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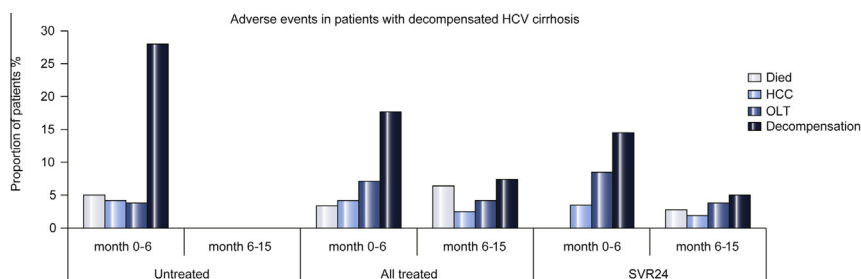
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Graphical abstract

**Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis**

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Michelle C.M. Cheung, Alex J. Walker, Benjamin E. Hudson, Suman Verma, John McLauchlan, David J. Mutimer, Ashley Brown, William T.H. Gelson, Douglas C. MacDonald, Kosh Agarwal, Graham R. Foster\*, William L. Irving, HCV Research UK



# Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis

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**Background & Aims:** Direct-acting antivirals have become widely used for patients with chronic hepatitis C virus infection with decompensated cirrhosis. Virological responses are excellent and early improvements in liver function, at least in a proportion of patients, have been observed but the longer term impact of viral clearance on end-stage liver disease complications is unclear.

**Methods:** Prospective study of patients with decompensated cirrhosis who received 12 weeks of all-oral direct-acting antivirals through the English Expanded Access Programme. Endpoints were deaths, liver transplantation, hepatocellular carcinoma, serious decompensation events, sepsis or hospitalisations, and MELD scores between start of therapy to 15 months post-treatment start. An untreated cohort of patients was retrospectively studied over 6 months for comparison.

**Results:** Amongst 317/406 patients who achieved sustained virological response at 24 weeks post-treatment, there were 9 deaths (3%), 17 new liver cancers (5%), 39 transplantations (12%) and 52 with serious decompensations (16%), over 15 months.

When compared to the first six months from treatment start and to untreated patients, there was a reduction in incidence of decompensations [30/406 (7%) in months 6–15 and 72/406 (18%) in months 0–6 for treated patients vs. 73/261 (28%) in untreated patients]. There was no significant difference in liver cancer incidence (10/406 (2.5%) in months 6–15 and 17/406

(4%) in months 0–6 for treated patients vs. 11/261 (4%) in untreated patients).

**Conclusions:** This study suggests that antiviral therapy in patients with decompensated cirrhosis led to prolonged improvement in liver function, with no evidence of paradoxical adverse impact nor increase in liver malignancy.

**Lay summary:** This is a report of a large group of patients in England who have hepatitis C virus (HCV) infection with advanced liver disease. They have been treated with new anti-HCV drugs, which cured the infection in the majority. This study looks at their outcomes a year following treatment, in terms of deaths, cancers and other complications of advanced liver disease. We conclude that in most patients anti-HCV treatment is beneficial even in advanced liver disease.

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## Introduction

All-oral, interferon (IFN)-free direct-acting antiviral (DAA) therapy for chronic hepatitis C virus (HCV) infection has allowed successful treatment of patients with advanced liver disease. Worldwide, large numbers of HCV-infected patients with decompensated cirrhosis have received antiviral therapy and although sustained virological response (SVR) rates are slightly reduced compared to patients with compensated disease, over 80% of treated patients still achieve viral clearance. Early analysis of patients who responded to therapy showed associated improvements in MELD and Child-Pugh scores [1–4], although some concerns have been expressed that the rate of malignancy may not change or may, paradoxically, increase [5,6]. Previous studies of IFN-based therapies have demonstrated that HCV clearance improves liver fibrosis, even in cirrhosis [7]. Moreover, patients who achieved SVR had reduced mortality, complications of cirrhosis and hepatocellular carcinoma compared to untreated patients or those who failed to achieve SVR [8–10]. However,

**Keywords:** Hepatitis C virus; Sofosbuvir; Ledipasvir; Daclatasvir; Decompensated cirrhosis; MELD score.

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**Abbreviations:** HCV, hepatitis C virus; DAA, direct-acting antiviral; MELD, model for end-stage liver disease; SVR, sustained virological response; EAP, expanded access programme; HCVUK, hepatitis C Research UK; SOF, sofosbuvir; LDV, ledipasvir; DCV, daclatasvir; RBV, ribavirin; OLT, orthotopic liver transplant; HCC, hepatocellular carcinoma; CI, confidence intervals.



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such studies involved patients with relatively 'early' cirrhosis and it remains unclear whether these long term benefits will be seen in patients treated for more advanced disease. Although there is little data on long term outcomes, international guidelines recommend that patients with decompensated cirrhosis should be urgently treated with IFN-free DAA therapy, regardless of eligibility for liver transplantation [11,12].

