Trends in decompensated cirrhosis and hepatocellular carcinoma among people with a hepatitis B notification in New South Wales
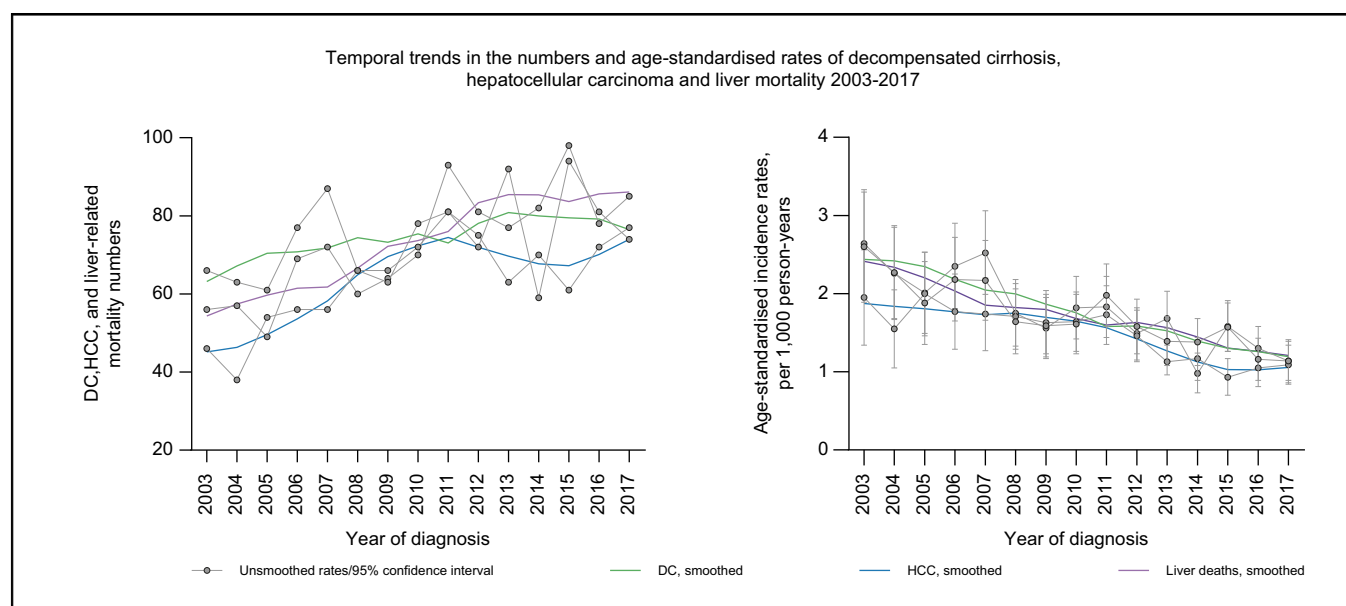
Authors

Syed Hassan Bin Usman Shah, Maryam Alavi, Behzad Hajarizadeh, Gail V. Matthews, Marianne Martinello, Mark Danta, Janaki Amin, Matthew G. Law, Jacob George, Heather Valerio, Gregory J. Dore

Correspondence

hbinusman@kirby.unsw.edu.au (S.H.B.U. Shah).

Graphical abstract

Temporal trends in the numbers and age-standardised rates of decompensated cirrhosis, hepatocellular carcinoma and liver mortality 2003-2017

Highlights

- The World Health Organization has set a 65% HBV mortality reduction target by 2030.

- Since the early 2000s, diagnoses of decompensated cirrhosis and HCC increased, but age-standardised incidence rates decreased.

- Age-standardised liver mortality rates decreased from 2.64 in 2003 to 0.97 per 1,000 person-years in 2017.

- Late HBV notification declined from 41% and 40% during 2001-2009 to 28% and 26% in 2010-2018, respectively.

- Hepatitis C co-infection and alcohol-use disorder are key modifiable risk factors associated with HBV disease burden.

Lay summary

Rising hepatitis B-related morbidity and mortality is a major public health concern. However, the development of highly effective medicines against hepatitis B virus (HBV) has brought renewed optimism for its elimination by 2030. This study shows a steady decline in HBV-related liver morbidity and mortality in New South Wales, Australia. Moreover, late hepatitis notification has also declined, allowing individuals with HBV to have access to timely antiviral treatment. Despite this, hepatitis C co-infection and alcohol use disorder are key modifiable risk factors associated with HBV disease burden. To attain the desired benefits from highly effective antiviral treatment, managing comorbidities, including hepatitis C and high alcohol use, must improve among individuals with hepatitis B.

Trends in decompensated cirrhosis and hepatocellular carcinoma among people with a hepatitis B notification in New South Wales

Syed Hassan Bin Usman Shah,[1,*] Maryam Alavi,[1] Behzad Hajarizadeh,[1] Gail V. Matthews,[1,2] Marianne Martinello,[1] Mark Danta,[2] Janaki Amin,[3] Matthew G. Law,[1] Jacob George,[4] Heather Valerio,[1] Gregory J. Dore[1]

[1]The Kirby Institute, University of New South Wales (UNSW) Sydney, NSW, Australia; [2]St Vincent's Hospital, Sydney, Australia; [3]Department of Health Systems and Populations, Macquarie University, Sydney, NSW, Australia; [4]Storr Liver Centre, Westmead Millennium Institute, University of Sydney and Westmead Hospital, Westmead, Australia

Background & Aims: Population-level trends and factors associated with HBV-related decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), and liver-related mortality are crucial to evaluate the impacts of therapeutic interventions.
Methods: Trends in HBV-DC and -HCC diagnoses and liver-related mortality in New South Wales, Australia, were determined through linkage of HBV notifications (1993-2017) to hospital admissions (2001-2018), mortality (1993-2018), and cancer registry (1994-2014) databases. Late HBV notification was defined as notification at or within 2 years of a DC or HCC diagnosis. Cox proportional-hazards regression and multivariable logistic regression analyses were performed to evaluate associated factors.
Results: Among 60,660 people with a HBV notification, 1,276 (2.0%) DC and 1,087 (1.8%) HCC diagnoses, and 1,219 (2.0%) liver-related deaths were documented. Since the early 2000s, the number of DC and HCC diagnoses increased; however, age-standardised incidence decreased from 2.64 and 1.95 in 2003 to 1.14 and 1.09 per 1,000 person-years in 2017, respectively. Similarly, age-standardised liver mortality decreased from 2.60 in 2003 to 1.14 per 1,000 person-years in 2017. Among people with DC and HCC diagnoses, late HBV notification declined from 41% and 40% between 2001-2009 to 29% and 25% in 2010-2018, respectively. Predictors of DC diagnosis included older age (birth <1944, adjusted hazard ratio [aHR] 2.06, 95% CI 1.57–2.69), alcohol use disorder (aHR 4.82, 95% CI 3.96–5.87) and HCV co-infection (aHR 1.88, 95% CI 1.53–2.31). Predictors of HCC diagnosis included older age (birth <1944, aHR 3.94, 95% CI 2.91–5.32) and male sex (aHR 3.79, 95% CI 3.05–4.71).
Conclusion: In an era of improved antiviral therapies, the risk of HBV-related liver morbidity and mortality has declined. HCV co-infection and alcohol use disorder are key modifiable risk factors associated with the burden of HBV.
Lay summary: Rising hepatitis B-related morbidity and mortality is a major public health concern. However, the development of highly effective medicines against hepatitis B virus (HBV) has brought renewed optimism for its elimination by 2030. This study shows a steady decline in HBV-related liver morbidity and mortality in New South Wales, Australia. Moreover, late hepatitis notification has also declined, allowing individuals with HBV to have access to timely antiviral treatment. Despite this, hepatitis C co-infection and alcohol use disorder are key modifiable risk factors associated with HBV disease burden. To attain the desired benefits from highly effective antiviral treatment, managing comorbidities, including hepatitis C and high alcohol use, must improve among individuals with hepatitis B.

