Supplementary Table 1. Types of HCV antiviral treatment regimens included in our study of VA patients from 1999-2015

	Regimen*	First Regimen N (%)	All Regimens N (%)
IFN ONLY	Interferon	3,872(5.4)	5,914(6.2)
	PEG	36,991(51.8)	46,245(48.6)
DAA + IFN	Boceprevir+PEG	3,185(4.5)	4,968(5.2)
	Telaprevir+PEG	498(0.7)	997(1.0)
	Simeprevir+PEG	14(0.0)	23(0.0)
	Sofosbuvir+PEG	1,046(1.5)	1,834(1.9)
DAA ONLY	Sofosbuvir (±daclatasvir)	3,473(4.9)	4,636(4.9)
	Sofosbuvir+Simeprevir	2,068(2.9)	3,331(3.5)
	Ledipasvir/Sofosbuvir	15,055(21.1)	20,539(21.6)
	Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir	5,255(7.4)	6,602(6.9)

* Regimens with or without ribavirin were included together

DAA = direct acting antivirals, IFN = interferon, PEG = pegylated interferon

Supplementary Table 2: Timing of HE vis-à-vis Treatment Initiation

	Number of patients who developed HE after start of treatment	Number who developed HE **Within 90 days** of start-date (%)	Number who developed HE **Within 180 days** of start-date (%)	Number who developed HE **Within 360** days of start-date (%)	Number who developed HE **before treatment end-date** (%)
IFN	4,270	149(3.5)	283(6.6)	526(12.3)	235(5.5)
IFN+DAA	234	28(12.0)	50(21.4)	86(36.8)	44(18.8)
DAA	601	115(19.1)	175(29.1)	291(48.4)	113(18.8)
SVR	1,056	112(10.6)	187(17.7)	319(30.2)	159(15.1)
No SVR	4,049	180(4.4)	321(7.9)	584(14.4)	233(5.8)

Supplementary Table 3: Varying Cohort Entry Dates with Respect to Treatment Initiation has a Limited Effect on the Risk Estimates for Hepatic Encephalopathy

		Number of patients (%)	Mean Follow-up (Years)	Number who developed HE (%)	HE incidence per 100 patient-years	Crude hazard ratio (95% CI)	Adjusted* hazard ratio (95%CI)
Analysis starting at 90 days from antiviral treatment initiation							
IFN-ONLY regimens	No SVR	34,006(66.7)	8.6	3,613(10.6)	1.24	1	1
	SVR	16,973(33.3)	10.6	508(3.0)	0.28	0.23 (0.21-0.26)	0.26 (0.23-0.30)
DAA+ IFN regimens	No SVR	3,198(42.4)	3.3	132(4.1)	1.26	1	1
	SVR	4,345(57.6)	5.2	74(1.7)	0.33	0.27 (0.20-0.37)	0.31 (0.22-0.43)
DAA-only regimens	No SVR	3,336(10.2)	2.7	124(3.7)	1.39	1	1
	SVR	29,414(89.8)	3.2	362(1.2)	0.39	0.28 (0.22-0.35)	0.41 (0.32-0.51)
Analysis starting at 180 days from antiviral treatment initiation							
IFN-ONLY regimens	No SVR	33,897(66.7)	8.6	3,504(10.3)	1.2	1	1
	SVR	16,948(33.3)	10.6	483(2.8)	0.27	0.22 (0.20-0.25)	0.25 (0.22-0.28)
DAA+IFN regimens	No SVR	3,182(42.3)	3.3	116(3.6)	1.1	1	1
	SVR	4,339(57.7)	5.2	68(1.6)	0.3	0.27 (0.20-0.37)	0.30 (0.22-0.43)
DAA-only regimens	No SVR	3,320(10.2)	2.7	108(3.3)	1.21	1	1
	SVR	29,370(89.8)	3.2	318(1.1)	0.34	0.28 (0.22-0.35)	0.39 (0.31-0.50)
Analysis starting at 360 days from antiviral treatment initiation							
IFN-ONLY regimens	No SVR	33,697(66.6)	8.7	3,304(9.8)	1.13	1	1
	SVR	16,905(33.4)	10.6	440(2.6)	0.24	0.21 (0.19-0.24)	0.24 (0.21-0.27)
DAA+	No SVR	3,160(42.2)	3.3	94(3.0)	0.9	1	1

