ORIGINAL ARTICLE

JOURNAL OF VIRAL HEPATITIS
JVH   WILEY

Impact of direct-acting antiviral agents on liver function in patients with chronic hepatitis C virus infection

Philip J. Johnson[1] | Sarah Berhane[1] | Alex J. Walker[2] | Fiona H. Gordon[3] |
Steven D Ryder[4,5] | Stuart McPherson[6] | Aravamuthan Sreedharan[7] |
Andrew A. Ustianowski[8] | Kosh Agarwal[9] | David Mutimer[10] | Takeshi Kumada[11] |
Hidenori Toyoda[12] | William L. Irving[5] | HCV Research UK

[1]Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, UK

[2]Centre for Evidence Based Medicine, Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

[3]Bristol Royal Infirmary, Bristol, UK

[4]Nottingham University Hospitals NHS Trust, Nottingham, UK

[5]NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, UK

[6]Newcastle upon Tyne Hospitals NHS Foundation Trust, Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK

[7]United Lincolnshire Hospitals NHS Trust, Lincoln, UK

[8]School of Medical Sciences, University of Manchester, Manchester, UK

[9]Institute of Liver Studies, King's College Hospital, London, UK

[10]University Hospitals Birmingham NHS Foundation Trust Queen Elizabeth Hospital, Queen Elizabeth Medical Centre, Birmingham, UK

[11]Department of Nursing, Faculty of Nursing, Gifu Kyoritsu University, Ogaki, Japan

[12]Department of Gastroenterology and Hepatology, Ogaki Municipal Hospital, Ogaki, Japan

Correspondence
Philip J. Johnson, Department of Clinical Cancer Medicine, Institute of Systems, Molecular and Integrative Biology, University of Liverpool, 2nd Floor, Sherrington Building, Ashton Street, Liverpool L69 3GE, UK.
Email: Philip.Johnson@liverpool.ac.uk

Present address
Sarah Berhane, NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust and University of Birmingham, Birmingham, UK and Institute of Applied Health Research, University of Birmingham, Birmingham, UK

Abstract

Whilst the benefit of direct-acting antiviral agents (DAAs) in achieving sustained virological response (SVR) is now well-accepted, their impact on liver function, particularly in relation to achievement of SVR, has not been well documented. We studied 2394 patients with chronic HCV infection, 1276 receiving DAAs and 1118 interferon-based therapy. Liver function was assessed by the albumin-bilirubin (ALBI) score or grade. Overall survival according to SVR status and baseline ALBI grade was examined. We also studied time to first decompensation according to ALBI grade, as well as longitudinal changes in ALBI score over time according to SVR. Among the patients receiving DAAs, 89% achieved SVR (Japan = 99%, UK = 78%). Amongst the decompensated patients in the UK cohort, three distinct risk groups according to ALBI grade at baseline were observed. The UK patients receiving DAAs, who had

- -

predominantly decompensated disease, showed clear evidence of improvement of liver function detectable within 2 years of the start of treatment, especially in those achieving SVR. These early changes in liver function were very similar to those observed in the first 2-3 years after interferon-based therapy. DAAs improve liver function especially in those with decompensated disease who achieve SVR. Experience with interferon-based therapy suggests that failure to achieve SVR is associated with long-term decline in liver function and, in contrast, patients who do achieve SVR can expect long-term disease improvement and subsequent stabilization of liver function. Our initial analysis suggests that those receiving DAAs are likely, in the long term, to follow a similar course.

KEYWORDS
ALBI score, direct-acting antivirals, hepatitis C virus, interferon therapy, liver function, sustained virological response

1 | INTRODUCTION

The clinical benefits of achieving a sustained virological response (SVR) to antiviral therapy in patients with chronic hepatitis C virus (HCV) infection have been extensively documented. These include a decrease in liver-related complications (such as hepatocellular carcinoma [HCC] and hepatic decompensation), non-liver-related complications (such as development of insulin resistance and lymphoma), together with improvements in quality of life for patients and economic benefit for healthcare providers.[1-5] Improvement in fibrosis and even reversal thereof has also been observed[6] and, it has been assumed, there is also improvement in liver function. Nonetheless, since DAAs have only recently been introduced, there is very short follow-up, leading a recent Cochrane review to conclude that 'there are no long-term trials that have assessed whether or not DAA treatment improves morbidity or mortality'[7] although this opinion has been robustly challenged.[1] Furthermore, it has even been suggested that the 'uncertain clinical benefit', along with the risks and costs of DAA therapy, should be discussed with patients to allow a shared decision on treatment to be made.[7]

We have recently shown that several of the factors involved in the Childs-Pugh score (CPS), the conventional measure of liver function, are 'redundant'. Thus, the CPS can be refined in a simple algorithm to involve only serum albumin and bilirubin (the albumin-bilirubin score [ALBI]).[8] The model was originally developed for patients with HCC and has been extensively validated.[9] More recently, the model has been validated in patients with chronic liver disease without HCC.[10] The ALBI score has the advantage that, as well as avoiding the necessity of using highly subjective variables (ascites and encephalopathy) as required for the Child-Pugh score, it has sufficient granularity to permit sensitive quantification of serial changes in liver function over time.

