Hepatitis C curada:
¿qué pacientes seguir en el hospital?

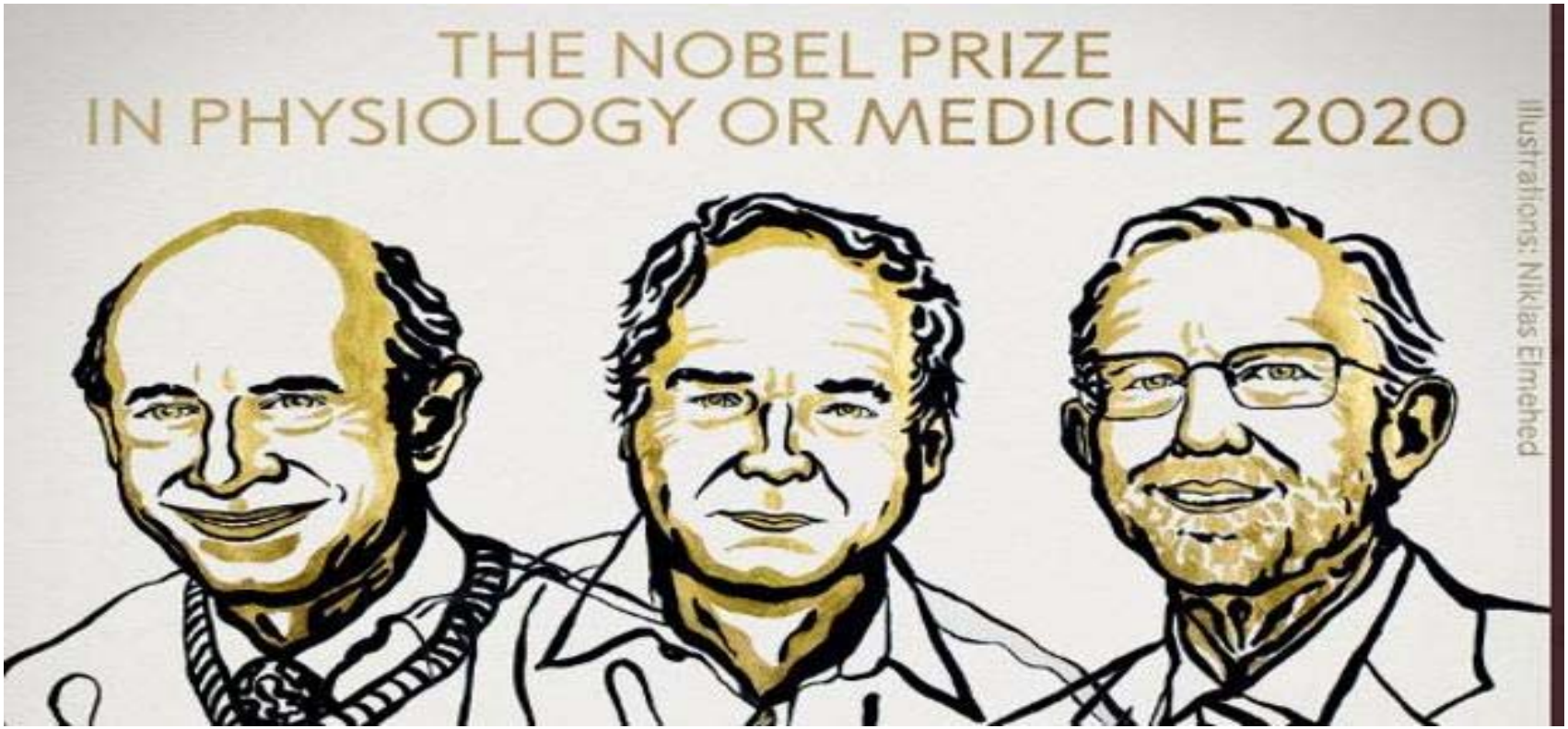
XIX Jornadas de Avances en Hepatología
Málaga, 8-9 de octubre de 2020

Javier García-Samaniego
Hospital Universitario “La Paz”
CIBERehd. IdiPAZ
Madrid

IdiPAZ
Instituto de Investigación
Hospital Universitario La Paz

ciberehd

Harvey J. Alter, Michael Houghton y Charles M. Rice, premio Nobel de Medicina 2020



ELIMINACIÓN DE LA HEPATITIS C: OBJETIVO GLOBAL

- La **OMS** ha planteado como objetivo la **eliminación de la hepatitis C** como problema de salud pública en el año **2030**[1,2]

90% Reducción de nuevas infecciones

Reducción de la mortalidad por hepatitis virales **65%**

- Más de 140.000 pacientes se han tratado y curado en España desde 2015

OMS: Organización Mundial de la Salud.

1. WHO. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. Disponible en: www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/. Último acceso: nov2019. **2.** Secretaría General de Sanidad y Consumo. Ministerio de Sanidad. Plan estratégico para el abordaje de la hepatitis C Crónica. Actualización línea estratégica 2. Junio 2017. Disponible en: http://www.mscbs.gob.es/ciudadanos/enfLesiones/enfTransmisibles/hepatitisC/PlanEstrategicoHEPATITISC/docs/actualizacionEstrategiaTerapeuticaJunio2017.pdf. Con acceso: nov 2019.

DOCUMENTO DE LA AEEH SOBRE LA ELIMINACIÓN DE LA HEPATITIS C EN ESPAÑA

Gastroenterol Hepatol. 2019;42(9):579–592

ELSEVIER

Gastroenterología y Hepatología

www.elsevier.es/gastroenterologia

GUÍA DE PRÁCTICA CLÍNICA

Eliminación de la hepatitis C. Documento de posicionamiento de la Asociación Española para el Estudio del Hígado (AEEH)☆

Javier Crespo[a,*], Agustín Albillos[b], María Buti[c], José Luis Calleja[d], Javier García-Samaniego[e], Manuel Hernández-Guerra[f], Trinidad Serrano[g], Juan Turnes[h], Enrique Acín[i], Juan Berenguer[j], Marina Berenguer[k], Joan Colom[l], Inmaculada Fernández[m], Conrado Fernández Rodríguez[n], Xavier Forns[o], Federico García[p], Rafael Granados[q], Jeffrey V. Lazarus[r], Jose María Molero[s], Esther Molina[t], Fernando Pérez Escanilla[u], Juan A. Pineda[v], Manuel Rodríguez[w], Manuel Romero[x], Carlos Roncero[y], Pablo Saiz de la Hoya[z] y Gloria Sánchez Antolín[aa]

1. Crespo J, *et al*. Eliminación de la hepatitis C. Documento de posicionamiento de la Asociación Española para el Estudio del Hígado (AEEH). Gastroenterol Hepatol. 2019;42(9):579-592.

