Hepatitis C Eradication Reduces Liver Decompensation, HIV progression, and Death in HIV/HCV-coinfected Patients with non-Advanced Liver Fibrosis

J. Berenguer[1], F. X. Zamora[2], C. Díez[1], M. Crespo[3], M. A. Von Wichmann[4], J. López-Aldeguer[5], M. J. Galindo[6], I. Santos[7], H. Esteban[8], C. Barros[9], J. J. Jusdado[10], C. Tural[11], T. Aldámiz[1], J. M. Bellón[1], and J. González-García[2], for the GESIDA HIV/HCV Cohort Study Group

[1]Hosp. Gregorio Marañón, Madrid, SPAIN, [2]Hosp. La Paz, Madrid, SPAIN, [3]Hosp. Vall d'Hebrón, Barcelona, SPAIN, [4]Hosp. Donostia, San Sebastián, SPAIN, [5]Hosp. La Fe, Valencia, SPAIN, [6]Hosp. Clínico, Valencia, SPAIN, [7]Hosp. La Princesa, Madrid, SPAIN, [8]Fundación SEIMC/GESIDA, Madrid, SPAIN, [9]Hosp. Móstoles, Móstoles, SPAIN, [10]Hosp. Getafe, Gefate, SPAIN, [11]Hosp. Germans Trias i Pujol, Badalona, SPAIN.

V CONGRESO NACIONAL DE GESIDA # P-013

Background

- The clinical benefits associated with eradication of HCV have been well characterized in patients with advanced fibrosis or cirrhosis but not in patients with less advanced stages of liver fibrosis [1-7].

- This is a relevant question, particularly in HIV/HCV–coinfected patients, for whom the delivery of effective HCV treatment could be a priority even in mild to moderate stages of liver fibrosis.

1) Bruno S. ***Hepatology 2007***; 45: 579. **2)** Veldt BJ. ***Ann Intern Med 2007***; 147: 677. **3)** Fernandez-Rodriguez CM. ***Am J Gastroenterol 2010***; 105: 2164. **4)** van der Meer AJ. ***JAMA 2012***; 308: 2584. **5)** Berenguer J. ***Hepatology 2009***; 50: 407. **6)** Berenguer J. ***Clin Infect Dis 2012***; 55: 728. **7)** Berenguer J. ***J Hepatol 2013***; 58: 1104-12.

Objective

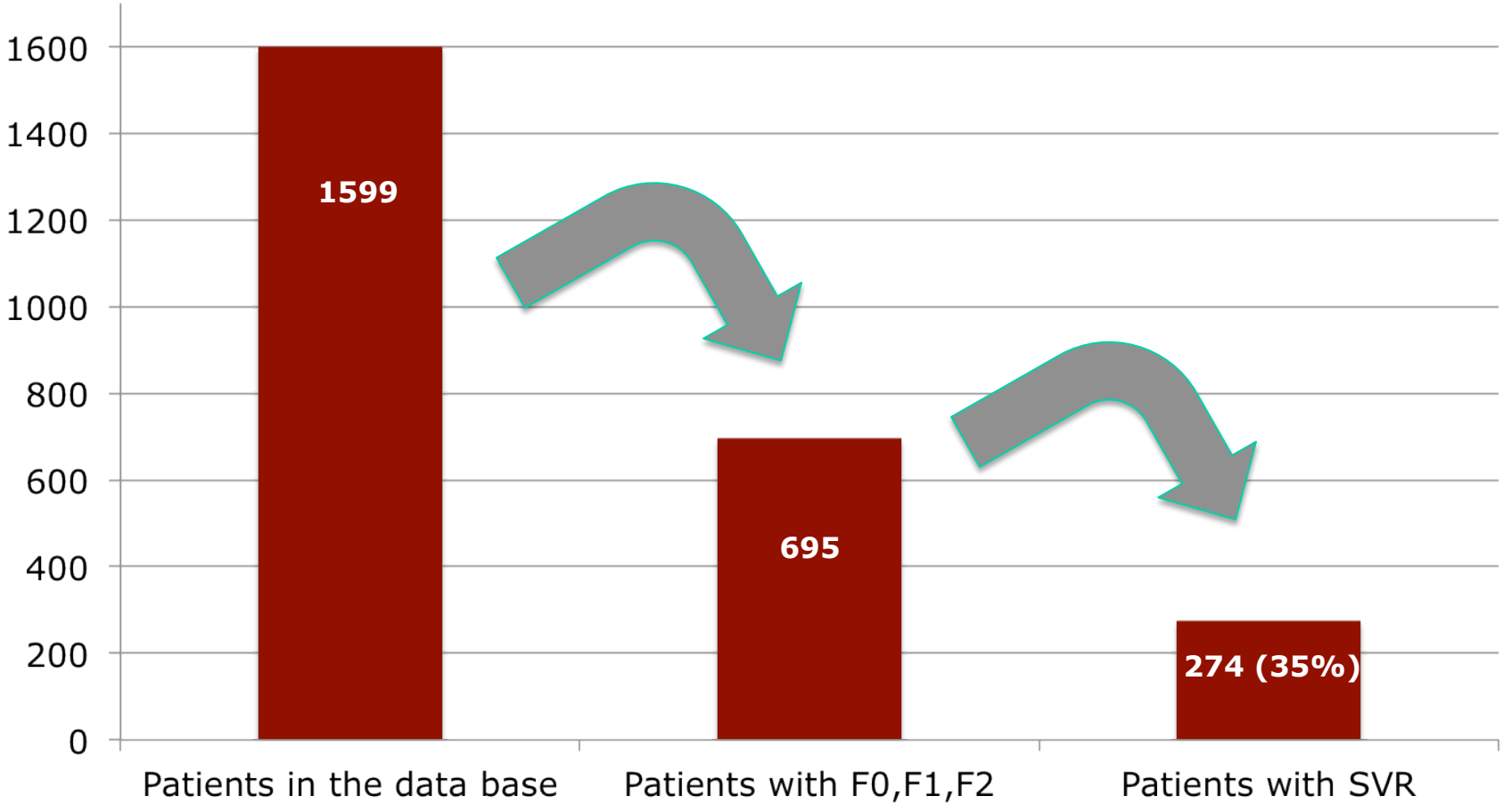
- To assess the effects of SVR following treatment with IFN+RBV on mortality and liver-related events, as well as on HIV progression, in HIV/HCV-coinfected patients with biopsy-proven nonadvanced liver fibrosis.

Study Design

Cohort Description	• HIV/HCV+ patients who started IFN-RBV between Jan 2000 and Jan 2008 [1-3] • 19 clinical centers in Spain • Centralized online CRF - Monitored • Assessment during FU: survival, liver decompensation, HIV-progression, ART, and labs. Liver biopsies and transient elastometry (TE) (if any).
Patient Selection	• Baseline liver biopsy (LB) with METAVIR F0,F1 or F2
Study Duration	• From IFN-RBV discontinuation until last FU visit or death • In retreated patients the FU was censored on the day the patient started the second course with IFN-RBV
Censoring Date	• July 31, 2010

1) Berenguer J, et al. ***Hepatology 2009***; 50(2): 407. **2)** Berenguer J, et al. ***Clin Infect Dis 2012***; 55(5): 728. **3)** Berenguer J, et al. ***J Hepatol*** 2013; 58: 1104-12.

