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McDonald, Scott A.; Barclay, Stephen T.; Innes, Hamish A.; Fraser, Andrew; Hayes, Peter C.; Bathgate, Andrew; Dillon, John F.; Went, April; Goldberg, David J.; Hutchinson, Sharon J.

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Scott A. McDonald, scott.mcdonald4@phs.scot, School of Health and Life Sciences, Glasgow Caledonian University and Health Protection Scotland, Glasgow, UK
Stephen T. Barclay, stephen.barclay@ggc.scot.nhs.uk, Glasgow Royal Infirmary, Glasgow, UK
Hamish A. Innes, hamish.innes@gcu.ac.uk, School of Health and Life Sciences, Glasgow Caledonian University and Health Protection Scotland, Glasgow, UK
Andrew Fraser, andrew.fraser@ggc.scot.nhs.uk, Aberdeen Royal Infirmary, Aberdeen, and Queen Elizabeth University Hospital, Glasgow UK
Peter C. Hayes, p.hayes@ed.ac.uk, Royal Infirmary of Edinburgh, Edinburgh, UK
Andrew Bathgate, andy.bathgate@nhslothian.scot.nhs.uk, Royal Infirmary of Edinburgh, Edinburgh, UK
John F. Dillon, j.f.dillon@dundee.ac.uk, School of Medicine, University of Dundee, Dundee, UK
April Went, april.went@phs.scot, Health Protection Scotland, Glasgow, UK
David J. Goldberg, david.goldberg@phs.scot, School of Health and Life Sciences, Glasgow Caledonian University and Health Protection Scotland, Glasgow, UK
Sharon J. Hutchinson, sharon.hutchinson@phs.scot, School of Health and Life Sciences, Glasgow Caledonian University and Health Protection Scotland, Glasgow, UK

Corresponding author
Dr Scott A McDonald
Glasgow Caledonian University, School of Health and Life Sciences
Cowcaddens Road, Glasgow G4 0BA, Scotland, UK
Email: smcdonald4@nhs.net

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ABSTRACT

Interferon-free DAA therapies have recently been licensed for patients infected with hepatitis C virus (HCV) who have decompensated cirrhosis (DC). Our aim was to describe factors associated with uptake of IFN-free DAAs in DC patients and to compare mortality risk and hospital admission rates between pre-DAA and DAA eras. This observational study used record-linkage between Scotland's HCV Clinical Database and national inpatient hospitalisation and mortality registers. For the DAA uptake analysis, the study population (*n*=297) was restricted to patients alive on 1 November 2014, and Cox regression was used to estimate uptake associated with various covariates. For the Cox regression of mortality comparing pre-DAA and DAA eras, the study population (*n*=624) comprised those diagnosed with DC in 2005–2018; follow-up was censored at two years. DAA uptake was 63% overall, and was significantly higher for treatment-experienced patients (adjusted hazard ratio (aHR)=1.64, 95% CI:1.14-2.34), genotype 1 vs. other genotypes (aHR=1.55. 95% CI:1.15-2.10), and lower for persons diagnosed with DC pre-2014 (0.47, 95% CI:0.33-0.68) and in Greater Glasgow (0.64, 95% CI:0.47-0.88). The intention-to-treat SVR rate was 89% (95% CI:83-93%). All-cause and liver-related mortality risk were significantly reduced among patients diagnosed with DC in the DAA era (Nov 2014–Dec 2018) compared with the pre-DAA era (2005–Oct 2014) (aHRs of 0.68, 95% CI:0.49-0.93; 0.69, 95% CI:0.50-0.95, respectively); in contrast, hospital admission rates were higher in the DAA era (aRR=1.14, 95% CI:1.04-1.26). The majority of HCV-infected DC patients engaged with specialist services can be treated with IFN-free DAAs. Improved survival among patients diagnosed with DC in the DAA era supports the beneficial impact of IFN-free therapies among those with advanced liver disease.

