

## Impact of previous hepatitis B infection on the clinical outcomes from chronic hepatitis C? A population-level analysis

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**Title:**

Impact of previous hepatitis B infection on the clinical outcomes from chronic hepatitis C? A population-level analysis.

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## Summary

Chronic coinfection with hepatitis C virus (HCV) and hepatitis B virus (HBV) is associated with adverse liver outcomes. The clinical impact of previous HBV infection on liver disease in HCV infection is unknown. We aimed to determine any association of previous HBV infection with liver outcomes using antibodies to the hepatitis B core antigen (HBcAb) positivity as a marker of exposure. The Scottish Hepatitis C Clinical Database containing data for all patients attending HCV clinics in participating health boards was linked to the HBV diagnostic registry and mortality data from Information Services Division, Scotland. Survival analyses with competing risks were constructed for time from the first appointment to decompensated cirrhosis, hepatocellular carcinoma (HCC) and liver-related mortality. Records of 8513 chronic HCV patients were included in the analyses (87 HBcAb positive & HBV surface antigen [HBsAg] positive, 1577 HBcAb positive & HBsAg negative, and 6849 HBcAb negative). Multivariate cause-specific proportional hazards models showed previous HBV infection (HBcAb positive & HBsAg negative) significantly increased the risks of decompensated cirrhosis (hazard ratio [HR]: 1.29, 95% CI: 1.01-1.65) and HCC (HR: 1.64, 95% CI: 1.09-2.49), but not liver-related death (HR: 1.02, 95% CI: 0.80-1.30). This is the largest study to date showing an association between previous HBV infection and certain adverse liver outcomes in HCV infection. Our analyses adds significantly to evidence which suggests HBV infection adversely affects liver health despite apparent clearance. This has important implications for HBV vaccination policy and indications for prioritisation of HCV therapy.

## Keywords

Cirrhosis, decompensation, hepatitis B core antigen, hepatocellular carcinoma, vaccination, viral hepatitis

## INTRODUCTION

Hepatitis C virus (HCV) infection is one of the leading causes of liver morbidity and mortality worldwide. It affects 2% of the population, being the leading global indication for liver transplant. However, while some patients have a rapidly progressive disease course, less than half of those chronically infected will go on to develop liver cirrhosis after 30 years of infection. The influences on disease progression are incompletely understood although environmental, viral and genetic variables have been shown to accelerate liver fibrosis. With the advent of effective but expensive direct acting antiviral (DAA) therapies for HCV, identifying those at the highest risk of liver disease progression is necessary to optimise the cost-utility of such therapies, which can vary greatly between individual clinical scenarios. One factor consistently associated with poorer outcome is the presence of additional liver pathologies.<sup>1-3</sup> As detailed in the AASLD/IDSA guidance on HCV treatment, these include alcohol excess and active coinfection with other hepatotropic viruses such as hepatitis B virus (HBV).<sup>3</sup> The majority of adults exposed to HBV will clear the virus from their serum. Despite this, HBV DNA has the potential to remain in hepatocytes as covalent closed circular DNA (cccDNA) long after viremia has resolved.<sup>4</sup> The effect of previous HBV infection on HCV associated liver disease has not yet been determined.

In the event of acute infection with HBV, 95% of healthy adults will appear to clear the infection with undetectable hepatitis B surface antigen (HBsAg) and development of hepatitis B surface antibodies (HBsAb) and hepatitis B core antigen (HBcAb) with undetectable serum HBV DNA using commercial assays. However, in the liver, HBV cccDNA has the potential to persist in hepatocytes for many years.<sup>4</sup> The replicative potential of this 'occult' HBV DNA is well recognized as HBV reactivation following immunosuppression is not uncommon. Indeed, for

