# Survival Following Hospitalization With Hepatocellular Carcinoma Among People Notified With Hepatitis B or C Virus in Australia (2000-2014)

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**We assessed trends in HCC survival in patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection in New South Wales, Australia. Data on HBV (n = 54,399) and HCV (n = 96,908) notifications (1993-2012) were linked to a hospitalization database (July 2000-June 2014), the New South Wales Cancer Registry, and the New South Wales Death Registry. A total of 725 (1.3%) first HBV-hepatocellular carcinoma (HCC) and 1,309 (1.4%) first HCV-HCC hospitalizations were included. Death occurred in 60.4% of HBV-HCC and 69.6% of HCV-HCC patients. Median survival following first HBV-HCC hospitalization improved from 0.6 years (95% confidence interval [CI] 0.39-1.28) in 2000-2004 to 2.8 years (1.54-5.54) in 2010-2014. Median survival following first HCV-HCC hospitalization was 0.8 years (0.45-1.33) in 2000-2004 and 0.9 (0.67-1.18) in 2010-2014. One-year HBV-HCC survival in 2010-2014 compared to 2000-2004 improved for those with (94% versus 81%) and without (42% versus 33%) potentially curative procedures (liver resection, liver transplantation, and radiofrequency ablation). Factors associated with improved survival following HBV-HCC were later study period (hazard ratio [HR] = 0.74; 95% CI, 0.57-0.97) and potentially curative procedures (liver resection, liver transplantation, and radiofrequency ablation) (HR = 0.23; 95% CI, 0.17-0.29), while male gender (HR = 1.37; 95% CI, 1.03-1.82), human immunodeficiency virus coinfection (HR = 3.06; 95% CI, 1.36-6.88), and Charlson Comorbidity Index ≥3 (HR = 1.81; 95% CI, 1.35-2.40) were associated with reduced survival. Factors associated with improved survival following HCC-HCV were Asia-Pacific country of birth (HR = 0.68; 95% CI, 0.55-0.84) and potentially curative procedures (HR = 0.21; 95% CI, 0.17-0.25), while age (HR = 1.01; 95% CI, 1.01-1.02), rural place of residence (HR = 1.46; 95% CI, 1.22-1.74), and human immunodeficiency virus coinfection (HR = 2.71; 95% CI, 1.19-6.15) were associated with reduced survival. *Conclusion:* All-cause survival following HBV-HCC has improved considerably, suggesting an impact of more effective antiviral therapy and earlier HCC diagnosis; in contrast, all-cause survival for HCV-HCC is unchanged. (*Hepatology Communications* 2017;1:736–747)**

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death worldwide.[1] Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the major causes of HCC,[2] responsible for around 80% of cases.[3] HCC has a very poor prognosis,[4] given the limited treatment options, with only a minority of patients being eligible for potentially curative strategies.[2,4]

Factors associated with HCC survival include HCC stage,[5,6] degree of liver function impairment, early HBV/HCV diagnosis and treatment,[7] HCC management received, and the presence of other clinical conditions at time of HCC diagnosis.[2,8] The past decade has witnessed improvements in HCC management and treatment of HCV and HBV.[9] The impact of these clinical management

*Abbreviations: CI, confidence interval; DAA, direct-acting antiviral; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; ICD-10-AM, International Classification of Diseases, Tenth Revision, Australian Modification; IQR, interquartile range; NSW, New South Wales; RFA, radiofrequency ablation; SLA, statistical local area.*

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changes on HCC survival at the population level is unclear.

The mandatory notification of HBV and HCV diagnoses in Australia since 1991 and well-established HCC surveillance systems through the New South Wales (NSW) Cancer Registry and the Admitted Patient Data Collection Database provide the opportunity to evaluate HCC survival at the population level.[10] The aims of this study were (1) to assess trends in HBV-HCC and HCV-HCC survival, including in those who received potentially curative HCC procedures, and (2) to identify factors associated with mortality risk.

# Patients and Methods

## STUDY POPULATION AND DATA SOURCES

The study population included all persons with HBV or HCV infection with first HCC hospitalization from July 1, 2000. HBV or HCV infection was based on notifications to the Notifiable Conditions Information Management System between January 1, 1993, and December 31, 2012. Under the Public Health Act 1991 all new HBV and HCV cases are notifiable to the NSW Department of Health.[10] A notifiable HBV case requires detection of HBV surface antigen or HBV DNA. A notifiable HCV case requires detection of anti-HCV antibody or HCV RNA. Personal identifiers were first recorded in the Notifiable Conditions Information Management System in 1992. HBV and HCV notifications were linked to administrative databases to assess potential factors associated with survival following HCC.

## HCC ASCERTAINMENT AND CASE DEFINITION

A case of HCC was defined by hospitalization with an HCC code (C22.0) as principal or additional diagnosis. Hospital admissions were obtained from the NSW Admitted Patient Data Collection Database, which includes inpatient hospitalizations from all public and private hospitals in NSW between July 1, 2000, and June 30, 2014. Data on each hospitalization are recorded at separation and include demographic and administrative data as well as the principle and any additional diagnoses coded according to the *International Classification of Diseases*, Tenth Revision,

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Australian Modification (ICD-10-AM). The validity of ascertainment of HCC cases through hospitalization-based codes was assessed by linkage to the NSW Cancer Registry, with data available for the period between January 1, 1994, and December 31, 2009.

*Potentially curative HCC procedures* were defined as ever receiving liver surgical resection (ICD-10-AM block 953; 30414-00 to 30421-00), liver transplantation (ICD-10-AM block 954; 90317-00), or radiofrequency ablation (RFA; ICD-10-AM block 95650950-00) during or following first HCC hospitalization as principle or additional procedure. Data for these variables were available through the hospitalization data sets for the entire study period (2000-2014).

