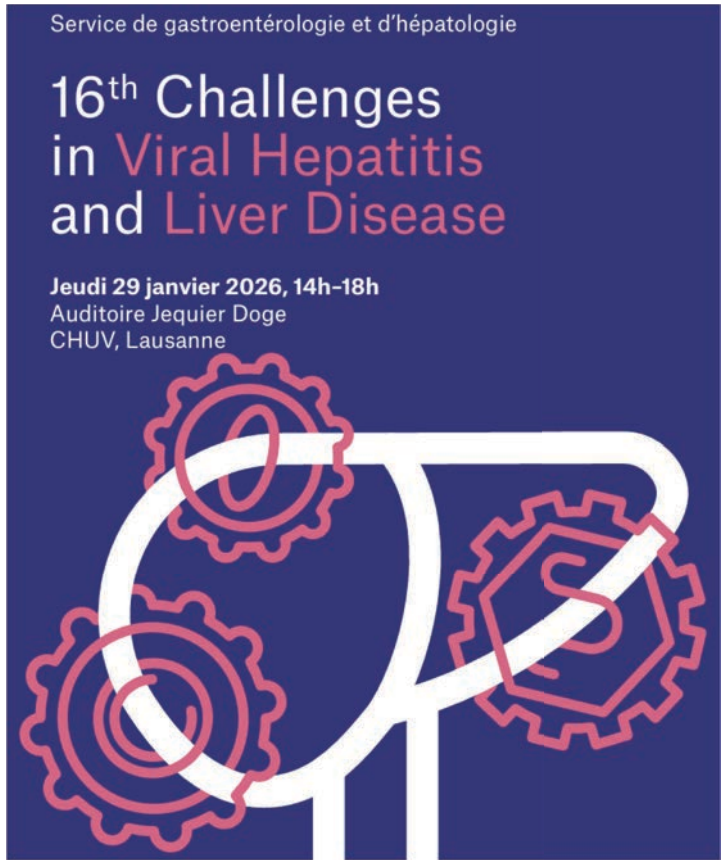


Clinical follow-up after cure of hepatitis C

Dr. Sabela Lens

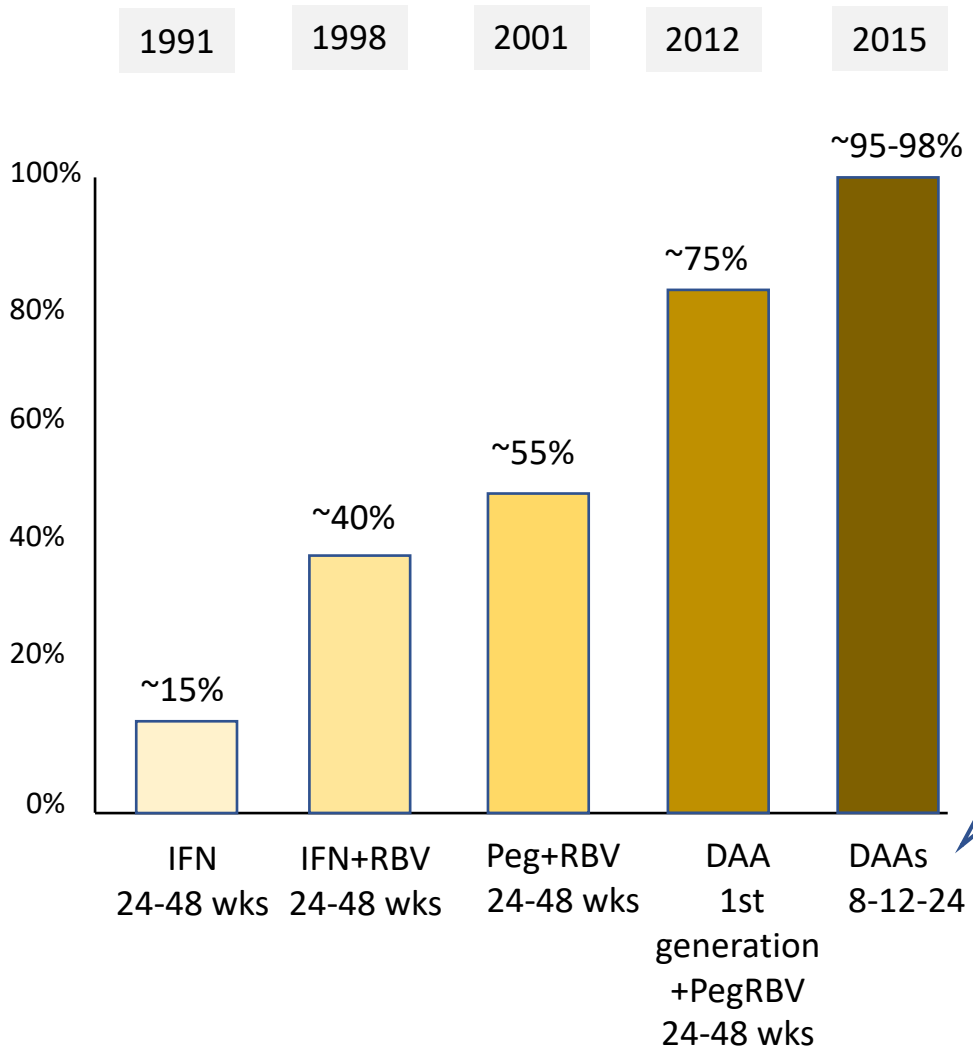
Liver Unit, Hospital Clinic, Barcelona

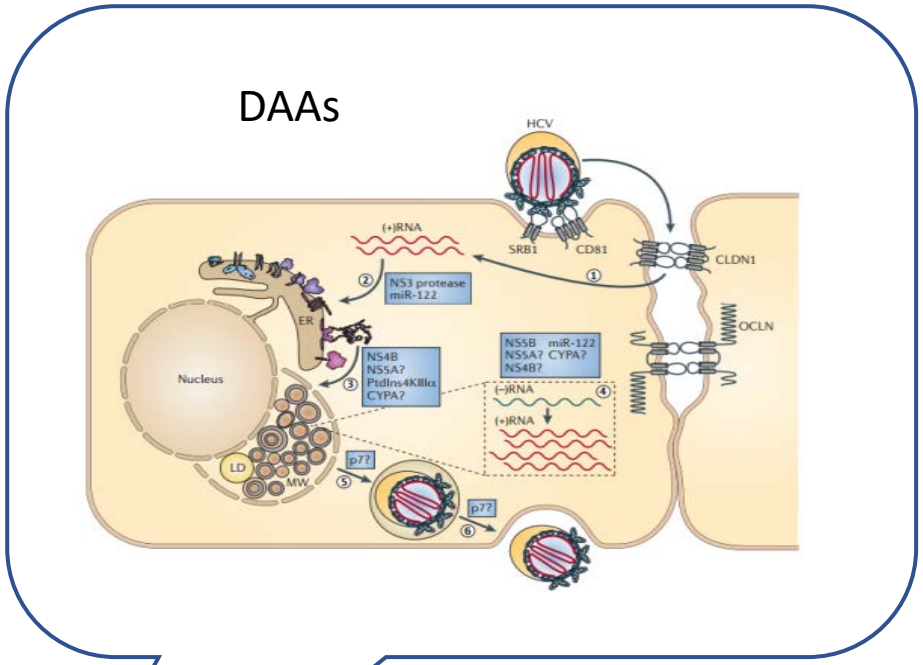
FCRB-IDIBAPS, CIBERehd, ERN-Liver

University of Barcelona

Clínic Barcelona | Universitat de Barcelona

HCV Antiviral Therapy evolution

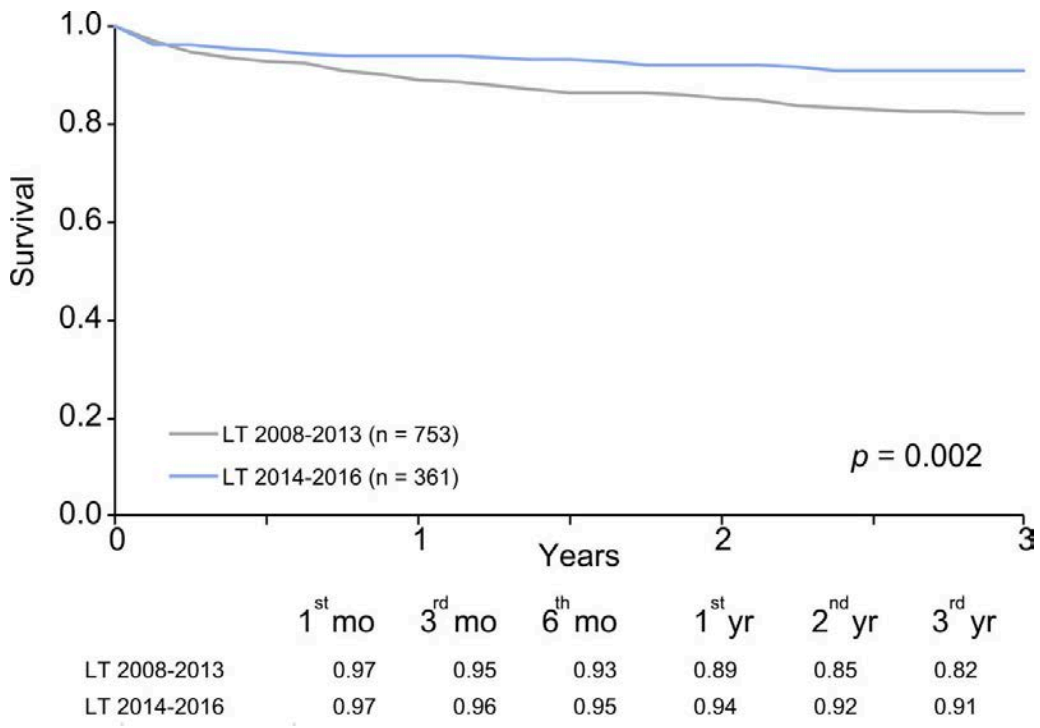




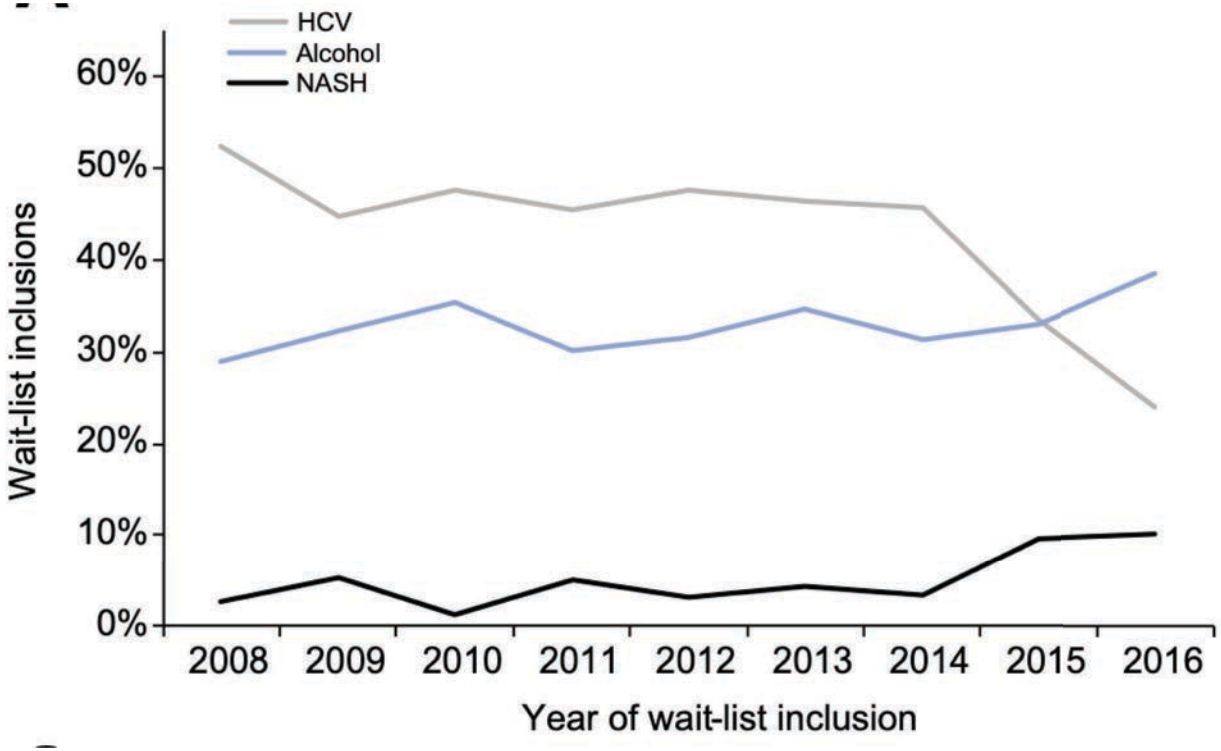
>SVR (%)
> Impact

McHutchison JG, *et al. N Engl J Med* 1998; 339:1485–1492; Manns MP, *et al. Lancet* 2001; 358:958–965; Fried MW, *et al. N Engl J Med* 2002; 347:975–982; Poordad F, *et al. N Engl J Med* 2011; 364:1195–1206; Jacobson IM, *et al. N Engl J Med* 2011; 364:2405–2416; Lawitz E, *et al. N Engl J Med* 2013; 368:1878–1887; Fichas Técnicas Daklinza, Epclusa, Harvoni, Olysio, Viekirax, and Zepatier .

