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The influence of hepatitis C and alcohol on liver-related morbidity and mortality in Glasgow's injecting drug user population

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SUMMARY. Infection with the hepatitis C virus (HCV) is associated with the development of severe liver disease, but cofactors – namely alcohol abuse – in Scotland's HCV-positive population complicate estimation of the unique contribution of HCV. We compared the risk of hospital admission/death for a liver-related cause in a large cohort of Glasgow's injecting drug users (IDUs) testing HCV-positive with IDUs testing HCV negative. Data for 6566 current/former IDUs who had been tested for anti-HCV and/or HCV RNA by polymerase chain reaction in Greater Glasgow health board between 1993 and 2007 were linked to the national hospitalization database and deaths registry to identify all admissions and deaths from a liver-related condition. Relative risks were estimated using Cox proportional hazards regression for recurrent events. Time at risk was censored at 2 years following an HCV test to address bias owing to unobserved seroconversion. The risk of hospitalization/death from a liver-related or an alcoholic liver-related condition following HCV testing was greater for those IDUs with no prior alcohol-related hospitalization who tested positive [adjusted hazard ratio (HR) = 3.2, 95% CI: 1.5–6.7; 4.9, 95% CI: 1.8–13.1, respectively], compared with those who tested anti-HCV negative, but not for those IDUs with a prior alcohol admission (HR = 0.8, 95% CI: 0.4–1.5; 0.8, 95% CI: 0.4–1.6). There was little evidence for an increased risk of hospitalization/death for an exclusively non-alcoholic liver condition for those testing positive (HR = 1.5, 95% CI: 0.8–2.7), after adjustment for previous alcohol-related admission. Within Glasgow's IDU population, HCV positivity is associated with an increased risk of a liver-related outcome, but this is not observed for those IDUs whose problem alcohol use already increases their risk.

Keywords: alcohol, hepatitis C, hospital admissions, injecting drug users, liver disease.

INTRODUCTION

In Scotland, of the 50 000 persons infected with the hepatitis C virus (HCV), approximately 90% are current or former injecting drug users (IDUs) (Hutchinson *et al.*, 2006). HCV infection is a known aetiological factor for cirrhosis and hepatocellular carcinoma [1,2], but it is often difficult to isolate the role of HCV infection from lifestyle factors – such as problem alcohol use – characteristic of the IDU population [1] in the development of severe liver disease.

Our goal was to determine liver-related morbidity, in terms of hospital utilization, in a large cohort of current/former IDUs who have tested HCV antibody positive (anti-HCV) and/or polymerase chain reaction (PCR) positive (HCV RNA) and compare the risk of hospitalization with those who tested anti-HCV and PCR negative (uninfected).

Abbreviations: GROS, General Register Office for Scotland; HCV, hepatitis C virus; HPS, Health Protection Scotland; ICD, International Classification of Diseases; IDU, injecting drug users; ISD, Information Services Division; PCR, polymerase chain reaction.

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METHODS

Design

The design was a retrospective cohort study, using record linkage between four national databases to estimate liver-related hospitalization/death rates for a large cohort of current/former IDUs who had been tested for HCV infection.

Study population and data sources

Health Protection Scotland (HPS) maintains a database – through sourcing records from the West of Scotland Specialist Virology Centre – of all persons who have been tested for HCV (anti-HCV/HCV RNA) in NHS Greater Glasgow health board. In 2008, for example, 18 000 anti-HCV tests were conducted in this health board (population 1.2 million), representing 25% of all tests Scotland-wide [2]. Test records contain the following non-named information: sex, date of birth, surname Soundex code and forename initial, as well as data concerning risk activities (classified into IDU reported and not-known). We used a deterministic approach (i.e. required complete matches on all identifiers) to map individual tests to distinct persons. Following this step, data for 97 250 individuals who had been tested at least once for HCV between 1993 and 2007 were available. Extra data on risk activities were obtained via deterministic record linkage to the national HIV test database (total of 415 555 HIV tests conducted over the period 1988–2007, among which 36 618 records mention IDU as risk activity) [3], also held by HPS. The study population thus consisted of those individuals tested for HCV in the period 1993–2007, with nonmissing data on sex and date of birth, and who had IDU indicated as risk activity (n = 6566).