Introduction

Worldwide, chronic hepatitis B (CHB) is a significant public health threat.[1,2] The World Health Organization (WHO) estimated that around 296 million people were living with CHB in 2019, with an estimated 820,000 deaths attributed to HBV-associated end-stage liver disease (ESLD),[3] most notably decompensated cirrhosis (DC) and hepatocellular carcinoma

(HCC).[1,3,4] Given the availability of highly effective antiviral regimens,[5] the WHO has defined a set of targets for eliminating HBV as a public health threat by 2030, including a 65% reduction in mortality.[2] While enhanced HBV diagnosis and timely linkage to care are required to achieve the WHO elimination targets, in many countries, including Australia, HBV diagnosis and treatment uptake remain suboptimal.[6] Further, the impact of the existing HBV programs is unknown in most settings, given limited capacity for evaluation of HBV liver disease burden at the population level.

Over their lifetimes, 15%–40% of people with CHB develop cirrhosis, liver failure, or HCC, and 15–25% are at risk of dying secondary to HBV-related ESLD.[7] The 5-year survival rate is 14-45% after DC [8] and 18-20% after HCC.[9] The prolonged subclinical

period and suboptimal screening can lead to late HBV diagnosis resulting in ESLD. Although potent and highly effective nucleos(t)ide analogue (NA) therapy reduces the risk of liver disease progression,[10] late hepatitis notification leads to a potential missed opportunity, limiting the chances of preventing hepatic carcinogenesis or fibrosis.[11–13] Moreover, other factors including alcohol use disorder (AUD), ageing, suboptimal treatment uptake, and HBV/HCV co-infection contribute to higher risk of liver morbidity and mortality.[14] In Australia, the epidemiology of HBV is complex, with a high prevalence among migrants from high- or intermediate HBV prevalence countries and Aboriginal or Torres Strait Islander peoples.[15,16] Over the past two decades, remarkable strides have been made in increasing HBV diagnosis, vaccination and treatment uptake [17] and understanding the epidemiology, risk factors, and molecular profiles of HBV-related DC and HCC.[18] However, enhanced HBV diagnosis and treatment uptake are needed if Australia is to achieve the WHO 2030 elimination targets.[6]

Australia is among the few countries with established national surveillance systems and mandatory HBV notification, thus providing an opportunity to evaluate HBV-related liver disease burden by linking notifications with hospitalisation and mortality databases.[11,19] This study aimed to evaluate trends and factors associated with HBV-related DC and HCC diagnoses, along with trends in liver-related mortality. Further, we assessed trends and factors associated with late notifications among people with an HBV notification in New South Wales (NSW), Australia.

Patients and methods

Study setting, data sources and record linkages
This study utilises routinely collected data from NSW, Australia. As of March 2018, the total NSW population was 7.95 million, and about 65% of the population lived in Sydney.[20] In 2018, an estimated 226,566 people were living with HBV in Australia, with 30% in NSW.[21]

Under the Public Health Act 1991, mandatory notification for all individuals with positive HBV and HCV serology tests is required in NSW.[22] This record is maintained at the NSW Notifiable Conditions Information Management System (NCIMS). NSW residents with an HBV notification (notifiable HBV cases require detection of HBV surface antigen or HBV DNA) and DC and/or HCC diagnosis or a history of AUD were identified through the NSW Admitted Patient Data Collection (APDC) for DC and AUD diagnoses, and APDC and NSW Cancer Registry (NSWCR) for HCC. APDC covers all inpatient admissions from public and private hospitals since 2001. Each hospitalisation record includes demographic, administrative and diagnostic information coded at discharge according to the ICD-10. People with HIV co-infection were identified through the National HIV Registry (NHR), receiving mandatory HIV notifications since 1985. Data on mortality was extracted from the Registry of Births, Deaths and Marriages (RBDM), which holds the information on all deaths registered in NSW since 1993.[22] People who received HBV treatment were identified through the Pharmaceutical Benefits Scheme (PBS) since 2010.

Data linkages occurred at 2 stages. First, HBV and HCV notifications were linked internally to identify people with HBV/HCV co-infection. Additionally, using demographic details (including full name, sex, date of birth, and address), probabilistic linkages were undertaken by the NSW Centre for Health Record Linkage,[22] which has deterministically linked NCIMS with NHR, using 2x2 name codes. Subsequently, the Australian Institute of Health and Welfare has probabilistically linked NCIMS with PBS records, using the aforementioned demographic details.[23]

Study population and period
The study population included people with an HBV notification in NSW, Australia, during 1993-2017. Linked data were extracted for the following periods: NCIMS (1 January 1993 - 31 December 2017); APDC (1 July 2001 - 30 June 2018); NSWCR (1 January 1993 - 31 December 2014); RBDM (1 January 1993 - 30 June 2018); NHR (1 January 1985- 31 December 2017); and PBS (1 April 2010 - 31 December 2018). Administrative data sources were extracted for different durations of time, depending on available periods for linkage. Hence, the study time period was restricted (2001-2018) to optimise data coverage.

Study outcomes
The primary outcomes of interest were HBV-related DC and HCC diagnoses and liver-related mortality. DC diagnosis was inferred using hospital discharge diagnosis code (ICD-10); primary or secondary diagnosis fields with following codes: DC ascites (R18.0), bleeding oesophageal varices (I85.0, I98.3, and I98.21), chronic hepatic failure (including hepatic encephalopathy; K72.1, K72.9), alcoholic hepatic failure (K70.4), or hepatorenal syndrome (K76.7).[11,19,24] Similarly, a hospital discharge diagnosis code was used to define HCC diagnosis, coded in either the principal or secondary diagnosis fields of a linked inpatient hospital record (C22.0) or identified through NSWCR records.[11,19,24] Hereafter, first-time DC and HCC hospitalisations or HCC diagnosis via cancer registry are referred to as DC and HCC diagnosis. Liver-related mortality was defined by any death following a DC and/or HCC diagnosis.

The secondary outcome was late HBV notification, defined by an HBV notification after, at the time or within 2 years before DC or HCC diagnosis.[12]

Exclusion criteria
Exclusion criteria were applied as follows: records where the data of HBV notification occurred after censoring (post-mortem HBV notifications); HBV notification without a Medicare (universal healthcare) number and duplicate HBV notifications; records where the date of HCC diagnosis or death was prior to 1 January 2001. Additionally, small cells (cell count with values <5) were not included in this analysis.

Statistical analysis
The linked dataset was cleaned, edited, and prepared for this study in the STATA software version 14.2 (StataCorp, College Station, Texas). Descriptive statistics including medians and interquartile ranges were calculated for continuous variables where the data was normally distributed, and frequencies with percentages were calculated for all categorical variables. Temporal trends in HBV-DC, HCC, and liver-related mortality were evaluated, including numbers and age-standardised incidence rates between 2001 to 2018. We calculated the rates where the denominator included all people with a HBV notification in NSW; people entered the cohort from the date of HBV notification and

observation time (for evaluation of DC and HCC) started from 2001, when both hospital admissions and cancer registry data were available. To reduce the potential for individuals to have the outcome of interest (DC and HCC) at study entry, a sensitivity analysis with an observation period of a 5-year look back window was adjusted to start from 2005. HCC diagnoses were obtained using hospital admission and cancer registry data; however, the cancer registry data was only available up to 2014. To evaluate whether the HCC diagnosis data source biased our results, an additional sensitivity analysis was carried out with only diagnoses through hospitalisation data available for the entire study period. Age-standardised rates (per 1,000 person-years) and corresponding 95% CIs were calculated assuming a Poisson distribution. Among people with a DC diagnosis, numbers and age-standardised incidence rates were evaluated overall and stratified by HBV/HCV co-infection notifications. Smoothing was carried out to create the impression of trends by ensuring that any fluctuation to a high or low value is amplified and the point-to-point distortion/variability is muted. Smooth trends were observed after averaging 4 values on each side and using a second-order smoothing polynomial. Standardisation was performed using the Australian Standard Population in 2013 (by 5-year age-grouping).