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

INTRODUCTION

The new generation of direct-acting antiviral (DAA) drugs for chronic hepatitis C virus (HCV) infection have opened the gates towards reducing the rising HCV-related liver disease burden. Ageing of the chronically-infected population in Scotland has led to an increasing trend in the numbers of HCV patients developing decompensated cirrhosis (DC),[1,2] with associated rise in mortality[3] and a steeply increasing burden on health-care resources such as hospital care.[4] The most recent UK, EASL, and WHO clinical guidelines recommend treatment with interferon-free (IFN-free) regimens for patients with advanced liver disease, including patients with cirrhosis who have progressed to the decompensated stage.[5–7] The new IFN-free therapies have the potential to improve health-related quality of life[8] and to reduce the HCV-related disease and economic burden in this patient population. While studies addressing the impact of DAAs on severe outcomes among patients with compensated cirrhosis or earlier stages of liver disease have been published, to date there has been scant evidence regarding the national-level uptake of IFN-free DAA treatment among DC patients, or on the longer-term impact these treatment regimens have had on important clinical endpoints such as mortality.

High sustained virologic response (SVR) rates – 75% from meta-analysis – have been achieved with IFN-free DAA regimens in Child-Pugh C patients,[9] and there is some evidence for longer-term improvements in severe clinical outcomes (such as mortality) associated with SVR achievement among IFN-treated DC patients.[10] Given the reported associations between improved survival and SVR achieved from IFN-free DAA therapy amongst HCV patients with compensated cirrhosis,[11–13] there is an expectation for similar effects among DC patients – as indicated by their inclusion within clinical guidelines – but the evidence base from clinical practice is scarce.[14] A recent early access study of DAA treatment and clinical outcomes among DC patients in the UK reported a beneficial effect of SVR on measures of liver function,[15] but found no association between SVR and hard clinical endpoints including mortality.[16] A larger study conducted in the USA among HCV patients with advanced liver disease,[12] reported a 67% mortality risk reduction associated with achievement of SVR following DAA-treatment (compared with non-SVR) among the subgroup of 3931 patients with a history of decompensated disease. Results of such study designs are however susceptible to potential bias even after extensive statistical adjustment, as patients cannot be

randomised to SVR or non-SVR groups.

Using a national-level cohort of chronically HCV-infected DC patients constructed from patients in HCV specialist care throughout Scotland, we aimed to provide a first report of actual DAA treatment levels and their potential impact on rates of the most severe clinical outcome – mortality – in this population over time. Thus, the objectives of our study are twofold: (i) to describe factors associated with the uptake of IFN-free DAA therapy in the DC patient population; and (ii) to compare all-cause and liver-related mortality and hospitalisation rates between pre-DAA and DAA eras, to establish if the availability and effectiveness of IFN-free DAA therapy has had an impact on these clinical outcomes.

METHODS

DAA uptake analysis

Data sources. Record-linkage between the Scottish Hepatitis C Clinical Database (a comprehensive record of all HCV patients attending specialist tertiary care within Scotland) and the national deaths registry (held by the National Records of Scotland) was conducted by Information Services Division (ISD) using probabilistic methods[17], with the resulting linkage anonymised before analysis. Data linkage was approved by the Scottish Public Benefit and Privacy Panel.

Study population and setting. The study population consisted of all DC patients on the HCV Clinical Database with active HCV infection (i.e., no evidence for having cleared HCV infection following prior antiviral treatment) at start of follow-up, and with date of first DC complication (defined as having ever been diagnosed with ascites and/or bleeding oesophageal varices and/or encephalopahy) in the period 1 January 2000 to 31 December 2018. The study population restricted further to those who were alive on 1 November 2014 (to ensure access to newly licensed IFN-free regimens), with last clinical contact within one year prior to entry to follow-up.

Regression modelling. Covariates of interest included sex, age-group (<45, 45-59, 60+ years), ethnicity, risk group (PWID, non-PWID/not known), historical alcohol use (self-reported: >50 units/week, ≤50 units/week, not known); period of DC diagnosis (2000-2013, 2014-2015, 2016-

2017; periods chosen to contain roughly equal numbers of outcomes), prior antiviral treatment, prior liver transplantation, prior hepatocellular carcinoma (HCC) diagnosis, prior ascites, prior bleeding varices, prior encephalopathy, HCV genotype category (G1, G3, Other/not known), and region (Greater Glasgow & Clyde, all other).

Entry to follow-up was defined as the later of date of DC diagnosis or 1 November 2014 (the approximate date at which IFN-free treatment became available for prescription; i.e., approval of daclatasvir by the Scottish Medicines Consortium[18]), and follow-up ended at the earliest of the start date of IFN-free therapy, death, or 1 December 2018. Multivariable Cox proportional-hazards regression analysis was conducted to estimate the relative risk (as hazard ratios) of DAA uptake associated with various factors. Both univariate and adjusted analyses were conducted; for the latter, covariates associated with uptake at the $p<0.30$ level of significance in the univariate analysis were included. Missing data on *risk group*, *historical alcohol use,* and *genotype category* were imputed using established multiple imputation methods[19,20] and the R package *mice* (see Supporting Information for further details).