Chronic HCV infection is the main indication for liver transplantation in the Western world, and universally recurs causing accelerated disease progression in the liver graft. Given the shortage of donor organs and costs of liver transplantation, DAA treatment may reduce the need for transplantation in patients with advanced cirrhosis and allow alternative uses for scarce organs. Pooled analysis of over 800 patients with decompensated cirrhosis showed that 60% of patients had an improvement in MELD score from baseline following therapy, but 23% deteriorated, at post-treatment weeks 4 to 12 [13]. The magnitude of improvement varied with a median of 2 MELD points. It is unclear whether this early change is clinically meaningful. Perhaps more importantly, minor reductions in MELD may adversely affect access to liver transplantation, if a patient no longer meets transplant criteria but is insufficiently improved with a reduced quality of life (so called 'MELD purgatory'). In such cases, therapy may not be beneficial.

We recently published data on the virological and clinical outcomes of patients with decompensated cirrhosis treated on the English Expanded Access Programme (EAP) with 12 weeks of sofosbuvir and a NS5A inhibitor with or without ribavirin [14]. Consistent with other studies, the majority of patients successfully achieved viral clearance associated with MELD improvements by post-treatment week 12. To assess the impact of antiviral therapy in patients with decompensated cirrhosis, the study compared treated patients to a retrospective cohort of patients with decompensation who were retreated for 6 months prior to the availability of DAAs. Treated patients had fewer decompensations, reduced deterioration in MELD, and overall adverse events, although there were no significant differences in rates of death, liver transplantation or hepatocellular carcinoma [14]. To address the longer term benefits of successful HCV clearance, here we report the outcomes in the same patient cohort followed-up for one year after completion of therapy.

### 121 Patients and methods

122 Patients who received DAA therapy through the English EAP were enrolled into  
123 the HCV Research UK (HCV RUK) registry for prospective data collection. Patients  
124 who started treatment between 1 April and 11 November 2014 were studied.  
125 Details of the EAP treatment and patient selection criteria were previously pub-  
126 lished [14]. In brief, treatment consisted of 12 weeks of sofosbuvir with ledipasvir  
127 or daclatasvir, with or without ribavirin. Treatment choice was according to local  
128 multidisciplinary meeting decisions by experienced clinicians. Eligible patients  
129 included those with past or current decompensated cirrhosis (with ascites, vari-  
130 ceal bleed or encephalopathy), Child-Pugh score B7 or above, extrahepatic HCV  
131 manifestations or exceptional circumstances which were determined by panel  
132 review. Presence of hepatocellular carcinoma was not an indication for treatment  
133 in the EAP unless one of the above criteria was also met.

134 An untreated cohort of patients with decompensated HCV cirrhosis were  
135 studied for 6 months to compare early outcomes with patients who underwent  
136 treatment on the EAP. They were not studied beyond 6 months of follow-up as  
137 data was retrospectively collected. Untreated patients were registered in HCV RUK  
138 either at least 6 months prior to the national start date of the EAP (1 April 2014),  
139 or 6 months before initiation of treatment for those patients who subsequently  
140 received DAAs. Further details on this comparator cohort have been described  
141 [14].

The study conforms to the ethical guidelines of the 1975 Declaration of Hel-  
sinki as reflected in *a priori* approval by the institution's human research commit-  
tee. Ethics approval for HCV RUK was given by the national research ethics service  
(NRES) committee East Midlands – Derby 1 (Research Ethics Committee reference  
11/EM/0314) and informed consent was obtained from each patient included in  
the study. Patients in the EAP who declined data collection (N = 13) were treated  
but were excluded from this analysis.

### Outcome measures

Data on virological response and clinical outcomes at 12 weeks post-treatment  
on consenting patients treated in the EAP was previously published [14]. Here  
we focus on the clinical outcomes in patients with decompensated cirrhosis fol-  
lowed for up to a year post completion of therapy (total follow-up 15 months  
since start of therapy). Data was collected for the period post-treatment week  
12 to month 12 (month 6 to 15), via standardised electronic forms. Sites were  
individually re-contacted by the central study team with any missing or invalid  
responses, to ensure completeness and accuracy of collected data. This data  
was combined with earlier data from treatment start to month 6.

Viral loads at 24 weeks post-treatment end or later were collected. We  
assessed the proportion of patients who achieved SVR after 24 weeks (SVR24),  
and those with late relapse after initial undetectable viral load at post-treatment  
week 12. All who relapsed were offered retreatment with 24 weeks therapy.

The following primary clinical endpoints were collected: deaths, liver trans-  
plantations and hepatocellular carcinoma at 15 months (3 months on treatment,  
12 months post-treatment). Endpoints were calculated as 15 months from treat-  
ment start date, to account for premature treatment discontinuations.

