**Title page**

**Comparison of the prognosis of patients with and without direct acting antiviral treatment for hepatitis C virus–related decompensated cirrhosis.**

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**Short running title**: Impact of DAAs on decompensated cirrhosis

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The authors declare the following:

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**Abstract**

**Background & Aims**: In patients with hepatitis C virus (HCV) infection and decompensated cirrhosis (DC), it is uncertain whether viral clearance is clinically meaningful and whether it decreases liver-related and non–liver-related mortality. The aim of this study was to assess whether viral eradication reduced liver-related and non–liver-related mortality in patients with HCV infection and DC.

**Methods**: To clarify the impact of viral eradication on liver-related and non–liver-related mortality, 433 patients with DC who received direct-acting antivirals (DAAs) and achieved sustained virological response (SVR) in the United Kingdom (DAA group) were compared with 621 patients with DC who did not receive DAAs and who underwent symptomatic treatment in Japan (Non-DAA group). Cox proportional hazards models were used for all-cause mortality and Fine and Gray proportional hazards models were used for liver-related and non–liver-related mortality.

**Results**: Cox’s proportional hazards model demonstrated that factors associated with all-cause mortality were age ≥ 65 years, male gender, albumin–bilirubin (ALBI) score ≥ −2.60, and Non-DAA group. Fine and Gray proportional hazards models showed that alcohol abuse, ALBI score ≥ −2.60, FIB-4 index ≤ 3.25, and Non-DAA group were independently associated with liver-related mortality. Fine and Gray proportional hazards models showed that age ≥ 65, male gender, no alcohol abuse, ALBI score ≥ −2.60, and FIB-4 index ≤ −3.25, and Non-DAA group were independently associated with non–liver-related mortality.

**Conclusion**: DAA-mediated viral eradication reduced not only liver-related mortality but also non–liver-related mortality in patients with HCV infection and DC. (248 words).

**Lay Summary**

It is uncertain whether viral clearance is clinically meaningful and whether it reduces liver-related and non–liver-related mortality in patients with hepatitis C virus infection and decompensated cirrhosis. We compared the prognosis of patients in the United Kingdom who were treated with direct-acting antivirals and achieved sustained virological response with untreated patients in Japan who did not receive direct-acting antiviral therapy. Eradication of hepatitis C virus reduced not only liver-related mortality but also non–liver-related mortality.

**What You Need to Know**

**Background**

It is uncertain whether viral clearance is meaningful and reduces liver-related and non–liver-related mortality in patients with hepatitis C virus infection and decompensated cirrhosis.

**Findings**

Eradication of hepatitis C virus reduced not only liver-related mortality but also non–liver-related mortality in patients with hepatitis C virus infection and decompensated cirrhosis.

**Implications for patient care**

Patients with hepatitis C virus infection and decompensated cirrhosis should be actively treated with antiviral therapy whenever possible, regardless of liver function.

**Key words**: hepatitis C virus (HCV); decompensated cirrhosis; direct-acting antiviral (DAA); sustained virological response (SVR), liver-related mortality; non–liver-related mortality.

**Introduction**

One of the most severe sequelae of chronic infection with the hepatitis C virus (HCV) is decompensated cirrhosis (DC) [1, 2]. Patients with DC have a poor prognosis and treatment options remain limited. Complications of DC include jaundice, variceal hemorrhage, ascites, and encephalopathy. Interferon-based treatment has not been recommended for HCV-infected patients with DC due to severity of adverse effects in this population [3, 4]. However, the introduction of oral direct-acting antiviral (DAA)-based HCV therapy has dramatically increased the number of patients who are eligible for antiviral therapy, and high response rates can be achieved with various combination treatment regimens [5, 6].

Viral eradication in patients with HCV infection and chronic hepatitis or compensated cirrhosis reduces all-cause mortality, including liver-related and non–liver-related mortality [7, 8, 9]. In a previous study of patients with DC, viral eradication was associated with a rapid improvement in liver function and complications [10, 11]. Two previous studies in patients with DC enrolled in a United Kingdom hepatitis C registry, HCV Research UK, had a follow-up period of less than 12 months [12, 13]. Therefore, in patients with HCV infection and DC, it is uncertain whether viral clearance is meaningful and whether it reduces liver-related and non–liver-related mortality.

