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## ORIGINAL ARTICLE

# Declining incidence of hepatitis C related hepatocellular carcinoma in the era of interferon-free therapies: A population-based cohort study

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## Abstract

**Background & aims:** The impact of interferon (IFN)-free therapies on the epidemiology of hepatitis C virus (HCV) related hepatocellular carcinoma (HCC) is not well understood at a population level. Our goal was to bridge this evidence gap.

**Methods:** This study included all patients in Scotland with chronic HCV and a diagnosis of cirrhosis during 1999-2019. Incident cases of HCC, episodes of curative HCC therapy, and HCC-related deaths were identified through linkage to nationwide registries. Three time periods were examined: 1999-2010 (pegylated interferon-ribavirin [PIR]); 2011-2013 (First-generation DAA); and 2014-2019 (IFN-free era). We used regression modelling to determine time trends for (i) number diagnosed and living with HCV cirrhosis, (ii) HCC cumulative incidence, (iii) HCC curative treatment uptake and (iv) post-HCC mortality.

**Results:** 3347 cirrhosis patients were identified of which 381 (11.4%) developed HCC. After HCC diagnosis, 140 (36.7%) received curative HCC treatment and there were 202 deaths from HCC. The average annual number of patients diagnosed and living with HCV cirrhosis was approximately seven times higher in the IFN-free versus the PIR era,

**Abbreviations:** aOR, adjusted odds ratio; DAA, direct acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C Virus; ICD, International Classification of Disease; IFN, Interferon; sdHR, subdistribution hazard ratio; SIMD, Scottish Index of Multiple Deprivation; SVR, sustained viral response.

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whereas the number of incident HCCs was four times higher. However, the cumulative incidence of HCC was significantly lower in the IFN-free versus PIR era (sdHR: 0.65; 95%CI:0.47-0.88;  $P = .006$ ). Among HCC patients, diagnosis in the IFN-free era was not associated with improved uptake of curative treatment (aOR:1.18; 95%CI:0.69-2.01;  $P = .54$ ), or reduced post-HCC mortality (sdHR: 0.74; 95%CI:0.53-1.05;  $P = .09$ ).

**Conclusions:** The cumulative incidence of HCC is declining in HCV cirrhosis patients, but uptake of curative HCC therapy and post-HCC survival remains suboptimal.

#### KEYWORDS

antiviral therapy, competing risks, DAAs, HCC, liver cancer, time trends

## 1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is a major cause of excess mortality in patients with hepatitis C virus (HCV) infection. From an epidemiological perspective, the number of HCC deaths occurring in a given time period depends on four main factors:

- **Size of the 'at risk' population** (For HCC, the major 'at risk' population are people with liver cirrhosis- ie the prevalence of cirrhosis in HCC patients exceeds 80%.<sup>1</sup>)
- **Cumulative incidence of HCC among the 'at risk' population** (Previous studies suggest the incidence of HCC among patients with HCV-related cirrhosis varies from 1-3 events per 100 person years of follow-up.<sup>2-6</sup>)
- **Uptake of HCC curative therapy following an HCC diagnosis** (Receiving curative HCC therapy is associated with improved survival,<sup>7</sup> but only patients with early stage HCC are eligible<sup>1,8</sup>).
- **Overall survival following HCC diagnosis** (HCC is a leading cause of cancer mortality<sup>9</sup>; Average survival after an HCC diagnosis is less than 1 year.<sup>10</sup>)

The arrival of interferon-free (IFN-free) direct acting antivirals (DAAs) from 2014 has not only revolutionised the treatment of chronic HCV infection but also offers new public health opportunities.<sup>11</sup> Whereas older treatments were long, arduous and ineffective, IFN-free therapies are short, tolerable and highly effective.<sup>12,13</sup> It is likely that IFN-free DAAs have already impacted the epidemiological landscape for HCV-related HCC. However, few studies have been able to quantify these changes at a population level, and so the picture remains uncertain. For example, the number of cirrhosis patients with cured HCV has probably increased dramatically in recent years, but precise numbers are not yet known. Similarly, although studies have shown that HCV cure is associated with reduced HCC incidence for cirrhosis patients,<sup>6,14</sup> this does not necessarily mean that HCC incidence is falling at a population level. The situation is complicated because HCV cure is also associated with a reduced risk of competing risk events (i.e. events that preclude the occurrence of HCC, such as death from decompensated cirrhosis), which may mitigate the population impact for HCC. By the same token, there is evidence that HCV cure is associated with improved post-HCC survival<sup>15,16</sup> – but

### Lay Summary

Individuals with hepatitis C cirrhosis are at high risk of developing hepatocellular carcinoma (HCC), which is the main form of primary liver cancer. Here, we showed that the incidence of hepatitis C related HCC has declined in recent years, following the introduction of new hepatitis C therapies. However, for individuals who do develop HCC, survival and uptake of curative treatment still remain poor.

this does not necessarily mean that overall survival at the population level has improved.

A better understanding of how these four aspects of the epidemiological landscape are shifting over time (if at all) is vital for policy makers and practitioners because they provide insight into the drivers of HCC mortality and indicate what innovations are likely to have the biggest impact on reducing deaths going forward (i.e. chemoprevention, risk-stratification for HCC screening, or drug-discovery for late stage disease). The main obstacle to carrying out this analysis is that it requires comprehensive and linkable health registries in order to follow patients from cirrhosis diagnosis through to death. Historical data for patients diagnosed in the era of IFN-based therapies are also essential. Scotland is one of the few settings anywhere in the world with the requisite database and linkage infrastructure to carry out this type of analysis. Thus, the main aim of this study was to determine the trends over a twenty-year period (1999 to 2019) in the aforementioned domains for HCV patients in Scotland.

## 2 | METHODS

### 2.1 | Study design and primary objective

We conducted a population-based cohort study to assess trends over time in relation to; (a) the number of individuals living with HCV cirrhosis, (b) HCC incidence, (c) receipt of HCC curative treatment, and (d) post-HCC mortality risk.

Secular trends were assessed using descriptive statistics and through competing risk multivariable regression models.

## 2.2 | Data Sources

We used data from four national health registries from Scotland to assess trends in HCV-related HCC over a period of 20 years (i.e. 1999 to 2019). First, the Scottish HCV clinical database records information on all patients attending a liver clinic in Scotland for care/management of their HCV infection. Second, the SMR01 database records all in-patient and day-case hospital admissions in Scotland. Third, the Scottish mortality register provides information on the date and cause of all deaths in Scotland. Fourth, the SMR06 registry provides detailed information on all cancer diagnoses in Scotland. Collectively, the SMR01, SMR06 and Scottish mortality register provide a means of following patients up over time. Linkage of these registries to the Scottish HCV clinical database was approved by Public Health Scotland Privacy Public Benefit Panel (application number: 1516-0457).

