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DOI:

[10.1016/j.jhep.2017.10.019](https://doi.org/10.1016/j.jhep.2017.10.019)

Publication date:

2018

Document Version

Peer reviewed version

[Link to publication in ResearchOnline](#)

Citation for published version (Harvard):

Alavi, M, Janjua, NZ, Chong, M, Grebely, J, Aspinall, EJ, Innes, H, Valerio, HM, Hajarizadeh, B, Hayes, PC, Krajdén, M, Amin, J, Law, MG, George, J, Goldberg, DJ, Hutchinson, SJ & Dore, GJ 2018, 'The contribution of alcohol-use disorder to decompensated cirrhosis among people with hepatitis C: an international comparison study', *Journal of Hepatology*, vol. 68, no. 3, pp. 393-401. <https://doi.org/10.1016/j.jhep.2017.10.019>

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The contribution of alcohol-use disorder to decompensated cirrhosis among people with hepatitis C: an international comparison

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Word Count (including the abstract, references, tables and figure legends)

4,886

Tables

4

Figures

2

List of abbreviations in the order of appearance

hepatitis C virus (HCV); direct acting antiviral (DAA); World Health Organization (WHO); alcohol-use disorder (AUD); British Columbia (BC); New South Wales (NSW); decompensated cirrhosis (DC); British Columbia Hepatitis Testers Cohort (BC-HTC); Classification of Diseases and Related Health Problems (ICD-10); Notifiable Conditions Information Management System (NCIMS); person-years (PY); population attributable fraction (PAF); adjusted hazard ratio (aHR).

Keywords

HCV; liver disease; alcohol-use disorder; population-based; data linkage

Conflict of interest statements

J Grebely has received research support and personal fees from Gilead Sciences and Merck. J Grebely has received research support from Abbvie, Bristol-Myers Squibb, and Cepheid. HI has received personal fees from Gilead Sciences. PCH has received research support and personal fees from Roche. PCH has received personal fees from MSD, Gilead Sciences, Abbvie, Janssen, Bristol-Myers Squibb, Pfizer, and Novartis. MK has received research support (via his institution) from Roche, Boehringer Ingelheim, Merck, Siemens Healthcare Diagnostics, and Hologic Inc. MGL has received research support from Boehringer Ingelheim, Merck, Bristol-Myers Squibb, Janssen, and ViiV HealthCare. MGL has received research support and personal fees from Gilead Sciences. MGL has received personal fees from Sirtex Pty Ltd. J George has received personal fees from MSD, Gilead Sciences, Bristol-Myers Squibb, Abbvie, and Pharmaxis. DJG has received personal fees from Gilead Sciences, Merck, and Abbvie. GJD has received research and travel support, and personal fees from Abbvie, Merck, Bristol-Myers Squibb, and Roche. GJD has received research support and personal fees from Janssen. GJD has received personal fees and travel support from Gilead Sciences. GJD has received personal fees from GlaxoSmithKline and Abbott Diagnostics. Other authors have no commercial relationships that might pose a conflict of interest in connection with this manuscript.

Financial support statement

The BC component of this work was supported by British Columbia Centre for Disease Control and the Canadian Institutes of Health Research [Grant # 201410PHE-337680-PHE-CAAA-179547]. The authors acknowledge the assistance of BC Centre for Disease Control, Provincial Health Services Authority Performance measurement and reporting, Information Analysts, BC Ministry of Health Data Access, Research and Stewardship, MSP, Discharge Abstract Database, and Medical Beneficiary and Pharmaceutical Services programme areas, BC Ministry of Health, and BC Cancer Agency and their staff involved in data access and procurement, and data management. The NSW component of this work was supported by the Kirby Institute. Kirby Institute is funded by the Australian Government Department of Health, under the agreement ID number 2-D3X513. This publication is part of the Bloodborne viruses and sexually transmissible infections Research, Strategic Interventions and Evaluation (BRISE) program, funded by the NSW Ministry of Health. This publication has received funding from the Sydney West Translational Cancer Research Centre (SW-TCRC) program “HOTTer-West: HCC Outcome improvements Through Translational research in WESTern Sydney. The Scottish component of this work was funded by the Scottish Government. The authors acknowledge the assistance of Health Protection Scotland, Information Services Division, Hepatitis C Clinical Database Monitoring Committee, the clinics and staff supporting the Hepatitis C Clinical Database, and the laboratories and staff supporting the Hepatitis C diagnosis and testing databases.