The aim of this study was to assess whether viral eradication decreased liver-related and non–liver-related mortality in patients with HCV infection and DC. The treatment cohort, based on data from HCV Research UK, was treated with DAAs, achieved sustained virological response (SVR), and was prospectively followed for 3 years, while the no-treatment cohort was based on data from one hospital in Japan and included only patients who did not receive DAAs.

**Materials and Methods**

**Ethics**

Ethics approval for HCV Research UK was given by the national research ethics service (NRES) Committee East Midlands - Derby 1 (Research Ethics Committee reference 11/EM/0314) and the proposal for the analysis reported herein was accepted by the HCVRUK Tissue and Data Access committee in January 2019, and informed consent was obtained from each patient included in the study. The study protocol was also approved by the institutional review board of Ogaki Municipal Hospital in March 2019 and was conducted in compliance with the Helsinki Declaration.

**Patients**

Between May 2015 and September 2015, 653 patients with a history of DC liver disease who received DAA therapy were enrolled in the HCV Research UK registry for prospective data collection. Inclusion criteria for DC included ascites, variceal bleeding, or hepatic encephalopathy (past or current). Treatment involved mainly ledipasvir/sofosbuvir, sofosbuvir/daclatasvir, or other regimens with or without ribavirin for a total of 12 weeks. Of the 653 patients, 22 who had a history of hepatocellular carcinoma (HCC), 55 who did not achieve SVR, 71 who developed HCC within 1 year after starting DAA therapy, and 64 with incomplete clinical information were excluded. The remaining 439 patients were analyzed as the “DAA group.”

As a control, an untreated cohort of patients with decompensated HCV cirrhosis who did not receive DAA therapy and who underwent symptomatic treatment was studied at Ogaki Municipal Hospital in Japan between 1995 and 2007. Of 6,638 consecutive patients whose data were collected retrospectively, 530 who had a history of HCC, 1,970 who received antiviral therapy including interferon-based therapy, 2,562 who had no history of decompensation, 472 who developed HCC within 1 year from the date of DC diagnosis, and 483 with incomplete clinical information were excluded. The remaining 621 patients were enrolled as the control “Non-DAA group” (Figure 1).

Observation was started on the first day of DAA treatment in the DAA group and on the day of DC diagnosis in the Non-DAA group. Observation was terminated on the day of death or the last visit in both groups.

At the start of follow-up, alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet count, albumin, total bilirubin, prothrombin time-international normalized ratio (PT-INR), creatinine, and estimated glomerular filtration rate (eGFR) [14] were measured. The FIB-4 index was calculated at the start of follow-up by the following formula: aspartate aminotransferase (AST) concentration (IU/L) × age (years) / (platelet count [109/L] × alanine aminotransferase [ALT] concentration1/2 [IU/L]) [15]. We used previously published cut-off values for the FIB-4 index. Patients with a FIB-4 value < 1.45 were defined as having no or moderate fibrosis, while those with a FIB-4 value > 3.25 were defined as having extensive fibrosis or cirrhosis [16]. In addition, the Child-Pugh classification, Child-Pugh score, model for end-stage liver disease (MELD) score, and albumin–bilirubin (ALBI) grade were used as indicators of liver function [3]. The ALBI grade was calculated using the following linear equation: (log10 bilirubin μmol/L × 0.66) + (albumin/L × −0.085) [17]. The continuous linear predictor was further categorized into three different grades for prognostic stratification purposes, as previously described: grade 1 (less than −2.60), grade 2 (between −2.60 and −1.39), and grade 3 (above −1.39) [17]. HCV genotype was assessed using PCR with genotype-specific primers to amplify core gene sequences. SVR was defined as undetectable serum HCV RNA at 12 weeks after the end of treatment.

In this study, causes of death were divided into liver-related disease, which included HCC, liver failure, and variceal bleeding, and non–liver-related disease. Causes of death in the UK were determined from the descriptions in the HCV Research UK database. Causes of death of patients who died at Ogaki Municipal Hospital in Japan were retrospectively identified by reviewing medical records; for patients who died elsewhere, for example in other hospitals, hospices, or their own homes, information regarding cause of death was obtained from the attending physician or the family physician.

**Statistical Analysis**

Continuous variables were expressed as medians (interquartile range). The Mann–Whitney *U* test was used to assess continuous variables. The chi-square test with Fisher’s exact test was used to evaluate categorical variables.