## 2.3 | Inclusion/exclusion criteria

All patients in Scotland with chronic HCV who received a diagnosis of cirrhosis between 1999 and 2019 were included in this study (N = 3350). Cirrhosis was defined as a diagnosis of compensated or decompensated cirrhosis made during the course of routine clinical investigation and follow-up at a specialist liver clinic. Typically, cirrhosis is diagnosed through a combination of liver biopsy; transient elastography; abdominal ultrasound; clinical examination; and routine liver function tests. The earliest date of cirrhosis diagnosis was obtained from the Scottish HCV clinical database.

Patients were excluded if HCC occurred before cirrhosis diagnosis, which we defined as an HCC diagnosis more than one year prior to cirrhosis diagnosis (N = 3). Thus, there were 3347 cirrhosis patients in our study population after applying the aforementioned exclusion criteria (see Figure 1).

## 2.4 | Outcome event definitions

Incident cases of HCC were identified through the presence of an ICD code for HCC (i.e. ICD10: C22.0; ICD9:155.0) in either a

cancer register, hospital admission or mortality record. Hospital admission and mortality records were only used to define HCC if they included an ICD code for HCC in the primary diagnostic/cause of death position. The date of HCC incidence was defined as the earliest HCC diagnosis/presentation date from across these three registries. All HCC presentations through to 31 Dec 2019 were counted.

Episodes of HCC treatment with curative intent were identified from surgical OPCS4 hospital procedure codes present in combination with an ICD10:C22.0 or ICD9:155.0 code in the primary discharge position. OPCS4 codes were included for ablation (J124; J127; J032; Y134; Y114; J083; J126; J125); resection (J023; J021; J022; J024; J031; J028; J026; J038) and liver transplantation (J011; J015; J012). These specific codes were identified through a two-stage process: (a) extracting all hospital admissions for HCV-related HCC occurring in Scotland in 1996-2019 (N = 4038); and then (b) reviewing and then categorising all OPCS4 codes included within these 4038 hospital admissions according to whether refer to instances of curative treatment or not, as defined by EASL clinical guidelines. [8] (see Table S1).

Deaths from HCC were identified by the presence of an HCC ICD code (ICD10: C22.0; ICD9:155.0) in any cause of death position.

## 2.5 | Definition of study covariates

The study outcome events were compared across three time periods, with each period corresponding to a distinct era of antiviral treatment. These three periods were (a) 1999-2010 (pegylated interferon-ribavirin); (b) 2011-2013 (First-generation DAA); and (c) 2014-2019 (IFN-free era).

Information on chronic HCV infection status was inferred from antiviral treatment history recorded on the HCV clinical database. Patients were assumed to have chronic infection through to the date of SVR achievement (if at all). The date of SVR achievement was defined as six months after the treatment completion date for episodes initiated before the year 2014 (i.e. SVR24); and three months after the

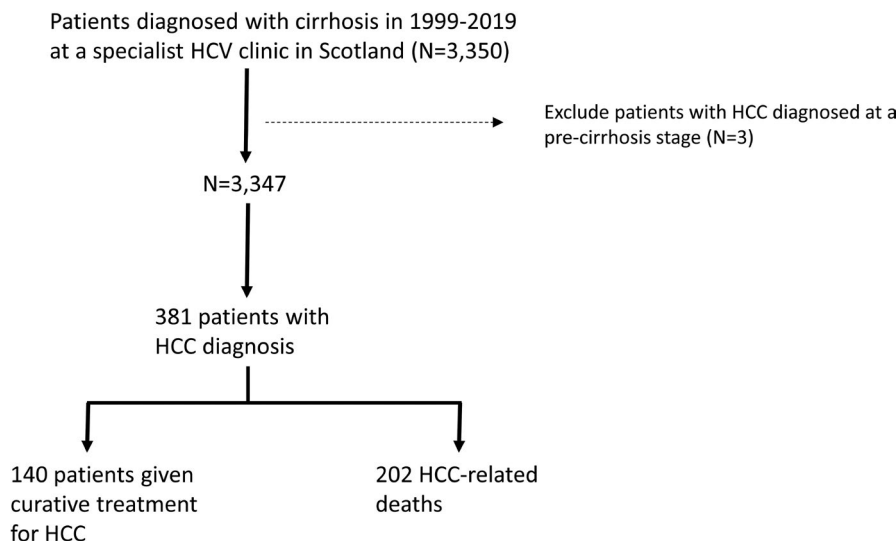


FIGURE 1 Derivation of study population

treatment completion date for episodes initiated from 2014 onwards (i.e. SVR12). This aligns with how SVR was defined by clinicians during the time frame of this study. A known history of heavy alcohol use was defined as self-reported consumption >50 units/week for a sustained period of six months or more. The deprivation status of participants was ascertained from the 2020 Scottish Index of Multiple deprivation (SIMD). SIMD scores were grouped into quintiles; quintile 1 represents the most deprived 20% of the Scottish population, whereas quintile 5 represented the least deprived 20% of the Scottish population. Decompensated cirrhosis was defined as diagnosis of bleeding oesophageal varices, ascites and/or hepatic encephalopathy. Individuals known to have a history of injecting drug use (IDU) were identified using information recorded on the HCV clinical database. Age refers to age at the date of cirrhosis and was treated as a continuous variable where appropriate. No individuals in our final sample were missing data for any of these aforementioned covariates.

## 2.6 | Statistical analyses

### 2.6.1 | Descriptive analysis

#### *'At risk' patients*

We determined the absolute number of patients living with HCV cirrhosis in Scotland for each calendar year between 1999 and 2019. The number of patients living with cirrhosis was broken down by calendar year; patients were counted as living with cirrhosis in a given year if they were alive at the mid-point of that year with a prior diagnosis of cirrhosis. In addition to calendar year, we also broke the number of patients down according to HCV infection status (i.e. chronic/SVR). Patients were categorised as SVR if they had achieved SVR by the year mid-point; otherwise, they were counted as having chronic infection for that year.

#### *HCC incidence*

We calculated the number of cirrhosis patients presenting with HCC in each calendar year according to chronic HCV infection status. Chronic HCV infection status at HCC diagnosis was inferred on the basis of whether the patient had achieved SVR prior to the HCC diagnosis date.

#### *Curative treatment*

We calculated the number of HCC patients who received curative HCC therapy. Again, we broke these numbers down according to calendar year and HCV infection status (i.e. chronic or SVR). Calendar year refers to the year of HCC diagnosis as opposed to the year of receiving therapy. Similarly, HCV infection status corresponds specifically to infection status at the time of HCC diagnosis, as opposed to the date of receiving therapy.

