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Clinical outcomes following DAA therapy in patients with HCV-related cirrhosis depend on disease severity

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Background & Aims: HCV-infected patients with cirrhosis achieve high sustained virological response (SVR) rates with direct-acting antivirals (DAAs) even after hepatic decompensation. We aimed to assess the clinical outcome following DAAs among patients with compensated and decompensated cirrhosis in relation to SVR and changes in model for end-stage liver disease (MELD) score.

Methods: Consecutive DAA-treated chronic HCV-infected patients with cirrhosis from 4 hepatology clinics were included. The primary endpoint in survival analyses was clinical disease progression, defined as liver failure, hepatocellular carcinoma, liver transplantation or death.

Results: In total, 868 patients were included with a median age of 59 (IQR 54–65) years; 719 (83%) with Child-Pugh A cirrhosis and 149 (17%) with Child-Pugh B/C cirrhosis. SVR was attained by 647 (90%) Child-Pugh A patients and 120 (81%) Child-Pugh B/C patients. During a median follow-up of 28 (IQR 20–36) months, 102 (14%) Child-Pugh A patients and 96 (64%) Child-Pugh B/C patients experienced clinical disease progression. SVR was independently associated with an improved event-free survival in patients with Child-Pugh A cirrhosis (adjusted hazard ratio [HR] 0.47; 95% CI 0.27–0.82, p = 0.007), but not in patients with Child-Pugh B/C cirrhosis (adjusted HR 1.23; 95% CI 0.67–2.26; p = 0.51). Twelve weeks post-DAAs, 28 (19%) patients with Child-Pugh B/C cirrhosis had ≥2-point MELD decline, but their 2-year event-free survival did not differ from those with a stable MELD (47.9%; 95% CI 28.7–67.1 *vs.* 48.9%; 95% CI 38.1–59.7, respectively, p = 0.99).

Conclusions: Among patients with chronic HCV infection, DAA-induced SVR was associated with a reduced risk of clinical disease progression in patients with Child-Pugh A cirrhosis but not in patients with Child-Pugh B/C cirrhosis. In Child-Pugh B/C cirrhosis, a ≥2-point MELD decline did not translate into improved clinical outcome.

Lay summary: Chronic HCV infection can be cured with antiviral therapy. In this study, we evaluated the long-term effects of antiviral therapy on liver-related complications in patients with cirrhosis. Our results suggest that patients with compensated cirrhosis who were cured of their HCV infection have a lower rate of complications. In contrast, the rate of complications was not related to virological cure among those with decompensated cirrhosis. While these patients seem to remain in need of liver transplantation, antiviral therapy may lower their priority on the liver transplantation waiting list.

Introduction

Worldwide, approximately 71 million people are chronically infected with HCV.[1] Chronic hepatic inflammation leads to fibrosis that may progress to cirrhosis, at which stage individuals are at risk of liver failure, hepatocellular carcinoma (HCC) and liver-related death.[2,3] In addition, HCV infection is associated with a number of non-hepatic complications. As a result, chronic HCV infection is associated with significantly impaired overall survival.[4]

Multiple long-term follow-up studies have shown that patients with compensated cirrhosis who achieve sustained virological response (SVR) with interferon (IFN)-based therapy have improved long-term outcomes.[2] Unfortunately, even optimized IFN regimens were hampered by a long treatment duration with substantial side-effects and limited virological efficacy, especially in the setting of advanced liver disease.[5] With direct acting antivirals (DAAs), however, even patients with compensated cirrhosis achieve SVR rates over 95%.[6–9]

Our group previously initiated a retrospective cohort study in which all patients with HCV-related cirrhosis treated with DAAs were included.[10] We found that treatment was safe and effective in this population, even in those with decompensated cirrhosis. For this group IFN-based therapy was contraindicated, leaving liver transplantation (LT) as the only option to improve their prognosis. Both clinical trials and real-world reports indicated

Keywords: HCV; Decompensated cirrhosis; MELD score; Delta MELD; Clinical outcome; DAAs.
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SVR rates around 80% with DAAs among patients with current or past decompensation.[10–16] The first studies on short-term outcomes after DAA therapy in patients with decompensated cirrhosis documented improvements in the model for end-stage liver disease (MELD) score and other biochemical parameters of liver function.[10–14,16,17] However, it is currently unclear how viral clearance and MELD score improvements relate to the occurrence of clinical events.

The aim of this study was to assess the relationship between DAA-induced SVR and clinical outcome in patients with chronic HCV infection and cirrhosis, both compensated and decompensated. The secondary aim was to evaluate the association between treatment-induced changes in MELD score and clinical outcomes in patients with decompensated cirrhosis.

Patients and methods

Study population and design

This international retrospective cohort study included all consecutive patients with chronic HCV infection and cirrhosis treated with IFN-free DAA regimens from 4 academic referral centres including 1 in the Netherlands (Erasmus MC, University Medical Center Rotterdam), 1 in Germany (Hannover Medical School) and 2 in Canada (Toronto Centre for Liver Disease and Gastrointestinal Research Institute Vancouver). The choice of DAA regimen was at the discretion of the treating physician. This study is an extension of our previously described cohort.[10] Patients who underwent a liver transplantation prior to the start of DAA treatment were excluded, as well as those co-infected with HIV or HBV. A single investigator reviewed all medical charts to acquire details on demographics, virologic and clinical data. Data were obtained on patient characteristics (sex, age, ethnicity, BMI), comorbidities (diabetes mellitus [DM] and a reported history of alcohol abuse [defined as more than 50 g/day]), HCV genotype and baseline laboratory parameters. A history of liver failure or HCC prior to the initiation of DAA therapy was recorded as well.

The protocol was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice and was reviewed and approved by the local ethics review board at each institution.

Definition of cirrhosis

Prior to the start of DAA therapy, the presence of cirrhosis was determined by liver biopsy or non-invasive measures of fibrosis. Cirrhosis was defined by a liver biopsy showing a METAVIR score of F4, a transient elastography result of ≥13.0 kPa, or at least 2 of the following: esophageal varices; platelet count below $140*10^9$/L; liver imaging showing a nodular liver, signs of portal hypertension, or ascites; non-invasive serum panels compatible with fibrosis stage 4 (FIB-4 >3.25, APRI >2 or FibroTest [BioPredictive, Paris, France] ≥0.75).[18–21] Baseline Child-Pugh score was calculated within 2 months of DAA initiation. Patients with Child-Pugh A cirrhosis were considered to have compensated cirrhosis, while patients with Child-Pugh B/C cirrhosis were considered to have decompensated cirrhosis.

Sustained virological response

Patients with undetectable HCV RNA ≥12 weeks after cessation of antiviral therapy were considered to have attained SVR. HCV RNA was measured using the COBAS AmpliPrep/COBAS TaqMan, version 2 (lower limit of detection, 15 IU/ml) (Roche, Pleasanton, CA) or the RealTime HCV assay (lower limit of quantification, 12 IU/ml) (Abbott Molecular, Des Plaines, IL) according to the manufacturer's instructions.