## HBV AND HCV TREATMENT

Overall estimates of HBV and HCV treatment dispensed over the study period were extracted from the Pharmaceutical Benefits Scheme (http://www.pbs.gov.au) and the Kirby Institute annual surveillance reports between 2003 and 2014.[11] Data on estimates of HBV treatment dispensed between 2003 and 2014 were available for entecavir, tenofovir, lamivudine, adefovir dipivoxil, interferon-alfa-2b, interferon-alfa-2a, peginterferon alfa-2a, and telbivudine. Data on estimates of HCV treatment dispensed between 2002 and 2014 were available for interferon + ribavirin, pegylated interferon, and pegylated interferon + ribavirin.

## OTHER DATA SOURCES AND DEFINITIONS

Data on human immunodeficiency virus (HIV) were obtained from the National HIV Registry that includes all individuals notified with HIV between January 1, 1993, and December 31, 2013. Data on deaths among those with HBV or HCV notification was obtained from the NSW Registry for Births, Deaths and Marriages between January 1, 1993, and June 18, 2014. HCV and HBV monoinfections were defined according to the earliest notification record available. HBV/HCV coinfections were defined according to date of notification of the latest infection and included in the HCV cohort.

*Alcohol-related hospitalization* was defined according to hospitalization with any of the following principal or additional ICD-10 codes: alcohol abuse counseling 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 behavioral disorders due to alcohol (F10). For HCC and alcohol dependency diagnoses, the first hospitalization as principle or additional diagnosis was used. All diseases listed in the Charlson Comorbidity Index as principle or additional diagnosis were analyzed, including acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular accident, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes mellitus, diabetes mellitus complications, paraplegia, renal disease, cancers, metastatic cancers, and severe liver disease.[12] The codes for HIV (B20-24) and malignant liver cancers (C22) were excluded from the Charlson Comorbidity Index to avoid overlapping with the main variables of HIV and HCC that were included separately in the analysis.[13] Time to HCC was calculated from date of HBV or HCV notification to date of first HCC hospitalization and categorized as follows: $\geq$2 years, <2 years, and at time of or after HCC.[14] *Decompensated cirrhosis* was defined as ever hospitalized with ascites (R18.0), bleeding esophageal 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). Codes for decompensated cirrhosis were removed from the Charlson Comorbidity Index in the multivariate analyses of this subpopulation.

## LINKAGE PROCESS

Data linkage was completed in two stages. First, HBV and HCV notifications were linked internally to identify patients with HBV/HCV coinfection. All notifications were then matched to all other data sets using probabilistic record linkage methods based on matching demographic data, using ChoiceMaker software.[10] The second stage involved HBV and HCV notification linkage to HIV notifications using deterministic methods based on a 100% match on name code, sex, and date of birth. Data linkage was done by the Centre for Health Record Linkage.[10]

## STATISTICAL ANALYSIS

Analyses of all-cause survival following HCC hospitalization were undertaken using Cox proportional hazards model. The start date was date of first HCC hospitalization. The end date was date of death or end of follow-up (June 31, 2014), whichever occurred first.

**TABLE 1. CHARACTERISTICS OF PEOPLE HOSPITALIZED WITH HCC AMONG THOSE WITH HBV NOTIFICATION IN NSW, AUSTRALIA (2000-2014)**

| Characteristic | Overall (N = 725) | 2000-2004 (n = 205) | 2005-2009 (n = 257) | 2010-2014 (n = 263) |
|---|---|---|---|---|
| Median year of birth (IQR) | 1950 (18) | 1944 (19) | 1950 (17) | 1954 (16) |
| Year of birth | | | | |
| Pre-1945 | 264 (36) | 110 (54) | 93 (36) | 61 (23) |
| 1945-1955 | 221 (31) | 47 (23) | 84 (33) | 90 (34) |
| 1956+ | 240 (33) | 48 (23) | 80 (31) | 112 (43) |
| Median age at HCC diagnosis, years (IQR) | 58 (17) | 58 (18) | 57 (17) | 58 (15) |
| Gender | | | | |
| Male | 604 (83) | 173 (84) | 206 (80) | 225 (85) |
| Place of residence* | | | | |
| Metro | 336 (46) | 87 (42) | 125 (49) | 124 (47) |
| Outer-metro | 341 (47) | 105 (51) | 114 (44) | 122 (46) |
| Rural | 44 (6) | 12 (6) | 17 (7) | 15 (6) |
| Missing | 4 (0.5) | 1 (0.5) | 1 (0.4) | 2 (0.7) |
| Place of birth | | | | |
| Australia | 41 (6) | 10 (5) | 13 (5) | 18 (7) |
| Asia Pacific | 529 (73) | 156 (77) | 190 (74) | 183 (69) |
| Europe | 68 (9) | 22 (11) | 32 (13) | 14 (5) |
| Other | 21 (3) | 2 (1) | 10 (4) | 9 (3) |
| Missing | 66 (9) | 15 (7) | 12 (5) | 39 (15) |
| HIV-positive | 8 (1) | 2 (1) | 4 (2) | 2(1) |
| Alcohol-related hospitalization | 55 (8) | 16 (8) | 16 (6) | 23 (9) |
| Charlson Comorbidity Index[†] | | | | |
| 0 | 174 (24) | 33 (16) | 60 (23) | 81 (30) |
| 1 | 242 (34) | 67 (33) | 92 (36) | 83 (31) |
| 2 | 67 (9) | 22 (11) | 24 (9) | 21 (8) |
| ≥3 | 242 (33) | 83 (40) | 81 (31) | 78 (29) |
| Median time from HBV notification, years (IQR)[‡] | 5 (10) | 2 (6) | 6 (9) | 10 (11) |
| Median time from NSW Cancer Registry diagnosis, months (IQR)[§] | 0.2 (0.9) | 0.2 (0.8) | 0.2 (0.8) | N/A |
| Potentially curative procedures[‖] | | | | |
| Liver resection | 227 (31) | 54 (26) | 80 (31) | 93 (35) |
| Liver transplantation | 27 (4) | 8 (4) | 14 (5) | 5 (2) |
| RFA | 41 (6) | 2 (1) | 20 (8) | 19 (7) |
| Died | 438 (60) | 156 (77) | 169 (64) | 113 (44) |
| Median age at death (IQR) | 61 (18) | 60 (16) | 60 (19) | 58 (15) |