For patients who achieved SVR24, the following secondary endpoints were  
measured: serious adverse events (decompensation, sepsis, hospitalisation for  
any cause) between month 6 and 15, MELD scores at 15 months (for non-  
transplanted patients only). For patients who did not attend clinic at month 15,  
laboratory data from visits within 1 month of the timepoint were included.  
Patients who did not achieve SVR24 were not included. SVR24 was defined as  
undetectable HCV RNA (measured at local laboratories with a lower limit of quan-  
tification of <30 IU/ml) at 24 weeks post-treatment. Where there was no result  
available at post-treatment week 24 but subsequent viral load was detectable, it  
was assumed that the patient had not achieved SVR24. MELD scores were calcu-  
lated using results provided by local accredited laboratories. Serious adverse event  
was defined as life-threatening, requiring hospitalisation or prolonged existing  
hospitalisation, resulting in persistent or significant disability, incapacity or death.

Statistical analysis was performed using Graphpad Prism 5. The following sta-  
tistical tests were performed: chi-squared test (for comparison of proportions), *t*  
test (for comparison of means) and log rank test (for comparison of survival).

## Results

### Patient population

A total of 480 patients received antiviral therapy through the EAP  
between the start of the programme on 1 April 2014 to 11  
November 2014 – 467 (97.3%) patients consented to provide data  
to the HCV RUK registry and 406 (87%) patients had decompen-  
sated cirrhosis and/or Child-Pugh score  $\geq$ B7, without previous  
liver transplantation, at treatment start. Sixty-one (13%) patients  
were treated for extrahepatic HCV disease or aggressive HCV  
recurrence in liver grafts.

Table 1 shows the demographics and baseline liver disease of  
patients with decompensation. The majority (295/406, 72.7%)  
were Child-Pugh B; 41 patients (10.1%) were Child-Pugh C. The  
remaining 70 patients (17.2%) had Child-Pugh A disease at base-  
line but a past history of liver decompensation. Most patients had  
significant portal hypertension represented by a median platelet  
count of  $75 \times 10^9/L$ .

### Virological outcomes

SVR after 12 weeks (SVR12) was achieved in 329 out of 406  
patients (81.0%), including 4 patients originally classified as

**Table 1. Baseline characteristics of patients according to treatment outcomes.** Virological failure included all patients with a detectable viral load at post-treatment week 24 or before, including re-treated patients. Non-SVR24 included in addition patients who died before post-treatment week 24 or without available viral load. Serious adverse events included all deaths, transplants, HCCs, decompensations, sepsis and hospitalisation to month 15.

Baseline characteristic	All decompensated	SVR24	Non-SVR24	Virological failure	SVR24 - serious adverse events	SVR24 - no serious adverse events
All N (%)	406	317 (78.1%)	89 (21.9)	53 (13.1)	135 (42.6%)	182 (57.4%)
SOF/LDV	18 (4.4)	12 (3.8)	6 (6.7)	4 (7.5)	7 (5.2%)	5 (2.7%)
SOF/LDV/RBV	228 (56.2)	187 (59.0)	41 (46.1)	30 (56.6)	78 (57.8%)	109 (59.9)
SOF/DCV	11 (2.7)	7 (2.2)	4 (4.5)	1 (1.9)	5 (3.7%)	2 (1.1%)
SOF/DCV/RBV	149 (36.7)	111 (35.0)	38 (42.7)	18 (34.0)	45 (33.3%)	66 (36.3%)
Genotype 1	198 (48.8)	174 (54.9)	24 (27.0)	11 (20.8)	75 (55.6%)	99 (54.4%)
Genotype 3	171 (42.1)	111 (35.0)	60 (67.4)	39 (73.6)	45 (33.3%)	66 (36.3%)
Other genotypes	37 (9.1)	32 (10.1)	5 (5.6)	3 (5.7)	15 (11.1%)	17 (9.3%)
Age (years) median, range	54, 28-79	54, 28-79	52, 30-74	52, 33-72	54, 33-76	55, 28-79
Bilirubin ( $\mu\text{mol/L}$ ) median, range	29, 4-433	28, 4-311	34, 7-433	33, 7-148	30, 4-311	26, 6-90
Albumin (g/L) median, range	31, 17-55	31, 17-49	29, 21-55	30, 21-40	31, 17-45	32, 17-49
Platelets ( $\times 10^9/\text{L}$ ) median, range	75, 3-321	75, 3-321	76, 20-277	76, 20-277	74, 20-237	76, 3-321
MELD median, range	12, 7-32	11, 7-32	13, 7, -25	12, 8-23	12, 7-32	11, 7-21
Child Pugh B	295 (72.7)	225 (71.0)	70 (78.7)	42 (79.2)	88 (65.3%)	137 (75.3%)
Child Pugh C	41 (10.1)	29 (9.1)	12 (13.5)	5 (9.4)	24 (17.8%)	5 (2.7%)
Baseline HCC	29 (7.1)	18 (5.7)	11 (12.4)	9 (17.0)	13 (9.6%)	5 (2.7%)