The Scottish Morbidity Records (SMR01) held by Information Services Division (ISD) is an episode-based patient record of all acute inpatient and day case hospital discharges from nonobstetric, nonpsychiatric specialities; the period of data used was 1981–2007. Discharge diagnoses are coded according to the World Health Organisation's International Classification of Diseases (ICD) Ninth Revision for discharges before 1996, and Tenth Revision for discharges between 1996 and 2006. ISD routinely combine the SMR01 data with death registrations held by the General Register Office for Scotland (GROS) to form a linked dataset.

Linkage procedure

Data linkage between these national databases provided HIV status and a comprehensive record of all inpatient hospital admissions and deaths for all IDUs on the Glasgow HCV test database. Linkage of records between individuals on the HCV test database and the SMR01/GROS data source was carried out by ISD using probabilistic record-linkage techniques [4]. ISD's probabilistic method involved calculating a score for each HCV test record as a potential match to each SMR01/GROS record. The linked dataset was anonymized before transfer to Health Protection Scotland for analysis. Linkages were approved by the Privacy Advisory Committee, which oversees confidentiality issues involving data held on NHS Scotland patients.

Data analysis

Outcome measures

For each IDU on the Glasgow HCV test database, the occurrence of any liver-related hospital admissions or death subsequent to their first HCV test was noted by searching the linked hospitalization/death records for liver-related discharge diagnosis/cause-of-death codes in either the main or a supplementary diagnosis/cause-of-death field. The relevant codes comprised alcohol-related: *alcoholic liver disease* (ICD-10 K70; ICD-9 571.0–571.2) and nonalcohol-related codes: *liver cancer* (ICD-10 C22; ICD-9 155), *nonalcoholic liver disease* (ICD-10 K71–77; ICD-9 570, 571.4–571.9, 572–573), *viral hepatitis* (ICD-10 B15–19; ICD-9 070), and *sequelae of viral hepatitis* (ICD-10 B94.2, R18, I85.0, I98.2; ICD-9 789.5, 456.0). Supplementary analyses were conducted for outcomes defined as at least one alcoholic liver-related code and for at least one nonalcoholic liver-related code (with the additional constraint that all other diagnosis/cause-of-death codes present for that episode did not specify an alcoholic liver-related condition). The latter analysis attempts to remove outcomes that may have been attributable to alcohol rather than HCV infection.

Epidemiological risk factors

Additional risk factors coded for each IDU were sex, age and a time-dependent variable for the occurrence of at least one previous alcohol-related hospitalization. Defining the latter covariate involved searching the linked hospital/death records for alcohol-related discharges occurring prior to the date of first mention of a liver-related condition, or at any time between 1 January 1981 and 31 December 2007 if the individual had never been admitted/died with a liver-related condition. This binary variable was included to adjust for the influence of problematic levels of alcohol intake. The relevant codes comprised *alcohol use* (ICD-10 Z72.1), *mental and behavioural disorders due to use of alcohol* (ICD-10 F10; ICD-9: 291, 303, 305), *degeneration of nervous system due to alcohol* (ICD-10 G31.2, G62.1, G72.1, I42.6, K29.2; ICD-9 357.5, 425.5, 535.3), *toxic effects of alcohol* (ICD-10 T51.0, T51.9; ICD-9 980.0), *alcohol-induced chronic pancreatitis* (ICD-10 K86.0), *evidence of alcohol involvement* (ICD-10 Y90-1), *finding of alcohol in blood* (ICD-10 R78.0; ICD-9 790.3), *alcohol rehabilitation* (ICD-10 Z50.2) and *accidental or intentional self-poisoning by and exposure to alcohol* (ICD-10 X45, X65; ICD-9 E860.0, E860.9).