Our primary aim here is to report changes in liver function in patients with decompensated disease consequent upon treatment with direct-acting antiviral agents (DAAs), but for comparison, we also include a large cohort of patients with compensated disease also treated with DAAs. A cohort of patients receiving interferon-based therapies is also included to give an indication of how liver function can change over the long term in response to effective antiviral treatment.

2 | PATIENTS AND METHODS

We studied 2394 patients with chronic HCV infection, 1276 receiving DAAs and 1118 receiving interferon-based therapy. Those receiving DAAs came from the UK (n = 602, median follow-up = 23.7 months [95% CI 23.5, 24.0], all with decompensated cirrhosis) and Japan (n = 674, median follow-up = 20.7 months [95% CI 20.5, 21.0], all with compensated disease). The Japanese cohort receiving interferon-based therapies (n = 1118, median follow-up = 11.0 years [95% CI 10.3, 11.8]) had, mainly, compensated disease. Other virology data recorded included the HCV genotype, viral load and whether the patient achieved sustained virological response (SVR). Demographic features and the range of clinical parameters for the entire patient population recorded are listed in Table 1. The time at which antiviral treatment was initiated is henceforth referred to as 'baseline'.

Patients were classified as having achieved SVR, relapse after initial response (REL) or no-response (NR) according to internationally agreed criteria.[11] Because there were only very minor differences between those with REL and NR with regard to any of the recorded parameters, REL and NR were combined and analysed as a 'non-SVR' cohort. A small group of Japanese patients who underwent a second course of DAA treatment (n = 17) were similarly classified; those who had response unclassified at the time of analysis were excluded.

2.1 | The UK DAA cohort

This observational cohort comprised 602 patients prospectively collected and treated for liver disease within the NHS England Expanded Access Programme (EAP), data for which are held by

TABLE 1 Demographic and clinical features of the three cohorts

Variable	DAA-treated HCV patients				IFN-treated HCV patients	
	Japan (N = 674)		UK (N = 602)		Japan (N = 1118)	
	Non-SVR (n = 9, 1.3%)	SVR (n = 665, 98.7%)	Non-SVR (n = 135, 22.4%)	SVR (n = 467, 77.6%)	Non-SVR (n = 459, 41.1%)	SVR (n = 659, 58.9%)
Age (years)	73 (66, 75) n = 9	69 (61, 76) n = 665	53 (48, 59) n = 135	54 (49, 60) n = 467	57 (50, 62) n = 459	53 (44, 60) n = 659
Male, n (%)	1 (11.1)	290 (43.6)	103 (76.3)	335 (71.7)	254 (55.3)	373 (56.6)
HCV genotype, n (%)						
1	7 (77.8)	479 (72.0)	33 (24.4)	258 (55.3)	330 (71.9)	296 (45.0)
2	2 (22.2)	186 (28.0)	0	0	129 (28.1)	353 (53.7)
3	0	0	96 (71.1)	156 (33.4)	0	2 (0.3)
Other (1/2)	0	0	6 (4.4)	53 (11.4)	0	7 (1.1)
Albumin (g/L)	44 (42, 46) n = 9	43 (40, 45) n = 665	30 (26, 35) n = 135	32 (28, 35) n = 467	41 (38, 43) n = 459	42 (40, 44) n = 659
Bilirubin (µmol/L)	8.6 (8.6, 12.0) n = 9	10.3 (8.6, 13.7) n = 665	31 (22, 47) n = 135	25 (16, 38) n = 467	10.3 (8.6, 13.7) n = 459	10.3 (8.6, 13.7) n = 659
Platelets	166 (99, 203) n = 9	165 (126, 211) n = 665	73 (51, 101) n = 131	76 (56, 106) n = 453	159 (121, 199) n = 459	178 (142, 222) n = 659
ALBI score	−3.07 (−3.21, −3.02) n = 9	−2.95 (−3.16, −2.74) n = 665	−1.61 (−2.03, −1.12) n = 135	−1.74 (−2.18, −1.37) n = 467	−2.78 (−3.03, −2.53) n = 459	−2.91 (−3.07, −2.68) n = 659
ALBI grade, n (%)						
1	8 (88.9)	559 (84.1)	4 (3.0)	48 (10.3)	326 (71.0)	553 (83.9)
2	1 (11.1)	103 (15.5)	84 (62.2)	296 (63.4)	132 (28.8)	106 (16.1)
3	0 (0)	3 (0.45)	47 (34.8)	123 (26.3)	1 (0.2)	0
Clinically significant deterioration, n (%)	1 (11.1)	2 (0.3)	51 (37.8)	68 (14.6)	Not recorded	Not recorded
Median time to clinically significant deterioration (95% CI)	Not reached n = 9	Not reached n = 665	Not reached n = 135	Not reached n = 467	Not recorded	Not recorded
Death, n (%)	1 (11.1)	8 (1.2)	50 (37.0)	34 (7.3)	99 (21.6)	35 (5.3)
Median follow-up, months (95% CI)	30.2 (16.1, 32.3) n = 9	20.6 (20.5, 21.0) n = 665	22.3 (21.4, 23.3) n = 135	23.9 (23.6, 24.0) n = 467	159.3 (144.3, 174.6) n = 459	115.6 (108.2, 126.4) n = 659
Median overall survival, months (95% CI)	Not reached n = 9	Not reached n = 665	Not reached n = 135	Not reached n = 467	Not reached n = 459	Not reached n = 659

Note: Highlighted figures represent the main differences between the cohorts.