IFN regimens	SVR	4,325(57.8)	5.2	54(1.2)	0.24	0.24 (0.17-0.34)	0.26 (0.18-0.38)
DAA-only regimens	No SVR	3,279(10.1)	2.7	67(2.0)	0.75	1	1
	SVR	29,295(89.9)	3.2	243(0.8)	0.26	0.33 (0.25-0.44)	0.43 (0.32-0.59)
Analysis starting at the time antiviral treatment was stopped							
IFN-ONLY regimens	No SVR	33,917(66.7)	8.6	3,524(10.4)	1.21	1	1
	SVR	16,943(33.3)	10.6	478(2.8)	0.27	0.22 (0.20-0.25)	0.25 (0.22-0.28)
DAA+ IFN regimens	No SVR	3,189(42.4)	3.3	123(3.9)	1.17	1	1
	SVR	4,335(57.6)	5.2	64(1.5)	0.28	0.24 (0.18-0.33)	0.28 (0.20-0.39)
DAA-only regimens	No SVR	3,335(10.2)	2.7	123(3.7)	1.37	1	1
	SVR	29,401(89.8)	3.2	349(1.2)	0.37	0.27 (0.22-0.34)	0.39 (0.31-0.49)

Supplementary Table 4. Propensity Matched Analysis of the Association between SVR and the Risk of Developing Incident HE

		Crude hazard ratio (95% CI)	Adjusted* hazard ratio (95%CI)	Crude hazard ratio with IPW± (95% CI)	Adjusted* hazard ratio with IPW± (95%CI)	Crude hazard ratio with trimmed IPW± (95% CI)	Adjusted* hazard ratio with trimmed IPW± (95%CI)
IFN-ONLY regimens	No SVR	1	1	1	1	1	1
	SVR	0.23 (0.21-0.26)	0.26 (0.23-0.30)	0.26 (0.23-0.30)	0.26 (0.23-0.30)	0.26 (0.23-0.30)	0.26 (0.23-0.30)
DAA+IFN regimens	No SVR	1	1	1	1	1	1
	SVR	0.27 (0.20-0.37)	0.32 (0.22-0.43)	0.32 (0.23-0.44)	0.31 (0.22-0.43)	0.30 (0.22-0.42)	0.30 (0.21-0.42)
DAA-only regimens	No SVR	1	1	1	1	1	1
	SVR	0.28 (0.22-0.35)	0.41 (0.32-0.51)	0.35 (0.27-0.44)	0.43 (0.34-0.54)	0.32 (0.25-0.41)	0.42 (0.33-0.53)

* Adjusted for regimen type, cirrhosis, decompensated cirrhosis, age, sex, race/ethnicity, body mass index, HBV co-infection, type 2 diabetes mellitus, ascites, varices, hepatocellular carcinoma, alcohol use disorders, substance use disorder, platelet count, serum bilirubin, serum creatinine, serum albumin, INR and blood hemoglobin levels. The laboratory tests were categorized into quartiles and modeled as dummy categorical variables.

±IPW Inverse probability weights based on propensity score estimates. Trimmed weights drop the largest and smallest 1% of propensity scores.

Supplementary Table 5. Association between SVR and the Risk of Developing Incident HE Accounting for the Competing Risk of Death

		Crude hazard ratio (95% CI)	Adjusted* hazard ratio (95%CI)	Crude sub-hazard± ratio (95% CI)	Adjusted* sub-hazard± ratio (95%CI)
IFN-ONLY regimens	No SVR	1	1	1	1
	SVR	0.23 (0.21-0.26)	0.26 (0.23-0.30)	0.24 (0.22-0.27)	0.29 (0.26-0.32)
DAA+IFN regimens	No SVR	1	1	1	1
	SVR	0.27 (0.20-0.37)	0.31 (0.22-0.43)	0.28 (0.21-0.38)	0.33 (0.24-0.46)
DAA-only regimens	No SVR	1	1	1	1
	SVR	0.28 (0.22-0.35)	0.41 (0.32-0.51)	0.29 (0.24-0.35)	0.43 (0.35-0.54)

* Adjusted for regimen type, cirrhosis, decompensated cirrhosis, age, sex, race/ethnicity, body mass index, HBV co-infection, type 2 diabetes mellitus, ascites, varices, hepatocellular carcinoma, alcohol use disorders, substance use disorder, platelet count, serum bilirubin, serum creatinine, serum albumin, INR and blood hemoglobin levels. The laboratory tests were categorized into quartiles and modeled as dummy categorical variables.
±With death as a competing risk.

