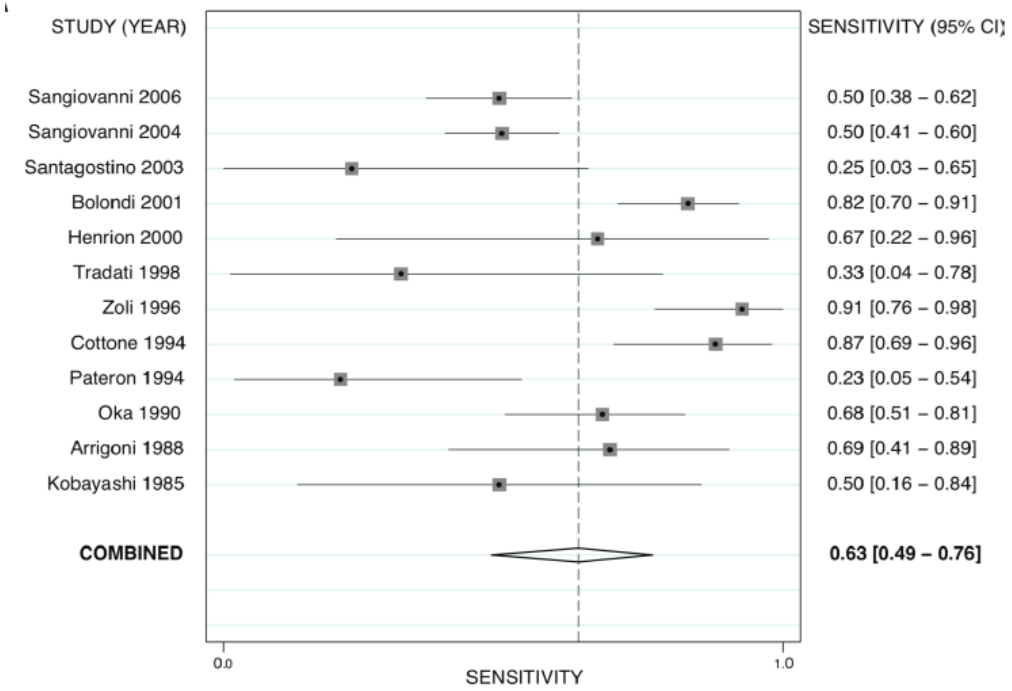
- What is the optimal HCC surveillance strategy in this patient?

HCC surveillance associated with improved survival in patients with cirrhosis

Author	Lead Time	Survival Rates	Significance
El-Serag 2011	70 days	Median survival 298 vs. 130 days	OR 0.81 (95%CI 0.70 – 0.94)
Tong 2010	118 days	3-year survival 62.5% vs. 36.6%	p=0.007
Wong 2008	236 days	2-year survival 49.4% vs. 28.6%	p=0.035
Tanaka 2006	238 days	Median survival 6.3 vs. 5.3 years	p=0.016
Trevisani 2002	98 - 239 days	Median survival 30 vs. 20 months	p<0.001

Singal et al. PLOS Medicine 2014

Ultrasound is efficacious for HCC surveillance



Singal et al. Aliment Pharm Ther 2009

Potential limitations of Ultrasound

- Operator characteristics
  - Variable experience and training of ultrasound technicians
- Patient characteristics
  - Obesity
  - Liver nodularity and echogenicity
  - Presence of ascites

Limitations of Ultrasound Sensitivity

- Retrospective cohort of 1170 ITA.LI.CA database patients
- Ultrasound failure in 28.9% of patients
  - Decreased from 33% in 1987-1999 to 26% in 2000 – 2008

Variable	Multivariate analysis
Annual vs. semiannual	2.20 (1.55 – 3.11)
Child Pugh B	1.60 (1.16 – 2.20)
Alpha fetoprotein (AFP)*	1.00 (1.00 – 1.00)