Since the earlier publication [4], 3 additional patients were confirmed as transplanted prior to DAA therapy, including one registered for therapy pre-transplant, grafted then initiated treatment. These patients were re-defined as post-transplant at treatment baseline, therefore 406 instead of 409 patients were included in this study.

non-SVR12 because no virology result was available, but who on further follow-up, were shown to be HCV RNA negative. Four patients relapsed after having a HCV RNA negative result at post-treatment week 12 and a further 8 died in the follow-up period after achieving SVR12. Therefore 317 (78.1%) patients achieved SVR24. Of note there were no late relapses after post-treatment week 12 amongst patients without baseline decompensated cirrhosis.

Amongst the 89 patients who did not achieve SVR24, 53 had virological failure (49 known before post-treatment week 12 and 4 late relapsers), 14 patients died before reaching post-treatment week 12, and another 12 between post-treatment 12–24 weeks. Ten patients had no available viral results at post-treatment week 24 although clinical outcomes data was still provided. See [Supplementary Table 1](#) for SVR24 according to genotype and treatment regimen.

Of the 53 patients with virological failure, 21 had viral relapse by post-treatment week 4, 24 patients by post-treatment week 12, and 4 relapsed after post-treatment week 12. Three patients did not clear virus by the end of therapy and one patient without a known virological result at post-treatment week 12 subsequently had documented relapse.

Forty-five of the patients with viral relapse were offered retreatment with a 24 week course of the same drug regime (switching NS5A inhibitor was not supported by the funders of the EAP), the outcomes of which will be reported separately. Eight patients declined retreatment.

#### Outcomes after 15 months in patients with decompensated cirrhosis

##### Mortality

In the 406 patients with decompensated cirrhosis there were 40 deaths over 15 months (9.9%) – 9 patients died who achieved SVR24 (2.8%), which was not statistically different to patients with known virological failure (3/53, 5.7%,  $p = 0.28$ ) ([Table 2](#)).

Although virological failure was predominantly seen in genotype 3 infected patients, the proportion who died did not differ between genotypes – there were 9 deaths amongst 24 genotype 1 infected patients without SVR24, compared to 21 deaths amongst 60 genotype 3 infected patients without SVR24 (37.5% vs. 35.0%,  $p = 0.83$ ). [Fig. 1](#) shows the survival rates over the study period.

##### Development of liver cancer

At treatment baseline, 29 of 406 total patients had a history of HCC (median days between diagnosis and DAA start was 287 days). Eighteen of these patients achieved SVR24 ([Table 1](#)). Two patients with pre-existing liver cancer history developed a new HCC (at 20 and 26 weeks from treatment start), both achieved SVR24. There were no recurrent HCCs amongst patients with previous cancer who did not achieve SVR24.

Amongst 317 patients who achieved SVR24, 17 (5.4%) developed a liver cancer ([Table 2](#)) over the follow-up period of 15 months (15 *de novo* and 2 recurrent). Five of the 17 (29.4%) new liver cancers developed in patients who achieved SVR24 occurred early, within 3 months of commencing treatment. There was a reduction (of borderline significance) in new cancer rates over 15 months between patients with and without SVR24 (17/317, 5.4% vs. 10/89, 11.2%,  $p = 0.049$ ) in patients with decompensated cirrhosis (hazard ratio 0.33, 95% CI 0.13–0.87) (see [Fig. 2](#)). This compares with 11/261 (4.2%) in untreated patients over 6 months.

##### Other outcomes

[Table 2](#) shows the outcomes for patients followed-up for 15 months. Amongst the 317 patients who achieved SVR24, 39 (12.3%) received a liver transplant. Forty-six patients experienced serious decompensation between months 0–6 (14.5%) which was markedly reduced in months 6–15 (16/317, 5.0%) ( $p = 0.00006$ ).



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**Table 2. Deaths, hepatocellular carcinomas (HCC), orthotopic liver transplants (OLT) and decompensations over 15 months for all treated patients according to treatment outcomes, compared to patients untreated for HCV (data for untreated patients derived from [4]).** Note all deaths up to post-treatment week 24 were defined as non-SVR24. Decompensation events were recorded for patients with SVR24 only.