The MELD score

The MELD score was calculated at baseline and during follow-up.[22] To compute delta MELD (ΔMELD), the baseline MELD score was subtracted from the MELD score at any specific timepoint during follow-up. The ΔMELD was categorized in 3 subgroups as these could have clinical relevance for the patient's outcome and/or prioritization on the LT waiting list. The subgroups were: ΔMELD ≤ -2 (MELD decline), -2 < ΔMELD < 2 (stable MELD), and ΔMELD ≥ 2 (MELD increase). In line with our prior report, a cut-off of 2 points was chosen as this was considered to potentially have a relevant impact on the individual's priority on the LT waiting list.[10]

Clinical outcomes

The primary endpoint was clinical disease progression, which is a combined endpoint of liver failure, HCC, LT or death, whichever came first. Liver failure was defined as: i) new-onset variceal bleeding, ascites, jaundice, or hepatic encephalopathy in patients with compensated cirrhosis; ii) worsening of a pre-existing symptom of decompensated cirrhosis (*i.e.* increased dose of diuretics, addition of rifaximin for pre-existing hepatic encephalopathy, or hospital admission for a new liver failure event); iii) a new liver failure event other than the event which was already present at baseline (for example newly developed hepatic encephalopathy in a patient with ascites at baseline). Hospital admission for recurring large volume paracentesis was not considered as a liver failure event. In sensitivity analyses worsening of a pre-existing symptom of decompensated cirrhosis was excluded from the definition of clinical disease progression. The HCC-free and LT-free survival, as more robust clinical outcomes, were considered as secondary endpoints due to the expected limited number of events.

Statistical analyses

Data are presented as median (IQR) or as proportions. For comparisons of categorical and continuous variables between patients with Child-Pugh A *vs.* Child-Pugh B/C cirrhosis the Student's *t* test, chi-square, Pearson correlation or the Mann-Whitney *U* test were used, where appropriate.

Baseline (t = 0) was defined as the initiation of treatment with DAAs. Patients were excluded if they were lost to follow-up or deceased prior to SVR determination. Outcomes were compared between patients with compensated (Child-Pugh A) and decompensated (Child-Pugh B/C) cirrhosis at baseline. Further survival analyses were stratified according to the Child-Pugh status at baseline, thereby dividing the cohort in a subgroup with Child-Pugh A cirrhosis and a subgroup with Child-Pugh B/C cirrhosis.

The Kaplan-Meier method was used to assess the cumulative event-free, HCC-free or LT-free survival. HCC-free survival was assessed in patients without HCC prior to the initiation of DAA therapy. Differences in the cumulative incidence for categorical variables were assessed through the log-rank test. Cox proportional hazards regression was used to evaluate the association between SVR or ΔMELD and clinical outcome, adjusted for other baseline variables in a stepwise approach. Patients were censored at their last follow-up or at the time of LT. As some patients without SVR were re-treated during follow-up, patients

Table 1. Baseline characteristics.

	Overall	Child-Pugh A cirrhosis				Child-Pugh B/C cirrhosis				
		Overall	SVR	Non-SVR	*p* value SVR *vs.* non-SVR	Overall	SVR	Non-SVR	*p* value SVR *vs.* non-SVR	*p* value Child-Pugh A *vs.* B/C
	(n = 868)	(n = 719)	(n = 647)	(n = 72)		(n = 149)	(n = 119)	(n = 30)		
Age, median (IQR), years	59 (54-65)	59 (54-65)	59 (54-65)	58 (54-64)	0.48	59 (53-65)	60 (54-66)	53 (48-58)	0.001	0.25
Male	553 (64%)	462 (64%)	410 (63%)	52 (73%)	0.10	91 (62%)	69 (58%)	22 (79%)	0.04	0.58
BMI (n = 733)	27 (24-30)	27 (24-30)	27 (24-30)	28 (24-32)	0.50	28 (25-31)	28 (25-31)	28 (27-31)	0.17	0.16
Diabetes mellitus	279 (21%)	145 (20%)	129 (20%)	16 (23%)	0.56	34 (23%)	30 (25%)	4 (14%)	0.22	0.43
HBV anti-core positive	202 (24%)	174 (25%)	156 (25%)	18 (27%)	0.69	28 (20%)	23 (21%)	5 (19%)	0.80	0.22
History of alcohol abuse (>5 g/day)	193 (22%)	143 (20%)	123 (19%)	20 (28%)	0.07	50 (34%)	35 (29%)	15 (50%)	0.03	<0.001
Genotype HCV										
1	623 (72%)	524 (73%)	485 (75%)	39 (54%)	0.001	99 (66%)	84 (71%)	15 (50%)	0.01	0.03
2	43 (5%)	35 (5%)	32 (5%)	3 (4%)		8 (5%)	7 (6%)	1 (3%)		
3	152 (18%)	119 (17%)	94 (15%)	25 (35%)		33 (22%)	19 (16%)	14 (47%)		
4	39 (5%)	33 (5%)	28 (4%)	5 (7%)		6 (4%)	6 (5%)	0 (0%)		
5	2 (0.2%)	0 (0%)	0 (0%)	0 (0%)		2 (1%)	2 (2%)	0 (0%)		
6	4 (0.5%)	4 (0.6%)	4 (0.6%)	0 (0%)		0 (0%)	0 (0%)	0 (0%)		
Mixed	2 (0.2%)	1 (0.1%)	1 (0.2%)	0 (0%)		1 (0.7%)	1 (0.8%)	0 (0%)		
Unknown	3 (0.3%)	3 (0.4%)	3 (0.5%)	0 (0%)		0 (0%)	0 (0%)	0 (0%)		
Treatment regimen										
NS3/4 NS5A	11 (1%)	11 (2%)	10 (2%)	1 (1%)	<0.001	0 (0%)	0 (0%)	0 (0%)	0.003	0.007
NS3/4 NS5B	116 (13%)	96 (13%)	90 (14%)	6 (8%)		20 (13%)	19 (16%)	1 (3%)		
NS3/4 NS5A/B	81 (9%)	78 (11%)	76 (12%)	2 (3%)		3 (2%)	3 (3%)	0 (0%)		
NS5B	158 (18%)	126 (18%)	85 (13%)	41 (57%)		32 (22%)	18 (15%)	14 (47%)		
NS5A/B	499 (58%)	407 (57%)	385 (60%)	22 (31%)		92 (62%)	77 (65%)	15 (50%)		
Unknown	3 (0.3%)	1 (0.1%)	1 (0.2%)	0 (0%)		2 (1%)	2 (2%)	0 (0%)		
Lab results median (IQR)										
Platelets, x10^9/L	114 (78-162)	121 (85-169)	123 (87-171)	104 (80-136)	0.05	78 (53-110)	78 (50-109)	79 (64-112)	0.60	<0.001
ALT, IU/L	79 (48-125)	88 (51-132)	87 (51-129)	98 (58-154)	0.09	57 (34-81)	57 (34-77)	56 (31-88)	0.88	<0.001
AST, IU/L	80 (54-117)	80 (53-120)	79 (52-118)	102 (68-140)	0.001	79 (55-107)	79 (52-105)	83 (62-122)	0.19	0.60
Albumin, g/L	38 (34-41)	39 (36-42)	39 (36-42)	37 (34-40)	0.004	30 (27-34)	30 (27-35)	31 (25-33)	0.05	<0.001
Total bilirubin, μmol/L	15 (10-22)	13 (10-19)	13 (10-19)	15 (11-20)	0.15	33 (20-47)	33 (20-46)	38 (23-49)	0.23	<0.001
INR	1.1 (1.1-1.3)	1.1 (1.1-1.2)	1.1 (1.0-1.2)	1.2 (1.1-1.3)	0.001	1.4 (1.2-1.6)	1.4 (1.2-1.5)	1.4 (1.2-1.6)	0.33	<0.001
Creatinine, μmol/L	71 (62-81)	71 (63-80)	72 (63-81)	66 (62-75)	0.007	72 (62-92)	72 (62-90)	71 (62-93)	0.82	0.19
Child-Pugh										
A	719 (83%)	719 (100%)	647 (100%)	72 (100%)	n.a.	0	0	0	0.18	n.a.
B	126 (15%)	0 (0%)	0 (0%)	0 (0%)		126 (85%)	103 (87%)	23 (77%)		
C	23 (3%)	0 (0%)	0 (0%)	0 (0%)		23 (15%)	16 (13%)	7 (23%)		
MELD score	8.5 (7.5-10.6)	8.0 (7.2-9.4)	8.0 (7.2-9.4)	8.3 (7.5-9.5)	0.05	13.4 (10.8-15.2)	13.0 (10.7-14.8)	13.5 (11.5-16.1)	0.37	<0.001
SVR on first treatment	767 (88%)	647 (90%)				119 (81%)				0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; MELD, model for end-stage liver disease; SVR, sustained virological response. Data are presented as n (%) unless otherwise noted. Data was available for 100% of the patients, except for the following characteristics in which it was available for: BMI in 733 (84.4%) patients, Genotype in 865 (99.7%) patients, platelets in 863 (99.4%) patients, ALT in 863 (99.4%) patients, AST in 866 (99.8%), albumin in 865 (99.7%), total bilirubin in 864 (99.5%) patients, INR in 856 (98.6%) patients, creatinine in 859 (99.0%) patients and MELD-score in 846 (97.5%) patients. To assess significance, the Student's *t*-test, Chi-square test, Pearson correlation or Mann-Whitney *U* test were used, where appropriate.

