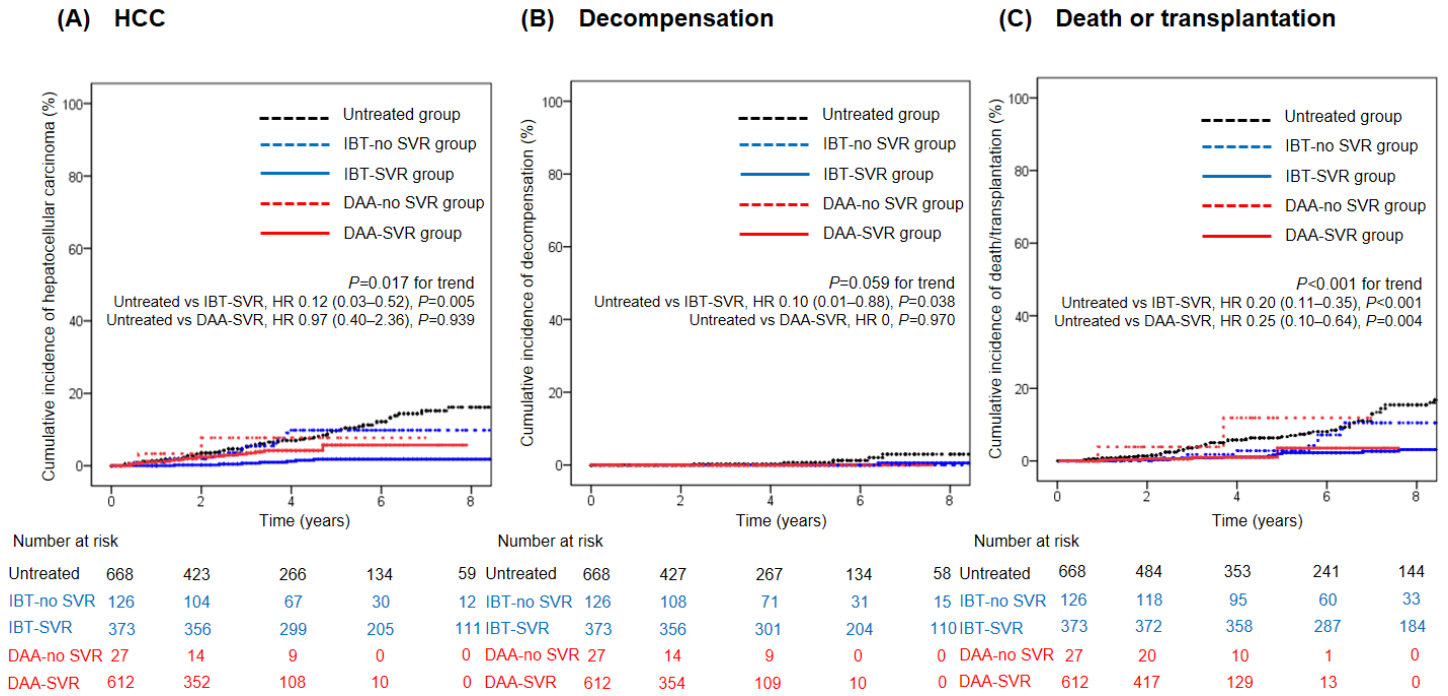


Supplementary Materials

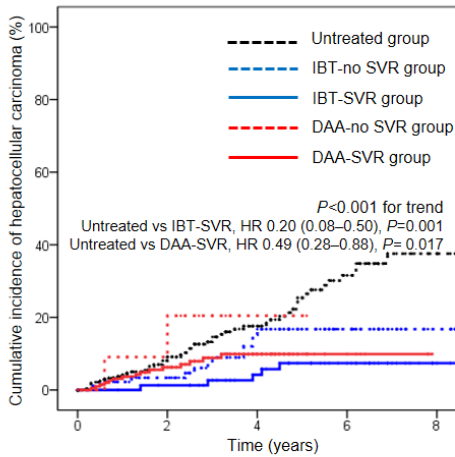
Gwang Hyeon Choi, et al.