Unadjusted and adjusted Cox proportional-hazards regression analyses were performed to evaluate factors associated with DC and HCC diagnoses. In unadjusted analysis, variables that did not violate the assumption of proportionality were considered for inclusion in the adjusted analysis. Covariates included age (birth cohort ≤1944, 1945-1964, and ≥1965), sex, country of birth, ethnicity, history of AUD, HBV-HCV/HIV co-infection, and local health district (LHD) of residence at the time of notification. Comorbidity burden was assessed using the Charlson comorbidity index (CCI).[25,26] The CCI was categorised from 0 to 3+ groups based on its score, where higher scores indicate a worse health condition.[26] The codes for moderate or severe liver morbidity were excluded from the CCI to avoid overlapping with the main variables that were included separately. Finally, HBV treatment trends among people with an HBV notification were calculated from 2010 to 2017. Given HBV treatment data was not available prior to 2010, HBV notifications were included in this analysis only for the 2009-2017 period. In all time-to-event analyses, time at risk started on HBV notification date and ended on date of DC or HCC diagnosis, death, or last follow-up (30 June 2018), whichever occurred first (depending on the outcome of interest in each analysis).

To assess the number of people with a late HBV notification, people with a DC or HCC diagnosis were stratified into 5 categories according to the time between their HBV notification and DC or HCC diagnosis [12]; people with an HBV notification a) after or at the time of DC or HCC diagnosis; b) less than 1 year before; c) between 1 and 2 years before; d) between 2 and 5 years before and; e) more than 5 years before. The proportion of those with a late HBV notification (categories a, b and c above) was calculated overall and during the 2001-2009 and 2010-2018 time periods. Following unadjusted analyses, multivariable logistic regression evaluated factors associated with late HBV notification, considering factors significant at the 0.20 level in the unadjusted models. Covariates included age, sex, country of birth, ethnicity, history of AUD, HBV-HCV/HIV co-infection, and LHD of residence at the time of DC or HCC diagnosis.[19] Further, the calendar period of DC and HCC diagnosis was hypothesised to be associated with late HBV notification, assuming late notification was more likely

to occur in the early 2010s, compared to later periods. In all analyses, LHD of residence at the time of HBV notification was defined by the 2011 NSW boundaries, including 8 LHDs covering metropolitan regions and 7 covering rural and regional locations.[27]

AUD is a standard term used to define continued drinking despite adverse mental and physical consequences. Liver-related consequences of alcohol use are not included in the definition of AUD.[28] AUD was defined according to hospitalisation with any of the following principal or additional ICD-10 codes: alcohol abuse counselling and surveillance (Z71.4), alcoholic cardiomyopathy (I42.6), alcohol-induced pseudo-Cushing's syndrome (E24.4), alcoholic myopathy (G72.1), alcoholic polyneuropathy (G62.1), alcohol rehabilitation (Z50.2), degeneration of nervous system due to alcohol (G31.2) or mental and behavioural disorders due to alcohol (F10).[28]

Results
Study participants
Between 1993 and 2017, there were 60,660 individuals with an HBV notification in NSW. The median year of birth was 1966 (interquartile range 1956-1977). Overall, 55% were male, 21% were born in Australia, 5% identified as Aboriginal and/or Torres Strait Islander, 4% had a history of AUD, 7% had HCV co-infection, and only 1% had HIV co-infection. During 2001–2018, there were 1,276 (2.0%) with a DC and 1,087 (1.8%) with an HCC diagnosis (Tables 1 and 2).

The number of people with an HBV notification who developed DC increased from 608 in 2001-2009 to 668 in 2010-2018. Compared to people without DC, individuals with DC were older (birth before 1945, 25% vs. 8% or during 1945-1964, 55% vs. 37%), more likely born in Australia (33% vs. 21%), and male (77% vs. 55%). Further, higher proportions had HBV/HCV co-infection (23% vs. 6%), history of AUD (30% vs. 3%), and lived in metropolitan areas at HBV notification (17% vs. 10%) (Table 1).

The number of people with an HBV notification who developed HCC increased from 481 in 2001-2009 to 606 in 2010-2018. Compared to people without HCC, individuals with HCC were older (birth before 1945, 31% vs. 8% or during 1945-1964, 57% vs. 37%) and more likely male (82% vs. 55%). A higher proportion of people with HCC were born overseas, predominantly in East Asia (33% vs. 28%) and Oceania/Southeast Asia (34% vs. 31%). Further, people with HCC were more likely to have HBV/HCV co-infection (12% vs. 6%), and a history of AUD (10% vs. 4%) (Table 2).

Temporal trends in DC and HCC diagnoses and liver-related mortality
Between 2003 and 2017, there was an increase in the number of annual DC diagnoses (66 to 74); however, age-standardised incidence declined from 2.64 (95% CI 1.95–3.33) to 1.14 (95% CI 0.86–1.41) per 1,000 person-years. In this period, HCC diagnosis numbers increased from 46 to 77, and age-standardised incidence declined from 1.95 (95% CI 1.34–2.56) to 1.09 (95% CI 0.84–1.34) per 1,000 person-years. Similarly, liver-related deaths increased from 56 in 2003 to 85 in 2017. However, the age-standardised incidence of liver mortality decreased from 2.60 (95% CI 1.89–3.30) in 2003 to 1.14 (95% CI 0.89–1.39) per 1,000 person-years in 2017 (Fig. 1). Additional sensitivity analysis (presented as Fig. S1) shows similar trends and rates for a 5-year look back window. Trends in HCC diagnoses based on hospitalisation data only, available for the entire study period, were

Table 1. Demographic characteristics among people with an HBV notification (1993-2017), by decompensated cirrhosis diagnosis status (2000-2018).

Characteristics (n, %)	All HBV	No DC 2001-2018	DC 2001-2018	Period of DC 2001-2009	2010-2018
	n = 60,660	n = 59,384	n = 1,276	n = 608	n = 668
Year of birth, median (IQR)*	1966 (56-77)	1967 (57-77)	1954 (45-62)	1951 (41-60)	1956 (47-65)
Birth cohort, n (%)*					
≤1944	4,908 (8)	4,589 (8)	319 (25)	199 (33)	120 (18)
1945-1964	22,583 (37)	21,882 (37)	701 (55)	320 (53)	381 (57)
≥1965	33,164 (55)	32,908 (55)	256 (20)	89 (14)	167 (25)
Male sex**	33,367 (55)	32,391 (55)	976 (77)	471 (78)	505 (76)
Aboriginal and Torres Strait Islander***	2,118 (5)	2,003 (5)	115 (9)	50 (8)	65 (10)
Place of birth****					
Australia	8,666 (21)	8,252 (21)	414 (33)	185 (31)	229 (34)
Americas, Europe, New Zealand	4,057 (10)	3,837 (10)	220 (17)	116 (19)	104 (16)
Africa	1,360 (3)	1,331 (3)	29 (2)	11 (2)	18 (3)
East Asia	11,661 (28)	11,431 (28)	230 (18)	114 (19)	116 (17)
Oceania and Southeast Asia	12,914 (31)	12,605 (31)	309 (24)	146 (24)	163 (25)
Western Asia	2,606 (6)	2,600 (6)	66 (5)	31 (5)	31 (5)
Co-infection					
With HCV	3,943 (7)	3,649 (6)	294 (23)	122 (20)	172 (26)
With HIV	394 (1)	364 (1)	30 (2)	19 (3)	11 (2)
LHD at the time of HBV notification*****					
Metropolitan NSW	6,049 (10)	5,832 (10)	217 (17)	107 (18)	110 (17)
Outer metropolitan NSW	27,773 (46)	26,198 (46)	575 (45)	263 (43)	312 (47)
Rural NSW	25,961 (43)	25,489 (44)	472 (37)	237 (39)	235 (36)
History of alcohol use disorder diagnosis	2,295 (4)	1,911 (3)	384 (30)	169 (28)	215 (32)

DC, decompensated cirrhosis; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; LHD, local health district; NSW, New South Wales.
* 5 had missing information.
** 387 had missing information.
*** 17,722 had missing information.
**** 19,336 had missing information.
***** 877 had missing information.

Table 2. Demographic characteristics among people with an HBV notification (1993-2017), by hepatocellular carcinoma diagnosis status (2000-2018).