Numbers in parentheses represent rounded percentage (column percentage) unless otherwise mentioned.
*Place of residence based on SLA at time of HBV notification.
[†]Charlson Comorbidity Index score indicates degree of health; higher scores indicate worse health condition.
[‡]Time from date of HBV notification to date of first HCC hospitalization.
[§]Time from diagnosis of the Central Cancer Registry to date of first HCC hospitalization.
[‖]Data from the NSW Cancer Registry available between January 1, 1994, and December 31, 2009: 4 (0.5%) received both resection and transplantation, 14 (2%) received RFA and resection, and 4 (0.5%) received RFA and transplantation.
Abbreviation: N/A, not available.

Records with missing date of birth, missing age at notification, or death date before the start of the study date (July 1, 2000) were excluded. HCC records with an HCC diagnosis through the NSW Cancer Registry prior to July 1, 2000, were excluded. Analyses were conducted to calculate median survival and probability of all-cause survival following first HCC hospitalization at 1, 2, and 5 years of follow-up.

The main explanatory variables included study period; updated age; gender; place of residence based on the statistical local area (SLA) at time of HBV or HCV notification, which was further grouped into rural, metropolitan, and outer-metropolitan SLAs; place of birth; HIV; HBV/HCV coinfection; alcohol-related hospitalization; Charlson Comorbidity Index; time to HCC diagnosis following HBV or HCV notification; and ever receiving HCC curative procedures. For variables that are clinically significant but with $P > 0.25$ in the univariate analysis, sensitivity analyses were done to assess the impact of their

**TABLE 2. CHARACTERISTICS OF PEOPLE HOSPITALIZED WITH HCC AMONG THOSE WITH HCV NOTIFICATION IN NSW, AUSTRALIA (2000-2014)**

| Characteristic | Overall (N = 1,309) | 2000-2004 (n = 231) | 2005-2009 (n = 394) | 2010-2014 (n = 684) |
|---|---|---|---|---|
| Median year of birth (IQR) | 1954 (14) | 1944 (22) | 1953 (13) | 1955 (10) |
| Year of birth | | | | |
| Pre-1945 | 367 (28) | 126 (54) | 111 (28) | 130 (19) |
| 1945-1955 | 410 (31) | 62 (27) | 134 (34) | 214 (31) |
| 1956+ | 532 (41) | 43 (19) | 149 (38) | 340 (50) |
| Median age at HCC diagnosis (IQR) | 56 (13) | 59 (21) | 54 (14) | 56 (10) |
| Gender | | | | |
| Male | 1,041 (80) | 175 (76) | 321 (81) | 545 (80) |
| Place of residence* | | | | |
| Metro | 487 (37) | 93 (40) | 163 (41) | 231 (34) |
| Outer-metro | 497 (38) | 98 (42) | 142 (36) | 257 (38) |
| Rural | 322 (25) | 40 (17) | 88 (22) | 194 (28) |
| Missing | 3 (0.2) | 0 (0) | 1 (0.2) | 2 (0.3) |
| Place of birth | | | | |
| Australia | 631 (53) | 66 (29) | 200 (51) | 365 (63) |
| Asia Pacific | 274 (23) | 82 (36) | 87 (22) | 105 (18) |
| Europe | 206 (17) | 60 (26) | 75 (19) | 71 (12) |
| Other | 75 (6) | 16 (7) | 22 (6) | 37 (6) |
| Missing | 123 (9) | 7 (3) | 10 (2) | 106 (15) |
| HBV coinfection | 79 (6) | 19 (8) | 21 (5) | 39 (6) |
| HIV-positive | 7 (1) | 0 (0) | 4 (1) | 3 (0·5) |
| Alcohol-related hospitalization | 429 (33) | 39 (17) | 122 (31) | 268 (39) |
| Charlson Comorbidity Index† | | | | |
| 0 | 142 (11) | 28 (12) | 42 (11) | 72 (11) |
| 1 | 526 (40) | 91 (40) | 131 (33) | 304 (44) |
| 2 | 193 (15) | 31 (13) | 64 (16) | 98 (14) |
| ≥3 | 448 (34) | 81 (35) | 157 (40) | 210 (31) |
| Median time from HCV notification, years (IQR)‡ | 8 (9) | 4 (6) | 8 (7) | 11 (10) |
| Median time from NSW Central Registry diagnosis, months (IQR)§ | 0.2 (2) | 0.4 (3) | 0.2 (1) | N/A |
| Potentially curative procedures‖ | | | | |
| Liver resection | 182 (14) | 31 (13) | 62 (16) | 89 (13) |
| Liver transplantation | 85 (7) | 23 (10) | 36 (9) | 26 (4) |
| RFA | 111 (8) | 2 (1) | 35(9) | 74(11) |
| Died | 911 (70) | 187(81) | 319 (81) | 405 (59) |
| Median age at death (IQR) | 58 (15) | 63 (20) | 55(15) | 57 (10) |

Numbers in parentheses represent rounded percentage (column percentage) unless otherwise mentioned.
*Place of residence based on SLA at time of HCV notification.
†Charlson Comorbidity Index score indicates degree of health; higher scores indicate worse health condition.
‡Time from date of HCV notification to date of first HCC hospitalization.
§Time from diagnosis of the NSW Cancer Registry to date of first HCC hospitalization.
‖Data from the NSW Cancer Registry available between January 1, 1994, and December 31, 2009: 5 (0.3%) received both resection and transplantation, 14 (1.1%) received RFA and resection, and 10 (0.7%) RFA and transplantation.
Abbreviation: N/A, not available.

inclusion on the adjusted model. Schoenfeld residuals were used to assess violation of the proportional hazards assumption. Analyses were performed using the Stata v14.0 (StataCorp, College Station, TX) and SAS software version 9.4 (SAS Institute, Cary, NC).