#### *HCC mortality*

The number of deaths related to HCC was also counted according to the calendar year of death and SVR status. Calendar

year corresponds to the year of HCC death, whilst HCV infection status relates to the infection status at the time of HCC diagnosis.

### 2.6.2 | Regression analyses

A range of multivariable regression models were fitted to assess time trends in relation to (a) HCC incidence; (b) receipt of curative therapy, and (c) post-HCC mortality risk. All models included statistical adjustment for relevant covariates to reduce bias from potential confounding.

#### *HCC incidence*

We performed time-to-event survival analysis to assess change in HCC incidence for cirrhosis patients over time, adjusting for relevant factors.

Time zero was defined as the date of first cirrhosis diagnosis. Patients were then followed up through to either the date of incident HCC (if at all), date of mortality (if at all) or the study completion date (31st Dec 2019). However, in a small number of patients, the date of cirrhosis diagnosis predated first appointment at an HCV specialist liver clinic. In these cases, survival time was left truncated (i.e. delayed entry) to avoid the potential introduction of immortal time bias between diagnosis of cirrhosis and the eventual first clinic appointment. Delayed entry means that whilst susceptibility to HCC begins from the date of cirrhosis diagnosis, only follow-up time occurring after the date of first appointment was counted in this analysis.

Fine-Gray regression, accounting for non-HCC mortality as a competing risk, was used to assess the association between time period and time to first HCC presentation. We included adjustment for age group, gender, decompensated cirrhosis, history of heavy alcohol use, SVR achievement, HCV genotype, IDU history, and deprivation status. Time period, SVR achievement, age, and decompensated cirrhosis were modelled as time-dependent variables—meaning they were able to change/update during the course of follow-up.

Two multivariate models were fitted to assess if the association between time period and HCC incidence is mediated by SVR achievement: one model including SVR achievement as a covariate and one omitting SVR achievement as a covariate.

We also performed sensitivity analyses where standard Cox regression models were fitted, in which competing risks are treated as censored observations.<sup>17</sup>

In this time-to-event analysis, we used the 'time window' method<sup>18</sup> to exclude all follow-up occurring in first six months since time zero. This was done to remove patients with 'prevalent' HCC (i.e. HCC already present at time zero) as opposed to incident HCC (ie HCC first emerging after time zero).

The cumulative incidence of HCC at specific time points was estimated using 'Stcomlist' command<sup>19</sup> in Stata version 17. Delayed entry patients were omitted from these calculations.

### Curative treatment

Logistic regression was used to identify factors associated with receiving curative therapy among those with incident HCC. The primary exposure variable of interest was time period, based on the year of HCC diagnosis. Covariates considered were: age at HCC diagnosis; history of heavy alcohol use; gender; SVR achievement, decompensated cirrhosis and SIMD deprivation quintile.

As with the HCC incidence analysis, models including and omitting SVR as a covariate were fitted to assess if SVR mediates the association between time period and HCC treatment uptake.

We also performed a sensitivity analysis where individuals diagnosed with HCC within 18 months of the study completion date of 31st Dec 2019 were excluded. This was to assess if recently diagnosed patients – who may not have had sufficient time to access therapy before the study completion data – could be biasing time period trends.

### HCC-related mortality

We performed time-to-event survival analysis to assess if time period was associated with risk of HCC mortality after HCC diagnosis. Follow-up time began at the date of HCC diagnosis and ended at the date of HCC mortality (if at all), date of non-HCC mortality (if at all) or the study completion date of 31st Dec 2019. As with our incidence analysis, a small number of patients were left truncated if their date of HCC diagnosis predated their first appointment at a specialist liver clinic.

Fine-Gray competing risk regression was used to determine the association between time period of HCC diagnosis and HCC mortality risk. Non-HCC death was treated as a competing risk. The primary exposure variable of interest was time period, which was based on the year of HCC diagnosis. Models included adjustment for age, history of heavy alcohol use, gender; age, SVR achievement at HCC diagnosis, decompensated cirrhosis at HCC diagnosis, HCV acquisition route and SIMD 2020 deprivation quintile. SVR achievement and HCC curative therapy were handled as time-dependent variables. Three separate models were fitted in total. Model 1 included all covariates except SVR and curative treatment status; Model 2 included all covariates except curative treatment status; Model 3 included all covariates. These separate models were fitted to gauge if SVR and receipt of curative treatment mediate the association between time period and HCC mortality risk.

## 3 | RESULTS

### 3.1 | Study population

A total of 3347 cirrhosis patients were included in our final study population (see Figure 1). The average-mean age at cirrhosis diagnosis was 47.6 years, and three-quarters were male (74.8%). Most

of the cohort were living in areas of high deprivation (i.e. 53.8% in SIMD quintile 1) and just under half were diagnosed with cirrhosis in the IFN-free era (i.e. 45%) (Table 1).

Of the 3347 patients in the final sample, 381 (11.4%) developed HCC, of which 140 (36.7%) were given curative treatment. There were 202 (53.0%) deaths from HCC (see Figure 1).

### 3.2 | Descriptive analyses

#### 3.2.1 | Diagnosed cirrhosis population

The number of patients living and diagnosed with HCV cirrhosis increased substantially over time, i.e. from an average of 282 per year in the pegylated interferon era to 1118 per year in the first-generation DAA era and to 2087 in the IFN-free era (Table 2 and Figure 2).

The proportion of living patients with an HCV cure has also risen considerably over time. From an average of 9.1% per year in the pegylated interferon/ribavirin era to 16.0% in the first-generation DAA era and to 52.5% in the IFN-free era. Since 2016, the number of cirrhotic patients living with cured HCV has exceeded the number of patients living with chronic HCV (Table 2 and Figure 2).

#### 3.2.2 | HCC incidence

The number of incident HCC cases also increased with time, from an average of 8 per year in the pegylated interferon and ribavirin era to 29 per year in the first-generation DAA era and to 34 per year in the IFN-free era. The proportion of HCC cases with SVR increased from 10.2% SVR in the pegylated interferon and ribavirin era; to 10.2% in the DAA first-generation era, to 53.0% in the IFN-free era (Table 2 and Figure 2).

#### 3.2.3 | Curative treatment

The number of HCC patients receiving curative therapy changed from an average of 3 per year in the pegylated interferon and ribavirin era to 13 per year in the first-generation DAA era and to 11 per year in the IFN-free era. The proportion of treated patients with an SVR was 12.7% in the pegylated interferon-ribavirin era, 10.8% in the first-generation DAA era, and 54.3% in the IFN-free era (Table 2 and Figure 2).