In sensitivity analysis, the study population was restricted to recent initial DC presentations (date of first DC complication from 1 November 2014) only, to avert confounding by disease stage (compared with recent DC, earlier DC diagnoses may have more advanced disease and be more/less likely to have been initiated on IFN-free DAA treatment).

Analysis of clinical outcomes across eras

Study population and setting: Record-linkage between Scottish HCV Clinical Database and SMR01/deaths registry. The study population consisted of all chronically HCV-infected DC patients on the Scottish HCV Clinical Database, for whom the first DC complication occurred on or later than 1 January 2005 and before the right censoring date of 31 December 2018. The follow-up period for each patient was defined to begin at date of DC and to end at date of death, date of outward migration, or 31 December 2018. This inclusion period – DC diagnoses since 2005 – was imposed to minimise possible selection bias from patients presenting to tertiary care with more advanced liver disease historically as compared with the recent past, and to allow an equal

number of years before and after the date when the IFN-free DAA treatment era was deemed to begin (1 November 2014). The study population for this analysis consisted of 400 DC patients.

Regression modelling. A limited set of covariates was defined: sex, age, risk group for acquisition (PWID, non PWID), alcohol use history, HCV genotype category, prior antiviral treatment (naive vs. experienced), liver transplantation (defined as a time-dependent variable), and the presence of HCC at baseline. Univariate and multivariable Cox models were fitted to the outcomes all-cause and liver-related mortality, and Cox regression with robust standard errors was conducted for the outcome hospital admission rate (with person-years at risk specified as offset).

Follow-up definitions. For mortality outcomes, the follow-up period for each DC patient was defined to begin at date of first DC complication, and to end at the earliest of two years following date of first DC complication, the date of death or the administrative right-censoring date. For hospital admissions, contiguous inpatient episodes without discharge from hospital, and transfers between specialty/consultant were counted as single admissions. For both mortality and hospitalisation outcomes, censoring at two years following DC diagnosis was conducted to reduce the potential impact of longer follow-up available for patients diagnosed in the pre-DAA era. To reduce potential bias in the fitted coefficients of the adjusted regression models, variable selection was carried out using the change-in-estimate approach.[21]

*Sensitivity analysis: length of pre-DAA era***.** As the length of the defined pre-DAA era is longer (9 years, 11 months) than the DAA era (4 years, 1 month), we wished to investigate if any observed difference in mortality risk would be influenced by the inclusion of patients diagnosed with DC further back in time. We therefore estimated the relative risk of mortality comparing three time periods of approximately equal size, by splitting the pre-DAA era into two periods: 2005–2009, and 2010 through 31 October 2014.

All statistical analyses were conducted in the R statistical programming environment, version 3.5.1.[22] Variable selection using the change-in-estimate approach (via augmented backward elimination) was implemented using the R package *abe*.[23]

RESULTS

DAA uptake analysis

The eligible study population consisted of 297 DC patients, of whom 63% (188/297) were ever initiated on IFN-free DAA therapy (Table 1). Mean follow-up time was 1.34 years (range: 0.29-4.16 years). The (intention-to-treat) SVR rate was 89% (95% CI: 83-93%). Eighty-seven patients (29%) died before the end of the study period. The cumulative incidence of DAA uptake over time (adjusting for the competing risk of mortality) is depicted in Supporting Information, Fig. S1).

Compared with 2016-2018, patients diagnosed with DC before 2014 were less likely to be initiated on IFN-free treatment (aHR=0.47, 95% CI: 0.32-0.68). A significantly increased relative risk of DAA uptake was observed for genotype 1, compared with G3/other (adjusted hazard ratio (aHR)=1.55, 95% CI: 1.15-2.10), and for treatment-experienced patients (aHR=1.64, 95% CI: 1.14-2.34). A reduced relative risk of DAA uptake was observed among those with a history of heavy alcohol history use (compared with ≤50 units/week or not known): aHR=0.73, 95% CI: 0.54-0.99, and those residing in Greater Glasgow & Clyde (aHR=0.64, 95%: 0.47-0.88).