Hepatocellular Carcinoma, Decompensation, and Mortality Incidences Based on Chronic Hepatitis C Treatment: A Prospective Cohort Study

Supplementary Figure

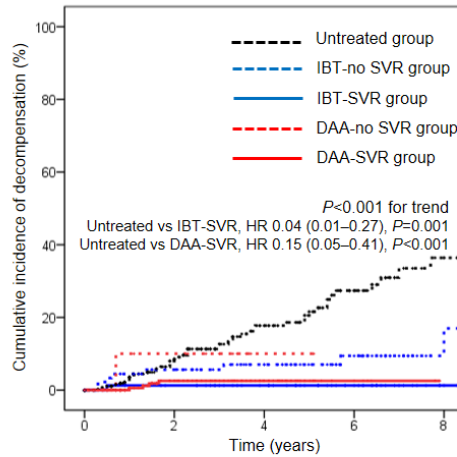


Supplementary Figure 1 Cumulative incidences of HCC, decompensation and death/transplantation in non-cirrhotic cohort. (A) Cumulative incidence of HCC in the untreated, IBT-no SVR, IBT-SVR, DAA-no SVR, and DAA-SVR groups. (B) Cumulative incidence of decompensation in the untreated, IBT-no SVR, IBT-SVR, DAA-no SVR, and DAA-SVR groups. (C) Cumulative incidence of death/liver transplantation in the untreated, IBT-no SVR, IBT-SVR, DAA-no SVR, and DAA-SVR groups. DAA, direct-acting antivirals; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IBT, interferon-based treatment; SVR, sustained virologic response

(A) HCC

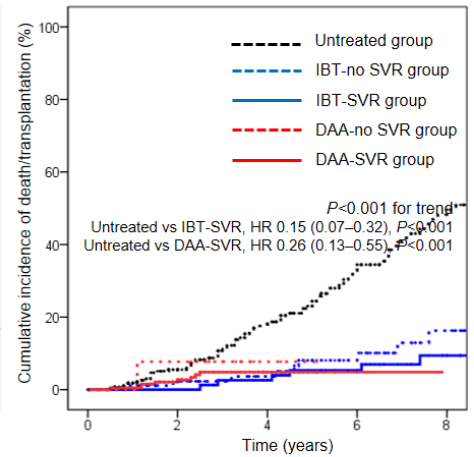
Number at risk

Untreated	296	173	98	46	14
IBT-no SVR	91	79	54	29	9
IBT-SVR	78	75	62	44	19
DAA-no SVR	13	8	1	0	0
DAA-SVR	205	126	51	7	0

(B) Decompensation

Number at risk

Untreated	296	173	104	52	21
IBT-no SVR	91	78	61	37	12
IBT-SVR	78	74	62	44	21
DAA-no SVR	13	8	1	0	0
DAA-SVR	205	130	54	7	0

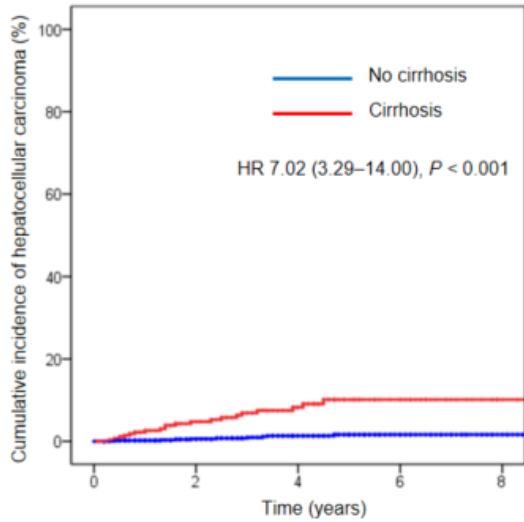
(C) Death or transplantation

Number at risk

Untreated	296	216	149	82	39
IBT-no SVR	91	84	68	45	25
IBT-SVR	78	78	73	62	34
DAA-no SVR	13	12	2	0	0
DAA-SVR	205	157	62	7	0

Supplementary Figure 2 Cumulative incidences of HCC, decompensation and death/transplantation in cirrhotic cohort. (A) Cumulative incidence of HCC in the untreated, IBT-no SVR, IBT-SVR, DAA-no SVR, and DAA-SVR groups. (B) Cumulative incidence of decompensation in the untreated, IBT-no SVR, IBT-SVR, DAA-no SVR, and DAA-SVR groups. (C) Cumulative incidence of death/liver transplantation in the untreated, IBT-no SVR, IBT-SVR, DAA-no SVR, and DAA-SVR groups. DAA, direct-acting antivirals; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IBT, interferon-based treatment; SVR, sustained virologic response