Finally, a time-dependent covariate with three levels was defined for HCV test result (anti-HCV negative, anti-HCV/HCV RNA positive and ±30 days around HCV test date, irrespective of whether positive or negative). The latter category was included to discount the effect of referral for an HCV test around the time of presentation/death with a liver-related condition. The first category includes persons for whom the PCR result is not known (or was not tested on the

same occasion); the second category also includes persons who tested HCV RNA negative, but the anti-HCV result is not known (or was not tested on the same occasion), on the assumption that PCR testing is routinely carried out on anti-HCV-positive individuals only. The first two categories are intended to represent (i) those who have never been infected with HCV (anti-HCV negative) and (ii) those who have been infected in the past with or without detectable viraemia, or with unknown PCR status (anti-HCV/HCV RNA positive).

Statistical analysis

Cox proportional hazards regression for recurrent events [5] was used to estimate the unadjusted relative risk of a liver-related hospital admission (or death with a liver-related cause) associated with sex, current age, HCV test result (time-dependent), previous alcohol-related admission (time-dependent) and HIV test result, among all IDUs. Adjusted relative risks were computed for HCV test result controlling for sex and current age only. Tests for an HCV test result by previous alcohol interaction were conducted; if inclusion of this interaction term significantly improved model fit according to the Akaike Information Criterion, the hazard ratios for HCV test result are presented separately for the two levels of previous alcohol-related admission.

To facilitate analysis of multiple outcomes for the same individual, time at risk was divided into risk periods, where the first risk period was defined to begin on the date of the first HCV test in which a positive or negative result was obtained (in the period 1993–2007), and subsequent risk periods were defined to begin at the date of discharge of the previous hospital episode (for any cause) or subsequent HCV test. Each risk period ended at the earlier of the next hospital admission (for any cause), death from any cause, 2 years following an HCV test if no subsequent test was carried out within this period (censoring at 2 years following an HCV test addresses potential bias owing to unobserved seroconversion or viral clearance), or 31 December 2007. For computational ease, only the first 10 HCV tests per individual were analysed in this way [0.5% of individuals had more than 10 tests performed in the period 1993–2007 (Table 1)]. Time at risk excluded stays in hospital (one cannot be at risk for admission if already in hospital). Data for 149 IDUs were excluded from analysis because their first test was post-mortem. Analysis was performed using data for the remaining 6417.

Rates were computed as the expected number of admissions/deaths per 1000 person-years of follow-up, under the assumption that counts are negative binomially distributed. Negative binomial distributions are to be preferred in the

Table 1 Baseline characteristics of the study population of 6417 IDUs who had undergone HCV testing in Greater Glasgow health board between 1 January 1993 and 31 December 2007, and for whom either a positive or a negative test result was obtained

			First HCV test result		
Variable	Level	Total (col%)	anti-HCV− (%)	anti-HCV+/ HCV RNA+ (%)	Prevalence
Sex	Male	4565 (71.1)	1877 (70.1)	2688 (71.9)	58.9
	Female	1852 (28.9)	802 (29.9)	1050 (28.1)	56.7
Age at 1st HCV test (years)	<25	1319 (20.6)	764 (28.5)	555 (14.8)	42.1
	25–34	3305 (51.5)	1368 (51.1)	1937 (51.8)	58.6
	35–44	1522 (23.7)	443 (16.5)	1079 (28.9)	70.9
	45+	271 (4.2)	104 (3.9)	167 (4.5)	61.6
Calendar period of 1st HCV test	1993–1998	1179 (18.4)	331 (12.4)	848 (22.7)	71.9
	1999–2001	1780 (27.7)	708 (26.4)	1072 (28.7)	60.2
	2002–2004	1944 (30.3)	917 (34.2)	1027 (27.5)	52.8
	2005–2007	1514 (23.6)	723 (27.0)	791 (21.2)	52.2
Previous alcohol-related admission	No	5029 (75.6)	2306 (86.1)	2723 (72.8)	54.1
	Yes	1388 (24.4)	373 (13.9)	1015 (27.2)	73.1
HIV status	Positive	84 (1.3)	25 (0.9)	59 (1.6)	70.2
	Negative	5801 (90.4)	2346 (87.6)	3455 (92.4)	59.6
	Not tested/NK	532 (8.3)	308 (11.5)	224 (5.0)	42.1
Number of HCV tests during 1993–2007	1 only	3725 (59.4)	1842 (68.7)	1883 (50.4)	50.6
	2–10	2658 (40.0)	827 (30.9)	1831 (49.0)	68.9
	>10	34 (0.6)	10 (0.4)	24 (0.6)	29.4