Patients included in the study



Baseline characteristics I

Characteristic	No SVR (n=421)	SVR (n=274)	Total (N=695)
Male sex *	314 (75)	190 (69)	504 (73)
Age – yr #	39.8 (36.5-43)	39.8 (36.3-42.4)	39.8 (36.3-42.7)
Weight – kg #	68 (60-75)	68 (59-75)	68 (60-75)
Low educational level *	211/333 (63)	132/222 (60)	343/555 (62)
Prior IDU *	349/420 (83)	225/271 (83)	574/691 (83)
CDC category C *	93/416 (22)	43/270 (16) ¶	136/686 (20)
CD4 + cells/uL #	536 (385-727)	562 (411-752)	546 (400-741)
HIV-RNA < LOQ *	267/410 (65)	182/266 (68)	449/376 (66)

*n (%); # median (IQR)
¶ P<.05 with the No SVR group

Abbreviations: ***IDU***, injection drug use; ***LOQ***, lower limit of quantification; ***LB***, liver biopsy; ***Rx***, treatment with IFN-RBV

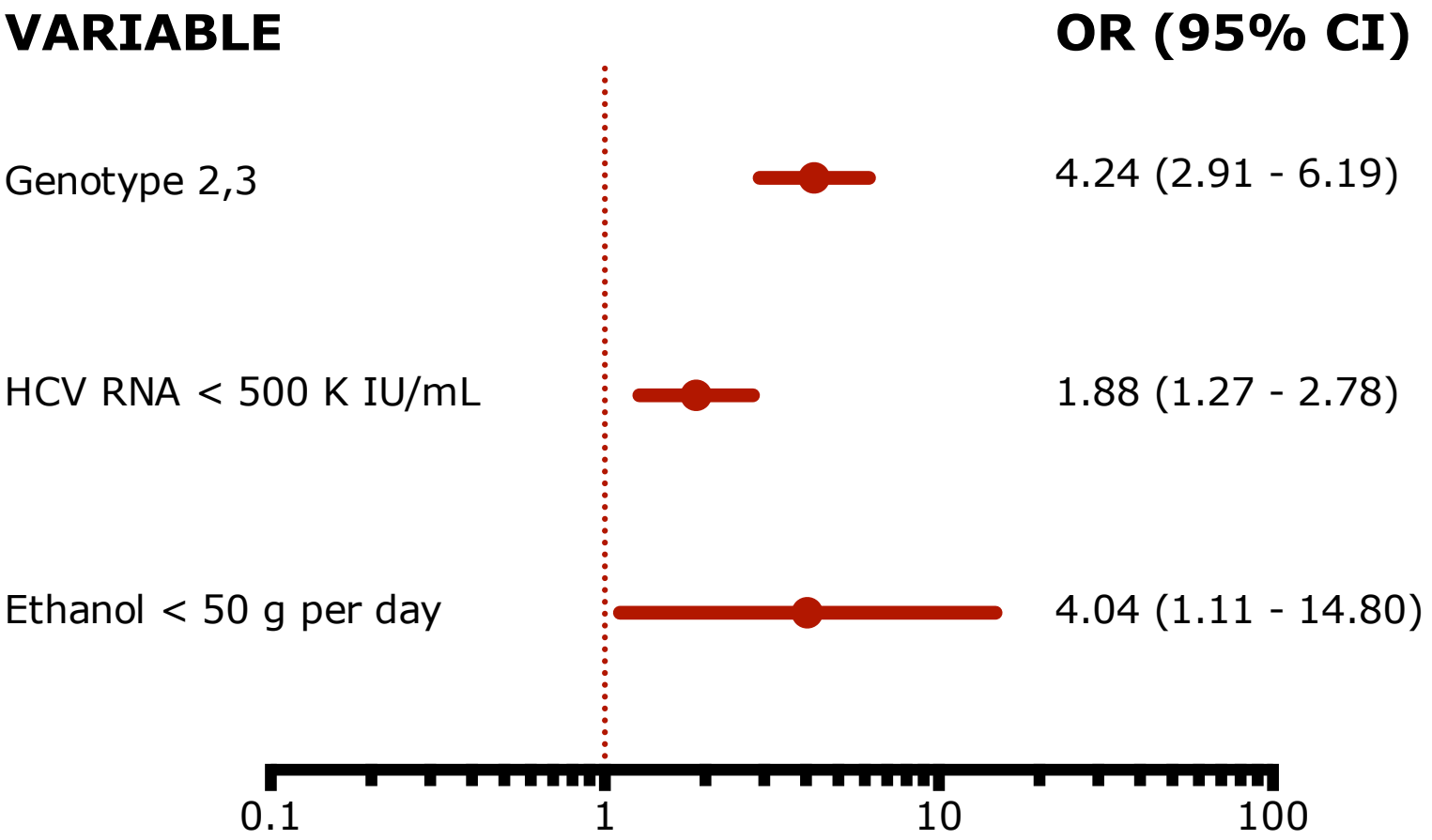
Baseline characteristics II

Characteristic	No SVR (n=421)	SVR (n=274)	Total (N=695)
HCV genotype*			
1 or 4	312 (76)	119 (44) ¶	431 (64)
2 or 3	97 (24)	149 (56) ¶	246 (36)
Unknown	12	6	18
HCV-RNA ≥ 500K IU/mL*	275/364 (76)	153/247 (62) ¶	428/611 (70)
METAVIR fibrosis score*			
F0, No. (%)	47 (11)	30 (11)	77 (11)
F1, No. (%)	169 (40)	121 (44)	290 (42)
F2, No. (%)	205 (49)	123 (45)	328 (47)
HBsAg positive*	12 (3)	7 (3)	19 (3)
Ethanol > 50 g/d*	22/383 (6)	4/262 (2) ¶	26/645 (4)
Methadone use	52/396 (13)	23/256 (9)	75/652 (12)
Δt LB – Rx initiation – mo #	4 (2 – 11)	6 (3 – 14)	5 (2 – 12)

*n (%); # median (IQR)