#### 3.2.4 | HCC-related mortality

The number of HCCs death increased from an average of 4 per year in the pegylated interferon-ribavirin era to 12 per year in the first-generation DAA era and to 22 per year in the IFN-free era. The proportion of patients dying with HCC who had achieved SVR was 6.5%

TABLE 1 Characteristics of: (A) study population with cirrhosis and (B) subgroup of patients with HCC

Characteristic	(A) Study population (N = 3347)	(B) Patients with HCC (N = 381)
	n (col %)	n (col %)
Time era (year of cirrhosis diagnosis)		
1999-2010	996 (29.8)	211 (55.4)
2011-2013	856 (25.6)	91 (23.9)
2014-2019	1495 (44.7)	79 (20.7)
SVR achievement		
Ever	2061 (61.6)	190 (49.9)
Never	1286 (38.4)	191 (50.1)
Gender		
Female	844 (25.2)	70 (18.4)
Male	2503 (74.8)	311 (81.6)
Age		
Mean (sd)	47.6 (sd:9.3)	53.8 (sd:8.6)
Decompensated cirrhosis		
Never	2676 (80.0)	252 (66.1)
Ever	671 (20.1)	129 (33.9)
Known history heavy alcohol use		
No	2010 (60.1)	226 (59.3)
Yes	1337 (40.0)	155 (40.7)
Scottish index multiple deprivation		
Q1 (most deprived)	1800 (53.8)	155 (40.7)
Q2	741 (22.1)	87 (22.8)
Q3	377 (11.3)	58 (15.2)
Q4	264 (7.9)	50 (13.1)
Q5 (least deprived)	165 (4.9)	31 (8.1)
HCV genotype		
Non-3	1651 (49.3)	158 (41.5)
3	1696 (50.7)	223 (58.5)
Known history of injecting drug use		
No	1147 (34.3)	197 (51.7)
Yes	2200 (65.7)	184 (48.3)

in the pegylated interferon era, 1.3% in the first DAA generation era, and 34.7% in the IFN-free era (Table 2 and Figure 2).

### 3.3 | Individual-level analyses

#### 3.3.1 | HCC incidence

A total of 3201 patients were included in the HCC incidence analysis after removing 146 individuals with less than six months follow-up (see previous explanation of 'time window' method). Of these 3201, survival time was left truncated (i.e. delayed entry) for 165 (5.2%) individuals (see Table S2). The average-mean duration of follow-up was 5.1 years per patient (median: 4.3 years). 288

incident HCCs were observed, equating to a crude incidence rate of 1.75 HCCs (95%CI: 1.56-1.97) per 100 person years of follow-up. The cumulative incidence of HCC after 1, 3 and 5 years was 1.3% (95%CI: 0.9-1.8); 4.1% (95%CI: 3.4-4.9); and 6.6% (95%CI: 5.7-7.6), respectively.

In multivariate Fine-Gray regression analysis, follow-up during the IFN-free era was associated with a reduction in the risk of HCC compared to follow-up during the era of pegylated interferon therapy (sdHR: 0.65; 95%CI: 0.47-0.88;  $P = .006$ ) (Table 3 and Figure 3). Other factors associated with higher HCC incidence were male gender (sdHR: 1.69; 95%CI: 1.26-2.25;  $P = .001$ ); older age (e.g. sdHR for  $\geq 60$  years versus 45-49 years; 4.30; 95%CI: 2.84-6.51;  $P < .001$ ); decompensated cirrhosis (sdHR: 1.64; 95%CI: 1.22-2.20;  $P = .001$ ) and HCV genotype 3 infection (sdHR: 1.57; 95%CI: 1.24-1.99;  $P < .001$ ).



TABLE 2 Average-mean number of people in Scotland: (A) living with HCV cirrhosis; (B) with incident HCC; (C) receiving curative HCC treatment; (D) dying from HCC, by time period

Time period	(A) Number living with HCV cirrhosis (N = 3347)		(B) Incident HCC (N = 381)		(C) Curative HCC treatment (N = 140)		(D) HCC deaths (N = 202)	
	Mean number, per year	% SVR	Mean number, per year	% SVR	Mean number, per year	% SVR	Mean number, per year	% SVR
1999-2010 (Pegylated interferon ribavirin)	282	9.1%	8	10.2%	3	12.7%	4	6.5%
2011-2013 (First-generation DAA)	1118	16.0%	29	10.2%	13	10.8%	12	1.3%
2014-2019 (IFN-free regimens)	2087	52.5%	34	53.0%	11	54.3%	22	34.7%
OVERALL	917	22.5%	18	20.9%	7	23.8%	10	12.8%

When SVR was included as a covariate, the association between follow-up in IFN-free era and HCC was only partly attenuated: sdHR:0.76; 95%CI:0.55-1.05;  $P = .10$  (Table 3). This observation is explored further in our post hoc analysis.

SVR achievement was associated with a lower risk of HCC incidence (sdHR:0.62; 95%CI:0.47-0.83;  $P = .001$ ) (Table 3). When a cause-specific model was fitted using standard Cox regression, the association between SVR and HCC incidence was HR:0.51; 95%CI:0.39-0.68;  $P < .001$  (Table S3).

### 3.3.2 | Curative HCC treatment

Of 381 HCC patients, 140 (36.8%) received curative HCC treatment. The only factor significantly associated with treatment uptake was decompensated cirrhosis (aOR: 0.51; 95%CI: 0.22-0.90;  $P = .02$ ) (Table 4). HCC diagnosis in the IFN-free era was not associated with higher uptake of curative treatment compared to the pegylated interferon/ribavirin era (aOR: 1.25; 95%CI: 0.72-2.18;  $P = .26$ ). Similarly, SVR achievement was not associated with receiving curative HCC treatment (aOR: 0.84; 95%CI:0.49-1.43;  $P = .52$ ). These associations were not materially altered in sensitivity analyses (Table S4).