MA is the recipient of a CASCADE International Fellowship. The research leading to these results has received funding from the People Programme (Marie Curie Actions) of the European Union’s Seventh Framework Programme (FP7/2007-2013) under REA grant agreement No PCOFUND-GA-2012-600181. J Grebely is supported by a National Health

and Medical Research Council (NHMRC) of Australia Career Development Fellowship. BH is supported by an NHMRC of Australia Early Career Fellowship. GJD is supported through an NHMRC of Australia Practitioner Fellowships. J George is supported by an NHMRC of Australia Program Grant (1053206), project grants (632630, 1049857), a Sydney West Translational Cancer Research Centre grant funded by the Cancer Institute NSW, and the Robert W. Storr Bequest to the Sydney Medical Foundation, University of Sydney

Ethics statement

This publication involved information already collected by population-based health administration registries; therefore, people have not been ‘recruited’ for the purposes of this research. A waiver of consent has been approved for each component of this work, by the relevant ethics committees in BC and NSW, and the Scottish Government. The BC component of this work has received ethics approval from the Behavioural Research Ethics Board, Office of Research Services, University of British Columbia (reference number H14-01649). The NSW component of this work has received ethics approval from NSW Population & Health Services Research Ethics Committee, Cancer Institute NSW (reference number HREC/13/CIPHS/63). The Scottish component of this work has utilised information within the surveillance framework of National Services Scotland. Approval for updating the linkage was granted by the National Services Scotland Public Benefit Privacy Panel.

Author contributions

MA, NZJ, and GJD contributed to study conception and design, data acquisition and analysis, interpretation of findings, and drafting of the manuscript; MC, J Grebely, EJA, HI, H MV, BH, and JA contributed to data acquisition and analysis and interpretation of findings, and;

PCH, MK, MGL, J George, DJG, and SJH contributed to study conception and design, data acquisition and analysis, and interpretation of findings.

Disclaimer

All inferences, opinions, and conclusions drawn in this publication are those of the author(s), and do not necessarily reflect the opinions or policies of the British Columbia Ministry of Health, Australian Government Department of Health, or the Scottish Government.

Abstract (261 words)

Background: The aim of this study was to evaluate the contribution of alcohol-use disorder to hepatitis C virus (HCV)-related decompensated cirrhosis diagnosis in three settings.

Methods: HCV notifications from British Columbia (BC), Canada, New South Wales (NSW), Australia, and Scotland (1995-2011/2012/2013, respectively) were linked to hospital admissions (2001-2012/2013/2014, respectively). Alcohol-use disorder was defined by non-liver-related hospitalisation due to alcohol use. Age-standardised decompensated cirrhosis incidence rates were plotted, associated factors were assessed using Cox regression, and alcohol-use disorder-associated population attributable fractions (PAFs) were computed.

Findings: Among 58,487, 84,529, and 31,924 people with HCV in BC, NSW, and Scotland, 2,689 (4.6%), 3,169 (3.7%), and 1,375 (4.3%) had a decompensated cirrhosis diagnosis, and 28%, 32%, and 50% of those with decompensated cirrhosis had alcohol-use disorder, respectively. Age-standardised decompensated cirrhosis incidence rates were considerably higher among people with alcohol-use disorder in NSW and Scotland. Decompensated cirrhosis was independently associated with alcohol-use disorder in BC, aHR 1.92, 95% CI 1.76, 2.10; NSW, aHR 3.68, 95% CI 3.38, 4.00, and; Scotland, aHR 3.88, 95% CI 3.42, 4.40. The PAFs of decompensated cirrhosis-related to alcohol-use disorder were 13%, 25%, and 40% in BC, NSW, and Scotland, respectively. **Interpretation:** Alcohol-use disorder was a major contributor to HCV liver disease burden in all settings, more distinctly in Scotland. The extent to which alcohol use would compromise the individual and population level benefits of direct-acting antiviral therapy (DAA) needs to be closely monitored. Countries, where appropriate, must develop strategies combining DAA treatment uptake promotion and alcohol-use disorder management, if World Health Organization 2030 HCV mortality reduction targets are to be achieved.

Lay Summary

The burden of advanced liver disease has been rising among people with hepatitis C globally. The prospect of increased access to direct-acting antiviral (DAA) therapies instigated the World Health Organization (WHO) to set ambitious targets for elimination of hepatitis C as a major public health threat by 2030. However, continued heavy alcohol intake is likely to impact potential benefits of DAA-based cure on individual-level liver disease progression and population-level liver disease burden. The aim of this study was to evaluate the contribution of alcohol-use disorder to hepatitis C-related decompensated cirrhosis diagnosis in British Columbia, Canada, New South Wales, Australia, and Scotland. Alcohol-use disorder was a major contributor to hepatitis C-related liver disease burden in all settings, more distinctly in Scotland. The extent to which alcohol use would compromise the individual and population level benefits of DAA-based therapies needs to be closely monitored. Countries, where appropriate, must develop strategies combining DAA treatment uptake promotion and alcohol-use disorder management, if WHO 2030 hepatitis C mortality reduction targets are to be achieved.

Introduction

The burden of advanced liver disease has been rising among people with hepatitis C virus (HCV) infection globally [1]. The prospect of increased access to direct-acting antiviral (DAA) therapies instigated the World Health Organization (WHO) to set ambitious targets for elimination of hepatitis C as a major public health threat by 2030 [2]. However, in settings with higher levels of alcohol-use disorder (AUD), the potential for HCV treatment programs to achieve the WHO liver mortality reduction target of 65% could be compromised, without developing concurrent strategies to reduce the consumption and impact of alcohol.

