

Association Between Sustained Virological Response and Adverse Liver-Related Events in Patients With Decompensated Hepatitis C Virus Cirrhosis



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Association Between Sustained Virological Response and Adverse Liver-Related Events in Patients With Decompensated HCV Cirrhosis

Study population



914 patients with decompensated HCV cirrhosis treated with direct-acting antivirals

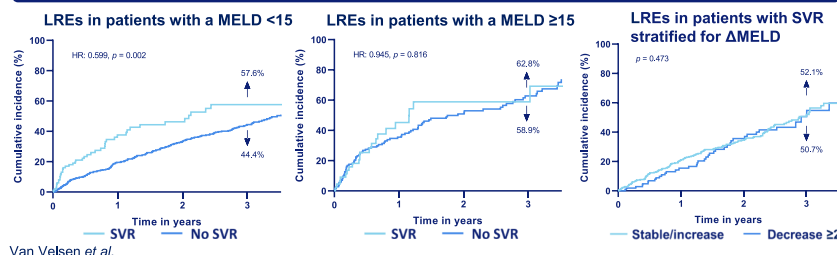


Association between sustained virological response (SVR) and liver-related events (LREs)

Key findings

- SVR reduces the risk of LREs in patients with a pretreatment MELD score <15
- No clinical benefit was observed in patients with higher pretreatment MELD scores, despite an SVR-associated MELD decrease

Results



Clinical Gastroenterology and Hepatology

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Abbreviations used in this paper: aHR, adjusted hazard ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUD, alcohol use disorder; BMI, body mass index; CI, confidence interval; CTP, Child-Turcotte-Pugh; DAA, direct-acting antiviral; DM, diabetes mellitus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; HR, hazard ratio; IFN, interferon; INR, international normalized ratio; IQR, interquartile range; LRE, liver-related event; LT, liver transplantation; MELD, Model for End-stage Liver Disease; PI, protease

inhibitor; SBP, spontaneous bacterial peritonitis; SVR, sustained viral response; VB, variceal bleed.



Most current article

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- BACKGROUND & AIMS:** Sustained virological response (SVR) improves prognosis in patients with chronic hepatitis C virus (HCV) with compensated cirrhosis, but whether a similar benefit can be obtained in decompensated patients is controversial. We studied the association between SVR and liver-related events (LREs) in patients with decompensated HCV cirrhosis.
- METHODS:** We included patients with decompensated HCV cirrhosis (Child-Turcotte-Pugh [CTP] ≥ 7 and/or history of decompensation) treated with direct-acting antivirals. The association between SVR and LREs, and between SVR-related change in Model for End-stage Liver Disease (MELD) score and LREs were assessed.
- RESULTS:** In total, 914 patients were included, with a median age of 54.7 years; 45% had alcohol use disorder, 87% CTP-B, and the median MELD score was 12.1. SVR was achieved in 834 patients (91.2%), with a median follow-up of 28 months. The 3-year cumulative incidence of LREs was 47.5% in patients with SVR compared with 58.6% in those without ($P < .001$). Findings were consistent in multivariable analysis (adjusted hazard ratio [aHR], 0.692; $P = .011$). SVR was associated with a reduced risk of LREs in patients with a pretreatment MELD < 15 (44.4% vs 57.6%; aHR, 0.601; $P = .004$), but not among patients with MELD ≥ 15 (62.8% vs 58.9%; aHR, 0.936; $P = .801$). Among patients with SVR, a ≥ 2 -point decrease in MELD was observed in 23.4% and was not associated with a reduced risk of LREs (52.1% vs 50.7%; $P = .473$). Findings were consistent in multivariable analysis (aHR, 0.730; $P = .122$), and in patients with a pretreatment MELD score ≥ 15 .
- CONCLUSIONS:** SVR was associated with a reduced risk of LREs in patients with decompensated HCV cirrhosis with a MELD score < 15 , whereas no clinical benefit was observed in those with higher MELD scores despite an SVR-associated MELD decrease.

Keywords: Decompensated Cirrhosis; Direct-Acting Antivirals; HCV; Liver-Related Events; MELD Score.

Chronic hepatitis C virus (HCV) infection remains a major cause of end-stage liver disease and hepatocellular carcinoma (HCC).¹ Currently available direct-acting antivirals (DAAs) have revolutionized the treatment of chronic HCV due to their excellent tolerability and high efficacy in patients with compensated liver disease.²⁻⁴ Despite somewhat attenuated rates of sustained virological response (SVR) among patients with decompensated cirrhosis, SVR can still be achieved in the vast majority of these patients.^{2,5-8} In several cohort studies, attainment of SVR virtually eliminated the risk of liver-related complications in patients without cirrhosis and markedly reduced the risk of these adverse liver-related outcomes among patients with compensated cirrhosis.^{5,9}

Whether achievement of SVR is associated with clinical benefits in patients with decompensated HCV cirrhosis remains controversial. Prior studies in this population indicated that SVR can be achieved in more than 80% of patients, and that SVR was associated with improvements in liver function tests, including a decrease in Model for End-stage Liver Disease (MELD) score.^{2,10,11} A recent study from India suggested that SVR was associated with recompensation in a subset of patients, whereas a multicenter study from Europe and Northern America did not observe a reduced risk of adverse liver-related events (LREs) in patients with SVR, despite improvements in MELD score.^{5,12}

These findings suggest that, although SVR could be beneficial in a subset of patients with decompensated HCV

cirrhosis, it may sometimes also have a potential unwanted negative effect, as it might not reduce the risk of adverse LREs, whereas an SVR-related decrease in MELD score would reduce the likelihood of receiving a liver allograft in patients eligible for liver transplantation (LT), because most organ allocation systems include MELD (or a comparable score) as part of the organ allocation process.

Therefore, the aim of this study was to study the association between SVR and adverse LREs in patients with HCV-related decompensated cirrhosis.

Patients and Methods

Study Population and Design

We conducted an international multicenter retrospective cohort study enrolling all consecutive patients with chronic HCV infection and decompensated cirrhosis (defined as having a diagnosis of cirrhosis with either a prior decompensation event and/or a Child-Turcotte-Pugh [CTP] score of ≥ 7) treated with an interferon (IFN)-free DAA regimen between 2014 and 2018. Patients were enrolled at 17 sites across Europe and North America. Patients who had a prior LT or a history of HCC were excluded.

Data Collection

Data were provided by the participating sites using a standardized digital case record form. Data were

collected on demographics (age, sex, ethnicity, body mass index [BMI]), comorbidities (diabetes mellitus [DM], a history of or current severe alcohol use disorder [AUD] defined as >50 g of alcohol intake per day), biochemistry, severity of liver disease (CTP score, MELD score), virology (HCV genotype, achievement of SVR), and LREs.

Definitions

SVR was defined as an undetectable HCV RNA at least 12 weeks after the end of treatment. HCV RNA was assessed using the local assay of each participating site. The CTP score at baseline was calculated using the prothrombin time, serum albumin, bilirubin, and clinical assessment by the local treating physician. The MELD score was calculated for the baseline visit and follow-up visits using serum bilirubin, creatinine, and international normalized ratio (INR). The change in MELD score from pretreatment to SVR (Δ MELD) was calculated by subtracting the MELD score at baseline from the MELD score at SVR assessment.

Assessment of Clinical Outcomes

The primary outcome of interest was the occurrence of LREs defined as the first of a composite of: (1) further decompensation (newly developed hepatic encephalopathy [HE] and/or a spontaneous bacterial peritonitis [SBP] and/or a first or recurrent variceal bleed [VB]); (2) development of HCC; (3) LT; or (4) death (all-cause mortality). Occurrence or worsening of ascites was not analyzed as an event in the primary study endpoint due to insufficient data on the severity and/or worsening of ascites.

Secondary outcomes were the cumulative incidence of HCC (censored for LT and death), a composite endpoint of HCC, LT, and death, and a composite endpoint of further decompensation, LT, and death.

Statistical Analysis

Normally distributed data were presented as mean and standard deviation; non-normally distributed data were presented as median with interquartile range (IQR). The χ^2 test, Student's *t*-test, and Mann-Whitney *U* test were used where appropriate.

Baseline was defined as the date when the first DAA regimen was started. Patients were excluded from analyses if there was insufficient data to assess SVR.

The association between SVR and clinical outcomes was visualized using survival curves based on the Kaplan-Meier method. Because patients without SVR could be retreated, we applied a clock-reset approach, as previously described.⁵ For this analysis, all patients were considered non-SVR at baseline, and those patients who achieved SVR were censored in the non-SVR group

What You Need to Know

Background

Sustained virological response (SVR) improves prognosis in chronic hepatitis C virus (HCV)-infected patients with compensated cirrhosis, but whether similar benefit can be obtained in decompensated patients is controversial.

Findings

SVR was associated with a reduced risk of adverse liver-related events among patients with a pretreatment Model for End-stage Liver Disease (MELD) score <15, whereas no risk reduction was observed in patients with a pretreatment MELD score $\geq$ 15, despite significant improvements in MELD score after successful direct-acting antiviral (DAA) therapy.

Implications for patient care

Our findings support DAA therapy in patients with decompensated HCV cirrhosis with a MELD score <15 but also suggest that DAA therapy could potentially have an unwanted negative effect in those with higher MELD scores, because these patients remain at risk for adverse liver-related events despite SVR, while they may be deprioritized for liver transplantation due to an SVR-related decrease in MELD score.

from the start of treatment that resulted in SVR, with subsequent follow-up time transferred to the SVR group. Comparisons across groups were performed using a Cox proportional hazards model with SVR as a time-varying covariate. We subsequently performed similar analyses after stratification by baseline MELD score (< or $\geq$ 15). A cutoff score of MELD 15 was used, as this cutoff score is often utilized to prioritize patients with end-stage liver disease for an LT.^{13,14}

To confirm the robustness of our findings, an additional sensitivity analysis was performed with baseline date set at SVR12 (12 weeks after cessation of therapy) of the first treatment regimen. For this analysis, we utilized the Kaplan-Meier method with the log-rank test. Next, we performed a sensitivity analysis in which we excluded all patients with HCC diagnosed in the first 3 months after the start of DAAs to exclude prevalent HCC prior to DAA therapy.

Finally, we assessed the association between Δ MELD and LREs in the overall population and in the group with a MELD score $\geq$ 15 at baseline. For this analysis, only patients who achieved SVR were included. The Δ MELD scores were divided into 2 groups: (1) a stable or increased MELD score (MELD score decrease <2 points or any increase); and (2) a decrease of $\geq$ 2 points of MELD score.⁵ The association between Δ MELD score with clinical outcomes was assessed using the Kaplan-

Meier method with the log-rank test and multivariable Cox regression.

A *P* value of $<.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics Windows version 28.0.1.0 (SPSS, Inc).

Ethics

This study was conducted according to the principles of Good Clinical Practice and the declaration of Helsinki. Patient data was obtained with permission from the local ethical committees.

Results

Patient and Cohort Characteristics

In total, data were collected on 1122 patients. After excluding noneligible patients with a CTP score ≤ 6 ($n = 52$), prior LT ($n = 32$), prior HCC ($n = 62$), and/or missing data on SVR ($n = 62$), 914 patients were included for analysis (Supplementary Figure 1). The majority of the population was male ($n = 620$; 67.9%), and the median age was 54.7 years (IQR, 48.8–60.8 years) (Table 1). DM was present in 219 patients (24.1%), and 397 (45.0%) had a current or past AUD. A total of 795 patients (87.0%) were CTP B, and 119 (13.0%) were CTP C. The median MELD score at baseline was 12.1 (IQR, 10.0–14.5), and 655 (78.5%) patients had a MELD score <15 . The treatment regimens used are specified in Table 1.

Compared with patients with a MELD score <15 , patients with a MELD ≥ 15 were generally younger, more frequently male, had a lower platelet count and albumin level, and less often achieved SVR after the first DAA therapy (Supplementary Table 1). DM was more common in patients with a MELD score <15 , whereas the presence of AUD was not different between patients with a MELD score <15 vs ≥ 15 .

Patients were followed for a median of 28 months (IQR, 13–39 months). A total of 616 events were recorded in 425 patients (46.5%) (71 HE, 31 SBP, 31 VB, 138 HCC, 156 LT, and 189 deaths).

Association Between SVR and LREs in the Overall Population

A total of 834 patients (91.2%) achieved SVR during follow-up; 757 after the first therapy, 68 after the second therapy, and 9 after a third treatment course. In the overall population, the 3-year cumulative incidence of LREs was significantly lower in patients who achieved SVR (47.5%; 95% confidence interval [CI], 43.4%–51.6%) compared with those who did not achieve SVR (58.6%; 95% CI, 48.4%–68.8%; hazard ratio [HR], 0.628; 95% CI, 0.486–0.811; $P < .001$) (Figure 1A). Findings were consistent in multivariable Cox regression

analysis; achievement of SVR was independently associated with a reduced hazard of LREs (adjusted hazard ratio [aHR], 0.692; 95% CI, 0.52–0.92; $P = .011$) (Table 2). Besides failure to achieve SVR, AUD, lower albumin, and higher MELD score at baseline were associated with an increased hazard of LREs.

Similarly, achievement of SVR was associated with a reduced risk of a composite of further decompensation, LT, and death in the overall population (57.6%; 95% CI, 46.8%–63.4% vs 41.6%; 95% CI, 37.5%–45.7%; HR, 0.646; 95% CI, 0.49–0.85; $P = .001$) (Figure 1B).

Achievement of SVR was also associated with a reduced risk of a composite of HCC, LT, and death (42.5%; 95% CI, 38.4%–46.6% vs 48.0%; 95% CI, 37.6–58.4; HR, 0.682; 95% CI, 0.51–0.90; $P = .008$) (Figure 1C).

Finally, the 3-year cumulative incidence of HCC was significantly lower in patients who achieved SVR (17.9%; 95% CI, 14.4%–21.4%) vs those who did not achieve SVR (29.7%; 95% CI, 19.1%–40.3%; HR, 0.497; 95% CI, 0.33–0.76; $P = .001$) (Figure 1D).

Findings were consistent in sensitivity analysis only considering the first treatment regimen (Supplementary Figure 2), and when excluding patients with HCC diagnosed in the first 3 months after start of DAA therapy (Supplementary Figure 3).

Association Between SVR and LREs Stratified by Baseline MELD Score

Among patients with a MELD score <15 at baseline, the 3-year cumulative incidence of LREs was significantly lower in patients who achieved SVR (44.4%; 95% CI, 39.5%–49.3%) compared with those who did not (57.6%; 95% CI, 44.9%–70.3%; HR, 0.599; 95% CI, 0.433–0.828; $P = .002$) (Figure 2A). Findings were consistent in multivariable Cox regression analysis, in which SVR was independently associated with a reduced hazard of LREs (aHR, 0.601; 95% CI, 0.43–0.85; $P = .004$) (Table 3). Besides failure to achieve SVR, higher age, AUD, diabetes mellitus, lower albumin, and higher MELD score at baseline were associated with an increased hazard of LREs.

Among patients with a MELD score ≥ 15 at baseline, SVR was not associated with a reduced incidence of LRE (3-year incidence: 62.8% [95% CI, 53.4%–72.2%] vs 58.9% [95% CI, 40.5%–77.3%]; HR, 0.945 [95% CI, 0.590–1.515]; $P = .816$) (Figure 2B). Findings were consistent in multivariable Cox regression analysis, in which achievement of SVR was not associated with a reduced hazard of LREs (aHR, 0.936; 95% CI, 0.56–1.56; $P = .801$) (Table 3).

Findings were consistent in sensitivity analyses only considering the first treatment regimen (Supplementary Figure 4), when considering a composite of further decompensation, LT, and death (Supplementary Figure 5), and for HCC (Supplementary Figure 6).

Table 1. Patient Characteristics at Baseline

Characteristics	Overall (N = 914)
Age, y	54.7 (48.8–60.8)
Male sex	620 (67.9)
Ethnicity	
Caucasian	723 (84.7)
Black	23 (2.7)
Asian	85 (10.0)
Other	23 (2.7)
Genotype	
1	381 (41.7)
2	26 (2.8)
3	257 (28.1)
Other	36 (3.9)
Unknown	214 (23.4)
BMI, kg/m ²	26.8 (23.9–30.8)
Normal weight	270 (32.4)
Overweight	283 (33.9)
Obese	281 (33.7)
DM	219 (24.1)
AUD	397 (45.0)
Platelets, × 10 ⁹ /L	76.0 (55.0–103.0)
ALT, U/L	52.0 (35.0–80.0)
AST, U/L	80.0 (55.0–116.0)
Albumin, g/L	32.0 (27.0–35.0)
Total bilirubin, mg/dL	1.8 (1.1–2.6)
INR	1.3 (1.2–1.5)
Creatinine, μmol/L	67.0 (58.0–82.0)
Prior decompensation	739 (80.9)
Treatment regimen	
Sofosbuvir	97 (10.6)
Sofosbuvir/ledipasvir	553 (60.5)
Sofosbuvir/velpatasvir	32 (3.5)
Sofosbuvir/simeprevir	47 (5.1)
Sofosbuvir/daclatasvir	176 (19.3)
Simeprevir/daclatasvir	1 (0.1)
Glecaprevir/pibrentasvir	6 (0.7)
Unknown	2 (0.2)
CTP	
B	795 (87.0)
C	119 (13.0)
MELD score	12.1 (10.0–14.5)
MELD <15	655 (78.5)

NOTE. Data are presented as median (interquartile range) or number (%).

NOTE. Prior decompensation was defined as a history of hepatic encephalopathy, spontaneous bacterial peritonitis, variceal bleed, and/or ascites.

NOTE. Overweight was defined by a BMI of ≥25 and <30 kg/m² in patients of non-Asian descent and ≥23 and <25 kg/m² in patients of Asian descent. Obesity was defined by a BMI of ≥30 kg/m² in patients of non-Asian descent and ≥25 kg/m² in patients of Asian descent.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUD, alcohol use disorder; BMI, body mass index; CI, confidence interval; CTP, Child-Turcotte-Pugh; DM, diabetes mellitus; INR, international normalized ratio; MELD, Model for End-stage Liver Disease.

Additionally, consistent findings were found when excluding patients with HCC diagnosed in the first 3 months after the start of DAA therapy ([Supplementary Figure 7](#)).

Association Between an SVR-Related Decrease in MELD and LREs

In total, 834 patients (91.2%) achieved SVR during the follow-up period, of which 98 patients (11.8%) were excluded from this analysis due to development of HCC or an LT prior to achieving SVR. The ΔMELD at 12 weeks after successful DAA therapy was available in 509 patients (69.2%). In this population, the median MELD score at start of therapy in which SVR was achieved was 11.7 (IQR, 9.8–14.1), and the median MELD score after achievement of SVR was 11.0 (IQR, 9.1–13.2). The median ΔMELD was −0.35 (IQR, −1.8 to 0.7); 119 patients (23.4%) had a MELD score decrease of ≥2 points, whereas 390 (76.6%) had a stable or increased MELD score. In patients with a MELD score ≥15 at the start of therapy, the median ΔMELD score was −1.7 (IQR, −4.0 to 0.3), with 40 patients (48.4%) achieving a decrease of ≥2 points.

