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Real-world impact following initiation of interferon-free hepatitis C regimens on liver-related outcomes and all-cause mortality among patients with compensated cirrhosis

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ABSTRACT

Few studies have investigated clinical outcomes among patients with cirrhosis who were treated with interferon (IFN)-free direct-acting antiviral (DAA). We aimed to quantify treatment impact on first decompensated cirrhosis hospital admission, first hepatocellular carcinoma (HCC) admission, liver-related mortality, and all-cause mortality among a national cohort of cirrhotic patients. Through record-linkage between Scotland's HCV Clinical Database and inpatient/day-case hospitalisation and deaths records, a study population comprising chronic HCV-infected patients with compensated cirrhosis and initiated on IFN-free DAA between 1 March 2013 and 31 March 2018 was analysed. Cox regression evaluated the association of each clinical outcome with time-dependent treatment status (on treatment, responder, non-responder, or non-compliant), adjusting for patient factors including Child-Pugh class. Among the study population (*n*=1,073) involving 1,809 years of follow-up, 75 (7.0%) died during (39 from liver-related causes), 47 progressed to decompensated cirrhosis, and 28 developed HCC. Compared with non-responders, treatment response (96% among those attending their 12 weeks post-treatment SVR test) was associated with a reduced relative risk of decompensated cirrhosis (hazard ratio [HR]=0.14; 95%CI: 0.05-0.39), HCC (HR=0.17; 95%CI: 0.04-0.79), liver-related death (HR=0.13; 95%CI: 0.05-0.34), and all-cause mortality (HR=0.30; 95%CI:0.12-0.76). Compared with responders, non-compliant patients had an increased risk of liver-related (HR=6.73; 95%CI: 2.99-15.1) and all-cause (HR=5.45; 95%CI:3.07-9.68) mortality. For HCV patients with cirrhosis, a treatment response was associated with a lower risk of severe liver complications and improved survival. Our findings suggest additional effort is warranted to address the higher mortality among the minority of cirrhotic patients who do not comply with DAA treatment or associated RNA testing.

Keywords: Hepatitis C virus; Compensated cirrhosis; Mortality; Antiviral treatment; Scotland.

Direct-acting antiviral (DAA) drugs for chronic hepatitis C virus (HCV) infection have prompted considerable optimism that the escalating HCV-related liver disease burden in countries may be reduced through treatment.[1,2] DAA regimens have produced sustained virological response (SVR) rates in excess of 90% for patients with compensated cirrhosis, more than twice the rate achieved by interferon-based regimens.[3] Given initial clinical guidelines and practice involving treatment prioritisation for those with advanced fibrosis,[4,5] an appreciable proportion of the 5 million people treated with DAAs globally to date will have had compensated cirrhosis.[6] Despite this, there remains relatively little evidence regarding the impact of IFN-free therapy for patients with compensated cirrhosis on important clinical outcomes, such as progression to decompensated cirrhosis (DC), development of HCC, and mortality.

There is robust and compelling evidence from the interferon treatment era that patients achieving SVR have significantly reduced risk of severe liver complications and all-cause mortality compared with non-SVR.[7,8] More recently, well-conducted clinical trials and real-world studies have demonstrated the ability of DAAs to effectively clear HCV from the host.[9-11] Yet the clinical utility of a DAA-induced SVR has been disputed by authors of a Cochrane review, who advocated that the impact of DAA therapy on HCV-related liver morbidity remains unproven;[12] an aim of our study was to provide real-world observational evidence to address this issue.

The main objective of our study was to evaluate the clinical benefit of IFN-free regimens through examination of the development of severe outcomes (including first DC admission, first hepatocellular cancer (HCC) admission, and liver-related and all-cause mortality) from the point of initiation on treatment for an entire national cohort of chronically HCV-infected patients diagnosed with compensated cirrhosis. In a real-world patient cohort, a significant minority of patients fail to complete treatment or do not return for RNA testing;[13] as a secondary objective we examined the same clinical outcomes in these patients. Although we would anticipate high rates of viral clearance among those compensated cirrhosis patients who do not return for HCV RNA testing upon completion of DAA therapy, the same behavioural factors associated with non-compliance may also lead to a heightened risk of liver disease progression and mortality.

METHODS

Data sources

The three principal data sources were the Scottish HCV Clinical Database (a comprehensive record of all HCV patients attending specialist tertiary care, covering all but one of 18 specialist liver clinics across Scotland, as previously described in Ref. 14), the national deaths registry (held by the National Records of Scotland) and the Scottish Morbidity Records (SMR; a database holding all acute inpatient and day-case hospital episodes held by the Information Services Division (ISD) of NHS Scotland). Record-linkage between these three databases was conducted by ISD using a combination of probabilistic and deterministic methods,[15,7] with the resulting linkage anonymised before analysis. The first step involved probabilistic linkage to the Community Health Index (CHI) database to retrieve a unique patient identifier (CHI number), which also allowed date of emigration from Scotland (if it had occurred) to be inferred, and the second step involved deterministic linkage to the deaths registry and SMR via the CHI number. Permission to link databases was obtained from the Public Benefit and Privacy Panel, National Services Scotland.