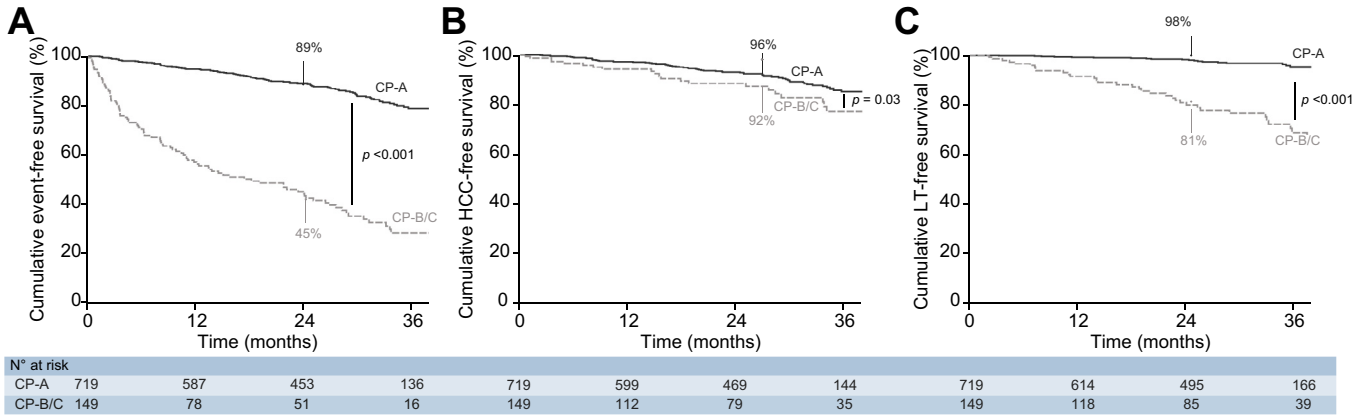

Fig. 1. Survival stratified for patients with Child-Pugh A and Child-Pugh B/C cirrhosis. Statistical significance was assessed with Log-rank test. CP-A, Child-Pugh A; CP-B/C, Child-Pugh B/C; HCC, hepatocellular carcinoma; LT, liver transplantation.

were able to switch from a without SVR to a with SVR status. SVR was therefore included in the Cox proportional hazards regression analyses as a time-dependent covariate. Survival curves according to SVR status were constructed using the clock-reset approach. Patients who switched from the without SVR to the with SVR group were censored in the without SVR group at the start of the treatment by which SVR was attained. The time was then set to zero for further follow-up in the SVR group.

Among patients with Child-Pugh B/C cirrhosis, ΔMELD was assessed 12 weeks after cessation of DAAs ($\Delta MELD_{12}$), at which