* Marker of aggressive tumor biology

Del Poggio et al. Clin Gastro Hep 2014

Limitations of Ultrasound Quality

- Retrospective cohort study of 941 patients with cirrhosis
- Ultrasound inadequate quality for surveillance in 134 (20.3%) patients

Variable	Multivariate analysis
Male gender	1.68 (1.14 – 2.48)
Child B or C cirrhosis	1.93 (1.32 – 2.81)
BMI category (BMI < 25 reference)	
Overweight (BMI 25 – 29.99)	2.29 (1.35 – 3.88)
Obesity class I (BMI 30-34.99)	2.95 (1.67 – 5.20)
Obesity class II (BMI 35-39.99)	6.37 (3.35 – 12.1)
Obesity class III (BMI ≥40)	8.22 (4.30 – 15.7)
Etiology (HCV reference)	
Hepatitis B	1.87 (0.79 – 4.39)
Alcohol-related	2.11 (1.33 – 3.37)
NASH	2.87 (1.71 – 4.80)

335

WWW.AASLD.ORG

Simmons et al. Aliment Pharmacol Ther (in press)

Potential solutions to improve effectiveness

- Better imaging quality
  - Improved ultrasound quality
  - Contrast enhanced CT or MRI
- Combining with biomarkers
  - Alpha fetoprotein (AFP)
  - AFP-L3% and DCP
  - Others: GP73, osteopontin, etc.

CT not recommended for HCC surveillance

Variable	Ultrasound (n=83)	CT (n=80)	p-value
Number of HCC	8 (10.8%)	8 (10.0%)	0.86
Proportion BCLC A	5 (55.5%)	5 (62.5%)	0.93
HCC-related mortality	5 (6.0%)	7 (8.8%)	0.46
False positive imaging	3 (3.6%)	9 (5.6%)	0.06
Cost per HCC	$17,041	$57,383	

Pocha et al. Aliment Pharm Ther 2013

MRI not recommended for HCC surveillance

- Prospective cohort study with 407 Child A-B patients
  - 1112 surveillance rounds over 1.5 years
  - Ultrasound and MRI done in all patients
- 35 patients with total of 40 HCC nodules
  - 26 patients had BCLC stage 0 and 8 BCLC stage A

Cohort	MRI	US	P-value
Sensitivity	97%	40%	P<0.001
Sensitivity for BCLC O	96%	42%	P<0.001
Specificity	94%	90%	P=0.049

Lim et al AASLD abstract 2014

Using AFP with ultrasound improves sensitivity for tumor detection in clinical practice

Surveillance Test	Sensitivity	Specificity
Ultrasound	92.0 (89.2 – 94.8)	74.2 (71.8 – 76.7)
AFP >20	52.9 (47.8 – 58.0)	93.3 (91.9 – 94.7)
Ultrasound and AFP >20	99.2 (98.2 – 100)	68.3 (65.7 – 70.9)
Ultrasound and AFP >20 and >2* from nadir	99.2 (98.2 – 100)	71.6 (69.0 – 74.0)