Multivariate Cox proportional hazards models were used to analyze factors related to all-cause mortality. Fine and Gray proportional hazards models for the subdistribution of a competing risk (18) were used to analyze factors related to liver-related and non–liver-related mortality. The cut-offs of analyzed factors were based on previous reports: age, 65 years [12]; ALBI score, −1.39 [17]; FIB-4 index, 3.25 [16]; and eGFR, 60 mL/min/1.73m2 [14].

In this study, we applied inverse probability weighting (IPW) to the Kaplan–Meier method for all-cause mortality, including liver-related and non–liver-related mortality, to adjust for potential imbalances [19]. SVR and non-SVR probabilities (propensities) were calculated using logistic regression analysis with a set of covariates deemed likely to have affected mortality in patients with DC; these included age, sex, presence or absence of diabetes mellitus, presence or absence of alcohol abuse, FIB-4 index, ALBI score, and eGFR. All of these variables were included, regardless of statistical significance. The inverse probability weights were defined as 1/ (propensity score) for the DAA group and 1/ (1−propensity score) for the Non-DAA group. Actuarial analysis of liver-related and non–liver-related mortality was performed using the cumulative incidence with the IPW competing risks method [20], and differences were tested using IPW-adjusted log-rank test.

Statistical significance was defined as p<0.05. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria) [21]. More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

**Results**

**Differences in baseline patient characteristics between the DAA and Non-DAA groups**

Table 1 shows the characteristics of patients in both the DAA and Non-DAA groups. The DAA group had a higher frequency of males, alcohol abuse, and smoking, and higher values for the Child-Pugh score, MELD score, BMI, ALT, AST, FIB-4 index, eGFR, total bilirubin, and PT-INR. By contrast, the Non-DAA group had a higher frequency of DM, greater age, and higher platelet count. The percentages of patients with HCV genotypes 1, 2, 3, and 4 in the DAA and Non-DAA groups were 54.5% (n=236) and 71.1% (n=275), 4.2% (n=18) and 28.9 (n=112), 35.8% (n=155) and 0.0% (n=0), and 5.5% (n=24) and 0.0% (n=0), respectively, indicating a significant difference between the two groups (*p*<0.0001). The proportions of individuals with liver-related versus non–liver-related death were 45.6% and 54.4% in the DAA group, respectively, and 46.7% and 53.3% in the Non-DAA group, respectively, indicating no difference between the two groups. The calculated propensity scores of patients in the DAA and Non-DAA groups were 0.80 (0.54–0.94) and 0.07 (0.02–0.19), respectively (p<0.001). In addition, the calculated IPW scores of patients in the DAA and non-DAA groups were 1.25 (1.06–1.85) and 1.08 (1.02–1.24), respectively (*p*<0.001).

**Factors associated with all-cause mortality**

Factors associated with all-cause mortality were analyzed using Cox’s proportional hazards model (Table 2). The analyzed factors were age, gender, alcohol abuse (presence or absence), DM (presence or absence), therapy (DAA vs. Non-DAA), FIB-4 index, ALBI grade, and eGFR. Age ≥ 65 years (hazard ratio [HR], 1.385, 95% confidential interval [CI], 1.119–1.714, *p*=0.0028), male gender (HR, 1.288, 95%CI, 1.053–1.576, *p*=0.0139), ALBI score ≥ −2.60 (HR, 1.885, 95%CI, 1.524–2.331, *p*<0.0001), and SVR (HR, 0.397, 95%CI, 0.275–0.6572, *p*<0.0001) were independently associated with all-cause mortality. Figure 2 shows that the IPW-adjusted cumulative all-cause mortality rates in the DAA and Non-DAA groups were 6.1% and 18.4% at 1 year, respectively, 13.1% and 23.7% at 2 years, respectively, and 16.8% and 30.0% at 3 years, respectively, indicating a significant difference (*p*<0.0001, IPW-adjusted log-rank test).

**Ratio of liver-related and non–liver-related mortality**

Figure 3 shows that the cumulative incidence rates of liver-related and non–liver-related mortality were 6.0% and 11.6% at 1 year, respectively, 9.7% and 15.8% at 2 years, respectively, and 13.8% and 19.8% at 5 years, respectively.