Impact on post-liver transplant survival and on the liver transplant waiting list composition



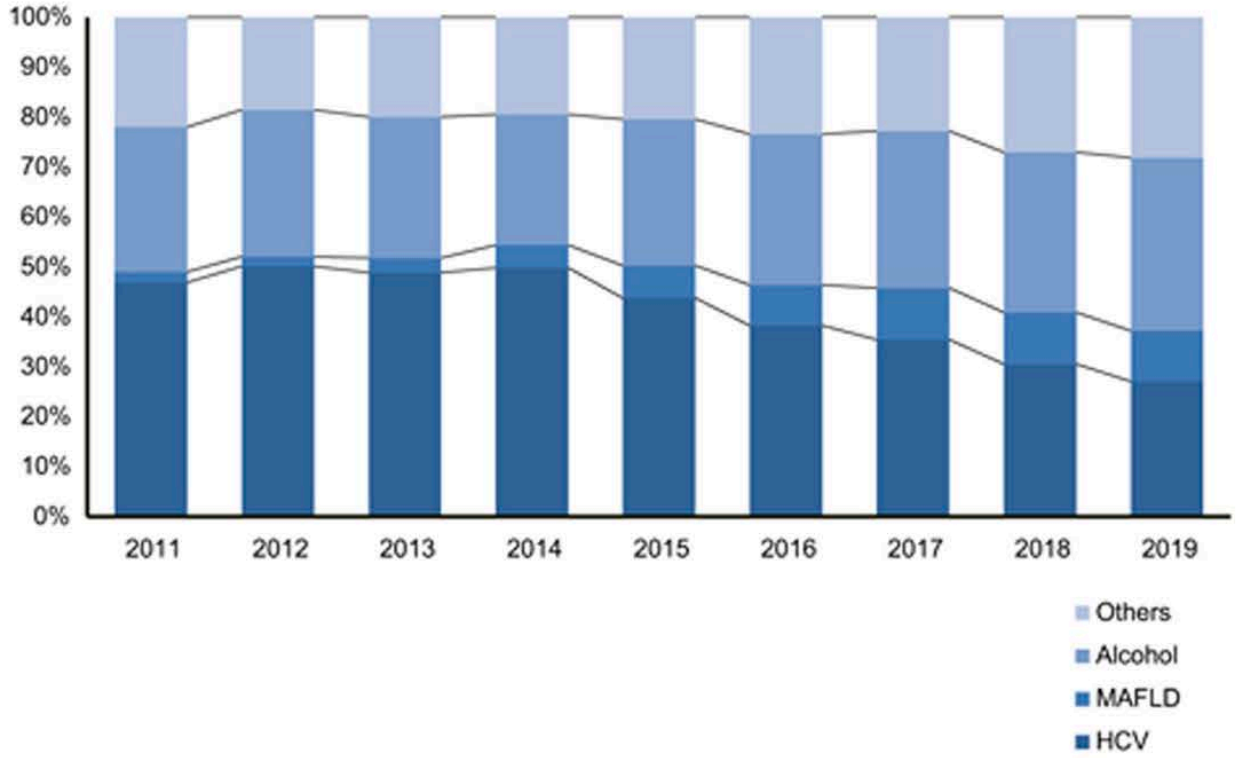
	1st mo	3rd mo	6th mo	1st yr	2nd yr	3rd yr
LT 2008-2013	0.97	0.95	0.93	0.89	0.85	0.82
LT 2014-2016	0.97	0.96	0.95	0.94	0.92	0.91



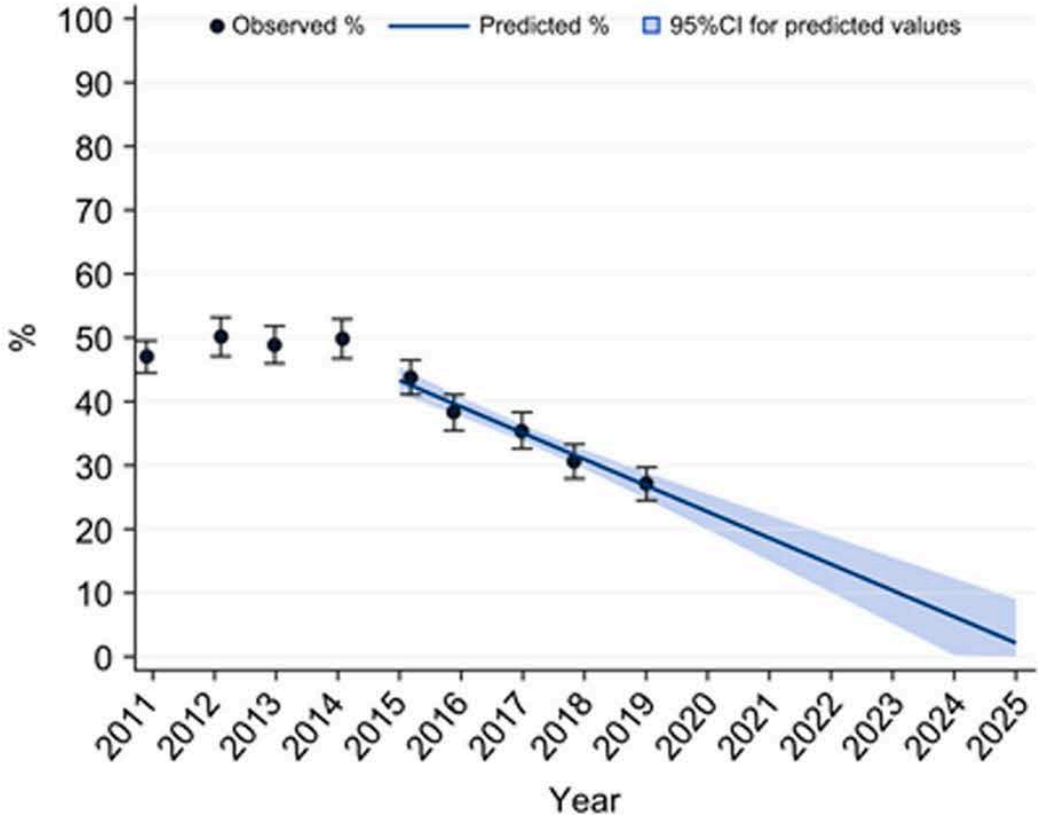
Crespo G et al. J Hepatol 2019

Impact of HCV antiviral therapy on hospital admissions

Changes in the number of admissions by etiology of cirrhosis from 2011 to 2019



Model predicting the evolution of HVC-related cirrhosis admissions in the future years



Rodríguez Tajes , et al. J Hepatology 2020

What is left in terms of clinical challenges after HCV SVR?

Individual

vs

Community

Clinical challenges after SVR

Clinical challenges in HCV elimination

Clinical Case (1) compensated cirrhosis

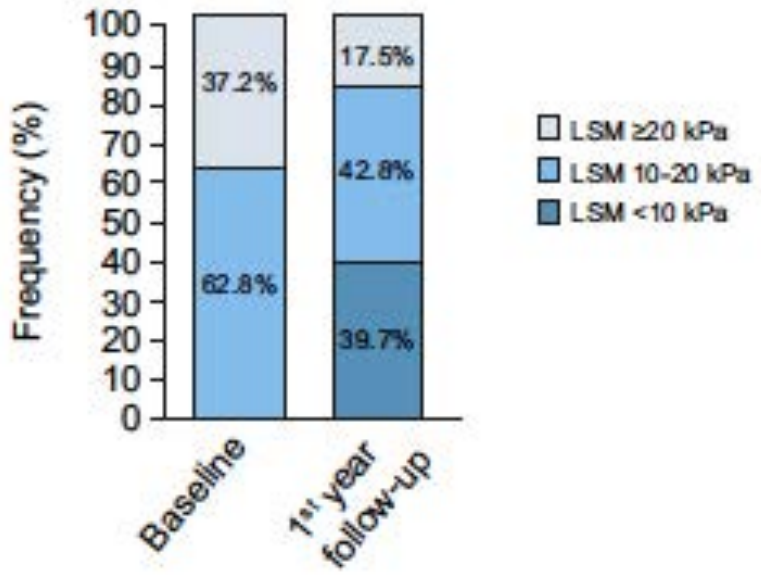
- Male 58 years old
- HCV genotype 1b cirrhosis, 80.000 platelets
- Child-Pugh A
- Liver Stiffness 21kPa → 11 kPa after SVR
- Esophageal varices

- To which extent will improve **fibrosis** and **portal hypertension**?
- Is the **risk of decompensation** null in the near future?
- Is the need for **HCC screening** reduced or persistent in long term?

Fibrosis regression: Who? When? How much?

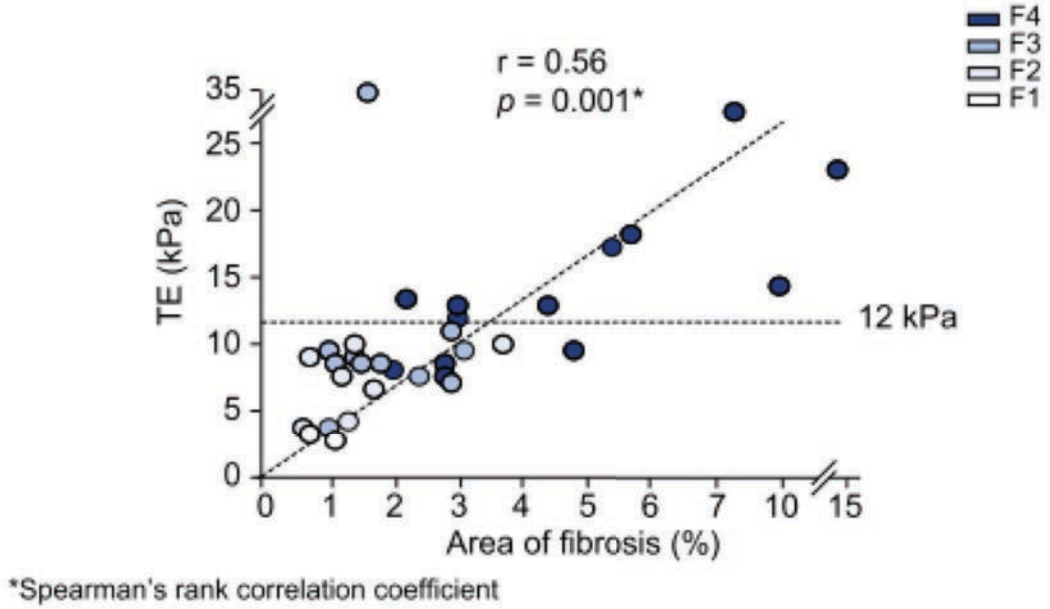
50–60% of patients show substantial LSM improvement over 2–5 years (~25–30% F3/F4 → F2)
rapid LSM decreases associated with high inflammatory/edematous components than with architectural remodeling

500 patients with cACLD treated with DAAs



Pons et al. J Hepatol 2020

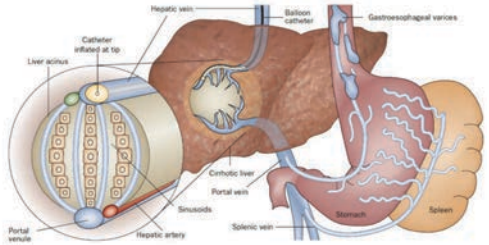
60% of 38 patients (IFN+RBV) ↓fibrosis stage (FU 5y)



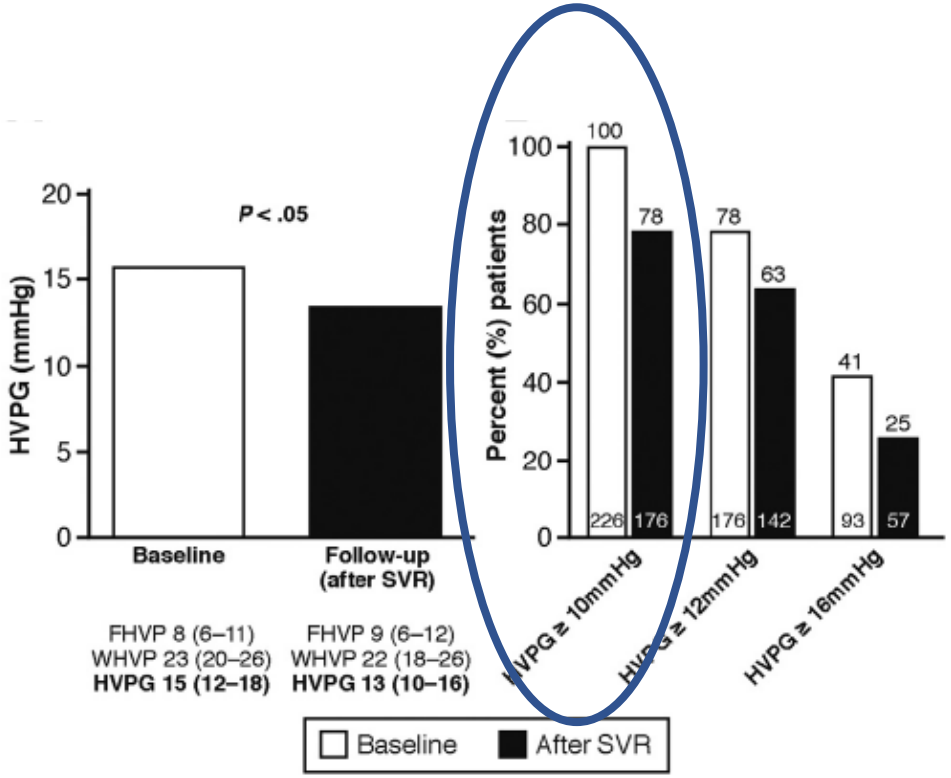
*Spearman's rank correlation coefficient

D'Ambrosio et al. J Hepatol 2013

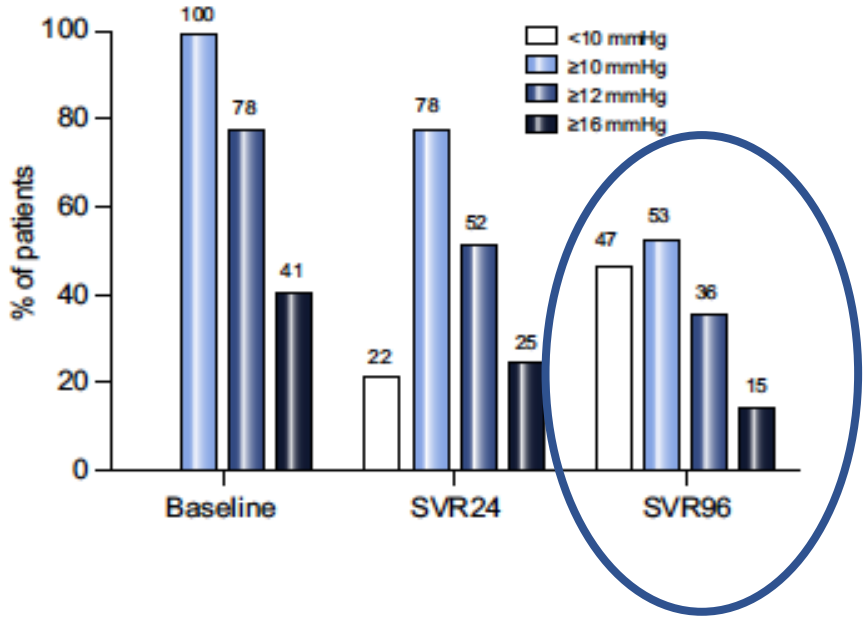
Impact on Portal Hypertension: short and long-term



226 patients with CSPH (*HVPG >= 10 mmHg)* + SVR: HVPG at 6 months and, if CSPH, again 2 years after EOT)