Study population

The study population was defined as all patients on the HCV Clinical Database who had ever been diagnosed with compensated cirrhosis on or following 1 January 1996 and who had been initiated on IFN-free treatment between 1 March 2013 and 31 March 2018 subsequent to date of cirrhosis diagnosis. Cirrhosis was determined based on biopsy, transient elastography (FibroScan®), abdominal ultrasound, clinical examination, routine liver function tests, or combinations of the above. Date of initiation (of the most recent IFN-free therapy course, if more than one) was defined as 'baseline'. The study population was further restricted to persons without decompensated disease or HCC at baseline.

Clinical outcomes

We investigated four principal endpoints subsequent to initiation on IFN-free treatment: first DC admission, first HCC admission, liver-related mortality, and all-cause mortality. This was based on the occurrence of a pre-defined set of ICD-10 (International Classification of Diseases, 10th Revision) codes in either the underlying or contributing cause of death fields (mortality) or either the main or supplementary discharge diagnosis fields (hospital admissions). For DC admissions, the set of ICD codes consisted of ascites (R18), bleeding oesophageal varices (I85.0, I98.3), chronic hepatic failure, including hepatic encephalopathy (K72.1, K72.9), alcoholic hepatic failure (K70.4),

and hepatorenal syndrome (K76.7); these ICD codes for defining DC admissions have been used in previous studies.[16,17] For HCC the single code was primary liver cancer (C22.0). For liver-related mortality, the set of DC and HCC codes was augmented by alcoholic liver disease (K70), non-alcoholic liver disease (K71-77), viral hepatitis (B15-19), and sequelae associated with viral hepatitis (B94.2, R17, I98.2).

Disease stage determination

Child-Pugh (CP) class was determined by the most recent laboratory test results for bilirubin, albumin, and prothrombin time within the 180 day period prior to treatment initiation (CP score is normally also derived using ascites and encephalopathy; these were absent as decompensated patients had been excluded). Patients who had not undergone a prothrombin time test in this period were assumed to be CP stage A if they had an albumin level of >3.5 g/dl, and bilirubin level of <2 mg/dl.[7] We quantified the degree of completeness in the covariates required to determine CP score, and used modern multiple imputation methods to impute missing values in regression analyses described further below.[18,19]

Analysis of outcomes associated with treatment outcome status

Follow-up time. Follow-up started at IFN-free treatment course start date, and ended at the earliest of the date of outcome, death, migration, or the administrative censoring date (31 March 2018).

Regression modelling. Separate Cox regression analyses were conducted for each of the four clinical endpoints. The exposure variable of interest, *treatment outcome status*, was defined as time-dependent (consisting of: *On treatment*, *Responder* (i.e., HCV RNA-ve), *Non-responder* (i.e., HCV RNA+ve, and *Non-compliant*)(see Supporting Information Fig. S1). *On treatment* status was included as it was possible for an outcome to occur while on treatment. Patients moved from *On treatment* status to one of the other three treatment statuses on the date that therapy ended (regardless of completion of the full prescribed course). Status *Non-responder* comprised those patients whose RNA test results at end of treatment (EOT), and thereafter at 12 weeks post-treatment, were HCV positive; the former patients switched from *On treatment* status to *Non-responder* status at EOT date, while relapsers moved from *Responder* to *Non-responder* status 12 weeks post-EOT. *Non-compliant* status consisted of those patients who either (a) did not complete

treatment and had unknown RNA status, (b) completed treatment and had unknown HCV RNA status, or (c) were an EOT responder (i.e., RNA-negative) but did not return for 12 week post-treatment RNA testing; patients in (a) and (b) switched to *Non-compliant status* at EOT date, while (c) switched at 12 weeks post-EOT. Failure to complete therapy was defined as such by the treating clinician and coded in the patient's HCV Clinical database record; no RNA testing was undergone by these patients. Our definition of non-compliance assumes that both failing to complete therapy and failing to return for planned RNA testing are indicators of non-compliant behaviour.

The status *Responder* comprises those who either achieved SVR or had an EOT response (i.e., tested HCV RNA-negative at that time); the latter group moved from responder to either non-responder (if RNA positive) or non-compliant (if RNA not known) status at 12 weeks post-EOT, as appropriate. *Responder* status (with the largest number of events) was set as the reference category but to facilitate interpretation of the value of a response to treatment failure, the reciprocal hazard ratio with *Non-responder* status as the reference category was also reported.