NÚMERO DE PACIENTES CON HEPATITIS C TRATADOS EN LA COMUNIDAD DE MADRID (2015-2020)

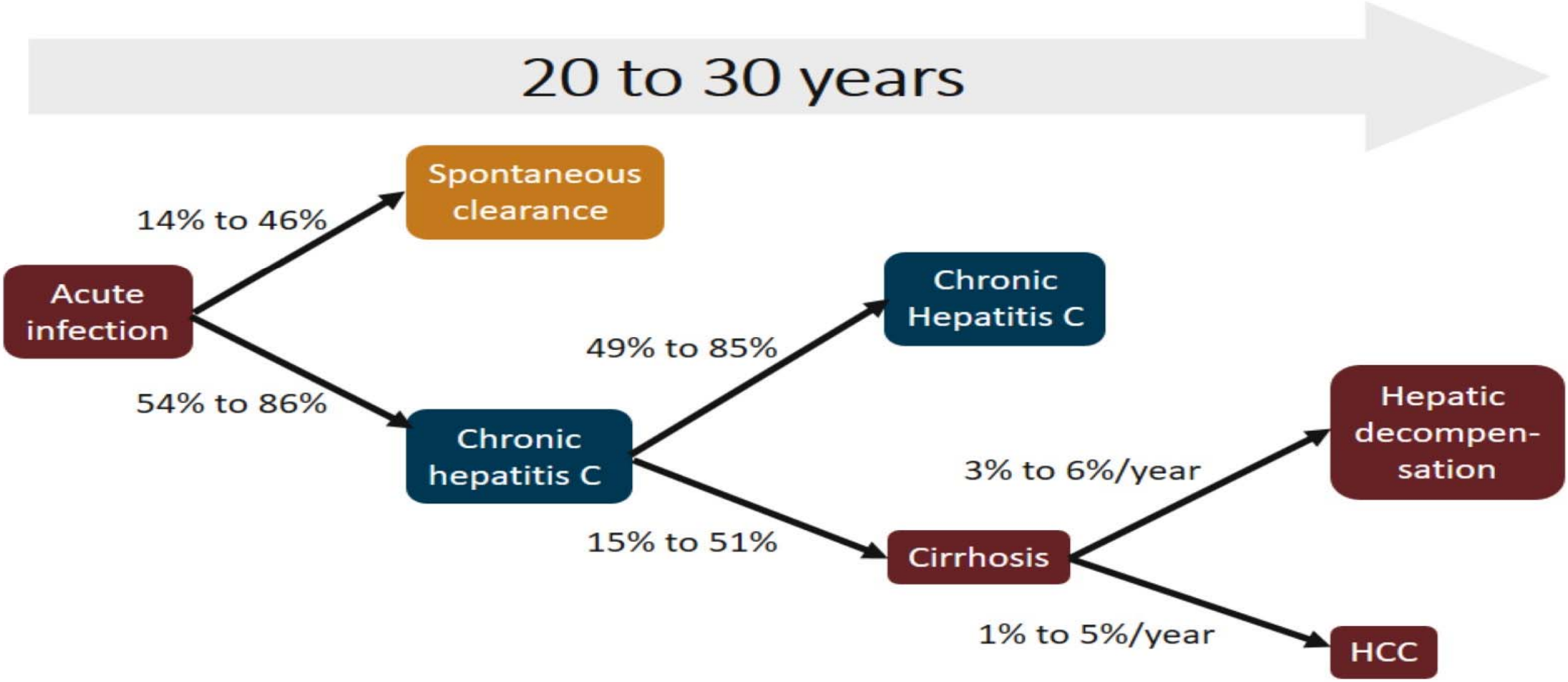
AÑO	Valor
2015	8.593
2016	4.712
2017	5.626
2018	3.075
2019	1.906
2020*	690
Total	24.602

*Hasta el 7 de octubre

Fuente: Registro de Utilización de Agentes Antivirales para el virus de la hepatitis C (RUA-VHC). Servicio Madrileño de Salud. Consejería de Sanidad. Comunidad de Madrid