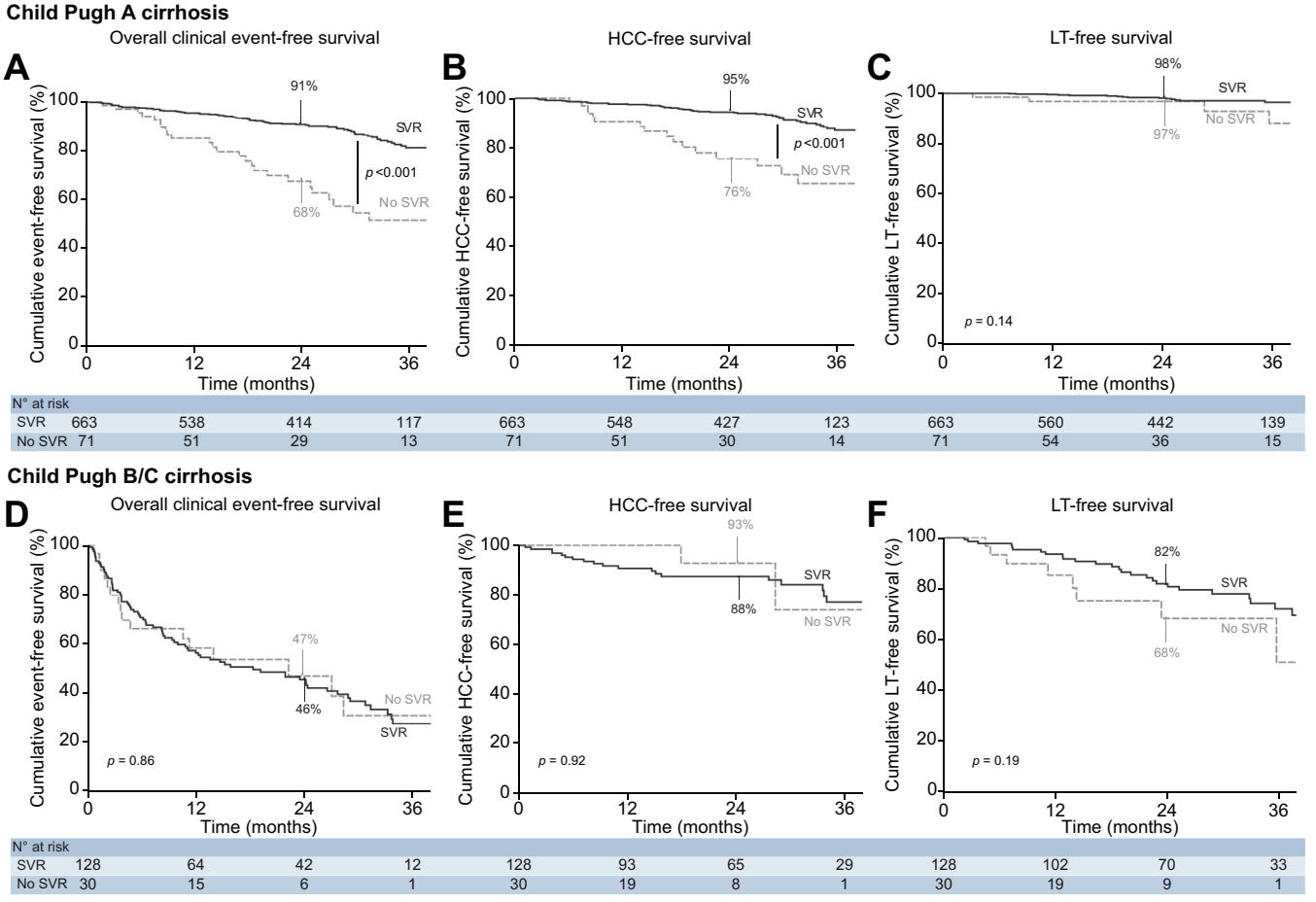

Fig. 2. Survival in patients with SVR vs. no SVR. (A-C) Child-Pugh A cirrhosis; (D-F) Child Pugh B/C cirrhosis. Statistical significance was assessed with Log-rank test. HCC, hepatocellular carcinoma; LT, liver transplantation; SVR, sustained virological response.

Table 2. Cox proportional hazards regression for event-free survival in patients with Child-Pugh A cirrhosis.

		Univariate		Multivariate	
Variables	**Incidence rate per 100 PY (95% CI)**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Age (per year)		1.03 (1.01-1.05)	0.005	1.04 (1.02-1.07)	0.002
<59	5.2 (3.6–6.8)				
≥59	7.9 (5.9–9.9)				
Sex					
Female	5.2 (3.3–7.0)	1 [Reference]		1 [Reference]	
Male	7.4 (5.7–9.1)	1.41 (0.92–2.16)	0.12	1.22 (0.77–1.95)	0.40
Genotype					
Non-genotype 3	5.6 (4.3–6.8)	1 [Reference]		1 [Reference]	
Genotype 3	12.0 (7.7–16.4)	2.17 (1.41–3.34)	<0.001	2.48 (1.45–4.24)	0.001
History of alcohol abuse					
No	6.0 (4.7–7.4)	1 [Reference]		1 [Reference]	
Yes	9.2 (5.7–12.6)	1.46 (0.94–2.27)	0.09	1.69 (1.01–2.84)	0.05
Diabetes mellitus					
No	6.2 (4.8–7.6)	1 [Reference]			
Yes	8.1 (4.9–11.3)	1.31 (0.84–2.06)	0.24		
BMI		0.96 (0.92–1.00)	0.05	0.96 (0.92–1.00)	0.07
<26.9	8.2 (6.0–10.4)				
≥26.9	5.0 (3.3–6.7)				
Anti-HBc					
No	5.6 (4.2–7.0)	1 [Reference]			
Yes	9.1 (6.0–12.2)	1.59 (1.04–2.42)	0.03		
PI-containing regimen					
No	7.6 (6.0–9.2)	1 [Reference]			
Yes	4.0 (2.2–5.9)	0.53 (0.32–0.89)	0.02		
Platelet count, x10^9/L		0.96 (0.92–0.99)	0.02	1.00 (1.00–1.00)	0.50
<121	8.3 (6.3–10.3)				
≥121	4.9 (3.3–6.4)				
ALT, IU/L		1.00 (1.00–1.00)	0.19		
<88	6.6 (4.8–8.4)				
≥88	6.0 (4.3–7.8)				
AST, IU/L		1.00 (1.00–1.00)	0.54		
<80	5.9 (4.2–7.6)				
≥80	7.0 (5.1–8.8)				
Albumin, g/L		0.93 (0.89–0.96)	<0.001	0.93 (0.89–0.97)	0.001
<39	8.8 (6.6–11.0)				
≥39	4.7 (3.3–6.2)				
Total bilirubin, μmol/L		1.02 (0.99–1.04)	0.17		
<13	5.6 (3.8–7.4)				
≥13	7.3 (5.5–9.0)				
INR		1.86 (0.81–4.28)	0.14		
<1.105	5.4 (3.8–7.1)				
≥1.105	7.6 (5.7–9.6)				
Creatinine, μmol/L		1.00 (1.00–1.00)	0.009		
<71	5.9 (4.2–7.7)				
≥71	6.7 (4.9-8.5)				
Virological response					
Without SVR	20.2 (12.4-27.9)	1 [Reference]		1 [Reference]	
With SVR	5.4 (4.2-6.6)	0.31 (0.20-0.49)	<0.001	0.47 (0.27-0.82)	0.007

ALT, alanine aminotransferase; Anti-HBc, anti-hepatitis B core antigen; AST, aspartate aminotransferase; HR, hazard ratio; INR, international normalized ratio; PI, protease inhibitor; PY, person-years; SVR, sustained virological response. Cut-offs for continuous variables were based on the median.

time the virological response was determined. The stability of the $\Delta MELD_{12}$ was assessed by comparing $\Delta MELD_{12}$ to the $\Delta MELD_{36}$, which is 24 weeks thereafter. Logistic regression analysis was used to assess which factors were associated with a $\Delta MELD_{12} \leq -2$.

All statistical analyses were 2-tailed and a *p* value of less than 0.05 was considered statistically significant. SPSS version 25 and 26 (SPSS Inc) were used for the analyses.