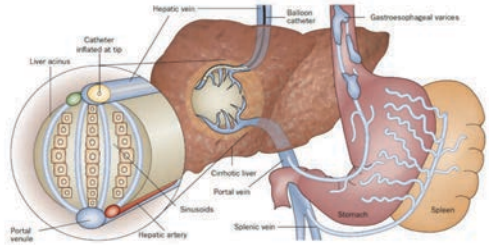


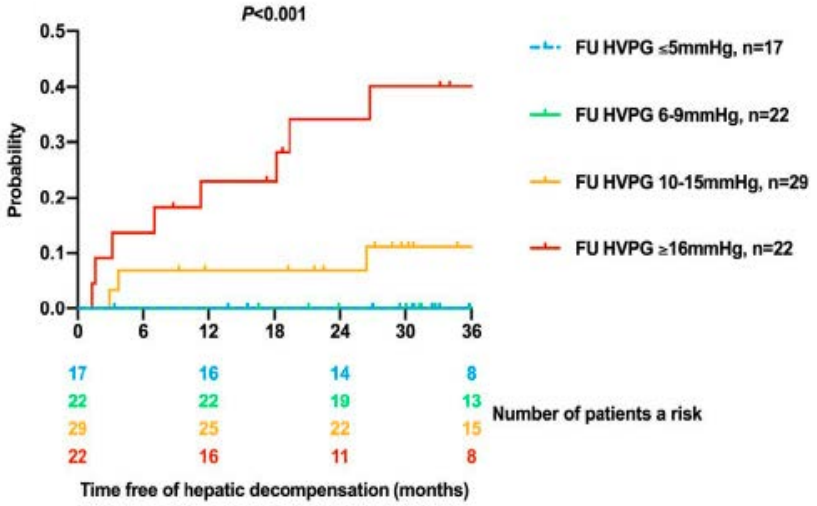
Lens et al. Gastroenterology 2017

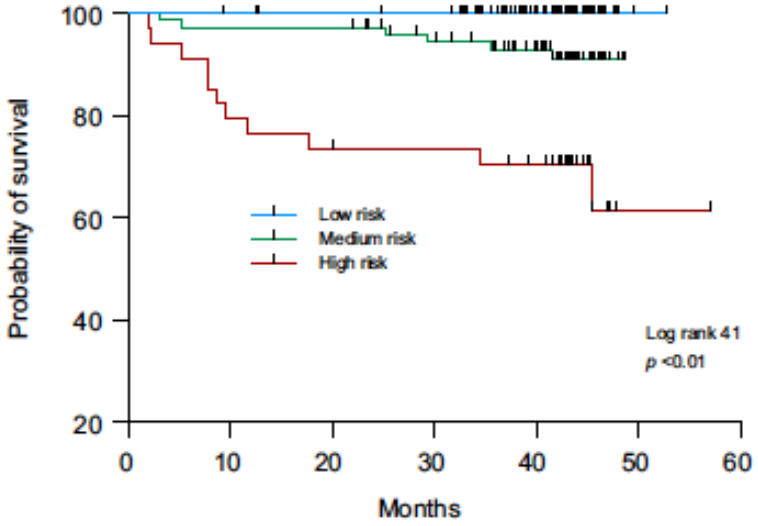


Lens and Baiges et al. J Hepatol 2020

Risk of Hepatic Decompensation based on CSPH







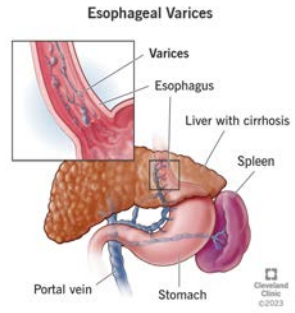
- ✓ 11 (12%) patients hepatic decompensation
  n=4 new and n=7 further
- ✓ 0.96/100 patient-years
- ✓ No patient with resolution of CSPH → decompensation

Mandorfer et al. Hepatology 2020

- ✓ De novo (n=5) or further decompensation (n=12) in 17 patients (7.5%)
- ✓ High risk: HVPG >=16 mmHg and previous ascites
- ✓ No patient with resolution of CSPH → decompensation

Lens and Baiges et al. J Hepatol 2020

Risk of CSPH-outcomes after SVR based on NITs



Overall cohort: n=675

- *Reiberger et al (2012) – n=80*
- *Lens et al (2015) – n=100*
- *Mandorfer and Kozbial et al (2016)/ Schwabl and Mandorfer et al (2018)/ Mandorfer et al (2020) – n=90*
- *Lens et al (2017)/ Lens and Baiges et al (2020) – n=226*
- *Puente et al (2017) – n=8*
- *Mauro et al (2018) – n=112*
- *Abadia et al (2019) – n=33*
- *Diez et al (2020) – n=26*

n=166 without paired HVPG-measurement before and after HCV-cure

n=59 without HCV-cure

n=32 without portal hypertension (HVPG≥6 mmHg) before HCV-cure

n=418 included in cohort for HVPG regression

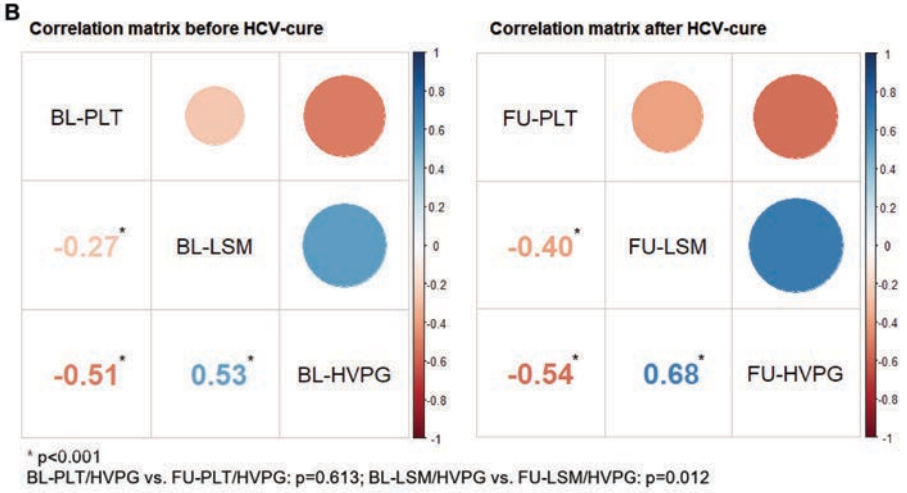
n=94 without paired NIT before and after HCV-cure

n=324 included in cohort for evaluation of NIT

n=241 with cACLD

n=274 with CSPH

n=184 with clinical evidence for CSPH



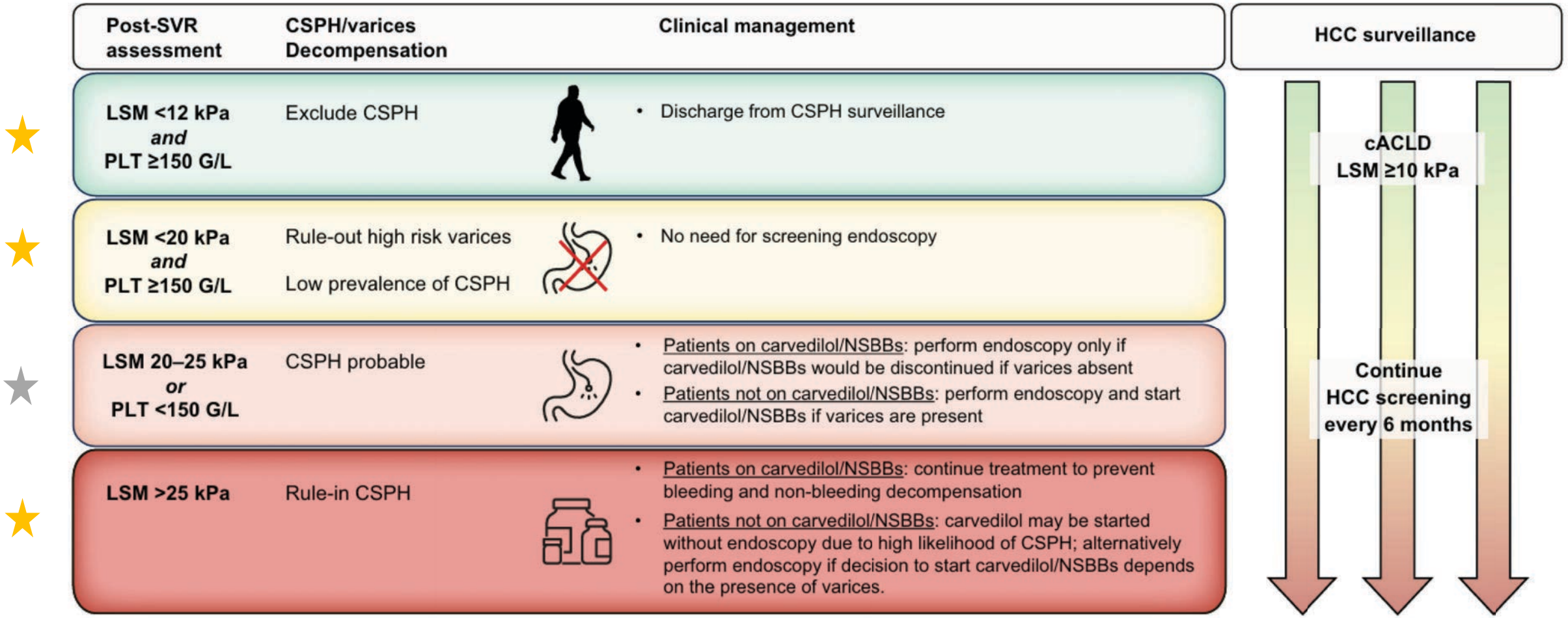
LSM <12kPa and PLT >150,000 can be discharged from portal hypertension surveillance *

✓they do not have CSPH
✓negligible risk of hepatic decompensation

*** IF no other risk factors!**

Semmler et al. J Hepatology 2022

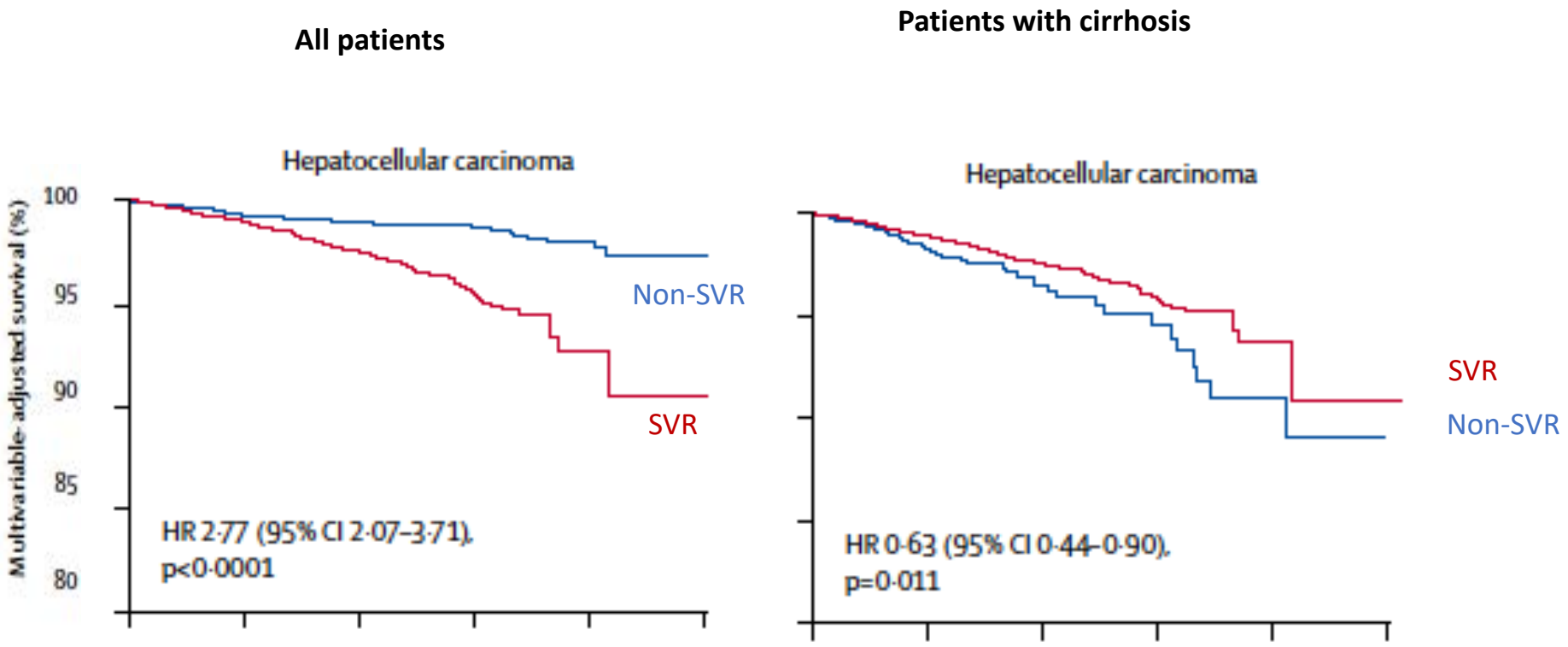
Risk of CSPH after SVR based on NITs



Reiberger and Lens et al. J Hepatology 2024

Risk of Hepatocellular Carcinoma

9895 patients (7344 receiving DAAs) mean FU of 2.8 years

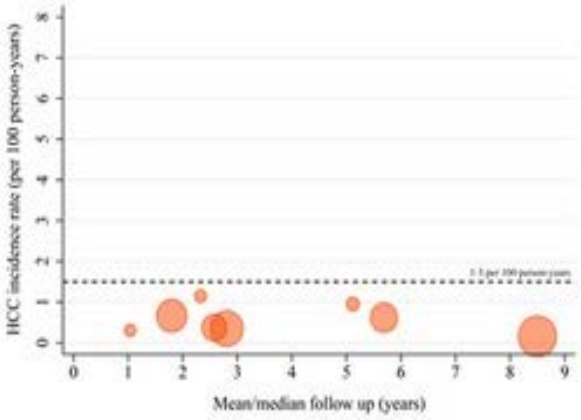


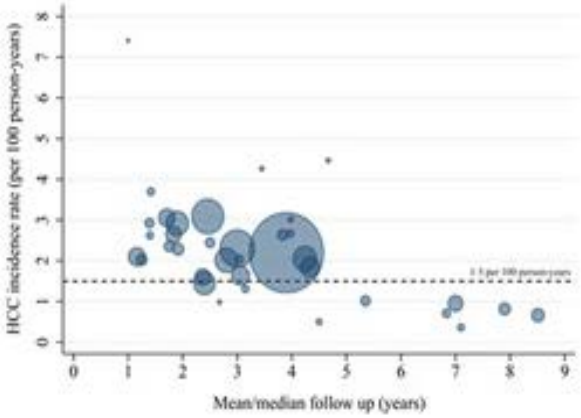
F3&F4 fibrosis stage at baseline → HCC screening with US / 6 months

Carrat et al. Lancet 2019

Risk of Hepatocellular Carcinoma in F3 vs F4

Systematic review and meta-analysis: 44 studies (107,548 person-years FU)
cirrhosis: 2.1 per 100 person-years (95% CI, 1.9–2.4) – age and decompensation-
F3 0.5 per 100 person-years (95% CI, 0.3–0.7)





Incidence of HCC after HCV cure among patients with F3 fibrosis:
0.5 per 100 person-years

Below current recommended incidence for cost-effective screening

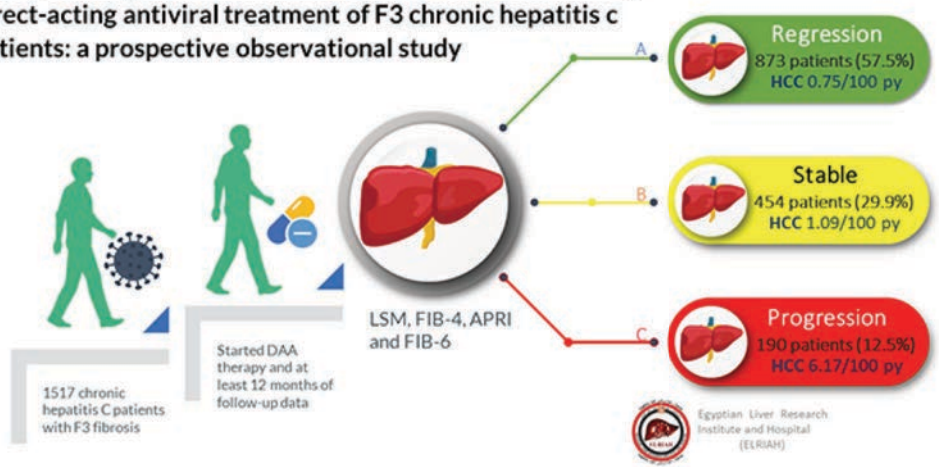
Incidence of HCC after HCV cure among patients with cirrhosis:
2.1 per 100 person-years