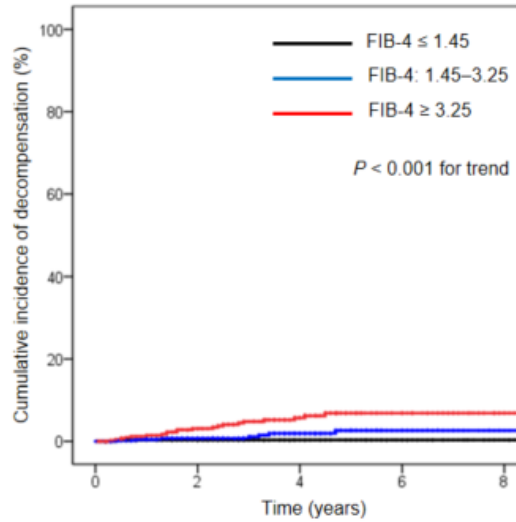
(A) Presence of cirrhosis



Number at risk

No cirrhosis	985	708	407	215	111
Cirrhosis	283	201	113	51	19

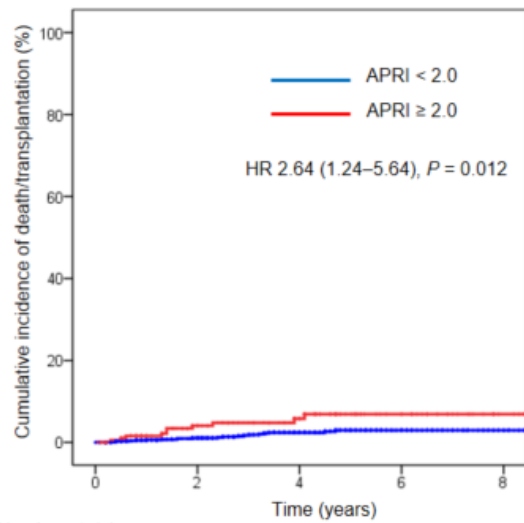
(B) FIB-4



Number at risk

≤ 1.45	312	247	151	93	52
1.45-3.25	481	334	181	83	38
≥ 3.25	439	320	186	88	40

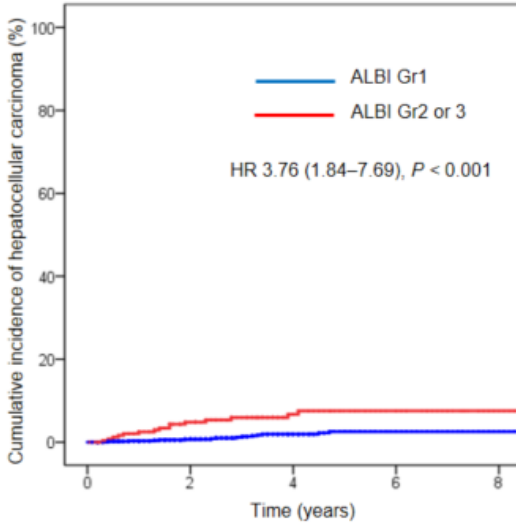
(C) APRI



Number at risk

< 2.0	1059	768	432	218	103
≥ 2.0	197	140	88	48	23

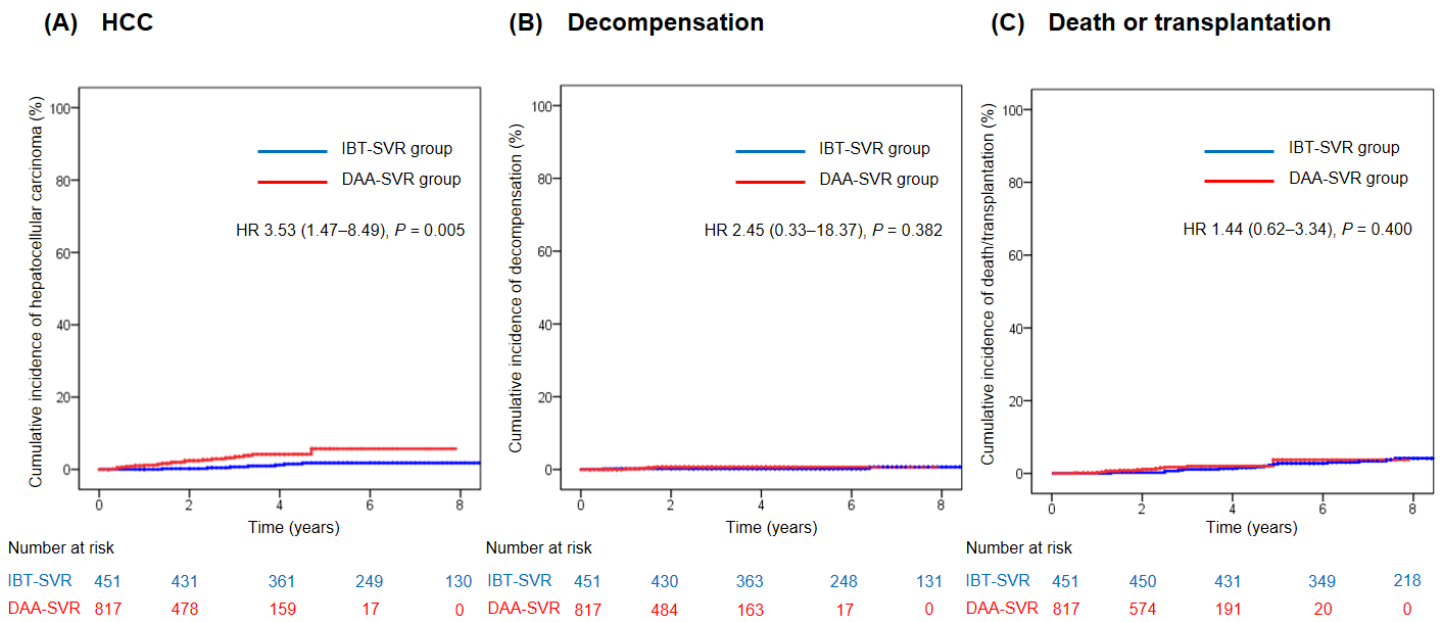
(D) ALBI



Number at risk

Gr1	1006	718	403	206	104
Gr 2 or 3	251	188	117	60	26

Supplementary Figure 3 Cumulative incidence of HCC according to the presence of cirrhosis and fibrosis score in the SVR cohort. (A) Cirrhosis. (B) FIB-4 index. (C) APRI score. (D) ALBI score. ALBI, albumin-bilirubin; APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4.



Supplementary Figure 4 Cumulative incidences of HCC, decompensation, and death/transplantation in the matched SVR cohort. (A) Cumulative incidence of HCC in the IBT-SVR and DAA-SVR groups. (B) Cumulative incidence of decompensation in the IBT-SVR and DAA-SVR groups. (C) Cumulative incidence of death/liver transplantation in the IBT-SVR and DAA-SVR groups. DAA, direct-acting antivirals; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IBT, interferon-based treatment; SVR, sustained virologic response.