Abbreviations: ALBI, albumin-bilirubin score; DAAs, direct-acting antiviral agents; HCV, hepatitis C virus; SVR, sustained virological response.

the UK Biobank, HCV Research UK. Patients eligible for treatment within the EAP were those at significant risk of death or irreversible damage from HCV infection within 12 months, regardless of genotype. Patients were treated with 12 weeks of Sofosbuvir along with either Daclatasvir or Ledipasvir (at clinician discretion) and ribavirin (at clinician discretion). All patients included within this study consented to contribute their data to the database.

All patients had decompensated chronic liver disease, with ascites, a history of variceal bleeding or encephalopathy or a Child-Pugh score greater than or equal to 7. Patients who had undergone liver transplantation before or after antiviral therapy were excluded since this would likely have a dramatic effect on liver function, making these patients less representative of those with severe liver disease. Additional patients were treated within the

EAP for extra-hepatic manifestations of HCV, but these patients were also excluded from the present study, which focuses on liver function. The present study comprises a cohort of patients treated between May 2014 and June 2015 giving a potential follow-up of 15 to 28 months.[12,13]

2.2 | The Japanese DAA cohort

Japanese patient data were prospectively collected between September 2014 and August 2016. A total of 674 patients with chronic HCV infection underwent anti-HCV therapy with IFN-free DAA regimens. No patients had decompensated cirrhosis since the use of DAAs is not permitted for patients with decompensated cirrhosis in Japan. Based on HCV genotype, patients received IFN-free DAA regimens that were approved by the Japanese National Medical Insurance system. Patients with HCV genotype 1 underwent a 24-week regimen with Daclatasvir (DCV) and Asunaprevir (ASV) [1], a 12-week regimen with Ledipasvir (LDV) and Sofosbuvir (SOF) [2], or a 12-week regimen with Ombitasvir (OMV), Paritaprevir (PRV) and Ritonavir (r) [3]. Patients with genotype 2 underwent a 12-week regimen with SOF and Ribavirin (RBV) [4].

2.3 | The Japanese interferon-based therapy cohort

We identified 1118 patients with chronic HCV infection treated with interferon-based therapy between August 1989 and September 2013, from Ogaki Municipal Hospital, Japan. Median follow-up was 11.1 years (95% CI 10.3, 11.8), and the number of recorded observations per patient ranged from 6 to 791 (median, 67). None of the patients received direct-acting antiviral agents.

2.4 | Statistical methods

All statistical analyses were carried out using Stata/SE 14.2. Median and interquartile range (IQR) were presented for the continuous variables and percentages for the categorical variables. SVR and non-SVR groups were analysed separately. Overall survival time (expressed in months) was calculated from date of start of treatment (ie, 'baseline') to date of death. Patients who were still alive at last follow-up time were censored. Time to clinically significant deterioration (new episode of encephalopathy, ascites, episode of variceal haemorrhage or admission with sepsis or death) was calculated from start of treatment to the date of first new decompensation event (ascites, paracentesis, encephalopathy and variceal bleed). Patients who did not decompensate were censored. Baseline variables available in all three cohorts were age, gender, HCV genotype, albumin (g/L), bilirubin (μmol/L), platelet count, date of start of treatment and date of death/last follow-up. Date of first decompensation was available for the DAA patients only.

ALBI score was the primary measure used in this study, defined as:

$$\left[\log_{10}(\text{bilirubin}) \times 0.66\right] + \left[\text{albumin} \times -0.085\right].$$

This produces a continuous score, which can either be used as is, or can be divided into ALBI grades according to the published cut-offs [8]: Grade 1, best liver function (≤−2.6), grade 2 (−2.6 to −1.39) and grade 3 (worst liver function(>−1.39).

Longitudinal data showing change in ALBI score over time were available for all three cohorts. Amongst the DAA patients, albumin and bilirubin were measured at baseline, then at pre-specified time intervals (typically, after 2, 4, 8 and 12 weeks during treatment) and a number of times after treatment. In the Japanese IFN cohort, samples were recorded at irregular intervals. Longitudinal data for FIB-4 and platelet count were available for the Japanese IFN and DAA cohorts, but not for the UK DAA patients.

2.5 | Kaplan-Meier survival analysis

Overall survival according to (a) each of the three cohorts, (b) SVR status and (c) baseline ALBI grade was assessed via Kaplan-Meier analysis. Time to decompensation according to ALBI grade was also generated for the DAA patients. Using Cox regression, hazard ratios and p-values were estimated for comparing between survival groups.

2.6 | Changes in the ALBI score

For a subset of patients with longitudinal data, to visualize changes in the ALBI score over time post-treatment, aggregate curves were generated for SVR and non-SVR patients separately via two methods:

(i) Fractional polynomial regression: A curve based on fractional polynomial (FP) regression was fitted to each patient so that values at fixed time points could be interpolated and an aggregate curve thereby generated. ALBI score was used as dependent variable and time post-treatment commencement as the explanatory variable. Specifically, in fitting these functions, we considered both first- and second-degree functions (FP1 and FP2, respectively). A selection procedure was then used to select the 'best' FP function model (ie the one with the lowest deviance). Using the selected FP function for each patient, we were able to generate predicted values for each patient at various time points. From these predictions, we calculated the median at regular six-monthly time points. 95% confidence intervals were generated by the bootstrap method.