Adverse event	Untreated N = 261			All treated N = 406		
	Month 0-6	Month 6-15	Overall	Month 0-6	Month 6-15	Overall
Died	13 (5.0%)	14 (5.4%)	27 (10.4%)	14 (3.4%)	12 (2.9%)	26 (6.4%)
HCC	11 (4.2%)+	6 (2.3%)	17 (6.5%)	17 (4.2%)	3 (0.7%)	20 (4.9%)
OLT	10 (3.8%)	19 (7.3%)	29 (11.1%)	17 (4.2%)	3 (0.7%)	20 (4.9%)
Decompensation	73 (28.0%)	16 (6.0%)	89 (34.0%)	72 (17.7%)	30 (7.4%)	102 (25.1%)

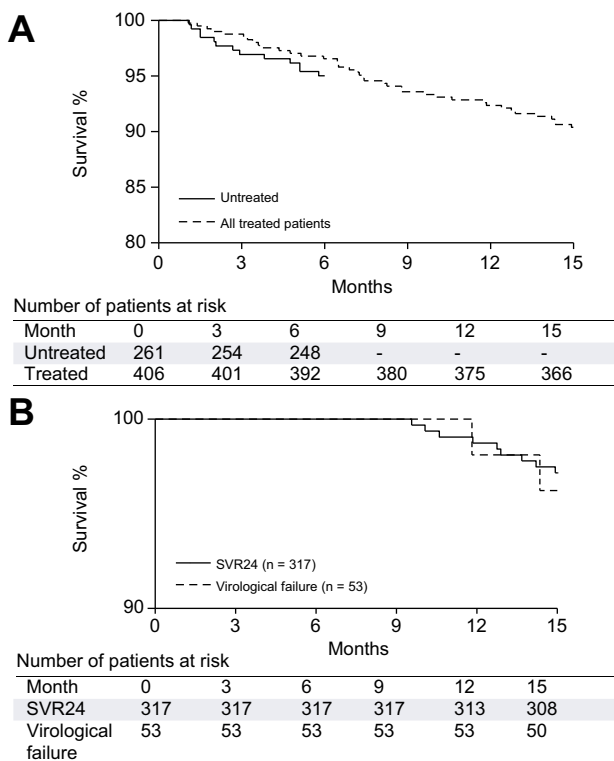
  

Adverse event	SVR24 N = 317			Non-SVR24 N = 89			Virological failure N = 53		
	Month 0-6	Month 6-15	Overall	Month 0-6	Month 6-15	Overall	Month 0-6	Month 6-15	Overall
Died	0 (0.0%)	9 (2.8%)	9 (2.8%)	14 (15.7%)	17 (19.1%)	31 (34.8%)	0 (0%)	3 (5.7%)*	3 (5.7%)
HCC	11 (3.5%)	6 (1.9%)	17 (5.4%)	6 (6.7%)	4 (4.5%)**	10 (11.2%)	3 (5.7%)	3 (5.7%)	6 (11.3%)
OLT	27 (8.5%)	12 (3.8%)	39 (12.3%)	2 (2.2%***)	5 (5.6%)	7 (7.9%)	1 (1.9%)	5 (9.4%)	6 (11.3%)
Decompensation	46 (14.5%)	16 (5.0%)	62 (19.5%)	26 (29.2%)	-	-	-	-	-

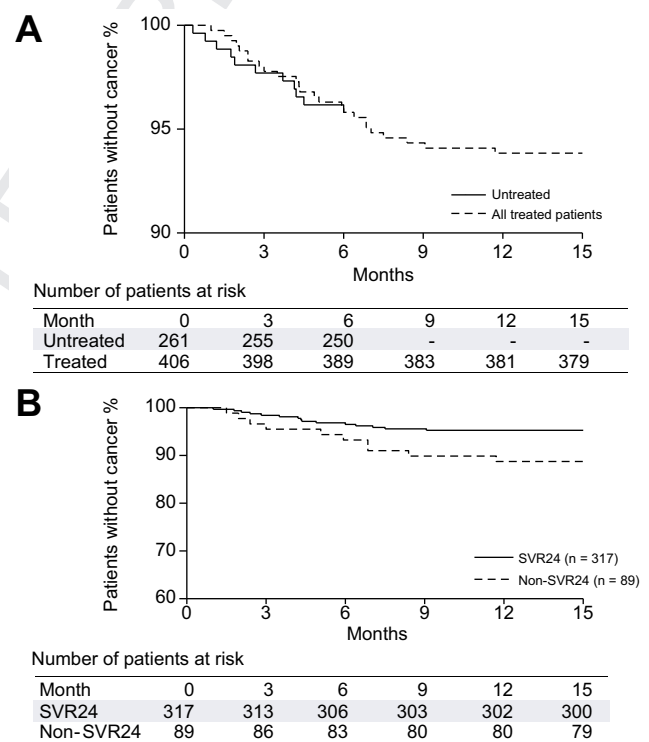
\*Denotes two patients who did not have known virological outcomes at 24 weeks post-treatment but had reported deaths, one of the two patients (marked by \*\*) also had a new liver cancer.

\*\*\*Denotes a patient transplanted by month 6 who did not have a known virological outcome at 24 weeks post-treatment.

†Figure updated from earlier publication.