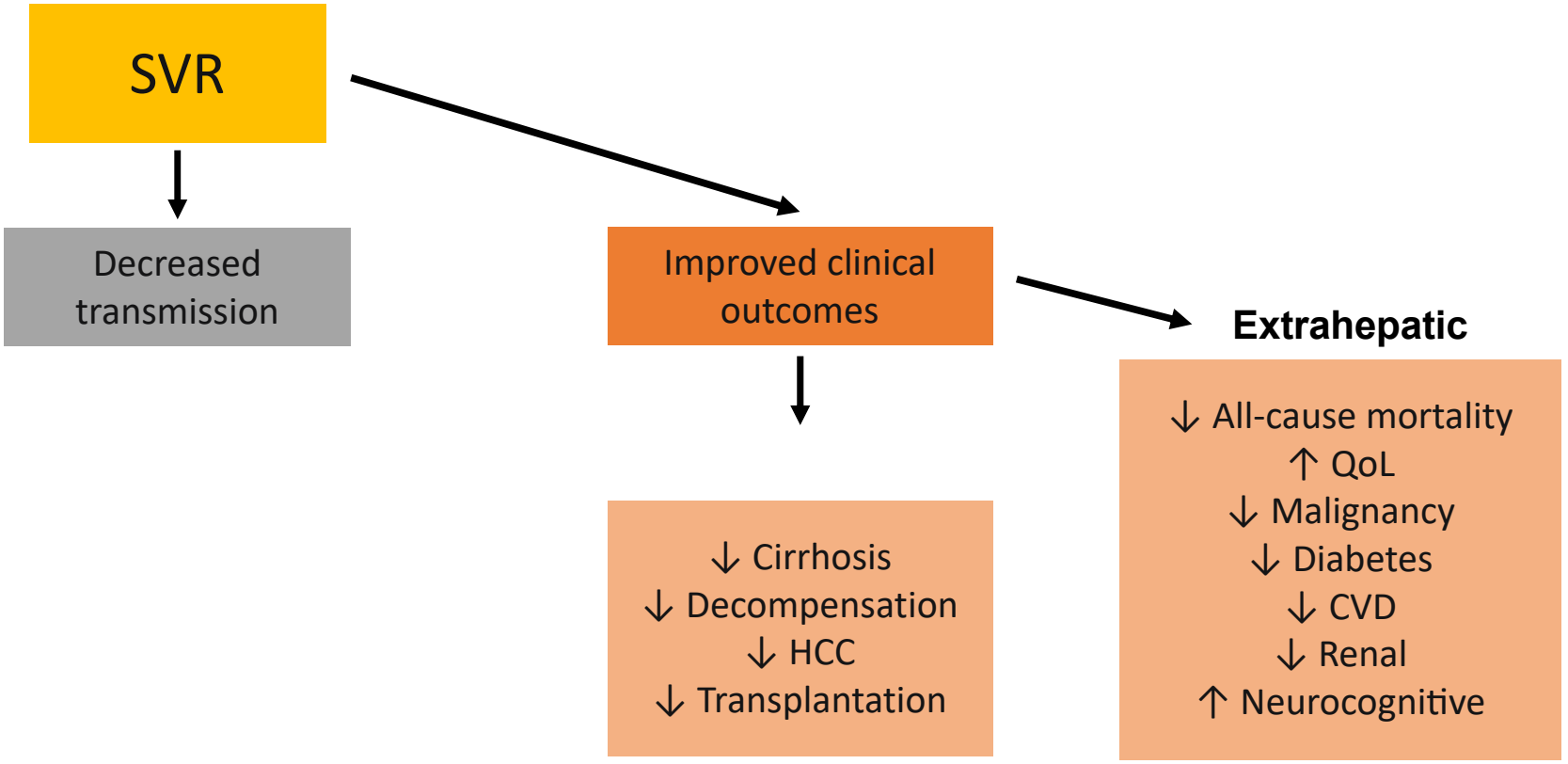
Comunidad de Madrid

Outline of HCV Long-Term Complications
Natural History of Hepatitis C



Maasoumy B, Wedemeyer H. *Best Pract Res Gastroenterol Hepatol*. 2012;26:401-412.

Benefits of Achieving SVR



Smith-Palmer J, et al. BMC Infect Dis. 2015;15:19. Negro F, et al. Gastroenterology. 2015;149:1345-1360.
George SL, et al. Hepatology. 2009;49:729-738.

Curación de la hepatitis C

La infección *prácticamente siempre* se cura

La enfermedad *NO siempre* se cura

Diagnóstico “tardío” de la hepatitis C
Concepto

Mauss et al. BMC Medicine (2017) 15:92
DOI 10.1186/s12916-017-0856-y

BMC Medicine

CORRESPONDENCE Open Access

Late presentation of chronic viral hepatitis for medical care: a consensus definition

Stefan Mauss[1,2], Stanislas Pol[2,9], Maria Buti[2,3], Erika Duffell[4], Charles Gore[5], Jeffrey V. Lazarus[6], Hilje Logtenberg-van der Grient[7], Jens Lundgren[6], Antons Mozalevskis[6,8], Dorthe Raben[6,10*], Eberhard Schatz[11], Stefan Wiktor[12], Jürgen K. Rockstroh[10,13] and on behalf of the European consensus working group on late presentation for Viral Hepatitis Care

Definición de diagnóstico tardío: ALD/LSLD. Consenso EASL (2015)

- estadio de fibrosis hepática ≥ F3 (elastometría, FIB-4, APRI, Fibrotest, biopsia)
- Cirrosis descompensada
- Diagnóstico de hepatocarcinoma…….

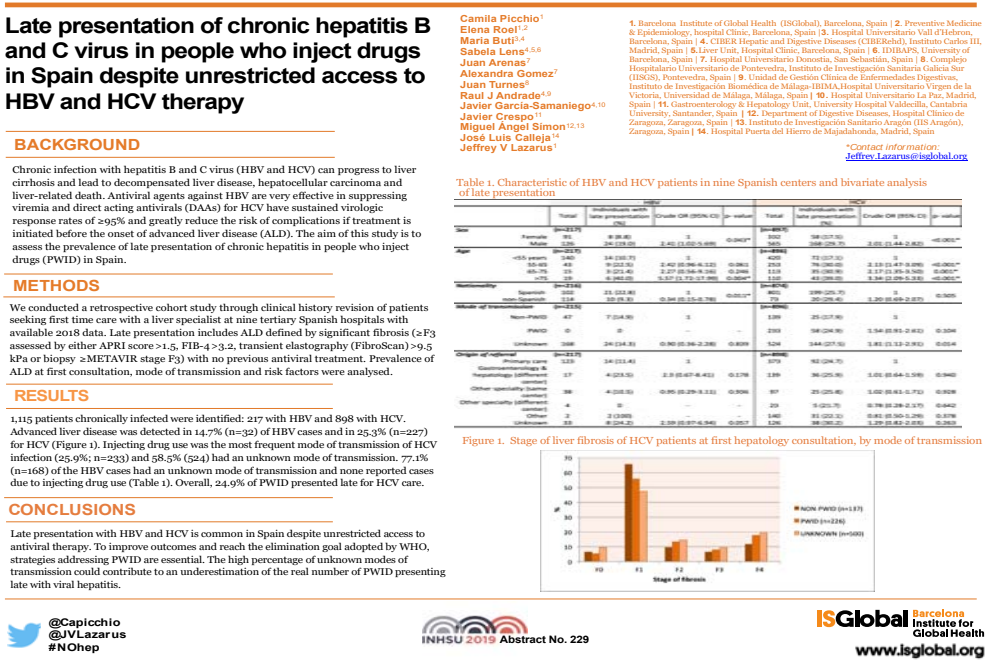
sin tratamiento antiviral previo

BMC Medicine 2017, 15: 92 - 99

Late presentation in PWID in Spain

- 1,115 patients (217 with HBV, 898 with HCV were included with 2018 data from 9 tertiary centers in Spain.
- Advanced liver disease was detected in 14.7% of HBV cases and in 25.3% of HCV cases.
- Injecting drug use was the most frequent reported mode of transmission of HCV infection (26%) and 59% had an unknown mode of transmission.
- Overall, 25% of PWID presented late for HCV care.

Source: Picchio et al. Abstract at INHSU 2019.