Prevalence, percentage of anti-HCV/HCV RNA positive; anti-HCV− refers to those who have never been infected with HCV; anti-HCV/HCV RNA positive refers to those who have been infected with HCV, with or without detectable viraemia; HCV, hepatitis C virus; IDU, injecting drug users.

presence of overdispersion (i.e. when the variance of event counts is larger than the mean) [6]. All statistical analyses were carried out using R version 2.7.2 [7].

RESULTS

Characteristics of the study population

Table 1 shows the characteristics of the IDU study population (n = 6417). The majority of those were men (71%), with 75% aged 25–44 years at first HCV test. Ninety-two per cent had ever been tested for HIV, and 1.3% tested HIV positive. On 38% (2364/6186) of the occasions in which an antibody test was carried out, a PCR test was also conducted (Table 2). Almost all (99%) of those who tested anti-HCV negative were not PCR tested on the same date; given the rare detection of HCV RNA positives among IDUs who test anti-HCV negative [8,9], then we estimate that the majority (>95%) of anti-HCV negatives will also be RNA negative. Among those who initially tested anti-HCV positive, 67% (2348/3506) were tested by PCR on the same occasion and 71% (1672/2348) of these tested HCV RNA positive; thus, we estimate that approximately 70% of IDUs initially testing anti-HCV positive (including those with PCR status not known/not tested) were also HCV RNA positive.

The prevalence of an anti-HCV positive and/or RNA positive first HCV test result was greatest for men (59%), those in the 35–44 years age group at first HCV test (71%), those first tested for HCV before 1999 (72%), those with a prior alcohol-related hospitalization (73%) and those who had tested HIV-positive (70%) (Table 1).

Liver-related hospitalization/death

Follow-up time ranged from 0 to 11.4 years (median: 2.0 years). There were a total of 1068 events (741 admissions/327 deaths) with mention of a liver-related condition among IDUs during follow-up (Table 3a). The fitted liver-related admission/death rate for the entire study population was 102 per 1000 person-years (95% CI: 83–125); 322/1000 (95% CI: 242–429) and 59/1000 (95% CI: 44–80) for those with and without a prior alcohol-related hospitalization, respectively. Figure 1 shows fitted rates for anti-HCV-negative and anti-HCV/HCV RNA-positive test results separately as a function of prior alcohol-related admission.

Table 2 Cross-tabulation of anti-HCV and HCV RNA test results at initial test, for 6417 IDUs who had undergone testing in Greater Glasgow health board only between 1 January 1993 and 31 December 2007 and for whom either a positive or a negative test result was obtained

	HCV RNA result at initial test			
anti-HCV at Initial Test	+	−	NK/NT	Total
+	1672	676	1158	3506
−	1	15	2664	2680
NK/NT	203	28	0	231
Total	1876	719	3822	6417

NK, not known; NT, not tested; HCV, hepatitis C virus; IDU, injecting drug users.