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3 those with evidence of previous HBV infection undergoing immunosuppressive therapy,  
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5 guidelines now recommend active monitoring and prophylactic antiviral therapy.<sup>5</sup>  
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8 The prevalence of DNA persistence in hepatocytes, also termed occult HBV infection  
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10 (OBI) following viral clearance is unknown. For those with serological markers of previous  
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12 infection such as HBcAb and HBV DNA, prevalence varies depending on sensitivity of testing.  
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14 Several papers have highlighted a link between OBI and poor liver outcomes. This has been  
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16 predominantly reported in the context of chronic HCV where detection of HBV DNA in the liver  
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18 is associated with accelerated liver fibrosis, increased risk of hepatocellular carcinoma (HCC)  
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20 and lower response rates to dual HCV therapy.<sup>6-9</sup> A study using nested HBV PCR in liver  
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22 biopsies of HCV positive, HBsAg negative patients to detect OBI revealed more severe liver  
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24 disease in the OBI positive group.<sup>10</sup> Recent meta-analyses have concluded OBI significantly  
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26 increases the risk of chronic liver disease and HCC.<sup>11</sup> However, most of the analyses included in  
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28 these studies are small and in selected population. In addition, previous research has not had  
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30 sufficient power to correct for possible confounding factors such as alcohol abuse and HCV  
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32 genotype, which have been shown to influence clinical outcomes in chronic HCV infection.  
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38 Determining the impact of PCR proven OBI in a large population of patients with HCV  
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40 would be impractical, particularly as liver biopsy has been largely replaced by non-invasive  
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42 methods in the routine assessment of HCV liver disease. However, it should be possible to  
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44 explore any effect associated with previous HBV infection using HBcAb positivity as a reliable  
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46 surrogate marker to identify individuals who have been exposed to HBV. The Scottish health  
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48 system provides a unique opportunity for epidemiological studies of HCV outcomes. The vast  
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50 majority of healthcare is provided by the state-funded sector with each individual being allocated  
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52 a unique identifier number, enabling their care to be tracked across different geographical  
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3 locations. We aimed to analyse the Scottish Hepatitis C Clinical Database linked to the hepatitis  
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5 B diagnostic registry data to determine if presence of a positive HBcAb status was associated  
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7 with adverse liver outcomes in patients diagnosed with chronic HCV infection. Primary  
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9 outcomes were development of decompensated cirrhosis, HCC, and liver-related mortality.  
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## 15 **MATERIALS AND METHODS**

### 16 **Data sources and linkage**

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18 The Scottish Hepatitis C Clinical Database consists of standalone Microsoft Access databases  
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20 installed across 17 of 18 Scottish HCV treatment centres. These databases hold information on  
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22 all aspects of HCV care and patient management, in addition to information on complications of  
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24 liver disease and other lifestyle factors such as alcohol excess and smoking status.  
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30 All HCV PCR or RNA positive records from the Scottish Hepatitis C Clinical Database  
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32 were electronically linked with HBV serology results extracted from the hepatitis B diagnostic  
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34 registry data (which contains all HBV testing records in Scotland), and to data from Scottish  
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36 Information Services Division, which provides accurate mortality information and has been used  
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38 successfully in several observational studies of the HCV-infected population.<sup>12,13</sup> Individuals  
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40 were excluded if they had never attended a HCV clinic appointment or if the date of clinical  
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42 outcomes (decompensated cirrhosis or HCC) predated the date of their first appointment.  
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47 Presence of decompensated cirrhosis was recorded if presence of ascites, jaundice,  
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49 bleeding oesophageal varices or encephalopathy was documented in the Hepatitis C Clinical  
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51 Database with the corresponding dates of laboratory tests. Although data on clinical diagnosis of  
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53 cirrhosis without decompensation were available from the database, frequency of surveillance for  
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55 cirrhosis varied between centres, therefore this was not included as a primary outcome in this  
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3 study. Diagnosis of HCC was by the treating clinician based on radiological findings, the tumour  
4 marker alpha-fetoprotein and, in some circumstances, biopsy according to UK guidelines.<sup>14</sup> The  
5 diagnosis was validated by the regional hepatobiliary cancer multidisciplinary teams. Date of  
6 HCC was recorded as the date of the first radiological examination suggesting the diagnosis of  
7 HCC. Date and causes of death were recorded in data from Information Services Division,  
8 Scotland. Liver-related mortality was determined through the International Classification of  
9 Disease (ICD) codes K70-K77, C22-C24 and B15-B19.