Supplementary Table 1 Clinical characteristics at the time of treatment initiation and clinical outcomes among IBT and DAA groups according to SVR status

Variable	IBT group			DAA group		
	IBT-SVR group (n=451)	IBT-No-SVR group (n=217)	<i>P</i>	DAA-SVR group (n=817)	DAA-No-SVR group (n=40)	<i>P</i>
Age, year	51.0 ± 10.6	54.1±11.2	<0.001	59.1 ± 11.4	58.3 ± 10.2	0.629
Male sex	209 (46.3)	103 (47.5)	0.785	394 (48.2)	18 (45.0)	0.690
HCV RNA, x log ₁₀ IU/mL	5.72 (4.77-6.37)	6.13 (5.54-6.58)	<0.001	6.04 (5.26-6.52)	6.03 (5.45-6.58)	0.696
HCV genotype			<0.001			0.346
1	167 (37.0)	134 (61.8)		464 (56.8)	27 (67.5)	
2	278 (61.6)	72 (33.2)		342 (41.9)	13 (32.5)	
Others/missing	6 (1.3)	11 (5.1)		11 (1.3)	0 (0)	
Diagnosis status			<0.001			0.294
Chronic hepatitis	373 (82.7)	126 (58.1)		612 (74.9)	27 (67.5)	
Compensated cirrhosis	78 (17.3)	91 (41.9)		205 (25.1)	13 (32.5)	
FIB-4 index			0.002			0.154
≤ 1.45	156 (34.8)	47 (21.9)		156 (19.9)	8 (20.0)	
1.45–3.25	155 (34.6)	80 (37.2)		326 (41.6)	11 (27.5)	
≥ 3.25	137 (30.6)	88 (40.9)		302 (38.5)	21 (52.5)	
APRI score			0.009			0.518
< 2.0	383 (85.1)	167 (77.0)		676 (83.9)	32(80.0)	
≥ 2.0	67 (14.9)	50 (23.0)		130 (16.1)	8 (20.0)	
ALBI score			0.034			0.130
≤ -2.60 (Grade 1)	360 (80.0)	157 (72.7)		639 (79.9)	35 (89.7)	
	90 (20.0)	59 (27.3)		161 (20.1)	4 (10.3)	