## ETHICS APPROVAL

Ethics approval for the study was granted by the NSW Population and Health Services Research Ethics Committee.

# Results

## PARTICIPANT CHARACTERISTICS

Among 54,399 HBV notifications and 96,908 HCV notifications over the period 1993-2012, a total of 725 (1.3%) HBV-HCC and 1,309 (1.4%) HCV-HCC first hospitalizations were identified through linkage in NSW, Australia, between 2000 and 2014. Participant characteristics for these 2,034 patients with

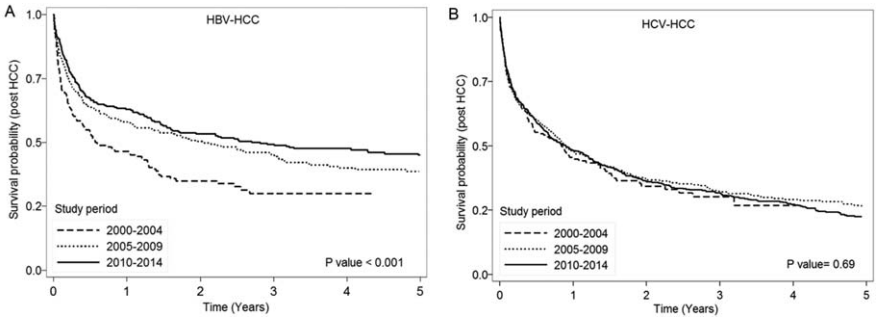


**FIG. 1.** Kaplan-Meier graphs of survival probability following first HCC hospitalization by study period among those with (A) HBV notification and (B) HCV notification in NSW, Australia, 2000-2014.

HCC are shown in Tables 1 and 2. Compared to HCV-HCC patients, HBV-HCC patients were older (median year of birth = 1950 versus 1954), more from a metropolitan place of residence (46% versus 37%), more often born in Asia (73% versus 23%), and diagnosed earlier (5 versus 8 years, from time of HBV or HCV notification). Potentially curative procedures were more commonly used in HBV-HCC than HCV-HCC patients (41% versus 29%). Death occurred in 60.4% of HBV-HCC and 69.6% of HCV-HCC patients during the study period (Tables 1 and 2).

## SURVIVAL FOLLOWING FIRST HCC HOSPITALIZATION

Median survival following first HCC hospitalization improved among HBV-HCC patients, from 0.6 years (95% confidence interval [CI] 0.39-1.28) in 2000-2004 to 2.0 years (95% CI 1.10-3.07) in 2005-2009 and 2.8 years (95% CI 1.54-5.54) in 2010-2014. Similarly, the probabilities of survival at 1 and 2 years of follow-up showed improvement in 2010-2014 (63%, 54%) compared to 2000-2004 (46%, 36%) (Table 3; Supporting Table S1; Fig. 1).

Median survival following first HCC hospitalization among HCV-HCC patients was stable: 0.8 years (95% CI 0.45-1.33) in 2000-2004, 0.9 years (95% CI 0.72-1.24) in 2005-2009, and 0.9 years (95% 0.67-1.18) in 2010-2014. The probabilities of survival at 1 and 2 years of follow-up showed no improvement in 2010-2014 (48%, 36%) compared to 2000-2004 (46%, 37%) (Table 3; Supporting Table S1; Fig. 1).

## SURVIVAL FOLLOWING HBV-HCC AND HCV-HCC HOSPITALIZATION IN PATIENTS WHO RECEIVED POTENTIALLY CURATIVE PROCEDURES

In HBV-HCC patients who received potentially curative procedures, 1-year and 2-year survival showed

**TABLE 3. SURVIVAL PROBABILITY AT 1, 2, AND 5 YEARS OF FOLLOW-UP FOLLOWING FIRST HCC HOSPITALIZATION AMONG THOSE WITH HBV OR HCV NOTIFICATION IN AUSTRALIA (NSW, 2000-2014) STRATIFIED BY RECEIVING POTENTIALLY CURATIVE PROCEDURES**

| | HBV-HCC | | | HCV-HCC | | |
|---|---|---|---|---|---|---|
| Study Period | Overall | Potentially Curative Procedures | No Curative Procedures | Overall | Potentially Curative Procedures | No Curative Procedures |
| 2000-2004 | | | | | | |
| 1 year | 46 (39, 54) | 81 (67, 89) | 33 (25, 41) | 46 (39, 53) | 82 (69, 90) | 33 (26, 41) |
| 2 years | 36 (29, 43) | 68 (53, 78) | 23 (16, 31) | 37 (30, 43) | 75 (61, 84) | 23 (17, 30) |
| 5 years | 28 (22, 35) | 56 (42, 68) | 18 (12, 25) | 25 (20, 32) | 56 (41, 70) | 15 (9, 21) |
| 2005-2009 | | | | | | |
| 1 year | 57 (51, 63) | 87 (78, 92) | 38 (30, 45) | 48 (42, 52) | 86 (78, 91) | 30 (25, 36) |
| 2 years | 50 (43, 55) | 83 (74, 89) | 28 (21, 35) | 35 (30, 40) | 76 (68, 83) | 17 (13, 22) |
| 5 years | 40 (34, 46) | 70 (60, 78) | 20 (14, 27) | 21 (17, 25) | 54 (45, 63) | 6 (4, 10) |
| 2010-2014 | | | | | | |
| 1 year | 63 (57, 69) | 94 (87, 97) | 42 (33, 50) | 48 (44, 52) | 90 (84, 94) | 32 (28, 36) |
| 2 years | 54 (47, 60) | 86 (78, 92) | 29 (22, 38) | 36 (32, 40) | 78 (71, 84) | 19 (15, 23) |
| 5 years | — | — | — | — | — | — |