The sensitivity analysis conducted for the study population restricted to recent DC diagnoses (i.e., from 1 November 2014) only yielded largely comparable results (Supporting Information, Table S2); 65% (109/166) had ever been initiated on IFN-free DAA therapy. Significantly reduced uptake was observed among those with a history of heavy alcohol history use (compared with ≤50 units/wk or not known), aHR=0.63, 95% CI: 0.41-0.96, and for those residing in Greater Glasgow & Clyde (aHR=0.65, 95%: 0.42-0.98), but there was no evidence for an association between uptake and period of DC diagnosis.

DAA era analysis

The annual numbers of all-cause deaths in the DC patient population (n=624) roughly decreased over the analysis period, from a high of 24 in 2007 to 8 in 2018; this trend was paralleled by the crude annual mortality rate, which was highest prior to 2010, and then slowly decreased until 2018. Fig. 1 plots the all-cause mortality rate among DC patients per calendar year of follow-up,

stratified by age-group. A more dramatic reduction in mortality rate into the DAA era was apparent for the 50+ years age-group compared with <50 years; the difference in mortality rates between age-groups also tended to decrease over time.

A total of 213 deaths occurred in the study period, of which 53 were in the DAA era. Table 2 shows the estimated relative risk of death (according to multivariable Cox regression models) associated with various patient factors. *Era* is defined as a time-dependent variable. The adjusted HR of both all-cause and liver-related mortality were significantly lower in the DAA compared with the pre-DAA era (aHRs: 0.68, 95% CI: 0.49–0.93; 0.69, 95% CI: 0.50-0.95. respectively).

Results of the sensitivity analysis in which the pre-DAA era was divided into two separate periods (2005-2009, 2010 to 31 Oct 2014) indicated that all-cause mortality risk was highest in the early period (aHR = 1.41, 95% CI: 1.03-1.93, compared with the second pre-DAA period), but the relative risk did not significantly decrease into the DAA period (aHR = 0.79, 95% CI: 0.56-1.12). For liver-related mortality, a similar pattern was apparent (Supporting Information, Table S3). However, 31 (13.1%) of the 236 patients in the second period (2010 to 31 Oct 2014) had been treated with IFN-free DAAs within two years of DC diagnosis (Supporting Information, Fig. S2). Eleven and three patients that had been diagnosed with DC during the second pre-DAA and the DAA period, respectively, had been initiated on IFN-containing treatment within two years of diagnosis (Supporting Information, Fig. S2), and 8/11 and 3/3 achieved SVR, respectively. In the second period, 1 out of 11 had been treated with pegylated interferon & ribavirin (pegIR) + boceprevir, 2/11 with pegIR + telaprevir, and 8/11 with pegIR + sofosbuvir. All three of the DAA era's IFN-containing patients received pegIR + sofosbuvir.

The overall hospital admission rate in our study population was 507 per 100 person-years; rates were 496/100 and 532/100 person-years in the pre-DAA and DAA eras, respectively (Fig. S3, Table 3). The estimated relative risk of both hospitalisation with any diagnosis and liver-related hospitalisation were significantly increased in the DAA era, after adjustment for patient factors (aRR=1.14, 95% CI: 1.04-1.26; aRR=1.14, 95% CI: 1.01-1.29, respectively). Liver-related hospital admission rates were notably raised for patients with prior ascites (aRR=1.37) and prior bleeding varices (aRR=1.33). This counterintuitive finding of an increase appears to be driven by the untreated DC patients; exploratory comparison between those treated and untreated (within two

years of DC diagnosis) indicated a halved admission rate among the treated subgroup in the DAA era: 346 compared with 652 admissions per 100 person-years (this remains exploratory because factors associated with initiation on DAA treatment are not controlled; i.e., confounding by indication),

DISCUSSION

Among Scotland's national DC patient population diagnosed in the period 2000–2018, the majority (63%) have been initiated on IFN-free therapy; lower uptake was observed for patients with a first DC complication prior to 2014. DAA uptake was associated with only a few of the variables investigated; namely, there was significantly lower uptake among patients in Greater Glasgow and Clyde (HR=0.6) and those with a history of heavy alcohol intake (0.7), and higher uptake among those with HCV genotype 1 (HR=1.6), compared with the genotype 3/other category. The latter finding is consistent with earlier availability of effective regimens for genotype 1 compared with genotype 3 infection. DAA uptake was also positively associated (HR=1.6) with being treatment experienced.