Results

Patient and cohort characteristics

In total, 945 chronic HCV-infected patients with cirrhosis were treated with DAAs. After excluding patients co-infected with HIV (n = 5), patients who underwent LT prior to start of DAAs (n = 45), patients lost to follow-up (n = 21) or deceased (n = 6) prior to SVR determination, the total study population consisted of 868 patients. Median (IQR) start date of DAA therapy was 06/2015 (01/2015 – 01/2016). Median age was 59 years (IQR 54–65) and 553 (64%) patients were male. Table 1 describes the baseline characteristics for the 719 (83%) patients with Child-Pugh A cirrhosis and the 149 (17%) patients with Child-Pugh B/C cirrhosis. A history of severe alcohol use and HCV genotype 3 were more frequently present among patients with Child-Pugh B/C cirrhosis. Liver-related biochemistry showed statistically significantly lower levels of alanine aminotransferase (ALT) and worse liver function parameters in those with Child-Pugh B/C

Table 3. Cox proportional hazards regression for event-free survival in patients with Child-Pugh B/C cirrhosis.

		Univariate		Multivariate	
Variables	**Incidence rate per 100 PY (95% CI)**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Age (per year)		1.01 (0.99–1.03)	0.50	1.02 (1.00–1.05)	0.07
<58.6	44.4 (32.0–56.9)				
≥58.6	41.2 (29.4–53.0)				
Sex					
Female	33.6 (21.8–45.4)	1 [Reference]		1 [Reference]	
Male	48.5 (36.6–60.3)	1.23 (0.80–1.89)	0.34	0.83 (0.52–1.34)	0.45
Genotype					
Non-genotype 3	38.4 (29.6–47.2)	1 [Reference]		1 [Reference]	
Genotype 3	66.9 (39.6–94.3)	1.49 (0.93–2.40)	0.10	2.10 (1.19–3.73)	0.01
History of alcohol abuse					
No	35.0 (25.8–44.2)	1 [Reference]		1 [Reference]	
Yes	62.2 (42.9–81.4)	1.59 (1.06–2.40)	0.03	1.75 (1.12–2.75)	0.02
DM					
No	42.1 (32.5–51.7)	1 [Reference]			
Yes	43.2 (24.7–61.7)	0.93 (0.57–1.52)	0.78		
BMI		1.02 (0.97–1.06)	0.50		
<27.5	47.2 (32.9–61.5)				
≥27.5	42.9 (30.0–55.9)				
Anti-HBc					
No	40.4 (30.8–50.0)	1 [Reference]			
Yes	46.8 (26.8–66.8)	1.45 (0.89–2.35)	0.13		
Child-Pugh					
Child-Pugh B	35.3 (27.2–43.3)	1 [Reference]		1 [Reference]	
Child-Pugh C	100 (78.3–100.0)	3.10 (1.92–5.00)	<0.001	1.63 (0.87–3.06)	0.13
PI-containing regimen					
No	39.7 (30.8–48.6)	1 [Reference]		1 [Reference]	
Yes	62.5 (34.4–90.6)	1.50 (0.91–2.48)	0.12	1.73 (1.01–2.95)	0.05
Platelet count, x10^9/L		0.97 (0.93–1.01)	0.10		
<78	46.6 (33.8–59.3)				
≥78	38.3 (26.8–49.7)				
ALT, IU/L		1.00 (0.99–1.00)	0.10		
<57	55.6 (40.8–70.4)				
≥57	33.3 (23.2–43.4)				
AST, IU/L		1.00 (1.00–1.00)	0.95		
<79	47.1 (33.9–60.2)				
≥79	39.1 (27.9–50.2)				
Albumin, g/L		0.91 (0.87–0.95)	<0.001	0.93 (0.89–0.98)	0.004
<30	72.3 (51.6–93.0)				
≥30	30.7 (22.1–39.3)				
Total bilirubin, μmol/L		1.02 (1.01–1.03)	0.001	1.01 (1.00–1.03)	0.04
<33	34.0 (23.2–44.8)				
≥33	50.9 (37.7–64.1)				
INR		1.35 (0.87–2.12)	0.19		
<1.37	29.4 (20.3–38.6)				
≥1.37	62.5 (46.0–79.0)				
Creatinine, μmol/L		1.00 (1.00–1.01)	0.27		
<72	38.1 (26.8–49.3)				
≥72	47.0 (34.1–59.9)				
Virological response					
Without SVR	44.5 (22.7–66.3)	1 [Reference]		1 [Reference]	
With SVR	42.4 (33.1–51.7)	1.05 (0.61–1.80)	0.86	1.23 (0.67–2.26)	0.51

ALT, alanine aminotransferase; Anti-HBc, anti-hepatitis B core antigen; AST, aspartate aminotransferase; DM, diabetes mellitus; HR, hazard ratio; INR, international normalized ratio; PI, protease inhibitor; PY, person-years; SVR, sustained virological response.
Cut-offs for continuous variables were based on the median.

cirrhosis (Table 1). With respect to DAAs, 185 (26%) patients with Child-Pugh A cirrhosis were treated with a NS3/4 protease inhibitor (PI) as opposed to 23 (15%) of the patients with Child-Pugh B/C cirrhosis (p = 0.007). In total, SVR was attained by 767 (88%) patients upon the initial DAA-regimen; 647 (90%) for Child-Pugh A cirrhosis and 120 (81%) for Child-Pugh B/C cirrhosis (p <0.001).

Median follow-up was 28 months (IQR 20–36) for patients with Child-Pugh A cirrhosis and 27 months (IQR 16–39) for patients with Child-Pugh B/C cirrhosis. Overall, 198 (23%) patients had a clinical event during follow-up; 102 (14%) patients with Child-Pugh A cirrhosis and 96 (64%) patients with Child-Pugh B/C cirrhosis (Table S1). In patients with Child-Pugh A cirrhosis, the first clinical disease progression event was liver failure in 35 (34%) patients, HCC in 61 (60%) patients, LT in 5 (5%) patients (all with HCC prior to DAA initiation) and death in 1 (1%) patient. In patients with Child-Pugh B/C cirrhosis, the first event was liver failure in 73 (49%) patients, HCC in 15 (10%) patients and LT or death in 8 (5%) patients. Among these 96 patients, the first clinical disease progression event was worsening of a pre-