Even though treatment completers would be a priori expected to achieve the same rates of viral clearance as *Responders*, patients who completed therapy but did not return for their end-of-treatment blood test were included in *Non-compliant* status, as non-compliance may be driven by the same factors that also lead to a raised risk of a clinical endpoint. Similarly, for those patients who were RNA-negative at EOT but did not return for their 12-week SVR blood test, lack of compliance may differentiate these patients from *Responders* who did return for their 12-week SVR test. We adopted this 'treatment status' covariate approach for two reasons: (i) we wished to examine the risk of clinical outcomes in the 'real-world' subpopulations of patients who are non-compliant; and (ii) this approach averts possible selection (and immortal time) bias if follow-up time is defined as starting at EOT or at SVR ascertainment date, since patients would need to survive to this date to obtain SVR status (normally determined at 12 weeks following EOT). In sensitivity analysis we further investigated *non-compliance*, by considering three subgroups relating to: (a) those who did not complete treatment and RNA status is unknown, (b) those who completed treatment and RNA status was unknown, and (c) those who had initially responded but RNA status was unknown from the point of SVR test, as they did not return for their 12-week RNA test. Subgroup (c) were by definition HCV RNA-negative at EOT.

The following set of covariates was defined: sex, age, risk group (person who injects drugs (PWID), non-PWID, not known), alcohol consumption history (self-reported: >50 units per week, ≤50 units per week/not known[20]), prior antiviral treatment, and Child-Pugh category (A, B). Univariate and multifactorial regression analyses were performed, and the Cox proportional hazards assumption was evaluated using graphical means.

All statistical analyses were conducted in the R statistical programming environment, version 3.5.1.[21] Multiple imputation using chained equations[18] was performed using the R package *mice* for risk group and the three test results needed for determining CP score (see above); models fitted to five imputation sets were combined. Due to a low event-to-covariate ratio for several endpoints, to reduce bias in the fitted regression coefficients variable selection for the multifactorial models was conducted using the change-in-estimate approach.[22] Specifically, augmented backward elimination using the R package *abe*[23] was performed for all imputation sets (with age, sex, Child-Pugh category and treatment status as compulsory inclusions), and covariates selected that were retained in ≥50% of 100 bootstrap re-samples.

Cumulative incidence functions for each endpoint (DC, HCC, liver-related mortality, and all-cause mortality), aggregating over treatment status, were computing within a competing risk framework[24] and presented graphically.

RESULTS

Patient cohort description

There were 1,073 eligible chronically HCV-infected patients diagnosed with compensated cirrhosis who had been initiated on IFN-free DAA therapy between 1 March 2013 and 31 March 2018. Demographic and other patient characteristics of the study population are provided in Table 1. Fifty-four percent (577/1073) of patients had been diagnosed with cirrhosis in 2015–2018, with only 7% (72/1073) diagnosed before 2009, and 27% (288/1073) had previously received treatment. Although 19% (204/1073) of patients were initiated on IFN-free DAA therapy within three months of cirrhosis diagnosis, 47% started therapy one year or later following diagnosis. Fifty-six percent (601/1073) were HCV genotype 1 (of all G1 with known subtype, 91% was G1A) and 38% (409/1073) were genotype 3. 96% (803/839) of patients were classified as Child-Pugh A.

The SVR proportion amongst those with RNA test results at 12 weeks following EOT was 96.4% (805/835). Among the entire study cohort, 75.0% (805/1073) achieved SVR; 2.8% (30/1073) did not achieve SVR (of whom 24 were relapsers), and for 22.2% (238/1073) SVR status was not measured or unknown. For the latter, 9.3% (100/1073) had insufficient follow-up as they were still on treatment. Among the study population excluding patients currently on treatment, 90.9% (884/973) responded to DAA therapy, with 11.1% (108/973) labelled as non-compliant. Among the study population including only those patients with an SVR test or with at least 15 weeks of follow-up post-EOT to allow opportunity for an SVR test, 96.6% (844/874) responded to DAA therapy (of whom 4.7% (40/844) were responders at EOT, had sufficient follow-up for SVR testing (i.e., 15 weeks; total of 28.6 person-years follow-up available from 15 weeks post-EOT), but SVR attainment was not known).

Cumulative incidence

Fig. 1 shows the cumulative incidence curves for each endpoint, aggregating over treatment status. The notably shallower cumulative incidence functions for responders compared to the remaining patient groups (aggregated together) are depicted in Supporting Information Fig. S2. Among our IFN-free DAA treated cirrhotic cohort, the 1-year cumulative risks of a first DC admission, first HCC admission, liver-related, and all-cause death were 3.0%, 1.7%, 1.2%, and 3.1%, respectively. The 2-year cumulative risks of the same endpoints were 4.7%, 2.8%, 4.1%, and 8.5%, respectively

Analysis of outcomes associated with treatment status

We analysed a total of 1809 person-years of follow-up (Table 2); mean follow-up time per patient was 1.69 person-years. Of the study population, 7.0% (n=75) had died by 31 March 2018, of which 39 deaths were defined as liver-related (with 15 due to DC or HCC, and the remainder coded as viral hepatitis, alcoholic cirrhosis, or unspecified cirrhosis of the liver). There were 47 first DC admissions and 28 first admissions for HCC (Table 2). The highest crude event rates were observed for *Non-responders*, across all endpoints (e.g., 119 deaths from any cause per 1,000 person-years; 95% CI: 39-278) except all-cause mortality, and the lowest crude event rates were observed for those who responded to treatment (17 deaths/1,000 person-years for liver-related mortality; 95% CI: 11-25). Patients considered to be non-compliant had very high rates of all-

cause mortality (183/1,000 person-years; 95% CI: 104-297).