### 22 **Study design and statistical analyses**

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24 Individuals included were grouped according to HBV status as either HBV infected (HBcAb  
25 positive, HBsAg positive), HBV exposed (HBcAb positive, HBsAg negative), HBV unexposed  
26 (HBcAb negative) and HBV status unknown. Demographic data was collected for all of these  
27 categories, however those with unknown HBV status were excluded from further univariate and  
28 multivariate survival analyses. Age at the first appointment was summarised as median with  
29 interquartile range and the other categorical variables were summarised as frequencies with  
30 percentages.

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41 As the majority of individuals in the Hepatitis C Clinical Database had no known date of  
42 HCV infection, date of first appointment was chosen as a starting point (baseline) for survival  
43 analyses. It was necessary to take account of the phenomenon of competing risks for our  
44 outcomes of interest, since an individual was at risk of more than one mutually exclusive event,  
45 and the occurrence of one of these would prevent any other event from happening. Specifically,  
46 in this study all-cause mortality might be a competing risk of decompensated cirrhosis and HCC,  
47 while non-liver related death might be a competing risk of liver-related death. Therefore cause-  
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3 specific hazard functions were modelled under a proportional hazards assumption to investigate  
4 the association between HBcAb positivity and decompensated cirrhosis, HCC and liver-related  
5 mortality. Time to decompensated cirrhosis and HCC was censored at the date of last follow-up  
6 (if recorded in the database) or date of death (if the last follow-up date was missing). Time to  
7 liver-related death was censored at the date of non-liver related death (if recorded).  
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15 For the univariate analyses, only the covariate 'HBV status' was included. For the  
16 multivariate analyses, other characteristics at baseline (date of the first appointment) recorded in  
17 the database (age, gender, ethnicity, HCV genotype, ever injection drug use [IDU], ever smoking,  
18 alcohol excess defined as a history of regular consumption of greater than 50 units per week, and  
19 HIV coinfection) were also included. Assuming that data was missing at random, multiple  
20 imputation procedures were conducted to impute missing baseline data on alcohol excess, HIV  
21 coinfection, ever smoking, HCV genotype, ever IDU and ethnicity. The imputation model  
22 included all variables related to the outcomes as well as the censoring indicator and the observed  
23 time to event, with binary logistic regression for two-level factors and polytomous logistic  
24 regression for factors have more than 2 levels. For each of the three outcomes of interest, cause-  
25 specific proportional hazards model was fitted to 5 imputed datasets. The estimates of hazard  
26 ratios and  $p$  values from each imputed dataset were combined to produce inferential results.  
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28 Proportional hazard assumptions were also tested by creating interactions with logarithm of time  
29 for all the covariates included in the models.  
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## RESULTS

### Study cohort

There were 21787 patients in the Scottish hepatitis B diagnostic registry data and 18603 patients in the Scottish Hepatitis C Clinical Database. After data linkage and exclusion of the patients who had developed primary outcomes prior to their first appointment, a total of 12209 patients were included in this study. The description of all the individuals included according to their HBV status is shown in Table 1. Of the 8513 patients with known HBV status, 87 (1%) were overtly HBV co-infected (HBcAb positive & HBsAg positive), 1577 (18.5%) had evidence of HBV exposure (HBcAb positive & HBsAg negative), and 6849 (80.5%) had no evidence of previous HBV exposure. The 3696 patients with HCV infection but unknown HBV status were only described for baseline demographics and were excluded in further analyses.

The HBV exposed group tended to be older at the first clinic appointment, with higher rates of reported alcohol excess, smoking, IDU and HIV coinfection than the unexposed group. For the 8513 patients with unknown HBV status, the median duration of follow-up from date of the first appointment to events or censoring was 3.3 years with the interquartile range 1.4 to 7.4 years. The variables with missing values were alcohol excess (32.9%), HIV coinfection (29.7%), ever smoking (25.9%), HCV genotype (12.4%), ever IDU (7.1%) and ethnicity (0.8%).