> -2.60 (Grade 2 or 3)						
Ever smoker	228 (50.8)	93 (43.7)	0.087	365 (44.9)	15 (37.5)	0.355
Alcohol intake			0.040			0.647
None	171 (38.0)	104 (48.6)		400 (49.0)	19 (47.5)	
Social	245 (54.4)	96 (44.9)		216 (26.4)	13 (32.5)	
Significant*	34 (7.6)	14 (6.5)		201 (24.6)	8 (20.0)	
Fatty liver disease on imaging study	77 (22.8), n=337	22 (15.6), n=141	0.075	131 (22.4), n=586	9 (32.1), n=28	0.228
Anti-HBc IgG positivity	25 (8.6), n=290	14 (8.7), n=161	0.978	62 (10.5), n=592	2 (6.7), n=30	0.503
BMI, kg/m ²	23.7 ± 3.0	24.1 ± 2.9	0.176	23.9 ± 3.1	23.6 ± 3.4	0.698
Diabetes mellitus	61 (13.6)	29 (13.4)	0.954	122 (14.9)	6 (15.0)	0.991
Hypertension	80 (17.7)	53 (24.4)	0.043	236 (28.9)	7 (17.5)	0.119
Cardiovascular disease	3 (0.7)	0 (0)	0.555	24 (2.9)	1 (2.5)	0.872
Cerebrovascular disease	2 (0.4)	3 (1.4)	0.336	19 (2.3)	1 (2.5)	0.943
Laboratory study						
WBC, /mm ³	4990 (3900-6100)	5010 (3770-6170)	0.876	5400 (4400-6630)	5680 (4240-5560)	0.446
Hemoglobin, g/dL	13.6 (12.6-14.9)	13.6 (12.5-14.7)	0.474	13.8 (12.8-14.8)	13.6 (12.6-14.8)	0.131
Platelet, ×1,000/mm ³	177 (136-220)	146 (108-187)	0.509	173 (130-216)	143 (121-201)	0.732
Albumin, g/dL	4.2 (4.0-4.5)	4.1 (3.9-4.4)	0.361	4.2 (4.0-4.4)	4.2 (4.1-4.4)	0.928
Total bilirubin, mg/dL	0.7 (0.6-1.0)	0.8 (0.6-1.1)	0.878	0.7 (0.6-1.0)	0.7 (0.6-1.2)	0.402
ALP, IU/L	80 (63-113)	85 (64-119)	0.475	122 (78-250)	100 (73-232)	0.417
AST, IU/L	50 (30-86)	51 (34-90)	0.362	46 (30-76)	57 (33-88)	0.439
ALT, IU/L	54 (29-105)	52 (32-104)	0.004	36 (22-70)	33 (21-75)	0.896
	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.050	0.8 (0.7-1.0)	0.8 (0.7-0.9)	0.210
						0.692

Creatinine, mg/dL	1.03 (0.98- 1.08)	1.05 (1.00- 1.12)		1.03 (0.97- 1.09)	1.04 (1.00- 1.11)	
PT, INR	3.3 (2.3-6.3)	5.9 (2.7-11.7)		3.8 (2.3-6.5)	5.3 (2.7-8.6)	
AFP, ng/dL						
Follow-up duration, year	7.8 (6.1-9.6)	5.7 (3.8-8.1)	<0.0 01	2.6 (1.7-3.8)	3.3 (2.3-4.2)	0.155

* Significant alcohol intake is defined as weekly ≥ 210 g for men and ≥ 140 g for women.

Data were presented as mean \pm standard deviation or median (interquartile range).

AFP, alpha-feto protein; ALBI, albumin-bilirubin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index; AST, aspartate aminotransferase; BMI, body mass index; DAA, direct acting antivirals; FIB-4, fibrosis-4; HCV, hepatitis C virus; IBT; interferon-based therapy; PT, prothrombin time; WBC, white blood cell.

