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# Hepatocellular carcinoma amongst Aboriginal and Torres Strait Islander peoples of Australia

Alan J Wigg[a,b,*], Sumudu K Narayana[a,b], Gunter Hartel[c], Linda Medlin[d], Greg Pratt[c], Elizabeth E. Powell[e,f], Paul Clark[g], Jane Davies[h,i], Kirsty Campbell[i], Maree Toombs[j], Michael Larkin[k], Patricia C Valery[c]

[a] *Hepatology and Liver Transplant Medicine Unit, Southern Adelaide Local Health Network, Adelaide, SA, Australia*
[b] *Flinders University of South Australia, Adelaide, South Australia, Australia*
[c] *QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia*
[d] *Aboriginal and Torres Strait Islander Health and Wellbeing, Central Queensland Hospital and Health Service, Queensland, Australia*
[e] *Department of Gastroenterology and Hepatology, Princess Alexandra Hospital, Brisbane, Queensland, Australia*
[f] *Centre for Liver Disease Research, Translational Research Institute, Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia*
[g] *Mater Hospitals, Brisbane, Queensland, Australia*
[h] *Menzies School of Health Research, Royal Darwin Hospital, Darwin, The Northern Territory, Australia*
[i] *Royal Darwin Hospital, Darwin, The Northern Territory, Australia*
[j] *University of Queensland, Herston, Queensland, Australia*
[k] *The Aboriginal Health Council of South Australia, Adelaide, Australia*

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ABSTRACT

*Background:* Liver disease and hepatocellular carcinoma (HCC) are important contributors to the mortality gap between Indigenous and non-Indigenous Australians. However, there is a lack of population based high quality data assessing the differences in HCC epidemiology and outcomes according to Indigenous status. The aim of this study was therefore to perform a large epidemiological study of HCC investigating differences between Indigenous and non-Indigenous Australians with HCC.

*Methods:* Study design was a retrospective cohort study. Data linkage methodology was used to link data from cancer registries with hospital separation summaries across three Australian jurisdictions during 2000–2017. Cumulative survival (Kaplan-Meier) and the differences in survival (Multivariable Cox-regression) by Indigenous status were assessed.

*Findings:* A total of 229 Indigenous and 3587 non-Indigenous HCC cases were included in the analyses. Significant epidemiological differences identified for Indigenous HCC cases included younger age at onset, higher proportion of females, higher rurality, lower socioeconomic status, and higher comorbidity burden (all $p < 0.001$). The distribution of cofactors was also significantly different for Indigenous Australians including higher prevalence of alcohol misuse, hepatitis B, and diabetes and more frequent presence of multiple HCC cofactors (all $p < 0.001$). Indigenous Australians received curative HCC therapies less frequently (6.6% vs. 14.5%, $p < 0.001$) and had poorer 5-year survival (10.0% vs. 17.3%, $p < 0.001$; unadjusted hazard ratio (HR) =1.42 96%CI 1.21–1.65) compared to non-Indigenous Australians. The strength of the association between indigenous status and survival was weaker and statistically non-significant after adjusting for rurality, comorbidity burden and lack of curative therapy (adjusted-HR=1.20 95%CI 0.97–1.47)

*Interpretation:* Such data provide a call to action to help design and implement health literacy, liver management and HCC surveillance programs for Indigenous people to help close the liver cancer mortality gap.



Research in context

* Corresponding author.
*E-mail address:* alan.wigg@sa.gov.au (A.J. Wigg).

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**Evidence before this study**

We searched PubMed for key articles describing the epidemiology of hepatocellular carcinoma in Indigenous Australians. The search terms 'liver cancer', 'hepatocellular carcinoma', 'Indigenous Australians', Aboriginal' and 'Torres Strait Islander' were used to select manuscripts of interest. We were unable to identify any studies reporting on HCC epidemiology involving data linkage across multiple State or Territory Jurisdictions, other than government reports describing basic epidemiology (incidence and mortality rates, age and gender).

**Added value of this study**

This study adds value to current literature because it provides the first large (across multiple state and Territory Australian Jurisdictions) epidemiological study of HCC in Indigenous Australians. It provides novel data on important sociodemographic factors associated with HCC in Indigenous Australians including; higher rurality, lower socioeconomic status, and higher comorbidity burden. The study found that the distribution of HCC cofactors was also significantly different for Indigenous Australians including higher prevalence of alcohol misuse, hepatitis B, and diabetes and more frequent presence of multiple HCC cofactors. Interestingly the survival difference was largely accounted for by factors others than Indigenous status including rurality, comorbidity burden and lack of curative therapy.