Action against AUD is particularly important given that people with HCV infection are more likely to engage in harmful consumption [3], and alcohol is a risk factor for higher liver-related mortality [4]. However, given the limited number of population-based studies, the relative contribution of AUD to the burden of liver disease in different HCV populations is not clear. The WHO HCV elimination strategy has highlighted the need to address alcohol use as a common co-morbidity among people with HCV infection [2]; yet, reducing the impact of alcohol is not included among target areas. Restriction of access to DAA treatment on the basis of ongoing alcohol use is present in many settings [5, 6], further potentially impacting treatment programs in WHO regions with higher per capita alcohol consumption [7].

Globally, British Columbia (BC), Canada, New South Wales (NSW), Australia, and Scotland are among the few settings with established surveillance systems that enable monitoring people with HCV infection, by linkage between HCV diagnosis databases and hospitalisation records. The aim of this study was to evaluate the contribution of AUD to population level decompensated cirrhosis (DC) diagnosis among people with an HCV notification.

Materials and methods

Data sources and record linkages

BC, Canada

The British Columbia Hepatitis Testers Cohort (BC-HTC) holds records of all individuals tested for HCV, HBV, and HIV at the BC Centre for Disease Control Public Health Laboratory, since 1992, or reported as a confirmed case of HCV, HBV, and HIV/AIDS, since 1990.[8] At the end of each episode of admission, all BC hospitals submit their hospitalisation records (including demographic, administrative, and diagnosis information) directly to the Canadian Institute of Health Information for inclusion in the Discharge Abstracts Database, since 1985 [9]. All hospitalisation records are coded using the 10th revision of the Classification of Diseases and Related Health Problems (ICD-10), since 2001. Information on all deaths registered in BC are held by the BC Vital Statistics Agency, since 1985 [10]. Using personal health numbers assigned to each individual in BC, BC-HTC records were deterministically linked to hospitalisation and mortality datasets. Record linkages were carried out by the BC Centre for Disease Control and BC Ministry of Health [8].

NSW, Australia

The NSW Notifiable Conditions Information Management System (NCIMS) holds records of all individual with positive HCV and HBV serology tests, notified of diagnoses via mandatory notification procedures, since 1991 [11]. National HIV Registry holds records of all notifications of HIV infection, since 1985 [12]. NSW Admitted Patient Data Collection covers all inpatient admissions from all hospitals in NSW, since 2001 [11]. Each hospitalisation record includes demographic, administrative and diagnosis information coded at discharge according to ICD-10 [11]. Information on all deaths registered in NSW are held

by the Registry of Births, Deaths and Marriages, since 1993 [11]. Using demographic details (including full name, gender, date of birth, and address), probabilistic linkages of records between the NCIMS, hospitalisation, and mortality datasets were undertaken by the NSW Centre for Health Record Linkage [11].

Scotland

Health Protection Scotland holds records of all individuals with positive HCV and HBV serology tests since 1991 and 1998, respectively [13]. Notifications of HIV diagnosis have been recorded since 1981 [13]. Hospital admission data are available from the Scottish Morbidity Records, comprising all Scottish hospitalisations since 1981, including demographic, administrative and diagnosis information coded at the end of each episode of admission (according to ICD-10 since 1996) [13]. Information on all deaths registered in Scotland are held by the National Records of Scotland, since 1980 [14]. Using unique identifiers and demographic details (including forename initial, surname Soundex, gender, date of birth, and postcode district of residence), a combination of deterministic and probabilistic linkages of records between the HCV notifications, hospitalisation, and mortality datasets were undertaken by Information Services Division Scotland [13].

Study period

In BC, NSW, and Scotland, HCV notifications were extracted for the study period between 1 January 1995 and 31 December 2011, 2012, and 2013, respectively, and; linked hospitalisation records were extracted for the study period between 1 January 2001 and 31 December 2012, 2013, and 2014, respectively. In each setting, linked mortality records were extracted for the study period between 1 January 1995 and the latest date of available hospitalisation data.

Study outcome

The primary outcome of interest was first-time hospitalisation due to DC. A hospital discharge diagnosis code (ICD-10) was used to infer diagnosis of DC; coded in either the principal or secondary diagnosis fields of a linked inpatient hospital record. The set of relevant codes included: ascites (R18), bleeding oesophageal varices (I85.0 and I98.3), chronic hepatic failure (including hepatic encephalopathy) (K72.1 and K72.9), alcoholic hepatic failure (K70.4), and hepatorenal syndrome (K76.7). Hereafter, a first-time DC hospital admission is referred to as DC diagnosis.

Exclusion criteria

Exclusion criteria were applied as follows: records where date of birth was missing, and records where the date of HCV notification occurred more than three months after date of death (post-mortem notification), or prior to January 1, 1995.

Statistical analysis

Among people with an HCV notification in each setting, trends in DC diagnosis numbers and age at DC diagnosis were evaluated. Age-standardised DC incidence rates [per 100 person-years (PY)], and corresponding 95% CIs were calculated assuming a Poisson distribution, overall and stratified by AUD. The European Standard Population 2013 was used for standardisation. The strength of association between risk factors and DC diagnosis was assessed using unadjusted and adjusted Cox proportional hazard regression analyses; covariates included birth cohort, gender, year of HCV notification, HBV and HIV co-infection, and AUD. The population attributable fractions (PAFs) and 95% CIs of DC diagnosis associated with AUD were computed based on the adjusted regression analyses, overall and stratified by birth in or after 1965 [15].