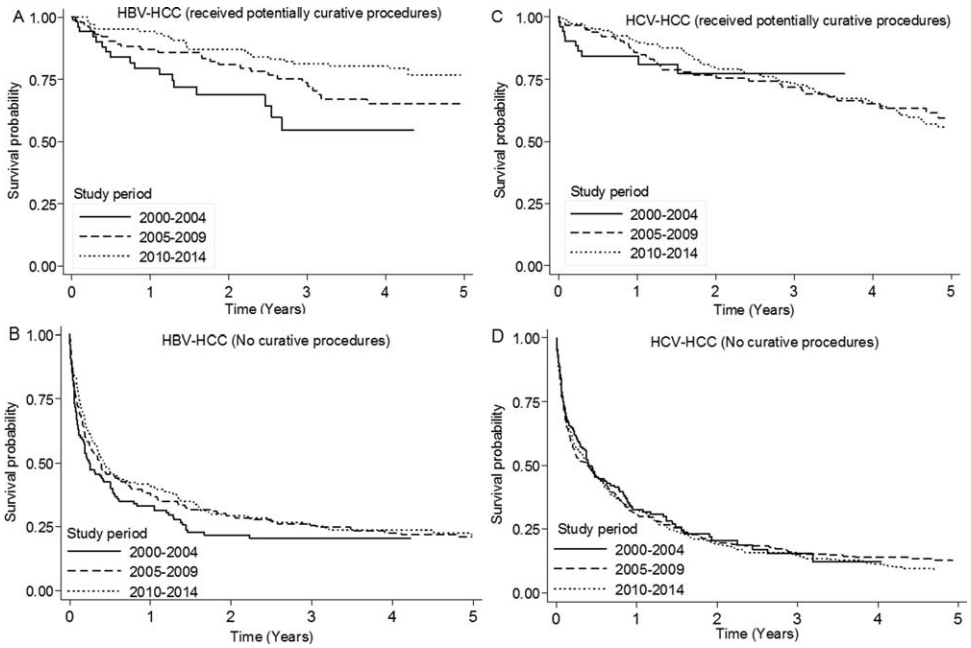


**FIG. 2.** Kaplan-Meier graphs of survival probability following first HCC hospitalization by study period among those with HBV notification who received (A) potentially curative procedures and (B) no curative procedures and among those with HCV notification who received (C) potentially curative procedures and (D) no curative procedures in NSW, Australia, 2000-2014.

clear improvement in 2010-2014 (94%, 86%) compared to 2000-2004 (81%, 68%) (Table 3 and Fig. 2). In HCV-HCC patients who received potentially curative procedures, 1-year and 2-year survival showed minimal improvement in 2010-2014 (90%, 78%) compared to 2000-2004 (82%, 75%) (Table 3 and Fig. 2).

## SURVIVAL FOLLOWING HBV-HCC AND HCV-HCC HOSPITALIZATION IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

In HBV-HCC patients with decompensated cirrhosis, 1-year and 2-year survival showed improvement in 2010-2014 (36%, 32%) compared to 2000-2004 (30%, 21%). In HCV-HCC patients with decompensated cirrhosis, 1-year and 2-year survival showed no improvement in 2010-2014 (27%, 19%) compared to 2000-2004 (31%, 27%).

## FACTORS ASSOCIATED WITH SURVIVAL FOLLOWING HCC HOSPITALIZATION

In the adjusted Cox proportional hazards analyses, factors associated with improved survival following first HCC hospitalization in HBV-HCC patients were later study period (hazard ratio [HR] = 0.74; 95% CI, 0.57-0.97; $P = 0.03$) and potentially curative procedures (liver resection, liver transplantation, and RFA) (HR = 0.23; 95% CI, 0.17-0.29; $P < 0.001$), while male gender (HR = 1.37; 95% CI, 1.03-1.82; $P = 0.03$), HIV coinfection (HR = 3.06; 95% CI, 1.36-6.88; $P < 0.01$), and Charlson Comorbidity Index $\geq 3$ (HR = 1.81; 95% CI, 1.35-2.40; $P < 0.001$) were associated with reduced survival (Table 4).

In adjusted Cox proportional hazards analyses, factors associated with improved survival following first HCC hospitalization in HCV-HCC patients were Asia-Pacific country of birth (HR = 0.68; 95% CI, 0.55-0.84; $P < 0.001$) and potentially curative procedures (HR = 0.21; 95% CI, 0.17-0.25; $P < 0.001$), while age (HR = 1.01; 95% CI, 1.01-1.02; $P < 0.01$), rural place of residence (HR = 1.46; 95% CI, 1.22-1.74; $P < 0.001$), and HIV coinfection (HR = 2.71; 95% CI, 1.19-6.15; $P = 0.01$) were associated with reduced survival (Table 5).

In a separate adjusted Cox proportional hazard analysis, combining HBV-HCC and HCV-HCC cohorts stratified by study period, survival was associated with HBV in the later study period (2010-2014 HR = 0.76; 95% CI, 0.62-0.93) but not the earlier study period (2000-2004 HR = 1.28; 95% CI, 0.95-1.72).

**TABLE 4. COX PROPORTIONAL HAZARDS ANALYSIS OF FACTORS ASSOCIATED WITH TIME TO DEATH FOLLOWING FIRST HOSPITALIZATION WITH HCC AMONG PEOPLE NOTIFIED WITH HBV**