Achievement of a decrease in MELD score of ≥2 points was not associated with superior outcomes; the cumulative incidence of LREs at 3 years was 50.7% (95% CI, 37.0%–64.4%) for those with a MELD decrease ≥2 vs 52.1% (95% CI, 44.7%–59.5%) in those with a stable or increased MELD ($P = .473$) ([Figure 3](#)). Findings were consistent in multivariable Cox regression analysis adjusted for baseline MELD, age, sex, AUD, overweight, presence of DM, and albumin level at baseline albumin: the aHR for change in MELD score was 0.730 (95% CI, 0.49–1.09; $P = .122$). Findings were consistent in patients with a baseline MELD ≥15.

Findings were consistent when a composite endpoint of HCC, LT, or death, and a composite of further decompensation, LT, or death was assessed ([Supplementary Figure 8](#)).

Discussion

This large international multicenter cohort study assessed the clinical outcomes after DAA therapy among 914 patients with decompensated cirrhosis due to chronic HCV infection. In the current study, SVR was associated with a reduced risk of adverse LREs among patients with a pretreatment MELD score <15. In contrast, no benefit of SVR could be demonstrated for patients with MELD scores ≥15, despite significant improvements in MELD score in these patients after SVR. These findings support treatment of patients with decompensated HCV-related cirrhosis with DAAs if the MELD score is <15 but also suggest that DAA therapy could potentially have an unwanted negative effect in

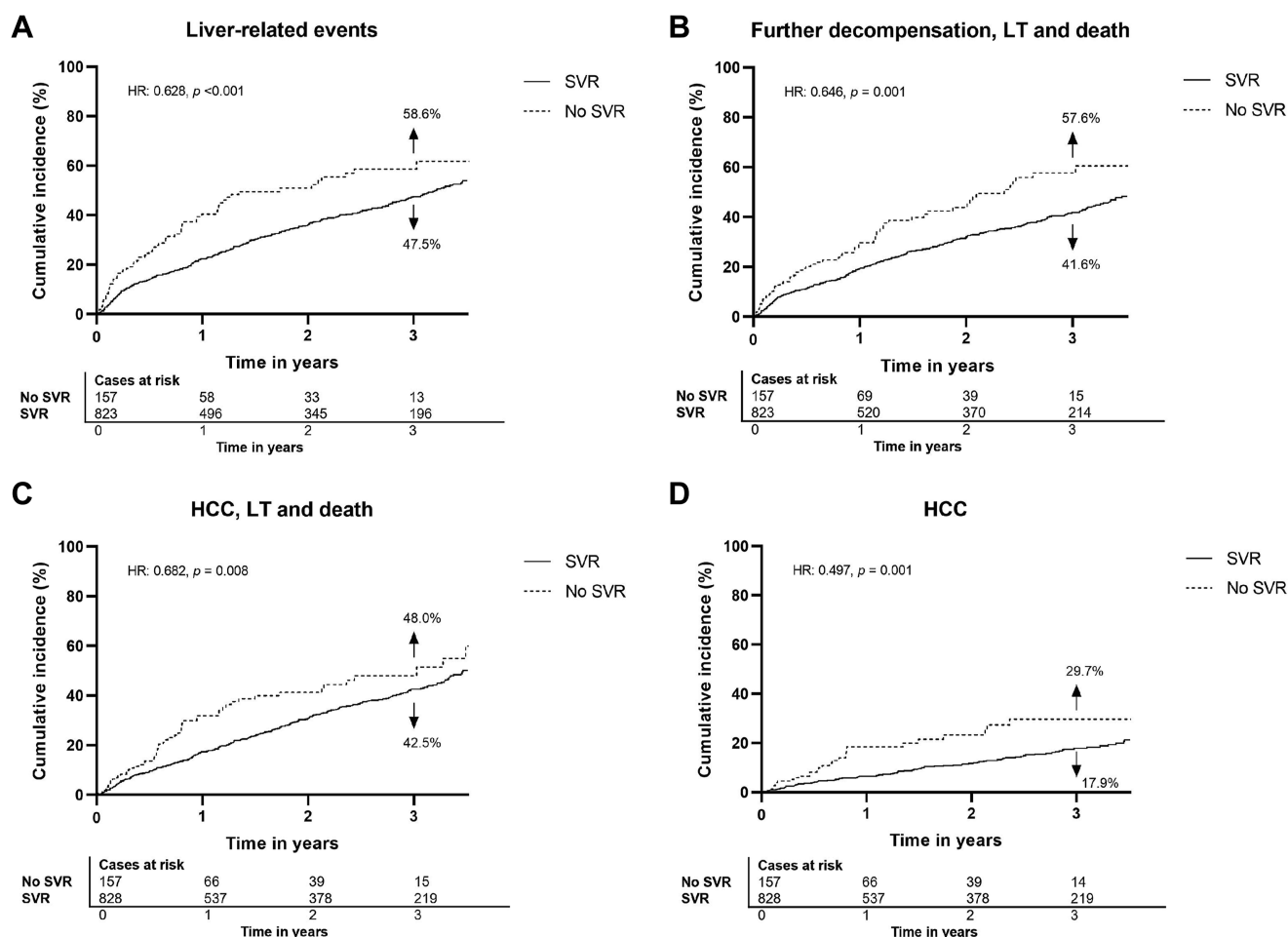


Figure 1. Cumulative incidence of liver-related events for patients with and without SVR. (A) LREs*; (B) Composite of further decompensation, LT, and death; (C) Composite of HCC, LT, and death; and (D) HCC. Kaplan-Meier curves were constructed using a clock-reset approach, in which patients who achieved SVR were censored in the non-SVR group, with subsequent follow-up time transferred to the SVR group. Comparisons were performed using Cox regression with SVR as a time-varying covariate. *LREs were defined as the first of a composite of: (1) further decompensation (newly developed HE and/or SBP and/or a first or recurrent VB); (2) development of HCC; (3) LT; or (4) death.

those with higher MELD scores because there is no evidence of clinical benefit, whereas there is a risk of reducing eligibility for LT through post-SVR decrease in MELD score.

With the widespread availability of DAAs, access to antiviral therapy is now a reality even for patients with advanced chronic HCV-related liver disease who were historically ineligible for treatment with pegIFN-based therapy. In this large real-world cohort, more than 82% of these patients achieved SVR after the first DAA therapy, aligning with previously published SVR rates from clinical trials.^{2,5-8,12,15} Furthermore, successful retreatment was performed in a subset of patients, resulting in SVR in over 90% of the enrolled patients. Given these excellent virological response rates, an important question is whether antiviral treatment should now be offered to all patients with decompensated HCV-related cirrhosis. This question remains relevant, as previous studies on the clinical benefits of SVR in patients with decompensated cirrhosis are conflicting. Although some studies reported improvements in liver function with SVR,^{10,12,16}

a previous study from our group suggested that, although SVR had marked clinical benefits among patients with compensated cirrhosis, SVR did not improve clinical outcomes in the small subset of patients with decompensated liver disease.⁵

In the current study, patients with SVR had a lower risk of LREs, although the risk reduction was attenuated when compared with observations from cohorts of patients with compensated cirrhosis, and a significant risk of adverse LREs persisted after SVR.⁹ These findings were consistent for various outcomes, including decompensation events, occurrence of HCC, and composite outcomes incorporating LT and mortality. These findings align with results of a VA study, in which SVR was associated with reduced all-cause mortality in patients with decompensated liver disease.¹⁷ A recent study by Premkumar et al found that 25% of patients with decompensated HCV cirrhosis recompensated after SVR, and that SVR was beneficial even in those who did not recompensate.¹² Interestingly, the incidence of LREs was higher in our cohort, which may relate to

Table 2. Determinants of LREs Based on Multivariable Cox Regression in the Overall Population

Variable	Univariable		Multivariable	
	HR (95% CI)	<i>P</i> value	aHR (95% CI)	<i>P</i> value
SVR	0.628 (0.486–0.811)	<.001	0.692 (0.520–0.920)	.011
Age, years	0.998 (0.989–1.008)	.753	1.010 (0.997–1.023)	.124
Female sex	0.715 (0.576–0.886)	.002	0.863 (0.664–1.120)	.267
AUD	1.496 (1.232–1.817)	<.001	1.465 (1.166–1.840)	.001
DM	1.071 (0.861–1.332)	.537	1.283 (0.996–1.653)	.054
BMI, kg/m ²	1.007 (0.990–1.023)	.434	–	–
Child-Pugh score	2.059 (1.620–2.617)	<.001	–	–
Platelet count, × 10 ⁹ /L	0.997 (0.995–1.000)	.017	0.999 (0.996–1.001)	.245
AST, U/L	1.000 (0.998–1.002)	.991	1.001 (0.998–1.005)	.514
ALT, U/L	0.996 (0.993–0.999)	.005	0.995 (0.991–1.000)	.058
Albumin, g/L	0.950 (0.934–0.967)	<.001	0.975 (0.955–0.995)	.016
Total bilirubin, mg/dL	1.168 (1.014–1.344)	.031	–	–
INR	1.845 (1.423–2.392)	<.001	–	–
Creatinine, μmol/L	1.001 (0.999–1.003)	.512	–	–
MELD score	1.082 (1.054–1.110)	<.001	1.073 (1.040–1.106)	<.001

NOTE. SVR was entered as a time-varying covariate.

NOTE. Boldface *P* values indicate statistical significance.

aHR, adjusted hazard ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUD, alcohol use disorder; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; INR, international normalized ratio; LRE, liver-related event; MELD, Model for End-stage Liver Disease; SVR, sustained viral response.

differences in access to LT (6 compared with 156 in our cohort), and the higher burden of both metabolic comorbidities as well as AUD in our cohort. Importantly, despite the lower incidence of LREs, Premkumar et al also reported that their patients remained at risk of further decompensation and HCC despite SVR.

Importantly, although SVR was associated with clinical benefits in some patients, a high risk of adverse LREs persisted in many patients. Further analysis of our cohort revealed that, although SVR was associated with a reduced risk of LREs in those with a baseline MELD of <15, no clinical benefit was observed in patients with a

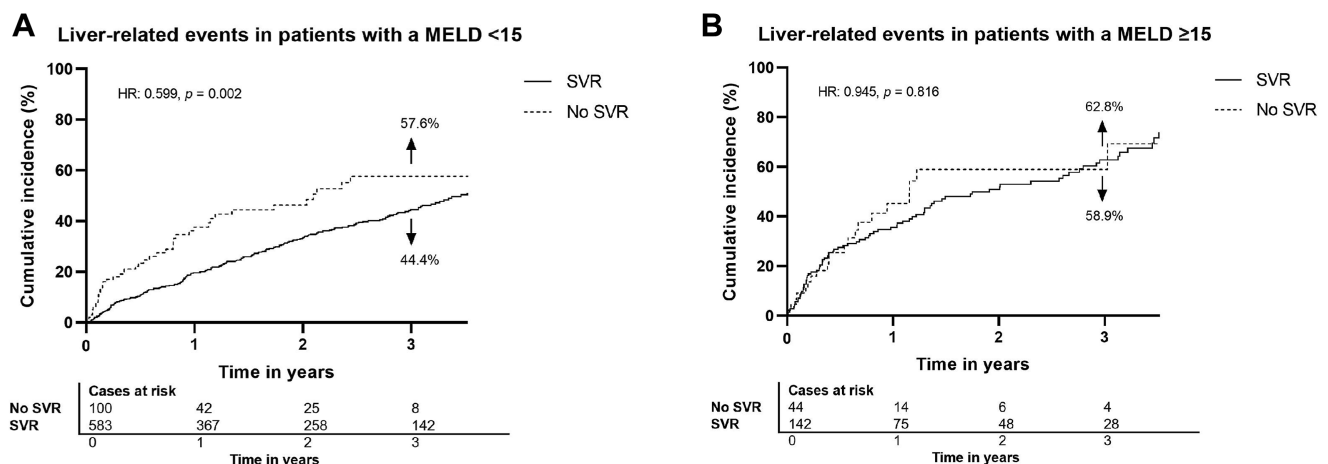


Figure 2. Cumulative incidence of LREs* stratified for MELD score shown for patients with and without SVR. (A) MELD score <15 at baseline; (B) MELD score ≥15 at baseline. Kaplan-Meier curves were constructed using a clock-reset approach, in which patients who achieved SVR were censored in the non-SVR group, with subsequent follow-up time transferred to the SVR group. Comparisons were performed using Cox regression with SVR as a time-varying covariate. *LREs were defined as the first of a composite of: (1) further decompensation (newly developed HE and/or SBP and/or a first or recurrent VB); (2) development of HCC; (3) LT; or (4) death.

Table 3. Determinants of LREs Based on Multivariable Cox Regression, Performed Separately for Patients With a MELD Score <15 and ≥15 at Baseline

Variable	MELD score <15 at baseline				MELD score ≥15 at baseline			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	P value	aHR (95% CI)	P value	HR (95% CI)	P value	aHR (95% CI)	P value
SVR	0.599 (0.433–0.828)	.002	0.601 (0.425–0.849)	.004	0.945 (0.590–1.515)	.816	0.936 (0.560–1.564)	.801
Age, years	1.000 (0.988–1.013)	.942	1.017 (1.001–1.033)	.035	1.002 (0.983–1.020)	.870	1.000 (0.977–1.024)	.992
Female sex	0.719 (0.553–0.935)	.014	0.816 (0.601–1.108)	.193	0.889 (0.573–1.380)	.601	1.047 (0.617–1.779)	.865
AUD	1.712 (1.342–2.182)	<.001	1.811 (1.360–2.410)	<.001	1.116 (0.765–1.628)	.569	1.087 (0.714–1.653)	.698
DM	1.175 (0.905–1.527)	.225	1.396 (1.043–1.869)	.025	1.018 (0.627–1.654)	.942	1.194 (0.686–2.077)	.531
BMI, kg/m ²	1.000 (0.979–1.022)	.992	–	–	1.006 (0.974–1.039)	.710	–	–
Child-Pugh score	1.881 (1.291–2.740)	.001	–	–	1.456 (1.002–2.116)	.049	–	–
Platelet count, × 10 ⁹ /L	0.998 (0.995–1.000)	.081	0.999 (0.996–1.002)	.393	0.999 (0.995–1.003)	.586	0.999 (0.994–1.004)	.652
AST, U/L	1.000 (0.998–1.003)	.782	1.003 (0.998–1.007)	.214	0.998 (0.994–1.001)	.195	0.999 (0.993–1.005)	.774
ALT, U/L	0.997 (0.994–1.000)	.071	0.994 (0.988–1.000)	.061	0.994 (0.988–0.999)	.032	0.996 (0.987–1.005)	.409
Albumin, g/L	0.954 (0.933–0.976)	<.001	0.968 (0.942–0.994)	.017	0.988 (0.957–1.019)	.441	0.993 (0.959–1.028)	.696
Total bilirubin, mg/dL	1.168 (1.014–1.344)	.031	–	–	1.010 (0.954–1.072)	.701	–	–
INR	3.084 (1.473–6.454)	.003	–	–	0.954 (0.629–1.447)	.823	–	–
Creatinine, μmol/L	1.000 (0.995–1.006)	.881	–	–	0.999 (0.997–1.002)	.625	–	–
MELD score	1.094 (1.035–1.156)	.002	1.079 (1.010–1.151)	.023	1.022 (0.950–1.099)	.560	1.035 (0.954–1.124)	.406

NOTE. SVR was entered as a time-varying covariate.

NOTE. Boldface values indicate statistical significance.

aHR, adjusted hazard ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUD, alcohol use disorder; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; SVR, sustained viral response.

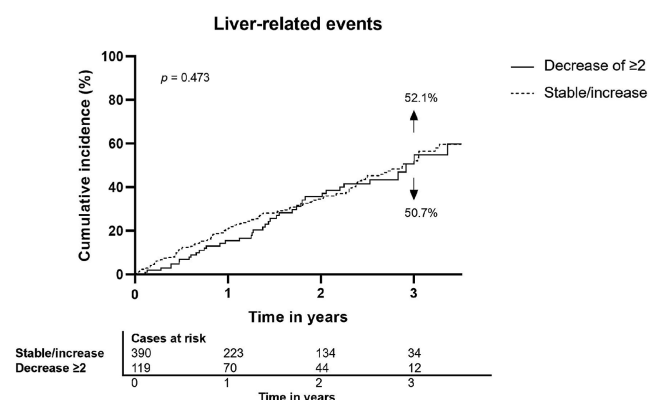


Figure 3. Cumulative incidence of LREs* stratified for Δ MELD. Patients were categorized into 2 subgroups: a MELD score decrease of minimal 2 points, or a stable or increase of MELD score. Statistical significance was assessed with the log-rank test. *LREs were defined as the first of a composite of: (1) further decompensation (newly developed HE and/or SBP and/or a first or recurrent VB); (2) development of HCC; (3) LT; or (4) death.

pretreatment MELD score ≥ 15 . In these patients, high rates of SVR were achieved, but this did not translate to a reduced risk of LREs.⁵ Even a MELD score improvement of ≥ 2 points after SVR, which was observed in almost 50% of patients with a pretreatment MELD ≥ 15 , was not associated with clinical benefits in this cohort.

These findings may have important clinical implications. Current guidelines recommend consideration of DAA therapy in patients with decompensated cirrhosis with a MELD score up to 18 to 20.^{18,19} Similar to the results in the overall group with MELD >15 , we found no benefit to SVR in both patients with a pretreatment MELD of 15 to 18 (HR, 0.986; 95% CI, 0.56–1.73; $P = .960$), and ≥ 18 (HR, 0.779; 95% CI, 0.32–1.88; $P = .579$). The current study suggests that the thresholds in the guidelines may warrant reconsideration, as the use of DAAs in patients with decompensated cirrhosis and a MELD ≥ 15 could actually have a potential unwanted negative effect, as these patients may not experience clinical benefit, but could be adversely affected by the decrease in LT waitlist priority due to a decrease in MELD score after SVR.¹¹ These patients are therefore at risk for ending up in a MELD purgatory state, where there is persistent (risk of) decompensation and HCC, but no priority for LT due to a post-SVR decrease in MELD score.

Besides HCV infection, almost 25% of this cohort had DM and 45% had AUD, predisposing these patients to a second liver disease potentially influencing LREs. Although both the presence of DM and AUD were associated with a higher risk of LREs, achievement of SVR was associated with a reduced risk of LREs in these patients if MELD was <15 (HR for patients with DM and/or AUD, 0.671; 95% CI, 0.460–0.979; $P = .038$; HR for patients without DM and AUD, 0.519; 95% CI, 0.273–0.984; $P = .045$) (Supplementary Figure 9), highlighting the importance of treating HCV even if other liver diseases coexist.

Protease inhibitor (PI)-containing regimens have been associated with hepatotoxicity in patients with advanced liver disease and are therefore contraindicated in patient with decompensated HCV cirrhosis or a prior decompensation event according to clinical guidelines.^{18,19} Importantly, in our study, 75 patients (8.2%) were treated with a PI-containing regimen and there were 2 cases of decompensation during therapy. PI treatment was not associated with an excess risk of decompensation, but this should be interpreted with caution due to potential confounding by (contra-)indication and the relatively small numbers of patients who received PI-based therapy.