AUD is a standard term used to define continued drinking despite adverse mental and physical consequences [16]. Liver-related consequences of alcohol use are not included in the definition of AUD [16]. A hospital discharge diagnosis code (ICD-10) at any point prior to DC diagnosis was used to infer the presence of AUD; coded in either the principal or a secondary diagnosis field of a linked inpatient hospital record. The set of relevant codes included: alcohol-induced Pseudo-Cushing's syndrome (E24.4), mental and behavioural disorders due to use of alcohol (F10), degeneration of nervous system due to alcohol (G31.2), alcoholic polyneuropathy (G62.1), alcoholic cardiomyopathy (I42.6), alcoholic myopathy (G72.1), alcohol rehabilitation (Z50.2), and alcohol abuse counselling and surveillance (Z71.4). Hereafter, having a history of at least one AUD-related hospital admission is referred to as AUD. AUD was not included as a time-dependent variable in Cox proportional regression analyses, given that it is considered to be an indicator of a long-standing condition. To calculate age-standardised DC incidence rates, assess factors associated with DC diagnosis, and evaluate PAFs, person-time at risk was defined to start six months post the date of HCV notification, and to end at whichever occurred first; death, or end of follow-up, assigned by year. Statistical analyses were carried out in STATA versions 12 and 13 or SAS version 9.4.

Role of the funding source

The funding sources did not have any role in study design, data collection and analysis, interpretation of data, writing of the report, and the decision to submit the paper for publication. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Study participants

There were 58,487 people with an HCV notification in BC, 84,529 in NSW, and 31,924 in Scotland (total n=174,940) during the study period. The BC population was older (70% born before 1965), compared to NSW (47%) and Scotland (28%). The proportion of people with AUD was highest in Scotland (27%), followed by BC (19%), and NSW (18%). There were 2,689 (4.6%) people with a DC diagnosis in BC, 3,169 (3.7%) in NSW and 1,375 (4.3%) in Scotland. Across the three settings, those with a DC diagnosis were more likely to be born during 1945-1964 and male. The proportion of people with a DC diagnosis and AUD was highest in Scotland (50%), followed by NSW (32%), and BC (28%) (Table 1).

Age at DC diagnosis

The age distribution at DC diagnosis varied across settings, with median age of 54 years [interquartile range (IQR) 48, 60] in BC, 50 years (IQR 45, 56) in NSW, and 46 years (IQR 39, 53) in Scotland. However, in all settings, compared to those without AUD, people with AUD had a younger age distribution, with median age of 52 vs. 56 years ($P<0.001$) at DC diagnosis in BC; 48 vs. 52 years ($P<0.001$) in NSW and; 43 vs. 49 years ($P<0.001$) in Scotland (Figure 1).

DC diagnosis numbers and rates

In BC, NSW, and Scotland, DC diagnosis numbers increased from 196, 192, and 68 in 2004 to 295 in 2011 ($P<0.001$), 351 in 2012 ($P<0.001$), and 157 in 2013 ($P<0.001$), respectively. Among people with AUD in the three settings, DC diagnosis numbers increased from 52, 57, and 36 in 2004 to 88 in 2011 ($P=0.025$), 145 in 2012 ($P=0.001$), and 72 in 2013 ($P=0.003$), respectively. Since 2004, age-standardised DC incidence rates have remained relatively stable

in all settings, although consistently higher among those with AUD in NSW and Scotland (Figure 2).

Factors associated with DC diagnosis

In unadjusted analyses, factors associated with DC diagnosis were consistent across all three settings. DC diagnosis was associated with older age, male gender, more recent HCV notification years (≥ 2007), HIV and HBV/HIV co-infection, and AUD. In unadjusted analyses, HBV co-infection was associated with DC diagnosis in BC and NSW (Table 2). Similar demographic and clinical factors were associated with DC diagnosis in adjusted analyses (Table 3). The association between DC diagnosis and more recent HCV notification years was driven by older age (Supplementary Table 1). In adjusted analyses across the three settings, AUD independently predicted DC diagnosis [adjusted hazard ratio (aHR) BC 1.92, 95% CI 1.76, 2.10; NSW 3.68, 95% CI 3.38, 4.00; and Scotland 3.88, 95% CI 3.42, 4.40] (Table 3).

Contribution of alcohol dependency to DC diagnosis

Overall, in BC, NSW, and Scotland, AUD was associated with a PAF of 13% (95% CI 11%, 15%), 25% (95% CI 23%, 27%), and 40% (95% CI 36%, 44%) of DC diagnoses, respectively. Among people born in or after 1965 in BC, NSW, and Scotland AUD was associated with a PAF of 21% (95% CI 16%, 25%), 36% (95% CI 32%, 40%), and 48% (95% CI 43%, 53%) of DC diagnoses, respectively (Table 4).