↓ Rate over time

Lockart et al. Hepatology 2022

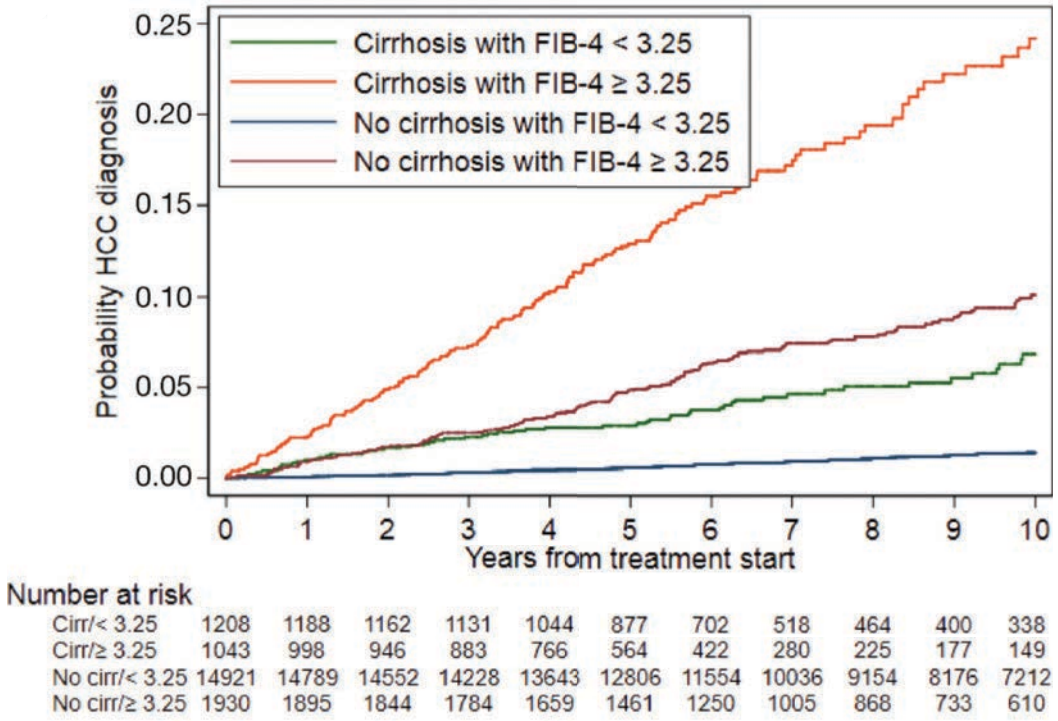
889 F3 patients (LSM 9.5-14-5 kPa)
If stable- worsening LSM → higher HCC risk

Changes in hepatic fibrosis and incidence of HCC following direct-acting antiviral treatment of F3 chronic hepatitis c patients: a prospective observational study



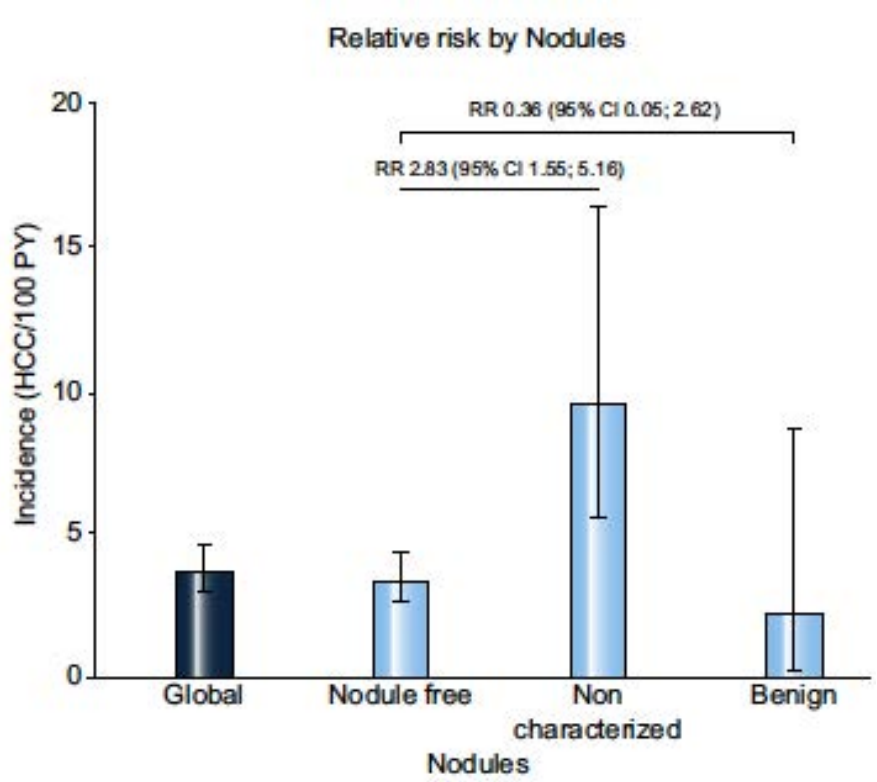
Shiha et al. Hepatoma research 2022

Is it possible to identify the potential predictors of HCC and stablish different surveillance modes tailored to risk classes?



Baseline FIB-4 ≥3.25 = 2-fold higher risk of HCC

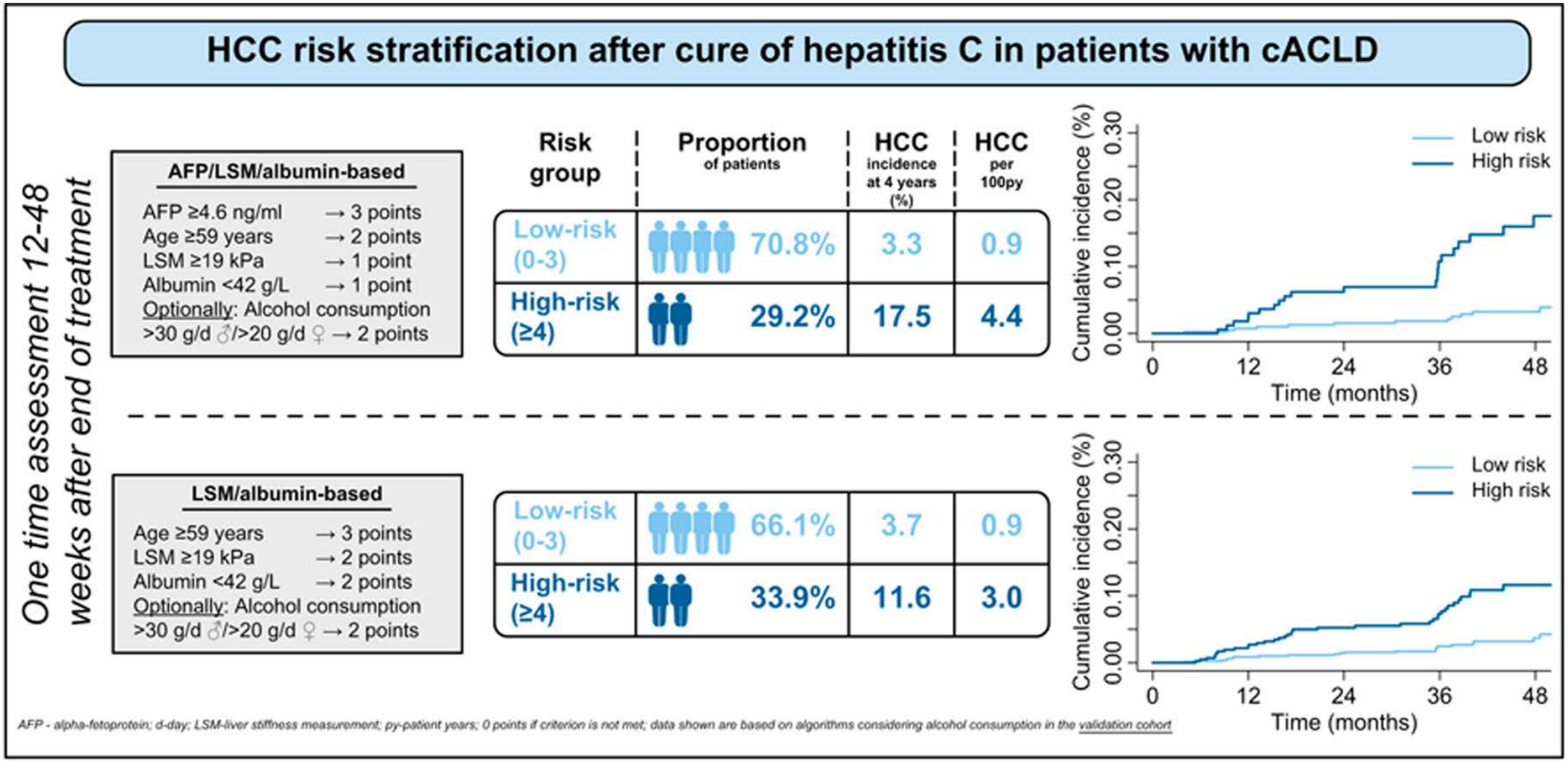
Ionnau G, Gastroenterology 2019



Non-characterized nodules before DAA therapy

Sanduzzi and Mariño et al. J Hepatol 2020

Is it possible to identify the potential predictors of HCC and stablish different surveillance modes tailored to risk classes?



Semmler et al. J Hepatol 2022
DOI: 10.1016/j.jhep.2021.11.025

Clinical Case (2) decompensated cirrhosis

- Male 64 years old

At presentation:

- HCV decompensated cirrhosis
- Ascites & HE grade II at admission
- Child-Pugh B

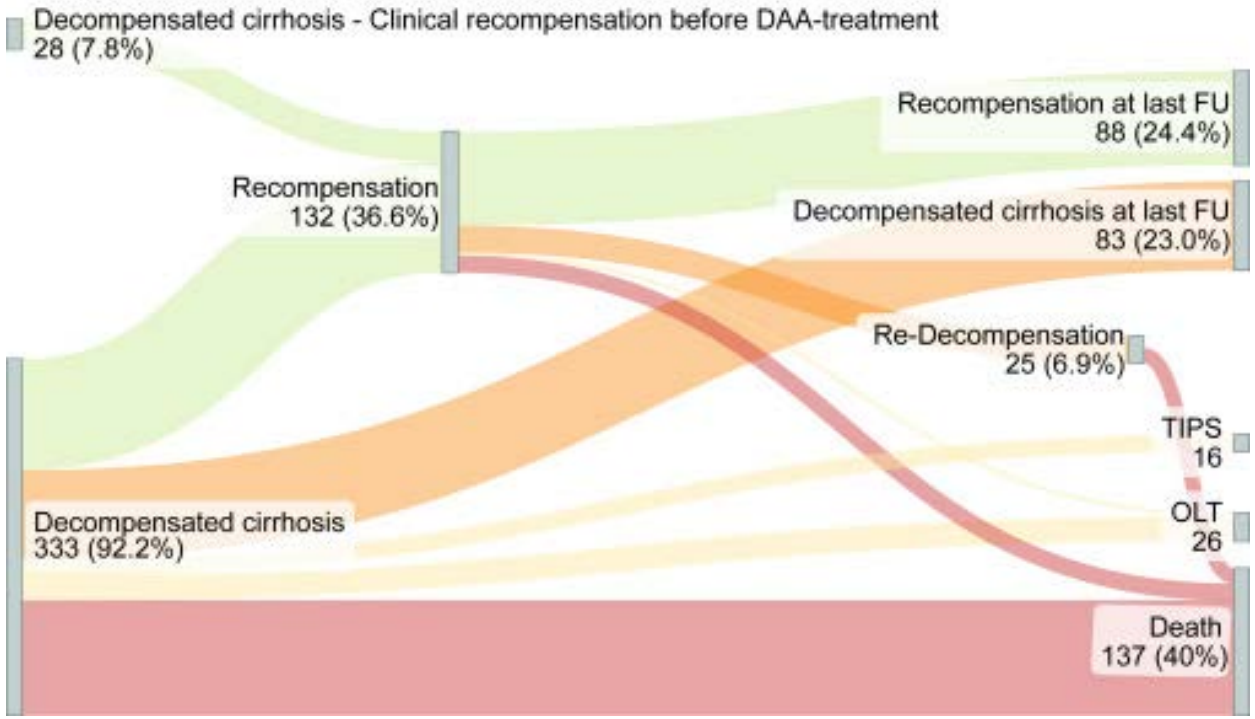
- What are the chances of achieving **recompensation***?
- Will recompensation have an impact on **survival** or **HCC**?

* Baveno VII criteria for recompensation:
- Resolution of ascites (no diuretics)
- Resolution of EH (no specific therapy)
- No re-bleeding within 12 months

J Hepatology 2022

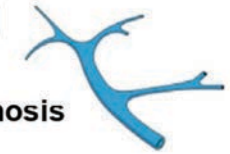
Recompensation after SVR

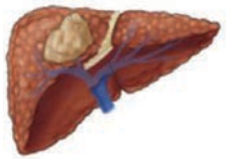
2570 cACLD, **36.6%** (132/361) achieve recompensation, median follow-up **8 years**



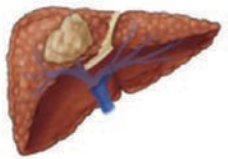
~3-fold lower risk for liver-related mortality & PVT

cACLD < recompensation < decompensated cirrhosis





Risk of HCC remains unchanged after recompensation



Albumin levels and diabetes are linked with recompensation

Semmler and Lens et al. Clin Gas Hep 2025
DOI: 10.1016/j.cgh.2025.04.026

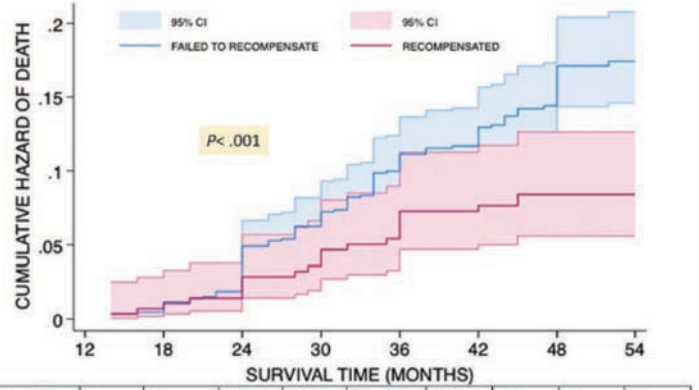
Recompensation after SVR

Prospective study 1152 patients with decompensated cirrhosis (ascites, GT-3)
24.7% (284/1152) recompensate (Baveno VII criteria)
median 16.5 months