Supplemental Table 6. Association between SVR and the Risk of Hospitalization with HE, <u>among patients without HE at baseline</u>.

		Number of patients (%)	Mean Follow-up (Years)	Number who were hospitalized for HE (%)	First HE hospitalization per 100 patient-years	Crude hazard ratio (95% CI)	Adjusted* hazard ratio (95%CI)
IFN-ONLY regimens	No SVR	34,006(66.7)	8.9	1,948(5.7)	0.65	1	1
	SVR	16,973(33.3)	10.7	292(1.7)	0.16	0.24(0.21-0.28)	0.28(0.24-0.33)
DAA+IFN regimens	No SVR	3,198(42.4)	3.3	43(1.3)	0.4	1	1
	SVR	4,345(57.6)	5.2	39(0.9)	0.17	0.39(0.26-0.61)	0.43(0.26-0.70)
DAA-only regimens	No SVR	3,336(10.2)	2.7	54(1.6)	0.6	1	1
	SVR	29,414(89.8)	3.2	298(1.0)	0.32	0.52(0.38-0.70)	0.59(0.43-0.81)

* Adjusted for regimen type, cirrhosis, decompensated cirrhosis, age, sex, race/ethnicity, body mass index, HBV co-infection, type 2 diabetes mellitus, ascites, varices, hepatocellular carcinoma, alcohol use disorders, substance use disorder, platelet count, serum bilirubin, serum creatinine, serum albumin, INR and blood hemoglobin levels. The laboratory tests were categorized into quartiles and modeled as dummy categorical variables.

Supplemental Table 7. Association between SVR and the <u>number of hospitalizations in the first three years after treatment start</u>, among patients without HE at baseline.

		Number of patients (%)	Mean number of hospitalizations for HE (SD)	Incident rate ratio of number of hospitalizations for HE	Adjusted* incident rate ratio of number of hospitalizations for HE
IFN-ONLY regimens	No SVR	34,006(66.7)	0.14(0.77)	1	1
	SVR	16,973(33.3)	0.03(0.32)	0.22(0.17-0.28)	0.25(0.21-0.31)
DAA+IFN regimens	No SVR	3,198(42.4)	0.03(0.29)	1	1
	SVR	4,345(57.6)	0.01(0.12)	0.34(0.21-0.55)	0.59(0.38-0.92)
DAA-only	No SVR	3,336(10.2)	0.02(0.15)	1	1

Supplementary Table 8. Propensity Matched Analysis of the Association between SVR and <u>Resolution of</u> Hepatic Encephalopathy

			Crude hazard ratio (95% CI)	Adjusted* hazard ratio (95%CI)	Crude hazard ratio with IPW± (95% CI)	Adjusted* hazard ratio with IPW± (95%CI)	Crude hazard ratio with trimmed IPW± (95% CI)	Adjusted* hazard ratio with trimmed IPW± (95%CI)
IFN-ONLY regimens	No SVR		1	1	1	1	1	1
	SVR		2.08 (1.62-2.68)	2.10 (1.57-2.82)	2.24 (1.70-2.97)	2.32 (1.76-3.07)	2.01 (1.50-2.68)	2.09 (1.55-2.81)
DAA+IFN regimens	No SVR		1	1	1	1	1	1
	SVR		1.88 (1.12-3.16)	1.39 (0.60-3.18)	1.86 (1.02-3.39)	1.34 (0.56-3.18)	2.09 (1.17-3.75)	1.39 (0.58-3.30)
DAA-only regimens	No SVR		1	1	1	1	1	1
	SVR		1.59 (1.21-2.09)	1.39 (1.03-1.87)	1.53 (1.13-2.07)	1.28 (0.95-1.72)	1.59 (1.17-2.15)	1.28 (0.95-1.74)

* Adjusted for regimen type, cirrhosis, decompensated cirrhosis, age, sex, race/ethnicity, body mass index, HBV co-infection, type 2 diabetes mellitus, ascites, varices, hepatocellular carcinoma, alcohol use disorders, substance use disorder, platelet count, serum bilirubin, serum creatinine, serum albumin, INR and blood hemoglobin levels. The laboratory tests were categorized into quartiles and modeled as dummy categorical variables.

±IPW Inverse probability weights based on propensity score estimates. Trimmed weights drop the largest and smallest 1% of propensity scores.