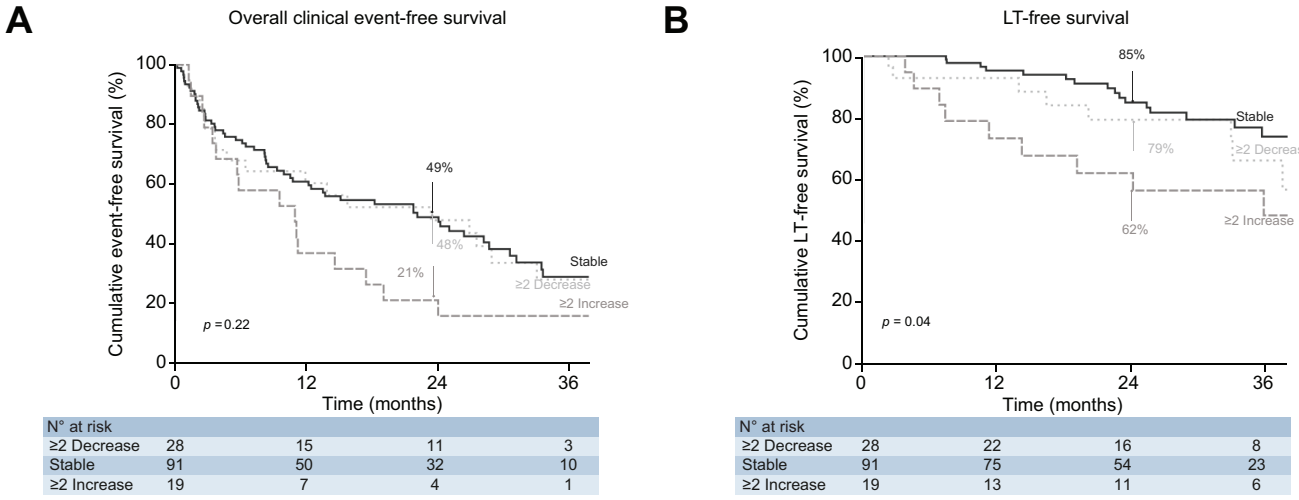

Fig. 3. Child Pugh-B/C cirrhosis: clinical outcome according to the delta MELD at 12 weeks after the end of treatment. Patients were categorized into 3 subgroups: delta MELD ≤-2 (MELD decline; dotted line), -2< delta MELD <2 (stable MELD; solid line), and delta MELD ≥2 (MELD increase; dashed line). Statistical significance was assessed through Cox proportional hazards regression after adjusting for the baseline MELD. LT, liver transplantation; MELD, model for end-stage liver disease.

existing symptom of decompensated cirrhosis in 21 patients, of whom 4 underwent LT or died thereafter. The cumulative 2-year event-free survival was 89.0% (95% CI 86.5%–91.6%) for those with Child-Pugh A cirrhosis compared to 45.2% (95% CI 36.8%-53.6%) for those with Child-Pugh B/C cirrhosis (p <0.001) (Fig. 1). In total, 67 (9%) Child-Pugh A patients and 22 (15%) Child-Pugh B/C patients were diagnosed with HCC, with a 2-year cumulative HCC-free survival of 95.6% (95% CI 93.8%–97.4%) *vs.* 91.7% (95% CI 86.4%–97.0%), respectively (p = 0.03). Nine (1%) Child-Pugh A patients and 19 (13%) Child-Pugh B/C patients underwent LT and 12 (2%) Child-Pugh A patients and 19 (13%) Child-Pugh B/C patients died, of whom 10 and 17 were liver-related deaths, respectively. The 2-year cumulative LT-free survival was 98.3% (95% CI 97.3%–99.3%) *vs.* 81.2% (95% CI 74.3%–88.1%), for Child-Pugh A and Child-Pugh B/C patients, respectively (p < 0.001).

Clinical outcome in patients with Child-Pugh A cirrhosis according to the virological response

Among patients with Child-Pugh A cirrhosis, the cumulative event-free survival at 2 years was statistically significantly higher among those who attained SVR (90.9%; 95% CI 88.6%–93.3%) than among those who did not attain SVR (67.8%; 95% CI 55.5%–80.2%) (p <0.001) (Fig. 2A). Attainment of SVR (adjusted hazard ratio [aHR] 0.47; 95% CI 0.27–0.82; p = 0.007) remained independently associated with clinical disease progression after controlling for age, male sex, HCV genotype 3, history of alcohol abuse, BMI, platelet count and albumin (Table 2).

Cumulative HCC-free survival at 2 years was 94.5% (95% CI 92.5%–96.5%) for those with SVR compared to 75.9% (95% CI 64.1%–87.7%) without SVR (p <0.001) (Fig. 2B). Achievement of SVR was independently associated with an improved HCC-free survival (aHR 0.17; 95% CI 0.09–0.33; p <0.001), in a model in which age, sex and alcohol abuse were also statistically significant predictors. This association remained after excluding HCCs which occurred within the first 6 months of follow-up (aHR 0.14; 95% CI 0.07–0.26; p <0.001).

Cumulative LT-free survival was 98.1% (95% CI 96.9%–99.3%) *vs.* 96.8% (95% CI 92.5%–100.0%) for patients with SVR and patients without SVR, respectively (p = 0.07) (Fig. 2C). In comparison to patients without SVR, those with SVR had a trend toward a favorable LT-free survival (HR 0.44; 95% CI 0.15–1.30; p = 0.14). Due to the limited number of LT or deaths in these patients, extensive multivariate analyses regarding this secondary endpoint were not possible. Controlling for either age, male sex, HCV genotype 3, history of alcohol abuse, albumin, total bilirubin, or platelet count had limited effect on the estimated HR of SVR (ranging between 0.44 and 0.57), which remained outside of the predefined level for statistical significance. In these analyses only HCV genotype 3 was statistically significantly associated with LT or death (for SVR-adjusted HR 3.87; 95% CI 1.58–9.48; p = 0.003).

Clinical outcome in patients with Child-Pugh B/C cirrhosis according to virological response

The cumulative event-free survival at 2 years did not differ significantly between those who attained SVR (46.0%; 95% CI 36.8%–55.2%) and those who did not attain SVR (47.4%; 95% CI 26.8%–68.0%, p = 0.93) (Fig. 2D). Further adjustment for age, male sex, HCV genotype 3, history of alcohol abuse, Child-Pugh C cirrhosis, PI-containing regimen, albumin and total bilirubin did not change this finding (aHR 1.23; 95% CI 0.67–2.26, p = 0.51) (Table 3). When worsening of a pre-existing symptom of decompensated cirrhosis was excluded from the definition of clinical disease progression, there was still no association between SVR and event-free survival (aHR 1.07; 95% CI 0.54–2.13; p = 0.85).

Cumulative HCC-free survival was 87.6% (95% CI 81.5%–93.7%) for those with SVR compared to 92.9% (95% CI 79.4%–100.0%) for those without SVR (p = 0.48) (Fig. 2E). SVR was not associated with improved HCC-free survival (aHR 1.18; 95% CI 0.26–5.47; p = 0.83) after controlling for albumin (aHR 0.85; 95% CI 0.76–0.95). Adjusting for other covariates or excluding HCCs which occurred within the first 6 months of follow-up did not alter the lack of an association between SVR and HCC-free survival.

Cumulative LT-free survival was 81.9% (95% CI 74.5%–89.3%) *vs.* 68.4% (95% CI 47.8%–90.0%) for patients with SVR and patients without SVR, respectively (p = 0.13) (Fig. 2F). Patients with SVR showed a non-significant trend toward favorable LT-free survival (HR 0.57; 95% CI 0.25–1.32; p = 0.19), which reduced with adjustment for alcohol abuse, albumin and total bilirubin (aHR 0.66; 95% CI 0.28–1.55; p = 0.34).