Supplementary Table 2 Annual incidence rates of hepatocellular carcinoma, decompensation and death/transplantation according to treatment response in the SVR cohort.

	Group	PY	No. of events	No./100 PY (95% CI)	HR (95% CI)	P	
Treated cohort	Hepatocellular carcinoma						
	IBT group	No SVR	988.8	16	1.62 (1.00-2.63)	Reference	-
		SVR	2,900.1	7	0.24 (0.12-0.51)	0.17 (0.07-0.41)	<0.001
	DAA group	No SVR	94.8	2	2.11 (0.54-8.31)	Reference	-
		SVR	2,063.2	23	1.11 (0.74-1.67)	0.52 (0.12-2.23)	0.381
	Decompensation						
	IBT group	No SVR	1051.6	8	0.76 (0.38-1.52)	Reference	-
		SVR	2,898.4	2	0.04 (0.07-0.27)	0.09 (0.02-0.44)	0.003
	DAA group	No SVR	96.1	1	1.04 (0.15-7.31)	Reference	-
		SVR	2,083.6	4	0.19 (0.07-0.51)	0.16 (0.20-1.40)	0.097
	Death or transplantation						
	IBT group	No SVR	1,311.6	21	1.60 (1.05-2.45)	Reference	-
		SVR	3,538.5	21	0.59 (0.39-0.91)	0.32 (0.17-0.59)	<0.001
	DAA group	No SVR	129.2	3	2.32 (0.76-7.10)	Reference	-
SVR		2,338.0	13	0.56 (0.32-0.96)	0.23 (0.07-0.82)	0.023	
No cirrhosis	Hepatocellular carcinoma						

	IBT group	No SVR	566.2	4	0.71 (0.27-1.88)	Reference	-	
		SVR	2,405.6	2	0.08 (0.02-0.33)	0.14 (0.03-0.76)	0.023	
	DAA group	No SVR	66.2	0	0	Reference	-	
		SVR	1,503.2	8	0.53 (0.27-1.06)	-	-	
	Decompensation							
	IBT group	No SVR	592.0	0	0	Reference	-	
		SVR	2,400.3	1	0.04 (0.01-0.30)	-	-	
	DAA group	No SVR	66.2	0	0	Reference	-	
		SVR	1,507.2	0	0	-	-	
	Death or transplantation							
	IBT group	No SVR	765.5	9	1.18 (0.61-2.25)	Reference	-	
		SVR	2,946.8	13	0.44 (0.26-0.76)	0.32 (0.14-0.76)	0.010	
	DAA group	No SVR	88.4	2	2.26 (0.57-8.90)	Reference	-	
		SVR	1,696.2	5	0.29 (0.12-0.71)	0.12 (0.02-0.63)	0.012	
Cirrhosis	Hepatocellular carcinoma							
	IBT group	No SVR	422.6	12	2.84 (1.63-4.96)	Reference	-	
		SVR	494.5	5	0.24 (0.12-0.51)	0.39 (0.14-1.12)	0.080	
	DAA group	No SVR	28.6	2	6.99 (1.84-26.62)	Reference	-	
		SVR	560.0	15	2.68 (1.63-4.41)	0.42 (0.10-1.84)	0.251	
	Decompensation							
	IBT group	No SVR	459.6	8	1.74 (0.88-3.46)	Reference	-	

		SVR	498.1	1	0.20 (0.03–1.42)	0.12 (0.02–0.99)	0.048
	DAA group	No SVR	29.9	1	3.34 (0.49–22.97)	Reference	–
		SVR	576.4	4	0.69 (0.26–1.84)	0.21 (0.02–1.89)	0.164
Death or transplantation							
	IBT group	No SVR	546.1	12	2.20 (1.26–3.85)	Reference	–
		SVR	591.7	8	1.35 (0.68–2.69)	0.52 (0.21–1.30)	0.162
	DAA group	No SVR	40.8	1	2.45 (0.35–16.98)	Reference	–
		SVR	641.8	8	1.25 (0.63–2.48)	0.57 (0.07–4.60)	0.601

CI, confidence interval; DAA, direct acting antivirals; HR, hazard ratio; IBT, interferon-based therapy;

PY, person-year, SVR, sustained virologic response

Cox proportional hazards model was used to determine hazards ratios and P values.