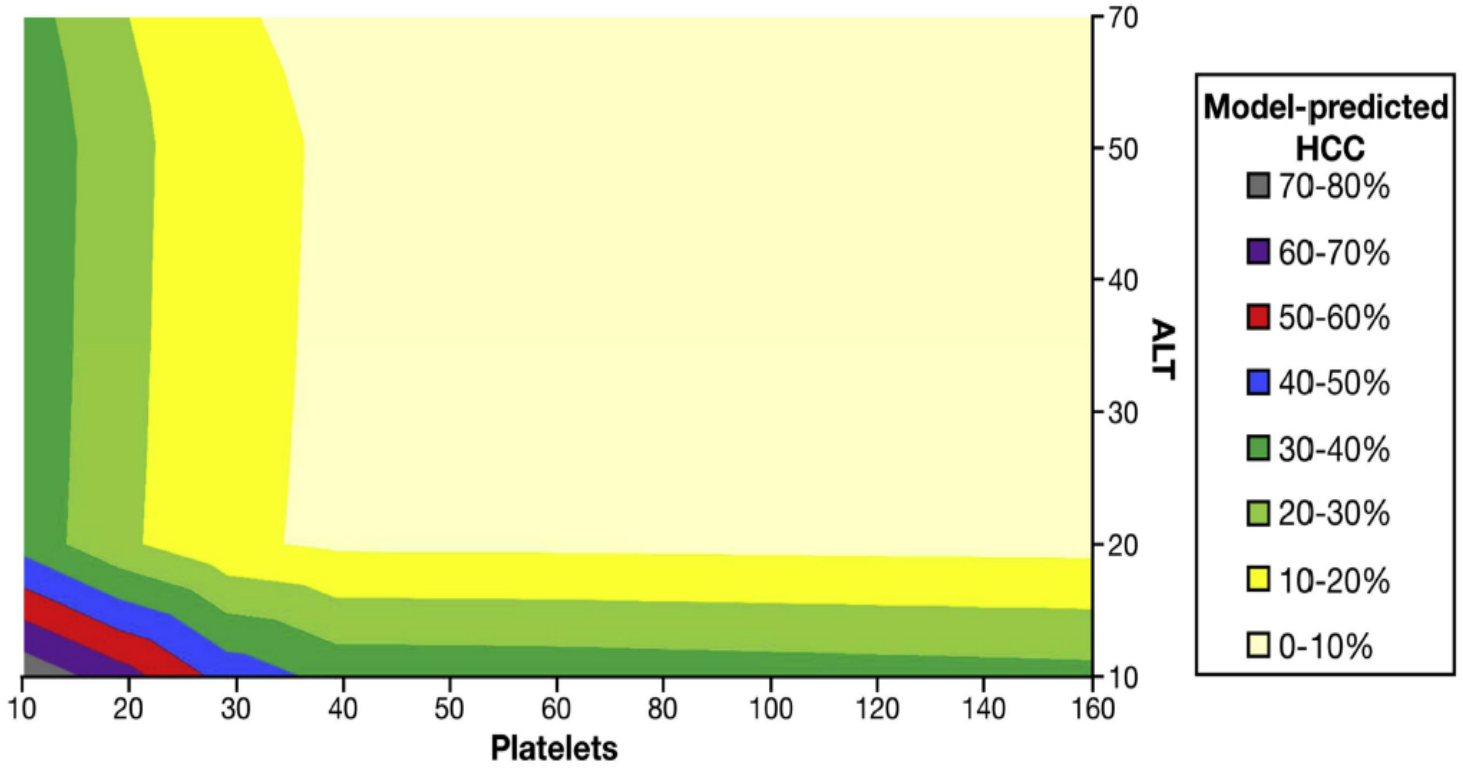
Chang et al Am J Gastro 2015

Using AFP with ultrasound improves sensitivity for early tumor detection in clinical practice

Test	Efficacy		Effectiveness	
	Sensitivity	Sensitivity Early Stage	Sensitivity	Sensitivity Early Stage
AFP alone	35/51 (69%)	25/51 (49%)	27/41 (65.9%)	19/41 (46.3%)
Ultrasound alone	43/51 (84%)	32/51 (63%)	18/41 (43.9%)	13/41 (31.7%)
Ultrasound and AFP	47/51 (92%)	35/51 (69%)	37/41 (90.2%)	26/41 (63.4%)

Singal et al Cancer Epi Biomark Prev 2012

AFP performance improved by adjusting for ALT



El Serag et al Gastro 2014

Key Questions

- What is the optimal HCC surveillance strategy?
  - Although ultrasound can be efficacious, it may have lower effectiveness given its operator dependent nature and differences in patient characteristics
  - There are no data supporting routine use of CT or MRI for surveillance purposes
  - AFP can improve sensitivity for early tumor detection and a combination of ultrasound/AFP may be the optimal surveillance strategy

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 March 2016
EMA/199242/2016

EMA reviews direct-acting antivirals for hepatitis C

Review to investigate possible hepatitis B re-activation

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