### 3.3.3 | Mortality risk after HCC diagnosis

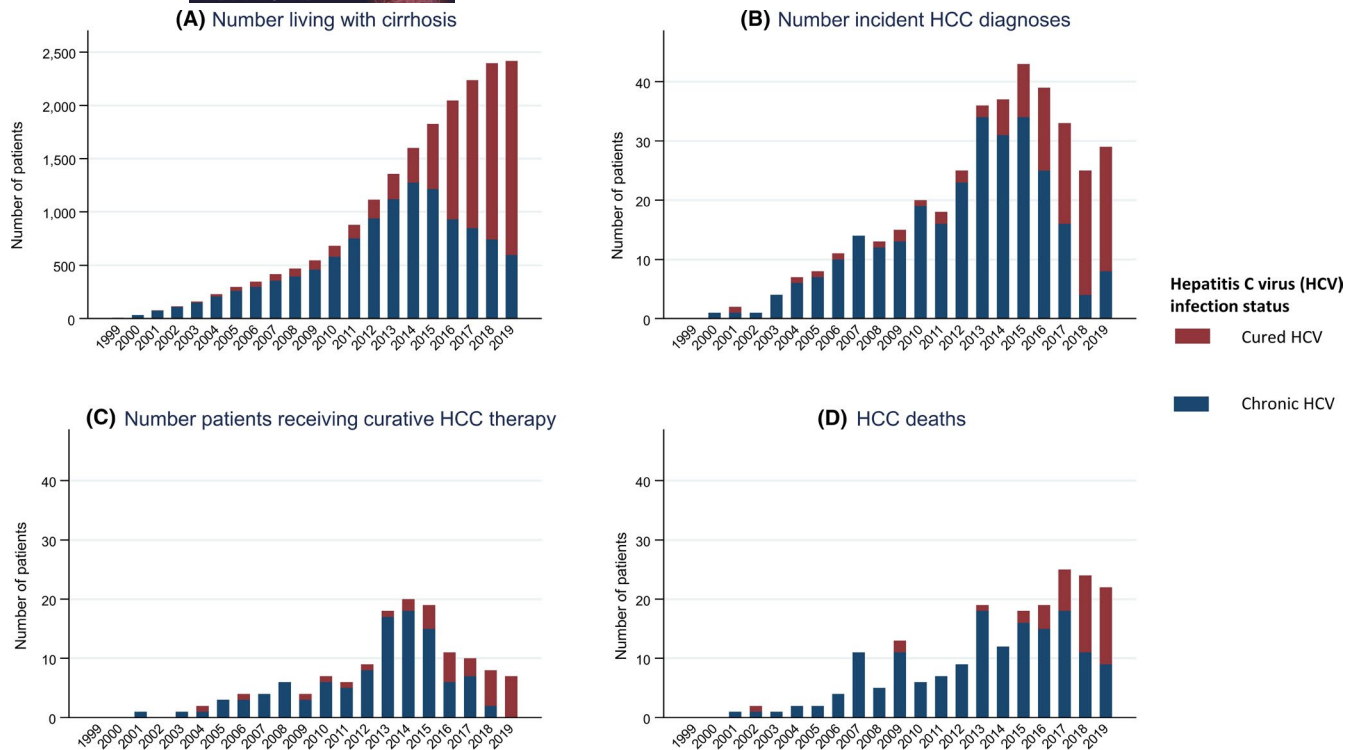
Of 381 HCC patients, 202 HCC deaths were observed during a mean of 2.9 years follow-up per patient (882 person years follow-up in total). Survival time was left truncated for 16 (4.2%) individuals (Table S2). The cumulative incidence of HCC mortality three years after HCC diagnosis was 47.8% (95%CI: 42.3-53.1) (Table S2).

In multivariable regression, there was a trend towards a reduced HCC mortality risk for patients diagnosed in the first-generation DAA era (sdHR: 0.68; 95%CI:0.48-0.97;  $P = .04$ ) and IFN-free era (sdHR: 0.74; 95%CI: 0.63-1.33;  $P = .09$ ) compared to the pegylated interferon-ribavirin era. (Table 5 and Figure 3). The strongest protective factor against HCC mortality was receiving curative HCC therapy (sdHR:0.27; 95%CI: 0.19-0.39;  $P < .001$ ). SVR achievement was also associated with a lower HCC mortality risk (sdHR:0.66; 95%CI:0.47-0.92;  $P = .03$ ), attenuating to sdHR:0.74 ( $P = .11$ ) after adjustment for curative HCC therapy (Table 5).

### 3.3.4 | Post hoc analysis

As previously described, the reduction in the cumulative incidence of HCC observed in the IFN-free era was only partly attenuated when adjusting for SVR achievement (ie from sdHR:0.67 to sdHR: 0.76). This may suggest that additional factors are contributing to the falling HCC incidence. Thus, we explored if severity of cirrhosis has changed over time, by calculating trends for the following liver-related blood tests: alanine aminotransferase (ALT); aspartate aminotransferase (AST); platelet count; albumin; bilirubin; and alpha





**FIGURE 2** Number of individuals with hepatitis C: (A) living with diagnosed cirrhosis; (B) diagnosed with first-time HCC; (C) receiving curative HCC therapy; (D) dying from HCC, over twenty years (1999-2019), according to infection status

fetoprotein (AFP). For each blood test and for each patient, we calculated the average value from all tests conducted within 6 months of cirrhosis diagnosis (i.e. because some patients will have, for example, multiple ALTs performed within this six-month time window).

This analysis shows that ALT; AST; bilirubin and AFP levels have all declined over time. For example, the median ALT was 74.4 IU/L for cirrhosis patients diagnosed in 1999-2010 versus 56.3 IU/L in 2014-2019. Conversely, platelet counts have increased over time from a median of 119.1 in 1999-2010 to 148.0 in 2014-2019 (Table S5).

## 4 | DISCUSSION

In this study, we show that the epidemiological landscape for HCV-related HCC has changed markedly during the last twenty years. The number of people diagnosed and living with cirrhosis has increased more than seven-fold, and from 2016, cured cirrhosis patients have outnumbered chronic cirrhosis patients. Another important milestone is that the majority of patients presenting with HCC now do so at a post-SVR stage. Perhaps the most important changes however have occurred with respect to the incidence of HCC. The absolute number of patients with incident HCCs has quadrupled, from 8 per year in the pegylated interferon era to 34 per year in the IFN-free era. Reassuringly, however, we show that the *cumulative incidence* of HCC—which takes account of the growing number of patients living with diagnosed cirrhosis—has actually fallen in the IFN-free era. Whilst the arrival of IFN-free therapies is likely to be the biggest factor behind this reduction, other concomitant trends appear to be

contributing too. For example, patients diagnosed with cirrhosis in the pegylated interferon-ribavirin era had significantly higher serum ALT, AST, bilirubin and AFP levels compared to patients diagnosed in IFN-free era. This may suggest that the diagnostic threshold for cirrhosis has fallen over time as new diagnostic technologies, such as transient elastography, have come into effect. Alternatively, it may be that cirrhosis is being diagnosed at an earlier more compensated stage. Whatever the explanation, the totality of these changes has important bearing on the feasibility of existing HCC screening guidelines.<sup>1,8</sup> Although the biannual screening recommendation has stayed more or less the same over the time period of this study, the shifting epidemiological landscape that we describe –i.e. more patients living with diagnosed cirrhosis compounded by a lower cumulative incidence of HCC – means that the resources required to deliver biannual screening have actually increased considerably. In other words, clinicians need to screen more patients in order to identify fewer HCCs. Alternatively, one could say that that the number needed to screen<sup>20</sup> (i.e. the number of cirrhosis patients that need to be screened to identify a single HCCs) is higher now than ever before. These data, therefore, provide important context to the current debate around the need for a more targeted approach to HCC surveillance.<sup>21,22</sup>