Late presentation of chronic hepatitis B and C virus in people who inject drugs in Spain despite unrestricted access to HBV and HCV therapy

Camila Picchio[1]
Elena Roe[1,2]
Maria Buti[3,4]
Sabela Lens[4,5,6]
Juan Arenas[7]
Alexandra Gomez[7]
Juan Turnes[8]
Raul J Andrade[4,9]
Javier Garcia-Samaniego[4,10]
Javier Crespo[11]
Miguel Ángel Simon[12,13]
José Luis Calleja[14]
Jeffrey V Lazarus[1]

1. Barcelona Institute of Global Health (ISGlobal), Barcelona, Spain | 2. Preventive Medicine & Epidemiology, hospital Clinic, Barcelona, Spain |3. Hospital Universitario Vall d'Hebron, Barcelona, Spain | 4. CIBER Hepatic and Digestive Diseases (CIBERehd), Instituto Carlos III, Madrid, Spain | 5.Liver Unit, Hospital Clinic, Barcelona, Spain | 6. IDIBAPS, University of Barcelona, Spain | 7. Hospital Universitario Donostia, San Sebastián, Spain | 8. Complejo Hospitalario Universitario de Pontevedra, Instituto de Investigación Sanitaria Galicia Sur (IISGS), Pontevedra, Spain | 9. Unidad de Gestión Clínica de Enfermedades Digestivas, Instituto de Investigación Biomédica de Málaga-IBIMA,Hospital Universitario Virgen de la Victoria, Universidad de Málaga, Málaga, Spain | 10. Hospital Universitario La Paz, Madrid, Spain | 11. Gastroenterology & Hepatology Unit, University Hospital Valdecilla, Cantabria University, Santander, Spain | 12. Department of Digestive Diseases, Hospital Clínico de Zaragoza, Zaragoza, Spain | 13. Instituto de Investigación Sanitario Aragón (IIS Aragón), Zaragoza, Spain | 14. Hospital Puerta del Hierro de Majadahonda, Madrid, Spain

*Contact information:
Jeffrey.Lazarus@isglobal.org

BACKGROUND

Chronic infection with hepatitis B and C virus (HBV and HCV) can progress to liver cirrhosis and lead to decompensated liver disease, hepatocellular carcinoma and liver-related death. Antiviral agents against HBV are very effective in suppressing viremia and direct acting antivirals (DAAs) for HCV have sustained virologic response rates of ≥95% and greatly reduce the risk of complications if treatment is initiated before the onset of advanced liver disease (ALD). The aim of this study is to assess the prevalence of late presentation of chronic hepatitis in people who inject drugs (PWID) in Spain.

METHODS

We conducted a retrospective cohort study through clinical history revision of patients seeking first time care with a liver specialist at nine tertiary Spanish hospitals with available 2018 data. Late presentation includes ALD defined by significant fibrosis (≥F3 assessed by either APRI score >1.5, FIB-4 >3.2, transient elastography (FibroScan) >9.5 kPa or biopsy ≥METAVIR stage F3) with no previous antiviral treatment. Prevalence of ALD at first consultation, mode of transmission and risk factors were analysed.

RESULTS

1,115 patients chronically infected were identified: 217 with HBV and 898 with HCV. Advanced liver disease was detected in 14.7% (n=32) of HBV cases and in 25.3% (n=227) for HCV (Figure 1). Injecting drug use was the most frequent mode of transmission of HCV infection (25.9%; n=233) and 58.5% (524) had an unknown mode of transmission. 77.1% (n=168) of the HBV cases had an unknown mode of transmission and none reported cases due to injecting drug use (Table 1). Overall, 24.9% of PWID presented late for HCV care.

CONCLUSIONS

Late presentation with HBV and HCV is common in Spain despite unrestricted access to antiviral therapy. To improve outcomes and reach the elimination goal adopted by WHO, strategies addressing PWID are essential. The high percentage of unknown modes of transmission could contribute to an underestimation of the real number of PWID presenting late with viral hepatitis.

Table 1. Characteristic of HBV and HCV patients in nine Spanish centers and bivariate analysis of late presentation

		HBV				HCV			
	Total	Individuals with late presentation (%)	Crude OR (95% CI)	p- value	Total	Individuals with late presentation (%)	Crude OR (95% CI)	p- value
Sex	(n=217)				(n=892)			
Female	91	8 (8.8)	1		392	58 (17.5)	1	
Male	126	24 (19.0)	2.41 (1.02-5.69)	0.043*	545	166 (29.7)	2.01 (1.44- 2.82)	<0.001*
Age	(n=217)				(n=891)			
<55 years	140	14 (10.7)	1		420	72 (17.1)	1	
55-65	43	9 (22.5)	2.42 (0.96-6.12)	0.061	253	76 (30.0)	2.13 (1.47- 3.09)	<0.001*
65-75	23	3 (21.4)	2.27 (0.54-9.56)	0.266	118	35 (30.9)	2.17 (1.35- 3.50)	0.001*
>75	10	6 (60.0)	5.57 (1.73-17.98)	0.004*	102	43 (39.2)	3.34 (2.29- 5.35)	<0.001*
Nationality	(n=216)				(n=874)			
Spanish	102	21 (12.8)	1	0.011*	801	199 (25.7)	1	0.505
non-Spanish	114	10 (9.1)	0.34 (0.15-0.78)		73	20 (29.4)	1.20 (0.69- 2.07)	
Mode of transmission	(n=224)				(n=894)			
Non-PWID	47	7 (14.9)	1		139	25 (17.9)	1	
PWID	0	0	-	-	233	58 (24.9)	1.54 (0.91- 2.61)	0.104
Unknown	168	24 (14.3)	0.90 (0.36- 2.28)	0.819	524	144 (27.5)	1.81 (1.13- 2.91)	0.014
Origin of referral	(n=217)				(n=894)			
Primary care	123	14 (11.4)	1		373	92 (24.7)	1	
Gastroenterology & hepatology (different center)	17	4 (23.5)	2.3 (0.67- 8.41)	0.178	139	36 (25.9)	1.01 (0.64- 1.59)	0.940
Other specialty (same center)	38	4 (10.5)	0.95 (0.29- 3.11)	0.936	97	25 (25.8)	1.02 (0.61- 1.71)	0.928
Other specialty (different center)	4	0	-	-	23	5 (21.7)	0.78 (0.28- 2.17)	0.642
Other	2	2 (100)			140	31 (22.1)	0.81 (0.50- 1.29)	0.378
Unknown	33	8 (24.2)	2.19 (0.87- 6.94)	0.057	126	38 (30.2)	1.29 (0.82- 2.05)	0.268

Figure 1. Stage of liver fibrosis of HCV patients at first hepatology consultation, by mode of transmission

@Capicchio
@JVLazarus
#NOhep

INHSU 2019 Abstract No. 229

ISGlobal Barcelona Institute for Global Health
www.isglobal.org

Viral hepatitis patients and late presentation risk factors

- 2,351 patients infected with HBV and HCV were included (544 HBV, 1,804 HCV) with available 2019 data from 11 centers
- ALD was detected in 12.7% of HBV cases and 29.5% for those with HCV infection. LSLD was reported in 10.8% of HBV cases and 10% of HCV cases.
- 58% and 64%of the cases were male for HBV and HCV, respectively.
- Half of HBV cases were in non-Spanish (45%) compared to 12% of those with HCV.