The determinants of uptake are multifactorial, but some insights are provided by our findings. Age and its confounder, ongoing risk behaviours, are likely the main drivers, with younger DC patients tending to be less likely to be initiated on treatment, for instance because of lifestyle factors that make engagement challenging. The initial high cost of DAAs led to restrictions on prescribing. Whilst patients with decompensated liver disease were eligible, the high cost of treatment (particularly for genotype 3) combined with fixed budgets, may have led to prioritisation of patients without unaddressed co-factors for liver disease mortality, such as ongoing problem alcohol use. Such decisions may have been more likely in health boards with higher burdens of HCV, such as Greater Glasgow & Clyde. Other patients may not have been offered treatment due to contraindications or life-threatening non-liver-related co-morbidities;[6] some patients with longstanding DC may have such advanced liver disease that there was no real justification for therapy (in the early part of the DAA era; current guidance is for unrestricted treatment) – and therefore these patients were effectively in a palliative care situation – or they may be awaiting liver transplantation. The sensitivity analysis restricting to more recent DC presentations partly

addresses this issue, by removing the very long-term individuals with DC from the study population. Overall DAA uptake in this patient cohort subset was almost identical (65%), and there were no notable differences in relative risks of uptake associated with patient characteristics (Supporting Information, Table S2).

Paralleling the significant reduction in progression to DC that was reported among compensated cirrhosis patients using the same data sources,[24] we observed a significant decrease in both all-cause and liver-related mortality risk in the DAA compared with the pre-DAA era among DC patients, with obtained adjusted HRs of 0.7. In their analysis of all-cause mortality comparing DAA-treated SVR-attaining and untreated DC patients, Cheung et al. did not observe any association between virological cure and mortality.[16] Although their study population was relatively large, a relatively small number of deaths were observed and conclusions were likely affected by the relatively short follow-up period of 15 months. The only other relevant research (to our knowledge) is a large study of HCV-infected American military veterans with advanced liver disease, in which an adjusted HR for mortality associated with SVR of 0.33 (95% CI: 0.26-0.42) was obtained among the subset of patients with a history of decompensated disease.[12]

In contrast to observational cohort studies of clinical outcomes among DAA-treated patients, in which virological cure cannot be randomised to participants, our approach of comparing mortality risk across time avoids this problem, under the assumption that newly diagnosed DC patients in the pre-DAA and DAA eras have a similar, before-treatment, prognosis. The between-era approach is also not susceptible to the potential for indication bias in DAA-treated vs. untreated patient comparisons, in which patients with an *a priori* favourable prognosis may be more likely to be initiated on DAA therapy.

Despite this design advantage, we found that the size of the pre-DAA period used as reference was influential, as sensitivity analysis exploring three follow-up periods indicated that the observed relative risk reduction in the main analysis was partly driven by the higher mortality risk in the early part of the pre-DAA period. This suggests that the decreasing trend in mortality risk began well before the introduction of IFN-free DAA treatment in the DC patient population. Our data

were insufficient to ascertain the reasons for this, but given that some of the patients diagnosed with DC in the later part of the second period (2010 to 31 Oct 2014) had been initiated on IFN-free DAA treatment and relatively few had undergone IFN-containing DAA treatment within two years (Supporting Information, Fig. S2), survival of these patients would be expected to be higher compared with patients diagnosed with DC in the first period (i.e., before 2010). Finally, improvements in patient care and management over time may have contributed to a rising trend in survival over the full analysis period.

In contrast to the mortality outcome results, rates of hospital admission with any diagnosis and rates with at least one liver-related diagnosis were higher in the DAA era (adjusted RRs of 1.14). At first glance, this appears to be at odds with the positive impact observed for mortality. However, given improving survival over our analysis period, DC patients are living longer with impaired liver function, which would suggest increasing hospitalisation rates, all else being equal. As the UK clinical guidelines for the management of HCV means that patients are preferably treated with IFN-free DAAs before cirrhosis has worsened, those HCV-infected patients who do progress to DC in the DAA era are not comparable to pre-DAA era DC patients, in that the former group consists of patients who were diagnosed late in disease progression, declined or did not adhere to treatment, or had advanced disease, comorbidities or behavioural risk factors that precluded initiation on therapy. Our exploratory comparison of hospitalisation rates between untreated and treated DC patients suggests that had treatment not been available, rates might have been even higher in the DAA era.