| | Person-Years (Total = 1,819) | Death (n = 416) | Rate (/100 Person-Years) | HR (95% CI) | Adjusted HR (95% CI) | P* |
|---|---|---|---|---|---|---|
| Study period | | | | | | |
| 2000-2004 | 188 | 115 | 61.1 | 1.00 | 1.00 | — |
| 2005-2009 | 611 | 146 | 23.8 | 0.68 (0.53-0.87) | 0.80 (0.62-1.04) | 0.10 |
| 2010-2014 | 1,020 | 155 | 15.2 | 0.59 (0.46-0.76) | 0.74 (0.57-0.97) | 0.03 |
| Age† | — | — | — | 1.01 (1.01-1.02) | 1.01 (0.99-1.01) | 0.90 |
| Gender | | | | | | |
| Female | 353 | 60 | 17.0 | 1.00 | 1.00 | — |
| Male | 1,466 | 356 | 24.2 | 1.36 (1.03-1.80) | 1.37 (1.03-1.82) | 0.03 |
| Place of residence | | | | | | |
| Metro | 919 | 175 | 19.0 | 1.00 | 1.00 | — |
| Outer-metro | 808 | 209 | 25.8 | 1.28 (1.04-1.56) | 1.18 (0.96-1.45) | 0.10 |
| Rural | 87 | 29 | 33.1 | 1.61 (1.08-2.38) | 1.13 (0.75-1.70) | 0.54 |
| Missing | 4 | 3 | 68.6 | 2.39 (0.76-7.51) | 1.33 (0.40-4.43) | 0.63 |
| Place of birth‡ | | | | | | |
| Australia | 38 | 30 | 78.6 | 1.00 | — | — |
| Asia Pacific | 1,431 | 291 | 20.2 | 0.47 (0.32-0.69) | — | — |
| Europe | 134 | 51 | 37.9 | 0.78 (0.50-1.23) | — | — |
| Other | 63 | 12 | 19.0 | 0.44 (0.22-0.85) | — | — |
| Missing | 152 | 32 | 21.1 | 0.42 (0.26-0.70) | — | — |
| HIV | | | | | | |
| No | 1,817 | 409 | 22.5 | 1.00 | 1.00 | — |
| Yes | 2 | 7 | 275.8 | 3.20 (1.51-6.78) | 3.06 (1.36-6.88) | <0.01 |
| Alcohol-related hospitalization | | | | | | |
| No | 1,737 | 378 | 21.7 | 1.00 | 1.00 | — |
| Yes | 83 | 38 | 45.9 | 1.49 (1.07-2.09) | 1.07 (0.74-1.54) | 0.70 |
| Charlson Comorbidity Index | | | | | | |
| 0 | 462 | 68 | 14.7 | 1.00 | 1.00 | — |
| 1 | 727 | 122 | 16.8 | 1.25 (0.93-1.69) | 1.15 (0.85-1.55) | 0.37 |
| 2 | 221 | 37 | 16.7 | 1.29 (0.86-1.93) | 1.03 (0.68-1.56) | 0.87 |
| ≥3 | 408 | 189 | 46.3 | 2.47 (1.87-3.26) | 1.81 (1.35-2.40) | <0.001 |
| Time to HCC§ | | | | | | |
| ≥2 years | 1,142 | 260 | 22.7 | 1.00 | 1.00 | — |
| <2 years | 506 | 118 | 23.3 | 1.26 (1.01-1.56) | 0.98 (0.78-1.24) | 0.91 |
| At time of or after HCC | 170 | 38 | 22.3 | 1.27 (0.90-1.78) | 0.99 (0.70-1.42) | 0.99 |
| Potentially curative procedures‖ | | | | | | |
| No | 698 | 337 | 48.3 | 1.00 | 1.00 | — |
| Yes | 1,121 | 79 | 7.0 | 0.21 (0.16-0.26) | 0.23 (0.17-0.29) | <0.001 |

*The overall adjusted *P* value for the study period = 0.07, place of residence = 0.18, Charlson Comorbidity Index <0.001, and time to HCC = 0.87.
†Age is calculated based on 5-year interval.
‡Excluded from the final model due to interaction with study period and Charlson Comorbidity Index ($P < 0.01$).
§Time calculated from date of HBV diagnosis to date of first HCC hospitalization.
‖Includes liver resection, liver transplantation, and RFA.

## TRENDS IN HCC MANAGEMENT

Over the study period, the proportion of HBV-HCV patients who received potentially curative procedures increased from 31% in 2000-2004 to 43% in 2010-2014 (Table 1). The proportion of HCV-HCC patients who received potentially curative procedures increased from 24% in 2000-2004 to 28% in 2010-2014 (Table 1).

## VALIDATION OF HOSPITALIZATION-BASED HCC DIAGNOSIS AND SURVIVAL ESTIMATES

Use of hospitalization coding data for diagnosis of HCC among people with HBV and HCV was based on its availability through 2014. In contrast, data on HCC cases recorded in the NSW Cancer Registry

**TABLE 5. COX PROPORTIONAL HAZARDS ANALYSIS OF FACTORS ASSOCIATED WITH TIME TO DEATH FOLLOWING FIRST HOSPITALIZATION WITH HCC AMONG PEOPLE NOTIFIED WITH HCV**