Adjusting for sex, current age, history of heavy alcohol consumption, route of HCV acquisition, previous treatment, and Child-Pugh class, there was a significantly decreased relative risk of progression to DC (HR=0.14; 95%CI: 0.05-0.39) associated with *Responder* (Table 3), compared with *Non-responder* status. Response to treatment was also strongly associated with a reduced risk of liver-related death (HR=0.13, 95% CI: 0.05-0.34), all-cause mortality (HR=0.30; 95%CI: 0.12-0.75) (Table 4), and of developing HCC (HR=0.17; 95%CI: 0.04-0.79). Compared with responders, non-compliant patients had a 5- to 7-fold increased risk of all-cause mortality or liver-related mortality (HR=5.45; 95% CI: 3.07-9.68; HR=6.73; 95% CI: 2.99-15.1, respectively). Models for all endpoints except all-cause mortality indicated significantly increased relative risks associated with age (HRs of 1.06 to 1.10 per year), and Child-Pugh class B was associated with a two-fold increased risk of DC (HR=2.52, 95% CI: 0.99-6.43).

Results of the sensitivity analysis in which follow-up for *non-compliant* status was separated into those who failed to complete treatment, those who completed therapy but whose RNA status was unknown, and those who tested RNA-negative at EOT but did not return for their 12-week SVR test indicated comparable results to the main analysis, taking into consideration the smaller numbers of outcomes recorded for each of these additional statuses (Table 5).

DISCUSSION

In the context of initially expensive DAA regimens and the large number of people infected with HCV, Scotland initially prioritised patients with advanced liver fibrosis (stage F2 to F4), but also set an ambitious target to reduce the incidence of HCV-related DC by 75% by 2020.[25] Among this large chronically HCV-infected cohort of compensated cirrhosis patients receiving IFN-free DAA therapy, treatment response was associated with a profound reduction in the relative risks of progression to decompensated liver disease and mortality. Before the advent of DAA therapy, the health burden in HCV-infected patients associated with development of DC was bleak, with a sustained increase in DC cases observed between 1994 and 2013.[26] The anticipated immediate reduction in HCV-driven disease with DAA scale-up of patients with advanced liver fibrosis emphasizes the credibility of using compensated cirrhosis as an early marker of DAA impact and success.[1] These record-linked national data challenge the perspective of Jakobsen and colleagues

regarding the unproven impact of viral clearance through DAA therapy on liver morbidity.[12,27] Although not proven with an idealised trial design, our observational study has nevertheless demonstrated clinically-relevant reduced risks of progression to both DC and HCC associated with SVR among a real-world national cohort of DAA-treated HCV patients with compensated cirrhosis.

In our cohort, non-compliant patients had a relatively high all-cause mortality rate (183/1,000 person-years), with eight of 16 deaths not related to liver disease (with underlying ICD-10 cause codes of X42 "Accidental poisoning by and exposure to narcotics and psychodysleptics" for three patients and R99 "Other ill-defined and unspecified causes of mortality" for three patients). The predominant risk factor for acquiring HCV infection in Scotland is drug use, and the period examined saw a large increase in drug related deaths[28] predominantly in older people with evidence of exposure to multiple illicit drugs, with or without problem alcohol use. It seems likely that non-compliance is a marker for ongoing drug use that is sufficient to impact on ability to engage with treatment and monitoring.

The relative risk of mortality among all three subgroups of non-compliant patients was either comparable to or higher than that for treatment non-responders (Table 5). Considering the aggregate subgroup of those who completed therapy but whose RNA status was unknown and those who tested RNA-negative at EOT but did not return for their 12-week SVR test, only five out of these 11 deaths were apparently related to HCV disease. Moreover, five deaths in this subgroup indicated ICD-10 X42 'Accidental poisoning by and exposure to narcotics and psychodysleptics' (n=2) or K46 'Alcoholic cirrhosis' (n=3) as underlying or contributing cause, which suggests that addiction or related behavioural factors may have contributed to their demise. This is in keeping with previous observations on the strong contribution of alcohol to HCV-related morbidity amongst people with HCV in Scotland.[20] Although we did adjust for alcohol history and PWID risk, there is likely to be residual confounding.