The relative risk of admission/death for a liver-related condition, adjusted for sex, current age and HCV test result, was much higher for those with a prior alcohol-related admission [hazard ratio (HR) = 16.6, 95% CI: 7.4–37.2]. The relative risk of admission/death for only those IDUs with no previous alcohol-related admission was greater for those who tested positive compared with those who tested negative (HR = 3.2, 95% CI: 1.5–6.7), and there was a very high relative risk of liver-related admission/death in the 30 day period surrounding an HCV test (HR = 20.9, 95% CI: 10.3–42.3). For those with at least one prior alcohol-related admission, there was an elevated relative risk associated with HCV test date ±30 days only (HR = 4.5, 95% CI: 2.7–7.5).

Adjusted hazard ratios for HCV test result in which the outcome was admission/death with mention of an alcoholic liver-related condition (Table 3b) were comparable to the hazard ratios obtained for any liver-related condition as outcome. First, there was a high relative risk of admission/death for an alcoholic liver-related condition for those with a previous alcohol-related admission (HR = 32.2, 95% CI: 11.6–89.1). For those IDUs with no previous alcohol-related admission, hazard ratios were: anti-HCV/HCV RNA-positive test result: HR = 4.9, 95% CI: 1.8–13.1; HCV test date ±30 days: HR = 28.4, 95% CI: 10.8–74.4. For those with at least one previous alcohol-related admission, hazard ratios were anti-HCV/HCV RNA-positive test result: HR = 0.8, 95% CI: 0.4–1.6; HCV test date ±30 days: HR = 4.2, 95% CI: 2.4–7.3.

In the analysis of admissions/deaths for exclusively non-alcoholic liver conditions (Table 3c) as the outcome (n = 321), including an interaction term did not improve model fit. There was an elevated, although nonsignificant, risk of a nonalcoholic liver-related admission/death following an anti-HCV/HCV RNA-positive (HR = 1.5, 95% CI: 0.8–2.7) test result and an elevated risk of HCV test date ±30 days (HR = 11.0, 95% CI: 6.0–20.3), compared with those who tested anti-HCV negative.

In supplementary analyses (not reported), we conducted regression analyses with the anti-HCV/HCV RNA-positive category separated into RNA positive (those who have been infected in the past, with viraemia detectable) and anti-HCV positive (those who have been infected but with no detectable viraemia, or with unknown PCR status); adjusted hazard ratios were very similar, with overlapping 95% confidence intervals, indicating that aggregation of the two

Table 3 Relative risk of hospitalization/death in the period 1 January 1993 to 31 December 2007 with a (a) liver-related diagnosis, (b) alcoholic liver-related diagnosis and (c) nonalcoholic liver-related diagnosis, in IDUs who have been tested for HCV in the Greater Glasgow health board (and with either a positive or a negative anti-HCV and/or HCV RNA test result) between 1 January 1993 and 31 December 2007. $N = 6417$