Even though this is an international multicenter cohort study encompassing data on a large cohort of DAA-treated patients with HCV and decompensated cirrhosis, there are some limitations. Due to the retrospective nature of data acquisition, we did not have detailed information on the severity of ascites, which made defining worsening of ascites challenging. Therefore, we opted to exclude development of ascites as an outcome in our analyses. For similar reasons, we were unable to study change in CTP over time. Furthermore, the clinical endpoints used in our analysis are inter-related, and we therefore used a composite endpoint comprising both decompensation, HCC, LT, and death for our primary analyses. To confirm the robustness of our findings, we also analyzed alternative endpoints (eg, only HCC, LT, or death, or death and LT-censored HCC) and found consistent results. In our study, we included all LREs, with no immortal time after therapy initiation. However, we performed additional sensitivity analyses excluding HCC cases that developed within the first 3 months and found consistent results (Supplementary Figures 3 and 7). Additionally, we found consistent results and comparable HRs when comparing the data from the country with the largest number of patients (the United Kingdom) and patients enrolled from other sites (Supplementary Figure 10). Another limitation of our study was that we used the MELD score and were unable to calculate the MELD-Na score due to missing data on sodium levels. Due to the retrospective nature of our study, data on previous or current AUD was collected at baseline, but no detailed information was available during follow-up. However, the findings were consistent regardless of the presence of AUD. Furthermore, detailed information on specific indications for LT listing were not available. In total, 156 patients underwent an LT with a median MELD score of 15.1 (IQR, 12.6–18.5) at time of transplantation. Notably, all 156 patients had a prior HCC or decompensating event before LT. Finally, criteria for (de)listing for LT vary across the sites participating in this study, as does the probability of being offered a graft, which could potentially influence time to transplant.

Conclusions

In conclusion, the current international retrospective cohort study of more than 900 patients with decompensated HCV cirrhosis shows that SVR is associated with

clinical benefit in patients with MELD scores <15. In patients with higher MELD scores, no clinical benefit was observed, whereas there is a potential risk of reducing eligibility for LT through post-SVR decrease in MELD score.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <https://doi.org/10.1016/j.cgh.2025.09.006>.

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Conflicts of interest

These authors disclose the following: Lisa M. van Velsen received a research grant from Gilead. Kosh Agarwal received consultancy fees from Aligos, ASC Therapeutics, Brii-bio, Barinthus, Chroma, DrugFarm, Gilead, GSK, Grifols, Janssen, PrecisionBio, Primmune, Roche, Surrozen, Tune, and Vir; and received grants from Gilead, GSK, and Abbott. Markus Cornberg is a consultant for Abbvie, AiCuris, AstraZeneca, Gilead, GSK, MSD Sharp & Dohme, and Roche; and gives sponsored lectures for Abbvie, Falk, Gilead, and MSD Sharp & Dohme. Robert J. de Knecht gives sponsored lectures for Abbvie, Echosens, Gilead, and Schallware; received research support from

Abbvie, Echosens, Gilead, GSK, and Johnson & Johnson; is a consultant for Echosens; and is on the advisory board of Gilead and Johnson & Johnson. Jose L. Calleja has served on the advisory board and given sponsored lectures for Gilead Sciences, Abbvie, and Roche. Maria Francesca Donato is on the speaker's bureau for Gilead Sciences. Harry L.A. Janssen received grants from Gilead Sciences, GlaxoSmithKline, Janssen, Roche, and Vir Biotechnology Inc; and is a consultant for Aligos, Gilead Sciences, GlaxoSmithKline, Grifols, Roche, Vir Biotechnology Inc, Precision Biosciences, Academic Medical Education, and H.C. Wainwright & Co. Bettina E. Hansen has consulted for and received grant/research support from Intercept Pharmaceuticals. Adriaan J. van der Meer received speakers' fees from GSK, Zambon, AOP Health, CymaBay, and Ipsen; received research support from Zambon, CymaBay, Intercept, and Mirum; and is a consultant for Intercept, CymaBay/Gilead, Ipsen, AOP Health, and Mirum. Jordan J. Feld has consulted for Abbott, AbbVie, Gilead, Enanta, and Roche; and has received grant/research support from AbbVie, Eiger, Gilead, Janssen, and Wako/Fujifilm. Milan J. Sonneveld receives speakers' fees from Gilead Sciences and Roche; receives research support from Roche, Gilead Sciences, GSK, and Fujirebio; and is a consultant for Gilead Sciences, Vir, Fujirebio, and Albireo/Ipsen. The remaining authors disclose no conflicts.

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Data Availability

Data was shared by independent sites and cannot be shared with external parties due to ethical restrictions.

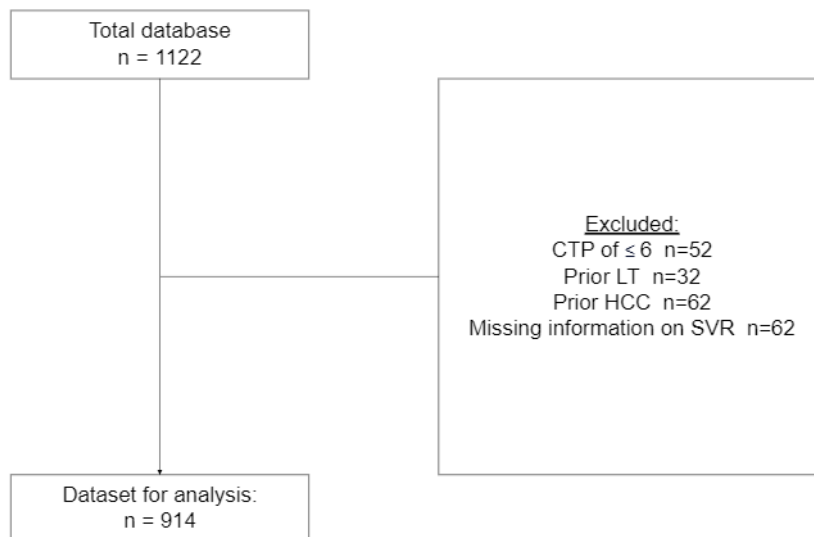
Supplemental information

Association Between Sustained Virological Response and Adverse Liver-Related Events in Patients With Decompensated Hepatitis C Virus Cirrhosis

Lisa M. van Velsen, Lisette A.P. Krassenburg, Grishma Hirode, Kosh Agarwal, Graham R. Foster, Zillah Cargill, Raoel Maan, Michael P. Manns, Heiner Wedemeyer, Markus Cornberg, Robert J. de Knegt, Gonzalo Crespo, Jose L. Calleja, Alnoor Ramji, Giuseppina Brancaccio, Maria Cristina Morelli, Ilaria Lenci, Chiara Mazzearelli, Raffaella Vigano, Paolo Angeli, Patrizia Burra, Maria Francesca Donato, Paola Carrai, Silvia Martini, Paolo Caraceni, Francesco Paolo Russo, Harry L.A. Janssen, Bettina E. Hansen, Adriaan J. van der Meer, Jordan J. Feld, and Milan J. Sonneveld

Supplementary Data

Title: Association between sustained virological response and adverse liver-related events in patients with decompensated HCV cirrhosis



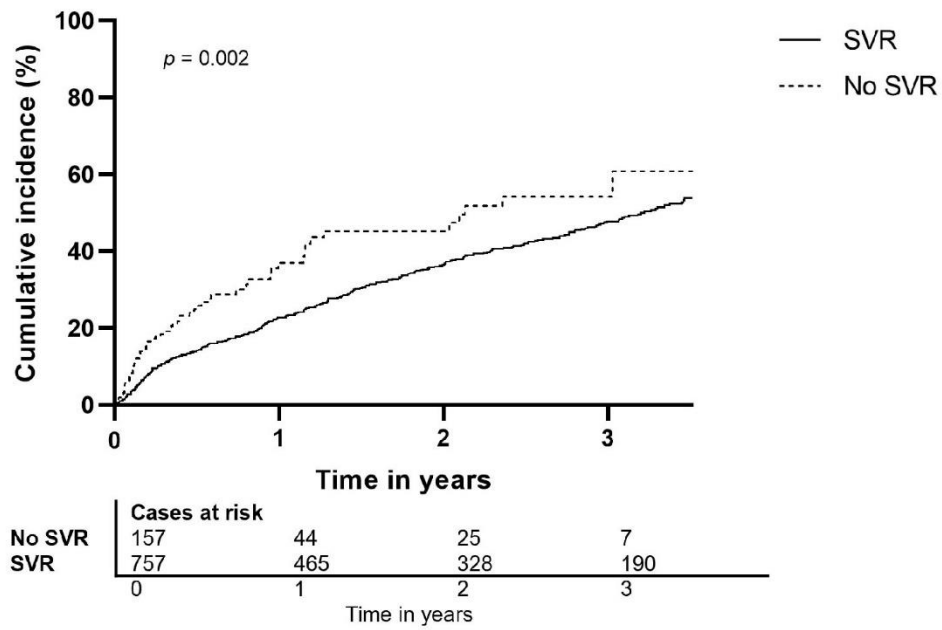
Supplementary figure 1. Patient disposition. Abbreviations: CTP, Child-Turcotte-Pugh; HCC, hepatocellular carcinoma; LT, liver transplantation; SVR, sustained virological response.

Supplementary table 1. Patient characteristics at baseline stratified by MELD score.

Characteristics	MELD <15 (n=655)	MELD ≥15 (n=179)	p value
Age, y,	55.5 (49.6-61.6)	53.0 (47.3-59.2)	0.011
Male gender, n (%)	431 (65.9)	136 (76.0)	0.010
Ethnicity, n (%)			0.590
• Caucasian	511 (84.3)	138 (84.1)	
• Black	17 (2.8)	4 (2.4)	
• Asian	59 (9.7)	19 (11.6)	
• Other	19 (3.1)	3 (1.8)	
Genotype, n (%)			<0.001
• 1	298 (45.5)	52 (29.1)	
• 2	21 (3.2)	4 (2.2)	
• 3	175 (26.7)	59 (33.0)	
• Other	28 (4.3)	7 (3.9)	
• Unknown	133 (20.3)	57 (31.8)	
BMI, kg/m ²	26.9 (24.0-30.8)	26.6 (24.2-30.3)	0.910
Diabetes Mellitus, n (%)	169 (25.8)	33 (18.4)	0.036
Alcohol use disorder, n (%)	287 (44.7)	81 (46.8)	0.623
Platelets, x10 ⁹ /L	78.0 (57.0-106.0)	67.0 (47.0-92.0)	<0.001
ALT, U/L	54.0 (37.0-83.5)	49.0 (33.0-75.0)	0.083
AST, U/L	79.0 (55.0-113.0)	91.5 (56.0-126.0)	0.085
Albumin, g/L	32.0 (29.0-36.0)	29.0 (25.0-33.0)	<0.001
Total bilirubin, mg/dL	1.5 (1.1-2.1)	3.3 (2.5-4.9)	<0.001
INR	1.3 (1.2-1.4)	1.6 (1.5-1.8)	<0.001
Creatinine, μmol/L	67.0 (58.0-80.0)	67.2 (57.7-92.0)	0.218
Prior decompensation, n (%)	544 (83.1)	129 (72.1)	<0.001
SVR on first treatment, n (%)	555 (84.7)	135 (75.4)	0.003
Child-Turcotte-Pugh, n (%)			<0.001
• B	609 (93.0)	111 (62.0)	
• C	46 (7.0)	68 (38.0)	
MELD score	11.2 (9.4-12.9)	17.3 (16.0-19.3)	<0.001

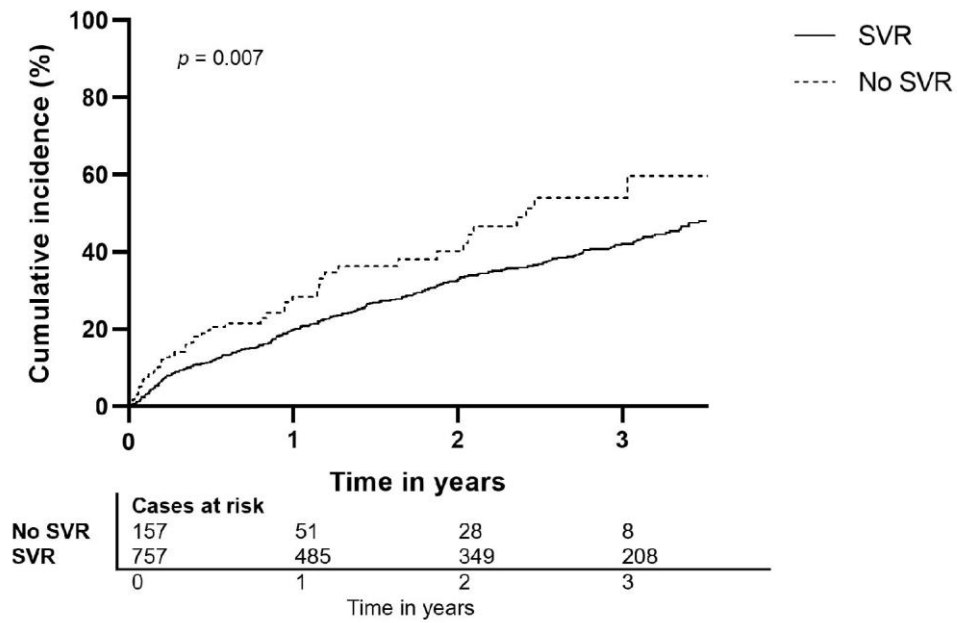
Data are presented as median (IQR), n (%). Comparisons between groups were made using Chi-square test and Mann Whitney U test where appropriate. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; INR, international normalized ratio; MELD, model for end-stage liver disease; SVR, sustained viral response.

Liver-related events

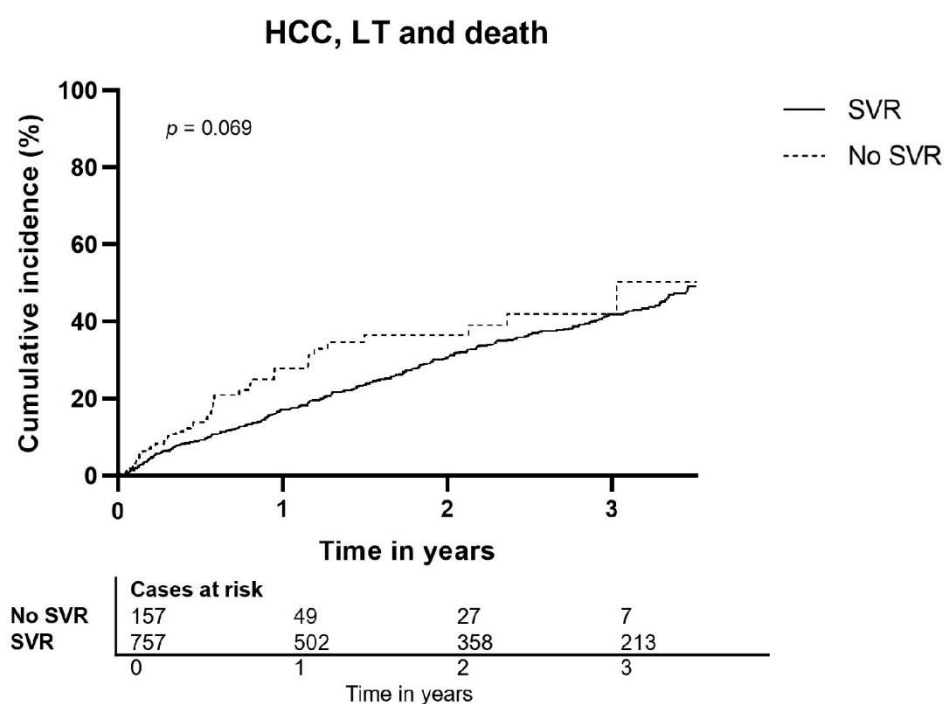


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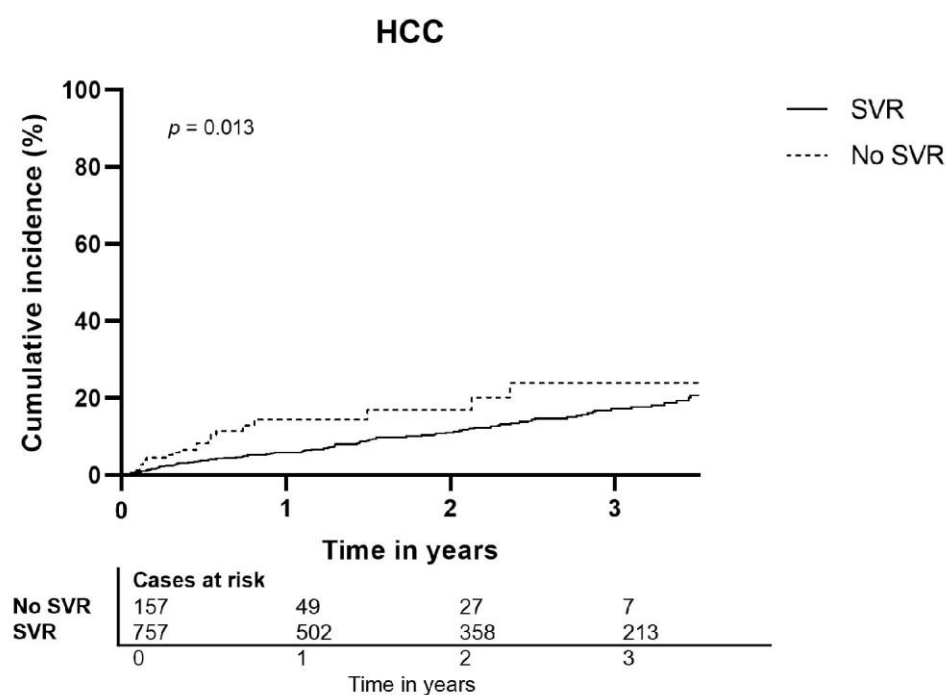
Further decompensation, LT and death



B.



C.

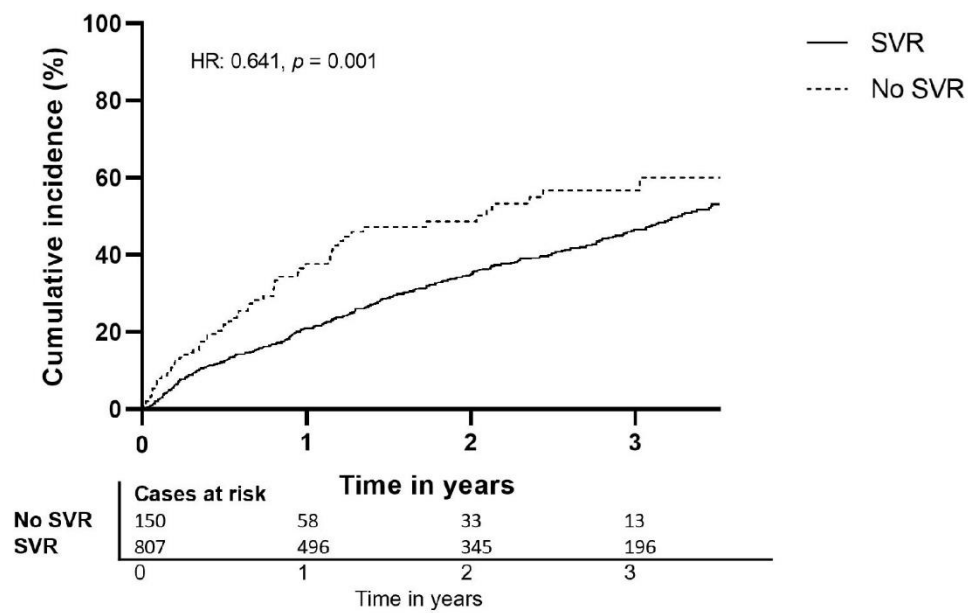


D.