**Implications of all the available evidence**

The study provides a framework for those involved in Indigenous Health in Australia to begin to address the incidence and mortality gap for HCC, the second most common cause of cancer death in this population. It is a call to action to help design effective interventions to reduce the HCC mortality gap.

## Introduction

Hepatocellular carcinoma (HCC) is a major global health problem and has the second highest rising incidence of any cancer in Australia [1]. Aboriginal and/or Torres Strait Islander peoples (hereafter respectfully referred to as Indigenous Australians) have an important place in the history of Hepatology, as serum from Indigenous Australians led to the discovery of Hepatitis B virus (HBV) or the "Australia antigen" in 1965 [2]. Data from national data registries have suggested that HCC in Indigenous Australians is a significant and under recognized current problem. Age-standardized incidence rates are 2.4-fold higher in Indigenous versus non-Indigenous Australians (15.5 versus 6.4 cases/100,000 persons), the largest difference in incidence for any cancer in Australia [1,3]. HCC in Indigenous Australians is also associated with a 2.4 fold higher age standardized mortality rate relative to non-Indigenous Australians and is the second most common cause of cancer death in Indigenous Australians [3]. This difference in mortality rates between Indigenous and non-Indigenous Australians is higher for HCC than any other cancer, other than cervical cancer [1].

The reasons for the higher incidence and mortality for HCC in Indigenous Australians have not been rigorously studied, with only one small retrospective study of 37 HCC cases providing detailed HCC epidemiology [4]. There is no information available on rates of diabetes and obesity, common conditions in Indigenous Australians that may increase the risk of HCC after controlling for other factors. Metabolic associated fatty liver disease (formerly known as non-alcoholic fatty liver disease) is strongly associated with diabetes mellitus and obesity, and now represents the greatest population attributable risk factor for chronic liver disease and HCC in the developed world [5]. Also lacking is information on the presence of multiple cofactors that may exist in HCC cases in Indigenous Australians.

In order to begin to address the significant problem of HCC in Indigenous Australians one of the starting points is a detailed epidemiological study. Therefore, the aim of this study was to perform a large retrospective cohort study of HCC epidemiology in Indigenous Australians, across multiple jurisdictions, using data linkage techniques.

## Methods

### *Study population and data sources*

All adults (18 years or older) diagnosed with HCC in Queensland (QLD; 2007–2017), South Australia (SA; 2000–2016) and the Northern Territory (NT; 2000–2015) were identified via relevant cancer registries using ICD code (9/10/O-3) C22.0. The cancer registry databases were linked to the corresponding state or territory admitted patient databases. Data linkage was managed by SA NT DataLink for the South Australian (SA) and Northern Territory (NT) data. The Queensland (QLD) Statistical Services Branch performed data linkage for QLD. Hospital separations were matched to cancer registry data using both deterministic and probabilistic methodologies. Deaths data (date and cause of death) were sourced from the Register of Births, Deaths and Marriages and the (Australian) National Death Index. Follow up for deaths was up to December 2016 for the NT, December 2017 for QLD, and December 2018 for SA.

### *Measures*

Indigenous status was identified via cancer registry coding and included all cases identified as Aboriginal and/or Torres Strait Islander. Patients' residential postcodes were used to determine area-based measures of remoteness of residence (Accessibility/Remoteness Index of Australia (ARIA+) score) [6] and socioeconomic advantage and disadvantage (IRSAD score) [7].

The specific aetiology of liver disease/HCC and presence of comorbidities were determined based on recorded primary or other diagnosis, coded using ICD-10-AM (10th edition). As exposures to risk factors are likely to have occurred over decades (e.g. cirrhosis, chronic viral hepatitis, excess alcohol, NAFLD), are inherited (e.g. Wilson's Disease), or may be diagnosed at an earlier time point when patients have compensated liver disease, we considered cases having presumed aetiology if they had the specific ICD codes as primary or other diagnosis in any admission during the study period. As the quality of documentation of ICD codes in elective day case admissions (e.g. for a procedures related to portal hypertension) has been reported to be poor [8], for comorbidities we considered co-existing conditions in any admission during the year of HCC diagnosis. Comorbidity was measured using the Charlson Comorbidity Index (CCI) [9]. All diseases listed in the CCI as primary or other diagnosis were analysed (excluding liver disease and HCC). Alcohol misuse as a cofactor was counted if any relevant ICD-10 codes pertaining to alcohol related disorders were identified from hospital coding. Curative HCC therapies were considered to be transplantation, liver resection or percutaneous ablation. The presence of cirrhosis was confirmed by relevant ICD-10 codes [8].