Change in MELD score following DAA therapy in patients with Child-Pugh B/C cirrhosis

The median MELD score at baseline was 13.4 (IQR 10.8–15.2) and the median MELD score 12 weeks after cessation of DAA therapy was 12.8 (IQR 10.3–18.1). The median $\Delta MELD_{12}$ was -0.32 (IQR -1.72 to 0.74); -0.29 (IQR -1.46 to 0.75) among patients with SVR *vs.* -0.95 (IQR -2.01 to 0.63) among patients without SVR (p = 0.54). Twelve weeks after therapy, 28 (19%) patients had an MELD decline of at least 2 points, 91 (61%) patients had a stable MELD and 19 (13%) patients had a MELD increase of at least 2 points. Only age (odds ratio [OR] 0.92; 95% CI 0.88–0.97, p = 0.004) and the MELD score at baseline (OR 1.22; 95% CI 1.04–1.44; p = 0.02) were statistically significantly associated with an MELD decline. SVR was not associated with ≥2-point decline of the MELD score (OR 1.02; 95% CI 0.31–3.30; p = 0.98).

In total, 23 (82%) patients with an MELD decline at 12 weeks remained with a MELD decline at 36 weeks; 86% of patients with SVR *vs.* 67% of patients without SVR (Table S1). None of the patients with an MELD increase and only 12% of patients with a stable MELD 12 weeks after DAA cessation reached a $\Delta MELD_{36}$ ≤-2. A MELD score decline in patients with SVR was reached through improvements of all 3 parameters of the score, whereas in patients without SVR an improvement was predominantly caused by a reduction of total bilirubin (Table S2).

Clinical outcome in patients with Child-Pugh B/C cirrhosis according to the ΔMELD

The cumulative 2-year event-free survival was 47.9% (95% CI 28.7%–67.1%) among patients with $\Delta MELD_{12}$ ≤-2, which was similar to patients with a stable MELD score (48.9%; 95% CI 38.1%–59.7%; p = 0.99) (Fig. 3A). After controlling for the baseline MELD score, an MELD decline ≥2 points was not statistically significantly associated with improved event-free survival (aHR 0.76; 95% CI 0.44–1.34; p = 0.34). This did not change in the sensitivity analyses in which worsening of a pre-existing symptom of decompensated cirrhosis was excluded as an outcome event (aHR 0.94; 95% CI 0.56–1.59; p = 0.82). When assessed continuously, having excluded patients with an MELD increase and adjusted for baseline MELD, the delta MELD at 12 weeks was not statistically significantly related to the event-free survival (HR 1.10; 95% CI 0.92–1.32; p = 0.29). In contrast, among patients with an MELD score increase of ≥2 points, the 2-year event-free survival was 21.1% (95% CI 2.7–39.5, p = 0.09 compared to patients with a stable MELD). With respect to the LT-free survival, patients with an MELD decline had a non-significantly worse outcome compared to those with a stable MELD (Fig. 3B), which did not change (aHR 1.32; 95% CI 0.55–3.15; p = 0.54) after controlling for baseline MELD. Sensitivity analyses among just patients with SVR or with a 3-point $\Delta MELD_{12}$ cut-off showed similar results for both endpoints.

Discussion

In this large international multicenter cohort study, including 868 patients with HCV-related cirrhosis treated with DAAs, achievement of SVR was independently associated with a 2.5-fold lower risk of cirrhosis-related complications or death in patients with compensated cirrhosis. In contrast, no clinical benefit was apparent with HCV eradication in patients with decompensated liver disease. Among patients with Child-Pugh B/C cirrhosis, the event-free survival and LT-free survival did not differ between those with SVR and those without SVR. A proportion of these patients showed a sustained decline of their MELD score of ≥2 points following DAA therapy, which was related to a higher baseline MELD score. However, MELD score improvement did not translate into a beneficial clinical outcome. Thus, DAA therapy may lower prioritization for LT through MELD score reduction, which is likely to primarily affect those with a more urgent need for a new liver.

In our real-world cohort, SVR was attained in 90% of patients with Child-Pugh A cirrhosis upon their initial course of DAA-based therapy.[6–9] Our group previously showed that, among 530 patients with advanced HCV-related liver disease, IFN-induced SVR was independently associated with a lower risk of HCC (aHR 0.19), as well as liver failure (aHR 0.06) and all-cause mortality (aHR 0.26).[23] In the current study the relative HCC risk reduction of DAA-induced SVR in patients with Child-Pugh A cirrhosis was almost identical to our previous study and other recent cohorts.[24–26] In addition, data from the Veterans Affairs (VA) system in the US have documented that in over 15,000 DAA-treated patients with advanced liver disease DAA-induced SVR was statistically significantly associated with a 4-fold reduction in all-cause mortality (aHR 0.26).[27] These comparable estimates, despite different timeframes, different patient populations and different treatment regimens, increase our confidence that SVR improves the clinical outcome of patients with chronic HCV infection with compensated liver disease.

The most novel findings of our study relate to patients with decompensated cirrhosis. The SVR rate of 81% among these patients in our study is in line with results from previous clinical trials and other real-world cohorts.[10–16] However, this is one of the first studies to evaluate clinical outcome after successful DAA therapy in patients with the most advanced liver disease. Importantly, and unlike in compensated cirrhosis, SVR was not associated with a lower rate of liver failure, HCC or death among the patients with decompensated cirrhosis at the start of DAA therapy. Our results thus question whether the clinical course of chronic HCV infection can still be altered by viral eradication at this advanced stage of disease. Studies on the hepatic venous pressure gradient (HVPG) indicated clinically relevant improvements shortly after DAA therapy in patients with HCV-related cirrhosis.[28,29] However, studies including predominantly patients with Child-Pugh A cirrhosis indicated that a higher HVPG at baseline was associated with smaller reductions in portal pressure and almost all of those with an HVPG ≥16 mmHg remained with clinically significant portal hypertension at SVR.[28,30] HVPG levels are generally higher among those with decompensated cirrhosis, in whom the HVPG is thus less likely to reduce below the risk threshold for future clinical events. Even though the HVPG was recently shown to continue to decline with time following SVR, 93% of those with HVPG >16 mmHg at baseline remained with clinically significant portal hypertension

2 years after viral eradication (while those with an unfavorable clinical course before that time could evidently not undergo a new pressure measurement).[31] Our clinical event data are in line with these results and suggests that patients with most advanced disease remain at significant risk of further cirrhosis-related events despite SVR. In line with our findings, El-Sherif and colleagues showed that DAA-induced SVR was not independently associated with recompensation to a Child-Pugh A status among 622 patients with Child-Pugh B/C cirrhosis at baseline.[32]

Belli *et al.* and Pascasio *et al.* reported their experience with DAA therapy in 103 and 122 HCV-infected patients on the LT waiting list, respectively.[17,33] The fact that in both studies ~20% of the patients could be delisted due to profound clinical improvements was a striking result, although it should be noted that their median MELD score at the start of DAA therapy was only 14, which is rather low for listed LT candidates. In a more recent nationwide registry study, 16% of patients on the LT waiting list were treated with a sofosbuvir-based DAA-regimen, of whom only <10% could be removed from the LT waiting list after 2 years of follow-up.[34] Still, these data suggest that there are some patients with decompensated cirrhosis that might benefit from DAA therapy, although the clinical course following delisting still needs further clarification. It is important to point out that our study is not arguing against these results. To explain, we assessed the occurrence of cirrhosis-related complications while these studies focused on clinical improvement, which is a very different outcome measure. We cannot exclude that some patients in our study (probably those without cirrhosis-related events) experienced clinical improvement following DAA therapy. Clinical improvement may have various definitions, such as a reduction in the severity of decompensation symptoms, resolution of decompensation symptoms or an improvement in the Child-Pugh score. However, as a result of the subjective nature of these endpoints, prospective studies with predefined definitions and evaluation methods are needed to reliably assess these endpoints of clinical improvement. Still, it remains relevant to point out that we did not find a statistically significant association between SVR and improved LT-free survival, as the most important and robust clinical endpoint. Longer follow-up in preferably prospectively followed larger cohorts will nevertheless be needed to better understand the association between DAA therapy and cirrhosis-related morbidity as well as its impact on the quality of life of HCV-infected patients with Child-Pugh B/C cirrhosis.