### Univariate and multivariate analyses

Univariate analyses (Table 2) revealed significantly higher risk of decompensated cirrhosis (HR: 1.50, 95% CI: 1.18 – 1.90) and HCC (HR: 1.57, 95% CI: 1.06 – 2.34) in the HBV exposed group (HBcAb positive & HBsAg negative) compared to those with known HBcAb negative status.

However, exposure to HBV did not significantly increase the risk of liver-related mortality (HR: 1.23, 95% CI: 0.98 – 1.56).

**Table 1. Description of study population (total number = 12209), according to HBV status.**

Demographics & outcomes	Subgroups according to HBV status			
	Co-infected (n = 87)	Exposed (n = 1577)	Unexposed (n = 6849)	Unknown (n = 3696)
Age at 1 <sup>st</sup> clinic appointment	34 (30 - 42)	39 (33 - 45)	35 (29 - 42)	37 (30 - 44)
Male gender	69 (79%)	1202(76%)	4836 (71%)	2524 (68%)
Ethnicity	White	81 (93%)	1455 (92%)	6454 (94%)
	Non-white	6 (7%)	108 (7%)	345 (5%)
	Unknown	0 (0%)	14 (1%)	50 (1%)
HCV genotype	1	32 (37%)	619 (39%)	2716 (40%)
	3	30 (34%)	696 (44%)	2864 (42%)
	Others	3 (3%)	89 (6%)	411 (6%)
	Unknown	22 (25%)	173 (11%)	858 (13%)
Ever IDU	Yes	54 (62%)	1218 (77%)	4810 (70%)
	No	19 (22%)	258 (16%)	1551 (23%)
	Unknown	14 (16%)	101 (6%)	488 (7%)
Ever smoking	Yes	44 (51%)	1075 (68%)	4383 (64%)
	No	9 (10%)	140 (9%)	611 (9%)
	Unknown	34 (39%)	362 (23%)	1805 (26%)
Alcohol intake	>50 u/w	20 (23%)	424 (27%)	1599 (23%)
	≤50 u/w	32 (37%)	696 (44%)	2938 (43%)
	Unknown	35 (40%)	457 (29%)	2312 (34%)
HIV coinfection	Yes	8 (9%)	72 (5%)	75 (1%)
	No	47 (54%)	1073 (68%)	4713 (69%)
	Unknown	32 (37%)	432 (27%)	2061 (30%)
Decompensated cirrhosis	6 (6.9%)	95 (6.0%)	239 (3.5%)	
HCC	2 (2.3%)	35 (2.2%)	80 (1.2%)	
Liver-related death	4 (4.6%)	96 (6.1%)	260 (3.8%)	

**Table 2. Hazard ratios (95% CI) and *p* values from univariate cause-specific hazard models for decompensated cirrhosis, HCC and liver-related mortality.**

	HR (95% CI)	<i>p</i>
<b>Decompensated cirrhosis</b>		
HBcAb[+] & HBsAg[+] vs HBcAb[-]	1.88 (0.83 – 4.22)	0.128
HBcAb[+] & HBsAg[-] vs HBcAb[-]	1.50 (1.18 – 1.90)	0.001
<b>HCC</b>		
HBcAb[+] & HBsAg[+] vs HBcAb[-]	1.78 (0.44 – 7.23)	0.423
HBcAb[+] & HBsAg[-] vs HBcAb[-]	1.57 (1.06 – 2.34)	0.025
<b>Liver-related mortality</b>		
HBcAb[+] & HBsAg[+] vs HBcAb[-]	1.06 (0.40 – 2.85)	0.904
HBcAb[+] & HBsAg[-] vs HBcAb[-]	1.23 (0.98 – 1.56)	0.080

Multivariate analyses (Table 3) showed that exposure to HBV (HBcAb positive & HBsAg negative) significantly increased the risk of decompensated cirrhosis (HR: 1.29, 95% CI: 1.01 – 1.65) and HCC (HR: 1.64, 95% CI: 1.09 – 2.49), while it did not significantly increase the risk of liver-related mortality (HR: 1.02, 95% CI: 0.80 – 1.30). We did not observed a statistically significant association between overt HBV infection (HBcAb positive & HBsAg positive) and the outcomes measured. The proportions of patients in this group developing decompensated cirrhosis (6.9%) and HCC (2.3%) suggested a trend to poorer liver outcomes compared to those unexposed to HBV (3.5% and 1.2% respectively). In the multivariate analysis of decompensated cirrhosis, there was a lower risk if ever IDU (HR: 0.56, 95% CI: 0.43 – 0.72) perhaps because people who injected drugs (PWID) might be diagnosed HCV infection earlier than those who did not due to screening. Since date at the first appointment was used as the starting time point, PWID would tend to be younger at the start of follow up and had a longer time to events interested. Violation of proportional hazard assumptions were not found in any of the multivariate models.