Overall, our findings of increased liver-related and all-cause mortality amongst those who are non-compliant are a stark reminder that HCV treatment without care and treatment for drug and alcohol use will not be sufficient to prevent deaths, and that linkage to, and integration of HCV

services with, harm reduction and addictions care are pivotal in achieving the goal of reducing overall morbidity and mortality amongst those with HCV.

For our treated cirrhotic patient cohort, the observed 1-year cumulative risks of progression from compensated cirrhosis to DC and HCC were relatively low, at 3.0% and 1.7%, respectively. Although the risk of progression is not reduced to zero through treatment with IFN-free DAA therapy, the clinical relevance of such therapy is demonstrated by comparing figures among untreated cirrhotic patients; for instance annual progression probabilities of 6.5% and 3.5% to DC and HCC, respectively, derived from pooled analysis.[29] This individual-level analysis corroborates emerging evidence of population-level effects reported from analysis of liver transplant registries[30] and record-linkage initiatives from Scotland and elsewhere.[31,32]

In a large study of a cirrhotic HCV-infected cohort by Backus et al.[33], DAA treatment and consequent SVR was strongly associated with a reduced rate of mortality (reported adjusted HR of 0.26 for SVR compared with non SVR), as well as a significant reduction in HCC. In the French ANRS CO22 Hepather study, treatment with DAAs of the subpopulation with cirrhosis was also associated with a decrease in all-cause mortality and HCC (adjusted HRs of 0.45 and 0.65, respectively, for treated compared with untreated patients).[34] The reductions in mortality associated with DAA treatment are comparable between the three distinct populations, which is reassuring. The significant reduction in the risk of HCC development observed with SVR in our cohort is consistent with Ioannou et al.'s[35] demonstration of a 52–71% reduction in HCC associated with IFN-containing or IFN-free DAA therapy. Increased diagnosis and scale-up of DAA therapy in HCV-infected populations is a public health imperative given the remarkable impact of such antivirals in those who are compliant.[7]

Strengths of our study include record-linkage of comprehensive national-level data sources and a moderately-sized study population, to allow the impact of IFN-free DAA therapy to be investigated in a 'real-world' cirrhotic cohort. In this study, we also specifically considered those with liver-related mortality, while Backus et al.[33] did not have information pertaining to reported cause of death and therefore could not address this issue. Finally, we looked separately at outcomes among non-compliant patients: namely, those patients who failed to complete IFN-free therapy or who did not return for planned HCV RNA testing. We consider these patients to

represent a 'real-world' category for whom clinical endpoints have previously been neglected. While DAAs are a potent intervention in those infected with HCV, this study further reiterates that non-compliant individuals have unique priorities, which increase their likelihood of mortality. Intensive and carefully coordinated efforts are required to re-engage with this minority of non-compliant patients to reduce the higher mortality observed in this cohort.

Our study is limited in several ways. In our observational study, response to DAA therapy among treated patients could not be randomised to participants. Although we adjusted for a number of important characteristics associated with the likelihood of being treated and responding to treatment in the analysis, a non-response after IFN-free therapy may be associated with more advanced liver disease. Even though we adjusted for disease stage using Child-Pugh class, a clinical measure of liver disease progression, low variability in this covariate means that we may have over-estimated the impact of treatment response on severe clinical outcomes. Data on potential confounders such as metabolic syndrome, diabetes and overweight were lacking in the HCV Clinical Database. Furthermore, we could not eliminate the impact of individual-level heterogeneity (unmeasured confounders) on outcomes; namely those patients who are less likely to respond to IFN-free treatment may be more likely to die or progress to DC or HCC.[36] We were unable to censor follow-up in the mortality endpoint analyses for liver transplantation; this limitation concerns mainly only those patients who failed to respond to IFN-free therapy, thus we may have underestimated the relative risk of death for this group. In addition, we defined as 'non-compliant' all patients lacking an expected HCV RNA test result, but for an unknown number of treatment completers worsening health may have led to early termination of therapy, and for other patients a post-EOT or SVR RNA test may have been performed but without their database record being updated. Furthermore, an unknown number of patients may have been classified as non-compliant because of issues in continuity of care (e.g. incarceration) that affected adherence to planned RNA testing rather than behavioural factors. Because the 12-week post-EOT RNA test may not have occurred exactly at 12 weeks, some follow-up time may have been misclassified between Responder and Non-responder status among patients who relapsed. Finally, incomplete data on the national HCV Clinical Database regarding HCC and DC status at baseline, potential misclassification of factors such as alcohol consumption or route of HCV acquisition, as well as record-linkage errors between this database and the national hospitalisation/deaths records may have lead to biased estimation of relative risks.

In conclusion, our study provides compelling national-level evidence of the profound impact of DAA therapy on the reduced propensity of compensated liver disease and mortality. However, it also provides a stark reminder that markedly worse outcomes are associated with non-compliance. Although we can now quantify the impact of achieving viral clearance through IFN-free DAA on the risk of disease progression among cirrhosis, treatment is not a panacea in this patient group. Our data indicate that additional efforts may be warranted – for instance, by strengthening links between HCV treatment and addiction and harm reduction services – to address the higher risk of mortality among the minority of cirrhotic patients who fail to comply with treatment or RNA testing.