Source: Buti, M Picchio C et al. AASLD 2020.

Hepatitis B virus (HBV) (n= 544)			Hepatitis C virus (HCV) (n= 1,804)		
Sex			**Sex**		
Male	315 (58.0)		Male	1,152 (63.9)	
Female	229 (42.0)		Female	650 (36.0)	
Missing	0 (0)		Missing	2 (0.1)	
Nationality			**Nationality**		
Spanish	244 (44.9)		Spanish	1576 (87.4)	
Non-Spanish	293 (53.9)		Non-Spanish	218 (36.0)	
Missing	7 (1.3)		Missing	10 (0.5)	
Late presentation to care*			**Late presentation to care***		
Yes	103 (18.9)		Yes	532 (29.5)	
No	441 (81.1)		No	1,272 (70.5)	
Advanced liver disease (ALD)**			**Advanced liver disease (ALD)****		
Yes	69 (12.7)		Yes	467 (25.9)	
	F3 fibrosis	18 (3.3)		**F3 fibrosis**	156 (8.7)
	F4 fibrosis	51 (9.4)		**F4 fibrosis**	311 (17.2)
No	400 (73.5)		No	1,242 (68.9)	
Missing	75 (13.8)		Missing	95 (5.3)	
Late stage liver disease (LSLD)***			**Late stage liver disease (LSLD)*****		
Yes	59 (10.8)		Yes	181 (10.0)	
	HCC	10 (1.8)		**HCC**	45 (2.5)
	Decomp. Cirrhosis	13 (2.4)		**Decomp. Cirrhosis**	78 (4.3)
	Liver complications^	52 (9.5)		**Liver complications^**	138 (7.6)
No	485 (89.1)		No	1,623 (90.0)	

*Late presentation to care includes those with ALD and LSLD, of which, 26 HBV and 116 HCV patients classified in both categories

**ALD is defined as significant fibrosis (≥ F3 assessed by either APRI score > 1.5, FIB-4 > 3.25, Fibrotest > 0.59 or alternatively transient elastography (FibroScan) > 9.5 kPa or liver biopsy ≥ METAVIR stage F3) with no previous antiviral treatment.

***LSLD is clinically defined by the presence of decompensated cirrhosis (at least one symptom of the following: jaundice, hepatic encephalopathy, clinically detectable ascites, variceal bleeding) and/or

^ Jaundice, hepatic encephalopathy, clinically detectable ascites, variceal bleeding, "other"

Post treatment follow-up of patients after SVR
EASL Guidelines 2020

- Patients with no to moderate fibrosis (METAVIR score F0– F2) with SVR and no ongoing risk behaviour should be discharged, provided that they have no other comorbidities (A1).
- Patients with advanced fibrosis (F3) or cirrhosis (F4) with SVR should undergo surveillance for HCC every 6 months by means of ultrasound, because the risk of de novo or incident HCC is reduced but not abolished by SVR (A1).
- In patients with cirrhosis, surveillance for oesophageal varices by endoscopy should be performed if varices were present at pre-treatment endoscopy, or if the platelet count falls below 150,000 and elastography increases to more than 20 kPa (A1).

Update EASL HCV guidelines J Hepatol 2020

Post treatment follow-up of patients after SVR
EASL Guidelines 2020

- Following SVR, monitoring for HCV reinfection through bi-annual or, at least, annual HCV RNA assessments should be undertaken in PWIDs or men who have sex with men with ongoing risk behaviour (A1).

- Retreatment should be offered without stigma or delay to those patients who are reinfected (A1).

- Untreated patients with chronic hepatitis C and those who definitively failed several prior treatment courses (incurable patients) should be regularly followed (A1).

Update EASL HCV guidelines J Hepatol 2020

Post treatment follow-up of patients after SVR
EASL Guidelines 2020

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Update EASL HCV guidelines J Hepatol 2020

Considerations after SVR in patients with mild/moderate liver disease

Consideration	Key Points and Recommendations
Alcohol use	▪ Alcohol use associated with liver fibrosis progression and HCC risk with chronic HCV infection; less evidence in post-SVR setting ▪ **Recommendations**: – Counsel avoidance of significant alcohol use in all pts and abstinence for pts with advanced liver fibrosis or cirrhosis
Obesity	▪ Fatty liver disease can cause fibrosis/cirrhosis; diabetes associated with unfavorable liver-related outcomes ▪ **Recommendations**: – Counsel lifestyle modifications, glycemic control

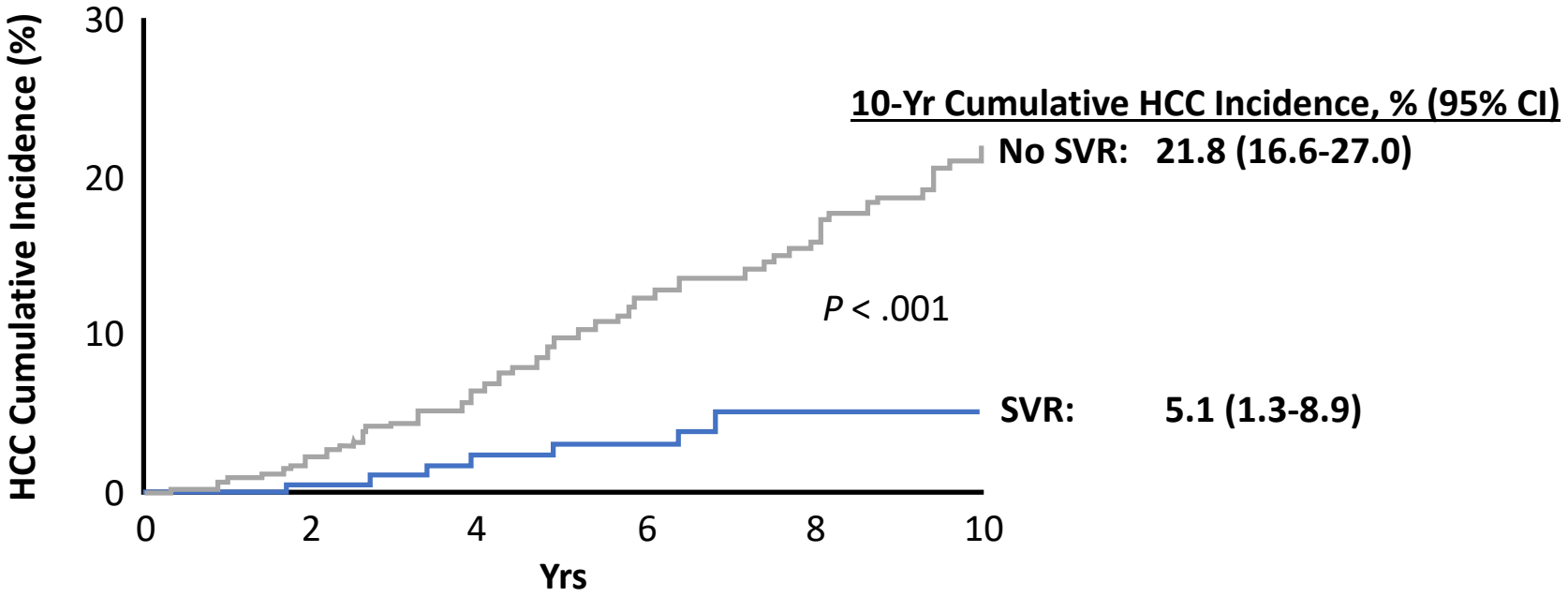
AASLD/IDSA Guidelines. September 2017.
Jacobson IM, et al. Gastroenterology. 2017;152:1578-1587
Update EASL HCV Guidelines 2020.