Factor	Level	*N*	Rate	95% CI	HR	95% CI	AdjHR	95% CI
(a) Admission/death with mention of a liver-related condition ($n = 1068$ outcomes)								
Sex	Female	222	69	46–102	Ref.			
	Male	846	116	92–148	1.75	1.51–2.03	1.54	1.00–2.36
Current age (years)*	<30	84	15	9–24	0.16	0.13–0.20	0.21	0.12–0.37
	30–39	686	127	97–167	Ref.			
	40+	298	305	213–438	1.30	1.13–1.49	1.12	0.76–1.63
Previous alcohol adm*	None	441	59	44–80	Ref.			
	Yes	627	322	242–429	5.51	4.88–6.23	16.6	7.40–37.2
No previous alcohol adm								
HCV test result	anti-HCV−	36	10	5–20	Ref.			
	anti-HCV/HCV RNA+	221	62	40–94	3.86	2.71–5.49	3.17	1.51–6.65
	±30 days of test	184	187	141.6–247.1	23.5	16.4–33.7	20.9	10.3–42.3
Previous alcohol adm								
HCV test result	anti-HCV−	87	166	94–292	Ref.			
	anti-HCV/HCV RNA+	320	271	184–399	1.01	0.80–1.28	0.77	0.39–1.49
	±30 days of test	220	957	705–1298	5.72	4.46–7.34	4.51	2.70–7.53
HIV status	Negative	902	94	75–117	Ref.			
	Positive	16	63	18–217	0.92	0.56–1.52	–	–
	NT/NK	150	211	118–375	1.65	1.38–1.97	–	–
(b) Admission/death with mention of an alcoholic liver-related condition ($n = 747$ outcomes)								
Sex	Female	139	49	27–90	Ref.			
	Male	608	85	62–118	1.99	1.65–2.39	1.74	0.99–3.06
Current age (years)*	<30	31	6	2–19	0.09	0.06–0.13	0.12	0.05–0.31
	30–39	507	100	71–141	Ref.			
	40+	209	214	132–346	1.18	1.00–1.39	0.99	0.63–1.55
Previous alcohol adm*	None	259	43	26–69	Ref.			
	Yes	488	239	168–339	7.37	6.34–8.58	32.2	11.6–89.1
No previous alcohol adm								
HCV test result	anti-HCV−	15	12	3–47	Ref.			
	anti-HCV/HCV RNA+	142	40	22–71	6.09	3.57–10.3	4.89	1.82–13.1
	±30 days of test	102	109	69–173	32.5	18.9–56.0	28.4	10.8–74.4
Previous alcohol adm								
HCV test result	anti-HCV−	72	131	70–248	Ref.			
	anti-HCV/HCV RNA+	251	182	116–287	0.98	0.75–1.27	0.75	0.36–1.58
	±30 days of test	165	720	501–1034	5.27	3.99–10.4	4.18	2.38–7.34
HIV status	Negative	631	67	49–92	Ref.			
	Positive	9	37	7–187	0.88	0.46–1.70	–	–
	NT/NK	107	177	82–383	1.57	1.28–1.94	–	–
(c) Admission/death with mention of a nonalcoholic liver condition, and this admission/death has no mention of an alcoholic liver-related condition ($n = 321$ outcomes)								
Sex	Female	83	20	14–29	Ref.			
	Male	238	25	20–32	1.36	1.06–1.75	1.20	0.80–1.80
Current age (years)*	<30	53	9	6–14	0.34	0.25–0.46	0.40	0.23–0.70
	30–39	179	26	19–34	Ref.			
	40+	89	67	46–97	1.65	1.27–2.14	1.51	0.99–2.30
Previous alcohol adm*	None	182	15	12–20	Ref.			
	Yes	139	68	49–93	2.88	2.30–3.59	2.41	1.67–3.48
HCV test result	anti-HCV−	36	6	4–9	Ref.			
	anti-HCV/HCV RNA+	148	23	17–31	2.16	1.50–3.11	1.47	0.79–2.73
	±30 days of test	137	109	85–140	15.0	10.4–21.7	11.0	6.01–20.3

Table 3 (Continued)

Factor	Level	*N*	Rate	95% CI	HR	95% CI	AdjHR	95% CI
HIV status	Negative	271	22	17–27	Ref.			
	Positive	7	27	8–86	1.00	0.46–2.13	–	–
	NT/NK	43	44	26–75	1.86	1.34–2.59	–	–

Previous alcohol adm refers to alcohol-related admission(s) prior to admission/death with mention of a liver-related code. *N*, number of hospital episodes; Rate, fitted number of episodes per 1000 person-years of follow-up, assuming negative binomially distributed data [6]; HR, hazard ratio; AdjHR, hazard ratio adjusting for sex, current age, anti-HCV/HCV RNA test result, and previous alcohol admission [with interaction with HCV test result in (a) and (b)]; CI, confidence interval; NT/NK, not tested/not known; HCV, hepatitis C virus; IDU, injecting drug users. *Time-dependent variable.