Supplementary Table 9. Competing Risks (Fine-Gray) Analysis of the Association between SVR and Resolution of Hepatic Encephalopathy

		Crude hazard ratio (95% CI)	Adjusted* hazard ratio (95%CI)	Crude sub-hazard± ratio (95% CI)	Adjusted* sub-hazard± ratio (95%CI)
IFN-ONLY regimens	No SVR	1	1	1	1
	SVR	2.08 (1.62-2.68)	2.10 (1.57-2.82)	2.32 (1.86-2.91)	2.26 (1.73-2.96)
DAA+IFN regimens	No SVR	1	1	1	1
	SVR	1.88 (1.12-3.16)	1.39 (0.60-3.18)	1.99 (1.21-3.28)	1.40 (0.63-3.15)
DAA-only regimens	No SVR	1	1	1	1
	SVR	1.59 (1.21-2.09)	1.39 (1.03-1.87)	1.75 (1.34-2.29)	1.51 (1.13-2.01)

* Adjusted for regimen type, cirrhosis, decompensated cirrhosis, age, sex, race/ethnicity, body mass index, HBV co-infection, type 2 diabetes mellitus, ascites, varices, hepatocellular carcinoma, alcohol use disorders, substance use disorder, platelet count, serum bilirubin, serum creatinine, serum albumin, INR and blood hemoglobin levels. The laboratory tests were categorized into quartiles and modeled as dummy categorical variables.

±With death as a competing risk.

Supplemental Table 10. Association between SVR and the Risk of Hospitalization with HE, <u>among patients who were on HE medications at baseline</u>

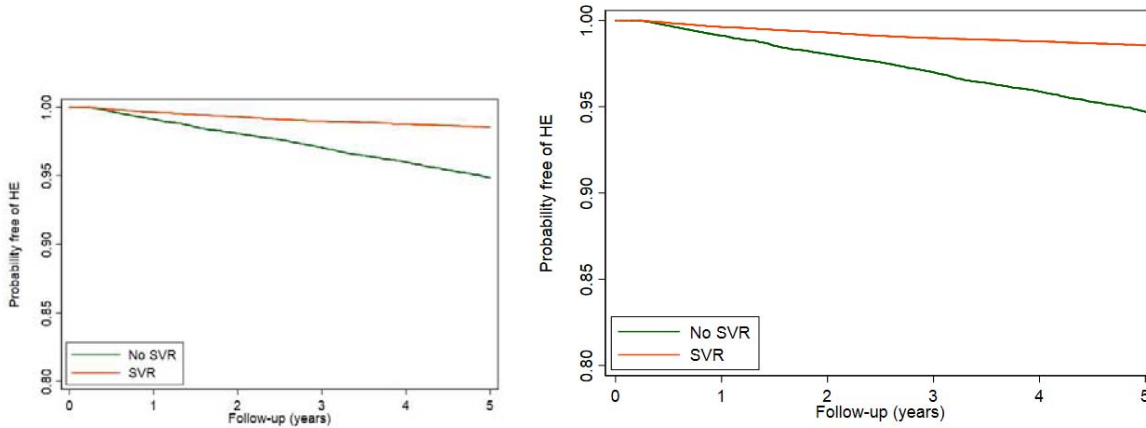|		Number of patients (%)	Mean Follow-up (Years)	Number who were hospitalized for HE (%)	First HE hospitalization per 100 patient-years	Crude hazard ratio (95% CI)	Adjusted* hazard ratio (95%CI)
IFN -ONLY regimens	No SVR	983(83.3)	5.9	239(24.3)	4.12	1	1
	SVR	197(16.7)	8.4	28(14.2)	1.69	0.44(0.28-0.69)	0.53(0.35-0.83)
DAA+IFN regimens	No SVR	167(59.9)	2.8	25(15.0)	5.37	1	1
	SVR	112(40.1)	4.4	10(8.9)	2.03	0.44(0.20-0.99)	0.52(0.15-1.83)
DAA-only regimens	No SVR	497(21.1)	2.1	58(11.7)	5.59	1	1
	SVR	1,861(78.9)	2.9	179(9.6)	3.35	0.67(0.49-0.91)	0.79(0.57-1.10)

* Adjusted for regimen type, cirrhosis, decompensated cirrhosis, age, sex, race/ethnicity, body mass index, HBV co-infection, type 2 diabetes mellitus, ascites, varices, hepatocellular carcinoma, alcohol use disorders, substance use disorder, platelet count, serum bilirubin, serum creatinine, serum albumin, INR and blood hemoglobin levels. The laboratory tests were categorized into quartiles and modeled as dummy categorical variables.