Discussion

This study outlines the rising absolute burden of HCV-related liver disease in BC, Canada; NSW, Australia; and Scotland. The increasing DC diagnosis numbers highlight the limited impact of interferon-containing HCV treatment programs across the three settings, as well as the combined effects of ageing and co-morbidities for liver disease progression. The impact of alcohol on liver disease progression among people with chronic HCV is evident through the younger age distribution of those with DC and AUD, and the higher attributable fractions for AUD among younger people with DC diagnosis. The overall contribution of AUD to DC diagnosis was highest in Scotland, the setting with the youngest age distribution, and lowest in BC, consistent with the older age demographic in this setting. Elimination of HCV infection as a public health threat by 2030 is defined by a 65% reduction in liver-related mortality and an 80% reduction in incidence compared with the 2015 baseline [2]. To reach the 65% mortality reduction component of the elimination target, concentrated policy action is required to enhance HCV treatment uptake, and where needed, improve AUD management at the national level. The availability of data on mandatory HCV notifications and the capacity for regular linkage to other administrative databases provides the opportunity for ongoing evaluation and comparison of HCV public health strategies in the DAA era between BC, NSW, and Scotland.

Across the three settings, suboptimal efficacy and uptake of interferon-based therapies were among the major gaps in the HCV care cascade during the 2000s-early 2010s [1]. Over the coming decade, enhanced uptake of highly effective interferon-free DAA therapies is expected to significantly reduce the burden of HCV-related liver disease [17]; however, the impact of different strategies needs to be closely monitored. Australia has adopted a broad DAA access strategy without liver disease stage or drug and alcohol restrictions since March

2016. Disease staging has been required for access to new therapies in BC and Scotland in 2016; however, eligibility criteria are opening to all disease stages as numbers of people with advanced liver disease diminish. Nonetheless, HCV-related liver disease is a multifactorial problem, to which antiviral therapy is only a partial solution [18]. The anticipated preventative impact of improved therapies has to be evaluated through linkage to individual-level treatment data, across the three settings. Such comparison should be possible in the near future, following procedures to enable access to government-subsidised treatment datasets.

The major contribution of AUD to DC diagnosis has important policy implications in all settings. Strong evidence exists for the effectiveness of several strategies to reduce harmful consumption at the population level, including those targeting the pricing, availability and marketing of alcohol [19]. Canada is among a handful of countries that has implemented and evaluated the impact of different forms of minimum alcohol pricing [20]. Increasing minimum prices in Canada have been shown to be associated with significant reductions in harmful patterns of use, and alcohol-related hospitalisation and mortality [21-23]. In most countries however, governments fail to follow the evidence on alcohol management policies, given lack of popular support and difficulties of implementation [19]. Intricate patterns of consumption and alcohol-related harm further complicate the application and evaluation of management policies. In Scotland, alcohol-related morbidity and mortality have declined in recent years; however, these declines are not consistently distributed among the population, with the greatest burden recorded among those living in the most deprived areas [24]. In Australia, overall levels of drinking have declined during the last decade; however, diverging drinking patterns indicate these declines are mostly concentrated among lighter drinkers, while the top ten percent of heavier drinkers are responsible for an increasing proportion of total consumption [25]. Despite these differences, in developing country-specific

management policies, tackling harmful consumption should remain integral to improving population level health outcomes and reducing social inequalities. After a prolonged battle with the well-organised and well-funded alcohol industry groups, Scotland has successfully passed legislation to introduce minimum unit pricing for alcohol. Ten years after implementation of this policy, the Scottish government estimates there would be at least 300 fewer alcohol-related deaths and 6,500 fewer hospital admissions each year [24]. In Australia, debates about minimising alcohol-related harm have increased in recent years [26, 27], instigating the Commonwealth government to explore the concept of a public interest case for minimum pricing of alcohol [28]. However, major alcohol policy reforms are yet to be implemented by the federal and state governments.

Across the three settings, older age was the strongest predictor of DC diagnosis. The causal relationship between ageing and increased risk of HCV-related complications is likely explained by a combination of longer duration of infection and ageing-related impaired repair mechanisms [29]. People born prior to 1945 were particularly at higher risk of developing DC. Interestingly, a recent study has demonstrated major acceleration in the development of HCV-related cirrhosis after the age of 50, irrespective of duration of infection [29]. Other predictors of DC diagnosis included AUD, male gender, and HBV/HCV/HIV co-infection. These characteristics are among well-defined risk factors for faster liver disease progression [30]. Defining an individual's risk of liver disease progression is often difficult, due to the non-linear nature of disease progression, and fluctuating lifestyle co-factors [31]. However, heavy alcohol use (>50 g/d) has been shown to be associated with end-stage liver disease diagnosis and liver-related mortality, independent of chronic HCV infection or viral eradication by therapy [32]. Given its significant impact, where needed, effects of AUD should be mitigated in order to lower the risk of liver disease progression among people with

HCV infection. Integration of alcohol dependency treatment in medical settings could optimise management of AUD and facilitate provision of treatment by multidisciplinary teams, including psychosocial interventions, pharmacological therapy, and medical management of AUD and liver disease [33].