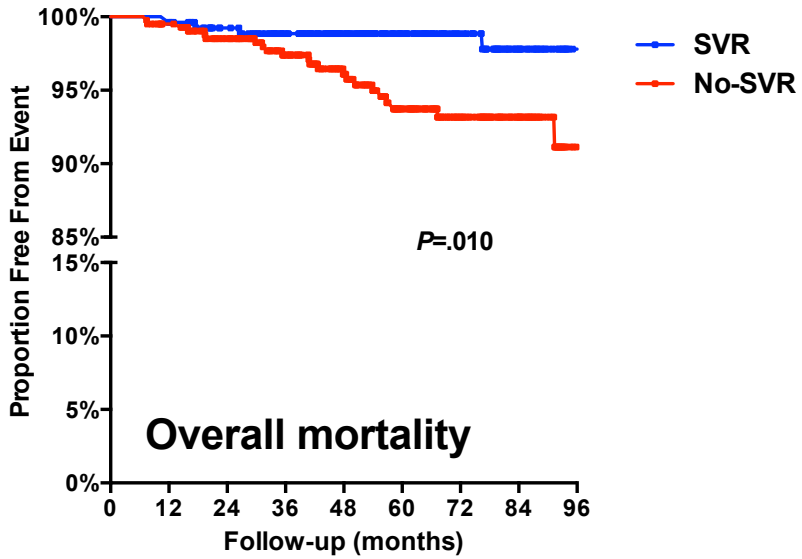
¶ P<.05 with the No SVR group

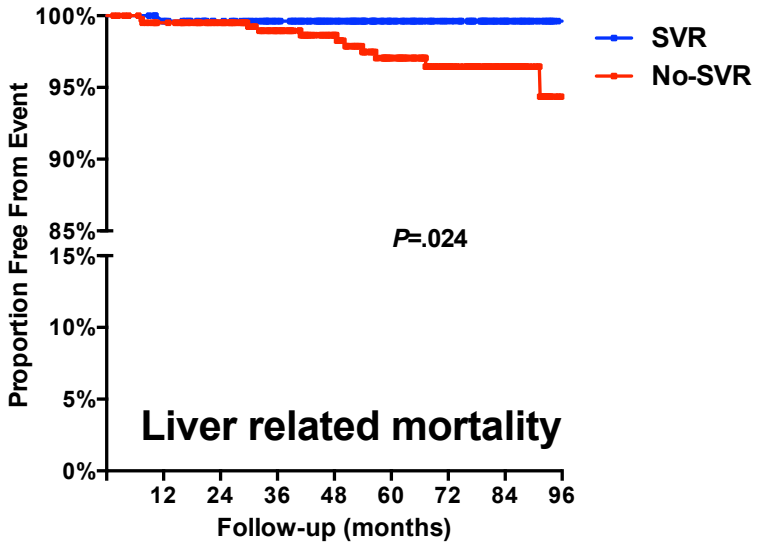
Variables associated with SVR

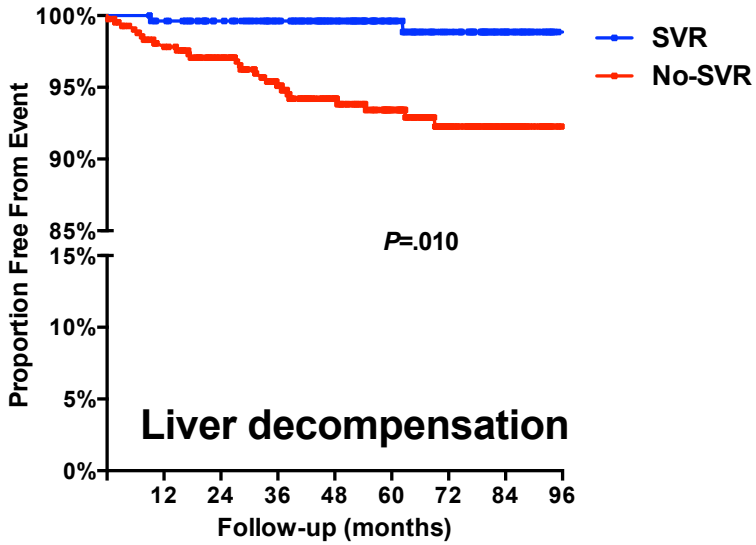


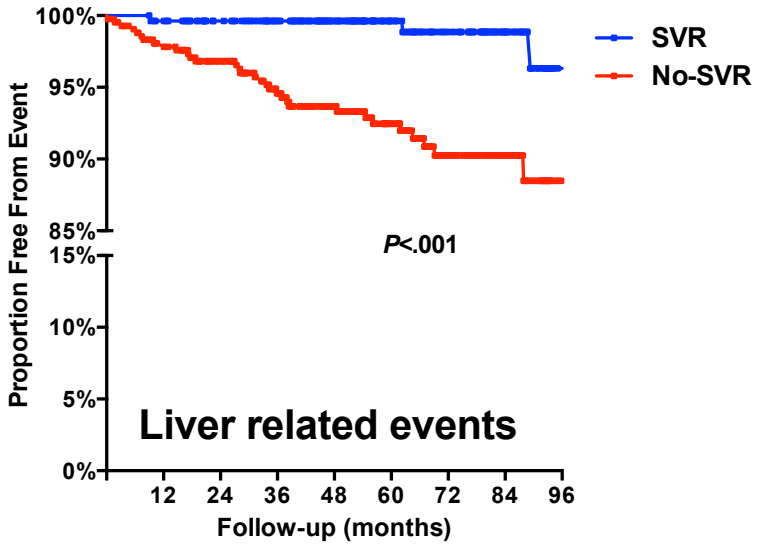
Kaplan Meier estimates of events

Median FU (IQR): **No SVR**: 59.3 mo (40.6 - 79.2); **SVR**: 59.5 (42.8 - 81.8)









Frequency of events during follow-up

	F0 to F2 (N=695)	
	No SVR	SVR
Nº of patients	421	274
Lost to follow-up	73 (17.3)	28 (10.2)*
Overall mortality	22 (5.2)	4 (1.5)*
Liver-related (LR)	11 (2.6)	1 (0.4)*
AIDS-related (AR)	1 (0.2)	0 (0)
Non–LR non–AR	9 (2.1)	3 (1.1)
CDC category C disease	14 (3.3)	2 (0.7)*
Liver decompensation	26 (6.2)	3 (1.1)*
Hepatocarcinoma	3 (0.7)	1 (0.4)
Liver transplantation	2 (0.5)	2 (0.7)