**Fig. 1. Survival of patients over 15 months.** (A) Survival in patients treated and untreated (log rank  $p = 0.32$ ). (B) Survival in treated patients with SVR24 and virological failure (log rank  $p = 0.38$ ). Note by definition no deaths occurred before month 9 (post-treatment week 24) in both groups.



**Fig. 2. Development of new hepatocellular carcinoma over 15 months.** (A) New hepatocellular carcinoma in untreated and treated patients (log rank  $p = 0.98$ ). (B) New hepatocellular carcinoma in patients with and without SVR24 (log rank  $p = 0.02$ ).

For patients who achieved SVR24, 135 (42.6%) experienced at least one serious adverse event (death, transplant, liver cancer, decompensation, sepsis or hospitalisation), therefore the transplant-free, adverse event free survival over 15 months was 57.4%. The group with adverse events contained a significantly

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Supplementary Table 2 shows the details of these events with incidences of decompensations, sepsis and all-cause hospitalisations which were graded as serious adverse events.

276 higher proportion of patients with Child-Pugh C disease at base-  
 277 line – 24/135 (17.8%) for patients with adverse events and 5/182  
 278 (2.7%) for patients without adverse events ( $p < 0.0005$ ) (see  
 279 Table 1). Fig. 3 shows that adverse events were most frequent  
 280 during the treatment period, and decreased over time.

281 Earlier we published on the baseline characteristics of the  
 282 untreated and treated patients, showing that the two cohorts  
 283 were similar apart from a higher proportion of patients using  
 284 alcohol (of any amount) at baseline amongst untreated patients  
 285 [14]. Supplementary Table 3 illustrates that after excluding active  
 286 alcohol users, adverse outcomes remained less frequent in treated  
 287 compared to untreated patients. Amongst untreated patients  
 288 who subsequently received DAAs when they became available,  
 289 and were studied as the treated cohort at least six months later,  
 290 there were numerically but not statistically significantly lower  
 291 incidences of liver cancers and decompensations following  
 292 treatment.

293 We previously proposed a model using baseline age and albu-  
 294 min to predict adverse outcomes at 6 months. Table 3 shows the  
 295 proportion of patients without adverse outcomes at month 15  
 296 based on age and serum albumin at treatment start, however  
 297 these baseline factors did not discriminate the likelihood of  
 298 developing adverse events or not. We did not include MELD score  
 299 change into the model due to the limited number of available  
 300 comparative scores.

#### 301 MELD scores for patients with decompensated cirrhosis who 302 achieved SVR24

303 The mean MELD score change from baseline at month 6 was  
 304  $-0.83 \pm 0.14$  (improvement) and  $+0.51 \pm 0.4$  at month 15 (deteri-  
 305 oration) ( $p < 0.0001$ ) based on 282 patients with available com-  
 306 parative scores at month 6 and 74 patients at month 15.  
 307 Supplementary Fig. 1 shows the waterfall plots for MELD score  
 308 changes between baseline and month 6 and month 15 for non-  
 309 transplanted patients who achieved SVR24. MELD improvement  
 310 was observed in patients with higher baseline score (see Supple-  
 311 mentary Table 4) but even in for those with baseline MELD  $>15$   
 312 the margin of improvement was smaller at 15 months than at  
 313 6 months. Supplementary Table 5 shows that based on the small  
 314 number of available results, there were no patients with baseline  
 315 MELD  $<9$  who worsened to above 15; for the majority group with  
 316 baseline MELD 10–14 there were similar proportions who

improved or deteriorated but 48.8% had no significant change  
 in MELD at month 15.

#### Discussion

The availability of highly effective all-oral antiviral regimens for  
 patients with chronic HCV infection has transformed the treat-  
 ment options for infected patients and most patients can now  
 achieve viral clearance. For patients with advanced liver disease  
 it is unclear whether viral eradication is beneficial and there  
 are some reports suggesting that it may be harmful. Indeed, the  
 definition of benefit following viral clearance, whether it is  
 patient survival, access to transplantation or avoidance of com-  
 plications, is debatable.

To evaluate the potential risks and benefits of antiviral ther-  
 apy in patients with end-stage liver disease we examined med-  
 ium term outcomes in the English Expanded Access  
 Programme. This involved a well-studied, prospectively enrolled  
 cohort of patients managed by experienced clinicians in a limited  
 number of centres. Data collection was to clinical trial standards  
 although external audit was not performed. Although observa-  
 tional studies in non-clinical trial conditions may be confounded  
 by subject or clinician non-compliance, the patient cohort in this  
 study all had advanced liver disease requiring regular medical  
 intervention and the treating centres were all experienced in data  
 handling techniques and were provided with support and  
 resources from the central administration. We therefore believe  
 that our dataset is likely to be accurate and complete with min-  
 imal errors from reporting or attendance failure.