(ii) Linear regressions: A curve based on linear regression models was fitted for each patient, using square and cubic terms where appropriate. ALBI score was used as dependent variables and time post-treatment as explanatory variable. For each patient, model-predicted values at various time points were generated. Median values of all patients at each of these time points were then calculated. 95% confidence intervals were produced by the bootstrap method.

The fractional polynomial method requires a minimum of 4 observations in order to construct a curve for a patient. Due to long follow-up, this was possible to undertake in the Japanese IFN patients. However, in the DAA cohorts, follow-up was shorter (about 24 months) and the average number of observations per patient was less. In this case, linear regression was used to construct the aggregate curves.

3 | RESULTS

There was a significant difference in survival between the UK group with decompensated disease and the Japanese with compensated disease (Figure 1). Those who achieved SVR survived longer in the UK cohort (P < .0001) but the number of events in the Japanese data set was too small for meaningful statistical analysis. (Figure 2). Of the 602 patients in the UK cohort, 467 (77.6%) achieved SVR at 12 weeks. Eighty-four died during follow-up and 119 were determined to have had a clinically significant deterioration event during a total follow-up time of 1033 person years. In the Japanese cohort, 99% achieved SVR although for a small percentage (1.9%), this required a second course of DAA therapy.

3.1 | Overall survival and clinically significant deterioration according to ALBI grade

There was some survival discrimination according to baseline ALBI grade in the UK decompensated cohort (Figure 3). In the same cohort, baseline ALBI grade also showed three distinct groups with different time to first decompensation (Figure 4). Equivalent analysis in the Japanese DAA patients was not possible as the number of patients with the relevant outcomes was very low.

3.2 | Changes in ALBI score over time—impact of treatment on the ALBI score

For a subset of patients, longitudinal data were available for 571 Japanese patients (including 9 achieving SVR) and 469 UK patients (including 77 achieving SVR). These were used to examine changes in ALBI score over time.
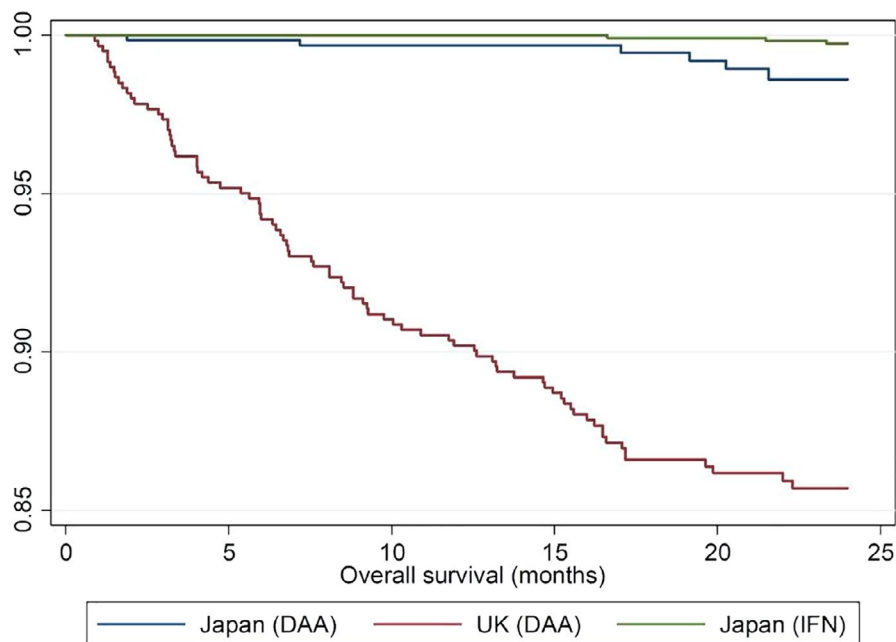
Overall survival by cohort					
Dataset	**% survival at 0.5 year (95% CI)**	**% survival at 1 year (95% CI)**	**% survival at 2 year (95% CI)**	**Hazard ratio (95% CI)**	**p-value**
Japan DAA	99.9 (98.9, 99.98)	99.7 (98.8, 99.9)	98.6 (96.8, 99.4)	1	reference
UK DAA	94.2 (92.0, 95.8)	90.2 (87.5, 92.3)	85.7 (82.6, 88.3)	14.3 (6.2, 32.7)	<0.0001
Japan IFN	100	100	99.7 (99.2, 99.9)	0.2 (0.1, 1.0)	0.045

FIGURE 1 Overall survival according to cohort. Kaplan-Meier plots. Note that the vertical axis starts as 0.85 to make the difference between the cohorts easier to visualize and the time (horizontal axis) is limited to 25 mo so that the cohorts are presented over a comparable time period

3.3 | UK DAA cohort

The mean ALBI score at baseline was −1.76 (CI −1.82, −1.72), while the mean ALBI score for the last ALBI was a significantly better (P < .01) at −2.04 (CI −2.09, −1.99). The median interval between these first and last measurements was 8.9 months (IQR 5.7, 15.2), meaning that for a large majority of patients, the last ALBI measurement was taken well after treatment was completed. Patients who achieved an SVR within 12 weeks of the end of treatment improved significantly more (change of −0.31) than those who did not (change of −0.14), P = .0031 (Figure 5A,B).