**Table 3. Hazard ratios (95% CI) and *p* values from multivariate cause-specific hazard models for decompensated cirrhosis, HCC and liver-related mortality.**

Covariates	Decompensated cirrhosis		HCC		Liver-related mortality	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Age at 1 <sup>st</sup> clinic appointment	1.07 (1.06 – 1.08)	<0.001	1.12 (1.10 – 1.14)	<0.001	1.10 (1.09 – 1.11)	<0.001
<b>Gender</b>						
Male vs Female	1.16 (0.90 – 1.49)	0.264	2.90 (1.70 – 4.93)	<0.001	1.31 (1.01 – 1.71)	0.041
<b>Ethnicity</b>						
White vs Non-white	0.88 (0.54 – 1.45)	0.632	1.87 (0.80 – 4.40)	0.152	1.60 (0.87 – 2.96)	0.140
<b>HCV genotype</b>						
Genotype 3 vs Genotype 1	1.10 (0.88 – 1.38)	0.431	1.42 (0.96 – 2.09)	0.101	1.40 (1.12 – 1.74)	0.003
Other types vs Genotype 1	0.62 (0.39 – 1.00)	0.053	0.37 (0.15 – 0.94)	0.037	0.64 (0.41 – 1.01)	0.065
<b>Ever IDU</b>	0.56 (0.43 – 0.72)	<0.001	0.65 (0.41 – 1.04)	0.077	1.12 (0.85 – 1.47)	0.437
<b>Ever smoking</b>	1.14 (0.80 – 1.63)	0.521	0.88 (0.53 – 1.47)	0.594	1.08 (0.77 – 1.53)	0.530
<b>Alcohol excess (&gt;50units/week)</b>	3.31 (2.61 – 4.20)	<0.001	1.78 (1.20 – 2.65)	0.006	2.78 (2.21 – 3.50)	<0.001
<b>HIV coinfection</b>	2.23 (1.39 – 3.57)	0.002	0.32 (0.05 – 2.31)	0.259	1.75 (1.02 – 2.98)	0.105
<b>HBV status</b>						
HBcAb[+] & HBsAg[+] vs HBcAb[-]	1.80 (0.79 – 4.07)	0.190	2.57 (0.62 – 10.52)	0.194	1.32 (0.49 – 3.57)	0.602
HBcAb[+] & HBsAg[-] vs HBcAb[-]	1.29 (1.01 – 1.65)	0.043	1.64 (1.09 – 2.49)	0.019	1.02 (0.80 – 1.30)	0.821

## DISCUSSION

Our data suggested a strong link between serological evidence of previous HBV infection and development of decompensated cirrhosis and HCC in patients with HCV. This association remains significant event once confounders such as history of alcohol excess, IDU, age at the first clinic appointment and smoking history have been taken into account. This is the largest study to confirm that previous HBV infection is an important factor in HCV liver disease outcomes, which may also have implications for other liver conditions.

Within Scotland, the majority of individuals who do become infected with HCV take part in risk prone behaviours such as IDU or are immigrants from highly endemic areas. Such individuals are also at risk of HBV exposure. Within HCV infected populations 2-10% have

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3 overt HBV infection.<sup>15</sup> In overt chronic coinfection with HBV and HCV viruses, one virus often  
4 replicates at lower levels which may lead to difficulties in diagnosis.<sup>16</sup> Despite apparent viral  
5 suppression, co-infected individuals have been reported to have higher rates of liver fibrosis and  
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10 HCC.