Predictors of recompensation

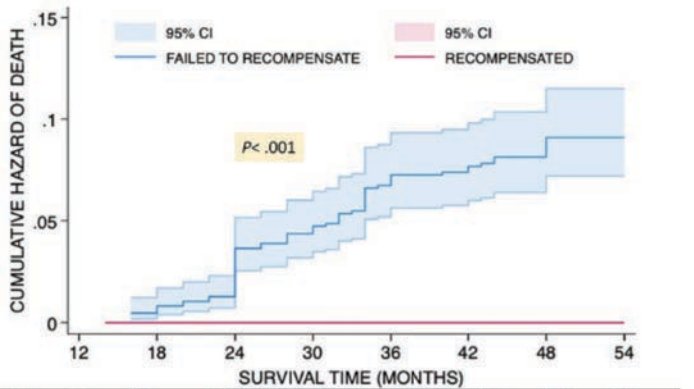
- Low bilirubin(aHR-0.6,95%CI-0.5-0.8,*P*<.001),
- INR(aHR-0.2,95%CI:0.1-0.3,*P*< .001),
- Absence of large esophageal varices(aHR-0.4,95%CI:0.2-0.9,*P*= .048), or
- Absence of gastric varices (aHR-0.5,95%CI:0.3-0.7,*P*= .022)

All cause mortality

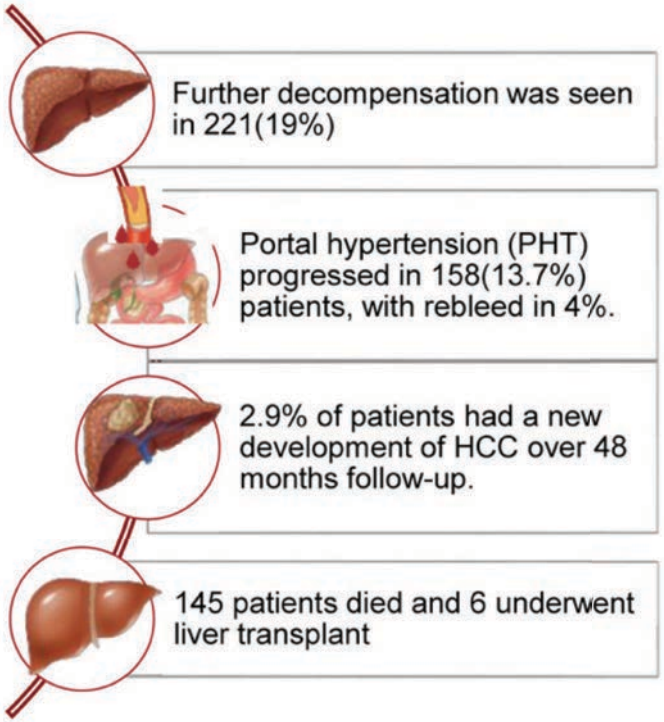


Time (Months)	0	6	12	18	24	30	36	42	48
Failed to recompensate	863	863	863	858	826	806	726	702	665
Recompensated	283	283	283	281	276	271	256	244	231

Liver-related mortality



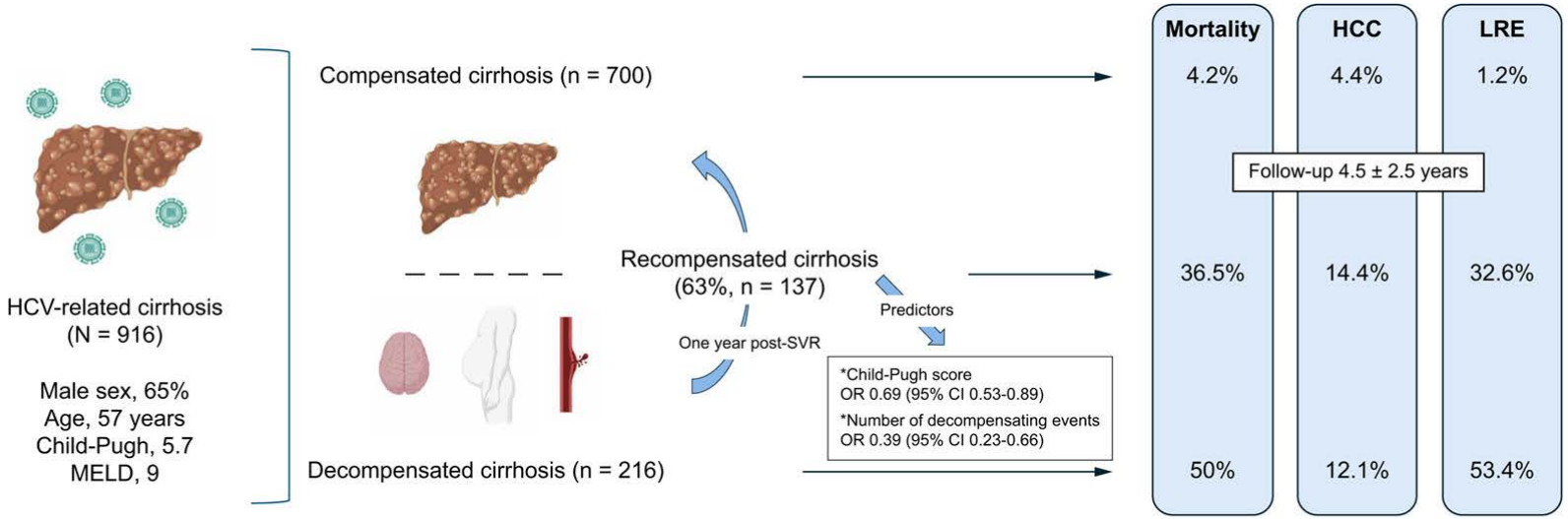
Time (Months)	0	6	12	18	24	30	36	42	48
Failed to recompensate	863	862	858	855	820	790	775	745	743
Recompensated	283	283	283	283	283	283	281	281	281



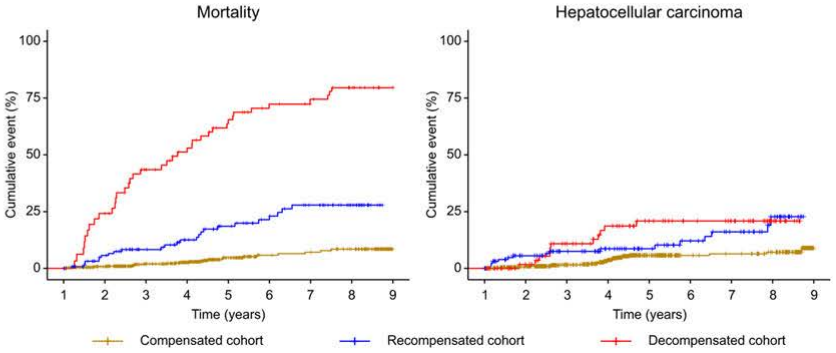
Premkumar et al. Gastroenterology 2024

Recompensation after SVR

63.4% (137/216) recompensate **12 months** post-SVR, predictors CPT (OR 0.69) and nº of decompensating events
"Recompensated" was defined as the absence of clinical decompensation events at the 12mo time point.



	Survival	Hepatocellular carcinoma	Liver-related events
Compensated cohort	HR 0.09 (95% CI 0.05-0.16)	Reference	Reference
Recompensated cohort	HR 0.30 (95% CI 0.19-0.49)	HR 2.12 (95% CI 1.06-4.25); $p = 0.035$	HR 11.81 (95% CI 5.39-25.87)
Decompensated cohort	Reference	HR 2.49 (95% CI 1.13-5.48); $p = 0.023$	HR 19.83 (95% CI 8.28-47.53)



Ampuero et al. J Hepatology 2025

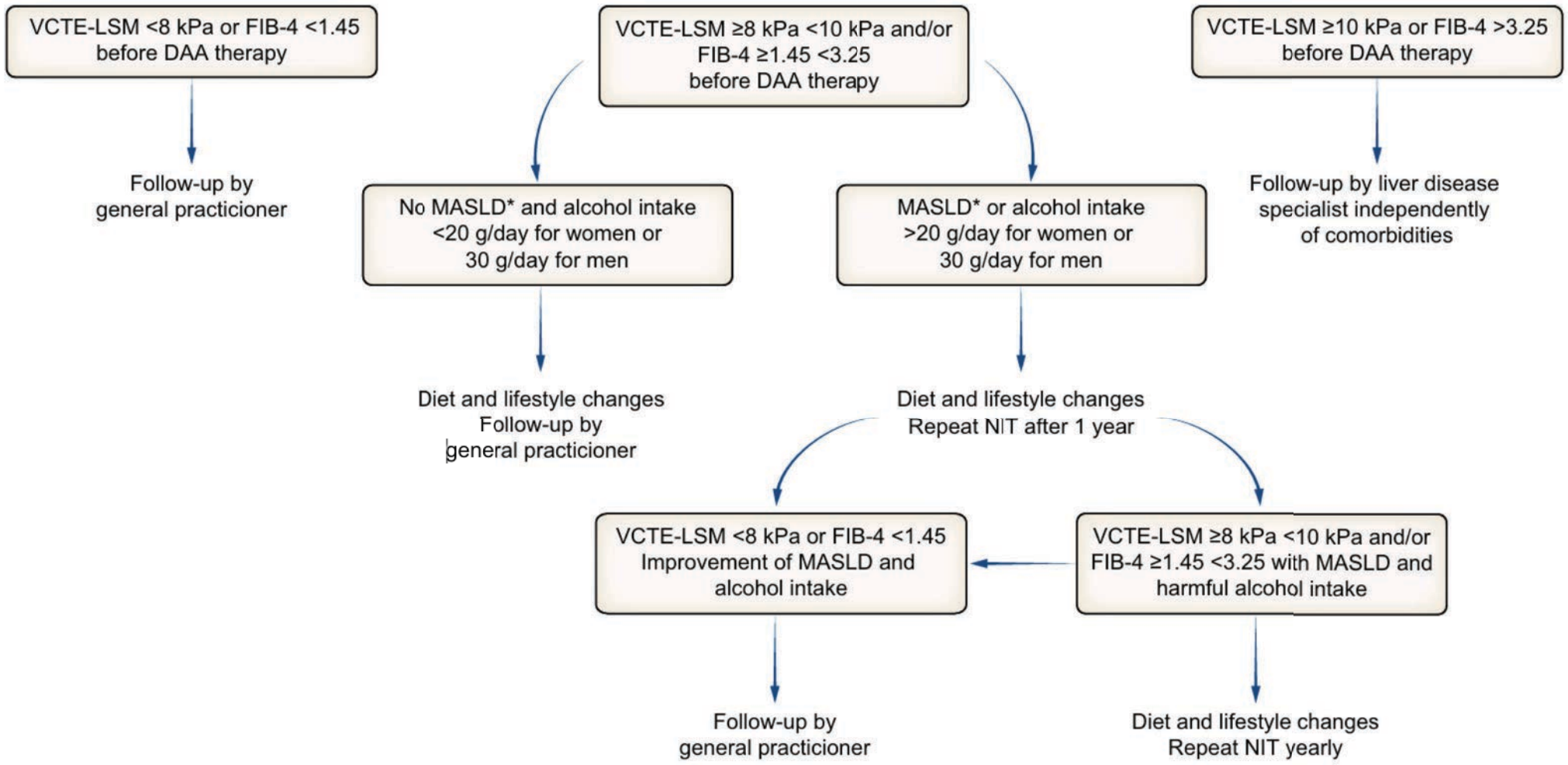
Clinical Case (3) no advanced fibrosis

- 67 years old
- Liver Stiffness 8 kPa → 6 kPa
- T2DM, Hypertension, overweight
- 2 alcohol drinks daily
- Liver steatosis (US), CAP 290

- 33 years old
- Liver Stiffness 5 kPa→ 5 kPa
- Ongoing drug use

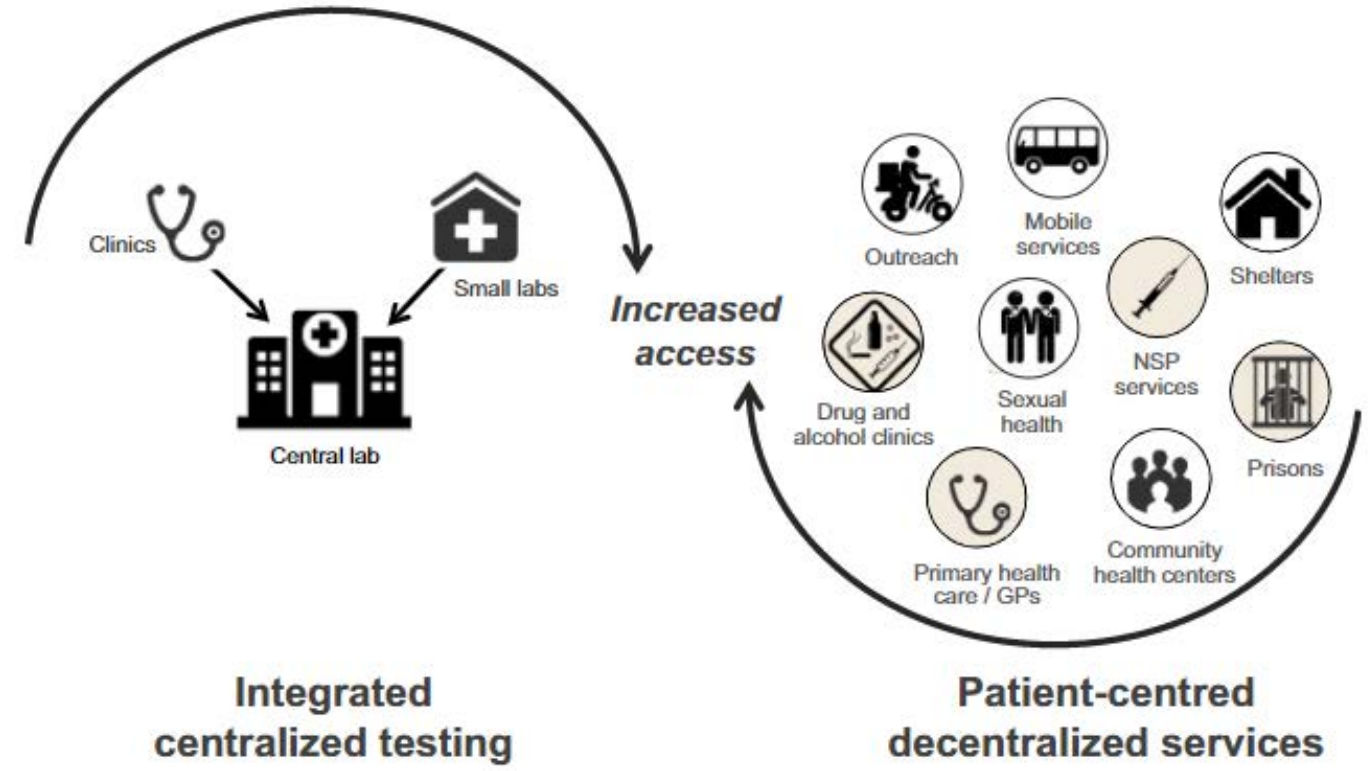
- What are the risks of **fibrosis** progression despite SVR?
- Is there **risk of reinfection** in the near future?

When can I discharge from specialized care?