**Factors associated with liver-related mortality**

Table 3 shows the factors associated with liver-related mortality according to Fine and Gray proportional hazards models. The analyzed factors were the same as those for all-cause mortality. Multivariate analysis showed that alcohol abuse (HR, 1.613; 95% CI, 1.079–2.413; *p*=0.0200), ALBI score ≥ −2.60 (HR, 1.619, 95%CI, 1.210–2.167, *p*=0.0012), FIB-4 index > 3.25 (HR, 3.301, 95%CI, 2.108–5.168, *p*<0.0001), and SVR (HR, 0.201, 95%CI, 0.079–0.364, *p*<0.0001) were independently associated with liver-related mortality. Figure 4 shows that the IPW-adjusted cumulative incidence rates of liver-related mortality with and without DAA therapy were 2.5% and 6.7% at 1 year, respectively, 5.8% and 9.4% at 2 years, respectively, and 6.5% and 12.6% at 3 years, respectively, indicating a significant difference between the two groups (*p*<0.0001, IPW-adjusted log-rank test).

**Factors associated with non–liver-related mortality**

Table 4 shows the factors associated with non–liver-related mortality according to Fine and Gray proportional hazards models. The analyzed factors were the same as those for all-cause mortality. Multivariate analysis showed that age ≥ 65 years (HR, 1.736, 95%CI, 1.304–2.309, *p*=0.0002), male gender (HR, 1.622, 95%CI, 1.213–2.168, *p*=0.0011), alcohol abuse (HR, 0.638; 95% CI, 0.415–0.981; *p*=0.0400), ALBI score ≥ −2.60 (HR, 1.472, 95%CI, 1.093–1.983 *p*=0.0110), FIB-4 index > 3.25 (HR, 0.385, 95%CI, 0.291–0.510, *p*<0.0001), and SVR (HR, 0.606, 95%CI, 0.393–0.934, *p*=0.0230) were independently associated with non–liver-related mortality. Figure 5 shows that the IPW-adjusted cumulative incidence rates of non–liver-related mortality with and without DAA therapy were 2.2% and 11.5% at 1 year, respectively, 7.3% and 14.3% at 2 years, respectively, and 10.3% and 16.5% at 3 years, respectively, indicating a significant difference between the two groups (*p*<0.0001, IPW-adjusted log-rank test).

**Discussion**

The advent of highly effective DAA drugs has transformed the treatment options for HCV-infected patients with DC [11, 12]. In this study, we examined a 12-week course of antiviral therapy in a large, heterogeneous group of patients with DC or life-threatening complications of HCV infection in the UK (HCV Research UK), and compared the outcomes of this group, who received DAAs and achieved SVR, with a group of patients in Japan who were not treated with DAAs. We found that viral eradication reduced not only liver-related mortality but also non–liver-related mortality in patients with HCV infection and DC.

All-cause mortality in this population was associated with high age, male gender, impaired liver function, and no viral eradication. There has previously been little information on how liver-related and non–liver-related mortality are affected by viral eradication in patients with HCV infection and DC. This study showed that in these patients, liver-related mortality was associated with alcohol abuse, impaired liver function, advanced fibrosis, and no viral eradication. Prognosis was closely related to HCV clearance, and the HR of the DAA group was about one-fifth of that in the Non-DAA group. It is clear that eradicating HCV is very important to reduce liver-related mortality. Impaired liver function, as indicated by ALBI grade 2 or 3, was associated with increased liver-related mortality. Judging from these results, it is considered that antiviral therapy should be started as early as possible during the period of mild liver injury. Liver-related mortality increased in patients with advanced fibrosis. The risk of hepatocarcinogenesis increases as hepatic fibrosis progresses [22, 23], and it is believed that the number of deaths from HCC does not decrease despite viral eradication in patients with advanced fibrosis and the risk of HCC development even in patients who achieve viral eradication remains elevated. In addition, excessive alcohol consumption was previously shown to be associated with increased liver-related mortality despite viral eradication [24]. On the other hand, in this study, non–liver-related mortality was associated with high age, male gender, no alcohol abuse, impaired liver function, mild fibrosis, and viral eradication. Many previous studies involving long-term follow-up of individuals receiving IFN-based therapy showed that viral eradication reduced not only liver-related mortality but also non–liver-related mortality in patients with chronic hepatitis and compensated cirrhosis [7, 8, 9]. Our study is the first to show that viral eradication reduces non–liver-related mortality even in patients with HCV infection and DC. HCV infection has been recognized as a systematic disease with both hepatic and extrahepatic manifestations [25, 26]. Chronic HCV infection is associated with pathophysiological changes outside the liver, including those involving the metabolic, cardiovascular, and neurological systems, as well as autoimmune and immune-mediated conditions such as mixed cryoglobulinemia, thyroid disease, and glomerulonephritis. Studies have also shown that treatment to eradicate HCV infection may improve some extrahepatic manifestations of HCV independently of the severity of underlying liver disease [23, 24]. In this study, excessive alcohol consumption was associated with decreased non–liver-related mortality. It is thought that liver-related mortality is increased in patients with excessive alcohol consumption [22], but decreases non–liver-related mortality. A similar phenomenon was observed in the FIB-4 index. Because advanced fibrosis is associated with increased liver-related mortality, especially in HCC [23], it is likely that advanced fibrosis resulted in a decrease in non–liver-related mortality.