3.4 | Japanese Interferon cohort of non-SVR patients

In the interferon-based group, survival at 20 years was 89.00% (95% CI 84.21, 92.41) in the SVR group compared to 66.13% (95% CI 59.25, 72.13) in the non-SVR group. Among the 134 patients in the Japanese interferon-based cohort who died, the major cause of death was HCC (45.5%) and, of these, the great majority (90.2%) occurred among the group who did not achieve SVR. Overall only 5.22% of those who died (or 0.63% overall) were recorded as dying from liver failure, the great majority of these (85.7%) also being in the non-SVR group.

Among the SVR cohort, the ALBI score improved slightly over the first 4 years and then remained largely stable for up to 24 years. By contrast, in the non-SVR group, after a small initial improvement there was a steady deterioration in liver function (Figure 5).

It is of particular interest to note that the early changes in ALBI, over the 2 years following initiation of DAA treatment, are very closely reflected in the first few years of the interferon-based treatment cohort in that in both SVR and non-SVR, there is an improvement in liver function. However, with insight into the long-term outcome it is apparent that among the SVR patients liver function stabilized whereas there was a steady deterioration in the non-SVR group.
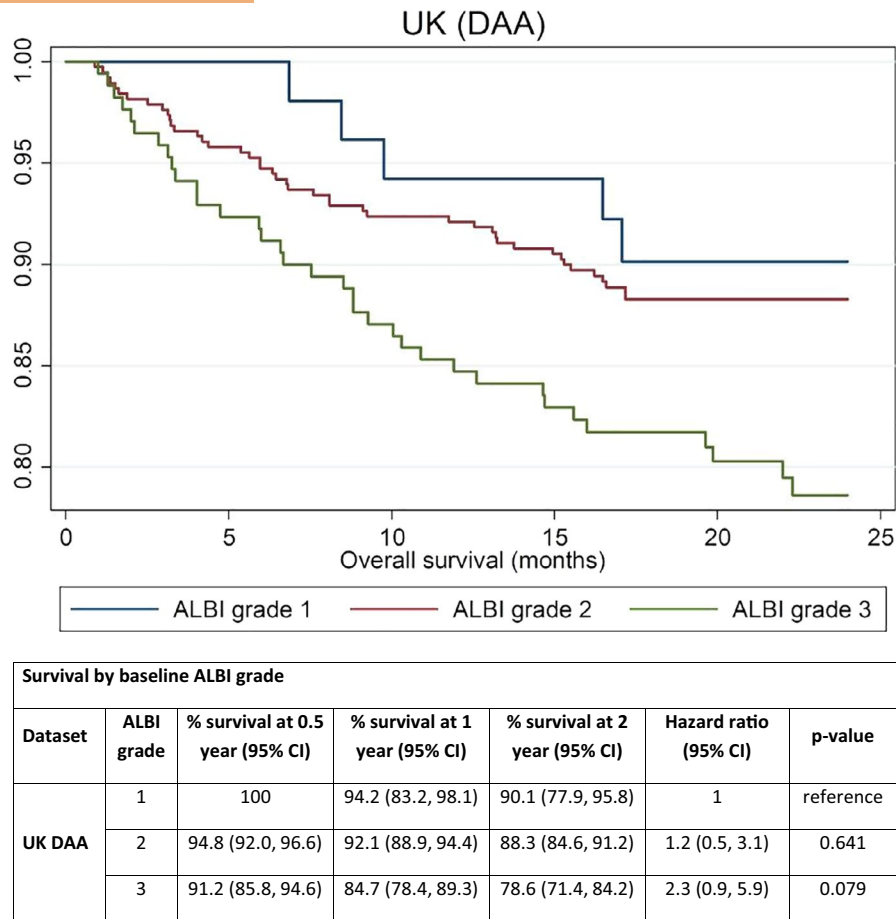
4 | DISCUSSION

Our study design permits us to assess the impact of a broad range of antiviral treatments on liver function, most pertinently the recently developed direct-acting antiviral agents in both the decompensated and compensated cirrhosis settings. Thus, in Japan the DAAs have been restricted to patients with compensated disease whereas in
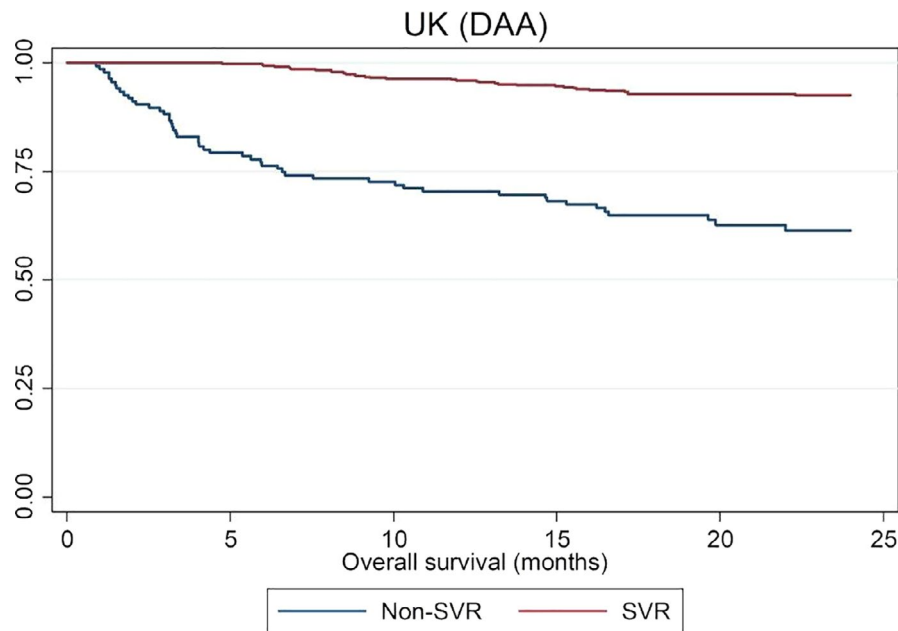
UK (DAA)