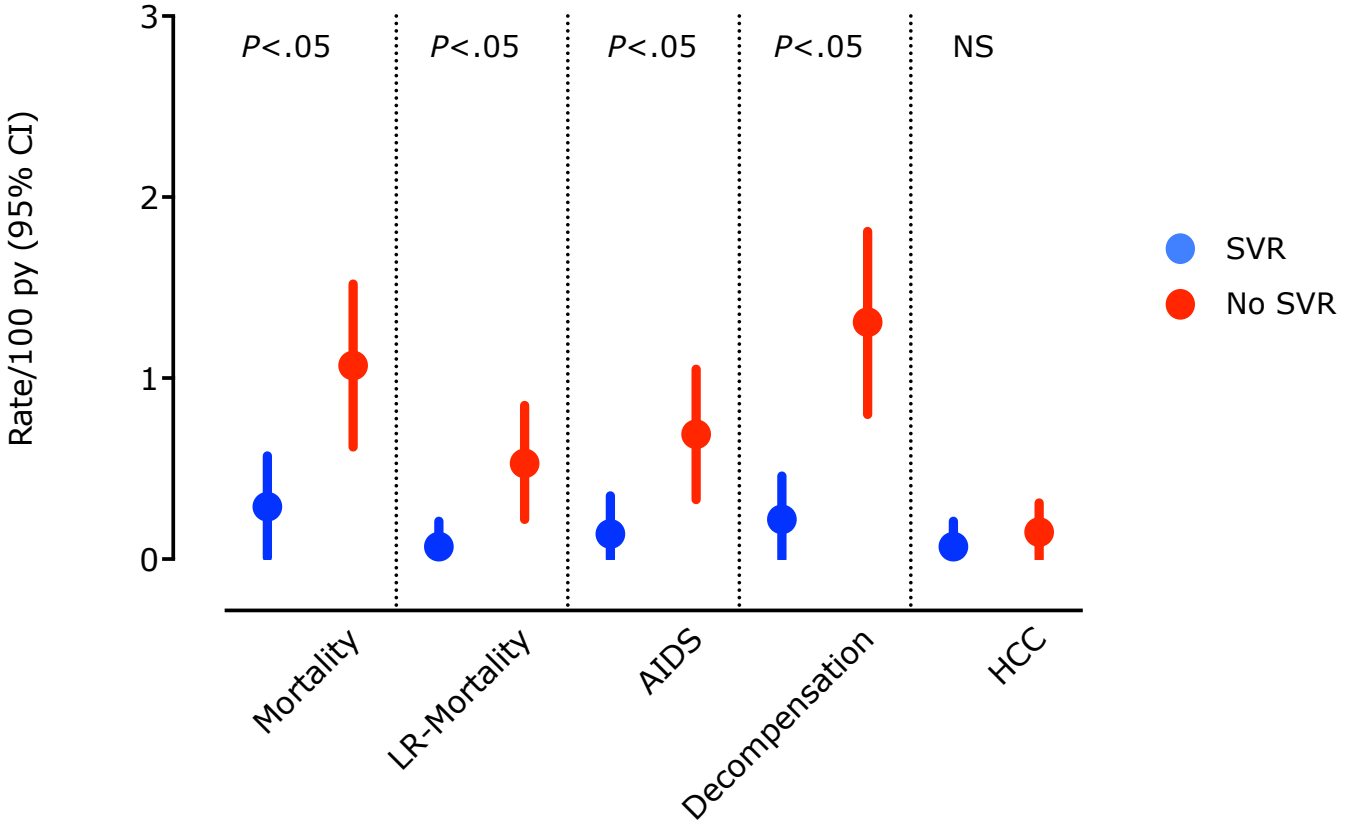
*P<.05 with the No SVR group.

Frequency of events during follow-up

	F0 to F2 (N=695)		F2 (n=328)		F0, F1 (n=367)	
	No SVR	SVR	No SVR	SVR	No SVR	SVR
Nº of patients	421	274	205	123	216	151
Lost to follow-up	73 (17.3)	28 (10.2)*	46 (22.4)	13 (10.6)*	27 (12.5)	15 (9.9)
Overall mortality	22 (5.2)	4 (1.5)*	15 (7.3)	1 (0.8)*	7 (3.2)	3 (2)
Liver-related (LR)	11 (2.6)	1 (0.4)*	10 (4.9)	1 (0.8)*	1 (0.5)	0 (0)
AIDS-related (AR)	1 (0.2)	0 (0)	0 (0)	0 (0)	1 (0.5)	0 (0)
Non–LR non–AR	9 (2.1)	3 (1.1)	4 (2)	0 (0)	5 (2.3)	3 (2)
CDC category C disease	14 (3.3)	2 (0.7)*	8 (3.9)	1 (0.8)	6 (2.8)	1 (0.7)
Liver decompensation	26 (6.2)	3 (1.1)*	17 (8.3)	1 (0.8)*	9 (4.2)	2 (1.3)
Hepatocarcinoma	3 (0.7)	1 (0.4)	3 (1.5)	0 (0)	0 (0)	1 (0.7)
Liver transplantation	2 (0.5)	2 (0.7)	0 (0)	0 (0)	2 (0.9)	2 (1.3)

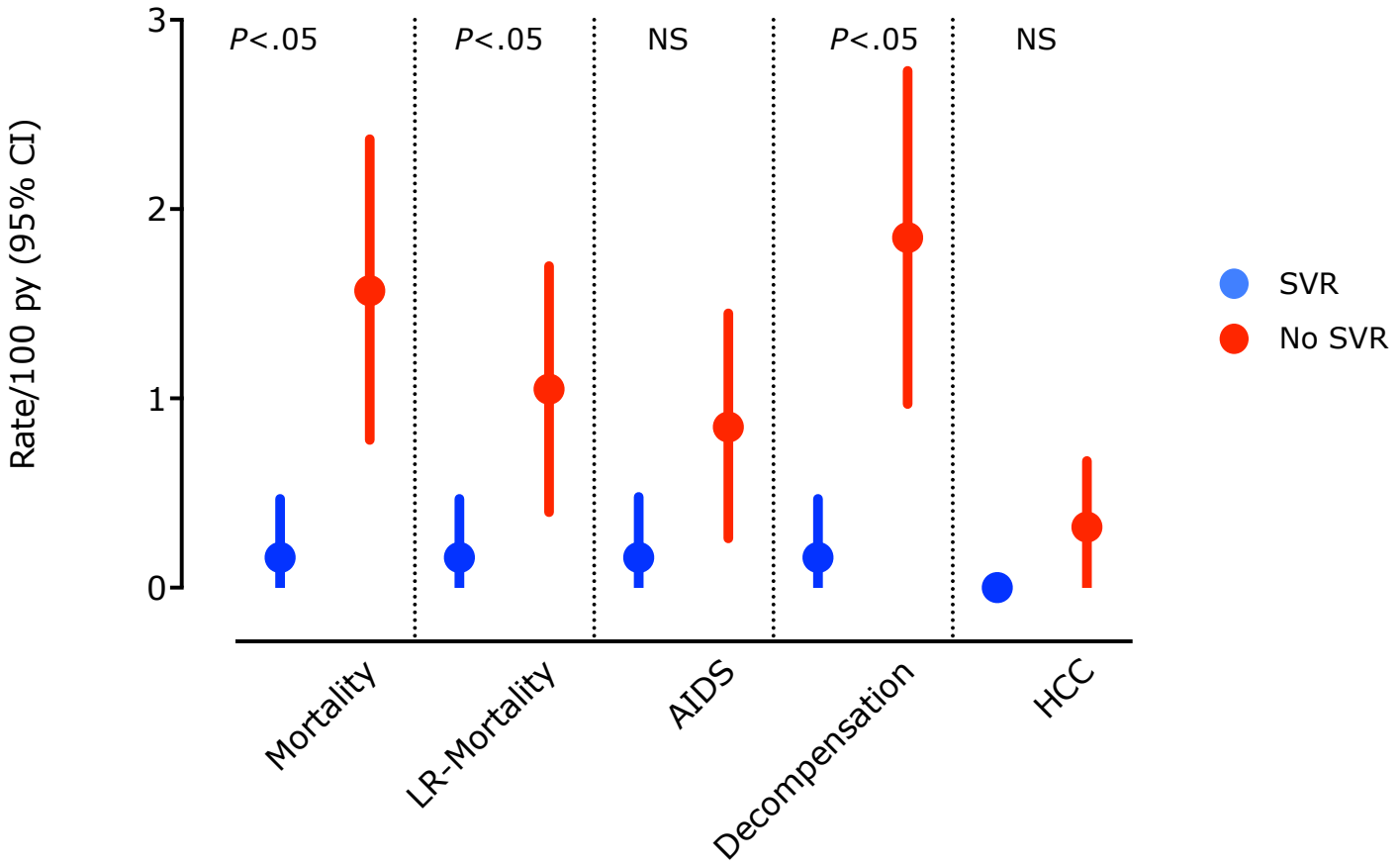
*P<.05 with the No SVR group.