Characteristics (n, %)	All HBV	No HCC 2001-2018	HCC 2001-2018	Period of HCC 2001-2009	2010-2018
	n = 60,660	n = 59,573	n = 1,087	n = 481	n = 606
Year of birth, median (IQR)*	1966 (56-77)	1967 (57-77)	1951 (42-59)	1947 (37-56)	1954 (46-61)
Birth cohort*					
≤1944	4,908 (8)	4,572 (8)	336 (31)	211 (44)	125 (21)
1945-1964	22,583 (37)	21,965 (37)	618 (57)	231 (48)	387 (64)
≥1965	33,164 (55)	33,032 (55)	132 (12)	38 (8)	94 (15)
Male sex**	33,367 (55)	32,475 (55)	892 (82)	393 (82)	499 (83)
Aboriginal and Torres Strait Islander***	2,118 (5)	2,092 (5)	26 (2)	9 (2)	17 (3)
Place of birth****					
Australia	8,666 (21)	8,549 (21)	117 (11)	37 (8)	80 (13)
Americas, Europe, New Zealand	4,057 (10)	3,908 (10)	149 (14)	76 (16)	73 (12)
Africa	1,360 (3)	1,328 (3)	32 (3)	12 (3)	20 (3)
East Asia	11,661 (28)	11,303 (28)	358 (33)	169 (35)	189 (31)
Oceania and Southeast Asia	12,914 (31)	12,545 (31)	369 (34)	156 (33)	213 (35)
Western Asia	2,606 (6)	2,612 (6)	54 (5)	28 (6)	26 (4)
Co-infection					
With HCV	3,943 (7)	3,815 (6)	128 (12)	43 (9)	85 (14)
With HIV	394 (1)	381 (1)	13 (1)	6 (1)	7 (1)
LHD at the time of HBV notification*****					
Metropolitan NSW	6,049 (10)	5,957 (10)	92 (9)	39 (8)	53 (9)
Outer metropolitan NSW	27,773 (46)	27,253 (46)	520 (48)	227 (47)	293 (49)
Rural NSW	25,961 (43)	25,496 (43)	465 (43)	212 (44)	253 (42)
History of alcohol use disorder diagnosis	2,295 (4)	2,148 (4)	111 (10)	36 (7)	75 (12)

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IQR, interquartile range; LHD, local health district; NSW, New South Wales.
* 5 had missing information.
** 387 had missing information.
*** 17,722 had missing information.
**** 19,336 had missing information.
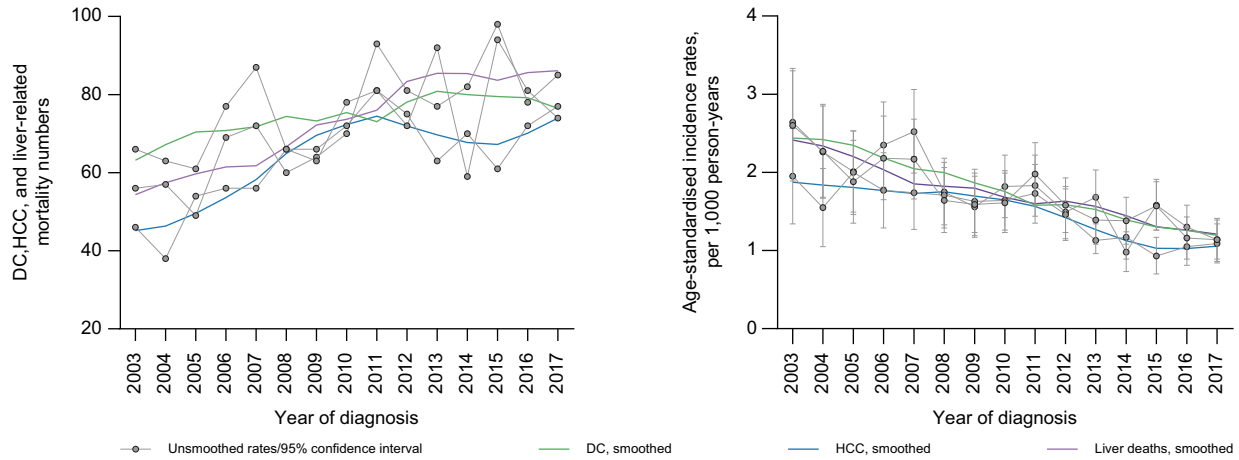***** 877 had missing information.

Fig. 1. Temporal trends in DC and HCC diagnoses, and liver-related mortality and age-standardised incidence rates in 2003-2017, among people with an HBV notification in NSW, 1993-2017. *2003-2017 was only chosen for visual display of data – the study period was 2001-2018. DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; NSW, New South Wales.

similar to those based on both hospitalisation and cancer registry data (combined HCC diagnosis, Fig. S2).

Trends in DC diagnosis, stratified by HBV/HCV co-infection notification

Between 2003 and 2017, DC diagnoses and age-standardised incidence declined from 58 to 54 and 2.52 (95% CI 1.82–3.23) to 0.88 (95% CI 0.63–1.13) per 1,000 person-years, respectively, among people with HBV mono-infection. However, the number and age-standardised incidence of DC among people with HBV/HCV co-infection increased from 6 to 20 and 4.02 (95% CI 0.53–7.51) to 6.14 (95% CI 4.31–7.96) per 1,000 person-years, respectively (Fig. 2).

Trends in antiviral treatment during 2010-2017

Between 2010 and 2017, the percentage of individuals on HBV treatment per calendar year increased from 3.8% to around 16.4% (Fig. 3).
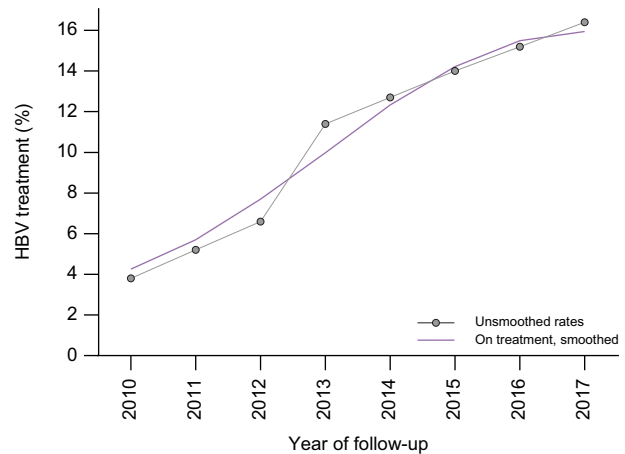
Fig. 3. Trends in antiviral treatment during 2010-2017 among people with an HBV notification (2009-2017), n = 17,340.
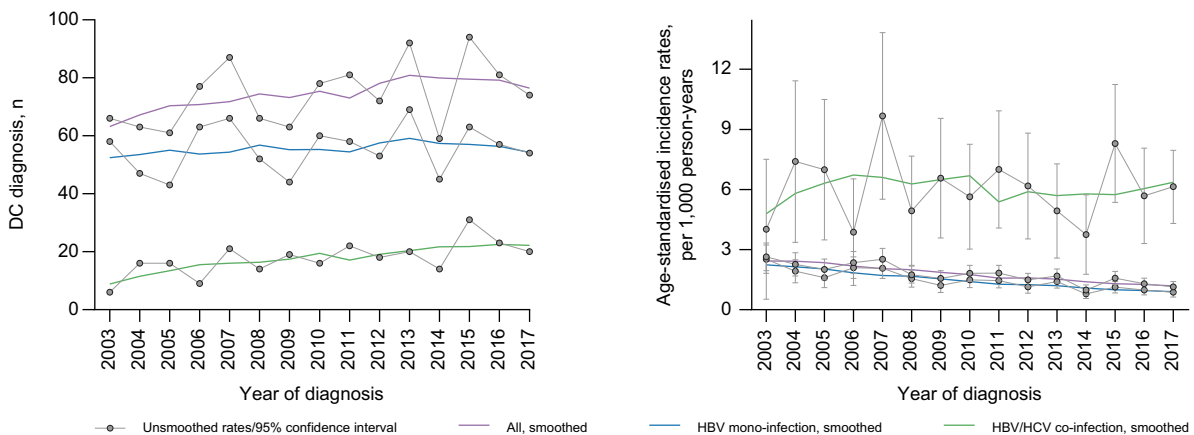
Fig. 2. Trends in DC diagnosis numbers and rates, overall and by HBV/HCV co-infection in 2003-2017, among people with an HBV notification in NSW, 1993-2017. *2003-2017 was only chosen for visual display of data – the study period was 2001-2018. DC, decompensated cirrhosis; NSW, New South Wales.