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Table 1. Characteristics of study population with chronic HCV infection diagnosed with compensated cirrhosis and initiated on IFN-free DAA therapy (n=1073), according to treatment status at the end of follow-up. For reasons of patient confidentiality broader categories for certain covariates are presented than are used in the Cox regression analyses.

	HCV RNA status known				HCV RNA status not known					
	Responder		Non-responder		Non-compliant		On Rx		Total	
Covariate	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
All pts	836		29		108		100		1073	(-)
Sex										
Female	214	(26)	7	(24)	23	(21)	29	(29)	273	(25)
Male	622	(74)	22	(76)	85	(79)	71	(71)	800	(75)
Age-group at baseline										
<45 yrs	210	(25)	8	(28)	47	(44)	32	(32)	297	(28)
45-54 yrs	356	(43)	11	(38)	42	(39)	46	(46)	455	(42)
55+ yrs	270	(32)	10	(34)	19	(18)	22	(22)	321	(30)
Period of cirrhosis diagnosis										
1996-2014	436	(52)	18	(62)	30	(28)	12	(12)	496	(46)
2015-2018	400	(48)	11	(38)	78	(72)	88	(88)	577	(54)
Risk group										
PWID	503	(60)	20	(69)	84	(78)	65	(65)	672	(63)
Non-PWID/NK	333	(40)	9	(31)	24	(22)	35	(35)	401	(37)
Alcohol use history										
>50 units/wk	244	(29)	14	(48)	35	(32)	31	(31)	324	(30)
≤50 units/wk or not known	592	(71)	15	(52)	73	(68)	69	(69)	749	(70)
Genotype										
G1†	486	(58)	14	(48)	49	(45)	52	(52)	601	(56)
G3/Other/NK	350	(42)	15	(52)	59	(55)	48	(48)	472	(44)
Previous antiviral treatment										
Experienced	251	(30)	10	(34)	17	(16)	10	(10)	288	(27)
Naive	585	(70)	19	(66)	91	(84)	90	(90)	785	(73)
Timing of initiation on IFN-free DAA treatment following date of cirrhosis diagnosis										
<6 months	288	(34)	9	(31)	47	(44)	59	(59)	403	(38)
6-24 months	240	(29)	6	(21)	37	(34)	28	(28)	311	(29)

24+ months	308	(37)	14	(48)	24	(22)	13	(13)	359	(33)
Child-Pugh class										
A	636	(76)	23	(79)	71	(66)	73	(73)	806	(75)
B	25	(3)	2	(7)	5	(5)	4	(4)	36	(3)
Missing	175	(21)	4	(14)	32	(30)	23	(23)	234	(22)

Note. †Total with genotype 1A was 401 (91% of all G1 with known subtype).

Table 2. Crude event rates (per 1,000 person-years; PY) for four clinical endpoints according to IFN-free treatment status, among study population with compensated cirrhosis and initiated on IFN-free DAA therapy (*n*=1073). Person-time was calculated as period from date of treatment initiation through the earliest of date of endpoint and censoring date.

Treatment outcome status (time-dependent)	DC n	DC PY	DC Rate	HCC n	HCC PY	HCC Rate	Liver-rel. mort. n	Liver-rel. mort. PY	Liver-rel. mort. Rate	All-cause mort. n	All-cause mort. PY	All-cause mort. Rate
Responder	26	1381	18.8 (12-28)	16	1392	11.5 (7-19)	24	1422	16.9 (11-25)	50	1422	35.2 (26-46)
Non-responder	5	41	121.5 (40-283)	2	41	49.2 (6-178)	5	42	118.9 (39-278)	5	42	118.9 (39-278)
Non-compliant	3	86	34.7 (7-101)	2	79	25.3 (3-91)	8	88	91.4 (39-180)	16	88	182.7 (104-297)
On treatment	13	255	51.0 (27-87)	8	256	31.2 (14-62)	2	258	7.8 (1-28)	4	258	15.5 (4-40)
All patients	47	1764	26.7 (20-35)	28	1768	15.8 (11-23)	39	1809	21.6 (15-30)	75	1809	41.5 (33-52)

Table 3. Association of HCV treatment status with the clinical outcomes first decompensated cirrhosis (DC) admission and first hepatocellular carcinoma (HCC) admission, among the study population with compensated cirrhosis who were initiated on IFN-free DAA therapy (*n*=1073).