This study has several limitations. First, DC diagnosis was defined by a limited number of conditions that appear to be strong indicators of the decompensated stage of cirrhosis; however, this definition has not been validated against the clinical diagnoses of DC and requires further validation studies. Second, using administrative data for defining AUD has clear limitations. In sensitivity analysis, across the three settings, 72-94% of people who had a first-time hospitalisation due to alcoholic liver failure also had a non-liver AUD-related admission; the majority of which (71-85%) were recorded before the first-time alcoholic liver failure hospitalisation. Further, a previous population-based study in Scotland has shown moderate and higher levels of self-reported alcohol consumption and binge drinking are major risk factors for subsequent alcohol-related hospitalisation (based on ICD codes) [34]. Finally, a validation study of administrative data (based on ICD codes) vs. chart notations has demonstrated 68% sensitivity and 97% specificity for the administrative data-based diagnosis of alcohol problem drinking [35]. Positive predictive value was 87%, and negative predictive value was 91%. Taken together, these findings suggest the current study has potential under-ascertainment of AUD, with potential overestimation of the impact on DC risk if more severe forms of AUD were more likely to be classified. Third, to improve the accuracy of trends in DC diagnosis numbers and age-standardised rates across the settings, these data were displayed and analysed since 2004. In Scotland, the pre-2004 DC trends were overestimated, given low HCV diagnosis rates during the early-mid 2000s (62% undiagnosed in 2006) [36]. Fourth, in the analysis of the association between DC diagnosis and more recent HCV

notification years, this study could not evaluate the potential impact of HCV diagnosis among people with more advanced liver disease in recent years. Previous findings from BC and NSW suggested the number of individuals with a late HCV notification has been declining in the 2000s (defined by an HCV notification before, at the time, or within two years before DC diagnosis); however, in the late 2000s, approximately 20% of people with HCV-related DC diagnosis still had a late HCV notification [37, 38]. Fifth, other factors might have contributed to lower age-standardised DC rates in BC, including residual confounding (attributed by unmeasured co-morbidities), and the older age distribution in this setting compared to the standard population. Sixth, HCV diagnosis for surveillance reporting is generally based on anti-HCV antibody detection and does not require HCV RNA confirmation. Thus, an estimated 25% of HCV notifications would have undergone spontaneous HCV clearance. Finally, the impact of antiviral therapy on DC diagnosis has not been evaluated in this study. Nevertheless, a minority of people would have received HCV treatment during the study period. These limitations should not have a major impact on the study findings, given the surveillance definition and systems in the three settings have been stable throughout the study period.

In conclusion, this international comparison of population level data provides evidence for the rising absolute burden of HCV-related advanced liver disease in BC, NSW, and Scotland, highlighting the combined impact of suboptimal HCV treatment efficacy and uptake, aging, and significant contribution of AUD to DC diagnosis. These findings suggest, where needed, action against AUD should form a strong component of HCV public health strategies. Continued heavy alcohol intake is likely to impact potential benefits of DAA-based cure on individual-level liver disease progression and population-level liver disease burden. Use of administrative databases for surveillance, particularly with the addition of individual-level

antiviral treatment data will be a valuable tool for ongoing evaluation and comparison of the impact of DAA-based therapies on the individual-level liver disease progression and population-level burden of HCV, given differences in the epidemiology of HCV and HCV public health strategies across the three settings.

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Table 1. Demographic characteristics among people with an HCV notification in BC, NSW, and Scotland, since 1995

Characteristics, n %	BC, Canada HCV notifications 1995-2011				NSW, Australia HCV notifications 1995-2012				Scotland HCV notifications 1995-2013			
	All		DC ^a		All		DC ^a		All		DC ^a	
	n=58,487	%	n=2,689	%	n=84,529	%	n=3,169	%	n=31,924	%	n=1,375	%
Birth cohort												
≥1965	17,397	30	210	8	45,298	54	611	19	22,889	72	602	44
1945-1964	35,616	61	1,981	74	34,518	41	2,171	69	8,051	25	681	50
≤1944	5,474	9	498	19	4,713	6	387	12	984	3	92	7
Male ^β	38,212	65	1,860	69	53,146	63	2,319	73	21,369	65	1,002	73
Year of HCV notification												
1995-2000	28,517	49	1,449	54	39,043	46	1,461	46	9,141	29	377	27
2001-2006	18,339	31	920	34	26,754	32	1,088	34	9,645	30	545	40
2007-2011/12/13	11,631	20	320	12	18,732	22	620	20	13,138	41	453	33
Co-infection status												
None	51,381	88	2,241	83	80,112	95	2,934	93	30,653	96	1,289	94
HBV	3,255	6	229	9	3,467	4	184	6	587	2	41	3
HIV	2,910	5	150	6	888	1	45	1	645	2	40	3
HBV/HIV	941	2	69	3	62	<1	6	<1	39	<1	5	<1
Alcohol-use disorder^γ	11,078	19	742	28	14,797	18	1,023	32	8,757	27	693	50

^aDC diagnosis during 2001-2012 in BC, 2001-2013 in NSW, and 2001-2014 in Scotland, ^βamong people with available information, ^γamong people with a DC diagnosis, Alcohol-use disorder was included if occurred prior to DC diagnosis