Supplementary figure 2. Cumulative incidence of liver-related events for patients with SVR versus without SVR after the first treatment regimen. (A) Liver-related events*, (B) Composite of further decompensation, LT and death, (C) Composite of HCC, LT and death,

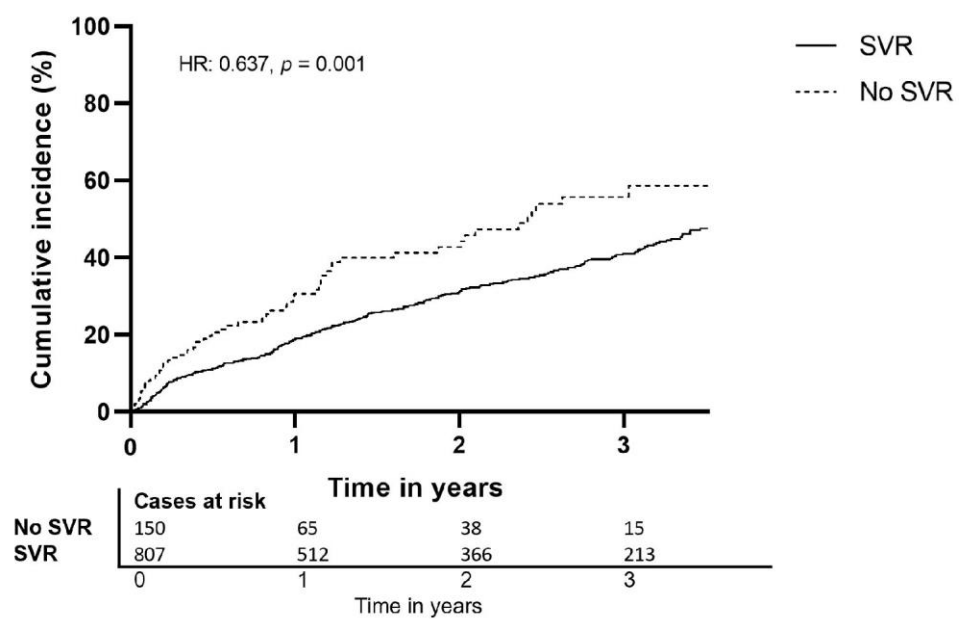
(D) HCC. Statistical significance was assessed with the Log-rank test. *Liver-related events were defined as the first of a composite of (1) further decompensation (newly developed hepatic encephalopathy and/or a spontaneous bacterial peritonitis and/or a first or recurrent variceal bleed, (2) development of HCC, (3) LT or, (4) death. Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; SVR, sustained virological response.

Liver-related events

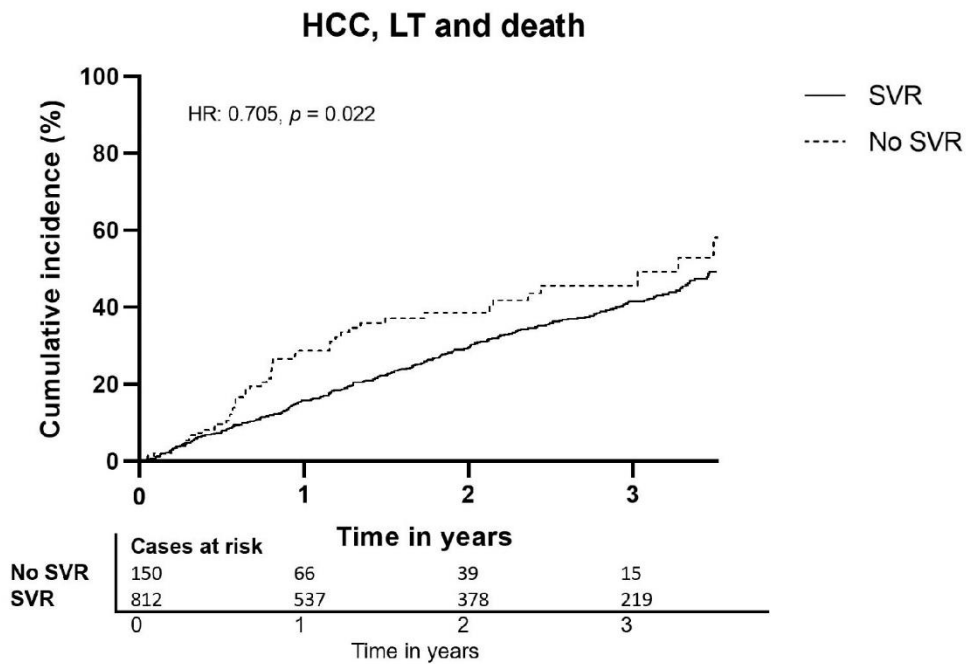


A.

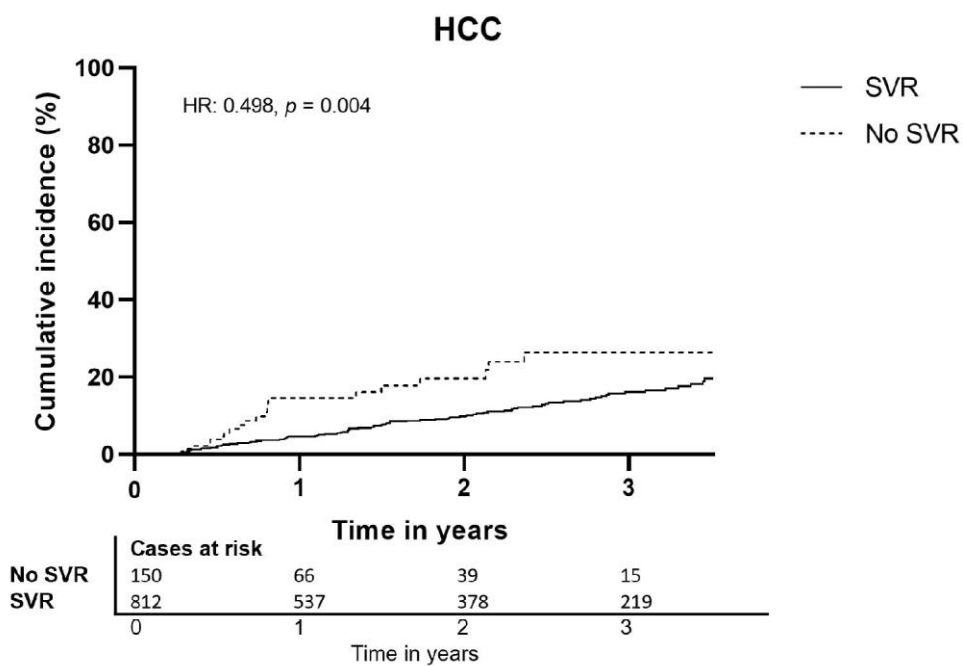
Further decompensation, LT and death



B.



C.



D.

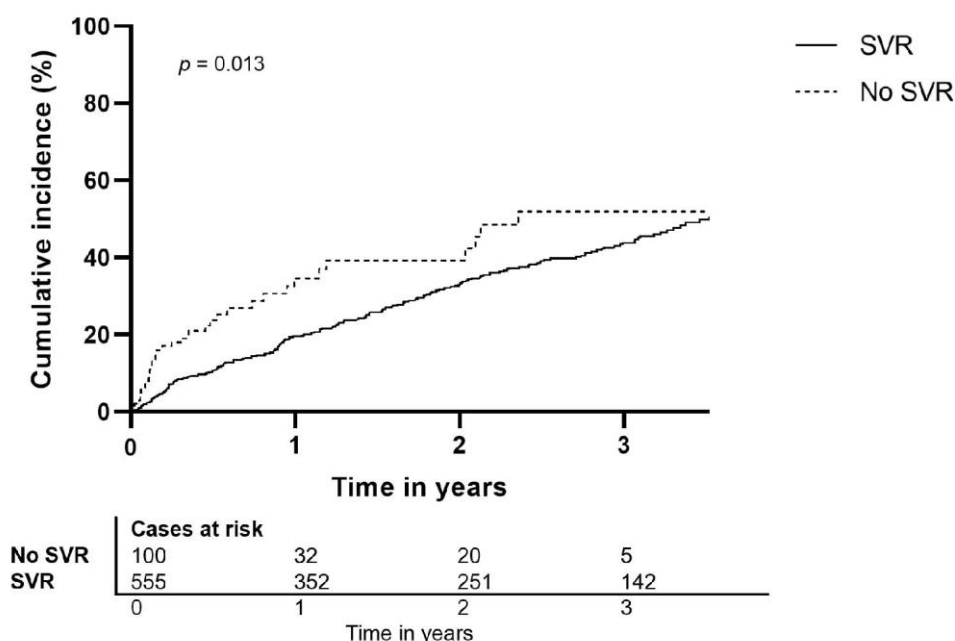
Supplementary figure 3. Cumulative incidence of liver-related events for patients with SVR versus without SVR excluding patients with HCC in the first 3 months after start of DAA therapy. (A) Liver-related events*, (B) Composite of further decompensation, LT and death, (C) Composite of HCC, LT and death, (D) HCC. Kaplan-Meier curves were constructed using a clock-reset approach, in which patients who achieved SVR were censored

in the non-SVR group, with subsequent follow-up time transferred to the SVR group.

Comparisons were performed using Cox regression with SVR as time-varying covariate.

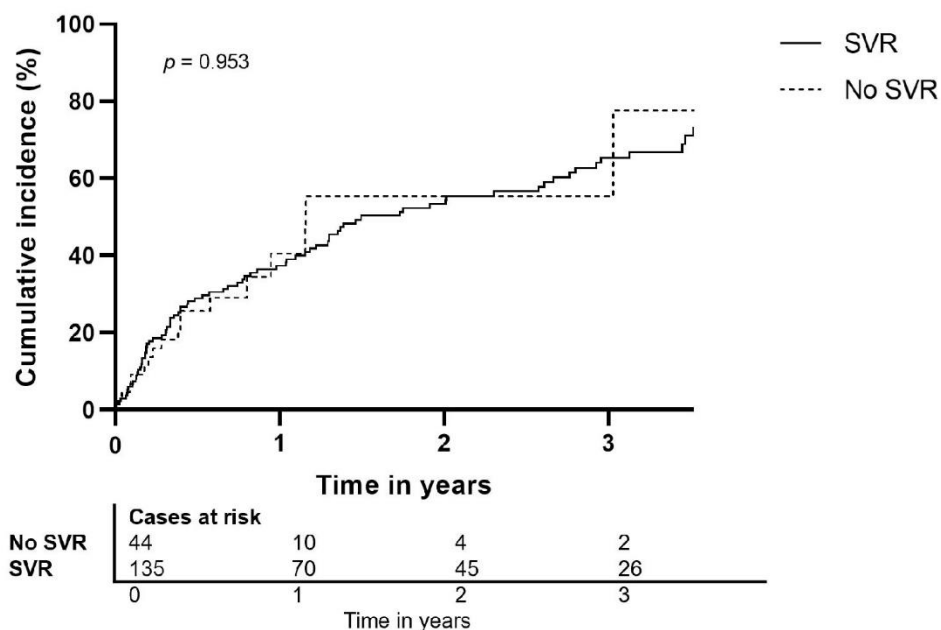
*Liver-related events were defined as the first of a composite of (1) further decompensation (newly developed hepatic encephalopathy and/or a spontaneous bacterial peritonitis and/or a first or recurrent variceal bleed, (2) development of HCC, (3) LT or, (4) death. Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; SVR, sustained virological response.

Liver-related events in patients with a MELD <15



A.

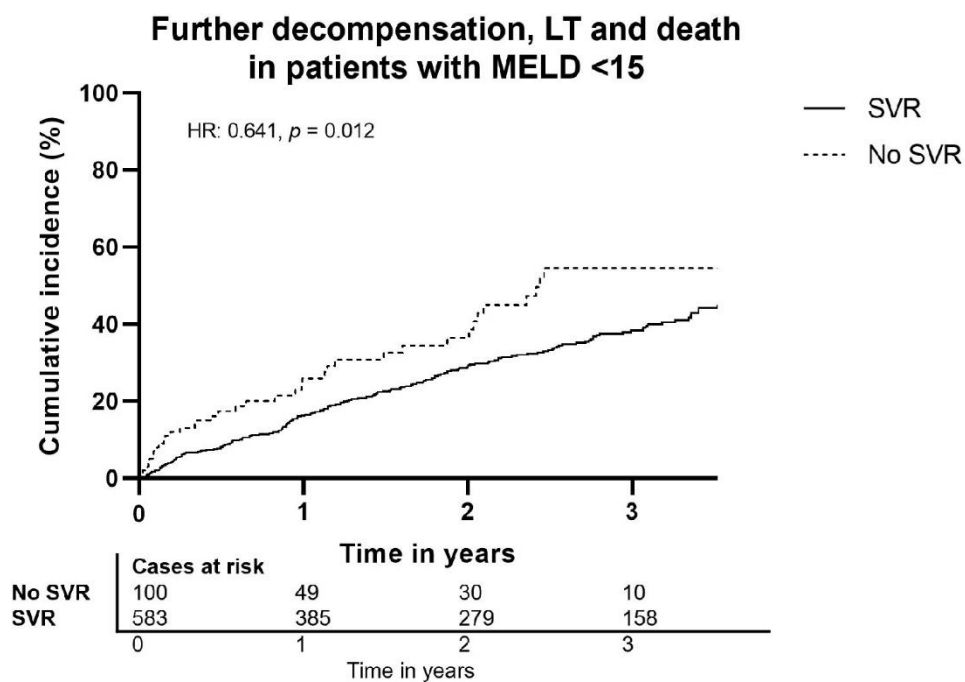
Liver-related events in patients with a MELD ≥ 15



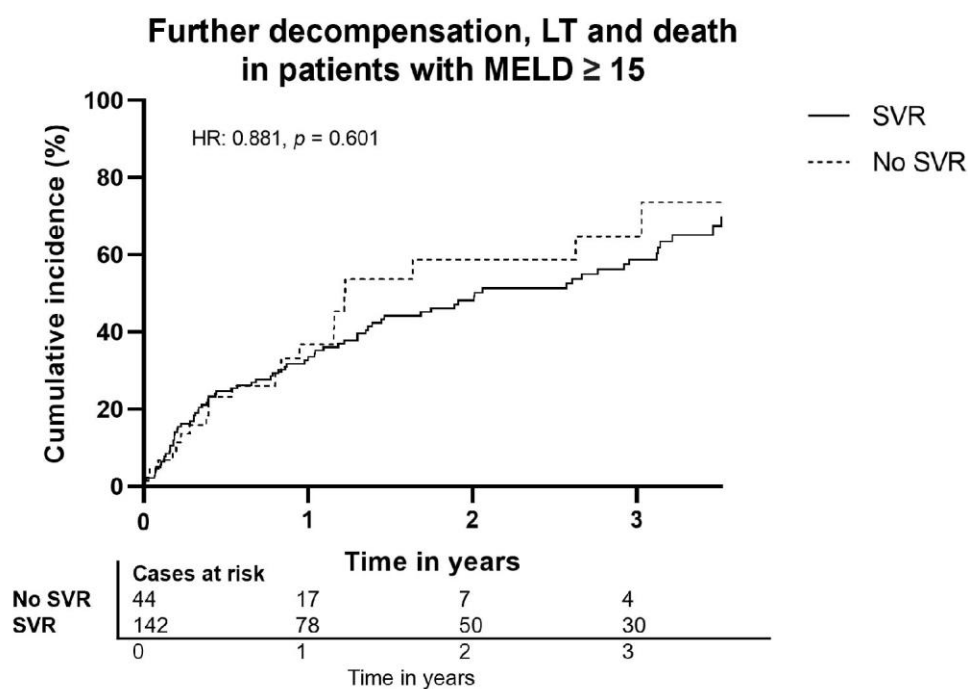
B.

Supplementary figure 4. Cumulative incidence of liver-related events* for patients with SVR versus without SVR after the first treatment regimen stratified for baseline MELD score. (A) MELD score <15 at baseline; (B) MELD score ≥ 15 at baseline. Statistical significance was assessed with the Log-rank test. *Liver-related events were defined as the first of a composite of (1) further decompensation (newly developed hepatic encephalopathy

and/or a spontaneous bacterial peritonitis and/or a first or recurrent variceal bleed, (2) development of HCC, (3) LT or, (4) death. Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; SVR, sustained virological response.



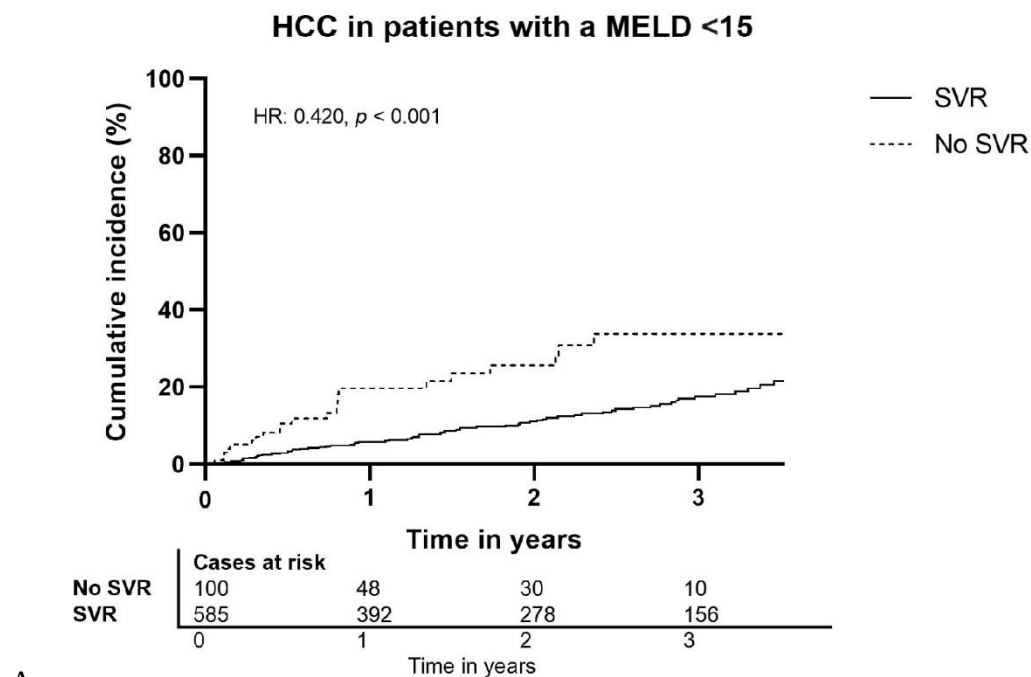
A.



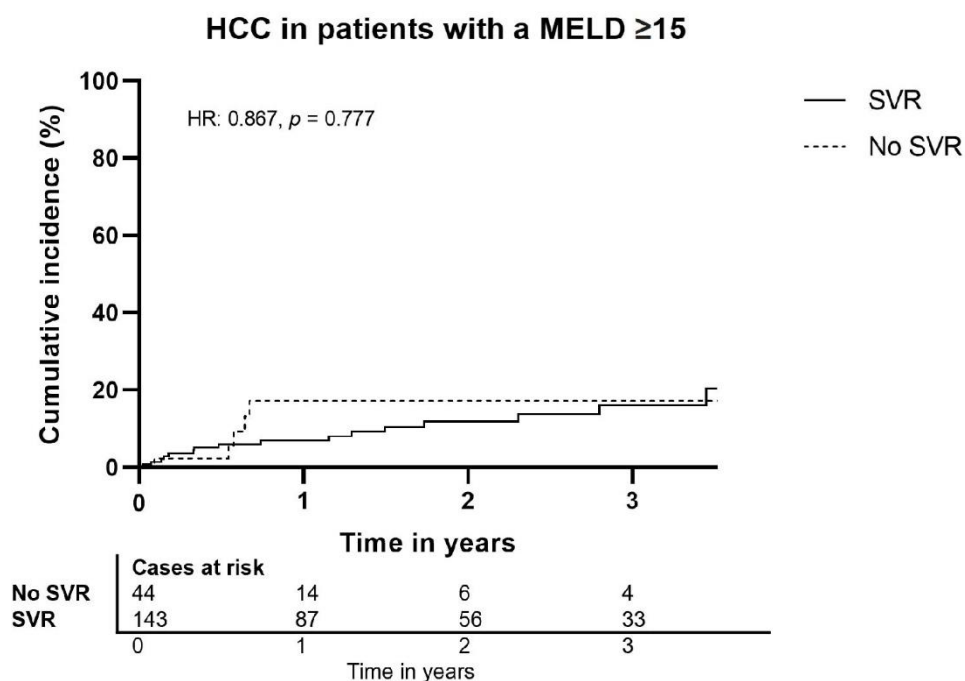
B.