| | Person-Years (Total = 2274) | Death (n = 881) | Rate (/100 Person-Years) | HR (95% CI) | Adjusted HR (95% CI) | P* |
|---|---|---|---|---|---|---|
| Study period | | | | | | |
| 2000-2004 | 181 | 120 | 66.1 | 1.00 | 1.00 | — |
| 2005-2009 | 685 | 263 | 38.4 | 0.92 (0.73-1.14) | 0.94 (0.75-1.17) | 0.56 |
| 2010-2014 | 1,407 | 498 | 35.4 | 0.96 (0.78-1.17) | 0.98 (0.78-1.21) | 0.84 |
| Age† | — | — | — | 1.01 (1.00-1.01) | 1.01 (1.01-1.02) | <0.01 |
| Gender | | | | | | |
| Female | 450 | 184 | 41.8 | 1.00 | 1.00 | — |
| Male | 1,824 | 697 | 38.2 | 0.96 (0.82-1.13) | 1.05 (0.88-1.25) | 0.54 |
| Place of residence | | | | | | |
| Metro | 947 | 309 | 32.6 | 1.00 | 1.00 | — |
| Outer-metro | 936 | 323 | 34.5 | 1.03 (0.88-1.20) | 1.23 (1.04-1.44) | 0.01 |
| Rural | 388 | 246 | 63.3 | 1.55 (1.31-1.83) | 1.46 (1.22-1.74) | <0.001 |
| Missing | 2 | 3 | 1.28 | 2.09 (0.67-6.54) | 3.26 (1.03-10.42) | 0.04 |
| Place of birth | | | | | | |
| Australia | 887 | 448 | 50.0 | 1.00 | 1.00 | — |
| Asia Pacific | 670 | 163 | 24.3 | 0.64 (0.53-0.76) | 0.68 (0.55-0.84) | <0.001 |
| Europe | 405 | 151 | 37.2 | 0.92 (0.77-1.11) | 0.80 (0.65-0.99) | 0.04 |
| Other | 137 | 52 | 37.8 | 0.85 (0.64-1.13) | 1.01 (0.75-1.37) | 0.94 |
| Missing | 173 | 67 | 38.6 | 0.68 (0.52-0.88) | 0.73 (0.55-0.96) | 0.02 |
| HBV | | | | | | |
| No | 2,149 | 829 | 38.6 | 1.00 | 1.00 | — |
| Yes | 125 | 52 | 41.5 | 0.97 (0.73-1.29) | 1.07 (0.81-1.43) | 0.60 |
| HIV | | | | | | |
| No | 2,265 | 875 | 38.6 | 1.00 | 1.00 | — |
| Yes | 10 | 6 | 62.5 | 1.89 (0.84-4.23) | 2.71 (1.19-6.15) | 0.01 |
| Alcohol-related hospitalization | | | | | | |
| No | 1,665 | 580 | 34.8 | 1.00 | 1.00 | — |
| Yes | 608 | 301 | 49.4 | 1.14 (0.99-1.31) | 0.98 (0.84-1.16) | 0.88 |
| Charlson Comorbidity Index | | | | | | |
| 0 | 221 | 85 | 38.3 | 1.00 | 1.00 | — |
| 1 | 1,036 | 304 | 29.3 | 0.79 (0.62-1.01) | 0.84 (0.66-1.08) | 0.17 |
| 2 | 363 | 127 | 34.9 | 0.91 (0.69-1.20) | 1.03 (0.78-1.36) | 0.82 |
| ≥3 | 652 | 365 | 55.9 | 1.29 (1.02-1.64) | 1.27 (0.99-1.62) | 0.05 |
| Time to HCC‡ | | | | | | |
| ≥2 years | 1,765 | 716 | 40.6 | 1.00 | 1.00 | — |
| <2 years | 420 | 118 | 28.1 | 0.90 (0.74-1.09) | 0.94 (0.76-1.15) | 0.53 |
| At time of or after HCC | 89 | 47 | 52.5 | 1.45 (1.07-1.95) | 1.13 (0.84-1.54) | 0.42 |
| Potentially curative procedures§ | | | | | | |
| No | 1,003 | 753 | 75.1 | 1.00 | 1.00 | — |
| Yes | 1,272 | 128 | 10.1 | 0.19 (0.16-0.24) | 0.21 (0.17-0.25) | <0.001 |

*The overall adjusted *P* value for the study period = 0.47, place of residence <0.001, place of birth = 0.05, Charlson Comorbidity Index <0.001, and time to HCC = 0.72.
†Age is calculated based on 5-year interval.
‡Time calculated from date of HCV diagnosis to date of first HCC hospitalization.
§Includes liver resection, liver transplantation, and RFA.

were only available through 2009. The availability of the two data sources for the period 2001-2009 provided the opportunity to validate hospitalization-based HCC diagnosis and survival estimates using both data sets. For the study period 2000-2009, the vast majority of HCC cases among individuals with HBV (90%) or HCV (91%) were also recorded in the NSW Cancer Registry and 93% of the HCV-HCC and 95% of the HBV-HCC Cancer Registry cases were recorded in the hospitalization data set. Over this period, median time from NSW Cancer Registry diagnosis to first HCC hospitalization was 0.2 months (interquartile range [IQR] = 0.9) for HBV and 0.2 months (IQR = 2) for HCV. Similar to the hospitalization estimates, median survival following HCC diagnosis based on NSW Cancer Registry showed improvement for HBV-HCC in 2007-2009 (2.50 years; 95% CI, 1.26-3.70) compared to 2001-2003 (1.27 years; 95% CI, 0.76-2.09) and no improvement for HCV-HCC (1.34 years; 95% CI, 0.92-1.81) in 2007-2009 compared to

2001-2003 (0.96; 95% CI, 0.63-1.55) (Supporting Table S2).

# Discussion

The global burden of HCC continues to escalate,[15] driven in most settings by aging populations of people with chronic HBV and HCV and poor access to and uptake of antiviral therapy. Trends in HCC-related mortality are similar due to the extremely poor survival following HCC.[4] Our study confirms the generally poor survival in patients with HBV-HCC and HCV-HCC, although it demonstrates improving survival in those with HBV-HCC. The availability of potent HBV antiviral therapy in Australia (entecavir, 2006; tenofovir, 2009) and the increased number of patients eligible for curative treatments are presumed to have been the major contributors to this improved survival.

The improvement in median survival following first HBV-HCC hospitalization from 0.6 to 2.8 years for the 2000-2004 and 2010-2014 study periods is striking. The high correlation of hospitalization-coded and Cancer Registry HBV-HCC cases (89.9%)[16] and the relatively short median period between diagnoses in these two data sets (0.2 months) provide reassurance of the validity of using hospitalization data to evaluate survival trends. Lead-time bias would be a potential explanation for some improved HBV-HCC survival if a temporal trend existed in favor of earlier HCC diagnosis (and thus earlier hospitalization). The higher proportion of HBV-HCC patients compared to HCV-HCC patients who received curative HCC treatments (41% versus 29%) and the increasing proportion for HBV-HCC patients during the study period (31% to 43%) would be consistent with higher and improving levels of HCC screening among at-risk patients with chronic HBV. The lack of clinical details on HCC screening and more detailed HCC staging prevent additional exploration of potential lead-time bias. However, the improvement in HBV-HCC survival in analyses stratified by receipt of potentially curative procedures (liver resection, liver transplantation, and RFA), a reliable surrogate for early-stage HCC diagnosis, reduces the risk that lead-time bias is the major explanation for improved survival. Of note, in HBV-HCC patients who received potentially curative strategies 1-year and 2-year survival probabilities have improved from 81% and 68% in 2000-2004 to 94% and 86% in 2010-2014. Improved HBV-HCC survival could be due to reducing progression to hepatic decompensation and reduced HCC recurrence, through more effective HBV antiviral therapy.