	1st DC admission				1st HCC admission			
	Univariate regression		Adjusted		Univariate regression		Adjusted	
Variable	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Treatment outcome status (time-dependent)								
Responder	Ref.		Ref.		Ref.		Ref.	
Non-responder	6.59	(2.49-17.4)	6.90	(2.59-18.4)	4.07	(0.91-18.1)	5.73	(1.26-26.1)
Non-compliant	1.89	(0.57-6.30)	2.12	(0.97-6.65)	2.29	(0.52-10.2)	2.94	(0.65-13.3)
On treatment	1.31	(0.24-7.12)	1.38	(0.27-7.07)	0.84	(0.08-8.82)	0.99	(0.11-8.76)
Sex								
Female	Ref.		Ref.		Ref.		Ref.	
Male	1.14	(0.58-2.24)	1.28	(0.63-2.58)	2.12	(0.74-6.12)	2.84	(0.93-8.61)
Age at start of therapy (per year)	1.04	(1.01-1.07)	1.05	(1.01-1.09)	1.06	(1.03-1.10)	1.10	(1.05-1.15)
Risk group								
PWID	Ref.		Ref.		Ref.		Ref.	
Non-PWID	1.10	(0.55-2.18)	0.72	(0.33-1.58)	0.87	(0.32-2.35)	0.28	(0.08-0.94)
Alcohol history								
<=50 units/wk or NK	Ref.		Ref.		Ref.			
>50 units/wk	1.35	(0.74-2.44)	—		0.65	(0.26-1.61)	0.48	(0.19-1.22)
Antiviral treatment								
Naive	Ref.		Ref.		Ref.			
Experienced	1.31	(0.73-2.38)	—		2.68	(1.25-5.71)	2.56	(1.16-5.62)
Child-Pugh class								
A	Ref.		Ref.		Ref.		Ref.	
B	2.52	(0.99-6.43)	2.51	(0.96-6.60)	1.35	(0.15-12.2)	1.37	(0.15-12.3)

Note. PWID = people who inject drugs. Reciprocal adjusted hazard ratios for Responder status (ie. equivalent to having Non-responder as reference category) are 0.14 (95% CI:0.05-0.39) and 0.17 (95% CI:0.04-0.79) for 1st DC admission and 1st HCC admission, respectively.

Table 4. Association of HCV treatment status with liver-related mortality and all-cause mortality, among the study population with compensated cirrhosis who were initiated on IFN-free DAA therapy (*n*=1073).

	Liver-related mortality				All-cause mortality			
	Univariate regression		Adjusted		Univariate regression		Adjusted	
Variable	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Treatment outcome status (time-dependent)								
Responder	Ref.		Ref.		Ref.		Ref.	
Non-responder	7.08	(2.69-18.7)	7.88	(2.93-21.2)	3.31	(1.32-8.31)	3.30	(1.31-8.35)
Non-compliant	6.10	(2.72-13.7)	6.73	(2.99-15.1)	5.39	(3.05-9.53)	5.45	(3.07-9.68)
On treatment	0.57	(0.04-7.36)	0.61	(0.05-7.60)	0.30	(0.05-1.93)	0.29	(0.05-1.89)
Sex								
Female	Ref.		Ref.		Ref.		Ref.	
Male	1.86	(0.81-4.30)	1.74	(0.77-3.93)	1.19	(0.70-2.05)	1.16	(0.66-2.02)
Age at start of therapy (per year)	1.04	(1.01-1.07)	1.05	(1.02-1.09)	1.00	(0.98-1.03)	1.02	(0.99-1.05)
Risk group								
PWID	Ref.		Ref.		Ref.		Ref.	
Non-PWID	1.09	(0.54-2.20)	0.77	(0.34-1.74)	0.67	(0.37-1.23)	0.60	(0.31-1.18)
Alcohol history								
<=50 units/wk or NK	Ref.		Ref.					
>50 units/wk	0.73	(0.35-1.54)	—		1.22	(0.75-1.97)	—	
Antiviral treatment								
Naive	Ref.		Ref.					
Experienced	0.95	(0.49-1.85)	—		0.94	(0.58-1.52)	—	
Child-Pugh class								
A	Ref.		Ref.		Ref.		Ref.	
B	1.18	(0.29-4.89)	1.09	(0.26-4.54)	1.48	(0.54-4.03)	1.47	(0.51-4.22)

Note. PWID = people who inject drugs. Reciprocal adjusted hazard ratios for Responder status (equivalent to having Non-responder as reference category) are 0.13 (95% CI:0.05-0.34) and 0.30 (95% CI:0.12-0.76) for liver-related and all-cause mortality, respectively.

Table 5. Results of sensitivity analysis dividing non-compliant patients at end of treatment into those who did not complete therapy and those who completed therapy but with unknown RNA status, and including a separate treatment outcome status for follow-up >12 weeks post-end of treatment for end of treatment responders who did not attend their 12-week SVR test. Multifactorial Cox regression analysis (see Methods) was used to estimate the association of HCV treatment status with the four clinical endpoints as adjusted hazard ratios (AdjHR), among the study population with compensated cirrhosis and initiated on IFN-free DAA therapy (*n*=1073).