Rate of events during FU for F0-F2
per 100 patients/years (95%CI)



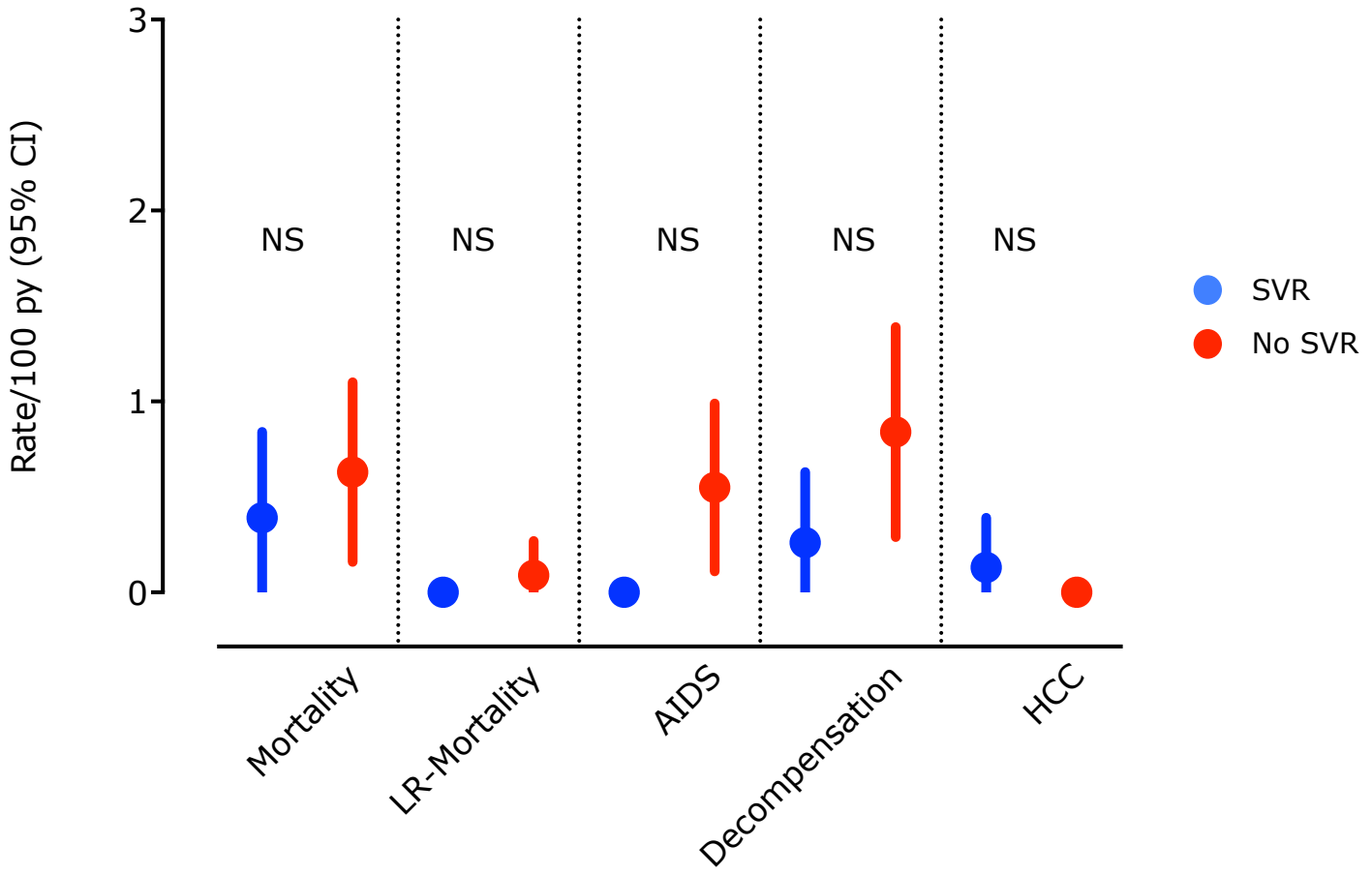
	Mortality	LR-Mortality	AIDS	Decompensation	HCC
SVR	0.29 (0.01-0.57)	0.07 (0-0.21)	0.14 (0-0.35)	0.22 (0-0.46)	0.07 (0-0.21)
No SVR	1.07 (0.62-1.52)	0.53 (0.22-0.85)	0.69 (0.33-1.05)	1.31 (0.8-1.81)	0.15 (0-0.31)

Rate of events during FU for F2
per 100 patients/years (95%CI)



	Mortality	LR-Mortality	AIDS	Decompensation	HCC
SVR	0.16 (0-0.47)	0.16 (0-0.47)	0.16 (0-0.48)	0.16 (0-0.47)	0 (0-0)
No SVR	1.57 (0.78-2.37)	1.05 (0.4-1.7)	0.85 (0.26-1.45)	1.85 (0.97-2.73)	0.32 (0-0.67)

Rate of events during FU for F0-F1
per 100 patients/years (95%CI)



	Mortality	LR-Mortality	AIDS	Decompensation	HCC
SVR	0.39 (0-0.84)	0 (0-0)	0.13 (0-0.39)	0.26 (0-0.63)	0.13 (0-0.39)
No SVR	0.63 (0.16-1.1)	0.09 (0-0.27)	0.55 (0.11-0.99)	0.84 (0.29-1.39)	0 (0-0)