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12 HBV is effectively prevented using a recombinant HBsAg-based vaccine, while many  
13 countries have now adopted universal HBV vaccination policies, within the UK vaccination is  
14 limited to individuals in high risk groups.<sup>17</sup> Despite being eligible for vaccination, up to 23% of  
15 the British PWID population have detectable antibodies to the HBcAb.<sup>18</sup> This suggests many  
16 were exposed to HBV prior to taking up vaccination, although some may have been infected  
17 before the vaccine was introduced. The challenges of identifying and vaccinating PWID during  
18 their most high-risk periods of use are well recognized, and worldwide HBcAb positivity is  
19 reported between 2-85% of PWID.<sup>19</sup>

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31 The association of HBcAb positivity with more rapid progressive liver disease has  
32 several possible explanations: (i) persistence of HBV DNA in a significant proportion of those  
33 with prior infection of HBV occurs and increases the risk of decompensated cirrhosis and HCC;  
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38 (ii) acute HBV infection and the inflammation associated with its clearance predisposes to a  
39 greater risk of cirrhosis with subsequent chronic HCV infection; (iii) failure of HBV vaccination  
40 and subsequent infection occurs in those with more severe liver disease; and (iv) previous HBV  
41 infection is simply a marker of certain individual traits, e.g. more chaotic / longer drug injecting  
42 history or poor compliance with medical intervention such as HBV vaccination which in turn  
43 could be associated with worse outcomes.  
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#### 54 **Persistent HBV DNA**

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3 Occult hepatitis B infection would present one of the most biologically plausible explanations for  
4 the excess liver morbidity in the HBV exposed group. If HBV DNA persistence and low levels  
5 of DNA replication are present in a significant proportion of those individuals previously  
6 infected, this could potentiate some of the molecular mechanisms of cellular damage induce by  
7 HCV in a similar way to overt coinfection. Of note, the European Medicines Agency has  
8 recently initiated an investigation of HBV reactivation following DAA therapy for HCV. This  
9 follows publication of case reports describing reactivation of HBV following successful DAA  
10 therapy for HCV, in two cases the only marker of HBV infection was HBcAb positivity.<sup>20,21</sup>  
11  
12 Suppression of one virus by another is well documented and these cases provide further evidence  
13 that in the context of chronic HCV infection, 'cleared' HBV may in fact be suppressed HBV  
14 with the potential to cause ongoing liver damage.<sup>22</sup>  
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29 The means by which coinfection induces higher levels of cellular damage are  
30 incompletely understood. However, there is evidence that HBV and HCV have shared  
31 mechanisms for inducing cellular stress which could become synergistic in the presence of both  
32 viruses to enhance fibrogenesis.<sup>23</sup> In addition, upregulation of proto-oncogenes are seen in both  
33 HBV and HCV which may predispose to liver damage and eventually HCC.<sup>24</sup> While we did not  
34 demonstrate a significant association between HBsAg positivity and adverse outcomes, these  
35 associations have been reported elsewhere and we did find a trend toward adverse outcomes and  
36 it is likely we were unable to detect an association due to the relatively small number of patients  
37 and events in this group in our cohort.<sup>1,15</sup>  
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49 Our study hinges on using HBcAb as a surrogate for OBI. In the setting of chronic HBV  
50 infection, HBcAb has a specificity of above 95% and an overall accuracy of 90% as a surrogate  
51 marker for ever infection,<sup>25</sup> we can assume that of those testing positive for HBcAb, at least 95%  
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3 will have been exposed to HBV. Association of outcomes with previous infection may be  
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5 weakened by individuals who lose HBcAb over time, however this does not introduce risk of a  
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7 Type I error in our study. The use of HBcAb to determine OBI is less clear cut. It has been found  
8  
9 that HBcAb has a sensitivity of 54% and specificity of 72% for OBI in a HCV positive  
10  
11 population, with a positive predictive value of 56%.<sup>10</sup> Similarly, another study found 62% of  
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13 those with HBcAb had evidence of viral DNA in their liver.<sup>26</sup> **It must be remembered that**  
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15 **extracting cccDNA from liver tissue that has been stored in various conditions for retrospective**  
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17 **analysis is not a ‘gold standard’ and thus more patients with HBcAb may have OBI. Even if we**  
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19 **accept that not all patients with HBcAb have OBI, it does not exclude our observation of**  
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21 **worsened outcome in those with HCV and HBcAb being attributable to OBI.** It is possible that  
22  
23 exposure to HBV infection could cause lasting liver damage by mechanisms other than DNA  
24  
25 persistence. Indeed, some studies have raised the possibility that previous HBV infection alone  
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27 may be linked to poorer liver disease outcomes without the presence of OBI.<sup>27,28</sup>  
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### 36 **Vaccination uptake and efficacy**