Supplemental Table 11. Association between SVR and <u>number of hospitalizations in the first three years after treatment start</u> for patients with treated HE at baseline

		Number of patients (%)	Mean number of hospitalizations for HE (SD)	Incident rate ratio of number of hospitalizations for HE	Adjusted* incident rate ratio of number of hospitalizations for HE
IFN -ONLY regimens	No SVR	983(83.3)	0.84(2.09)	1	1
	SVR	197(16.7)	0.31(1.17)	0.38(0.17-0.84)	0.28(0.19-0.41)
DAA+IFN regimens	No SVR	167(59.9)	0.29(0.79)	1	1
	SVR	112(40.1)	0.14(0.55)	0.49(0.21-1.12)	0.56(0.25-1.26)
DAA-only regimens	No SVR	497(21.1)	0.28(0.89)	1	1
	SVR	1,861(78.9)	0.19(0.67)	0.70(0.51-0.96)	0.80(0.60-1.07)

* Adjusted for regimen type, cirrhosis, decompensated cirrhosis, age, sex, race/ethnicity, body mass index, HBV co-infection, type 2 diabetes mellitus, ascites, varices, hepatocellular carcinoma, alcohol use disorders, substance use disorder, platelet count, serum bilirubin, serum creatinine, serum albumin, INR and blood hemoglobin levels. The laboratory tests were categorized into quartiles and modeled as dummy categorical variables
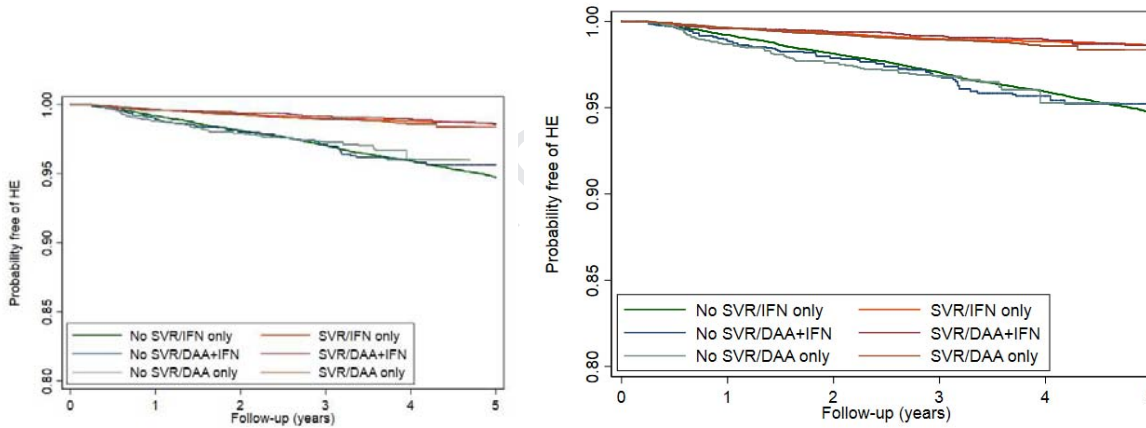
Supplementary Figure 1. Kaplan-Meier curves comparing the cumulative incidence of HE development in patients who achieved SVR versus those who did not, among all patients or clinically-relevant subgroups.

NOTE: Left plots use inverse probability weights (IPW) based on the propensity scores (PS). Plots on the right use trimmed (largest and smallest PS dropped) IPW
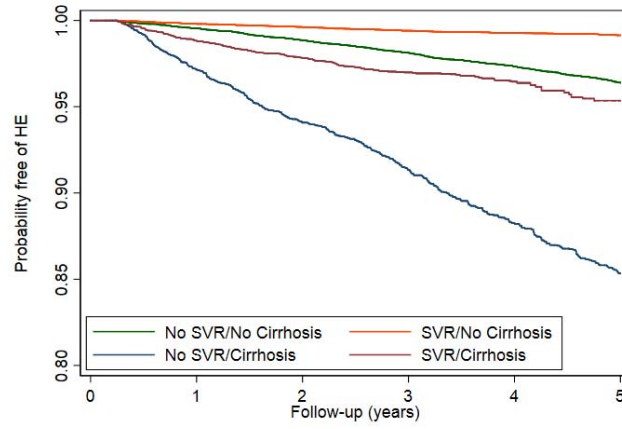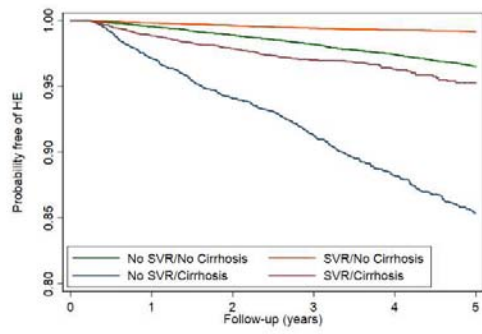
<u>**A. ALL PATIENTS**</u>