The main limitation in this study was the nature of the control subjects. Untreated Japanese patients with DC were selected based on the same criteria as treated patients in the UK. While it would have been preferable to conduct a randomized control trial of treatment versus no treatment, this would have been unethical. There were significant differences in the background factors of the DAA group in the UK and the Non-DAA group in Japan. Patients in Japan were an average of 17 years older and were more likely to be men and to have DM than those in the UK. In contrast, patients in the UK had a higher BMI and higher rates of alcohol abuse and smoking than those in Japan. Genotype 3 was present in the UK, but not in Japan. However, there was no difference between the two groups in Child-Pugh class, ALBI score, or ALBI grade, all of which were used as indicators of liver function. The FIB-4 index, used as a marker of fibrosis, was higher in the UK than in Japan. In order to reduce the confounding effects of covariates, we used the Cox proportional hazards model for overall mortality and Fine and Gray proportional hazards models with competitive risk for liver-related and non–liver-related mortality in this study. In addition, we applied IPW to the Kaplan–Meier method for all-cause, liver-related, and non–liver-related mortality, to adjust for potential imbalances between the DAA and Non-DAA groups [19, 20]. The results of the analysis demonstrated that the DAA group survived longer than the Non-DAA group despite their different background factors. Another limitation is the presence of racial differences such as underlying diseases and life expectancy. The effects of these differences were not clear in this study.

There were some patients with compensated cirrhosis in both groups. Specifically, 14.1% of patients in the UK (DAA group) and 14.7% of patients in Japan (Non-DAA group) were Child-Pugh class A at baseline, but had past decompensation events.

In conclusion, SVR obtained by DAA therapy for DC prolongs survival. Moreover, this effect applies not only to liver-related mortality but also to non–liver-related mortality.

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**Figure Legends**

Figure 1. Flowchart of the patient selection process.

HCV, hepatitis C virus; DAA, direct-acting antiviral; SVR, sustained virological response; HCC, hepatocellular carcinoma

Figure 2. All-cause mortality with and without DAA therapy and adjusted by IPW.

The cumulative all-cause mortality rates in the DAA and Non-DAA groups were 6.1% and 18.4% at 1 year, respectively, 13.1% and 23.7% at 2 years, respectively, and 16.8% and 30.0% at 3 years, respectively, indicating a significant difference between the two groups (*p*<0.0001, IPW-adjusted log-rank test).

IPW, inverse probability weighting; SVR, sustained virological response

Figure 3. Liver-related and non–liver-related mortality

The incidence rates of liver-related and non-liver related mortality were 6.0% and 11.6% at 1 year, respectively, 9.7% and 15.8% at 2 years, respectively, and 13.8% and 19.8% at 5 years, respectively.

SVR, sustained virological response

Figure 4. Liver-related mortality with and without DAA therapy and adjusted by IPW.

The cumulative incidence rates of liver-related mortality with and without DAA therapy were 2.9% and 8.4% at 1 years, respectively, 5.8% and 9.4% at 2 years, respectively, and 6.5% and 12.6% at 3 years, respectively, indicating a significant difference between the two groups (*p*<0.0001, IPW-adjusted log-rank test).

IPW, inverse probability weighting; DAA, direct-acting antiviral; SVR, sustained virological response.

Figure 5. Non–liver-related mortality with and without DAA therapy and adjusted by IPW.

The cumulative incidence rates of non–liver-related mortality with and without DAA therapy were 2.2% and 11.5% at 1 year, respectively, 7.3% and 14.3% at 2 years, respectively, and 10.3% and 16.5% at 3 years, respectively, and there was a significant difference between the two groups (*p*<0.0001, IPW-adjusted log-rank test).

IPW, inverse probability weighting; DAA, direct-acting antiviral; SVR, sustained virological response.