*Data analysis*

Statistical analyses were performed using Stata/SE (version 15; Stata Corporation, College Station, TX, USA). The data was checked for potential errors and inconsistencies. Descriptive analyses were presented as frequency (percentages,%), mean (standard deviation, SD) or median (interquartile range, IQR) value depending on data distribution. Group comparisons were made using Student's *t*-test, the Mann-Whitney test, the Chi-squared test, or Fisher's exact test, as appropriate. All tests were two-tailed and a p-value of less than 0.05 was considered statistically significant. Amongst Indigenous cases with HBV, individual annual risk of HCC was estimated as previously described by Parker et al. [4] Age-specific crude incidence rates calculated for Indigenous Australians were divided by the reported prevalence of HBV in Indigenous Australians [10] and the result multiplied by the age-specific proportion of HCC attributable to HBV in the study cohort. This analysis was restricted to HBV related HCC as HBV is the only diagnosis where HCC surveillance guidelines, in non-cirrhotic individuals, can very according to ethnicity, age and sex.

Cumulative overall survival estimates by Indigenous status were calculated using the Kaplan–Meier method. All cases were followed until date of death, or the last day of the year of 2016 for the NT, 2018 for SA and 2017 for QLD, whichever came sooner. Multivariable Cox regression analysis was used to assess the differences by Indigenous status and reported in terms of hazard ratios (HRs) with associated 95% confidence intervals (CIs). Informed by previous Australian studies which examined differences in survival by Indigenous status [4,11,12], we included in the main effects model factors that could influence overall survival, such as patients' sociodemographic characteristics, HCC aetiology, comorbidities, cirrhosis, receipt of potentially curative HCC treatment, period of HCC diagnosis and state of residence at diagnosis. Violations of the proportional hazards assumption were assessed by visual inspection of Kaplan Meier curves and in Schoenfeld residuals tests. The vce (robust) option was used to obtain robust standard errors for the parameter estimates to control for mild violation of underlying assumptions.

*Ethics approvals*

This study was approved by the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (2019–3365), SA Department for Health (HREC/19/SAH/45), Aboriginal Health Research Ethics Committee (04–19–829), QIMR Berghofer Medical Research Institute (P3506), and Queensland Health (HREC/17/QPAH/23).

*Role of funding source*

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the datasets received from relevant governmental data custodians the used for the study analyses. The corresponding author had the final responsibility to submit for publication.

*Adherence to record guidelines*

The manuscript adhered strictly to RECORD guidelines and a checklist is included as Supplementary Table 1.

## Results

A total of 248 Indigenous and 4063 non-Indigenous HCC cases were identified (Fig. 1). A total of 229 Indigenous and 3587 non-Indigenous HCC cases who had at least one hospital admission were included in analyses.

*Clinical and sociodemographic characteristics of HCC*

Clinical and sociodemographic characteristics for HCC in Indigenous and non-Indigenous cases are shown in Table 1. Indigenous Australians were younger when diagnosed with HCC with mean age at diagnosis 59.9 years (SD = 12.0) vs. 65.4 years (SD = 11.9, $p < 0.001$). In addition a significantly higher proportion of Indigenous Australians were diagnosed with HCC at an age less than 50 years (17.0% vs. 7.1%, $p < 0.001$). The relative proportion of Indigenous women (31.4%) with HCC was higher than that seen in the non-Indigenous population (18.4%, $p < 0.001$). Data on tumour characteristics was only available for NT HCC cases. Tumour size was significantly greater in Indigenous vs. non-Indigenous patients (79.0 mm vs 50.5 mm, $p < 0.001$), indicative of more advanced disease at presentation. Tumours were predominantly single nodules at presentation with no differences in multifocal presentation between the groups.

Over half of Indigenous people with HCC lived in remote/very remote areas (52.8% vs. 2.8% in non-Indigenous, $p < 0.001$), and in areas of most disadvantage (48.1% vs. 20.7% in non-Indigenous, $p < 0.001$). Indigenous Australians had a higher comorbidity burden reflected by a significantly higher median Charlson comorbidity index (3.1 vs. 2.5, $p < 0.001$). Diabetes (48.0% vs. 29.3%, $p < 0.001$), chronic renal disease (28.8% vs. 10.1%, $p < 0.001$), chronic pulmonary disease (12.2% vs. 6.0%), ischaemic heart disease (5.7% vs. 2.9%, $p = 0.017$), and dementia (4.8% vs. 1.8%) were significantly more common in the Indigenous HCC cohort.