Time to DC diagnosis after an HBV notification

Overall, among 1,276 people with a DC diagnosis, 33% (n = 427) had a late HBV notification, declining from 41% (244 of 594) in 2001-2009 to 29% (192 of 659) in 2010-2018. Compared to people with an HBV mono-infection notification, those with HBV/HCV co-infection had a slightly larger decline in the proportion with late HBV notification (41% and 37% in 2001-2009 vs. 30% and 21% in 2010-2018, respectively) (Fig. 4). Among 379 people with a history of AUD and DC diagnosis, 31% (n = 118) had a late HBV notification, declining from 39% (64 of 165) in 2001-2009 to 25% (54 of 214) in 2010-2018 (Table S1). In adjusted analysis, late HBV notification was associated with older age at the time of HBV notification (≥47 years, median) (adjusted odds ratio [aOR] 2.91, 95% CI 1.97–4.31), Aboriginal and Torres Strait Islander ethnicity (aOR 0.41, 95% CI 0.17–0.94) and period of DC diagnosis (≥2014, aOR 0.58, 95% CI 0.41–0.83) (Table 3).

Time to HCC diagnosis after an HBV notification

Overall, among 1,087 people with an HCC diagnosis, 31% (n = 339) had a late HBV notification, declining from 40% (188 of 475) in 2001-2009 to 25% (151 of 601) in 2010-2018. People with an HBV mono-infection notification and those with HBV/HCV co-infection had a similar decline in the proportion of late HBV notification (40% and 37% in 2001-2009 vs. 26% and 22% in 2010-2018, respectively) (Fig. 4). In adjusted analysis, late HBV notification among those with an HCC diagnosis was associated with older age at the time of HBV notification (≥50 years, median) (aOR 4.98, 95% CI 3.25, 7.63) (Table 3).

Factors associated with DC diagnosis during 2009-2018

In adjusted analysis, DC diagnosis was associated with older age (birth before 1944) (adjusted hazard ratio [aHR] 2.06, 95% CI 1.57–2.69), history of AUD (aHR 4.82, 95% CI 3.96–5.87), HCV co-infection (aHR 1.88, 95% CI 1.53–2.31), and male sex (aHR 1.93,
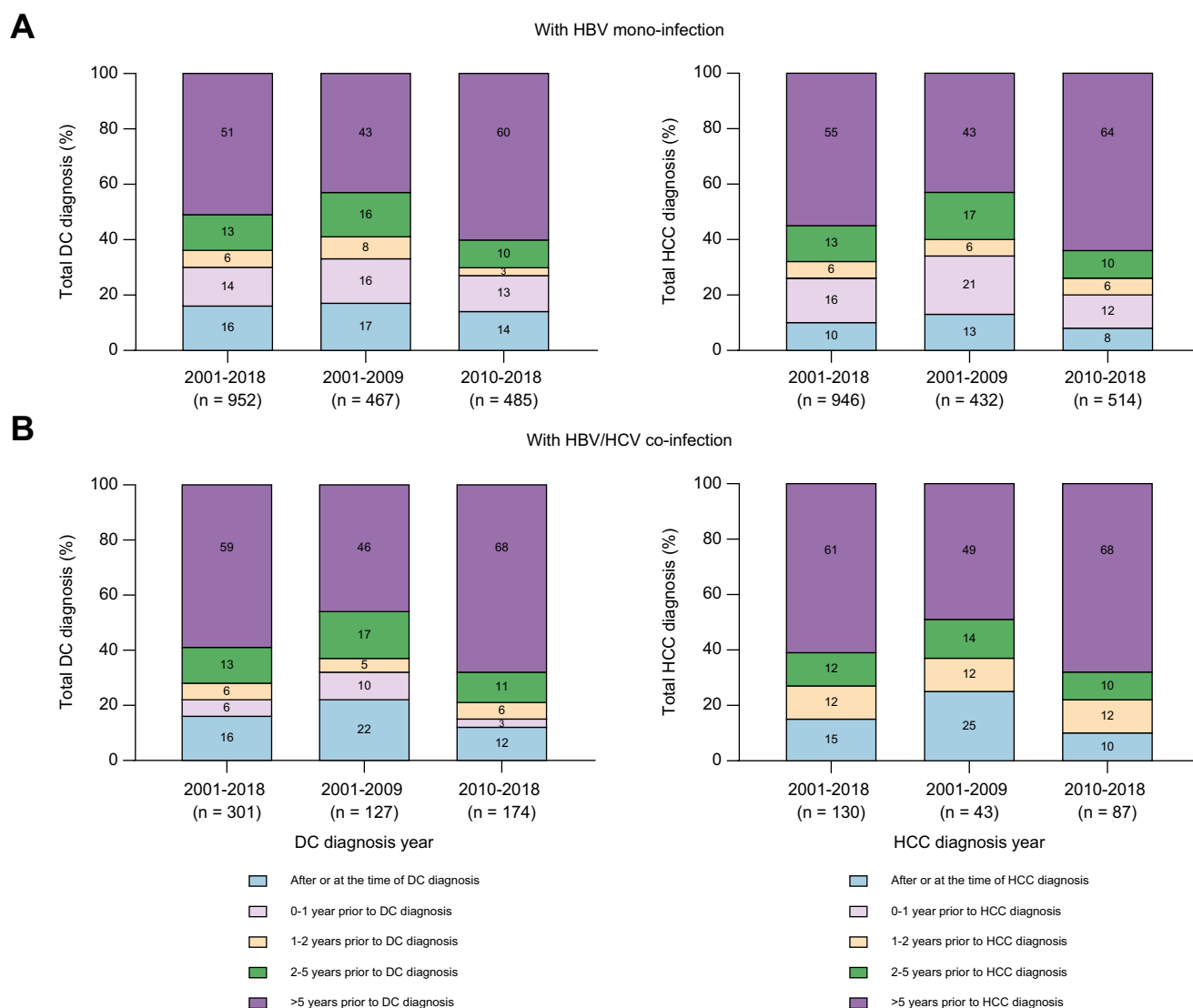
A

B

Fig. 4. Time from HBV notification to decompensated cirrhosis or hepatocellular carcinoma diagnosis. Among (A) people with an HBV mono-infection notification (n = 952 for DC and n = 946 for HCC), and (B) people with an HBV/HCV co-infection notification (n = 301 for DC and n = 130 for HCC). *(B) (for HCC) combined 2 categories, small cells (<5). DC, decompensated cirrhosis; HCC, hepatocellular carcinoma.

Table 3. Logistic regression analysis, evaluating factors associated with late HBV notification among people with decompensated cirrhosis (n = 668) and hepatocellular carcinoma (n = 606).