Post-SVR Monitoring for HCC

Which Patients Need It?

HCC Risk After IFN-Based Treatment

- Long-term follow-up study of people with HCV infection and Ishak score 4-6 fibrosis (N = 530) treated with IFN

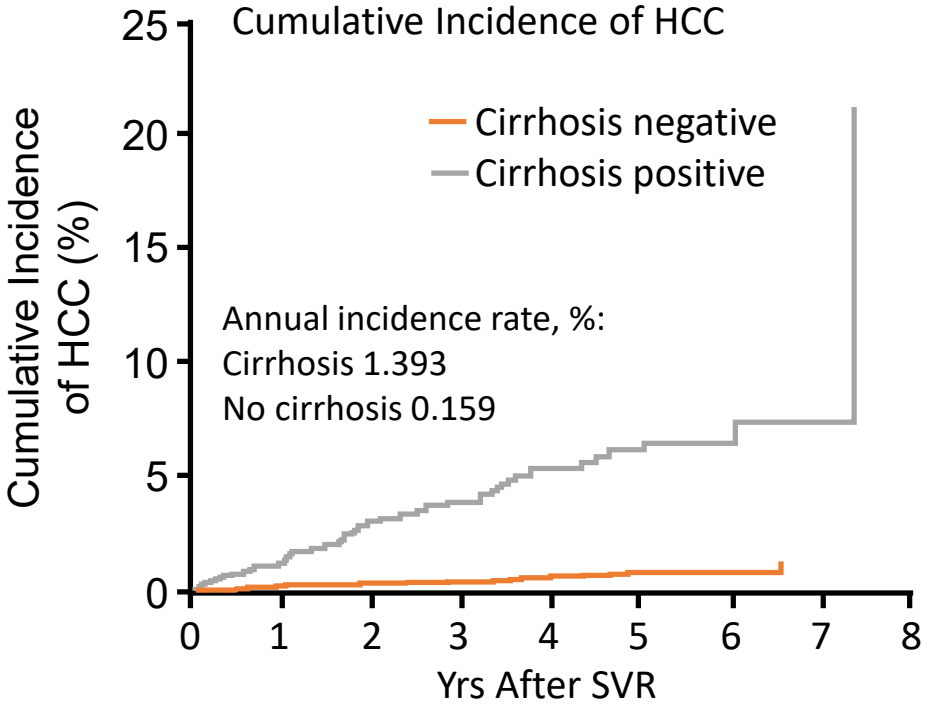


SVR with IFN reduces but does not eliminate the risk of HCC

van der Meer. JAMA. 2012;308:2584.

Fibrosis Stage and Incidence of HCC in Pts Achieving SVR: Retrospective US VA Study

- Retrospective cohort study of de novo HCC incidence in pts achieving SVR on IFN-based therapy in VA Healthcare System 1999-2010 (N = 10,738)



Incidence of HCC Following SVR

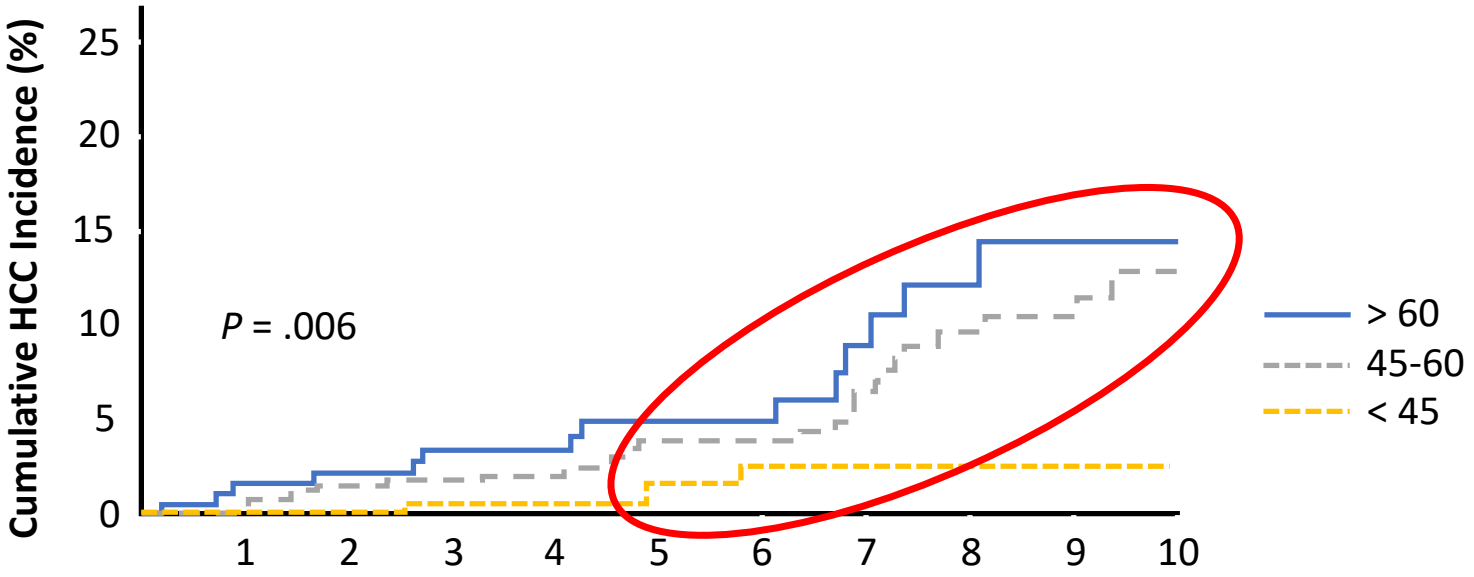
Baseline Status		n	HCC, n	Annual Incidence, %
Cirrhosis	High APRI*			
No	No	6832	11	0.055
No	Yes	2358	31	0.476
Yes	No	584	9	0.526
Yes	Yes	964	49	1.997

*> 2.0.