Our real-world DC patient population obtained SVR rates – 89% overall – that were comparable to rates reported using IFN-free regimens from clinical trials (>80% overall in advanced cirrhosis[25,26]), from clinical studies involving selected patient populations (up to 90% depending on genotype and prescribed regimen[15]), and in real-world settings (up to 84% in a patient population of which 70-75% had prior decompensation[27]).

Limitations of our findings and interpretation thereof are as follows. In our observational record-linkage study, we relied on an assumption that (after adjustment for known confounders), survival

in HCV patients newly diagnosed with DC was similar across time. Although the between-era comparison approach is powerful in eliminating the limitation of unmeasured confounding factors for initiation on treatment, the attainment of virological cure, and survival, other – unknown – factors temporally consistent with the roll-out of DAAs may have also contributed to the reduced all-cause mortality risk over the analysis period. An additional limitation concerns the unknown impact of incomplete data on the HCV Clinical Database regarding prior decompensation, HCC status, and heavy alcohol use. Finally, record-linkage errors between this database and the national deaths registry may have lead to biased estimation of relative risks.

Conclusions. Among Scotland's chronically HCV-infected DC population, uptake of IFN-free treatment was 63% overall, with a notable lower uptake observed for treatment-naive vs. experienced patients, and among patients who had been diagnosed with DC before 2014. Real-world IFN-free therapy uptake in this patient population may be improved through knowledge of the factors associated with reduced uptake. The IFN-free virological cure rate among HCV patients with decompensated cirrhosis was high (89%) in this real-world setting, and the significant reduction in mortality risk observed in the DAA era suggests that a combination of moderate uptake and the relatively high SVR rate has had a favourable impact on survival for Scotland's HCV-infected DC patients. Together with the potential for DAA treatment to offer an improved health-related quality of life for this patient group, being diagnosed with DCC in an era with growing access to DAAs appears to translate to a decreased risk of severe clinical outcomes such as mortality.

Significance statement

In Scotland and elsewhere, effective treatments - direct acting antivirals (DAA) - have recently come available for patients infected with hepatitis C virus who are in the most severe stage of liver disease. Although the majority of this patient group can be treated, uptake can be improved beyond the 63% currently achieved. These new DAA treatments are effective in improving survival in this patient group, as demonstrated by our study's finding of a 32% lower risk of all-cause mortality since DAAs became available, compared with preceding years when they were not.

Conflict of interest declaration

STB reports receipt of speakers fees from Abbvie, Gilead, and advisory board fees from Abbvie, BMS, Gilead, MSD. JFD reports grants and personal fees from Roche, MSD, Janssen, Gilead and Abbvie, personal fees from BMS, and grants from GSK. PCH has received personal support from Roche, Janssen, MSD and Gilead. DJG reports personal fees from Abbvie and personal fees from Gilead and MSD. SJH has received honoraria for presenting at meetings/conferences from Gilead. All other authors report no potential conflicts of interest.

Data availability statement

Data involve clinical NHS patient records linked to national hospitalisation and mortality registries and as such are not publicly available. Access to these individual-level data can be sought through approval of the Public Benefit and Privacy Panel for health and social care (www.informationgovernance.scot.nhs.uk/pbpphsc/home/for-applicants/).

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Table 1. Characteristics of study population: uptake of IFN-free DAA treatment among all DC patients on the HCV Clinical Database who were alive on 1 November 2014 and with active infection (i.e., no evidence for viral clearance following prior treatment) at start of follow-up (later of date of DC diagnosis or 1 November 2014), with date of first DC complication in the period 1 January 2000 to 31 December 2018 (n=297). The outcome (DAA uptake) is defined as initiation on most recent course of DAA by censoring date (earlier of death or 31 December 2018. Regression results reflect the imputation of missing data on *risk group* and *genotype category*.