Supplementary figure 5. Cumulative incidence of further decompensation, LT and death for patients with SVR versus without SVR stratified for baseline MELD score. (A) MELD score <15 at baseline; (B) MELD score ≥ 15 at baseline. Kaplan-Meier curves were constructed using a clock-reset approach, in which patients who achieved SVR were censored in the non-SVR group, with subsequent follow-up time transferred to the SVR group.

Comparisons were performed using Cox regression with SVR as a time-varying covariate. Further decompensation was defined as: newly developed hepatic encephalopathy and/or a spontaneous bacterial peritonitis and/or a first or recurrent variceal bleed. Abbreviations: LT, liver transplantation; MELD, model for end-stage liver disease; SVR, sustained virological response.



A.

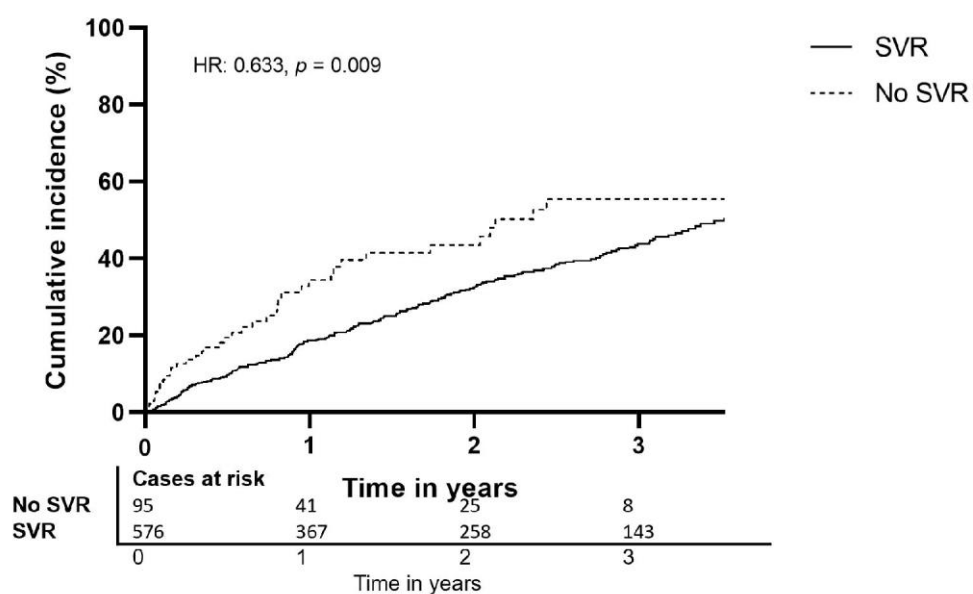


B.

Supplementary figure 6. Cumulative incidence of HCC for patients with SVR versus without SVR stratified for baseline MELD score. (A) MELD score <15 at baseline; (B) MELD score ≥ 15 at baseline. Kaplan-Meier curves were constructed using a clock-reset approach, in which patients who achieved SVR were censored in the non-SVR group, with

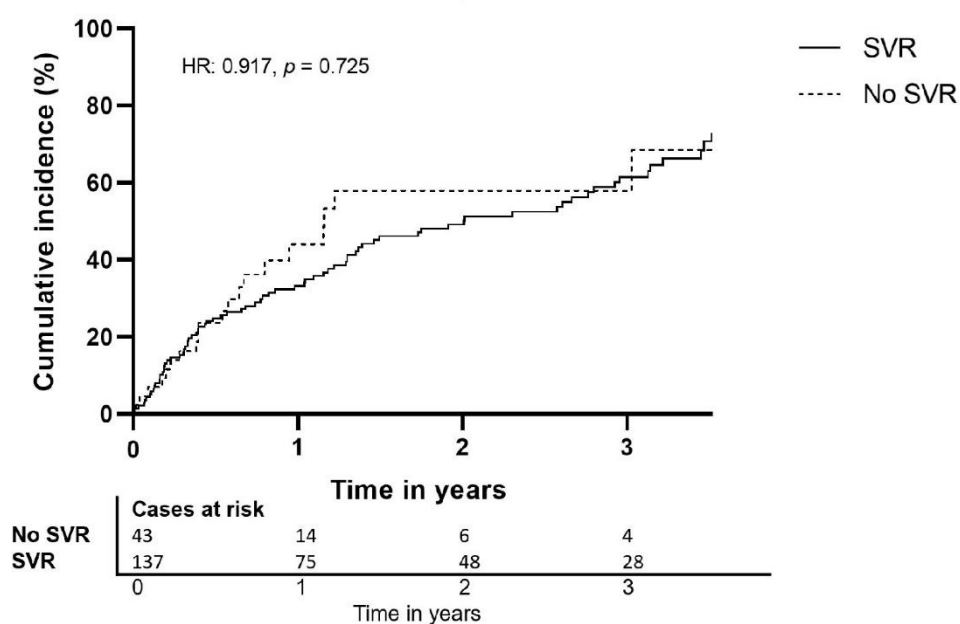
subsequent follow-up time transferred to the SVR group. Comparisons were performed using Cox regression with SVR as a time-varying covariate. Abbreviations: HCC, hepatocellular carcinoma, MELD, model for end-stage liver disease; SVR, sustained virological response.

Liver-related events in patients with a MELD <15



A.

Liver-related events in patients with a MELD ≥ 15



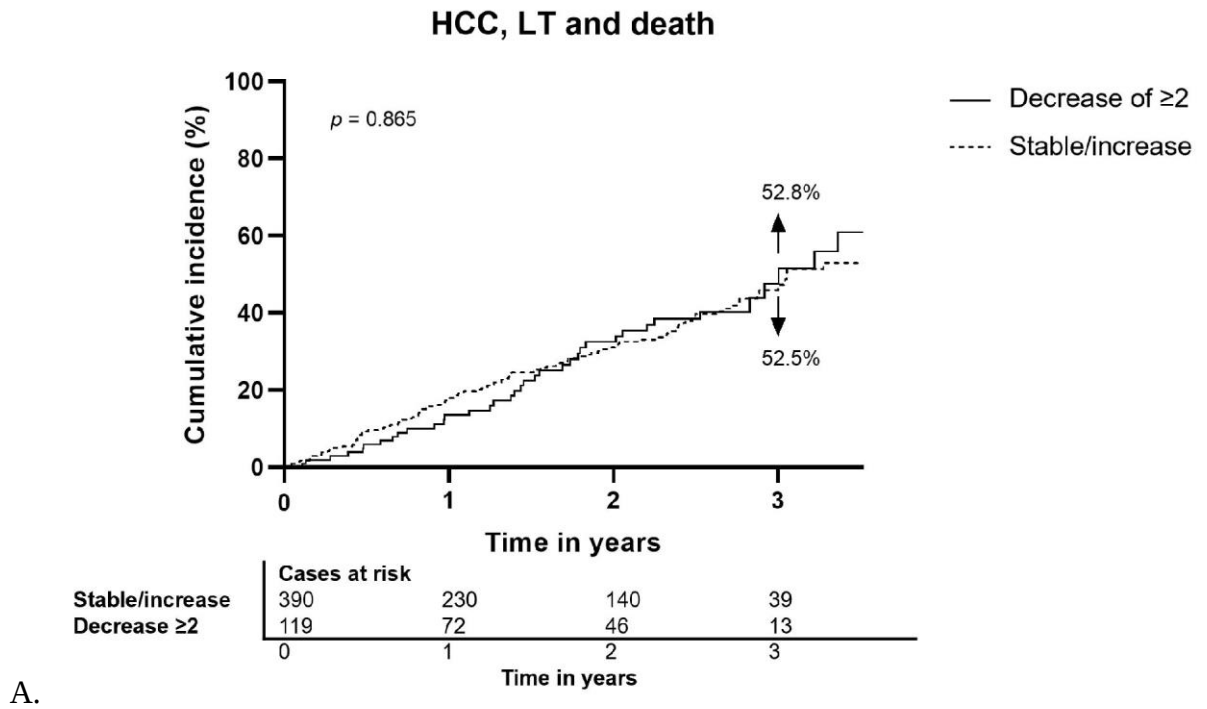
B.

Supplementary figure 7. Cumulative incidence of liver-related events* for patients with SVR versus without SVR stratified for baseline MELD score, excluding patients with HCC in the first 3 months after start of DAA therapy. (A) MELD score <15 at baseline; (B) MELD score ≥ 15 at baseline. Kaplan-Meier curves were constructed using a clock-reset approach, in which patients who achieved SVR were censored in the non-SVR group, with

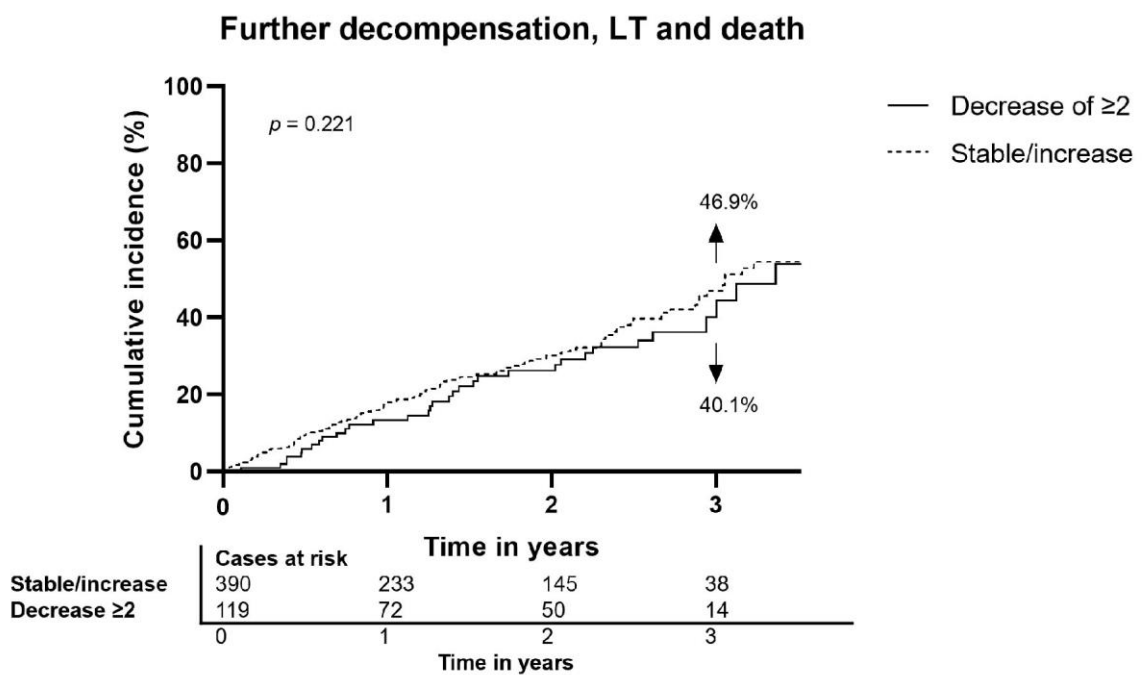
subsequent follow-up time transferred to the SVR group. Comparisons were performed using Cox regression with SVR as a time-varying covariate.

*Liver-related events were defined as the first of a composite of (1) further decompensation (newly developed hepatic encephalopathy and/or a spontaneous bacterial peritonitis and/or a first or recurrent variceal bleed, (2) development of HCC, (3) LT or, (4) death.

Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease, SVR, sustained virological response.



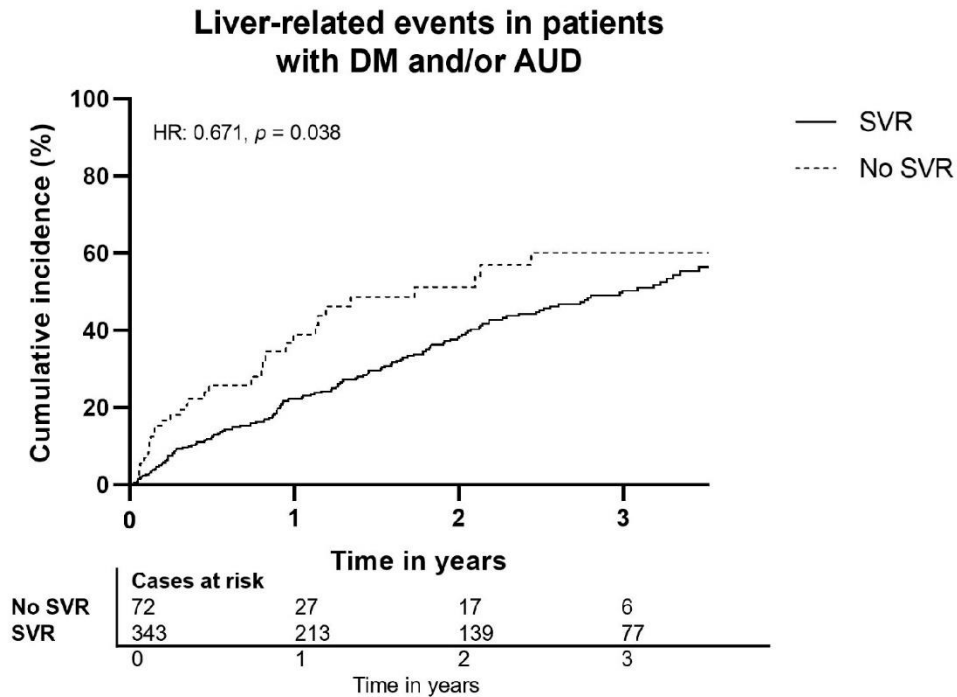
A.



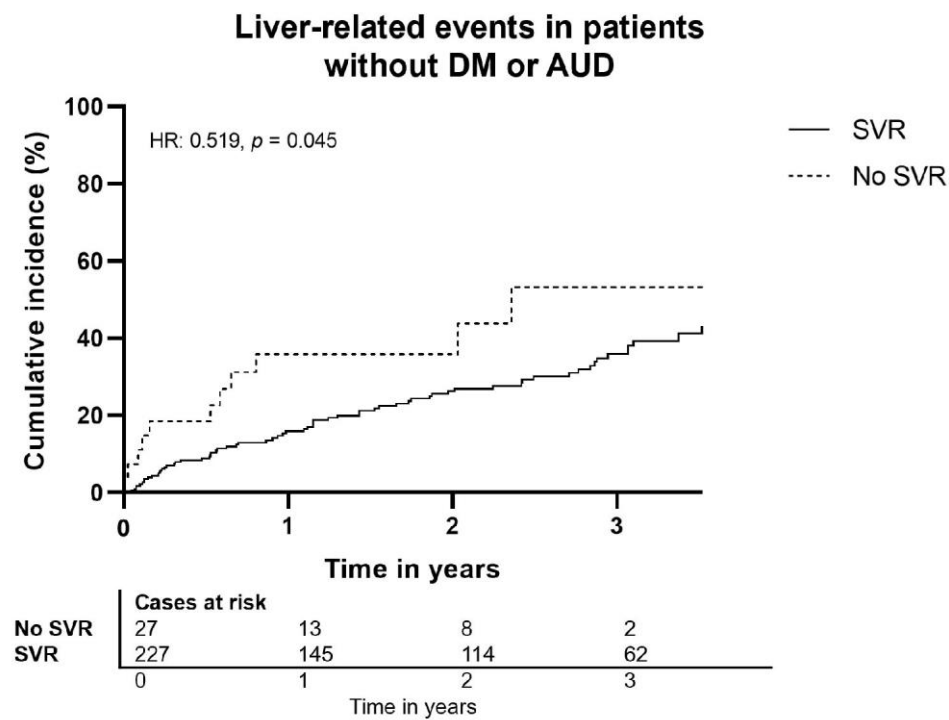
B.

Supplementary figure 8. Cumulative probability of liver-related events stratified for Δ MELD. (A) Composite of HCC, LT and death, (B) Composite of further decompensation, LT and death. Patients were categorized into 2 subgroups: a MELD score decrease of minimal 2 points, or a stable or increased MELD score. Statistical significance was assessed with the

Log-rank test. Further decompensation was defined as newly developed hepatic encephalopathy and/or a spontaneous bacterial peritonitis and/or a first or recurrent variceal bleed. Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease.



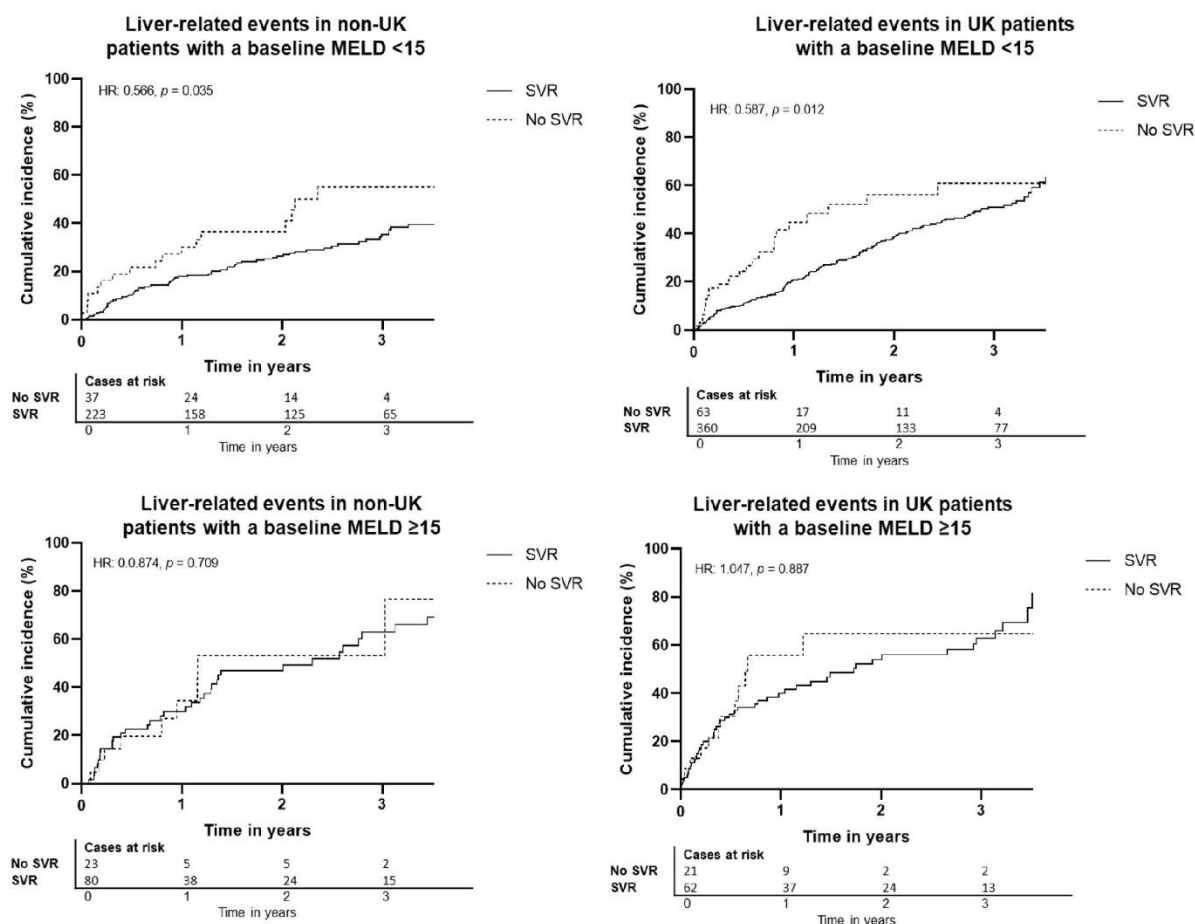
A.