Focusing on mortality as a solitary endpoint, the recent VA study reported a sensitivity analysis in which DAA-induced SVR was associated with reduced all-cause mortality (HR 0.33; 95% CI 0.26–0.42) among patients with a history of hepatic decompensation.[27] In the actively decompensated patients in our study, the association between SVR and a reduced risk of LT or death (aHR 0.66) was less strong than in the VA study, and not statistically significant. The current 5-year overall survival following LT in patients with chronic HCV infection is expected to be around 75%, as HCV recurrence no longer limits the post-LT outcome due to effective DAA therapy.[35,36] Only a limited number of HCV-infected patients with decompensated cirrhosis and SVR may be able to achieve such survival without LT, but further studies are needed on how to select those prior to antiviral therapy.

In parallel to other reports, the patients with Child-Pugh B/C cirrhosis in our study showed a modest decrease in MELD score following DAA therapy.[13–17,37] In almost 20% of patients the MELD score decline was at least 2 points at 12 weeks following the end of therapy. One of the largest real-world studies including 409 DAA-treated patients with decompensated cirrhosis showed a mean $\Delta MELD_{12}$ of -0.85 compared to +0.75 in untreated patients.[15] However, our data showed no association between $\Delta MELD_{12}$ and the virological response. Still, among patients with SVR, the MELD decline was largely sustained and based on improvements of all 3 parameters of the score (international normalized ratio, bilirubin and creatinine). The reports of MELD score decline with DAA therapy have been highlighted as evidence of benefit, however, our long-term clinical follow-up in decompensated patients may temper this enthusiasm. Despite a MELD decline following DAA therapy, no benefit was seen in terms of clinical disease progression or LT-free survival. While the need for LT may thus persist, biochemical improvements could lower the patient's chance of receiving a donor liver in MELD-based allocation systems. This potential downside of antiviral therapy appears to be more relevant for those in higher need of LT, because patients with higher MELD scores were more likely to achieve a profound MELD score decline in line with prior reports.[16,37] Yet, patients with high MELD scores at baseline were also most likely to have subsequent clinical events after therapy. Further analyses could not identify clear predictors of a substantial MELD decline apart from age, with older patients being less likely to have a MELD decline.

PI use has been related to hepatoxicity in patients with advanced cirrhosis.[38] Therefore, both the FDA and clinical practice guidelines advise against the use of PIs in patients with Child-Pugh B/C cirrhosis.[39,40] Our results support these recommendations as PI use was associated with an unfavorable clinical outcome among patients with decompensated cirrhosis.

This study has several limitations. Cirrhosis-related events were frequent in patients with decompensated cirrhosis and unrelated to the virological response, but we could not assess differences in the severity of these events between those with and those without SVR as a relative measure of clinical benefit. Hereto, the Child-Pugh score over time could be a relevant endpoint, but this is difficult to ascertain retrospectively due to the subjective nature of the score. The LT-free survival was evaluated as a more robust endpoint. However, despite the respectable study size, the few deaths precluded in-depth analyses regarding the association between SVR and this most solid clinical endpoint. While the median follow-up of 2.2 years was somewhat limited, it may be considered long given the natural history of patients with decompensated cirrhosis.[41,42] Increasing the sample size of this group with most advanced disease will nevertheless be needed to better understand the association and absolute impact of DAAs on clinical outcome, also because the high virological efficacy of DAA therapy left a limited number of patients without SVR. Due to the retrospective nature of this study, our study is not suited to assess the exact relation between health behavior and clinical outcome in DAA-treated patients with decompensated cirrhosis. Exact amounts of alcohol use and changes in alcohol use during follow-up were not available. However, it is unlikely that differences in alcohol use between the virological response groups would explain the lack of an association between SVR and clinical outcome in patients with Child-Pugh B/C cirrhosis. Also, exclusion of patients with a history of alcohol abuse from our analyses did not change the lack of an association between SVR or MELD decline and

improved clinical outcome (data not shown). Another limitation is the relative low range of MELD scores (median 13.4) and lacking sodium among the patients with decompensated cirrhosis in our study. This MELD score range is understandable as we included the first Child-Pugh B/C patients who were treated in our centers. Also, guidelines have relatively quickly adopted MELD-based decision strategies regarding the timing of DAAs before or after LT.[2,40] Patients with higher MELD scores were advised to be treated after LT rather than before LT. Our results may be considered to support this approach. Had we included patients with more advanced disease our findings might have been even more pronounced. Perhaps the most important limitation remains the lack of an untreated control group, although with the current favorable safety profile of the DAAs one should expect substantial selection bias in studies with such methodology.

In conclusion, in this international multicenter cohort study, chronic HCV-infected patients with compensated cirrhosis showed an improved clinical outcome with SVR. In patients with decompensated cirrhosis, however, there was no association between SVR and clinical outcome. Among these patients, a decline of the MELD score of ≥2 points appeared durable in those with SVR but was not associated with improved prognosis. Patients with HCV-related decompensated cirrhosis who start DAA therapy may thus be at risk of a persisting need of LT at a lower priority on the LT waiting list.

Abbreviations

aHR, adjusted HR; DAAs, direct-acting antivirals; DM, diabetes mellitus; HCC, hepatocellular carcinoma; HR, hazard ratio; HVPG, hepatic venous pressure gradient; IFN, interferon; LT, liver transplantation; MELD, model for end-stage liver disease; ΔMELD, delta MELD; $\Delta MELD_{12}$, delta MELD at 12 weeks after the end of therapy; $\Delta MELD_{36}$, delta MELD at 36 weeks after the end of therapy; PI, protease inhibitor; SVR, sustained virological response; VA, Veterans Affairs.

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Conflict of interest

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors took part in study concept and design, acquisition of data and critical revision of the manuscript. Analysis and interpretation of data: L Krassenburg, B Hansen, J Feld, A van der Meer. Drafting of manuscript: L Krassenburg, J Feld, A van der Meer.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

Supplementary data

Supplementary data to this article can be found at https://doi.org/10.1016/j.jhep.2020.11.021.

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