Table 2. Unadjusted analysis of factors associated with DC diagnosis among people with an HCV notification in BC, NSW, and Scotland, since 1995

Characteristics, n %	BC, Canada HCV notification, 1995-2011 n=55,873					NSW, Australia HCV notification, 1995-2012 n=82,526					Scotland HCV notification, 1995-2013 n=30,746				
	DC ^a n=2,443	%	HR ^b	95% CI	P	DC ^a n=2,559	%	HR ^b	95% CI	P	DC ^a n=1,020	%	HR ^b	95% CI	P
Birth cohort															
≥1965	198	1	1.00	-	-	479	1	1.00	-	-	466	2	1.00	-	-
1945-1964	1,804	5	4.21	3.64, 4.88	<0.001	1,750	5	4.59	6.81, 9.01	<0.001	490	7	2.97	2.61, 3.37	<0.001
≤1944	441	10	9.18	7.77, 10.86	<0.001	330	8	7.83	4.15, 5.08	<0.001	64	8	4.45	3.43, 5.79	<0.001
Gender															
Female	749	4	1.00	-	-	690	4	1.00	-	-	287	3	1.00	-	-
Male	1,694	5	1.24	1.14, 1.35	<0.001	1,860	4	1.63	1.50, 1.78	<0.001	732	4	1.28	1.11, 1.46	<0.001
Year of HCV notification															
1995-2000	1,443	5	1.00	-	-	1,355	4	1.00	-	-	274	4	1.00	-	-
2001-2006	792	4	1.14	1.04, 1.25	0.003	879	3	1.11	1.01, 1.23	0.032	397	4	1.28	1.09, 1.51	0.002
≥2007	208	2	1.31	1.12, 1.53	0.001	325	2	1.51	1.30, 1.75	<0.001	249	2	1.42	1.16, 1.75	0.001
Co-infection status															
None	2016	4	1.00	-	-	2,387	3	1.00	-	-	958	3	1.00	-	-
HBV	214	7	1.60	1.39, 1.84	<0.001	132	4	1.35	1.13, 1.61	0.001	26	5	1.39	0.94, 2.05	0.100
HIV	144	5	1.32	1.12, 1.57	<0.001	36	4	1.66	1.20, 2.31	0.002	31	5	1.82	1.27, 2.60	0.001
HBV/HIV	69	8	2.01	1.58, 2.56	<0.001	4	7	3.57	1.34, 9.53	0.011	5	14	5.48	2.27, 13.19	<0.001
Alcohol-use disorder^c															
No	1,775	4	1.00	-	-	1,672	2	1.00	-	-	464	2	1.00	-	-
Yes	668	7	1.82	1.67, 1.99	<0.001	887	6	2.96	2.73, 3.21	<0.001	556	7	3.62	3.20, 4.10	<0.001

^aDC diagnosis during 2001-2012 in BC, 2001-2013 in NSW, and 2001-2014 in Scotland, ^b hazard ratio, ^camong people with a DC diagnosis, AUD was included if occurred prior to DC diagnosis

Table 3. Adjusted analysis of factors associated with DC diagnosis among people with an HCV notification in BC, NSW, and Scotland, since 1995

Characteristics, n %	BC, Canada HCV notification, 1995-2011 n=55,873					NSW, Australia HCV notification, 1995-2012 n=82,526					Scotland HCV notification, 1995-2013 n=30,746				
	DC ^a n=2,443	%	aHR ^b	95% CI	P	DC ^a n=2,559	%	aHR ^b	95% CI	P	DC ^a n=1,020	%	aHR ^b	95% CI	P
Birth cohort															
≥1965	198	1	1.00	-	-	479	1	1.00	-	-	466	2	1.00	-	-
1945-1964	1,804	5	4.55	3.93, 5.28	<0.001	1,750	5	5.13	4.63, 5.69	<0.001	490	7	3.07	2.70, 3.49	<0.001
≤1944	441	10	11.13	9.40, 13.19	<0.001	330	8	11.90	10.30, 13.75	<0.001	64	8	7.09	5.43, 9.25	<0.001
Gender															
Female	749	4	1.00	-	-	690	4	1.00	-	-	287	3	1.00	-	-
Male	1,694	5	1.15	1.06, 1.26	0.001	1,860	4	1.43	1.31, 1.56	<0.001	732	4	1.15	1.00, 1.32	0.048
Year of HCV notification															
1995-2000	1,443	5	1.00	-	-	1,355	4	1.00	-	-	274	4	1.00	-	-
2001-2006	792	4	1.36	1.24, 1.49	<0.001	879	3	1.25	1.13, 1.37	<0.001	397	4	1.46	1.24, 1.72	<0.001
≥2007	208	2	1.81	1.55, 2.12	<0.001	325	2	1.87	1.61, 2.17	<0.001	249	2	1.81	1.48, 2.23	<0.001
Co-infection status															
None	2016	4	1.00	-	-	2,387	3	1.00	-	-	958	3	1.00	-	-
HBV	214	7	1.55	1.35, 1.79	<0.001	132	4	1.40	1.17, 1.67	<0.001	26	5	1.34	0.94, 1.99	0.138
HIV	144	5	1.55	1.31, 1.84	<0.001	36	4	1.61	1.16, 2.24	0.005	31	5	1.50	1.04, 2.14	0.028
HBV/HIV	69	8	2.37	1.86, 3.02	<0.001	4	7	2.66	1.00, 7.10	0.051	5	14	5.50	2.28, 13.27	<0.001
Alcohol-use disorder^γ															
No	1,775	4	1.00	-	-	1,672	2	1.00	-	-	464	2	1.00	-	-
Yes	688	7	1.92	1.76, 2.10	<0.001	887	6	3.68	3.38, 4.00	<0.001	556	7	3.88	3.42, 4.40	<0.001