Characteristic, n %	Late HBV notification (DC), n = 187	aOR	95% CI	*p* value	Late HBV notification (HCC), n = 152	aOR	95% CI	*p* value
Age at HBV notification, by median								
<47 years	57 (17)	1.00			34 (11)	1.00		
≥47 years	130 (38)	2.91	1.97–4.31	<0.001	118 (39)	4.98	3.25, 7.63	<0.001
Sex								
Female	47 (29)				24 (23)			
Male	140 (28)	-	-	-	128 (26)	-	-	-
Aboriginal and Torres Strait Islander*								
No	178 (30)	1.00			-	-	-	-
Yes	8 (12)	0.41	0.17–0.94	0.037				
Country of birth								
Australia	57 (25)	1.00			20 (25)			
Americas/Europe, New Zealand	27 (26)	0.56	0.31–1.01	0.054	19 (26)	-	-	-
Africa	7 (35)	1.64	0.57–4.74	0.356				
East Asia	35 (30)	0.68	0.38–1.22	0.200	50 (26)	-	-	-
Oceania and Southeast Asia	50 (31)	0.75	0.44–1.27	0.289	51 (24)	-	-	-
Western Asia	9 (26)	0.57	0.23–1.38	0.216	6 (23)	-	-	-
Co-infection with HCV								
No	150 (30)	1.00			133 (26)			
Yes	37 (21)	0.82	0.50–1.34	0.437	19 (22)	-	-	-
LHD of residence at the time of HBV notification								
Rural NSW	27 (25)				14 (26)			
Outer metro NSW	88 (28)				72 (25)	-	-	-
Metro NSW	69 (29)				65 (26)	-	-	-
History of alcohol use disorder								
No	132 (29)				132 (25)			
Yes	55 (26)				20 (27)	-	-	-
Period of DC/HCC diagnosis								
≤2013	108 (33)	1.00			82 (28)	1.00		
≥2014	79 (23)	0.58	0.41–0.83	0.003	70 (22)	0.68	0.46, 1.01	0.060

Levels of significance: *p* <0.05 (multivariable logistic regression analysis).
aOR, adjusted odds ratio; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LHD, local health district.
* Not shown, small n (<5).

95% CI 1.60–2.31). Moreover, CCI groups 1-2 and 3+ were significantly associated with a higher risk of DC diagnosis (aHR 3.74, 95% CI 3.04–4.60 and 10.29, 95% CI 8.46–12.51), respectively (Table 4). The association between DC diagnosis and HCV co-infection was driven by the LHD of residence at the time of HBV notification (aHR 2.42, 95% CI 1.73–3.40 for outer metro LHD residents and aHR 1.74, 95% CI 1.17–2.59 for people living in metro NSW) (Table S2).

Factors associated with HCC diagnosis during 2009-2018

In adjusted analysis, HCC diagnosis was associated with older age (birth before 1944) (aHR 3.94, 95% CI 2.91–5.32), male sex (aHR 3.79, 95% CI 3.05–4.71), history of AUD (aHR 2.18, 95% CI 1.66–2.86), and HCV co-infection (aHR 2.06, 95% CI 1.59–2.66). Moreover, CCI groups 1-2 and 3+ were associated with a significantly higher risk of HCC diagnosis (aHR 1.73, 95% CI 1.37–2.20 and 6.23, 95% CI 5.11–7.59), respectively. Further, compared to people born in Australia, those born in Africa (aHR 3.12, 95% CI 1.85–5.26), East Asia (aHR 3.73, 95% CI 2.70–5.15), and Oceania & Southeast Asia (aHR 3.05, 95% CI 2.24–4.15) had a higher risk of an HCC diagnosis (Table 4).

Discussion

Our study demonstrated important trends in DC and HCC diagnosis, and liver-related mortality among people with an HBV notification in NSW, Australia. Between 2003 and 2017, the number of first hospitalisation for DC and HCC, and liver-related deaths increased. In contrast, age-standardised incidence rates for these events declined. An increase in the population-level burden of advanced HBV-related liver disease, in the context of increasing therapeutic intervention uptake and declining individual-level risk, is explained by an expanding and ageing HBV-infected population. Improved HBV therapies (entecavir or tenofovir) were introduced from the mid-2000s, with progressively increasing treatment initiation rates.[29,30] Further potential advanced liver disease risk reductions were limited by late HBV diagnosis, HCV co-infection, and AUD. Thus, enhanced HBV screening, HCV cure, improved AUD management, and increases in HBV therapeutic uptake all have the potential to reduce the burden of advanced HBV-related liver disease.[31,32]

Suboptimal HBV screening and CHB latency that can span decades has limited opportunities to prevent progression to ESLD.[14] Overall, during this period, 33% and 31% of HBV-related DC and HCC cases were diagnosed late (from 2 years prior to after these events), respectively, consistent with the recent estimates of under-diagnosis in the overall Australian HBV-infected population (31-40%).[12,15] Encouragingly, the proportion of late diagnosis has declined over time; continued population-level screening and surveillance efforts, including consideration of one-off universal HBV testing, are required.[33]

Achieving higher HBV therapeutic coverage among the eligible population is clearly a goal to address continued disease burden. Even in patients with DC, appropriate antiviral therapy can ameliorate hepatic dysfunction.[34,35] Although antiviral therapy also improves survival following HCC,[36,37] prognosis

Table 4. Cox proportional-hazards regression analysis, evaluating factors associated with decompensated cirrhosis and hepatocellular carcinoma diagnosis (2009-2018) among people with an HBV notification (1993-2017), n = 60,660.

	DC				HCC			
Characteristic, n %	n = 668*	aHR	95% CI	p value	n = 606*	aHR	95% CI	p value
Birth cohort								
Born ≥1965	167 (1)	1.00			94 (<1)	1.00		
Born 1945-1964	381 (2)	2.07	1.70–2.52	<0.001	386 (2)	3.69	2.90–4.68	<0.001
Born ≤1944	120 (2)	2.06	1.57–2.69	<0.001	125 (3)	3.94	2.91–5.32	<0.001
Sex								
Female	161 (1)	1.00			104 (<1)	1.00		
Male	505 (2)	1.94	1.60–2.31	<0.001	498 (2)	3.79	3.05–4.71	<0.001
Aboriginal and Torres Strait Islander								
No	599 (1)	1.00			576 (1)	1.00		
Yes	65 (3)	0.88	0.66–1.18	0.417	17 (1)	0.78	0.46–1.32	0.362
Country of birth								
Australia	229 (3)	1.00			80 (1)	1.00		
Americas, Europe, New Zealand	104 (3)	1.00	0.77–1.29	0.995	73 (2)	1.60	1.12–2.27	0.008
Africa	18 (1)	1.18	0.72–1.93	0.505	20 (1)	3.12	1.85–5.26	<0.001
East Asia	116 (1)	1.14	0.87–1.50	0.331	188 (2)	3.73	2.70–5.15	<0.001
Oceania and Southeast Asia	163 (1)	1.11	0.87–1.42	0.361	213 (2)	3.05	2.24–4.15	<0.001
Western Asia	35 (1)	0.87	0.59–1.29	0.510	26 (1)	1.48	0.93–2.37	0.096
Co-infection with HCV								
No	494 (1)	1.00			518 (1)	1.00		
Yes	174 (4)	1.88	1.53–2.31	<0.001	87 (2)	2.06	1.59–2.66	<0.001
LHD of residence at HBV								
Rural NSW	110 (2)	1.00			53 (1)	1.00		
Outer metro NSW	312 (1)	1.22	0.97–1.55	0.092	293 (1)	1.26	0.91–1.75	0.152
Metro NSW	235 (1)	0.99	0.77–1.27	0.981	252 (1)	1.13	0.81–1.57	0.442
History of alcohol use disorder								
No	453 (1)	1.00			530 (1)	1.00		
Yes	215 (9)	4.82	3.96–5.87	<0.001	75 (3)	2.18	1.66–2.86	<0.001
†**Charlson comorbidity index**								
0	133 (1)	1.00			292 (1)	1.00		
1-2	219 (5)	3.74	3.04–4.60	<0.001	99 (2)	1.73	1.37–2.20	<0.001
3+	316 (9)	10.29	8.46–12.51	<0.001	210 (7)	6.23	5.11–7.59	<0.001

Levels of significance: p <0.05 (cox proportional-hazards regression analyses).
aHR, adjusted hazard ratio; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LHD, local health district; NSW, New South Wales.
* Missing values were included in all adjusted models.
† Charlson comorbidity index score indicates degree of health; higher scores indicate worse health condition.

remains poor.[36,38] Thus, the primary focus for reducing advanced liver disease burden and mortality relies heavily on preventing disease progression.[39] Recent systematic reviews reinforce the favourable response of timely antiviral therapy by demonstrating an estimated 30% to 75% reduction in HCC risk.[34,35]