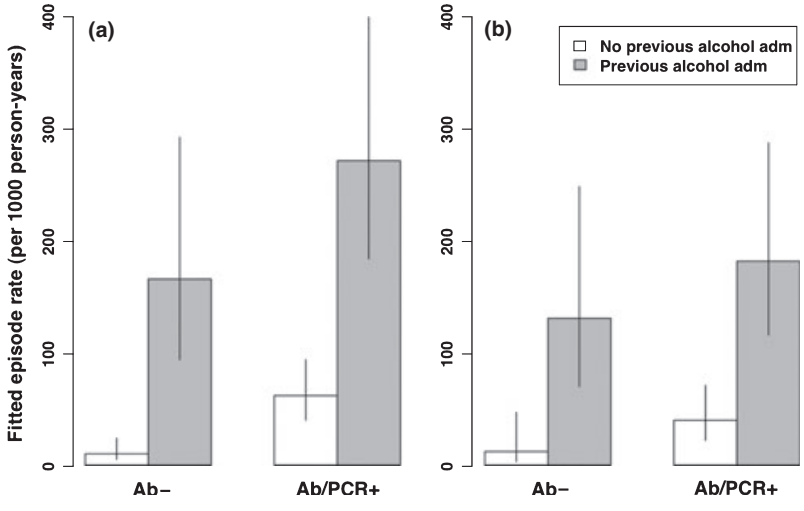

Fig. 1 Fitted admission/death rates as a function of hepatitis C virus test result and whether the individual had a previous alcohol-related hospitalization, for (a) episodes with any liver-related discharge diagnosis/cause of death and (b) episodes with at least one alcoholic liver-related diagnosis/cause of death. Lines indicate 95% confidence intervals.

positive HCV test status categories in the analysis was justified.

DISCUSSION

Injecting drug users in Scotland's Greater Glasgow health board who tested anti-HCV positive and/or HCV RNA positive for HCV infection had an up to threefold increased risk of developing liver disease, as indexed by hospital admission/death for a liver-related condition. Importantly, this study compared IDUs testing HCV positive with those testing negative, within the same geographical region, and so a degree of control regarding lifestyle factors and socio-economic variables was attained. Additional control for problem alcohol use, thus clarifying the unique association between HCV infection and liver disease, was carried out via inclusion of an indicator variable for previous alcohol-related hospitalization and fitting an interaction between this variable and HCV test result in the regression analysis.

Risk was significantly increased for those testing anti-HCV/HCV RNA positive compared with anti-HCV negative, but for only those IDUs with no previous alcohol-related hospital admission. As the latter variable serves as a proxy for problem alcohol use [10], the lack of statistically significant association between a positive HCV test result and a liver-related outcome for those who had a previous alcohol-related admission may relate to a high baseline risk of hospital admission/death for a liver-related condition in this relatively young cohort of IDUs (median age = 31.2 years at start of follow-up) and suggests that alcohol is the predominant factor responsible for liver disease progression. This is consistent with the results of the subanalysis where the outcome definition was restricted to alcohol liver-related codes, in which there was a stronger association between an anti-HCV/HCV RNA-positive test result and outcome for those IDUs who had no previous alcohol-related hospital admission (adjusted HR of 4.9 compared with 3.1 for all liver conditions). In addition, prior alcohol-related admission was strongly associated with outcome in the main analysis and in both subanalyses (adjusted HRs ranged from 2.4 to 32.2).

Results of the subanalysis restricting the outcome definition to nonalcoholic liver-related admission/deaths, where no other diagnosis/cause-of-death code mentioned alcoholic liver disease, suggest that for our relatively young study population, the risk of developing nonalcoholic liver disease within the follow-up period (median time to first admission

of 1.4 years, interquartile range: 0.3–3.9 years) was not appreciably elevated by HCV infection alone, after adjustment for previous alcohol-related admission which appeared to be a strong cofactor.

We observed a highly elevated relative risk of a liver-related admission/death within 30 days preceding or following an HCV test, indicating that referral for HCV testing often occurred around the time of clinical presentation with severe disease. By specifying HCV test result as a time-dependent covariate with an explicit level for within ±30 days of test in the regression analysis, we were able to reduce the effects of referral bias.