El-Serag HB, et al. Hepatology. 2016;64:130-137.

Persistence of HCC Risk After SVR

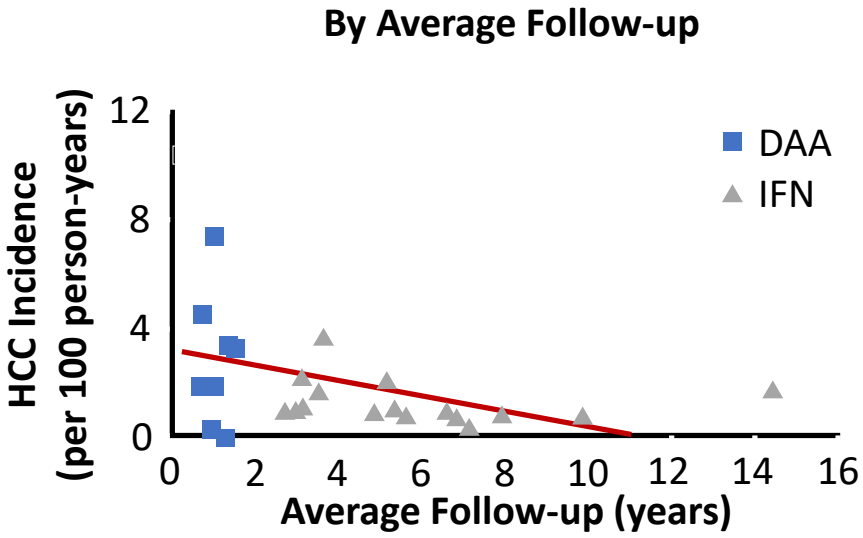
- Pooled analysis of people with bridging fibrosis or cirrhosis and SVR after HCV treatment with IFN (N = 1000)
  - After median follow-up of 5.7 yrs, n = 51 with HCC, approximately 1% annual risk

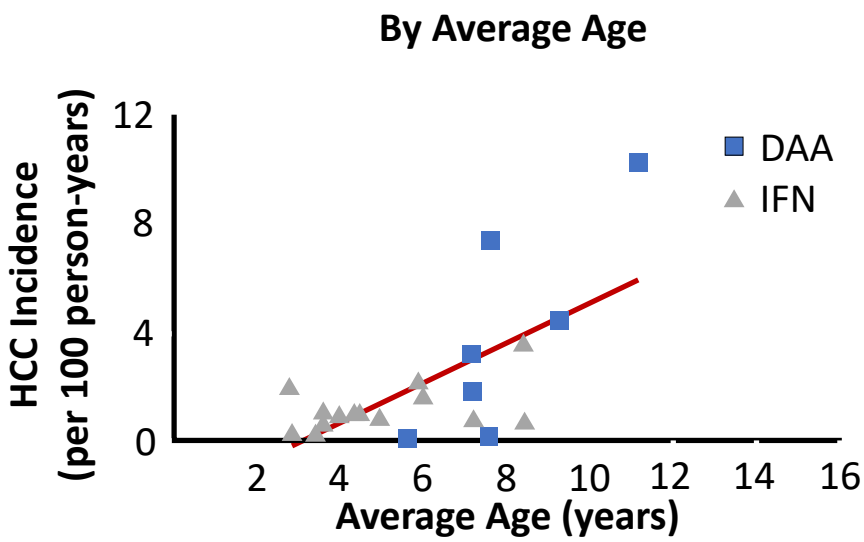


van der Meer. J Hepatol. 2017;66:485.

HCC occurrence in DAA vs IFN treated patients

- Systematic review and meta-regression of 26 studies on de novo HCC occurrence after SVR in IFN- vs DAA-treated patients





- **DAA studies:** shorter follow-up and older patients with more severe liver disease than in IFN studies
- **"Controlling for follow-up" and age:** similar HCC risk in DAA and IFN studies

Waziry. J Hepatol. 2017;67:1204.

Indefinite HCC Surveillance

Guideline/Guidance	HCC Surveillance Recommendations		
	F0-F2	F3	F4
AASLD/IDSA (HCV)[1]	Same as for those never infected with HCV	Ultrasound every 6 mos	
EASL[2]	None	Ultrasound every 6 mos	
AASLD/IDSA (HCC)[3]	None	None (incidence < 1.5%/yr)	Ultrasound every 6 mos (incidence 3% to 5%/yr)

1. AASLD/IDSA Guidelines. September 2018. 2. EASL Guidelines. 2020. 3. Marrero. Hepatol. 2018;68:723.

Post treatment follow-up of patients after SVR
EASL Guidelines 2020

- Patients with no to moderate fibrosis (METAVIR score F0– F2) with SVR and no ongoing risk behaviour should be discharged, provided that they have no other comorbidities (A1)
- Patients with advanced fibrosis (F3) or cirrhosis (F4) with SVR should undergo surveillance for HCC every 6 months by means of ultrasound, because the risk of de novo or incident HCC is reduced but not abolished by SVR (A1)
- **In patients with cirrhosis, surveillance for oesophageal varices by endoscopy should be performed if varices were present at pre-treatment endoscopy, or if the platelet count falls below 150,000 and elastography increases to more than 20 kPa (A1).**