In Australia, the number of individuals on HBV therapy has increased since the mid-2000s[29]; however, considerable gaps remain in the HBV cascade of care, given that modelling estimates that two-thirds of eligible individuals are not receiving treatment.[40] Our study does, however, show a steady increase in treatment uptake over time. Enhancing HBV antiviral therapy coverage and increasing screening are clear priorities within the Australian Hepatitis B Strategy.[41] Broadened antiviral therapy prescription through general practitioners has commenced but should be accelerated. Similarly, improved HBV screening strategies facilitated by primary care electronic health systems need to be implemented, including pop-up reminders of high-risk groups, particularly based on country of birth.[33]

Although later study period (2010-2018) was associated with reduced individual risk of HBV-related DC and HCC, several associated factors persisted: older age, male sex, history of AUD, and HCV co-infection. These factors have a known association with fibrosis progression or advanced liver disease,[42,43] but importantly HCV co-infection is modifiable. Most HCV infections (more than 80%) are diagnosed in Australia, and since 2016, an

unrestricted HCV direct-acting antiviral therapy program has facilitated high treatment uptake.[44] However, those with HBV/HCV co-infection appear to have had relatively lower uptake.[45] Therefore, a particular emphasis should be placed on HCV cure in this population, given their higher risk of advanced liver disease. Further efforts are also required to improve AUD management, including cross-discipline education and training for practitioners involved in HBV management.

Interestingly, most cases of HBV-related DC were observed among individuals born in Australia, given a higher rate of AUD and HCV co-infection among them.[46] In contrast, most HBV-related HCC diagnoses were among people born overseas, predominantly in the Asia-Pacific region. It is unclear why the non-Australian country of birth is a common risk factor for developing HBV-related HCC; literature suggests a higher prevalence of IFNλ3 gene polymorphisms among Asians that may be associated with fibrosis progression.[47,48] Moreover, the prevalence of oncogenic HBV genotype (genotype C) in Asian populations has a potential relationship with HCC development.[49]

Older age was associated with late HBV notification among people with DC and HCC, congruent with other Australian and Canadian studies.[12,50] This raises considerable concern of a "missed opportunity" for this older cohort to have had access to effective and timely antiviral therapy. In contrast, after accounting for other factors in another Canadian study, people in

the older birth cohort did not show an association with late diagnosis.[13] Nonetheless, there remains a need to further reduce the late diagnosis of hepatitis.[12,13]

There are several limitations to our study. First, HBV notifications in NSW are predominantly based on evidence of chronic infection as defined by HBV serology. However, the number of individuals with active viral replication could not be evaluated. Second, we relied on hospitalisation coding data to diagnose DC and HCC, which could introduce misclassification (over-diagnosis) or missed cases (under-diagnosis). A Canadian validation study of health administrative data *vs.* a tertiary care hepatology clinic demonstrated 90% sensitivity and 88% specificity for the diagnosis of DC and 78% sensitivity and 99% specificity for diagnosing HCC through administrative data.[51] Similarly, an NSW linkage study demonstrated high (around 90%) HCC diagnostic concordance between hospitalisation data and the NSWCR. However, sensitivity analysis for validating DC events through hospital admission records has not been undertaken in NSW.[12,19,24] Third, in NSW, administrative data sources were available for different periods of time. Hence, to improve the accuracy of trends in DC and HCC diagnosis numbers and age-standardised rates and to minimise biased estimations of time to DC or HCC diagnosis, the study time period was restricted. We also undertook a sensitivity analysis evaluating trends in hospitalisation-based HCC diagnoses (excluding cancer registry cases) which were available for the total study period, with similar findings. Fourth, to study the real-world mortality among individuals with HBV notifications in NSW, liver-related mortality was based on deaths following hospital admissions for DC or HCC and thus excludes liver-related deaths which occurred without a previous hospitalisation and may include some deaths unrelated to liver disease.[24] Information on cause-specific mortality from death certificates will be available in the future, but there are also limitations with cause of death ascertainment. Fifth, although compensated cirrhosis is a major risk factor for both DC and HCC, ICD-10 coded hospitalisation data does not have a code for compensated cirrhosis. Sixth, data on Aboriginal ethnicity and the place of birth was unavailable for many individuals. In the analyses of factors associated with DC and HCC diagnoses, missing information of each variable were identified and included in the unadjusted and adjusted models. Lastly, using administrative data to define AUD has clear limitations, given the low sensitivity of administrative data (68% sensitivity and 97% specificity for the diagnosis of heavy alcohol intake).[52]

In conclusion, this population-level study provides evidence for declining risk of HBV-related DC, HCC, and liver-related mortality, suggesting an impact of highly effective antiviral therapy from the mid-2000s. The proportion of HBV-related DC and HCC cases with late hepatitis notification has also declined. Further strategies to reduce HBV disease burden include enhanced HBV screening and earlier diagnosis, increased HBV treatment coverage for eligible individuals, and addressing modifiable co-factors such as HCV co-infection and AUD.

References

Author names in bold designate shared co-first authorship

[1] World Health Organization. Global hepatitis report, 2017 [Internet]. Geneva: World Health Organization; 2017 [cited 2021 Oct 17]. Available from: https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/pdf.

[2] World Health Organization. Global health sector strategy on viral hepatitis 2016–2021 [Internet]. Geneva: World Health Organization; 2016 [cited 2021 Oct 17]. Available from: https://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/.

[3] World Health Organization. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Accountability for the global health sector strategies 2016–2021: actions for impact. Geneva: World Health Organization; 2021 [cited 2021 Oct 17]. Available from: https://www.who.int/publications/i/item/9789240027077.

[4] **Asrani SK**, **Devarbhavi H**, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol 2019;70(1):151–171.

[5] Lok AS, McMahon BJ, Brown Jr RS, Wong JB, Ahmed AT, Farah W, et al. Antiviral therapy for chronic hepatitis B viral infection in adults: a systematic review and meta-analysis. Hepatology (Baltimore, Md) 2016;63(1):284–306.

[6] **Howell J**, **Pedrana A**, Cowie BC, Doyle J, Getahun A, Ward J, et al. Aiming for the elimination of viral hepatitis in Australia, New Zealand, and the Pacific Islands and Territories: where are we now and barriers to meeting World Health Organization targets by 2030. J Gastroenterol Hepatol 2019;34(1):40–48.

[7] Bertuccio P, Turati F, Carioli G, Rodriguez T, La Vecchia C, Malvezzi M, et al. Global trends and predictions in hepatocellular carcinoma mortality. J Hepatol 2017;67(2):302–309.

[8] Poordad FF. Presentation and complications associated with cirrhosis of the liver. Curr Med Res Opin 2015;31(5):925–937.

[9] **Pascual S**, **Miralles C**, **Bernabé JM**, **Irurzun J**, **Planells M**. Surveillance and diagnosis of hepatocellular carcinoma: a systematic review. World J Clin cases 2019;7(16):2269–2286.

[10] Cholongitas E, Papatheodoridis GV, Goulis J, Vlachogiannakos J, Karatapanis S, Ketikoglou J, et al. The impact of newer nucleos(t)ide analogues on patients with hepatitis B decompensated cirrhosis. Ann Gastroenterol 2015;28(1):109–117.

[11] Waziry R, Grebely J, Amin J, Alavi M, Hajarizadeh B, George J, et al. Trends in hepatocellular carcinoma among people with HBV or HCV notification in Australia (2000-2014). J Hepatol 2016;65(6):1086–1093.

[12] Alavi M, Law MG, Grebely J, Amin J, Hajarizadeh B, George J, et al. Time to decompensated cirrhosis and hepatocellular carcinoma after an HBV or HCV notification: a population-based study. J Hepatol 2016;65(5):879–887.

[13] Samji H, Yu A, Kuo M, Alavi M, Woods R, Alvarez M, et al. Late hepatitis B and C diagnosis in relation to disease decompensation and hepatocellular carcinoma development. J Hepatol 2017;67(5):909–917.

[14] Papatheodoridis GV, Chan HL, Hansen BE, Janssen HL, Lampertico P. Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. J Hepatol 2015;62(4):956–967.