Treatment outcome status (time-dep.)	1st DC admission AdjHR (95% CI)	1st HCC admission AdjHR (95% CI)	Liver-related mort. AdjHR (95% CI)	All-cause mortality AdjHR (95% CI)
Responder†	Ref.	Ref.	Ref.	Ref.
Non-responder	7.03 (2.65-18.7)	5.82 (1.29-26.3)	7.91 (2.95-21.2)	3.31 (1.31-8.35)
Did not complete Rx, RNA status NK	‡	‡	10.9 (3.11-38.4)	8.06 (3.07-21.2)
Completed treatment, RNA status NK	3.24 (0.75-14.0)	‡	6.31 (1.85-21.5)	4.03 (1.58-10.3)
EOT responder, no SVR test	2.56 (0.34-19.2)	10.1 (2.19-46.2)	4.58 (1.06-19.7)	5.59 (2.36-13.3)
On treatment	1.24 (0.22-7.11)	0.83 (0.09-7.88)	0.67 (0.06-7.93)	0.34 (0.05-2.13)

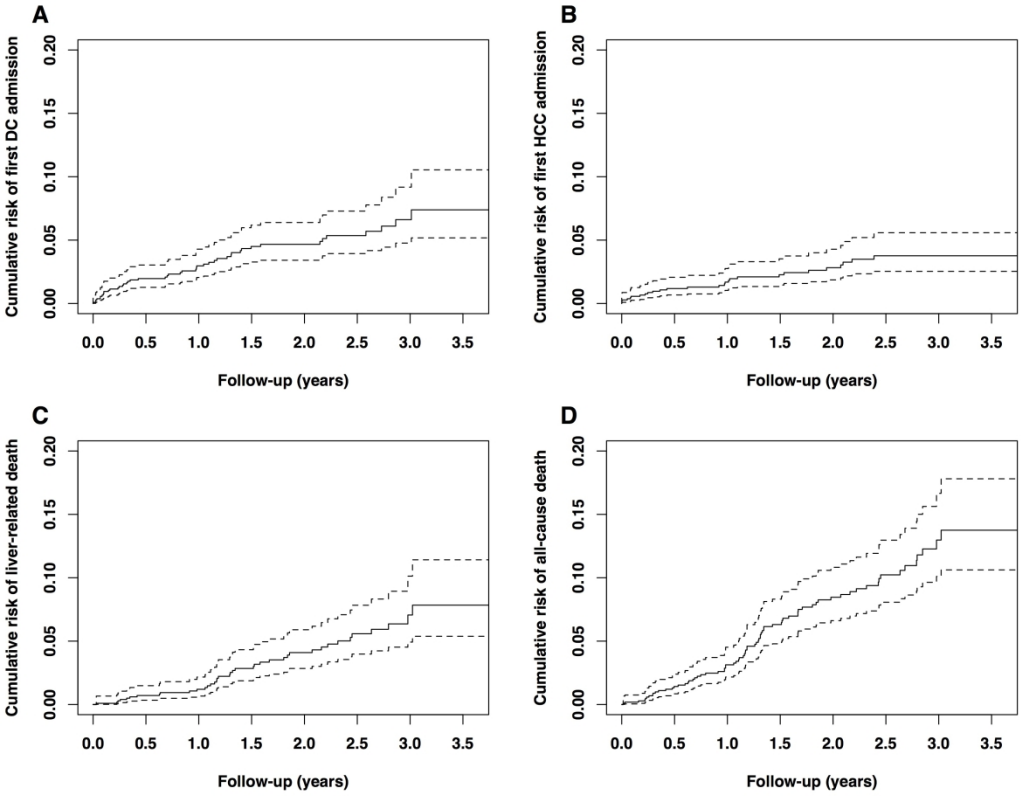
Note. NK = not known; EOT = end of treatment; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; AdjHR = adjusted hazard ratio (adjusted for sex, age, risk group, and Child-Pugh class for all outcomes, and for 1st HCC admission outcome only additionally for alcohol history and antiviral treatment history). Reciprocal adjusted hazard ratios for Responder status (ie. equivalent to having Non-responder as reference category) are 0.14 (95% CI:0.05-0.38), 0.17 (95% CI:0.04-0.79), 0.13 (95% CI:0.05-0.34), 0.30 (95% CI:0.12-0.76) for 1st DC admission, 1st HCC admission, liver-related mortality, and all-cause mortality, respectively.

† Responder status excludes follow-up time >12 weeks post-EOT, for EOT responders without SVR test only

‡ No outcomes

FIGURE LEGENDS

Fig. 1. Cumulative incidence of four specified endpoints among cirrhotic patients following IFN-free DAA therapy initiation. Displayed are: first DC hospital admission (A), first HCC hospital admission (B), liver-related death (C), and all-cause death (D). Dashed lines indicated 95% confidence intervals.



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