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38 There were insufficient clinical data to determine if any of those with positive HBcAb status had  
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40 taken up vaccination which was subsequently unsuccessful, with or without the influence of  
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42 advanced liver disease. However, rates of vaccine efficacy are almost 90% in those with  
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44 compensated cirrhosis and higher in those without significant liver disease.<sup>29</sup> Given the low rates  
45  
46 of vaccine uptake in PWID population it is improbable that the association with HBcAb and  
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48 cirrhosis is due to vaccine non-response and then subsequent infection with HBV is already in  
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50 cirrhotic individuals.  
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While it is possible that those exposed to HBV have riskier behaviours, a study of Australian PWID shows that individuals who are unvaccinated against HBV are more likely to be male and do not have more high-risk patterns of drug use.<sup>30</sup> To explore this hypothesis in the Scottish population, we also analysed the relationship between HBV status and all-cause mortality. This analysis showed a strong association between IDU and mortality but no significant increase in all-cause mortality risk with HBcAb positivity (Table 4).

**Table 4. Hazard ratios (95% CI) and *p* values from multivariate cause-specific hazard models for all-cause mortality.**

<b>Covariates</b>	<b>HR (95% CI)</b>	<b><i>p</i></b>
<b>Age at 1<sup>st</sup> clinic appointment</b>	1.07 (1.06 – 1.08)	< 0.001
<b>Gender</b>		
Male vs Female	1.21 (1.03 – 1.42)	0.018
<b>Ethnicity</b>		
White vs Non-white	1.47 (0.94 – 2.31)	0.103
<b>HCV genotype</b>		
Genotype 3 vs Genotype 1	1.41 (1.23 – 1.61)	< 0.001
Other types vs Genotype 1	1.10 (0.85 – 1.42)	0.520
<b>Ever IDU</b>	1.79 (1.49 – 2.16)	< 0.001
<b>Ever smoking</b>	1.21 (0.95 – 1.53)	0.214
<b>Alcohol excess (&gt; 50 units/week)</b>	1.96 (1.71 – 2.25)	< 0.001
<b>HIV coinfection</b>	1.56 (1.13 – 2.15)	0.017
<b>HBV status</b>		
HBcAb[+] & HBsAg[+] vs HBcAb[-]	1.48 (0.88 – 2.49)	0.114
HBcAb[+] & HBsAg[-] vs HBcAb[-]	0.88 (0.76 – 1.03)	0.146

A sub-analysis of the HBcAb negative cohort was also preformed to determine any differences between those with evidence of vaccination (HBsAb positive) and those without (Table 5). In this cohort, vaccinated individuals were more likely to be younger, male, Caucasian, having a history of IDU, and be smokers compared to unvaccinated individuals ( $p < 0.001$  for these characteristics). In addition to the 18.5% of the HCV population known to be exposed to HBV, 62% of the Scottish HCV population had not been vaccinated at the point of presenting

with HCV which suggests that historically the UK vaccination policy was failing to adequately protect individuals at risk of HBV.