B.

Supplementary figure 9. Cumulative probability of liver-related events* for patients with SVR versus without SVR and a baseline MELD <15 stratified for patients with and without DM and/or AUD. (A) Patients with DM and/or AUD; (B) Patients without DM and/or DM. Kaplan-Meier curves were constructed using a clock-reset approach, in which

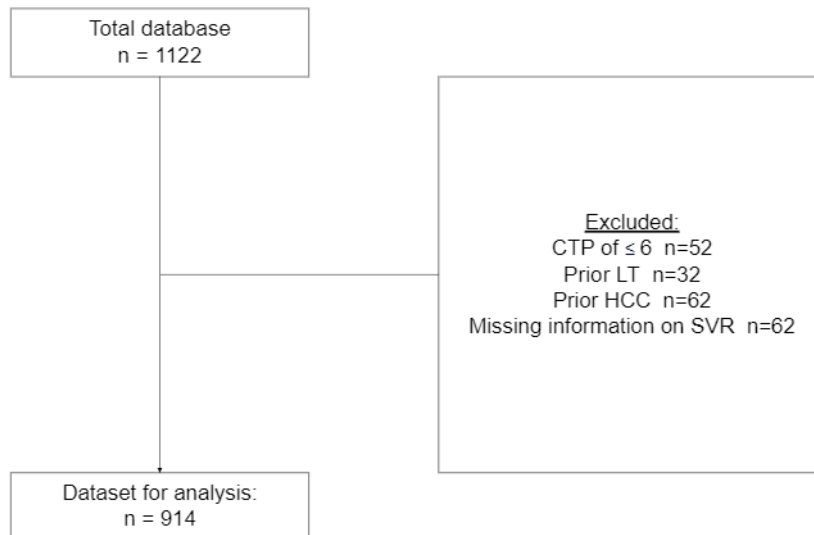
patients who achieved SVR were censored in the non-SVR group, with subsequent follow-up time transferred to the SVR group. Comparisons were performed using Cox regression with SVR as a time-varying covariate. *Liver-related events were defined as the first of a composite of (1) further decompensation (newly developed hepatic encephalopathy and/or a spontaneous bacterial peritonitis and/or a first or recurrent variceal bleed, (2) development of HCC, (3) LT or (4) death. Abbreviations: AUD, alcohol use disorder; DM, diabetes mellitus; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease, SVR, sustained virological response.



Supplementary figure 10. Cumulative probability of liver-related events* for patients with SVR versus without SVR and a baseline MELD <15 stratified for patients from the UK versus non-UK. Kaplan-Meier curves were constructed using a clock-reset approach, in which patients who achieved SVR were censored in the non-SVR group, with subsequent follow-up time transferred to the SVR group. Comparisons were performed using Cox regression with SVR as a time-varying covariate. *Liver-related events were defined as the first of a composite of (1) further decompensation (newly developed hepatic encephalopathy and/or a spontaneous bacterial peritonitis and/or a first or recurrent variceal bleed, (2) development of HCC, (3) LT or (4) death. Abbreviations: AUD, alcohol use disorder; DM, diabetes mellitus; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease, SVR, sustained virological response.

Supplementary Data

Title: Association between sustained virological response and adverse liver-related events in patients with decompensated HCV cirrhosis



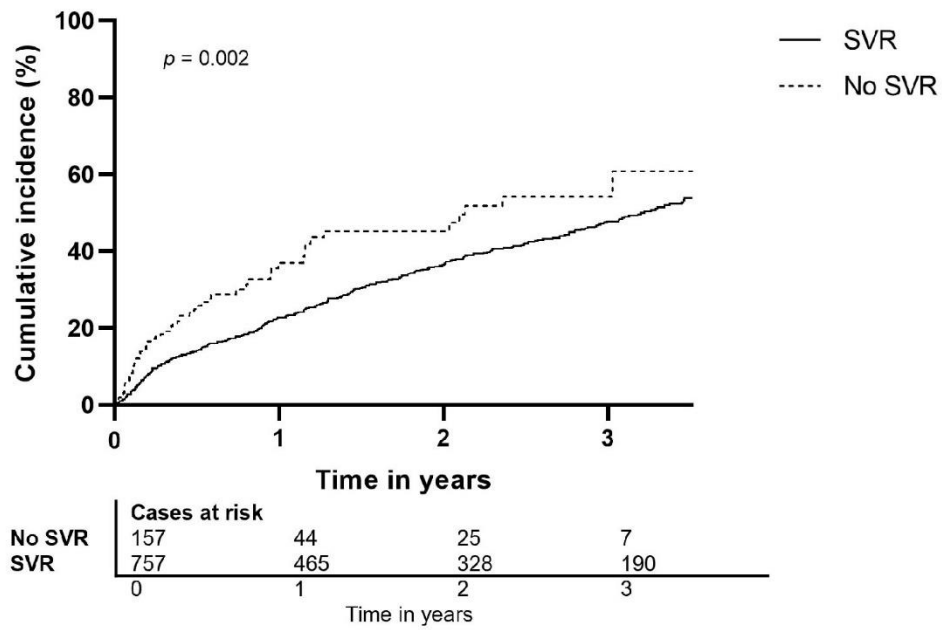
Supplementary figure 1. Patient disposition. Abbreviations: CTP, Child-Turcotte-Pugh; HCC, hepatocellular carcinoma; LT, liver transplantation; SVR, sustained virological response.

Supplementary table 1. Patient characteristics at baseline stratified by MELD score.

Characteristics	MELD <15 (n=655)	MELD ≥15 (n=179)	p value
Age, y,	55.5 (49.6-61.6)	53.0 (47.3-59.2)	0.011
Male gender, n (%)	431 (65.9)	136 (76.0)	0.010
Ethnicity, n (%)			0.590
• Caucasian	511 (84.3)	138 (84.1)	
• Black	17 (2.8)	4 (2.4)	
• Asian	59 (9.7)	19 (11.6)	
• Other	19 (3.1)	3 (1.8)	
Genotype, n (%)			<0.001
• 1	298 (45.5)	52 (29.1)	
• 2	21 (3.2)	4 (2.2)	
• 3	175 (26.7)	59 (33.0)	
• Other	28 (4.3)	7 (3.9)	
• Unknown	133 (20.3)	57 (31.8)	
BMI, kg/m ²	26.9 (24.0-30.8)	26.6 (24.2-30.3)	0.910
Diabetes Mellitus, n (%)	169 (25.8)	33 (18.4)	0.036
Alcohol use disorder, n (%)	287 (44.7)	81 (46.8)	0.623
Platelets, x10 ⁹ /L	78.0 (57.0-106.0)	67.0 (47.0-92.0)	<0.001
ALT, U/L	54.0 (37.0-83.5)	49.0 (33.0-75.0)	0.083
AST, U/L	79.0 (55.0-113.0)	91.5 (56.0-126.0)	0.085
Albumin, g/L	32.0 (29.0-36.0)	29.0 (25.0-33.0)	<0.001
Total bilirubin, mg/dL	1.5 (1.1-2.1)	3.3 (2.5-4.9)	<0.001
INR	1.3 (1.2-1.4)	1.6 (1.5-1.8)	<0.001
Creatinine, μmol/L	67.0 (58.0-80.0)	67.2 (57.7-92.0)	0.218
Prior decompensation, n (%)	544 (83.1)	129 (72.1)	<0.001
SVR on first treatment, n (%)	555 (84.7)	135 (75.4)	0.003
Child-Turcotte-Pugh, n (%)			<0.001
• B	609 (93.0)	111 (62.0)	
• C	46 (7.0)	68 (38.0)	
MELD score	11.2 (9.4-12.9)	17.3 (16.0-19.3)	<0.001

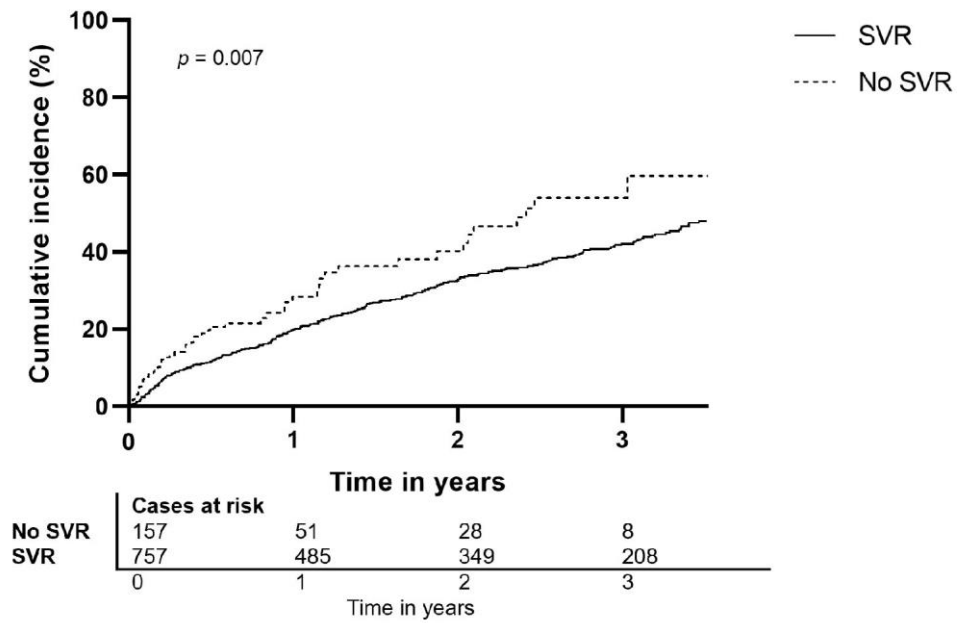
Data are presented as median (IQR), n (%). Comparisons between groups were made using Chi-square test and Mann Whitney U test where appropriate. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; INR, international normalized ratio; MELD, model for end-stage liver disease; SVR, sustained viral response.

Liver-related events

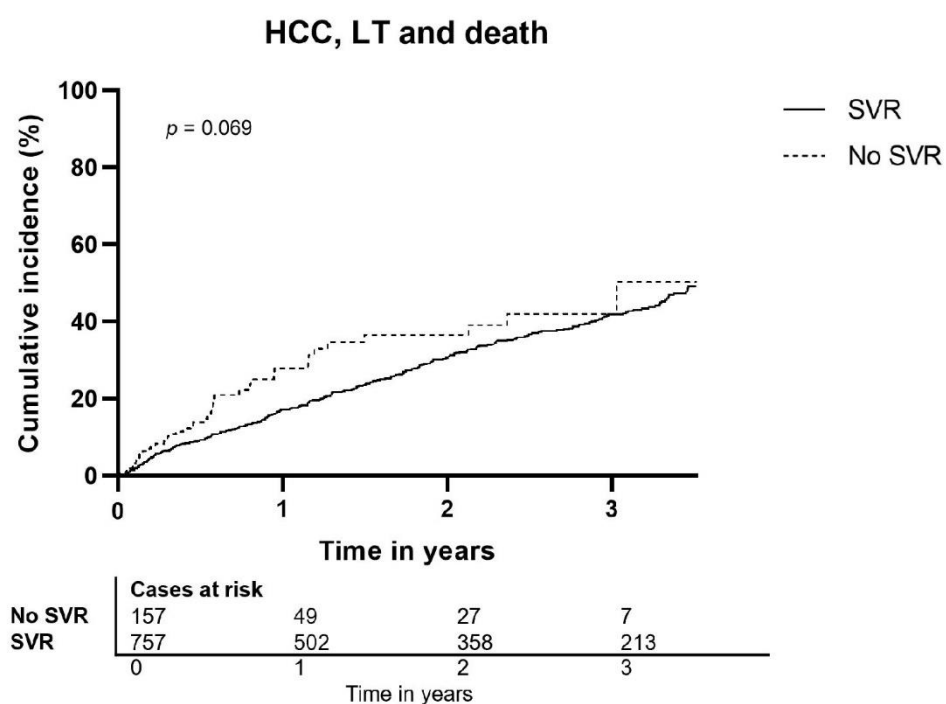


A.

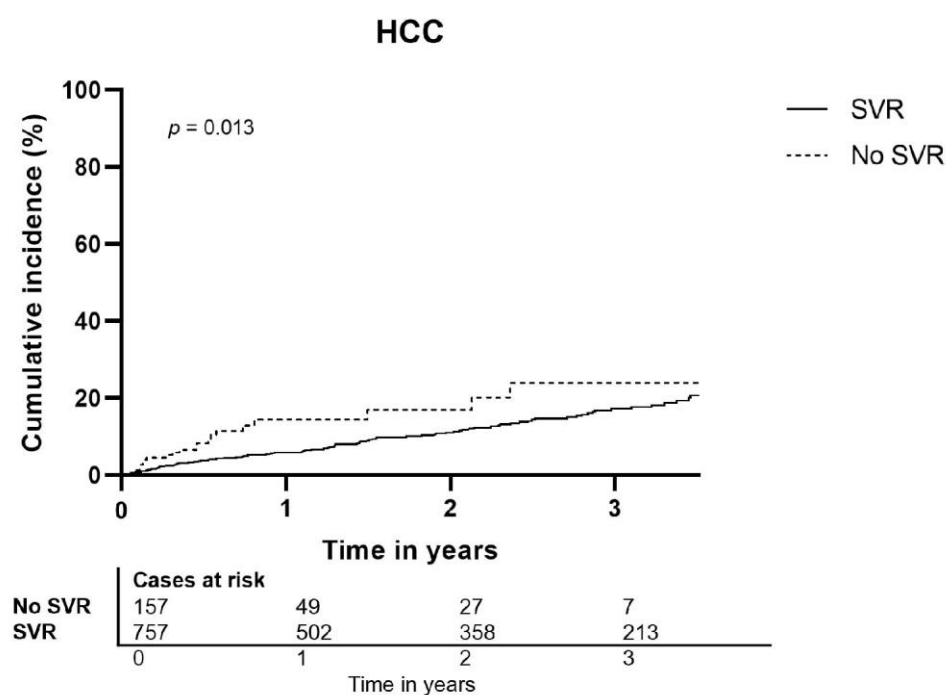
Further decompensation, LT and death



B.



C.

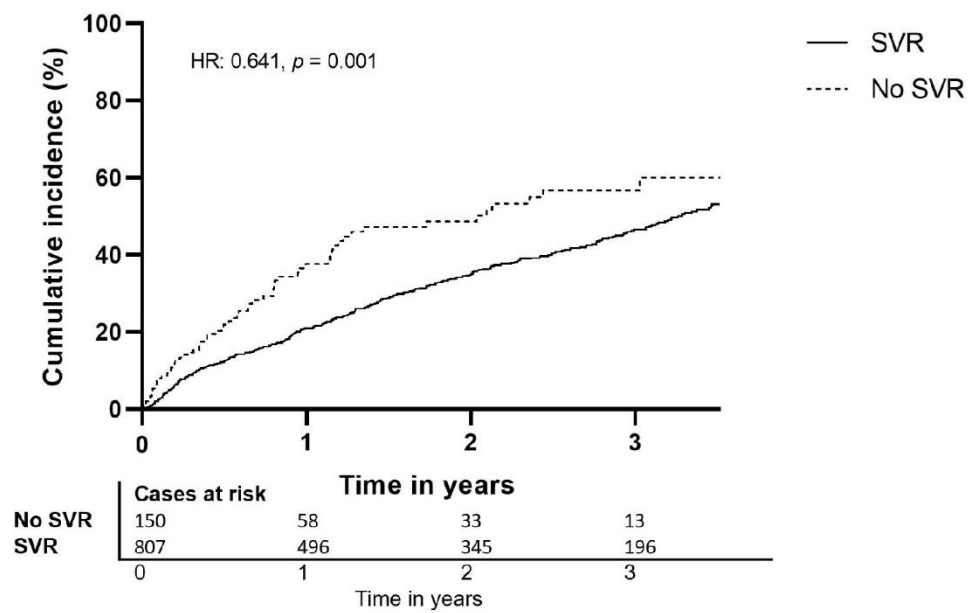


D.

Supplementary figure 2. Cumulative incidence of liver-related events for patients with SVR versus without SVR after the first treatment regimen. (A) Liver-related events*, (B) Composite of further decompensation, LT and death, (C) Composite of HCC, LT and death,

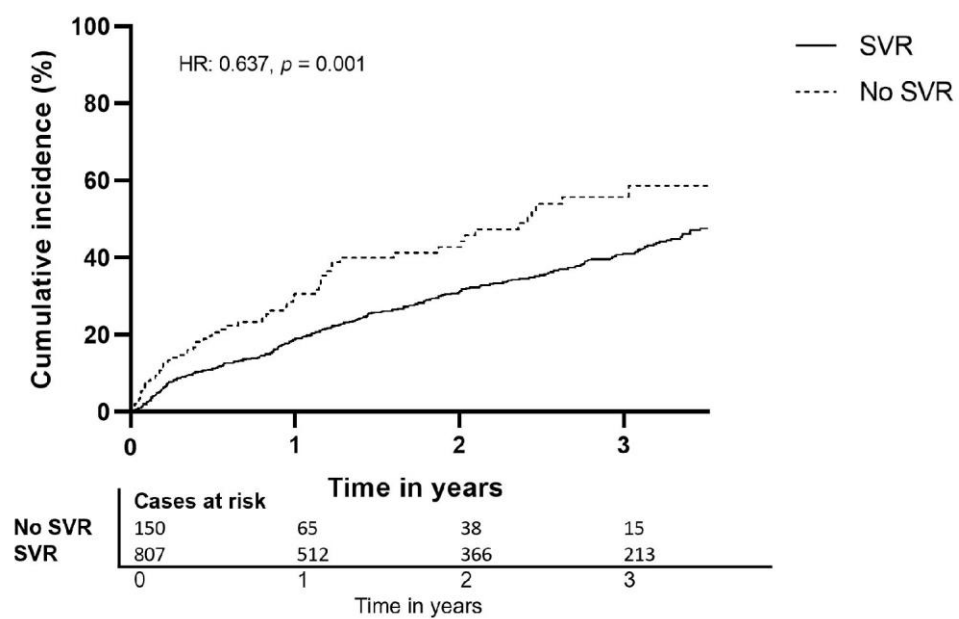
(D) HCC. Statistical significance was assessed with the Log-rank test. *Liver-related events were defined as the first of a composite of (1) further decompensation (newly developed hepatic encephalopathy and/or a spontaneous bacterial peritonitis and/or a first or recurrent variceal bleed, (2) development of HCC, (3) LT or, (4) death. Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; SVR, sustained virological response.