This study adds to the research base on the risk of severe liver disease associated with HCV infection [11], through retrospective follow-up of a study population at risk of accelerated progression caused by excessive alcohol consumption [1,12]. The ethical, inexpensive record-linkage technique we used allowed investigation of our research question using a much larger cohort of IDUs than is normally viable if conducted with clinical study populations [13,14]. Although other population-based studies have reported excess liver-related morbidity, (i.e. hospital admissions) in individuals diagnosed with HCV [15,16], we have demonstrated an increased relative risk of a liver-related hospitalization/death in individuals testing anti-HCV and/or HCV RNA positive compared with those testing negative, in Scotland's largest regional IDU population.

We found an overall prevalence of anti-HCV and/or HCV RNA positive of 58% at first HCV test among 6417 IDUs tested in 1993–2007; this is lower than the prevalence of 72% observed among 1949 IDUs interviewed during community-wide voluntary anonymous surveys in Glasgow during 1990–1996 [17], because IDUs will tend to be younger and to have been injecting for fewer years at the time of their first HCV test.

The primary limitation of our methods was the limited recording of IDU status on the Glasgow HCV test database (of those anti-HCV/HCV RNA positive at first test, only 7.3% were reported as IDU from routine virology test forms; this increased to 41% after linkage to the HIV test database). The second limitation was the lack of regular (annual) HCV testing of IDUs. To put our findings in perspective, among 947 IDUs recruited in 2008/2009 from needle-exchange services across Glasgow using a cross-sectional voluntary anonymous survey approach, 72% had ever been tested for HCV but only 26% had been tested in the last year [18]. To minimize information bias owing to unobserved seroconversion or spontaneous viral clearance, we discounted follow-up time 2 years subsequent to an HCV test if a further test was not carried out within that period. Seroconversion within this 2 year period would result in the incorrect assignment of follow-up time to anti-HCV-negative test status. However, we carried out sensitivity analyses (not reported) on the size of this period from 1 to 3 years, in 6 months steps, and found the estimated relative risks to be quite robust.

A third limitation concerns variation in the length of time between the event of an IDU becoming infected with HCV and being referred for their first HCV test (this is particularly an issue for the early part of the analysis period, when HCV test uptake in Greater Glasgow among patients with end-stage liver disease was lowest [13% for 1993–1997] [19]). The risk of developing severe liver disease will be much higher for those IDUs infected many years before their first HCV test. Indeed, 33% of those IDUs whose first HCV test was positive were 35 years of age or older; but, given that the age of commencement of injecting drug use averages 20 years, then many in this age group will have been first tested at least 15 years after first injecting drugs (and acquiring the virus). Because we lacked information on date of infection, the relative risk estimated for a positive test result will be attenuated owing to 'missing' HCV-positive follow-up time that more accurately reflects the natural history of HCV infection. A related concern is the unknown degree of presentation bias: those IDUs who are tested for HCV (e.g. those admitted to hospital) may be at higher risk of developing liver disease than IDUs in general.

Finally, an unknown degree of bias will be present because of the limitations of record linkage with incomplete or missing identifiers, which will influence our estimates of the relative risks associated with HCV test result. Unrecovered linkages between the HCV test database and the SMR01/GROS records will result in attenuated relative risks if positive outcome HCV tests fail to be linked to a liver-related hospital admission.

This is the largest study to our knowledge that estimates the relative risk of a liver-related outcome in a regional population of HCV-tested current/former IDUs. Using inexpensive electronic record linkage of national data sources, the current study provides evidence, for health service policy-makers and providers, of the need to dedicate resources to the prevention, diagnosis and treatment of HCV infection. However, associated problem drinking is common in this cohort and is also important to address. The main finding of our study is that excessive alcohol use causes major pathology in this population, and together with HCV infection, this results in an increased risk of admission/death from liver disease.

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CONFLICT OF INTEREST

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