Reiberger and Lens et al. J Hepatology 2024

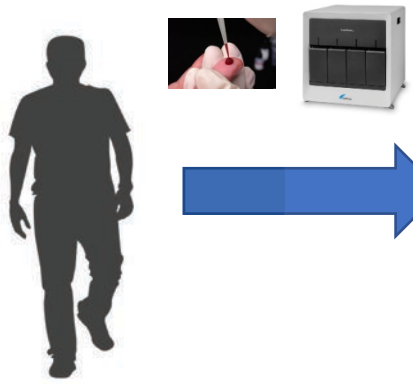
Decentralization in HCV management

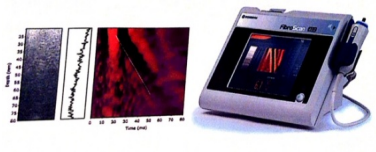


hepatitis C virus (HCV) testing models at both (*A*) integrated centralized, tertiary or district laboratories and (*B*) patient-centered decentralized primary health care services are required for global elimination. GPs, general practitioners; NSP, needle/syringe program.

Applegate TL, et al. Hepatitis C Virus Diagnosis and the Holy Grail. Infect Dis Clin N Am 2018;32:425-445.

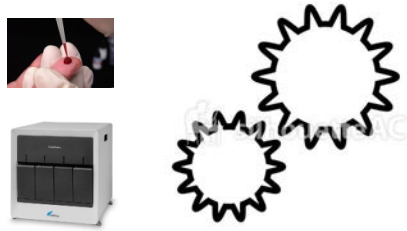
Experience in the Harm Reduction Center ‘La Mina’, Barcelona





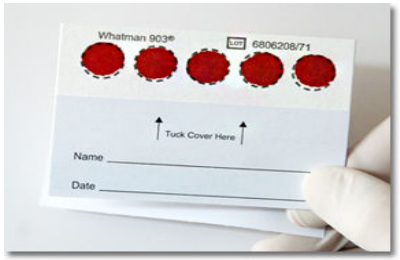
Portable FibroScan (5-10')
Drug interactions
Quality of Life Questionnaire
Education

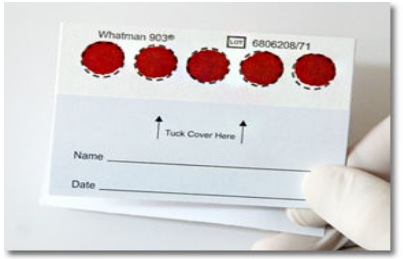
Medication at the center
Adherence monitoring
Daily administration



SVR Evaluation
Reinfection test

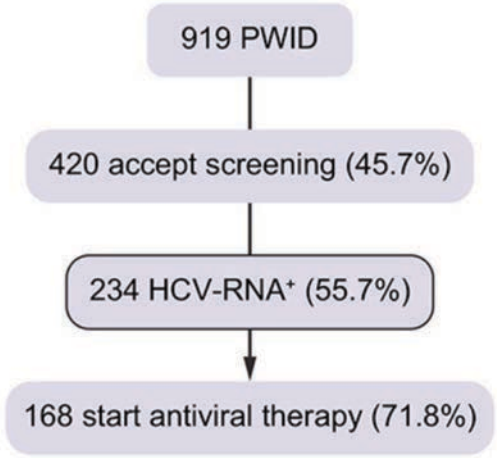
HCV RNA test at HRC





CHIME- Gilead Sc funded Project in collaboration Hospital Clínic Barcelona with Public Agency of Catalonia and Elisa Martrò Lab

HCV microelimination in harm reduction centres has benefits beyond HCV cure but is hampered by high reinfection rates



Variables	Total HCV-RNA+ n = 234
Age (years)	41 (34–47)
Male	207 (88)
Foreign nationality	116 (49)
Homeless	82 (35)
Family support	124 (53)
Unemployment	151 (65)
Previously incarcerated*	123 (60)
Educational level*:	
None	4 (2)
Primary education	91 (44)
Secondary education	49 (24)
Highschool	15 (7)
University degree	25 (12)
Vocational training	13 (6)
Healthcare system attendance:	
Primary care	66 (28)
Hospital	43 (18)
Drug injection (previous 6 months):	
>Once/day	132 (56)
Once/day	25 (11)
Weekly	30 (13)
<Weekly	41 (17)
None	6 (3)
Drug consumption (previous 6 months):	
Cocaine	207 (88)
Heroin	208 (89)
Cocaine and heroin	174 (79)
Cannabis	113 (48)
Speedball	171 (73)
Syringe sharing (previous 6 months)*	36 (18)
Paraphernalia sharing (previous 6 months)*	77 (38)
Risky sexual relationships (previous 6 months)†	77 (44)
Alcohol consumption (previous 6 months)	72 (31)
>28 units/week	27 (12)
Opioid substitution therapy (OST)	104 (44)
Concomitant psychiatric medication*	
Benzodiazepines	80 (39)
Antidepressants	34 (17)
Antipsychotics	23 (11)
HIV+	47 (20)
TARGA therapy among HIV+	27/47 (57)
Previous HCV+ diagnosis	152 (65)
Previous HCV antiviral therapy	36 (15)
HCV-RNA (IU/ml)	538,000 (91,300–1,875,000)
Baseline FibroScan® (kPa)	n = 199
Fibrosis stage	6 (4.9–7.5)
F0–1	150 (75)
F2	27 (14)
F3	12 (6)
F4	10 (5)
Advanced fibrosis (LSM ≥9.5 kPa)	22 (11)

88% male

41 (34-47) y.o

49% foreign

35% homeless

65% unemployed

67% daily drug use

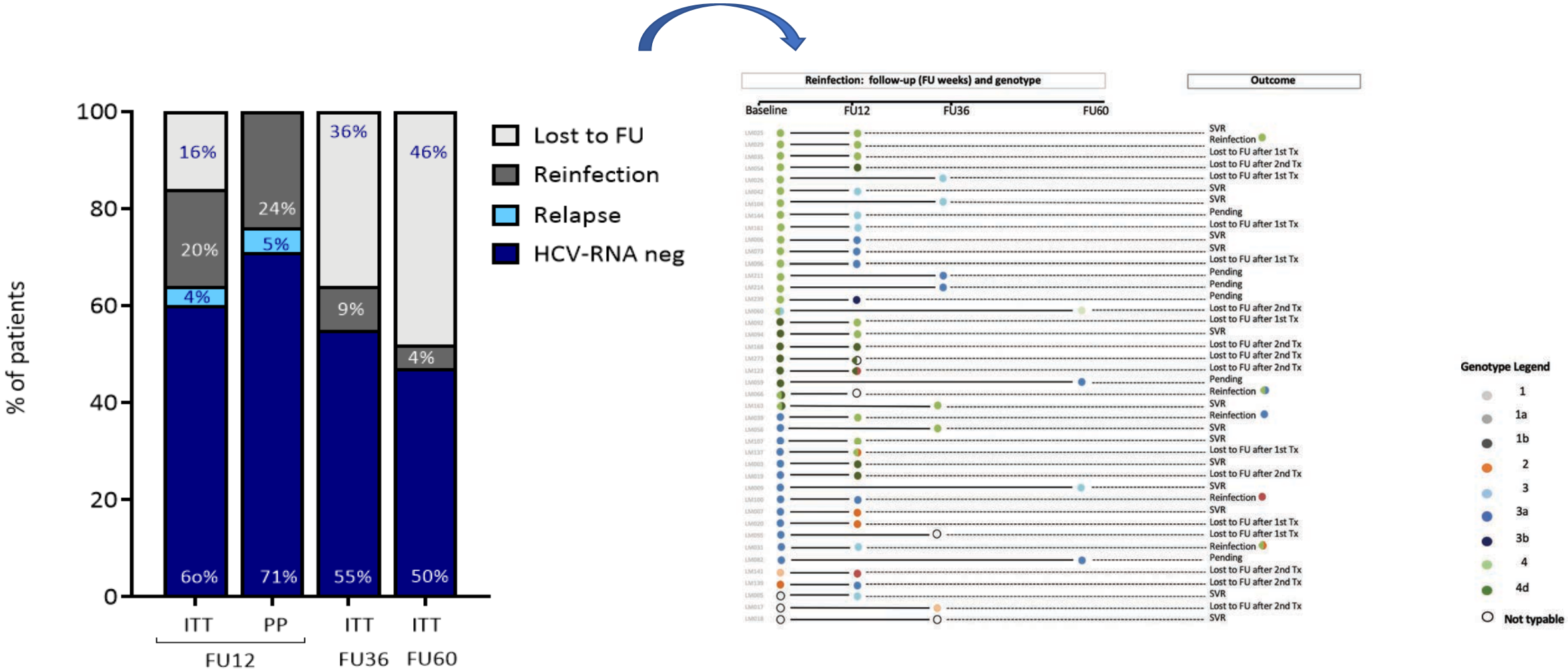
48% risk transmission

20% HIV+

11% F3-F4

Lens S et al. J Hep Reports 2022

HCV microelimination in harm reduction centres has benefits beyond HCV cure but is hampered by high reinfection rates



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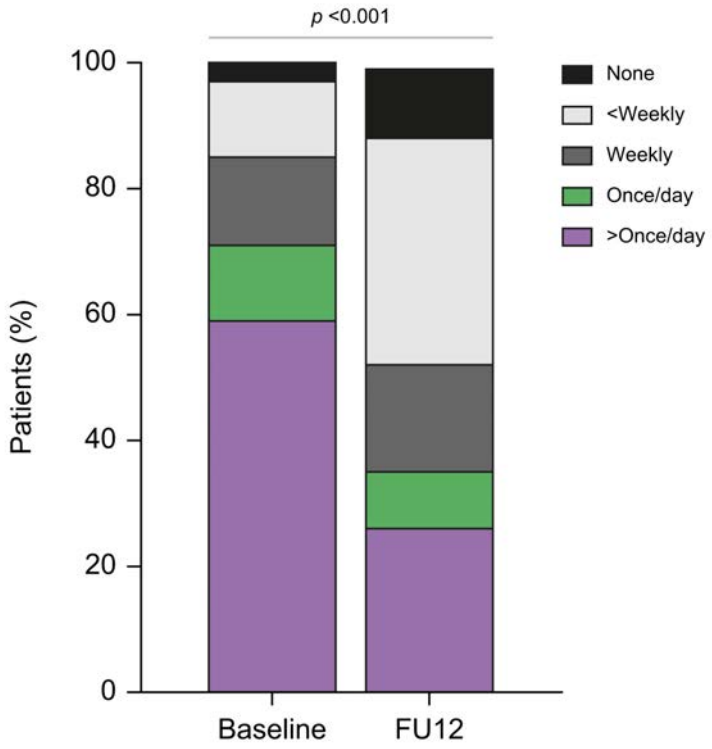
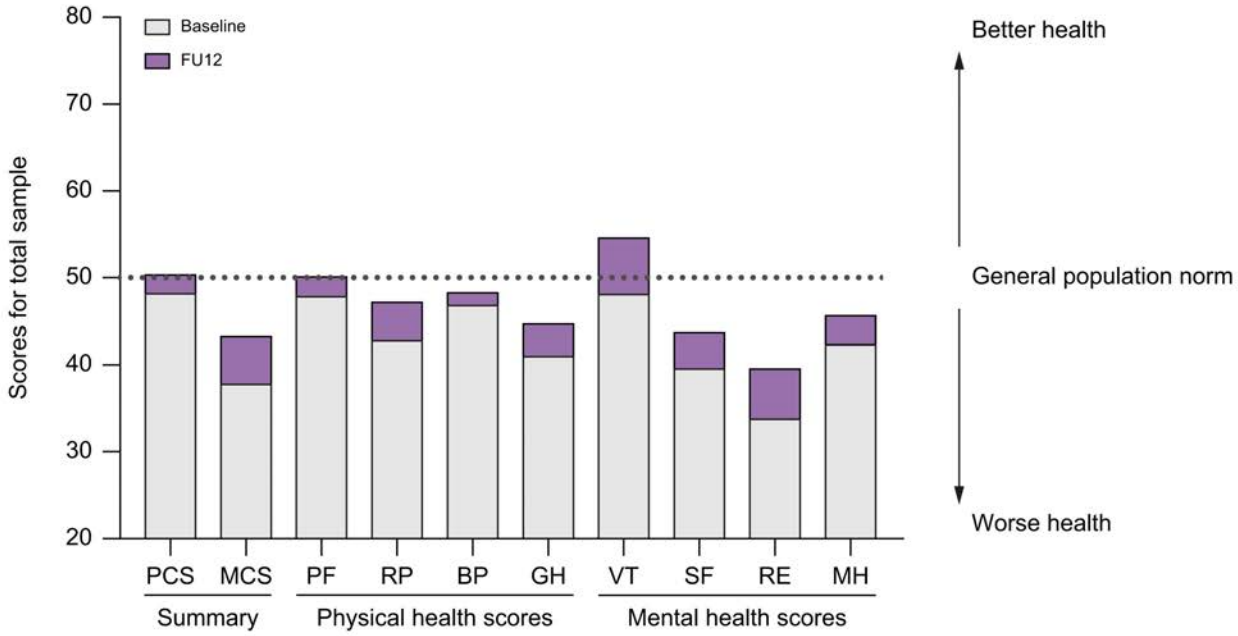
HCV microelimination in harm reduction centres has benefits beyond HCV cure but is hampered by high reinfection rates

Reduction in drug injection frequency



Improvement in QoL



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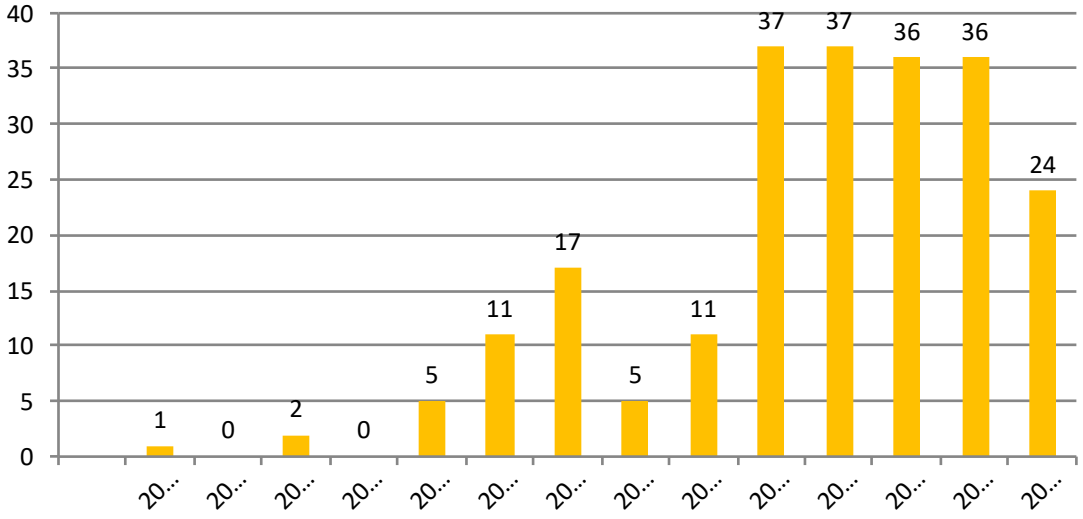
MSM and HCV (re)infection