There were 35 'Torres Strait Islanders only/and Aboriginal' cases included in the study. Except for age at diagnosis, they had similar demographic characteristics as Aboriginal cases (gender $p = 0.99$, rurality of residence $p = 0.087$, socioeconomic advantage and disadvantage $p = 0.30$). 'Torres Strait Islanders only/and Aboriginal' were significantly older than Aboriginal cases (63.6 years vs 59.2 years, $p = 0.043$)

*Rates of cirrhosis and cirrhosis-related complications*

Rates of cirrhosis and cirrhosis-related complications are shown in Table 2. The majority of HCC occurred in patients with known cirrhosis in both Indigenous and non-Indigenous groups (89.1% vs 92.4%, $p = 0.071$). The most common complication of cirrhosis in both groups was ascites, with approximately one-in-four (26.6% of Indigenous vs. 27.9% of non-Indigenous cases; $p = 0.670$) having at least one hospital admission where ascites was documented. Only one complication of cirrhosis, hepatic encephalopathy, significantly varied between the groups, with 14.0% of Indigenous HCC cases having at least one hospital admission with documented hepatic encephalopathy (vs. 6.6% for non-Indigenous cases; $p < 0.001$).

*Aetiology and cofactors for HCC*

Aetiology and cofactors for HCC in Indigenous and non-Indigenous Australians are shown in Table 3. Alcohol was an aetiological factor in over half of Indigenous and over one-third of non-Indigenous HCC (54.1% vs. 39.6%, $p < 0.001$). HCC secondary to chronic HBV occurred in Indigenous people about 2.5 times more frequently than non-Indigenous (25.3% vs. 9.9%, $p < 0.001$). In contrast, HCC secondary to chronic hepatitis C infection (HCV) was more frequent in the non-Indigenous cohort (27.1% vs 16.6%, $p < 0.001$). Although coding could not capture significant differences between groups for non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH), a surrogate

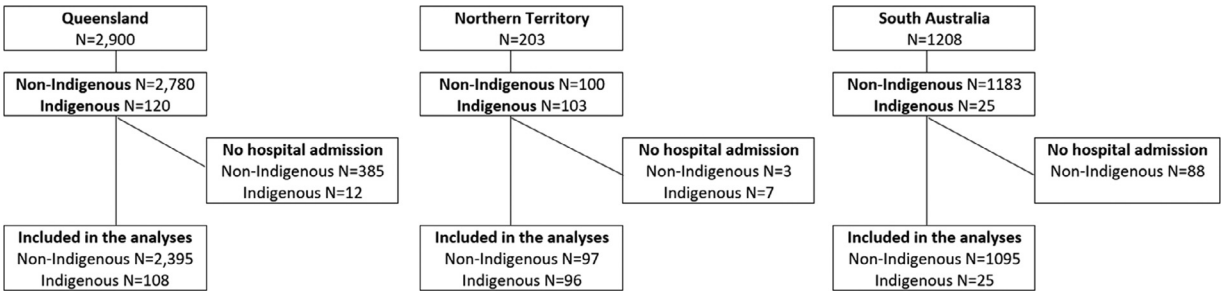


**Fig. 1.** Flow chart of HCC case ascertainment.

**Table 1**
Clinical and sociodemographic characteristics of HCC in Indigenous and non-Indigenous Australians.

| | | Non-Indigenous $N = 3587$ | Indigenous $N = 229$ | Total $N = 3816$ | p-value |
|---|---|---|---|---|---|
| **Age at diagnosis** (years; mean, SD) | | 65.4 (11.9) | 59.9 (12.0) | 65.1 (12.0) | <0.001 |
| **Less than 50 years at diagnosis** | | 254 (7.1%) | 39 (17.0%) | 293 (7.7%) | <0.001 |
| **Gender** | Male | 2926 (81.6%) | 157 (68.6%) | 3083 (80.8%) | <0.001 |
| | Female | 661 (18.4%) | 72 (31.4%) | 733 (19.2%) | |
| **Maximum tumour size** (mm; mean, SD)* | | 50.5 (27.0) | 79.1 (47.4) | | <0.001 |
| **Multiple tumour nodules*** | | 7 (7%) | 3 (3%) | | 0.33 |
| **Rurality of residence (ARIA+)** | Major city | 2227 (65.5%) | 30 (13.8%) | 2257 (62.4%) | <0.001 |
| | Inner regional | 563 (16.6%) | 10 (4.6%) | 573 (15.8%) | |
| | Outer regional | 514 (15.1%) | 63 (28.9%) | 577 (15.9%) | |
| | Remote/very remote | 96 (2.8%) | 115 (52.8%) | 211 (5.8%) | |
| **Socioeconomic advantage and disadvantage (IRSAD)** | Q1 most affluent | 359 (12.0%) | 15 (8.3%) | 374 (11.8%) | <0.001 |
| | Q2 | 628 (21.0%) | 23 (12.7%) | 651 (20.6%) | |
| | Q3 | 629 (21.1%) | 26 (14.4%) | 655 (20.7%) | |
| | Q4 | 750 (25.1%) | 30 (16.6%) | 780 (24.6%) | |
| | Q5 most disadvantaged | 618 (20.7%) | 87 (48.1%) | 705 (22.3%) | |
| **Charlson comorbidity index** (median, IQR) | | 2.5 (2.9) | 3.1 (3.0) | 2.5 (2.9) | 0.002 |
| **Charlson comorbidity group** | CCI=0 (no comorbidity) | 1455 (40.6%) | 61 (26.6%) | 1516 (39.7%) | <0.001 |
| | CCI=1 | 360 (10.0%) | 22 (9.6%) | 382 (10.0%) | |
| | CCI=2 | 525 (14.6%) | 39 (17.0%) | 564 (14.8%) | |
| | CCI≥3 | 1247 (34.8%) | 107 (46.7%) | 1354 (35.5%) | |