Variable	N	DAA-treated n	(row%)	Univariate Cox HR	(95% CI)	Multivariable Cox HR	(95% CI)
Total	297	188	(63%)				
Sex							
Female	93	61	(66)	Ref.		–	
Male	204	127	(62)	1.06	(0.78-1.44)	–	
Age-group (at 1 Nov 2014)							
<45 yrs	110	60	(55)	0.72	(0.52-1.00)	0.70	(0.49-0.99)
45-54	130	86	(66)	Ref.		Ref.	
55+	57	42	(74)	1.14	(0.79-1.65)	1.04	(0.68-1.58)
Ethnicity							
White	278	174	(63)	Ref.		–	
Non-white	19	14	(74)	0.97	(0.56-1.67)	–	
Risk group							
PWID	191	117	(61)	Ref.		Ref.	
Non-PWID	39	31	(79)	1.46	(1.03-2.08)	1.04	(0.67-1.62)
NK	67	40	(60)	–		–	
Alcohol use history							
>50 units/wk	176	97	(55)	0.58	(0.43-0.77)	0.73	(0.54-0.99)
≤50 units/wk or NK	121	81	(75)	Ref.		Ref.	
Period of first DC complication							
2000-13	103	67	(65)	0.45	(0.31-0.64)	0.47	(0.32-0.68)
2014-15	81	53	(65)	0.71	(0.49-1.02)	0.88	(0.60-1.28)
2016-18	113	68	(60)	Ref.		Ref.	
Genotype							
1	125	92	(74)	1.60	(1.19-2.14)	1.55	(1.15-2.10)
3/Other	151	95	(63)	Ref.		Ref.	
NK	21	1	(5)	–		–	
Previous antiviral treatment							
Naive	243	137	(56)	Ref.		Ref.	
Experienced	54	51	(94)	1.72	(1.25-2.39)	1.64	(1.14-2.34)
HCC status (prior to most recent DAA course, or ever if never DAA-treated)							
No	265	171	(65)	Ref.		–	
Yes	32	17	(53)	0.77	(0.47-1.27)	–	
Liver transplantation (prior to most recent DAA course, or ever if never DAA-treated)							
No	275	169	(61)	Ref.			
Yes	22	19	(86)	0.91	(0.56-1.46)	–	
Prior ascites							
No	54	37	(69)	1.21	(0.84-1.73)	–	
Yes	243	151	(62)	Ref.		–	
Prior bleeding varices							
No	261	168	(64)	Ref.		Ref.	
Yes	36	20	(56)	0.66	(0.41-1.05)	0.65	(0.39-1.06)
Prior encephalopathy							
No	214	130	(61)	Ref.		Ref.	
Yes	83	58	(70)	1.32	(0.97-1.81)	1.25	(0.90-1.73)
Region							
Greater Glasgow & Clyde	150	83	(55)	0.56	(0.42-0.75)	0.64	(0.47-0.89)
Other	147	105	(71)	Ref.		Ref.	

Note. HR = hazard ratio. Covariates for multivariable regression were selected based on P<0.30 in univariate analysis.

Table 2. All-cause mortality rates and hazard ratios for all-cause mortality and liver-related mortality associated with characteristics of the study population of chronically HCV-infected DC patients attending specialist liver centres in Scotland. *Era* was defined as a time-dependent binary covariate, with value switching from '0' in the pre-DAA era (January 2005 to October 2014) to '1' in the DAA era (November 2014 to December 2018) on 1 November 2014. Follow-up censored at two years following first DC complication. *N*=624.

		N	Person-years	Deaths [liver-related]	Rate (per 100 pyrs)	Unadjusted all-cause HR	Adjusted all-cause HR (95% CI)	Adjusted liver-related HR (95% CI)
Total		624	933	213 [202]	22.8	–		–
Era	Pre-DAA	–	609	160 [151]	26.3	Ref.	Ref.	Ref.
	DAA	–	324	53 [51]	16.3	0.66 (0.48-0.90)	0.68 (0.49-0.93)	0.69 (0.50-0.95)
Sex	Female	174	284	49 [45]	17.3	Ref.	Ref.	Ref.
	Male	450	649	164 [157]	25.3	1.44 (1.05-1.98)	1.39 (1.01-1.92)	1.44 (1.03-2.01)
Age at DC	<50 yrs	374	585	119 [110]	20.4	Ref.	Ref.	Ref.
	50+ yrs	250	348	94 [92]	27.0	1.30 (0.99-1.71)	1.21 (0.91-1.61)	1.27 (0.95-1.70)
Risk group for HCV acquisition	PWID	373	568	123 [115]	21.7	Ref.		
	Non-PWID	105	156	38 [37]	24.3	1.09 (0.77-1.55)		
	NK †	146	209	52 [50]	24.9	–		
Alcohol use history	>50 units/wk	368	544	135 [128]	24.8	1.23 (0.93-1.62)	1.23 (0.92-1.63)	1.24 (0.92-1.66)
	≤50 units/wk or NK	256	389	78 [74]	20.1	Ref.	Ref.	Ref.
Ascites	No	107	162	28 [27]	17.3	Ref.	Ref.	Ref.
	Yes	517	771	185 [175]	24.0	1.38 (0.93-2.06)	1.23 (0.82-1.83)	1.19 (0.79-1.80)
Bleeding varices	No	575	854	201 [191]	23.5	Ref.		
	Yes	49	79	12 [11]	15.2	0.66 (0.37-1.18)		
Encephalopathy	No	529	797	183 [173]	23.0	Ref.		
	Yes	95	135	30 [29]	22.0	0.96 (0.65-1.41)		
HCC prior to DC diagnosis	No	581	882	187 [176]	21.2	Ref.	Ref.	Ref.
	Yes	43	51	26 [26]	50.6	2.30 (1.53-3.47)	2.10 (1.36-3.23)	2.19 (1.42-3.38)