[15] MacLachlan JH, Allard N, Towell V, Cowie BC. The burden of chronic hepatitis B virus infection in Australia, 2011. Aust N Z J Public Health 2013;37(5):416–422.

[16] MacLachlan JH, Cowie BC. Cultural and linguistic diversity of people living with chronic hepatitis B in 2011-2016: changing migration, shifting epidemiology. Aust N Z J Public Health 2018;42(5):441–443.

[17] Xiao Y, Howell J, van Gemert C, Thompson AJ, Seaman CP, McCulloch K, et al. Enhancing the hepatitis B care cascade in Australia: a cost-effectiveness model. J Viral Hepat 2020;27(5):526–536.

[18] Robotin MC, Masgoret X, Porwal M, Goldsbury D, Khoo C, George J. Using a chronic hepatitis B Registry to support population-level liver cancer prevention in Sydney, Australia. Clin Epidemiol 2018;10:41–49.

[19] Alavi M, Grebely J, Hajarizadeh B, Amin J, Larney S, Law MG, et al. Mortality trends among people with hepatitis B and C: a population-based linkage study, 1993-2012. BMC Infect Dis 2018;18(1):215.

[20] Australian Bureau of Statistics. National, state and territory population [Internet]. Canberra (ACT): Australian Bureau of Statistics; 2021 [cited 2021 Oct 17]. Available from: https://www.abs.gov.au/statistics/people/population/national-state-and-territory-population/mar-2021.

[21] The Kirby Institute. Hepatitis B and C in Australia annual surveillance report supplement 2016 [Internet]. NSW (AU): The Kirby Institute; 2016 [cited 2021 Oct 17]. Available from: https://kirby.unsw.edu.au/sites/default/files/kirby/report/SERP_HepBandC-Annual-Surveillance-Report-Supp-2016.pdf.

[22] The centre for health record linkage (CHeReL). 2021. Available from: https://www.cherel.org.au/.

[23] Australian Institute of Health and Welfare. Data linkage [Internet]. Canbera (ACT): Australian Institute of Health and Welfare; 2021 [cited 2021 Oct 17]. Available from: https://www.aihw.gov.au/our-services/data-linkage.

[24] Alavi M, Law MG, Valerio H, Grebely J, Amin J, Hajarizadeh B, et al. Declining hepatitis C virus-related liver disease burden in the direct-acting antiviral therapy era in New South Wales, Australia. J Hepatol 2019;71(2):281–288.

[25] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J chronic Dis 1987;40(5):373–383.

[26] Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 2011;173(6):676–682.

[27] NSW Health. Local health districts and specialty networks [Internet]. NSW (Au): NSW Health; 2018 [cited 2021 Oct 17]. Available from: https://www.health.nsw.gov.au/lhd/pages/default.aspx.

[28] Friedmann PD. Alcohol use in adults. New Engl J Med 2013;368(17):1655–1656.

[29] MacLachlan J, Smith C, Towell V, Cowie B. Viral hepatitis mapping project: national report 2018–19. Darlinghurst: Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM); 2020.

[30] Matthews G, Robotin M. All you wanted to know about hepatitis B: a guide for primary care providers. Sydney: Australasian Society for HIV Medicine and Cancer Council NSW; 2008.

[31] **Mathurin P**, **Bataller R**. Trends in the management and burden of alcoholic liver disease. J Hepatol 2015;62(1 Suppl):S38–S46.

[32] Pimpin L, Cortez-Pinto H, Negro F, Corbould E, Lazarus JV, Webber L, et al. Burden of liver disease in Europe: epidemiology and analysis of risk factors to identify prevention policies. J Hepatol 2018;69(3):718–735.

[33] Allard NL, MacLachlan JH, Tran L, Yussf N, Cowie BC. Time for universal hepatitis B screening for Australian adults. Med J Aust 2021;215(3):103–105.e1.

[34] Papatheodoridis GV, Lampertico P, Manolakopoulos S, Lok A. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. J Hepatol 2010;53(2):348–356.

[35] Govan L, Wu O, Xin Y, Hutchinson SJ, Hawkins N. Comparative effectiveness of antiviral treatment for hepatitis B: a systematic review and Bayesian network meta-analysis. Eur J Gastroenterol Hepatol 2015;27(8):882–894.

[36] Thein HH, Walter SR, Gidding HF, Amin J, Law MG, George J, et al. Survival after diagnosis of hepatocellular carcinoma and potential impact of treatment in a hepatitis B or C infected cohort. Hepatol Res Off J Jpn Soc Hepatol 2012;42(12):1175–1186.

[37] Papatheodoridis GV, Idilman R, Dalekos GN, Buti M, Chi H, van Boemmel F, et al. The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. Hepatology (Baltimore, Md) 2017;66(5):1444–1453.

[38] Zhong JH, Ke Y, Gong WF, Xiang BD, Ma L, Ye XP, et al. Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. Ann Surg 2014;260(2):329–340.

[39] Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. PLoS Med 2014;11(4):e1001624.

[40] McCulloch K, Romero N, MacLachlan J, Allard N, Cowie B. Modeling progress toward elimination of hepatitis B in Australia. Hepatology (Baltimore, Md) 2020;71(4):1170–1181.

[41] Department of Health Australian Government. Third national hepatitis B strategy [Internet]. Canbera (ACT); 2018 [cited 2021 Oct 17]. Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/ohp-bbvs-1/$File/Hep-B-Third-Nat-Strategy-2018-22.pdf.

[42] Wong GL. Prediction of fibrosis progression in chronic viral hepatitis. Clin Mol Hepatol 2014;20(3):228–236.

[43] Wu YJ, Xu MY, Lu LG. Clinical advances in fibrosis progression of chronic hepatitis B and C. J Clin Translational Hepatol 2014;2(4):222–227.

[44] Hajarizadeh B, Grebely J, Matthews GV, Martinello M, Dore GJ. Uptake of direct-acting antiviral treatment for chronic hepatitis C in Australia. J viral Hepat 2018;25(6):640–648.

[45] Valerio H, Alavi M, Law M, Tillakeratne S, Amin J, Janjua NZ, et al. High hepatitis C treatment uptake among people with recent drug dependence in New South Wales, Australia. J Hepatol 2021;74(2):293–302.

[46] Valery PC, McPhail S, Stuart KA, Hartel G, Clark PJ, O'Beirne J, et al. Changing prevalence of aetiological factors and comorbidities among Australians hospitalised for cirrhosis. Intern Med J 2021;51(5):691–698.

[47] Eslam M, Hashem AM, Leung R, Romero-Gomez M, Berg T, Dore GJ, et al. Interferon-λ rs12979860 genotype and liver fibrosis in viral and non-viral chronic liver disease. Nat Commun 2015;6:6422.

[48] Eslam M, Ahlenstiel G, George J. Interferon lambda and liver fibrosis. J Interferon Cytokine Res Off J Int Soc Interferon Cytokine Res 2019;39(10):627–635.

[49] Wong GL, Chan HL, Yiu KK, Lai JW, Chan VK, Cheung KK, et al. Meta-analysis: the association of hepatitis B virus genotypes and hepatocellular carcinoma. Aliment Pharmacol Ther 2013;37(5):517–526.

[50] Lapointe-Shaw L, Chung H, Holder L, Kwong JC, Sander B, Austin PC, et al. Diagnosis of chronic hepatitis B pericomplication: risk factors and trends over time. Hepatology (Baltimore, Md) 2021;73(6):2141–2154.

[51] Lapointe-Shaw L, Georgie F, Carlone D, Cerocchi O, Chung H, Dewit Y, et al. Identifying cirrhosis, decompensated cirrhosis and hepatocellular carcinoma in health administrative data: a validation study. PloS one 2018;13(8):e0201120.

[52] Kim HM, Smith EG, Stano CM, Ganoczy D, Zivin K, Walters H, et al. Validation of key behaviourally based mental health diagnoses in administrative data: suicide attempt, alcohol abuse, illicit drug abuse and tobacco use. BMC Health Serv Res 2012;12:18.