Overall survival by SVR						
Dataset	SVR status	% survival at 0.5 year (95% CI)	% survival at 1 year (95% CI)	% survival at 2 year (95% CI)	Hazard ratio (95% CI)	p-value
UK DAA	Non-SVR	76.3 (68.2, 82.6)	70.4 (61.9, 77.3)	61.3 (52.1, 69.3)	1	reference
	SVR	99.4 (98.0, 99.8)	95.9 (93.7, 97.4)	92.5 (89.7, 94.6)	0.2 (0.1, 0.2)	<0.0001

FIGURE 2 Overall survival in UK patients receiving direct-acting antiviral agents (DAAs) according to sustained virological response (SVR) status. Kaplan-Meier plots

Survival by baseline ALBI grade

Dataset	ALBI grade	% survival at 0.5 year (95% CI)	% survival at 1 year (95% CI)	% survival at 2 year (95% CI)	Hazard ratio (95% CI)	p-value
UK DAA	1	100	94.2 (83.2, 98.1)	90.1 (77.9, 95.8)	1	reference
	2	94.8 (92.0, 96.6)	92.1 (88.9, 94.4)	88.3 (84.6, 91.2)	1.2 (0.5, 3.1)	0.641
	3	91.2 (85.8, 94.6)	84.7 (78.4, 89.3)	78.6 (71.4, 84.2)	2.3 (0.9, 5.9)	0.079

FIGURE 3 Overall survival in the entire UK cohort according to baseline albumin-bilirubin (ALBI) grade. Kaplan-Meier plots

the UK, they were initially confined to patients with decompensated disease on the grounds that these were at the most imminent risk of death from liver failure. However, in both instances the follow-up is, of necessity, short, and therefore, our long-term data on the impact of interferon-based therapy on survival and liver function allow us to reasonably extrapolate DAA-related changes in liver function over the longer term.

Here, we document that liver function improves in patients receiving DAAs, particularly in those who achieve SVR, and most strikingly in those who have decompensated disease. The changes in the DAA cohort in a 3-year period are very similar in character to those seen in the interferon-treated groups over the first 3 years suggesting that the DAA cohort is likely to experience similar beneficial changes over the longer term as was seen in the interferon-treated group.

Our method of irregular time series analysis, together with the extensive serial data and use of the ALBI score (rather than the Child-Pugh score), allows us to visualize and quantify these changes over time. It is apparent, in all datasets, that even in those who do not achieve SVR, there is modest improvement in liver function over the first 3 years after initiation of therapy. We assume that even in the non-SVR group, there is transient improvement in liver function associated with a fall in viral load on treatment (indeed we know
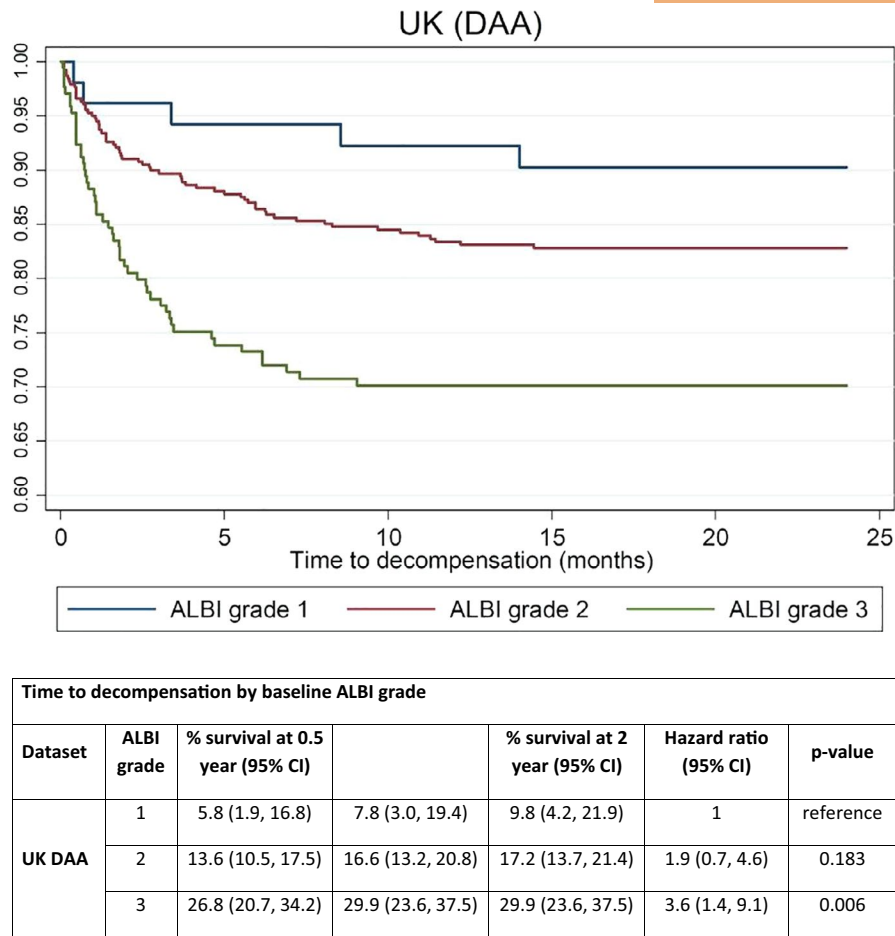
this to be the case because they include some patients who relapsed after initial response) that persists for a short time following treatment, but recurs with the post-treatment rise in viral load and subsequent recurrence of liver injury.