Liver stiffness (TE) following IFN-RBV

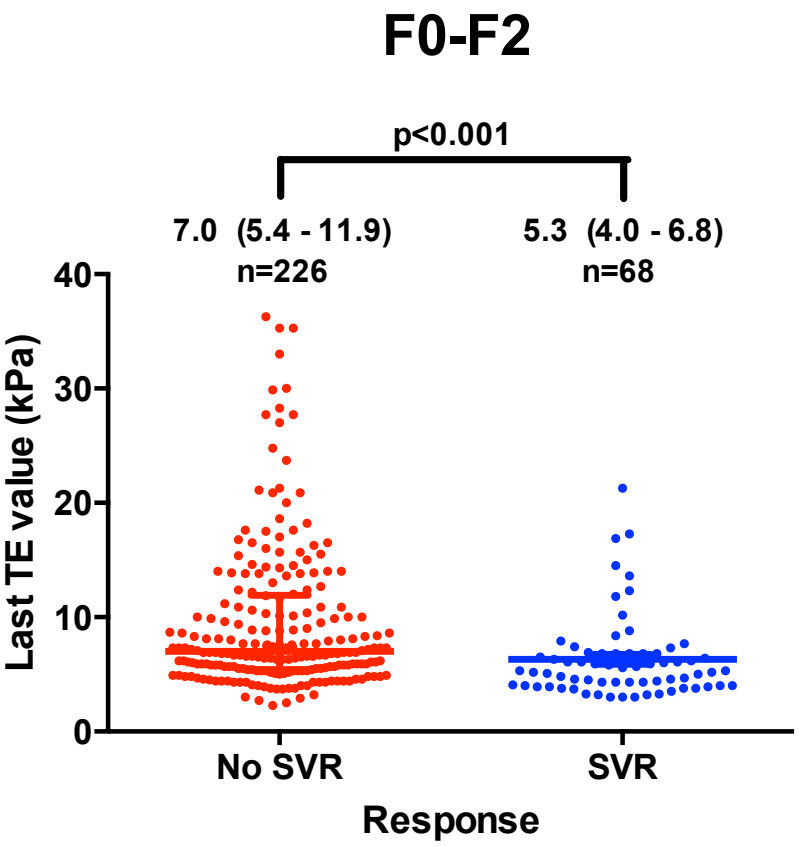
294 patients studied with TE during FU

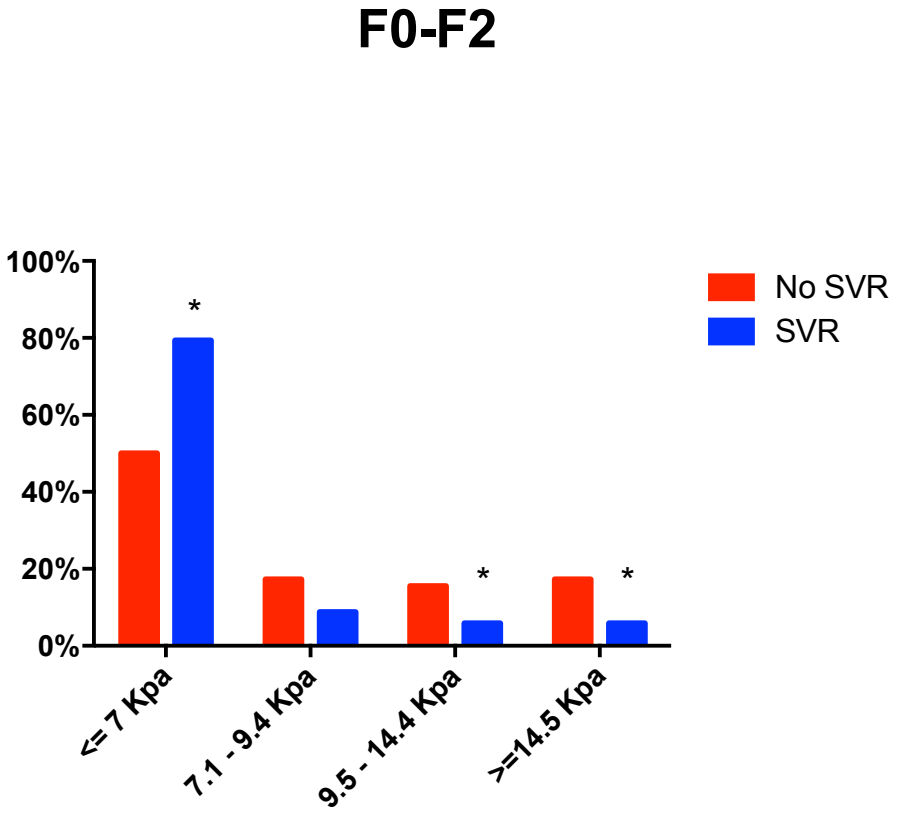
- 226 SVR
- 68 No SVR

	No SVR N = 68	SVR N = 226	P
Baseline fibrosis*			NS
• F0	9 (13)	24 (11)	
• F1	28 (41)	97 (43)	
• F2	31 (46)	105 (47)	
Δt (mo) to last TE#	61.2 (41.9–80.1)	51.7 (32.9–70.4)	<.05

*n (%); # median (IQR)