<u>**B. ACCORDING TO ANTIVIRALREGIMEN**</u>
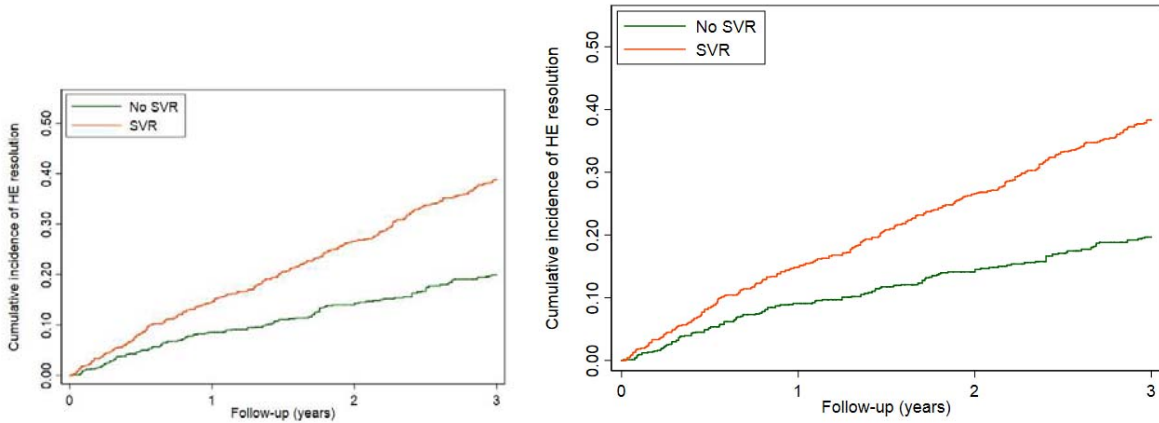

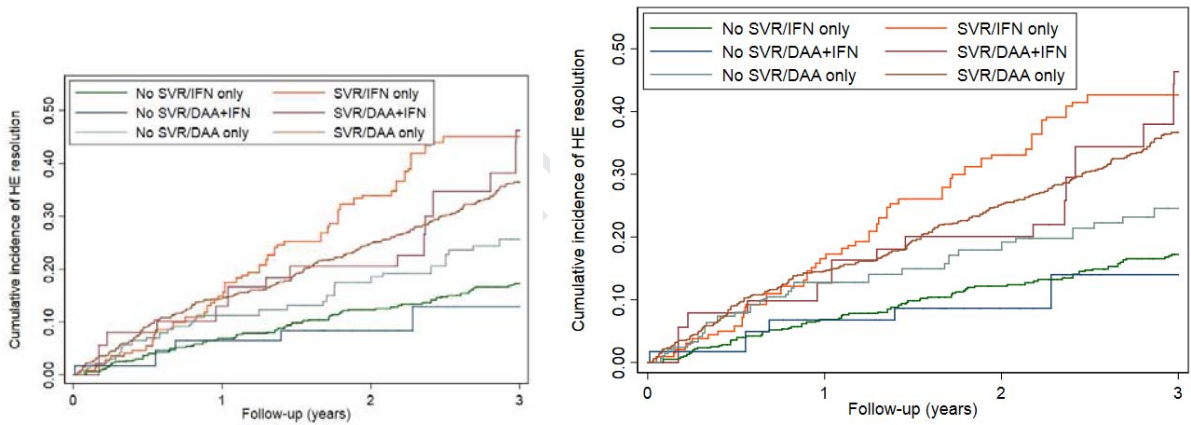<u>**C. ACCORDING TO PRESENCE/ABSENCE OF CIRRHOSIS**</u>

Supplementary Figure 2. Cumulative-probability curves comparing the resolution of HE in patients with SVR versus those without SVR among all patients or clinically-relevant subgroups.

NOTE: Left plots use inverse probability weights (IPW) based on the propensity scores (PS). Plots on the right use trimmed (largest and smallest PS dropped) IPW

A. ALL PATIENTS

B. BY ANTIVIRAL REGIMEN

C. BY MELD CATEGORY