One limitation of the study is the choice of control subjects –  
 untreated patients with decompensated cirrhosis were selected  
 based on the same criteria as treated patients, from the same reg-  
 istry, but were not otherwise matched. Treated and untreated  
 patients had similar demographics and baseline liver disease,  
 apart from the proportion of active alcohol users which was  
 higher in untreated patients. Excluding patients using any  
 amount of alcohol at baseline, who had additional risks for dis-  
 ease progression and potentially poorer engagement with medi-  
 cal input, treated patients remained with fewer decompensations  
 and total adverse events compared to untreated [14]. Although  
 patients during treatment were followed-up more closely, all  
 patients were regularly reviewed due to their advanced liver dis-  
 ease. The study evaluated serious adverse events which were  
 actively monitored for (all patients were offered HCC surveil-  
 lance) or resulted in hospitalisations. Therefore, reporting of such  
 events between treated and untreated patients were not likely to  
 be biased by differences in the frequency of routine follow-up.  
 The majority of the untreated cohort subsequently received DAAs  
 when they became available, and about half were included in the  
 treated cohort. Thus the same patients were studied at least six  
 months later, during their treatment period, and there was no  
 increase in the incidences of decompensations and liver cancers.

Recent studies highlighting the possibility of an increased  
 incidence or recurrence of liver malignancy in patients with  
 decompensated cirrhosis who achieve viral clearance with DAA  
 regimens has led some to question the value of treating such  
 patients [5,6]. In the English EAP, patients with liver cancer were  
 not indicated for treatment unless they had decompensated cir-  
 rhosis. We did not see any evidence of an increase in liver cancer  
 during therapy and the following 12 months. Nearly a third of the

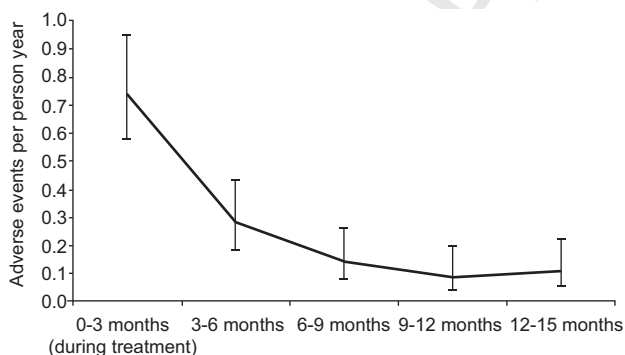


Fig. 3. Combined adverse event rate (death, liver transplant, HCC, decompensation, sepsis, all-cause hospitalisation) per person over time, for patients with SVR24 (n = 307). Error bars represent 95% confidence intervals.

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**Table 3. Proportion of patients without adverse events (death, transplantation, liver cancer, decompensation, sepsis or hospitalisations) according to baseline characteristics.** Total 182 patients out of 317 who achieved SVR24.

	N	No adverse events (n)	
Age <65 Albumin ≥35	74	47	63.5%
Age <65 Albumin <35	212	120	56.6%
Age ≥65 Albumin <35	21	10	47.6%
Age ≥65 Albumin ≥35	10	5	50.0%




375 newly detected liver cancers occurred in the first 3 months of  
376 therapy, suggesting this was growth from cancers which were  
377 radiologically undetectable at treatment baseline, rather than  
378 *de novo* development. There is potential bias that in a cohort of  
379 patients with decompensated cirrhosis, development or detec-  
380 tion of liver cancer is masked by death driven by advanced liver  
381 disease. We observed a reduction in cancer rates in patients with  
382 SVR compared to virological failure, but the relatively short dura-  
383 tion of follow-up and the low incidence of such events prevent a  
384 clear conclusion at this stage.

385 In the IFN era, antiviral therapy in patients with cirrhosis was  
386 associated with reduced hepatocellular carcinoma [9]. Large  
387 cohorts such as HALT-C have demonstrated that reduced cancer  
388 development may be an effect of IFN, which has anti-tumour  
389 properties, rather than viral clearance alone, although this was  
390 only observed after four years from treatment [15]. The magni-  
391 tude of the impact of clearing HCV with DAAs on liver cancers  
392 may require data pooling from studies with longer follow-up,  
393 and may differ depending on the degree of cirrhosis or whether  
394 there is previous history of HCC. The reduction in liver cancer  
395 rates from 4% in 261 untreated patients over 6 months to 1.9%  
396 over 9 months after achieving viral clearance in 317 successfully  
397 treated patients reassures us that induction of liver cancer in our  
398 patients did not occur.


399 The long term benefits of viral eradication on liver function  
400 and the complications of portal hypertension remain unclear.  
401 However, in our cohort there was a marked reduction in liver  
402 related serious adverse events in those patients who cleared  
403 virus, with decreasing adverse events rates over time. We specu-  
404 late that patients will continue to benefit long term although fur-  
405 ther data will be required to confirm this.