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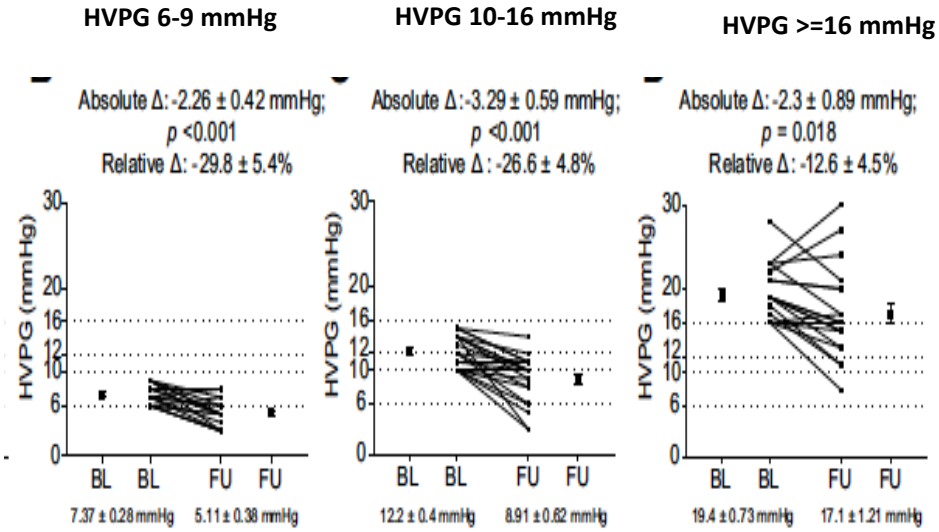
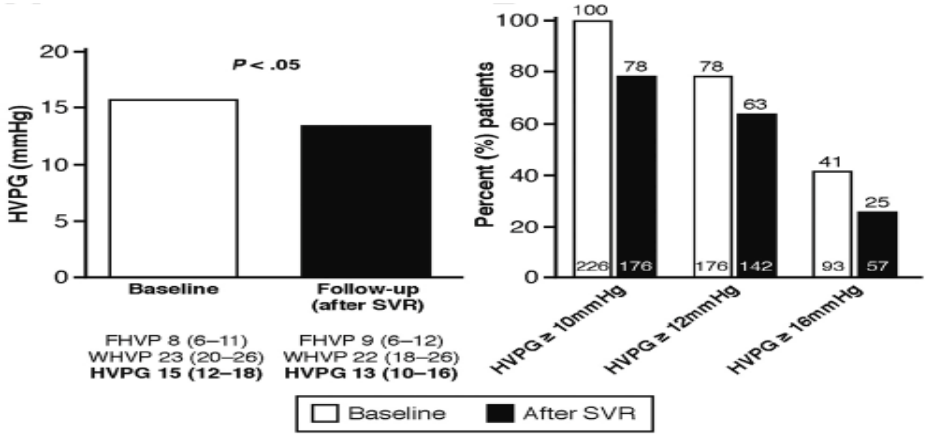
Impact of SVR on portal hypertension (short term)

60 patients with paired HVPG



Mandorfer et al. J Hepatol 2016

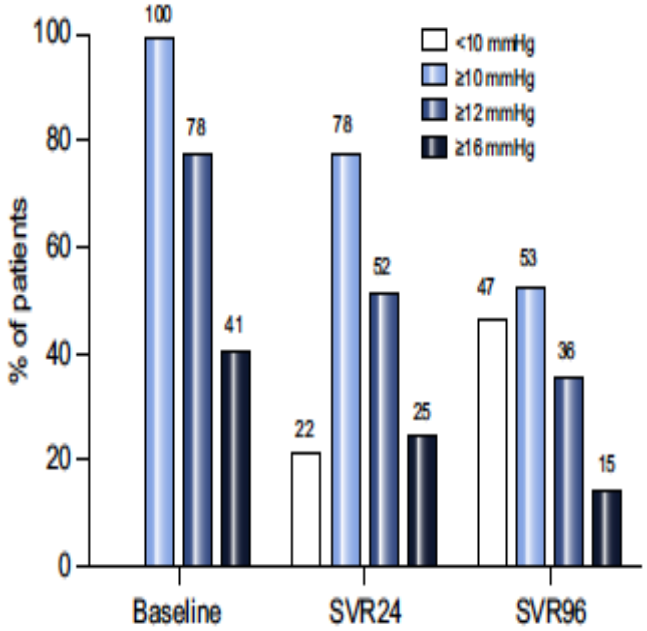
226 patients with CSPH + SVR (6 months after EOT)

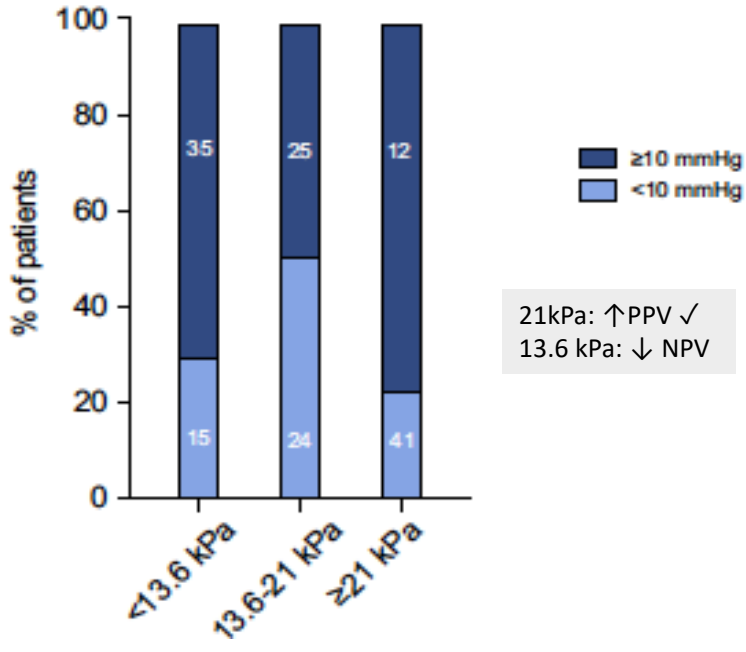


Lens et al. Gastroenterology 2017

Impact of SVR on portal hypertension (long term)

226 patients with CSPH + SVR (6 months and 2 years after EOT)





21kPa: ↑PPV ✓
13.6 kPa: ↓ NPV

Lens and Baiges et al. J Hepatol 2020

CONCLUSIONES

- El número de diagnósticos tardíos continúa siendo muy elevado en España y esto tiene importantes consecuencias clínicas y epidemiológicas.
- Al menos uno cada cuatro nuevos diagnósticos se da en pacientes con enfermedad hepática avanzada. Una elevada proporción de ellos pertenece a colectivos vulnerables.
- La evidencia disponible apoya el cribado **indefinido** de CHC en pacientes con fibrosis avanzada/cirrosis con periodicidad semestral.
- A pesar de que los pacientes con RVS experimentan una reducción de la hipertensión portal, al menos la mitad de ellos continúan con CSPH dos años después de la eliminación de la infección.

- **La eliminación de la hepatitis C solo será posible en el entorno de 2024 si se sigue avanzando en políticas de cribado y mejora de la continuidad asistencial**