* Data of tumour size and number was only available from the Northern Territory and included 96 Indigenous and 97 non-Indigenous HCC cases.

**Table 2**
Cirrhosis and cirrhosis-related complications according to Indigenous status.

| | Non-Indigenous $N = 3587$ | Indigenous $N = 229$ | Total $N = 3816$ | *p*-value |
|---|---|---|---|---|
| **Cirrhosis** | 3314 (92.4%) | 204 (89.1%) | 3518 (92.2%) | 0.071 |
| **Ascites** | 1002 (27.9%) | 61 (26.6%) | 1063 (27.9%) | 0.670 |
| **Hepatic encephalopathy** | 237 (6.6%) | 32 (14.0%) | 269 (7.0%) | <0.001 |
| **Jaundice** | 38 (1.1%) | 3 (1.3%) | 41 (1.1%) | 0.720 |
| **Hepatorenal syndrome** | 115 (3.2%) | 6 (2.6%) | 121 (3.2%) | 0.620 |
| **Spontaneous bacterial peritonitis** | 151 (4.2%) | 14 (6.1%) | 165 (4.3%) | 0.170 |
| **Oesophageal/gastric varices with/without bleeding** | 752 (21.0%) | 44 (19.2%) | 796 (20.9%) | 0.530 |
| **Variceal bleeding** | 302 (8.4%) | 15 (6.6%) | 317 (8.3%) | 0.320 |

**Table 3**
Cofactors for HCC in Indigenous and non-Indigenous Australians.

| | | Non-Indigenous $N = 3587$ | Indigenous $N = 229$ | Total $N = 3816$ | *p*-value |
|---|---|---|---|---|---|
| Alcohol | | 1421 (39.6%) | 124 (54.1%) | 1545 (40.5%) | <0.001 |
| HBV | | 355 (9.9%) | 58 (25.3%) | 413 (10.8%) | <0.001 |
| HCV | | 972 (27.1%) | 38 (16.6%) | 1010 (26.5%) | <0.001 |
| NAFLD/NASH | | 279 (7.8%) | 14 (6.1%) | 293 (7.7%) | 0.360 |
| Diabetes | | 1051 (29.3%) | 110 (48.0%) | 1161 (30.4%) | <0.001 |
| Obesity | | 237 (6.6%) | 17 (7.4%) | 254 (6.7%) | 0.630 |
| Cumulative risk ** | 0 | 1054 (29.4%) | 32 (14.0%) | 1086 (28.5%) | <0.001 |
| | 1 | 1368 (38.1%) | 80 (34.9%) | 1448 (37.9%) | |
| | ≥2 | 1165 (32.5%) | 117 (51.1%) | 1282 (33.6%) | |
| Combined aetiology groups | | | | | |
| | Alcohol + HBV | 127 (3.5%) | 31 (13.5%) | 158 (4.1%) | <0.001 |
| | Alcohol + HCV | 564 (15.7%) | 30 (13.1%) | 594 (15.6%) | 0.290 |
| | Alcohol + HBV or HCV | 595 (16.6%) | 57 (24.9%) | 652 (17.1%) | 0.001 |
| | NAFLD/NASH + HBV or HCV | 67 (1.9%) | 5 (2.2%) | 72 (1.9%) | 0.730 |