Our analysis also sheds new light on outcomes downstream of HCC diagnosis that have crucial bearing on the overall epidemiological picture. In particular, we show that only about one-third of patients receive curative treatment and that this proportion has not improved over time. Thus, the uptake of curative therapy in the IFN-free era remains about the same as what it was in the era of

TABLE 3 Factors associated with HCC incidence among patients diagnosed with cirrhosis (N = 3201)

Characteristic	Univariate		Multivariate: model 1		Multivariate: model 2	
	sdHR (95% CI)	P	sdHR (95% CI)	P	sdHR (95%CI)	P
<b>Time era</b>						
1999-2010	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-
2011-2013	0.80 (0.56-1.16)	0.24	0.78 (0.53-1.13)	0.19	0.77 (0.53-1.13)	0.19
≥2014	0.67 (0.50-0.89)	0.006	0.65 (0.47-0.88)	0.006	0.76 (0.55-1.05)	0.10
<b>SVR achievement</b>						
No	1.00 (REF)	-	-	-	1.00 (REF)	-
Yes	0.70 (0.55-0.90)	0.006	-	-	0.62 (0.47-0.83)	0.001
<b>Gender</b>						
Female	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-
Male	1.29 (0.97-1.70)	0.08	1.69 (1.26-2.25)	<0.001	1.68 (1.25-2.24)	<0.001
<b>Age group</b>						
<40	0.10 (0.02-0.41)	0.002	0.09 (0.2-0.39)	0.001	0.09 (0.02-0.38)	0.001
40-44	0.25 (0.11-0.57)	0.001	0.24 (0.11-0.54)	0.001	0.24 (0.11-0.54)	<0.001
45-49	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-
50-54	1.72 (1.15-2.57)	0.009	1.74 (1.15-2.63)	0.008	1.76 (1.17-2.66)	0.01
55-59	3.49 (2.38-5.11)	<0.001	3.55 (2.39-5.28)	<0.001	3.62 (2.43-5.38)	<0.001
≥60	4.12 (2.83-5.99)	<0.001	4.30 (2.84-6.51)	<0.001	4.43 (2.92-6.73)	<0.001
<b>Decompensated cirrhosis</b>						
No	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-
Yes	1.49 (1.13-1.97)	0.005	1.64 (1.22-2.20)	0.001	1.52 (1.12-2.06)	0.007
<b>Known history heavy alcohol use</b>						
No	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-
Yes	0.87 (0.69-1.11)	0.26	0.91 (0.71-1.17)	0.46	0.89 (0.69-1.15)	0.38
<b>Scottish index multiple deprivation</b>						
Q1 (most deprived)	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-
Q2	1.45 (1.07-1.96)	0.016	1.20 (0.87-1.65)	0.26	1.16 (0.84-1.60)	0.37
Q3	1.88 (1.34-2.63)	<0.001	1.25 (0.87-1.78)	0.23	1.28 (0.90-1.82)	0.18
Q4	2.16 (1.49-3.11)	<0.001	1.34 (0.91-1.97)	0.49	1.33 (0.90-1.97)	0.15
Q5 (least deprived)	2.18 (1.41-3.37)	<0.001	1.52 (0.95-2.43)	0.08	1.54 (0.96-2.47)	0.07
<b>HCV genotype</b>						
Non-3	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-
3	1.37 (1.08-1.72)	0.008	1.57 (1.24-1.99)	<0.001	1.60 (1.26-2.03)	<0.001
<b>Known history of injecting drug use</b>						
No	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-
Yes	0.52 (0.41-0.66)	<0.001	0.96 (0.74-1.25)	0.76	0.95 (0.73-1.23)	0.68

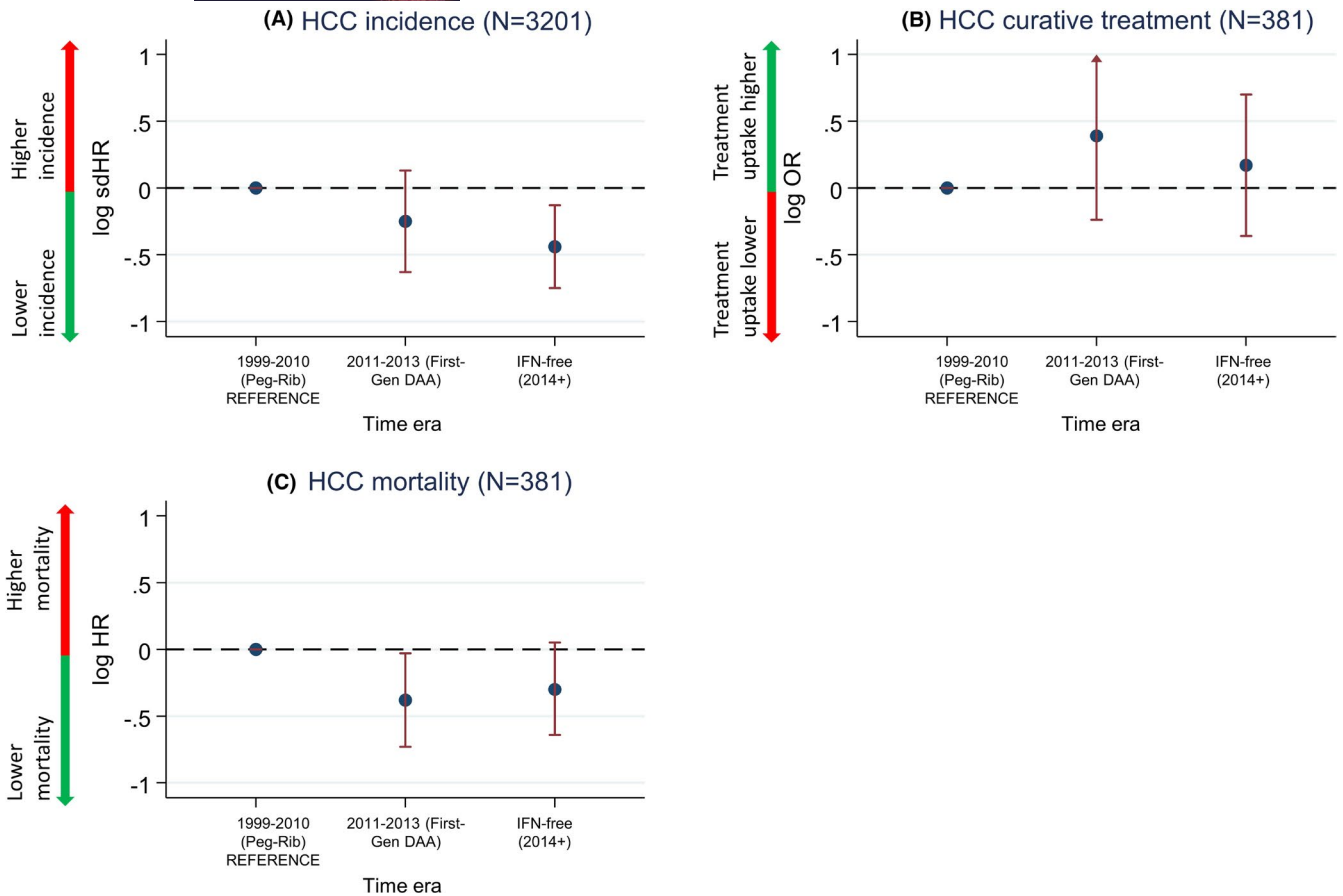
Time era, SVR achievement and decompensated cirrhosis are modelled as time-dependent variables.