It is also striking that, associated with the improvement in liver function, there is, in the UK cohort with decompensated disease, clear evidence of survival benefit in those achieving SVR (compared to those not achieving SVR) even over the short period of follow-up. Again, extrapolating from the Interferon-treated group there is clear evidence of long-term survival benefit with the achievement of SVR although it is important to note that this benefit is consequent upon the decreased incidence of HCC rather than any improvement in mortality from liver failure, the incidence of which was, in fact, very low.

The marked reduction in deaths from HCC, consequent on achieving SVR, has also been widely reported but it has been noted that, although the risk of HCC is decreased in the SVR group, it is not abrogated completely. Indeed, in the largest study to date of HCC arising *after* SVR it is striking that the HCCs occurred very shortly after SVR with a median development time of only 1.66 years.[14]

In summary, we have demonstrated that DAA treatment results in improved liver function and survival particularly in patients who achieve SVR, compared to those who do not. Amongst patients with decompensated liver disease, liver function clearly impacts on

UK (DAA)

Time to decompensation by baseline ALBI grade						
Dataset	ALBI grade	% survival at 0.5 year (95% CI)		% survival at 2 year (95% CI)	Hazard ratio (95% CI)	p-value
UK DAA	1	5.8 (1.9, 16.8)	7.8 (3.0, 19.4)	9.8 (4.2, 21.9)	1	reference
	2	13.6 (10.5, 17.5)	16.6 (13.2, 20.8)	17.2 (13.7, 21.4)	1.9 (0.7, 4.6)	0.183
	3	26.8 (20.7, 34.2)	29.9 (23.6, 37.5)	29.9 (23.6, 37.5)	3.6 (1.4, 9.1)	0.006

FIGURE 4 Time to decompensation (clinically significant deterioration) according to baseline albumin-bilirubin (ALBI) grade in the entire UK cohort. Kaplan-Meier plots
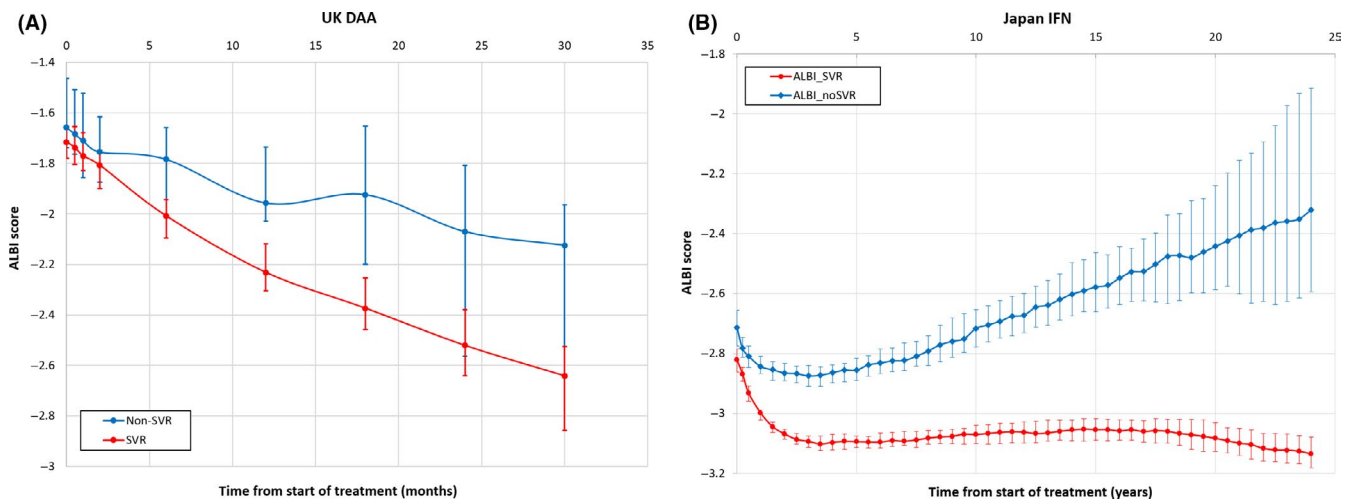
FIGURE 5 A and B, Changes in albumin-bilirubin (ALBI) score over time in the (A) UK DAA and the (B) Japanese interferon cohorts. Note the similarity in the changes between the two cohorts over the first 3 y

survival and the likelihood of further adverse liver-related events. The changes in liver function and survival with DAAs mirror, in the short term over which they have been observed, analogous results in a population receiving interferon-based therapy. In the latter cohort, such changes were, on long follow-up, associated with improved liver function and survival. It is likely that the DAA-mediated improvement of liver function in patients who achieve SVR will translate into survival benefit.