** Count of risk factors namely alcohol, HBV, HCV, obesity, and diabetes;.

**Table 4**
HCC treatment in Indigenous and non-Indigenous Australians.

| | Non-Indigenous $N = 3587$ | Indigenous $N = 229$ | Total $N = 3816$ | $p$-value |
|---|---|---|---|---|
| **Liver resection** | 263 (7.3%) | 8 (3.5%) | 271 (7.1%) | 0.028 |
| **Ablation** | 176 (4.9%) | 5 (2.2%) | 181 (4.7%) | 0.060 |
| **Trans arterial chemoembolization** | 762 (21.2%) | 24 (10.5%) | 786 (20.6%) | <0.001 |
| **Transplant** | 139 (3.9%) | 5 (2.2%) | 144 (3.8%) | 0.280 |
| **Any HCC treatment** | 1035 (28.9%) | 36 (15.7%) | 1071 (28.1%) | <0.001 |
| **Curative HCC therapy given*** | 519 (14.5%) | 15 (6.6%) | 534 (14.0%) | <0.001 |

* liver resection, ablation, or transplant.

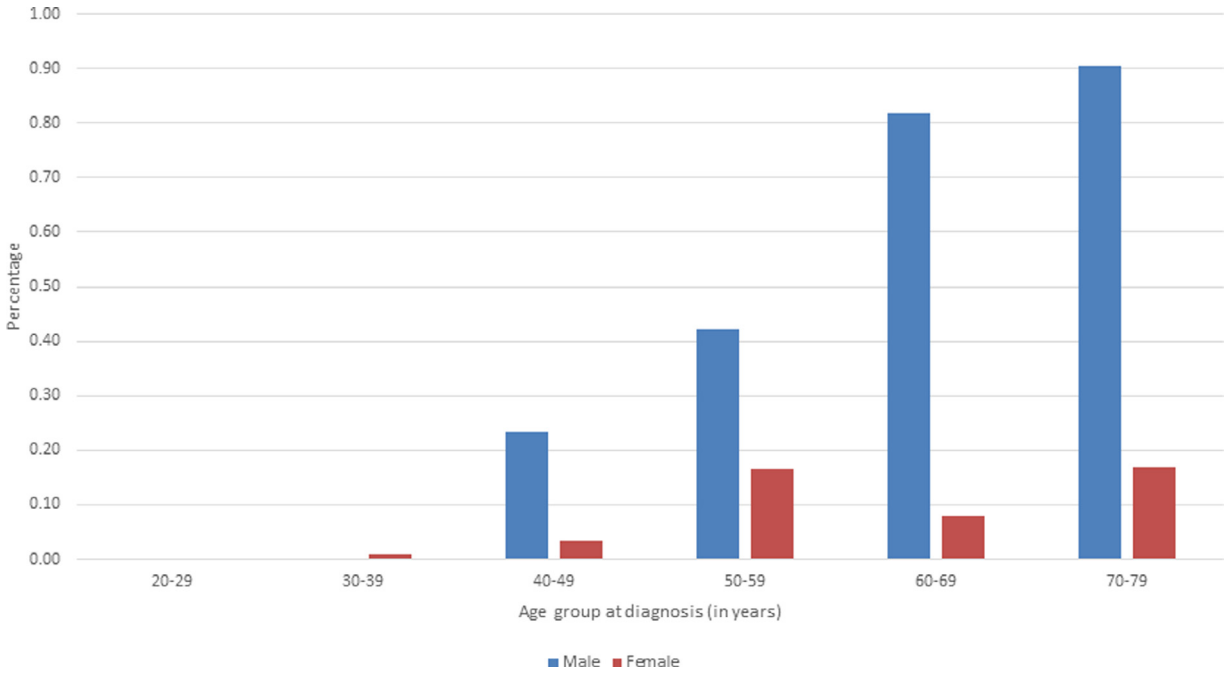


**Fig. 2.** Annual risk of HCC in HBV-infected Indigenous Australians.

for metabolic associated fatty liver disease, diabetes, was significantly more common in Indigenous HCC patients (48.0% vs. 29.3%, $p < 0.001$).

Clustering of cofactors was significantly more common in the Indigenous group, with a higher cumulative number of cofactors (alcohol, HBV, HCV, obesity and diabetes) amongst Indigenous Australians ($p < 0.001$). Indeed the majority of Indigenous cases had at least two cofactors for HCC (51.1% vs. 32.5%, $p < 0.001$). The most common cluster of cofactors in Indigenous HCC cases was the combination of alcohol and viral hepatitis (either HBV or HCV), present in 24.9% of the Indigenous cohort, compared with 16.6% of non-Indigenous cases ($p = 0.001$).

### *HCC treatment*

Indigenous cases were less likely to undergo HCC treatment (Table 4). 15.7% of Indigenous cases received any HCC treatment vs. 28.9% of non-Indigenous cases with HCC receiving treatment ($p < 0.001$). Curative-intent treatment was provided less frequently to Indigenous people with HCC than non-Indigenous (6.6% vs. 14.5%; $p < 0.001$).