Model 1 omits SVR achievement as a covariate.

Model 2 includes SVR achievement as a covariate.

pegylated interferon and ribavirin treatment. New initiatives to increase early HCC detection have the potential to save many lives. One option could be to adopt a 'precision medicine' approach to HCC screening, where biannual ultrasound examinations are targeted at patients who stand to gain the most benefit (which should

take into consideration both a patient's risk of developing HCC as well as the likelihood of receiving curative therapy if HCC is detected at an early stage). New risk prediction tools are needed to support this approach. However, despite the lack of improvement in curative treatment uptake, we still observed a trend towards lower



**FIGURE 3** Association between time period and: (A) HCC incidence; (B) curative HCC treatment uptake; and (C) HCC mortality risk. Estimates are adjusted for age, gender, decompensated cirrhosis, history of heavy alcohol use, deprivation, HCV genotype and HCV acquisition route. Estimates are not adjusted for SVR. The dashed line corresponds to the line of null effect. Effect sizes are presented on log scale to ensure Y axis is symmetrical around the line of null effect

HCC-related mortality risk in the IFN-free era (albeit this was not statistically significant;  $P = .09$ ). This putative survival improvement may be a corollary of the higher SVR prevalence, given that SVR itself was associated with a lower HCC mortality risk in our analysis (as has also been noted elsewhere<sup>15,16</sup>).

Finally, our results suggest a mixed picture with respect to the influence of deprivation on HCC outcomes. There was no indication that deprivation was associated with a higher HCC incidence among cirrhosis patients (indeed, if anything, the reverse was true). However, both uptake of curative treatment and survival appeared to be adversely affected by higher levels of deprivation (Figure S1).

Overall, our analysis is consistent with many strands of prior research. For example, like other studies<sup>6,14</sup> we show that an HCV cure is associated with decreased HCC incidence compared to untreated patients and treatment failures. We also show that an HCV cure may be associated with improved survival after HCC, which has also been reported elsewhere.<sup>15,16</sup> This study also chimes with previous population-based studies showing a reduction in all-cause mortality,<sup>23</sup> incident decompensated cirrhosis<sup>24</sup> and HCC mortality<sup>25</sup> in the IFN-free era. However, our finding of a reduced HCC incidence in the IFN-free era is novel and to the best of our knowledge has not been shown before. Therefore, this study will lend further

confidence to patients, clinicians and policy makers regarding the utility of IFN-free therapies. At the same time, it also highlights the need now to focus on increasing curative treatment uptake for the full impact of IFN-free therapies to be realised.

The metier of this study is that we have been able to present twenty-year time trends across several domains relevant to the epidemiology of HCV-related HCC. Moreover, we have been able to do this at a national level, drawing on the world-leading hepatitis databases and data linkage infrastructure available in Scotland. This study has limitations too that warrant mention. First, data for some relevant covariates were not available to us. This includes BMI and hepatitis B infection status which are associated with HCC risk. However, because there have not been any extreme changes in these risk factors over time, we do not consider this limitation a serious one. Second, we did not have recourse to individual-level data on abdominal ultrasound examinations performed in an HCC screening context. As a result, we were not able to quantify how the uptake of abdominal ultrasound screening for HCC has changed over time (if at all). It is conceivable that screening uptake has fallen in the IFN-free era due to the more chaotic circumstances of patients treated with IFN-free therapies. This may explain why uptake of curative treatment has not improved.

TABLE 4 Factors associated with uptake of curative HCC therapy among patients with incident HCC (N = 381)

Characteristic	Univariate		Multivariate: model 1		Multivariate: model 2	
	OR (95%CI)	P	OR (95%CI)	P	OR (95% CI)	P
Time era <sup>a</sup>						
1999-2010	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-
2011-2013	1.43 (0.77-2.66)	0.25	1.48 (0.79-2.79)	0.23	1.47 (0.78-2.78)	0.23
2014-2019	1.15 (0.69-1.91)	0.60	1.18 (0.69-2.01)	0.54	1.25 (0.72-2.18)	0.26
SVR achievement at HCC diagnosis						
No	1.00 (REF)	-	-	-	1.00 (REF)	-
Yes	0.82 (0.51-1.32)	0.40	-	-	0.84 (0.49-1.43)	0.52
Gender						
Female	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-
Male	0.73 (0.43-1.24)	0.24	0.62 (0.35-1.10)	0.10	0.63 (0.35-1.11)	0.11
Age at HCC diagnosis						
per 1 year increase	0.99 (0.97-1.02)	0.58	0.97 (0.94-1.00)	0.10	0.97 (0.94-1.01)	0.10
Decompensated cirrhosis						
No	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-
Yes	0.60 (0.36-1.01)	0.05	0.51 (0.29-0.88)	0.02	0.51 (0.29-0.88)	0.02
Known history heavy alcohol use						
No	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-
Yes	0.91 (0.60-1.40)	0.67	1.03 (0.65-1.63)	0.89	1.04 (0.66-1.65)	0.86
Scottish index multiple deprivation						
Q1 (most deprived)	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-
Q2	1.07 (0.61-1.85)	0.82	1.04 (0.59-1.84)	0.88	1.04 (0.59-1.84)	0.88
Q3	1.18 (0.63-2.20)	0.61	1.31 (0.69-2.52)	0.41	1.33 (0.69-2.55)	0.39
Q4	1.28 (0.67-2.47)	0.46	1.33 (0.66-2.65)	0.43	1.33 (0.67-2.68)	0.41
Q5 (least deprived)	1.58 (0.73-3.46)	0.25	1.59 (0.72-3.51)	0.26	1.60 (0.72-3.53)	0.25
HCV genotype						
non-3	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-
3	1.10 (0.72-1.68)	0.66	1.07 (0.69-1.67)	0.55	1.07 (0.68-1.66)	0.78
Known history of injecting drug use						
No	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-
Yes	0.85 (0.56-1.29)	0.44	0.76 (0.47-1.21)	0.25	0.77 (0.48-1.24)	0.29

Model 1 omits SVR achievement as a covariate.