Liver-related events

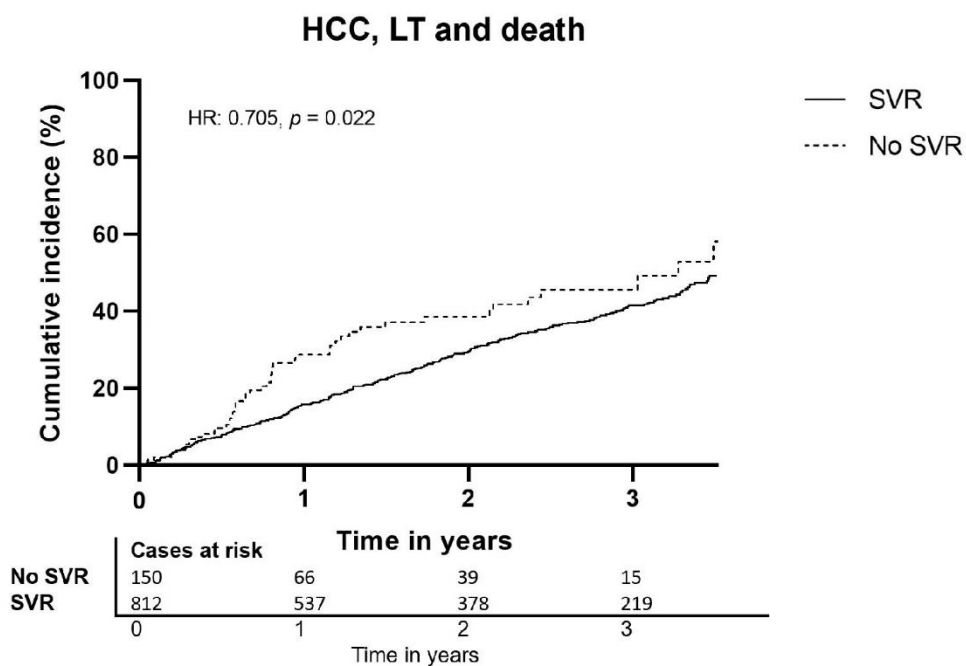


A.

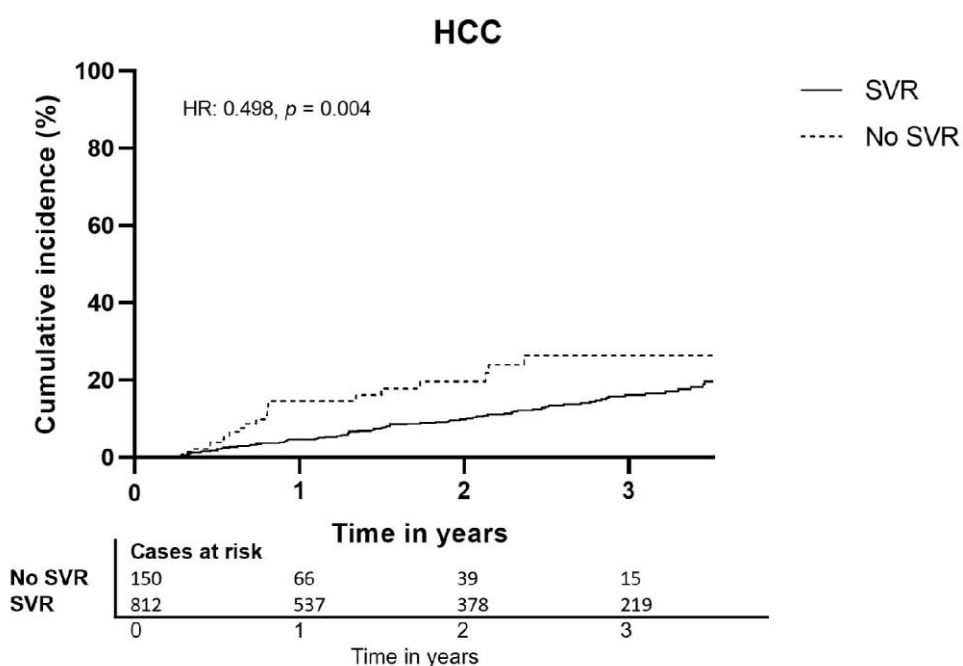
Further decompensation, LT and death



B.



C.



D.

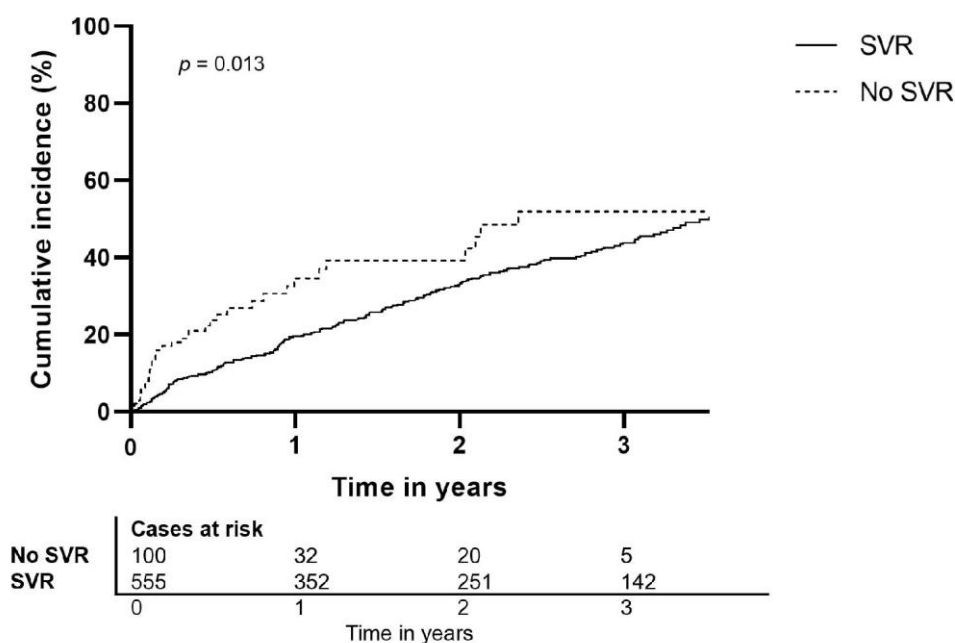
Supplementary figure 3. Cumulative incidence of liver-related events for patients with SVR versus without SVR excluding patients with HCC in the first 3 months after start of DAA therapy. (A) Liver-related events*, (B) Composite of further decompensation, LT and death, (C) Composite of HCC, LT and death, (D) HCC. Kaplan-Meier curves were constructed using a clock-reset approach, in which patients who achieved SVR were censored

in the non-SVR group, with subsequent follow-up time transferred to the SVR group.

Comparisons were performed using Cox regression with SVR as time-varying covariate.

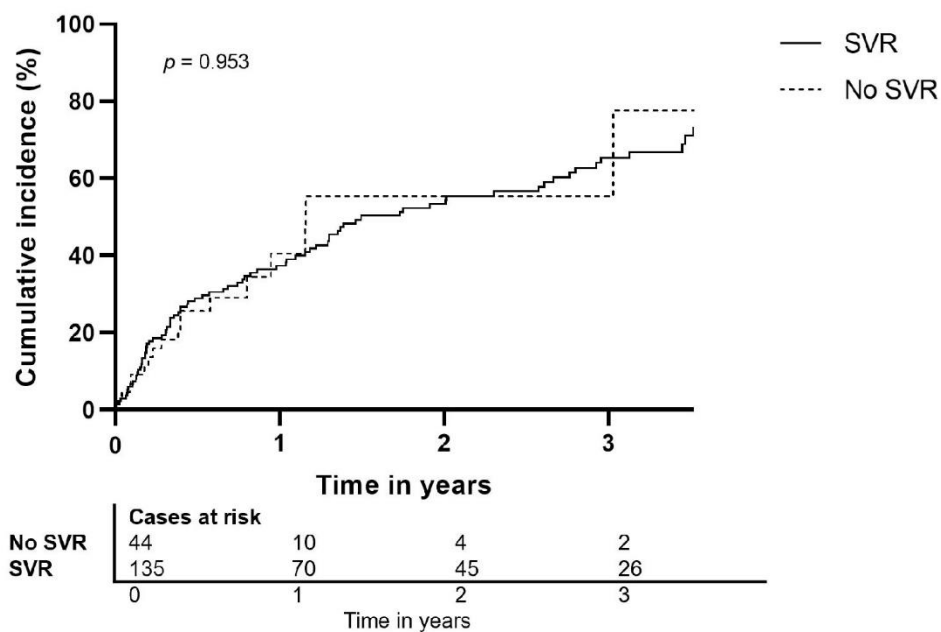
*Liver-related events were defined as the first of a composite of (1) further decompensation (newly developed hepatic encephalopathy and/or a spontaneous bacterial peritonitis and/or a first or recurrent variceal bleed, (2) development of HCC, (3) LT or, (4) death. Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; SVR, sustained virological response.

Liver-related events in patients with a MELD <15



A.

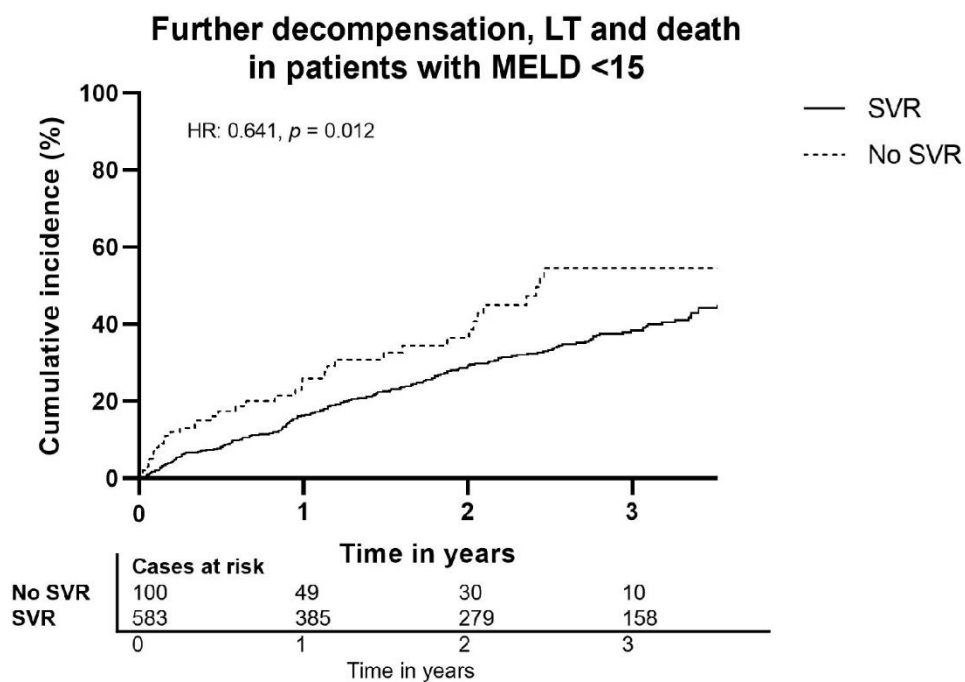
Liver-related events in patients with a MELD ≥ 15



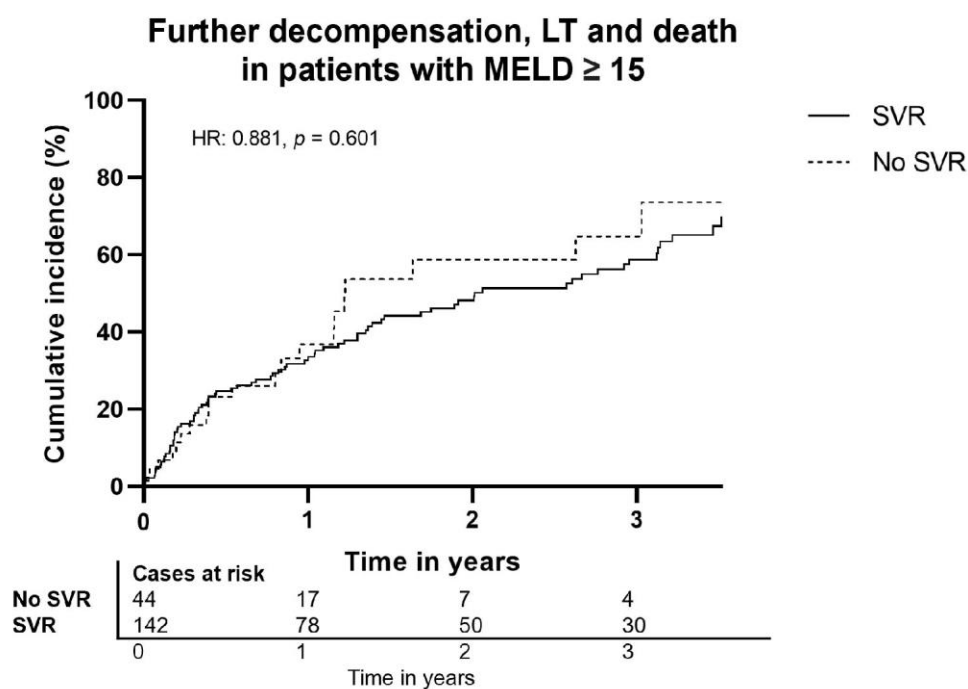
B.

Supplementary figure 4. Cumulative incidence of liver-related events* for patients with SVR versus without SVR after the first treatment regimen stratified for baseline MELD score. (A) MELD score <15 at baseline; (B) MELD score ≥ 15 at baseline. Statistical significance was assessed with the Log-rank test. *Liver-related events were defined as the first of a composite of (1) further decompensation (newly developed hepatic encephalopathy

and/or a spontaneous bacterial peritonitis and/or a first or recurrent variceal bleed, (2) development of HCC, (3) LT or, (4) death. Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; SVR, sustained virological response.



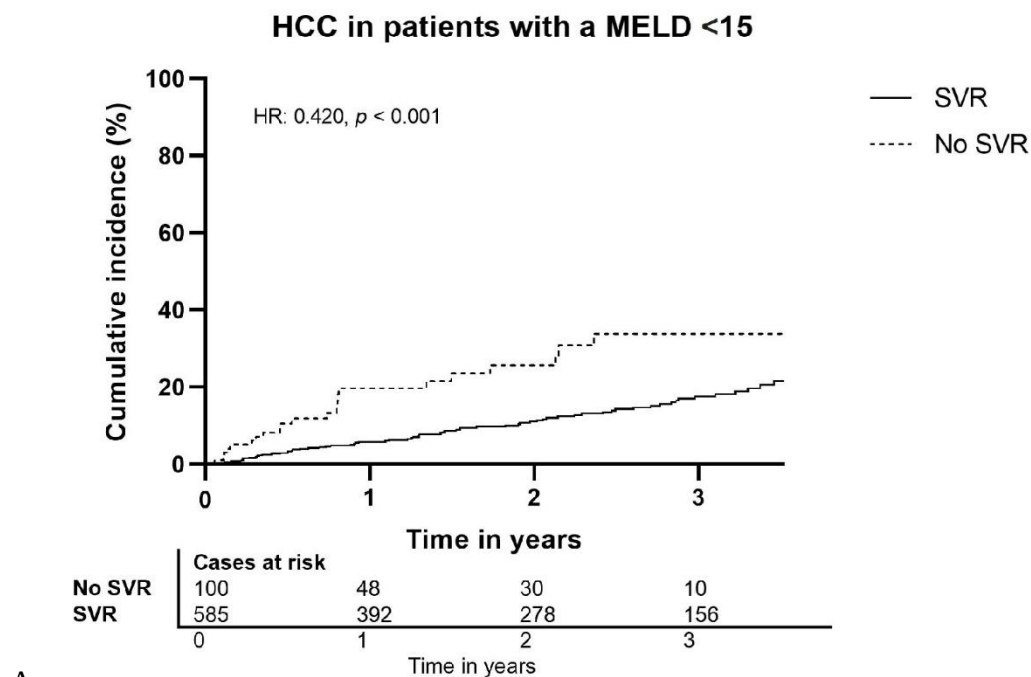
A.



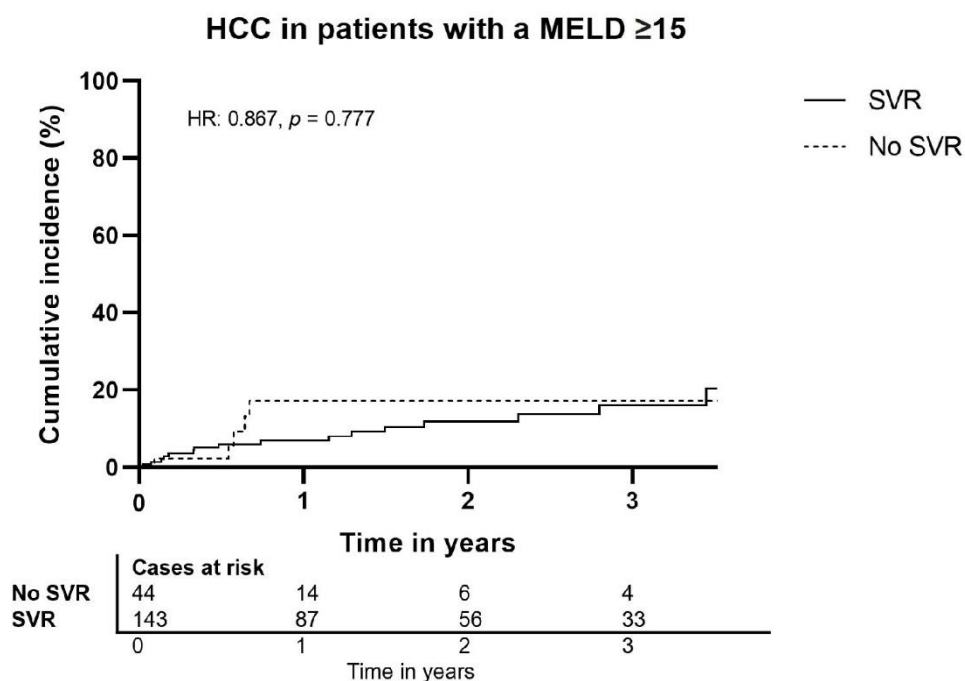
B.

Supplementary figure 5. Cumulative incidence of further decompensation, LT and death for patients with SVR versus without SVR stratified for baseline MELD score. (A) MELD score <15 at baseline; (B) MELD score ≥ 15 at baseline. Kaplan-Meier curves were constructed using a clock-reset approach, in which patients who achieved SVR were censored in the non-SVR group, with subsequent follow-up time transferred to the SVR group.

Comparisons were performed using Cox regression with SVR as a time-varying covariate. Further decompensation was defined as: newly developed hepatic encephalopathy and/or a spontaneous bacterial peritonitis and/or a first or recurrent variceal bleed. Abbreviations: LT, liver transplantation; MELD, model for end-stage liver disease; SVR, sustained virological response.



A.