Increased incidence of HCV among MSM patients



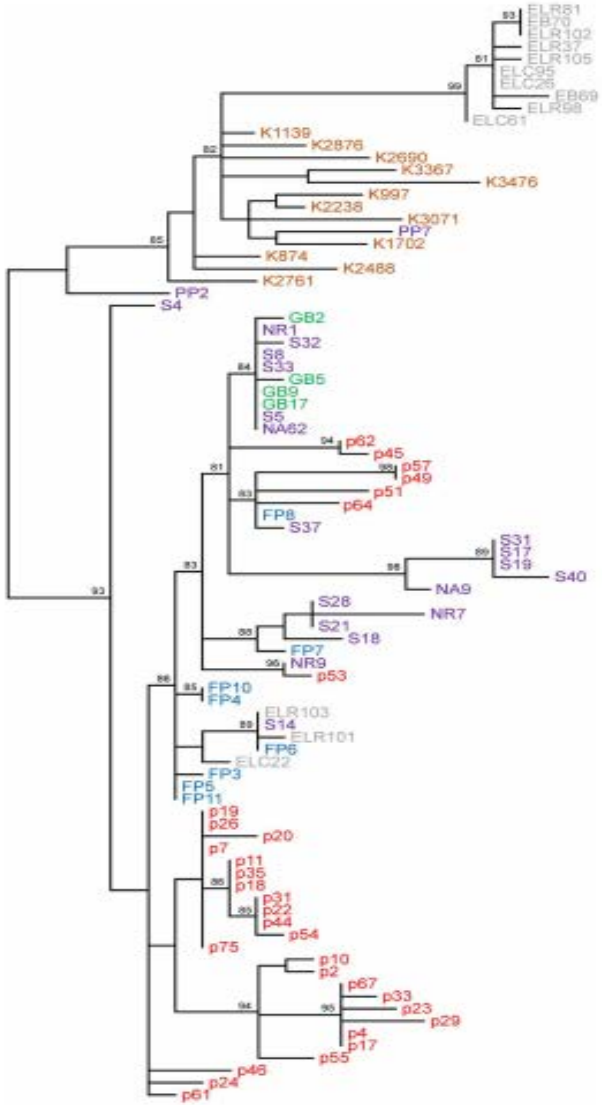
Incidence of acute hepatitis C: cases/year (5000 HIV positive patients followed at HIV Hosp Clinic Unit)

98% MSM

31% Symptomatic

50% had associated an STD (LUES, LGV)

Martínez-Rebollar et al. Enferm Infecc Microbiol Clin. 2015

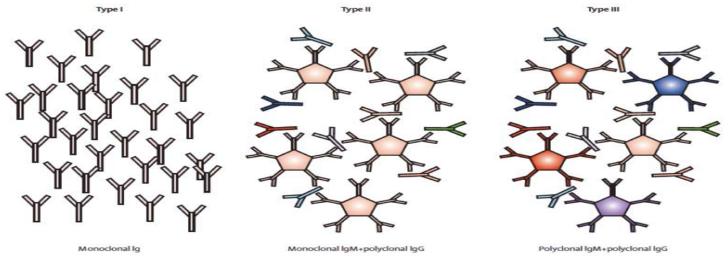


The **Phylogenetic analysis** shows a Local network in Barcelona related to other networks in Europe

Caro-Perez N, J Clinicl Virol 2017

HCV care cascade (updated)

Clinical Case (3) cryoglobulinemic vasculitis

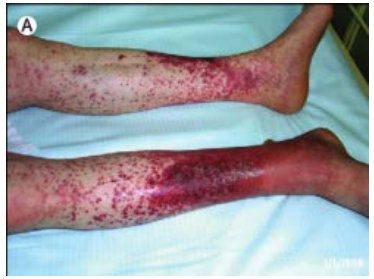


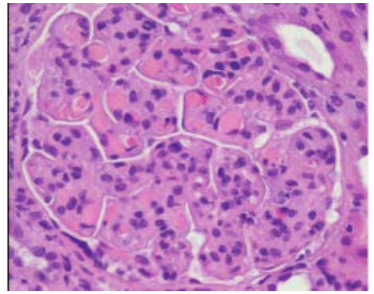
- Woman 59 years old
- Liver Stiffness 4.8 kPa
- CryoVas: Purpura, myalgia, arthralgias, BVas 4

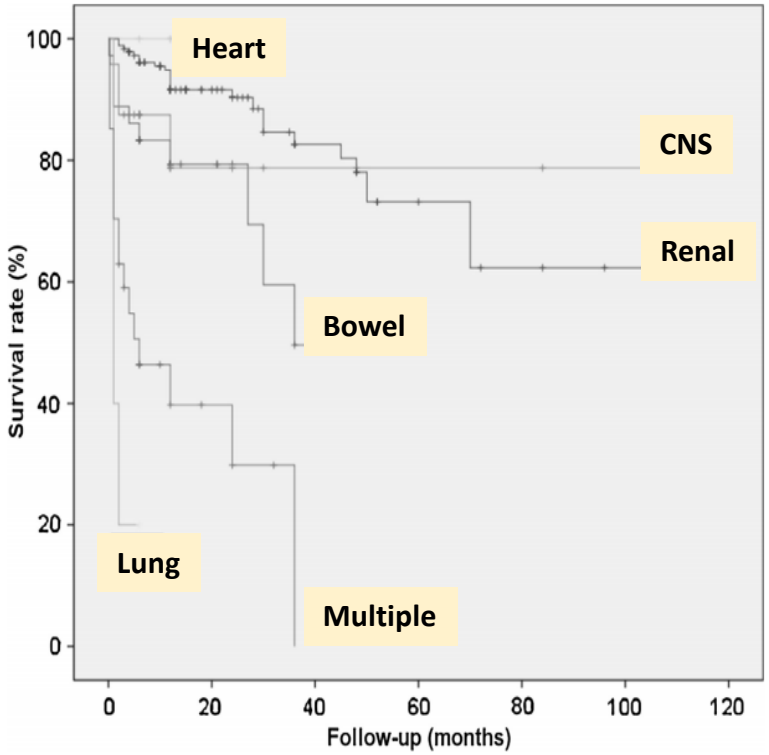
- What are the possibilities of CryoVas **remission** after SVR?
- Is there **risk of CryoVas relapse** in the future?

Cryoglobulinemic Vasculitis

Clinical Manifestations CV	
General symptoms:	fever≥ 38°C, weakness, myalgias, and arthralgias
Cutaneous signs:	purpura, distal ulcers or ischemic lesions
Peripheral and central nervous system involvement:	peripheral neuropathy (motor and/or sensory, confirmed by electromyography), stroke, spinal cord lesions or seizures
Renal involvement:	Membranoproliferative glomerulonephritis (proteinuria, hematuria)
Others:	Gastrointestinal tract , cardiac or pulmonary involvement





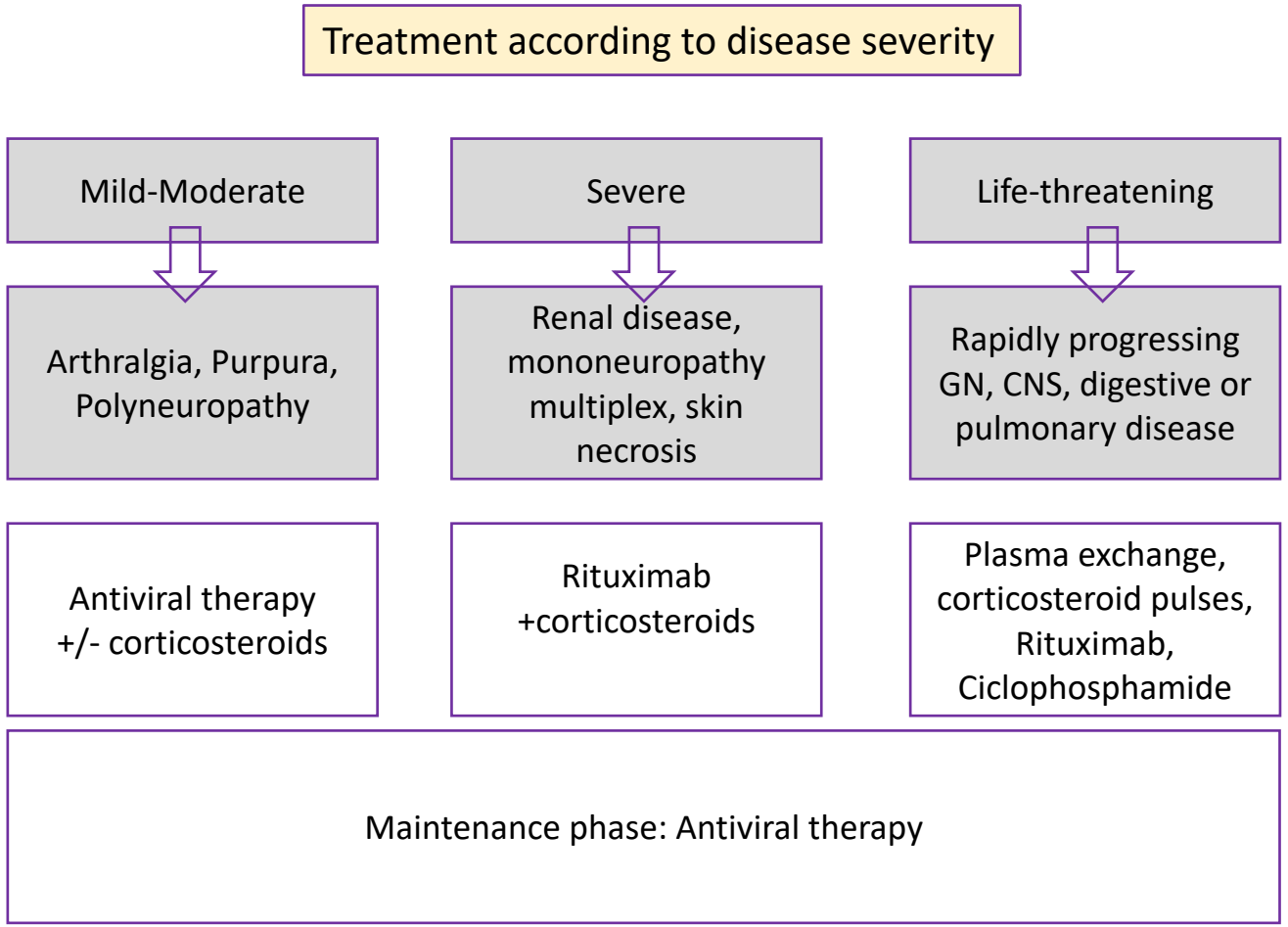


The most common presentation, the triad of purpura, arthralgia, and weakness (Meltzer), is reported in 80% of patients at disease onset

Ramos-Casals, et al. Med Clin (Barc). 2015;144(9):410–417

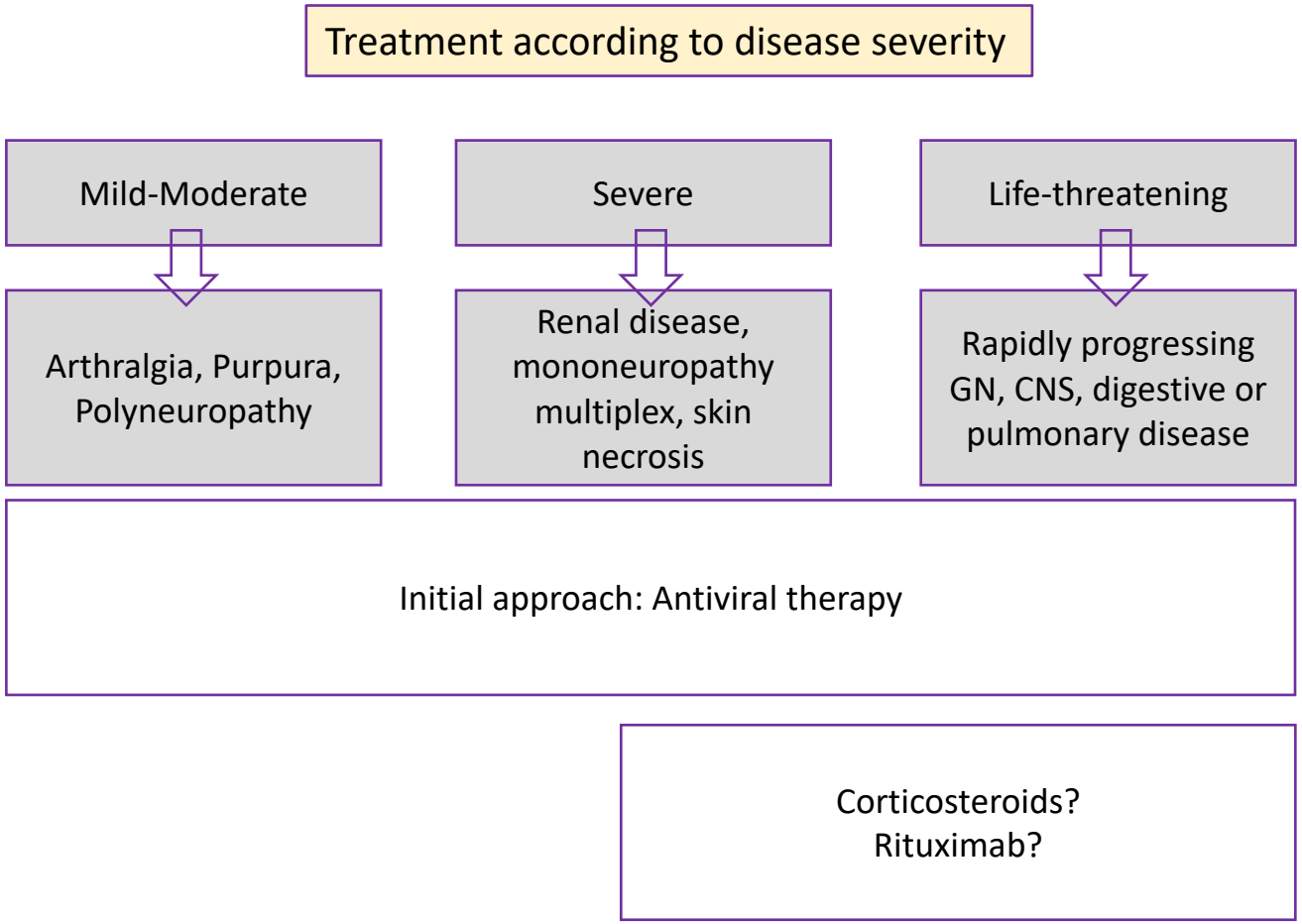
Retamozo, et al. Medicine (Baltimore). 2013