### *Attributable risk of HCC in HBV-infected Indigenous Australians*

Amongst Indigenous cases with chronic HBV infection, individual annual risk of HCC was estimated assuming that the prevalence of chronic HBV infection in Indigenous Australian adults is 2.5%.[10] As illustrated in Fig. 2, the individual annual risk of HCC in HBV-infected Indigenous men aged 40–49 years was 0.23%, 0.42% for 50–59 years, 0.82% for 60–69 years and 0.91% for 70–79 years. Corresponding estimates for Indigenous women were 0.03%, 0.16%, 0.08% and 0.17%, respectively.

In an analysis restricted to HBV-related HCC amongst Indigenous Australians, alcohol as aetiology varied according to age group. Alcohol plus HBV as aetiological factors were present in 86.0% of Indigenous cases <50 years at HCC diagnosis (vs. 43.0% of Indigenous patients 50+ years, $p = 0.005$). There were no other significant differences between the groups for cofactors or cumulative cofactor risk. The majority of patients were cirrhotic in both age groups of HBV-related HCC (93% >50 years and 100% < 50 years, $p = 0.32$).

### *Survival*

The median time from diagnosis to death was shorter in Indigenous people; 150 days (IQR 55–473) vs. 290 days for non-Indigenous cases (IQR 79–781), with median survival time 276 days (IQR 76–761) overall. The probability of 5-year survival was 10.0% (95%CI 5.5%–16.0%) versus 17.3% (95%CI 15.8%–18.8%; $p < 0.001$), as demonstrated in Fig. 3. This disparity was reflected in the unadjusted hazard rate, which was 42% higher for Indigenous cases compared to their counterparts (HR=1.42 95%CI 1.21–1.65, $p < 0.001$; Table 5).