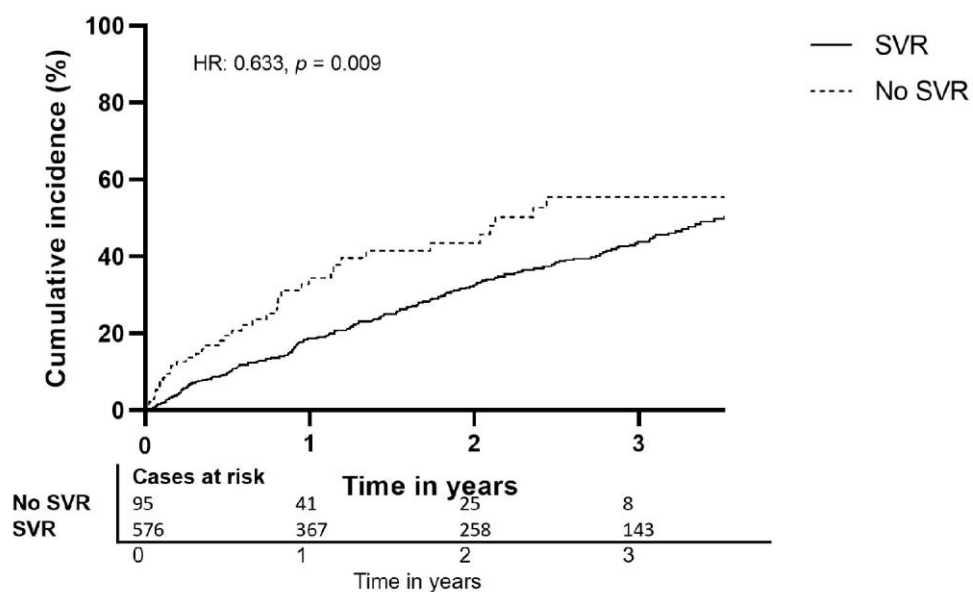


B.

Supplementary figure 6. Cumulative incidence of HCC for patients with SVR versus without SVR stratified for baseline MELD score. (A) MELD score <15 at baseline; (B) MELD score ≥ 15 at baseline. Kaplan-Meier curves were constructed using a clock-reset approach, in which patients who achieved SVR were censored in the non-SVR group, with

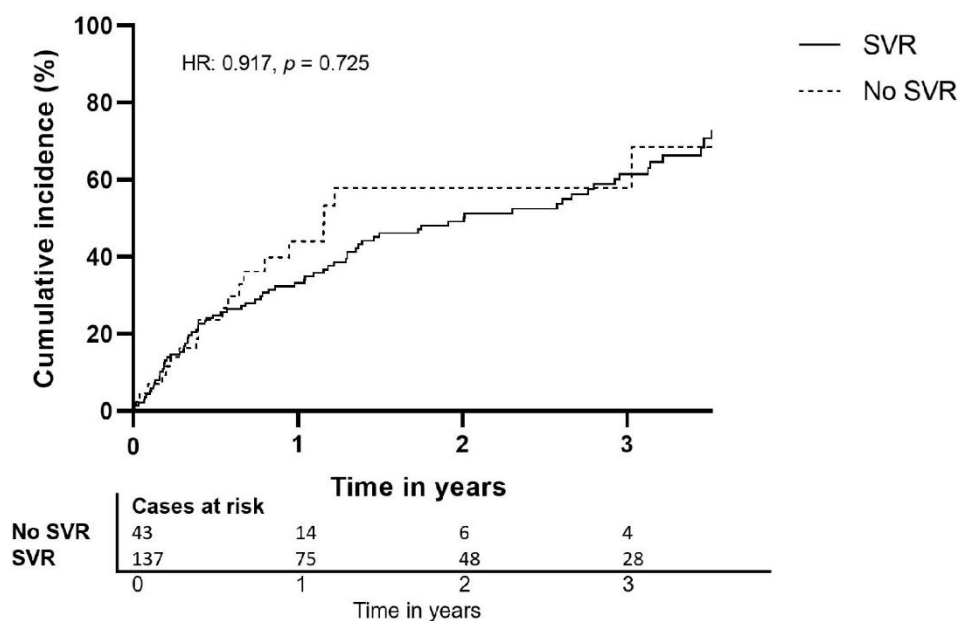
subsequent follow-up time transferred to the SVR group. Comparisons were performed using Cox regression with SVR as a time-varying covariate. Abbreviations: HCC, hepatocellular carcinoma, MELD, model for end-stage liver disease; SVR, sustained virological response.

Liver-related events in patients with a MELD <15



A.

Liver-related events in patients with a MELD ≥ 15



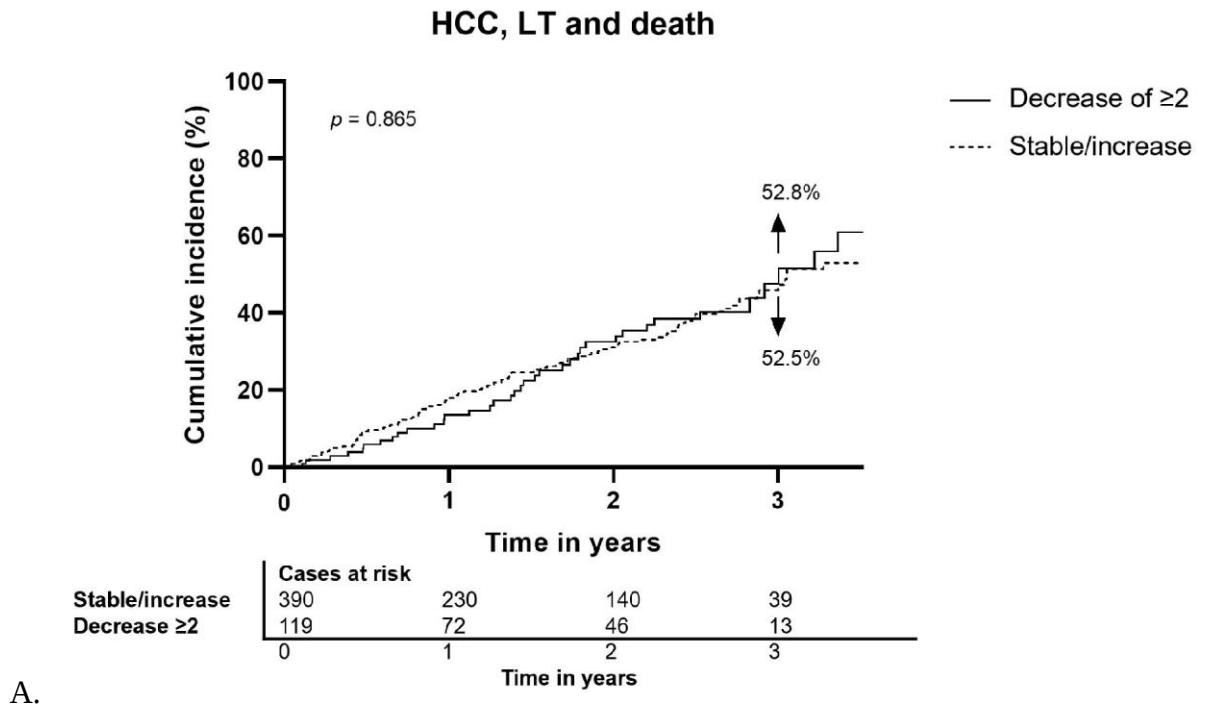
B.

Supplementary figure 7. Cumulative incidence of liver-related events* for patients with SVR versus without SVR stratified for baseline MELD score, excluding patients with HCC in the first 3 months after start of DAA therapy. (A) MELD score <15 at baseline; (B) MELD score ≥ 15 at baseline. Kaplan-Meier curves were constructed using a clock-reset approach, in which patients who achieved SVR were censored in the non-SVR group, with

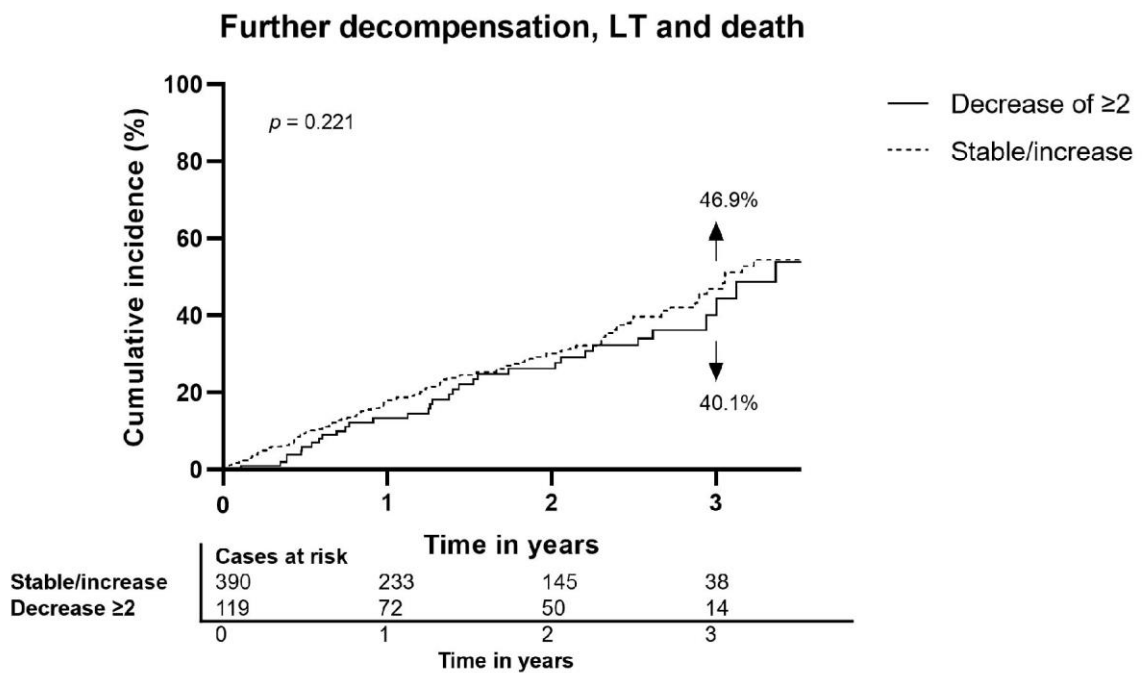
subsequent follow-up time transferred to the SVR group. Comparisons were performed using Cox regression with SVR as a time-varying covariate.

*Liver-related events were defined as the first of a composite of (1) further decompensation (newly developed hepatic encephalopathy and/or a spontaneous bacterial peritonitis and/or a first or recurrent variceal bleed, (2) development of HCC, (3) LT or, (4) death.

Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease, SVR, sustained virological response.



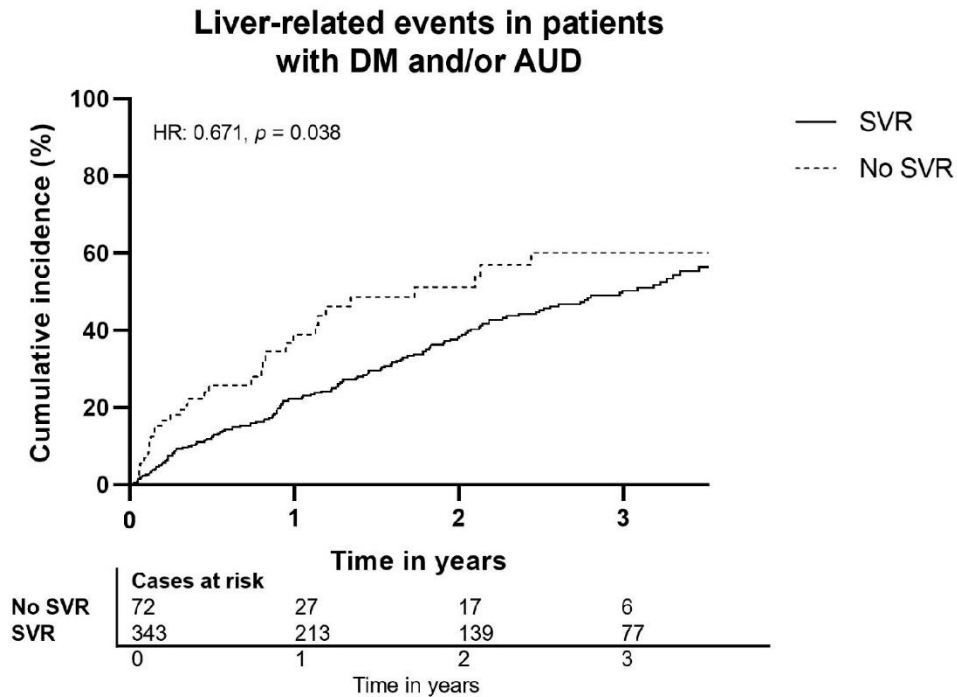
A.



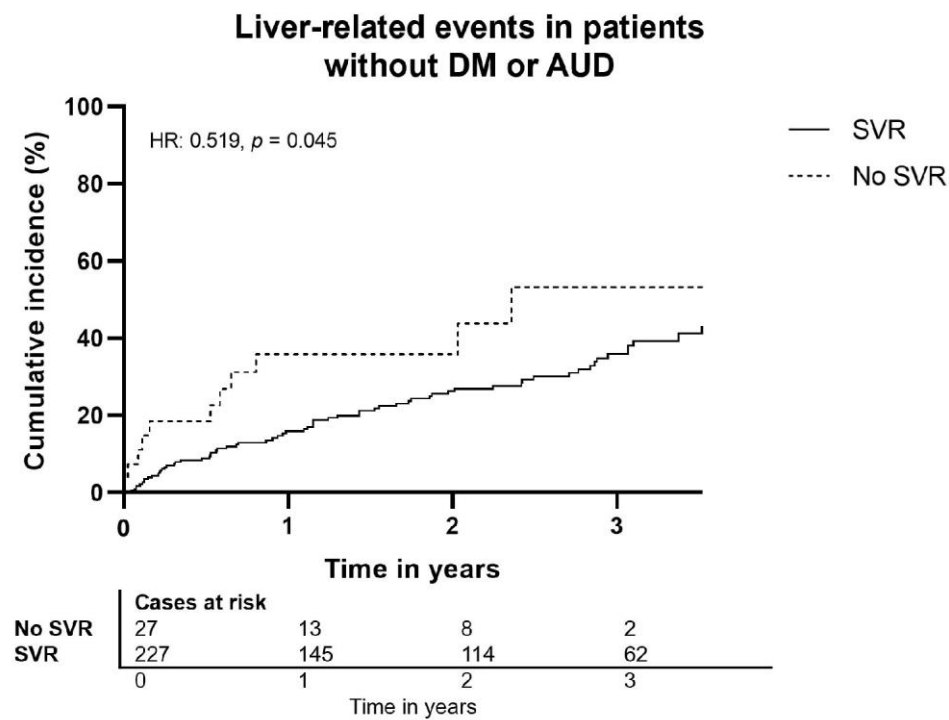
B.

Supplementary figure 8. Cumulative probability of liver-related events stratified for Δ MELD. (A) Composite of HCC, LT and death, (B) Composite of further decompensation, LT and death. Patients were categorized into 2 subgroups: a MELD score decrease of minimal 2 points, or a stable or increased MELD score. Statistical significance was assessed with the

Log-rank test. Further decompensation was defined as newly developed hepatic encephalopathy and/or a spontaneous bacterial peritonitis and/or a first or recurrent variceal bleed. Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease.



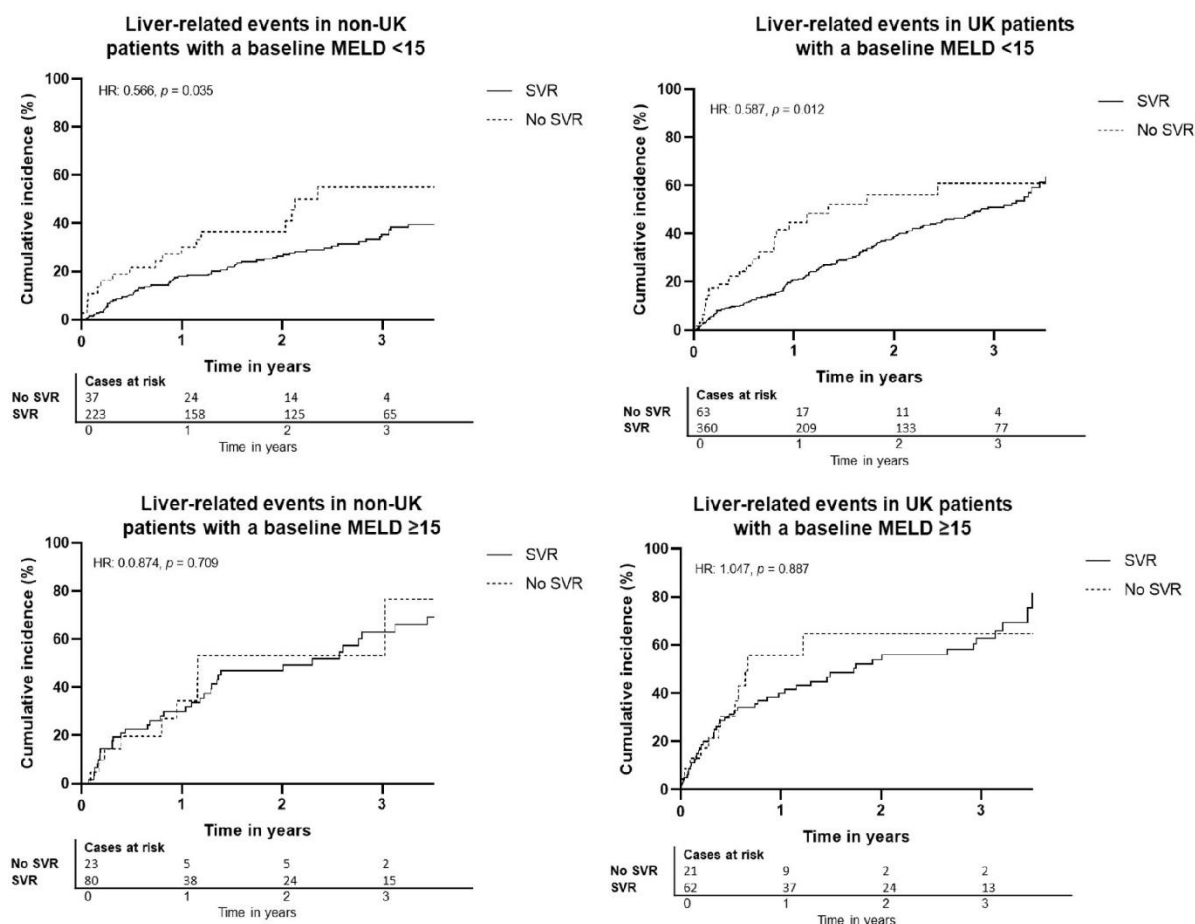
A.



B.

Supplementary figure 9. Cumulative probability of liver-related events* for patients with SVR versus without SVR and a baseline MELD <15 stratified for patients with and without DM and/or AUD. (A) Patients with DM and/or AUD; (B) Patients without DM and/or DM. Kaplan-Meier curves were constructed using a clock-reset approach, in which

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Supplementary figure 10. Cumulative probability of liver-related events* for patients with SVR versus without SVR and a baseline MELD <15 stratified for patients from the UK versus non-UK. Kaplan-Meier curves were constructed using a clock-reset approach, in which patients who achieved SVR were censored in the non-SVR group, with subsequent follow-up time transferred to the SVR group. Comparisons were performed using Cox regression with SVR as a time-varying covariate. *Liver-related events were defined as the first of a composite of (1) further decompensation (newly developed hepatic encephalopathy and/or a spontaneous bacterial peritonitis and/or a first or recurrent variceal bleed, (2) development of HCC, (3) LT or (4) death. Abbreviations: AUD, alcohol use disorder; DM, diabetes mellitus; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease, SVR, sustained virological response.