Improvement in HBV-HCC survival is clearly contrasted by a lack of improvement in survival following first hospitalization for HCV-HCC. The continued extremely poor survival in HCV-HCC patients is consistent with limited improvement in three clinical and public health areas. First, it suggests that HCC screening remains poor at the population level. Increased screening should have been reflected in a higher proportion with earlier stage of HCC diagnosis and subsequent improved survival through receipt of potentially curative procedures (*true improvement*) and lead-time bias (*artificial improvement*). Second, although there have been advances in HCC management over the last decade, with the advent of new local (microwave ablation, DC beads) and systemic (sorafenib) treatment modalities,[17-19] these potential individual-level improvements have not yet translated into significant population-level benefits in the HCV-HCC cohort given the generally late stage at diagnosis. Third, improving HCV clinical management over the last decade had no significant impact on HCV-HCC survival. HCV treatment remained interferon-based, and overall treatment uptake remained low (1%-2%) in Australia through 2014.[20,21] The additional analyses within the combined HBV-HCC and HCV-HCC cohort, demonstrating a relationship between HBV and improved survival in the later study period (2010-2014), provide further confirmation of contrasting HBV-HCC and HCV-HCC survival impact.

In adjusted analyses, factors associated with poorer HBV-HCC and HCV-HCC survival included HIV, comorbidities (borderline for HCV), and lack of curative HCC procedures. Later study period and female gender were associated with improved HBV-HCC survival. Younger age, nonrural residence, and Asia-Pacific birth were associated with improved HCV-HCC survival. The explanation for improved HCV-HCC survival in people born in Asia-Pacific countries (also improved HBV-HCC survival in unadjusted analysis) may be lower comorbidities of alcohol use (thus, residual confounding) or higher levels of HCC screening with earlier diagnosis. The proportion of HCV-HCC patients with curative HCC procedures was 36% for Asia-Pacific-born and 22% for Australian-born, consistent with higher levels of HCC screening among patients born in Asia-Pacific countries.

We studied temporal trends in survival in HBV-HCC and HCV-HCC patients at the population

level. Three population-based studies have observed temporal improvement in HCC survival in Canada (1990-2009), the United States (2003-2011), and The Netherlands (1989-2009)[22-24]; however, survival was not analyzed based on HCC etiology. Recent clinic-based cohorts have also shown improved survival in HBV-HCC compared to HCV-HCC,[4,25,26] with an estimated 5-fold increase in median survival in HBV-HCC patients following antiviral therapy (80 months) compared to untreated patients (16 months).[27] A study from Germany reported improved overall survival in HBV-HCC (from 11.0 to 18.6 months) compared to HCV-HCC (from 17.7 to 18.5 months) in patients diagnosed between 1998 and 2009.[4]

The advent of interferon-free direct-acting antiviral (DAA) therapy provides considerable optimism that high cure rates will translate into both individual-level and population-level liver disease burden reductions. Reduced HCV-related liver disease progression through DAA-based cure should clearly impact on HCC risk, but the potential impact of DAA treatment on survival following HCV-HCC is unknown.[28,29] We have hypothesized that improved HBV-HCC survival in our study is related to the introduction of highly effective HBV antiviral therapy from 2006 and resultant reduction in risk of HCC recurrence and hepatic decompensation. In contrast, preliminary evidence suggests that DAA therapy may not have a similar effect on HCC recurrence, with even a suggestion that risk could be increased.[28] There are contrasting views and evidence on HCC risk in the DAA era,[28,29] but this is clearly a crucial area for ongoing clinical and epidemiological research.

The study has several limitations that need to be considered. First, we have relied on hospitalization-coded HCC events due to the longer period of available data (2000-2014 versus 2000-2009 in the NSW Cancer Registry). As mentioned, high correlation and short duration between first hospitalization-coded and Cancer Registry HCC diagnoses provide reassurance. Second, the absence of information on liver disease stage is a limitation. Further, the incomplete data on HCC stage at diagnosis led to the exclusion of this variable from the time-to-event analyses. We therefore used hospitalization-coded information on potentially curative procedures (liver resection, liver transplantation, and RFA) to evaluate the impact of earlier-stage HCC diagnosis. These data may be somewhat incomplete as RFA is often administered as a day-only procedure (not recorded in the hospitalization data set). Individual data on HBV antiviral therapy would have been useful to evaluate more directly the impact of improved HBV clinical management. Uptake of HBV antiviral therapy has increased markedly in Australia over the last decade, with the estimated number of people dispensed HBV antiviral drugs increasing from about 2,095 in the first quarter of 2003 to more than 38,015 in the last quarter of 2014,[30] with the assumption that this would also be the case within the HBV-HCC subpopulation. Finally, our population-based estimates of HCC incidence might appear low compared to other studies.[31] However, antiviral HBV therapy would have reduced HBV-HCC risk, and our HCV study population included individuals without chronic HCV (as diagnosis and notification are generally based on anti-HCV antibody detection).

Our findings highlight the generally poor survival following HBV-HCC and HCV-HCC but indicated that enhanced HCC screening, earlier HCC diagnosis, and access to highly effective antiviral therapy could provide considerable population-level improvements in survival. Broad access to HBV and HCV antiviral therapy has the potential to prevent HCC development; therefore, reductions in HCC incidence and improvements in HCC survival should lead to a turnaround in the escalating burden of HCC and related mortality.

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# Supporting Information

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