Cryoglobulinemic Vasculitis: Treatment



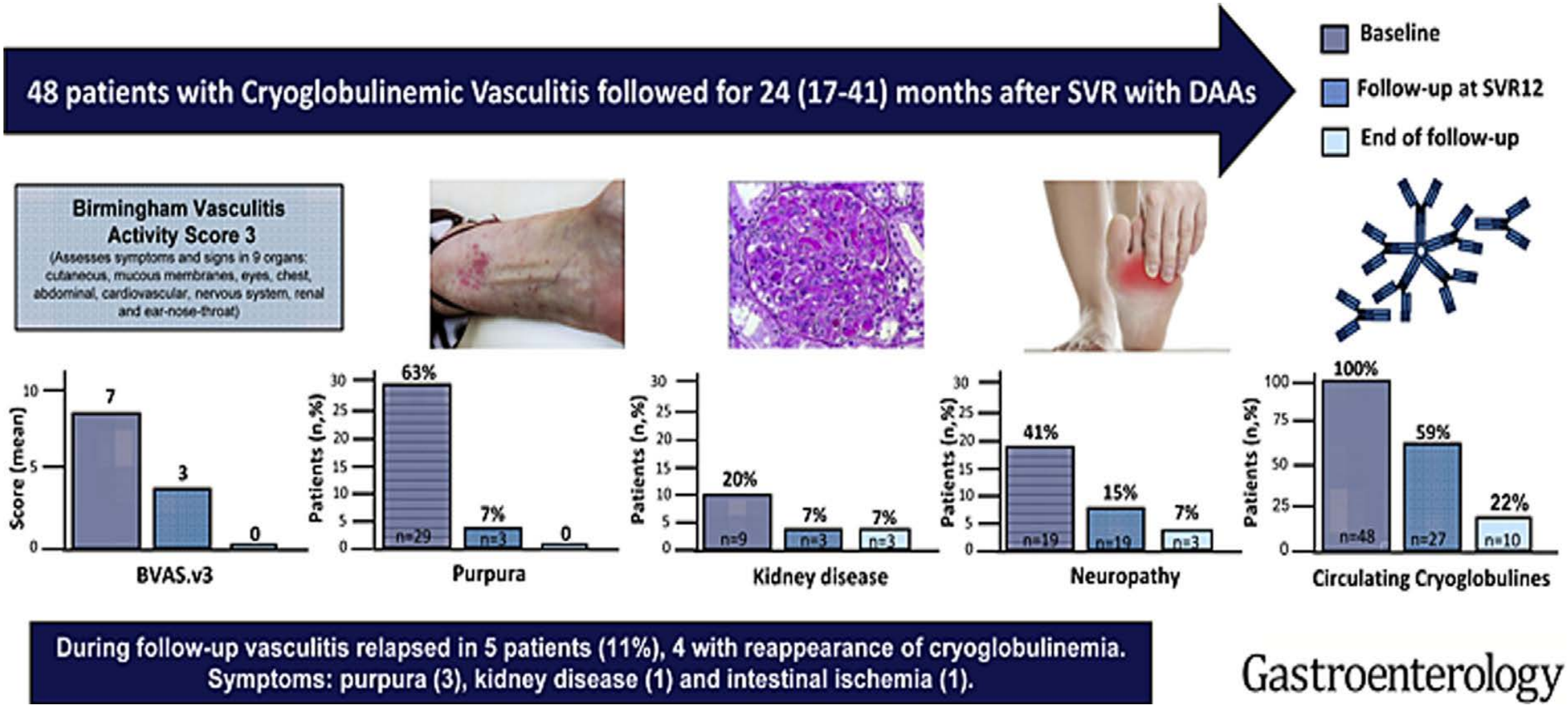
Cacoub, et al. The Am J Medicine 2015; 169 (9)
Ramos-Casals, et al. Lancet 2012; 379: 348–60

Cryoglobulinemic Vasculitis: Treatment



Cacoub, et al. The Am J Medicine 2015; 169 (9)
Ramos-Casals, et al. Lancet 2012; 379: 348–60

SVR Long term clinical impact on CryoVas

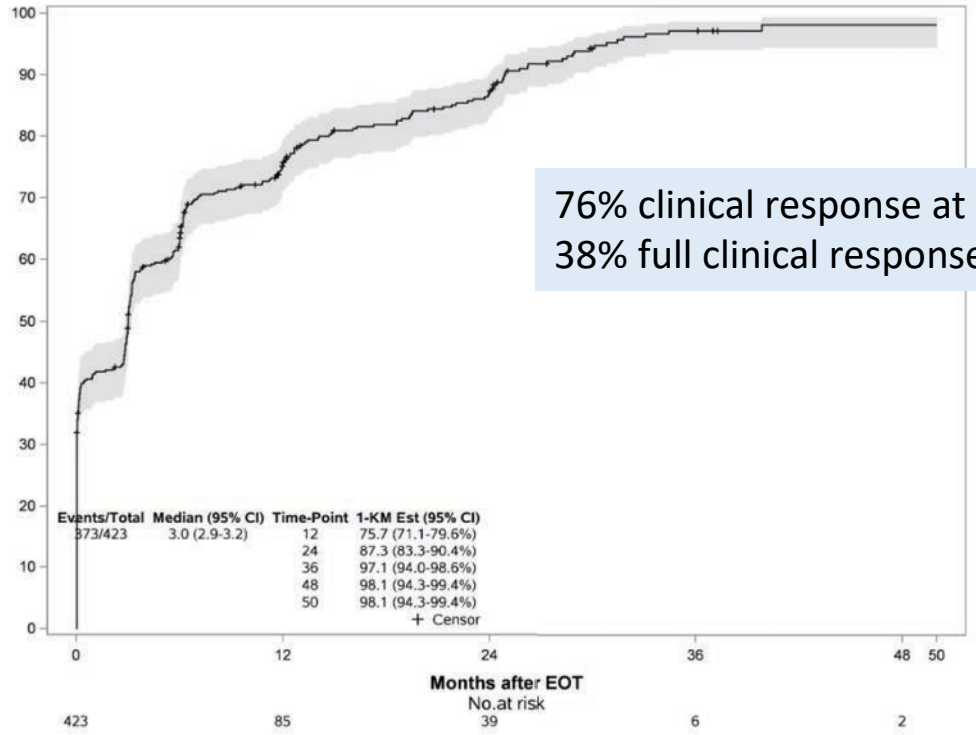


Bonacci et al, Gastroenterology 2018

SVR Long term clinical impact on CryoVas

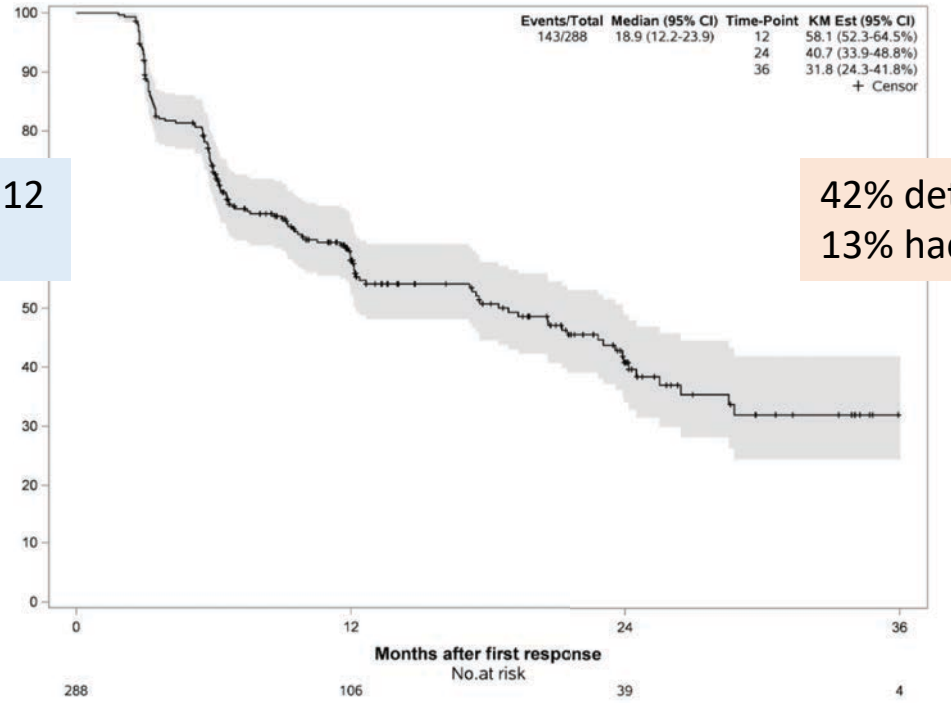
Italian multicenter cohort 423 patients with Cryo-Vas and SVR

Clinical response



76% clinical response at month 12
38% full clinical response (FCR)

Clinical deterioration



42% deterioration
13% had a relapse

Age and renal involvement → non clinical response
FCR was inversely associated with age, neuropathy, and high cryocrit levels

Kondili L, et al. Hepatology 2022

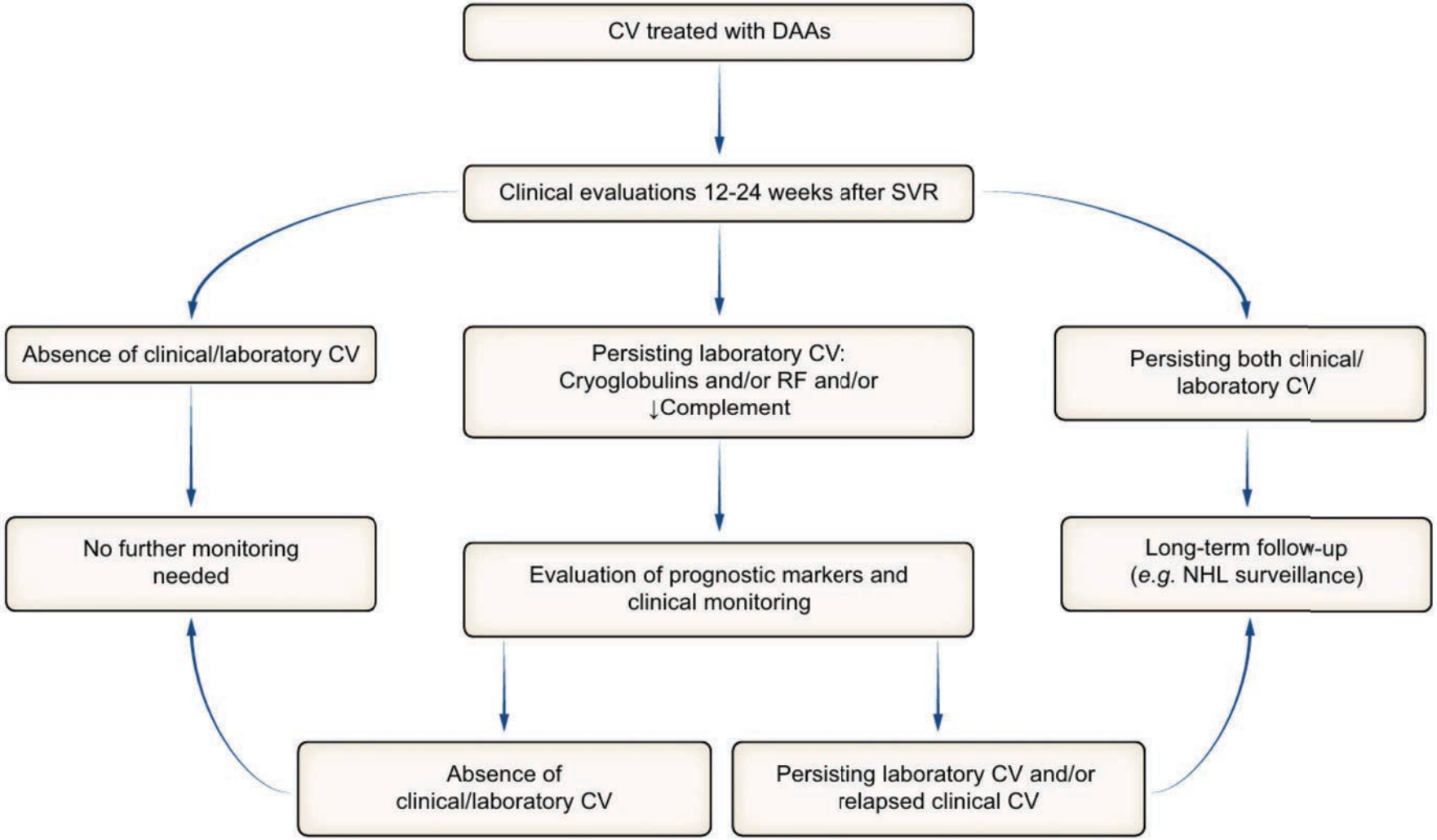
Relapse of CryoVas after SVR

Table 2. Relapses/flares of CV after treatment with DAAs with suggested triggering events or predisposing conditions.

First author, year, [ref]	Patients with CV flares (total patients, %)	Mean FU after EOT	Suggested triggering event or predisposing conditions	Pre-DAA clinical	Flare characteristics and evolution (transient/ persistent)
Sollima, 2016[119]	1 (7, 14%)	3 months	Triggering event: Influenza vaccine	Purpura, nephropathy	†CV
Visentini, 2018[120]	3 (ND)	22.8 months	Triggering events: Respiratory infection, lung carcinoma	Nephropathy 2/4, neuropathy 4/4, purpura 3/4, ulcers 1/4, arthralgia 1/4	Nephropathy 2/4, purpura 1/4, skin ulcers 1/4 (2 transient, 1 death, 1 ND)
Bonacci, 2018[121]	5 (46, 10.8%)	24 months	Predisposing condition: Cirrhosis	Purpura 3/5, neuropathy 2/5, nephropathy 1/5	Purpura (transient) 3/5, nephropathy 1/5, fatal acute mesenteric ischaemia 1/5
Sollima, 2018[122]	1 (ND)	18 months	Triggering event: Influenza vaccine	Purpura, nephropathy	Purpura, nephropathy, serum CGs (transient)
*Visentini, 2022[123]	9 (71, 12.7%)	ND	Triggering event: COVID-19 vaccine	8/71 +NHL	†CV
*Vacchi, 2023[124]	22 (416, 5.3%)	ND	Triggering event: COVID-19 vaccine	CV	Mainly neuropathy or purpura
Kondili 2022[125]	18 (137, 13%)	15 (13-27) months	Predisposing condition: High RF values	Purpura, weakness, SS, neuropathy	Purpura, neuropathy, other (transient in 66.7%)
Gragnani, 2023[126]	20 (374, 5%) post- vaccination 10 (51, 14%) post-COVID-19	137 (72–290) weeks	Triggering events: COVID-19 vaccine COVID-19	CV	†CV

*Studies also involving HCV-negative CV: 13 out of 71 patients, and 3 out of 6 relapsing ones in the study by Visentini *et al.*;[108] 127 out of 416 patients in the study by Vacchi *et al.*;[109]
†CV: disease relapses were mostly characterised by worsening of previous manifestations of CV. CGs, cryoglobulins; CV, cryoglobulinemic vasculitis; EOT, end of treatment; FU, follow-up; NHL, non-Hodgkin lymphoma; RF, rheumatoid factor; SS, sicca syndrome; ND, not done/specified.

How to manage CryoVas after SVR



Reiberger and Lens et al. J Hepatology 2024

Take-home messages

Patients with mild-moderate fibrosis who achieve SVR have an excellent liver-related **prognosis** and can generally be **discharged** from specialised care. However, those with comorbidities (metabolic, alcohol) may require continued risk-based monitoring.

The risk of liver decompensation if resolution of CSPH is neglible. Post-SVR CSPH surveillance should rely on **dynamic** risk stratification using liver **stiffness** and **platelet** count.

Although SVR can result in clinical improvement and even **recompensation** in 1/3 of patients with prior decompensated cirrhosis, the risk for **HCC** remains.

In patients with F3 fibrosis after HCV cure, EASL currently recommends continued HCC surveillance, although emerging data and risk scores suggest that a substantial proportion may have a very low HCC risk, highlighting the need for **personalised surveillance strategies** rather than a one-size-fits-all approach.

HCV cure leads to remission of **cryoglobulinemic** vasculitis in most patients, but **persistence or relapse** may occur despite SVR.

Gracias!!!!!!!!!!!!

Viral, Genetic and Immune-mediated Hepatitis Group

IDIBAPS, Hospital Clínic, Barcelona, Spain

PI18/00079; PI19/00036; PI20/00609
IFI18/00006; CM21/00081