Note. † Category not used in Cox regression as missing values were imputed, using the R package *mice*. Variable selection for the adjusted model was conducted using the change-in-estimate approach [20].

Table 3. Recurrent hospital admission rates associated with DC patient characteristics. Number of admissions and hazard ratios for admission with a liver-related diagnosis code are also shown. Follow-up was censored at two years following first DC complication. *N*=624.

		N	Person -years	Admissions [liver-related]	Rate (per 100 pyrs)	Unadjusted HR	Adjusted HR (95% CI)	Adjusted liver-related HR (95% CI)
Total		624	841	4266 [3564]	507	–		–
Era	Pre-DAA	–	585	2901 [2426]	496	Ref.	Ref.	Ref.
	DAA	–	256	1365 [1138]	532	1.13 (1.03-1.24)	1.14 (1.04-1.26)	1.14 (1.01-1.29)
Sex	Female	174	256	1164 [952]	455	Ref.	Ref.	Ref.
	Male	450	585	3102 [2612]	530	1.07 (0.95-1.19)	1.06 (0.95-1.18)	1.09 (0.95-1.25)
Age at DC	<50 yrs	374	530	2642 [2168]	498	Ref.	Ref.	Ref.
	50+ yrs	250	311	1624 [1396]	523	1.01 (0.92-1.12)	0.99 (0.89-1.09)	1.02 (0.90-1.15)
Risk group for HCV acquisition	PWID	373	527	2526 [2082]	480	Ref.	Ref.	Ref.
	Non-PWID	105	137	712 [608]	521	1.05 (0.93-1.18)	1.06 (0.94-1.19)	1.10 (0.96-1.26)
	NK †	146	178	1028 [874]	459	–	–	–
Alcohol use history	>50 units/wk	368	621	2691 [2266]	517	1.00 (0.90-1.10)		
	≤50 units/wk or NK	256	320	1575 [1298]	492	Ref.		
Ascites	No	107	112	523 [401]	469	Ref.	Ref.	Ref.
	Yes	517	729	3743 [3163]	513	1.06 (0.94-1.19)	1.23 (1.09-1.40)	1.37 (1.17-1.61)
Bleeding varices	No	575	756	3648 [3047]	483	Ref.	Ref.	Ref.
	Yes	49	85	618 [517]	727	1.17 (1.05-1.33)	1.29 (1.16-1.44)	1.33 (1.18-1.49)
Encephalo-pathy	No	529	693	3427 [2873]	494	Ref.	Ref.	Ref.
	Yes	95	148	839 [691]	568	1.08 (0.95-1.22)	1.13 (1.00-1.29)	1.14 (0.97-1.33)
HCC prior to DC diagnosis	No	581	772	3781 [3141]	490	Ref.	Ref.	Ref.
	Yes	43	69	485 [423]	707	1.12 (0.99-1.26)	1.10 (0.97-1.24)	1.10 (0.97-1.25)

Note. † Category not used in Cox regression as missing values were imputed, using the R package *mice*. Pre-DAA era refers to the period 1 January 2005 to 31 October 2014, and DAA era to the period 1 November 2014 to 31 December 2018. Variable selection for the adjusted model was carried out using the change-in-estimate approach [20].

FIGURE LEGENDS

Fig. 1. All-cause mortality rate among chonically HCV-infected DC patients (date of first decompensation 1 January 2005 to 31 December 2018; follow-up time for all patients was censored at two years following DC date) per calendar year, stratified by age-group at DC date (<50, 50+ years). *N*=624.