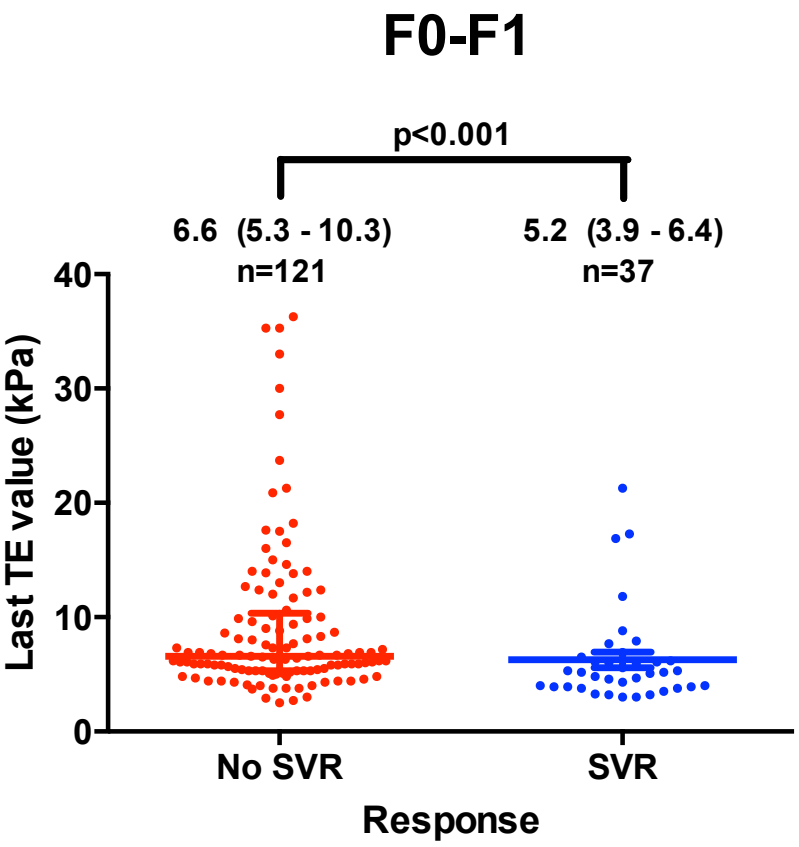
Liver stiffness (TE) following IFN-RBV

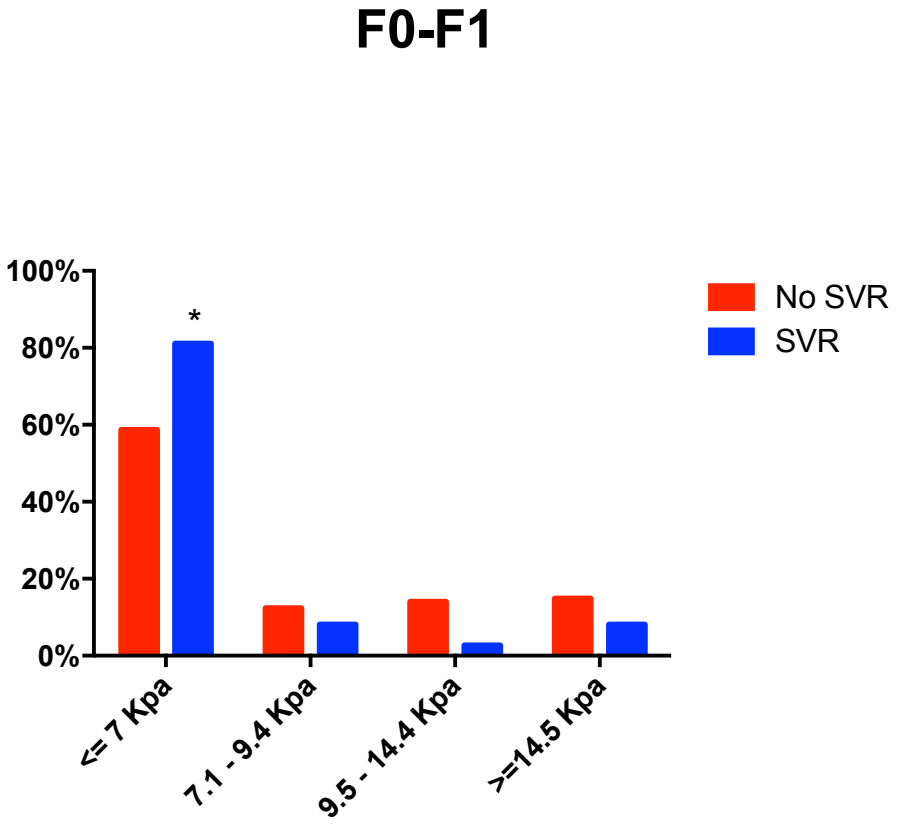




* P<.05 with the No SVR group

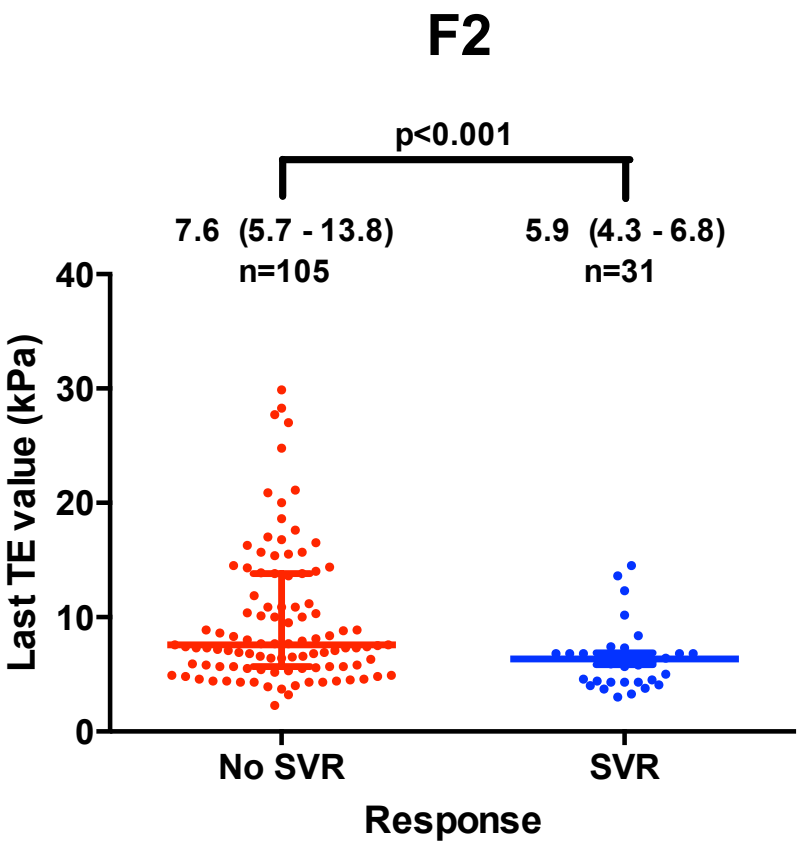
Liver stiffness (TE) following IFN-RBV

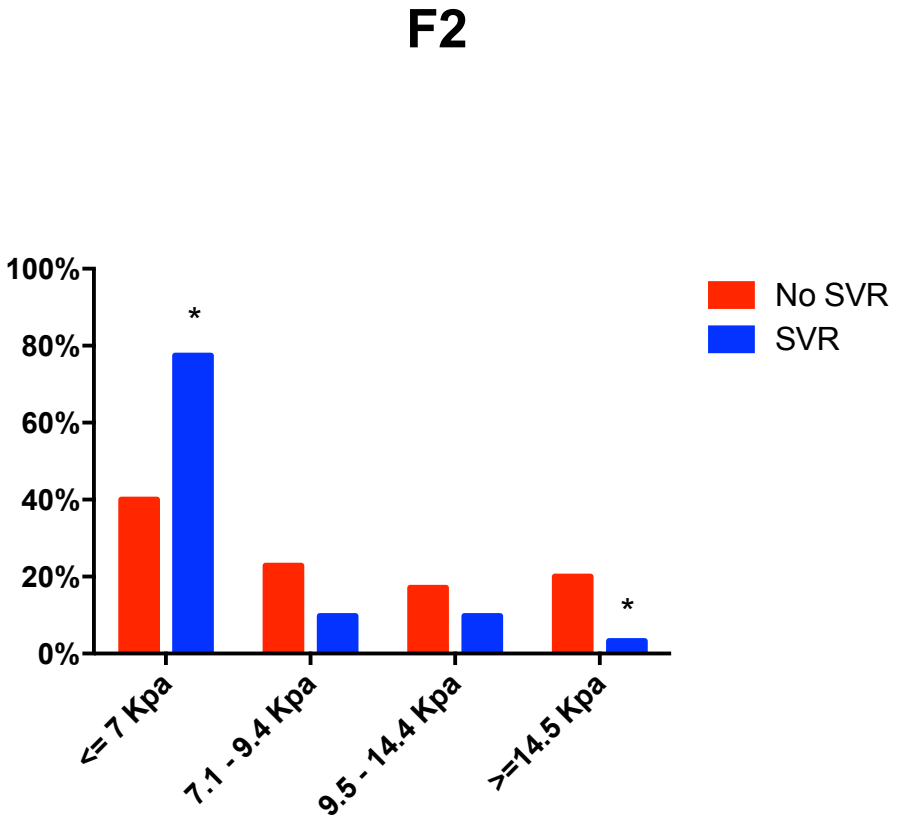




* P<.05 with the No SVR group

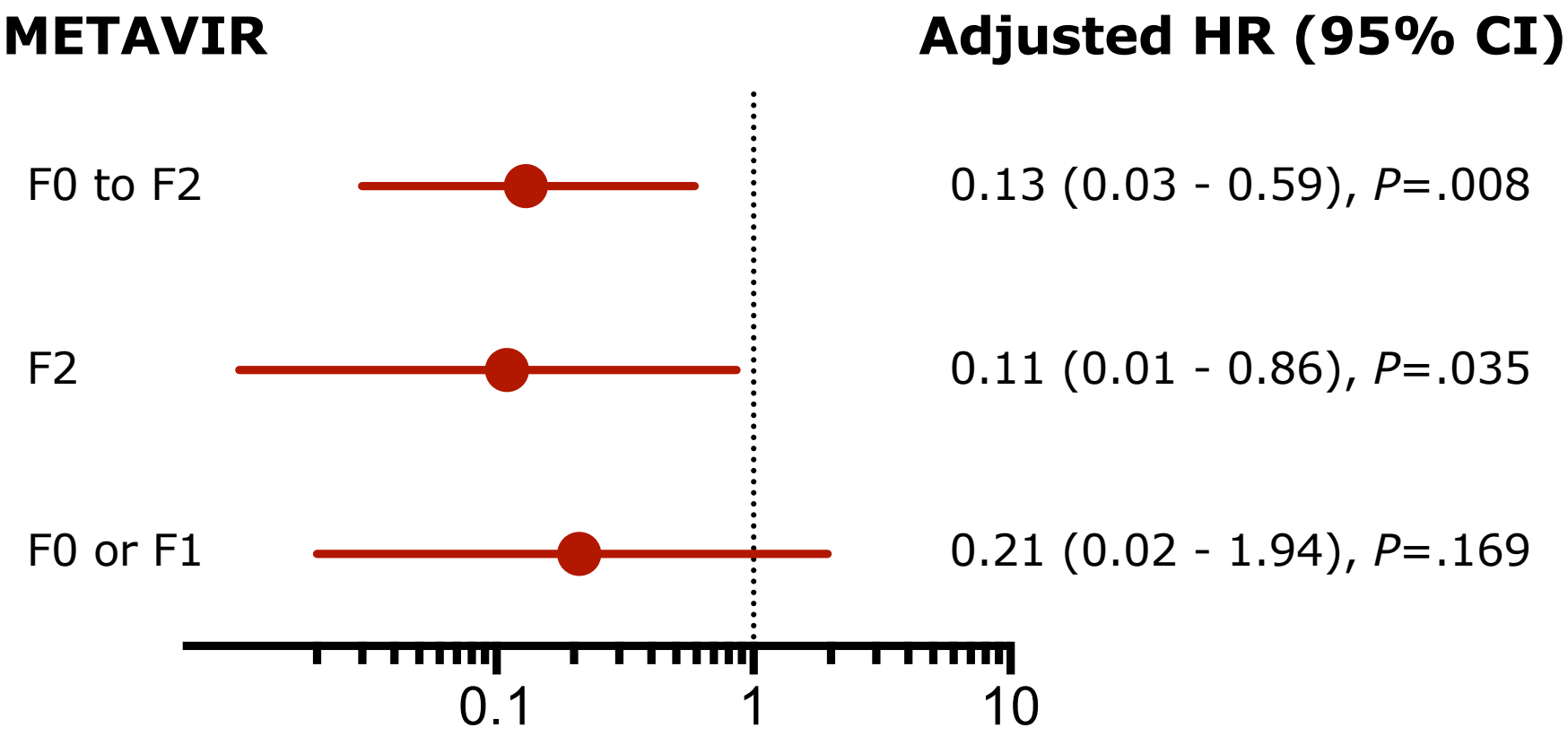
Liver stiffness (TE) following IFN-RBV





* P<.05 with the No SVR group

Hazard of liver-related events according to fibrosis stage in patients with SVR (Cox regression analysis)



Adjusted for: age, sex, history of IDU, CDC clinical category, CD4+ cell count, HCV genotype, and HCV RNA viral load

Conclusions

- Eradication of HCV in HIV/HCV-coinfected patients with nonadvanced liver fibrosis (F0 to F2), and, more specifically, with moderate stages of liver fibrosis (F2), is associated with a reduction in the risk of mortality and liver-related events.

- These findings constitute a strong rationale for considering anti-HCV treatment in this population group, particularly treatment based on the newer and more effective direct antiviral agents.

The GeSIDA 3603 Team

Principal Investigators
J Berenguer, J Gonzalez

Study Coordinators
E Barquilla, H Esteban

Statistician
JM Bellón

H. Gregorio Marañón, Madrid
T Aldámiz, JM Bellón, J Cosín, I Gutiérrez, JC López, P Miralles, B Padilla, A Carrero, F Tejerina, C Diez, M Ramírez, M Sánchez-Conde, J Berenguer,