406 The value of antiviral therapy in patients with decompensated  
407 cirrhosis will remain a subject for debate until very large cohorts  
408 have been evaluated for extended periods of time. Our data on  
409 12 months follow-up after treatment of a large English cohort  
410 indicates that there are benefits for many patients, although in  
411 patients with Child-Pugh C disease viral clearance may have the  
412 least impact on liver complications. In our view it is important  
413 that liver transplantation remains available for patients with very  
414 advanced disease who achieve viral clearance, as such patients  
415 may not improve to a level commensurate with a high quality  
416 of life.

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### Conflict of interest

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### Authors' contributions

434 The study was designed and led by GRF and WI. MC, BH, SV man-  
435 aged patients in the study, collated the data and assisted in the  
436 analysis. MC and AW performed the data and statistical analysis.  
437 WI and JM supervised sample collection, data management and  
438 assisted with study design and implementation. DJM, AB, WG,  
439 DCM and KA led the recruitment and data collection. All authors  
440 participated in data analysis and participated in the preparation  
441 of the manuscript. 442

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### Supplementary data

453 Supplementary data associated with this article can be found, in  
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### References

- 457 *Author names in bold designate shared co-first authorship* 458
- 459 [1] Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS, et al. 460  
Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in 461  
patients with advanced liver disease. *Gastroenterology* 2015;149:649–659. 462
  - 463 [2] Curry MP, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, et al. 464  
Sofosbuvir and velpatasvir for HCV in patients with decompensated 465  
cirrhosis. *N Engl J Med* 2015;373:2618–2628. 466
  - 467 [3] Leroy V, Hezode C, Metivier S, Tateo M, Conti F, Nguyen-Khac E, et al. 468  
Daclatasvir plus sofosbuvir with or without ribavirin in patients with HCV 469  
infection and decompensated cirrhosis: interim analysis of a French 470  
multicentre compassionate use programme European association for the 471  
study of the liver. Barcelona, Spain: The International Liver Congress; 2016. 472



- 470 [4] Petersen J, Welzel T, Herzer K, Ferenci P, Gschwantler M, Cornberg M, et al. 493  
 471 Daclatasvir plus sofosbuvir with or without ribavirin for the treatment of 494  
 472 chronic HCV infection in patients with decompensated cirrhosis: results of a 495  
 473 European Multicentre Compassionate Use Programme. European Association 496  
 474 for the Study of the Liver. Barcelona, Spain: The International Liver Congress; 497  
 475 2016. 498  
 476 [5] Reig M, Mariño Z, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, et al. 499  
 477 Unexpected early tumor recurrence in patients with hepatitis C virus - 500  
 478 related hepatocellular carcinoma undergoing interferon-free therapy: a note 501  
 479 of caution. *J Hepatol* 2016. 502  
 480 [6] Buonfiglioli F, Conti F, Andreone P, Crespi C, Foschi G, Lenzi M, et al. 503  
 481 Development of hepatocellular carcinoma in HCV cirrhotic patients treated 504  
 482 with direct acting antivirals. European Association for the Study of the 505  
 483 Liver. Barcelona, Spain: The International Liver Congress; 2016. 506  
 484 [7] Poynard T, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, et al. 507  
 485 Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in 508  
 486 patients with chronic hepatitis C. *Gastroenterology* 2002;122:1303–1313. 509  
 487 [8] van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. 510  
 488 Association between sustained virological response and all-cause mortality 511  
 489 among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 512  
 490 2012;308:2584–2593. 513  
 491 [9] Shiratori Y, Ito Y, Yokosuka O, Imazeki F, Nakata R, Tanaka N, et al. Antiviral 514  
 492 therapy for cirrhotic hepatitis C: association with reduced hepatocellular 515  
 carcinoma development and improved survival. *Ann Intern Med* 2005;142:105–114.  
 [10] Bruno S, Stroffolini T, Colombo M, Bollani S, Benvegnù L, Mazzella G, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology* 2007;45:579–587.  
 [11] Liver EASo. EASL recommendations on treatment of hepatitis C 2015. *J Hepatol* 2015;63:199–236.  
 [12] Panel AIHG. Hepatitis C guidance: AASLD-IDS recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology* 2015;62:932–954.  
 [13] Bunchorntavakul C, Reddy KR. Treat chronic hepatitis C virus infection in decompensated cirrhosis - pre- or post-liver transplantation? The ironic conundrum in the era of effective and well-tolerated therapy. *J Viral Hepat* 2016;23:408–418.  
 [14] **Foster GR, Irving WL**, Cheung MC, Walker AJ, Hudson BE, Verma S, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol* 2016.  
 [15] Lok AS, Everhart JE, Wright EC, Di Bisceglie AM, Kim HY, Sterling RK, et al. Maintenance peginterferon therapy and other factors associated with hepatocellular carcinoma in patients with advanced hepatitis C. *Gastroenterology* 2011;140:840–849, quiz e812.

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