CONFLICT OF INTEREST

The authors have no conflict of interest.

AUTHOR CONTRIBUTIONS

PJ, WI and SB involved in study concept and design and drafting of manuscript. All authors involved in acquisition of data and critical revision of the manuscript for intellectual content. SB, AW, PJ and WI involved in analysis and interpretation of the data. SB and AW involved in statistical analysis. PJ, HT and WI involved in study supervision.

ORCID

Philip J. Johnson https://orcid.org/0000-0003-1404-0209
Stuart McPherson https://orcid.org/0000-0002-5638-2453
Kosh Agarwal https://orcid.org/0000-0002-4754-828X
Takeshi Kumada https://orcid.org/0000-0003-2211-495X
Hidenori Toyoda https://orcid.org/0000-0002-1652-6168
William L. Irving https://orcid.org/0000-0002-7268-3168

REFERENCES

1. Smith-Palmer J, Cerri K, Valentine W. Achieving sustained virologic response in hepatitis C: a systematic review of the clinical, economic and quality of life benefits. *BMC Infect Dis.* 2015;15:19.
2. Nahon P, Bourcier V, Layese R, et al. Eradication of hepatitis C virus infection in patients with cirrhosis reduces risk of liver and non-liver complications. *Gastroenterology.* 2017;152:142-156.e142.
3. Marino Z, Darnell A, Lens S, et al. Time association between hepatitis C therapy and hepatocellular carcinoma emergence in cirrhosis: relevance of non-characterized nodules. *J Hepatol.* 2019;70(5):874-884.
4. Singal AG, El-Serag HB. Hepatocellular carcinoma from epidemiology to prevention: translating knowledge into practice. *Clin Gastroenterol Hepatol.* 2015;13:2140-2151.
5. van der Meer AJ, Berenguer M. Reversion of disease manifestations after HCV eradication. *J Hepatol.* 2016;65:S95-S108.
6. Schiff ER, Lee SS, Chao YC, et al. Long-term treatment with entecavir induces reversal of advanced fibrosis or cirrhosis in patients with chronic hepatitis B. *Clin Gastroenterol Hepatol.* 2011;9:274-276.
7. Jakobsen JC, Nielsen EE, Feinberg J, et al. Direct-acting antivirals for chronic hepatitis C. *Cochrane Database Syst Rev.* 2017;9:CD012143.
8. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. *J Clin Oncol.* 2015;33:550-558.
9. Pinato DJ, Sharma R, Allara E, et al. The ALBI grade provides objective hepatic reserve estimation across each BCLC stage of hepatocellular carcinoma. *J Hepatol.* 2017;66:338-346.
10. Chen RC, Cai YJ, Wu JM, et al. Usefulness of albumin-bilirubin grade for evaluation of long-term prognosis for hepatitis B-related cirrhosis. *J Viral Hepat.* 2017;24:238-245.
11. Jacobson IM, Poordad F, Brown RS Jr, Kwo PY, Reddy KR, Schiff E. Standardization of terminology of virological response in the treatment of chronic hepatitis C: panel recommendations. *J Viral Hepat.* 2012;19:236-243.
12. Cheung MCM, Walker AJ, Hudson BE, et al. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol.* 2016;65:741-747.
13. Foster GR, Irving WL, Cheung MC, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol.* 2016;64:1224-1231.
14. El-Serag HB, Kanwal F, Richardson P, Kramer J. Risk of hepatocellular carcinoma after sustained virological response in Veterans with hepatitis C virus infection. *Hepatology.* 2016;64:130-137.

How to cite this article: Johnson PJ, Berhane S, Walker AJ, et al. Impact of direct-acting antiviral agents on liver function in patients with chronic hepatitis C virus infection. *J Viral Hepat*. 2021;28:168–176. https://doi.org/10.1111/jvh.13408

APPENDIX 1

K. Agarwal (Kings College Hospital, London), M. Aldersley (St James's University Hospital, Leeds), A. Ala (Frimley Park Hospital), R. Aspinall (Queen Alexandra Hospital, Portsmouth), E. Barnes (John Radcliffe Hospital, Oxford), A. Brown (St Mary's Hospital, London), L. Corless (Hull Royal Infirmary), M. Cramp (Derriford Hospital, Plymouth), D. Forton (St George's Hospital, London), G. Foster (The London Hospital), M. Foxton (Chelsea & Westminster), W. Gelson (Addenbrookes Hospital, Cambridge), D. Gorard (Wycombe Hospital), F. Gordon (Bristol Royal Infirmary), S. Khakoo (Southampton General Hospital), A. Lawson (Royal Derby Hospital), S. McPherson (Freeman Hospital, Newcastle), S. Moreea (Bradford Teaching Hospitals NHS Foundation Trust), D. Mutimer (Queen Elizabeth Hospital, Birmingham), M. Prince (Manchester Royal Infirmary), P. Richardson (Royal Liverpool University Hospital), W. Rosenberg (Royal Free Hospital & University College Hospital), S. Ryder (Queen's Medical Centre, Nottingham), A. Sreedharan (Lincoln County Hospital), B. Stone (Royal Hallamshire Hospital, Sheffield), A. Ustianowski (North Manchester General Hospital), S. Verma (Royal Sussex County Hospital, Brighton), M. Wiselka (Leicester Royal Infirmary)