**Table 5. Demographics summary of HCV patients with HBcAb negative and known HBsAb status.**

Demographics		HBcAb(-) & HBsAb(+) (n = 2034)	HBcAb(-) & HBsAb(-) (n = 4511)	<i>P</i>
Age at 1 <sup>st</sup> clinic appointment		32 (27 - 38)	36 (29 - 43)	< 0.001
Male gender		1512 (74%)	3103 (69%)	< 0.001
Ethnicity	White	1974 (97%)	4195 (93%)	< 0.001
	Non-white	49 (2%)	284 (6%)	
	Unknown	11 (1%)	32 (1%)	
HCV genotype	1	811 (40%)	1769 (39%)	0.354
	3	893 (44%)	1871 (41%)	
	Others	112 (5%)	277 (6%)	
	Unknown	218 (11%)	594 (13%)	
Ever IDU	Yes	1600 (79%)	3012 (67%)	< 0.001
	No	319 (16%)	1174 (26%)	
	Unknown	115 (6%)	325 (7%)	
Ever smoking	Yes	1394 (69%)	2809 (62%)	< 0.001
	No	146 (7%)	497 (11%)	
	Unknown	494 (24%)	1205 (27%)	
Alcohol intake	>50 u/w	464 (23%)	1063 (24%)	0.322
	≤50 u/w	811 (40%)	1995 (44%)	
	Unknown	759 (37%)	1453 (32%)	
HIV coinfection	Yes	28 (1%)	42 (1%)	0.182
	No	1447 (71%)	3106 (69%)	
	Unknown	559 (27%)	1363 (30%)	

*P* value was obtained from Mann-Whitney test for age at 1<sup>st</sup> clinic appointment, and from Chi-squared test for the others.

### Implications for HCV therapy

Although recent guidance of National Institute for Health and Care Excellence has suggested direct acting antivirals can be used for all HCV infected patients with genotype 1 infection, the cost of provision for all HCV infected individuals will be considerable. Ideally, healthcare providers should prioritise treatment for patients where this will result in the biggest

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3 improvement in health outcomes. Early access programmes in the UK have largely been targeted  
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5 at those with more advanced disease. Identifying individuals whose liver disease may progress  
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7 more rapidly, e.g. those with previous HBV exposure, may help target those who will benefit  
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9 most from treatment in earlier stages of the disease.  
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### 15 **Limitations of analysis**

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17 One common limitation encountered in observational research in HCV infected populations is  
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19 uncertainty around time of infection. In this study, the majority of individuals do not have a  
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21 known date of infection with HCV or exposure to HBV. Various studies have reported ways of  
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23 accounting for this, either by assuming infection at a certain age or at a specific point following  
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25 date of reported commencement of IDU. In this study we have used date of first clinic  
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27 appointment as a surrogate while including age at first clinic appointment as a covariate in the  
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29 multivariate analysis and excluding those developing primary outcomes prior to first  
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31 appointment. This approach introduces risk of a Type II error by automatically excluding any  
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33 individual with decompensated cirrhosis or HCC at diagnosis but should not falsely inflate the  
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35 rate of adverse liver outcomes in one particular group. In addition, as HCV clearance does not  
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37 always prevent future progression to decompensated cirrhosis or HCC, particularly in the  
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39 presence of other liver pathologies, we chose not to include it in this study.  
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### 48 **Conclusions**

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50 This is the largest study to date to show an association between previous HBV infection and  
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52 adverse liver outcomes (decompensated cirrhosis and HCC) in a large, unselected population of  
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54 individuals with chronic HCV. Our results confirm a growing body of evidence which suggests  
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3 HBV infection may have adverse effects on liver health despite apparent viral clearance. Our  
4 data also suggest that UK vaccination policies failed to prevent HBV infection in a substantial  
5 number of individuals at risk although novel approaches targeting high risk groups may be more  
6 effective. The current HCV therapy guideline focussed on prioritizing patients with advanced  
7 disease should be reconsidered to include HBV coinfection and prior exposure. Our findings  
8 have important implications for the UK HBV vaccination policy and global HCV therapy  
9 policies.  
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#### 36 **STATEMENT OF INTERESTS**

37  
38 There is no conflict of interest to disclose and no specific funding was obtained.  
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#### 44 **AUTHORS CONTRIBUTIONS**

45  
46 HW, RS, ET, HAI, PRM and JFD conceived the analysis presented in this study. HW, RS and  
47 HAI were involved in data extraction and data linkage. HW performed the statistical analyses.  
48 All authors assisted with drafting and/or appraising the manuscript. PRM and JFD supervised  
49 this study.  
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