^aDC diagnosis during 2001-2012 in BC, 2001-2013 in NSW, and 2001-2014 in Scotland, ^badjusted hazard ratio, ^γamong people with a DC diagnosis, AUD was included if occurred prior to DC diagnosis

Table 4. Population attributable fraction of DC diagnosis associated with alcohol-use disorder among BC, NSW, and Scotland people with an HCV notification, since 1995

	BC HCV notification, 1995-2011 n=55,879				NSW HCV notification, 1995-2012 n=82,526				Scotland HCV notification, 1995-2013 n=30,746			
	DC diagnosis 2001-2012, n=2,443				DC diagnosis 2001-2013, n=2,559				DC diagnosis 2001-2014, n=1,020			
	Alcohol-use disorder, n	%	PAF ^a	95% CI	Alcohol-use disorder, n	%	PAF ^a	95% CI	Alcohol-use disorder, n	%	PAF ^a	95% CI
All	688	7	13	11, 15	887	6	25	23, 27	556	7	40	36, 44
Born ≥1965	90	3	21	16, 25	247	3	36	32, 40	309	5	48	43, 53
Born <1965	598	9	12	10, 14	640	13	22	20, 24	247	12	33	28, 37

^a population attributable fraction, computed based on adjusted regression analysis in each setting

Figure 1. Age at DC diagnosis among people with an HCV notification in BC, NSW, and Scotland, by alcohol-use disorder, since 1995

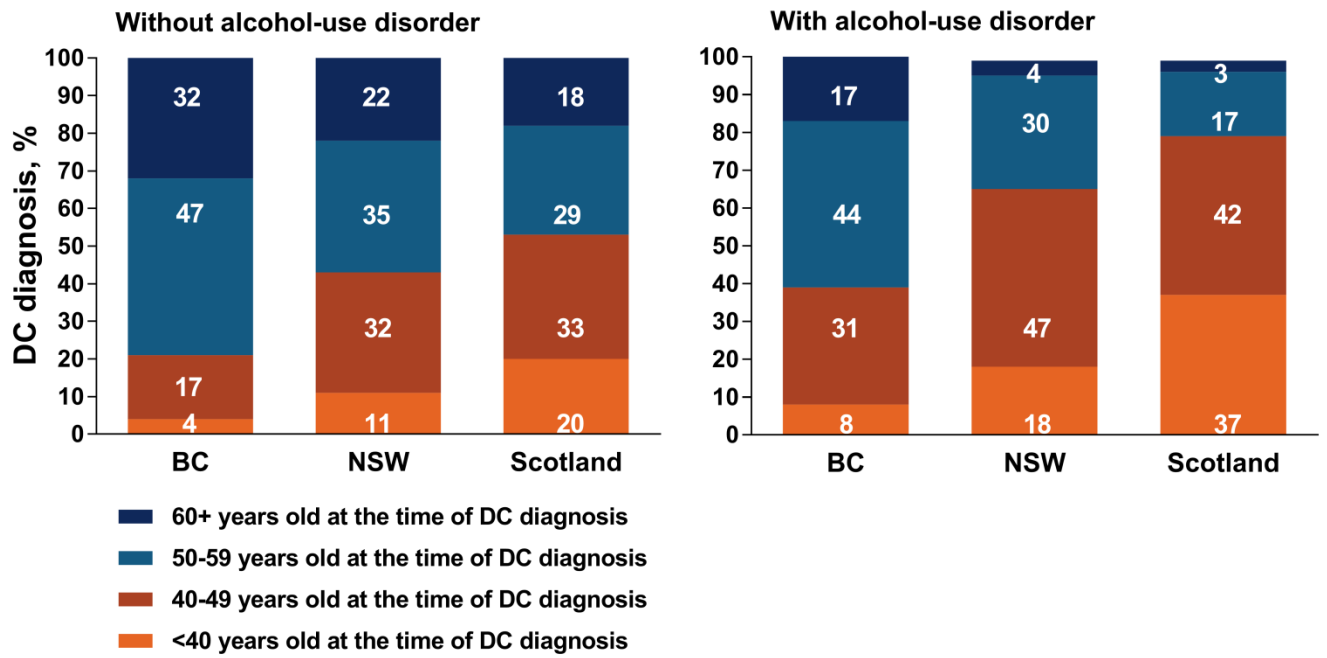


Figure 2. Temporal trends in DC diagnosis numbers and age-standardised incidence rates among people with an HCV notification in BC, NSW, and Scotland, by alcohol-use disorder, since 1995