H. 12 de Octubre, Madrid
MA Hernando, F Pulido, V Rodríguez, R Rubio

H. Clinic, Barcelona
P Callau, JM Gatel, J Mallolas, JM Miro

H. Clínico Univ de Valencia, Valencia
A Ferrer, MJ Galindo

H. Clínico San Carlos, Madrid
MJ Téllez, J Vergas

H. Donostia, San Sebastián
J Arrizabalaga, JA Iribarren, MA Von Wichmann

H. General de Valencia, Valencia
E Ortega, L Ortiz

H. La Paz, Madrid
J Alvarez, JR Arribas, I Bernardino, M Mora, F Pascual, JM Peña, E Rodríguez, I Valero, F Zamora, J González,

H. Germans Trias i Pujol Badalona
B Clotet, A Jou, C Tural

H. Getafe, Madrid
G Gaspar, G Pérez

H. Guadalajara, Guadalajara
M Rodríguez, ML Montes

H. La Fe, Valencia
S Cuellar, J López-Aldeguer

H. La Princesa, Madrid
I Santos, J Sanz

H. Móstoles, Madrid
C Barros, E Condés

Fund SEIMC-GESIDA, Madrid
E Aznar, E Barquilla, H Esteban, B Moyano

H. Príncipe Asturias, Madrid
A Arranz, J de Miguel, J Sanz

H. Ramón y Cajal, Madrid
A Moreno, S Moreno, C Quereda, MA Sanfrutos

H. Santa Creu i Sant Pau Barcelona
P Domingo, JM Guardiola

H. Severo Ochoa, Madrid
M Cervero, JJ Jusdado, R Torre

H. Vall d´Hebron, Barcelona
M Crespo, E Van den Eynde

Funding

- **FIPSE** (Refs. 36443/03, 36702/07, 361020/10)
- **FIS** (Refs. EC07/90734, PI11/01556, EC11/241)
- **RIS** (Ref RD12/0017)
- **I3SNS** (J Berenguer) (Refs. INT10/009, INT12/154)