Model 2 includes SVR achievement as a covariate.

<sup>a</sup>Time era is based on year of HCC diagnosis.

Future studies should ideally align data on HCC incidence, curative treatment and survival with information on ultrasound screening uptake. We also did not have data on the BCLC HCC stage at diagnosis. Thus, we cannot say what proportion of HCCs were diagnosed at an early stage and how this has changed over time. However, uptake of curative HCC therapies can be viewed as a proxy for early HCC detection because these therapies are contraindicated in patients with intermediate- or advanced-stage HCC. Another caveat is that the deprivation score we use relates

to the year 2020 which is at the upper end of time period of this study. Thus, there is a small potential for misclassification of high/low deprivation areas- but this will be minimal because in general, areas of high deprivation do not suddenly become areas of low deprivation within twenty years (and vice versa). Another limitation is that there is no specific OPCS4 code to capture stereotactic ablative radiotherapy, which is increasingly being adopted as a form of curative ablative therapy. Thus, it is possible that some cases of curative HCC treatment have been missed. Finally, our

TABLE 5 Factors associated with HCC-related mortality after diagnosis of HCC (N = 381)

Characteristic	Univariate		Multivariate: model 1		Multivariate: model 2		Multivariate: model 3		
	sdHR (95% CI)	P	sdHR (95% CI)	P	sdHR (95% CI)	P	sdHR (95% CI)	P	
Time era <sup>a</sup>									
1999-2010	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-	
2011-2013	0.72 (0.51-1.03)	0.07	0.68 (0.48-0.97)	0.04	0.74 (0.51-1.05)	0.09	0.69 (0.48-0.99)	0.05	
2014-2019	0.82 (0.58-1.16)	0.27	0.74 (0.53-1.05)	0.09	0.91 (0.63-1.33)	0.64	0.75 (0.51-1.09)	0.13	
SVR achievement at HCC diagnosis									
No	1.00 (REF)	-	-	-	1.00 (REF)	-	1.00 (REF)	-	
Yes	0.67 (0.49-0.91)	0.01	-	-	0.66 (0.47-0.92)	0.02	0.74 (0.52-1.06)	0.11	
Gender									
Female	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-	
Male	1.11 (0.77-1.61)	0.58	1.26 (0.85-1.86)	0.24	1.28 (0.87-1.88)	0.21	1.09 (0.76-1.58)	0.63	
Age at HCC diagnosis									
per 1 year increase	1.02 (1.00-1.04)	0.06	1.03 (1.01-1.05)	0.004	1.03 (1.01-1.05)	0.003	1.03 (1.00-1.05)	0.04	
Decompensated cirrhosis									
No	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-	
Yes	1.19 (0.86-1.65)	0.30	1.38 (0.98-1.93)	0.07	1.33 (0.94-1.88)	0.10	1.23 (0.87-1.73)	0.25	
Known history heavy alcohol use									
No	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-	
Yes	1.03 (0.78-1.36)	0.84	0.90 (0.67-1.21)	0.48	0.90 (0.67-1.21)	0.47	0.93 (0.69-1.26)	0.09	
Scottish index multiple deprivation									
Q1 (most deprived)	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-	
Q2	0.94 (0.65-1.34)	0.72	0.90 (0.62-1.31)	0.58	0.91 (0.63-1.34)	0.65	1.01 (0.69-1.47)	0.96	
Q3	0.86 (0.58-1.30)	0.48	0.77 (0.50-1.18)	0.24	0.78 (0.51-1.19)	0.27	0.84 (0.55-1.31)	0.45	
Q4	0.56 (0.34-0.91)	0.02	0.52 (0.32-0.85)	0.009	0.52 (0.32-0.85)	0.01	0.54 (0.33-0.88)	0.01	
Q5 (least deprived)	0.69 (0.42-1.11)	0.12	0.68 (0.42-1.11)	0.13	0.73 (0.45-1.19)	0.21	0.83 (0.51-1.36)	0.46	
HCV genotype									
non-3	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-	
3	0.90 (0.68-1.19)	0.45	0.88 (0.64-1.21)	0.44	0.96 (0.72-1.29)	0.78	1.00 (0.74-1.35)	1.00	
Known history of injecting drug use									
No	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-	1.00 (REF)	-	
Yes	1.15 (0.88-1.52)	0.31	1.31 (0.94-1.83)	0.11	1.32 (0.98-1.79)	0.07	1.31 (0.96-1.79)	0.09	
Receipt of curative HCC treatment									

TABLE 5 (Continued)

Characteristic	Univariate		Multivariate: model 1		Multivariate: model 2		Multivariate: model 3	
	sdHR (95% CI)	P	sdHR (95% CI)	P	sdHR (95% CI)	P	sdHR (95% CI)	P
No	1.00 (REF)	-	-	-	-	-	1.00 (REF)	-
Yes	0.27 (0.19-0.38)	<0.001	-	-	-	-	0.27 (0.19-0.39)	<0.001

SVR achievement and receipt of curative treatment are modelled as time-dependent variables.

Model 1 omits SVR achievement and curative treatment as covariates.

Model 2 includes SVR but omits curative treatment.

Model 3 includes both SVR and curative treatment as covariates.

<sup>a</sup>Time era is based on year of HCC diagnosis.

study does not provide information on trends in the development of HCC in non-cirrhotic patients nor does it provide the bigger picture in terms of trends in the total chronic HCV diagnosed population. Nevertheless, patients with cirrhosis represent the main risk group for HCC and are also targeted for biannual HCC screening. Thus, these data are highly relevant to the ongoing debate about the sustainability of the biannual screening recommendation in cirrhosis SVR patients.

In conclusion, the epidemiological landscape for HCV-related HCC has changed considerably over the last two decades, particularly with respect to the number of diagnosed cirrhosis patients and the cumulative incidence of HCC. These changes have important implications for the implementation and sustainability of existing HCC screening guidelines.

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None.

**CONFLICTS OF INTEREST**

There are no conflicts of interest to disclose.

**DATA AVAILABILITY STATEMENT**

The data used in this study are not publicly available, but can be acquired through a successful application to the Public Benefit and Privacy Panel for Health and Social Care (<https://www.information.gov.scot.nhs.uk/pbpphsc/home/for-applicants/>).

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#### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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