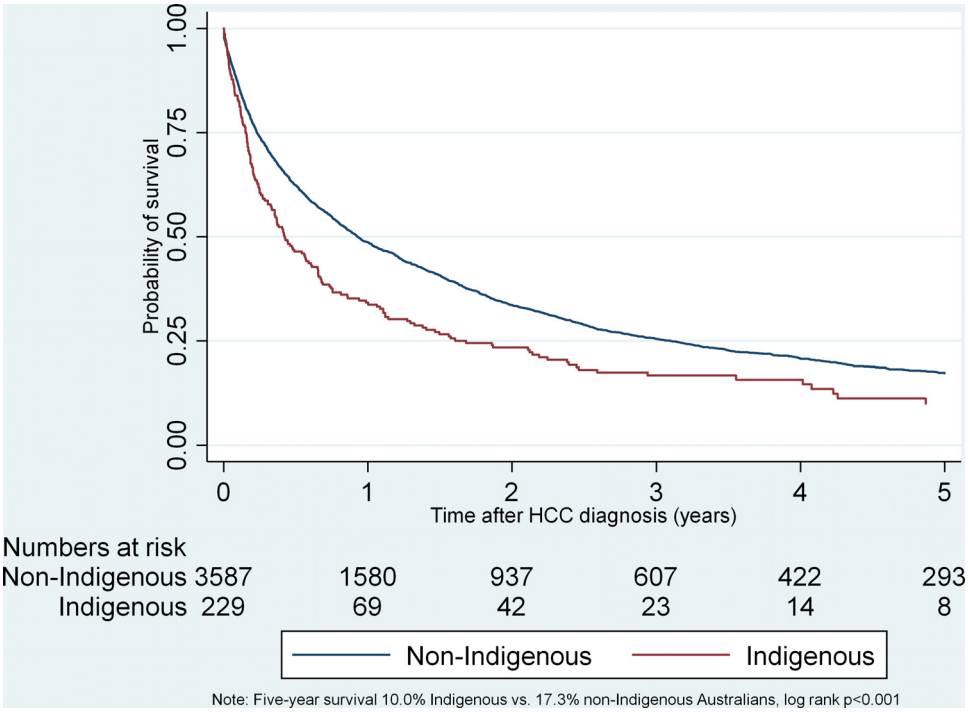


**Fig. 3.** Kaplan Meier survival curve for HCC in Indigenous and non-Indigenous Australian.

**Table 5**
Predictors of mortality amongst Indigenous and non-Indigenous Australians with HCC.

| | | Unadjusted | | | Adjusted | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95%CI | p-value | HR | 95%CI | p-value |
| **Indigenous status** | Indigenous (vs. non-Indigenous) | 1.42 | 1.21–1.65 | <0.001 | 1.20 | 0.97–1.47 | 0.087 |
| **Gender** | Female (vs. male) | 1.15 | 1.05–1.26 | 0.003 | 1.07 | 0.97–1.18 | 0.181 |
| **Age group** | <50 years | 1.02 | 0.87–1.19 | <0.001* | 0.97 | 0.82–1.16 | <0.001* |
| | 50–59 years | 1.00 | | | 1.00 | | |
| | 60–69 years | 1.18 | 1.07–1.31 | | 1.07 | 0.95–1.19 | |
| | 70 years and over | 1.74 | 1.58–1.90 | | 1.27 | 1.14–1.43 | |
| **Period of diagnosis** | 2000–2009 | 1.12 | 1.02–1.22 | 0.038* | 1.01 | 0.91–1.12 | 0.751* |
| | 2010–2013 | 1.01 | 0.92–1.10 | | 0.98 | 0.89–1.07 | |
| | 2014–2017 | 1.00 | | | 1.00 | | |
| **State of residence** | Queensland | 1.00 | | 0.134* | 1.00 | | <0.001* |
| | Northern Territory | 1.18 | 1.00–1.39 | | 0.66 | 0.52–0.83 | |
| | South Australia | 1.00 | 0.93–1.08 | | 0.60 | 0.55–0.67 | |
| **Rurality of residence** | Major city | 1.00 | | <0.001* | 1.00 | | <0.001* |
| **(ARIA+)** | Inner regional | 1.18 | 1.06–1.32 | | 1.07 | 0.96–1.19 | |
| | Outer regional | 1.35 | 1.22–1.50 | | 1.24 | 1.11–1.38 | |
| | Remote/very remote | 1.44 | 1.23–1.68 | | 1.26 | 1.02–1.56 | |
| **Charlson comorbidity group** | CCI=0 (no comorbidity) | 1.00 | | <0.001* | 1.00 | | <0.001* |
| | CCI=1 | 1.08 | 0.95–1.24 | | 1.16 | 1.01–1.34 | |
| | CCI=2 | 1.21 | 1.08–1.36 | | 1.41 | 1.23–1.63 | |
| | CCI≥3 | 1.97 | 1.81–2.14 | | 1.89 | 1.70–2.10 | |
| **Diabetes** | (vs. not) | 1.04 | 0.96–1.12 | 0.385 | 0.75 | 0.64–0.89 | 0.001 |
| **Obesity** | (vs. not) | 0.68 | 0.58–0 0.81 | <0.001 | 0.73 | 0.59–0.91 | 0.004 |
| **Alcohol** | (vs. not) | 0.89 | 0.82–0.96 | 0.001 | 0.98 | 0.84–1.15 | 0.838 |
| **HBV** | (vs. not) | 0.70 | 0.61–0.80 | <0.001 | 0.82 | 0.70–0.97 | 0.020 |
| **HCV** | (vs. not) | 0.65 | 0.60–0.71 | <0.001 | 0.86 | 0.73–1.00 | 0.057 |
| **NAFLD** | (vs. not) | 0.56 | 0.48–0.64 | <0.001 | 0.69 | 0.59–0.82 | <0.001 |
| **Cumulative risk** ** | 0 | 1.00 | | <0.001* | 1.00 | | 0.725* |
| | 1 | 0.87 | 0.80–0.95 | | 1.06 | 0.89–1.24 | |
| | ≥2 | 0.70 | 0.64–0.77 | | 1.05 | 0.77–1.43 | |
| **Cirrhosis** | (vs. not) | 0.43 | 0.37–0.50 | <0.001 | 0.63 | 0.53–0.74 | <0.001 |
| **Curative HCC therapy**** | (vs. not) | 0.20 | 0.18–0.23 | <0.001 | 0.22 | 0.19–0.26 | <0.001 |

* Overall significance.
** Count of risk factors namely alcohol, HBV, HCV, obesity, and diabetes.
*** liver resection, ablation, or transplantation.

In multivariable analysis, the disparity in survival between Indigenous and non-Indigenous cases was mostly explained by differences in sociodemographic factors, comorbidities, obesity, cirrhosis, diabetes, state of residence, period of diagnosis, and receipt of curative treatment. Adding sociodemographic factors (age, sex, remoteness of residence, and state of residence at diagnosis; adj-HR = 1.34 95%CI 1.10–1.64), comorbidities, diabetes, obesity and cirrhosis (adj-HR=1.32 95%CI 1.13–1.55), and receipt of curative treatment (adj-HR=1.28 95%CI 1.09–1.50), one at a time, decreased the hazard ratio slightly. Adding presence of multiple cofactors, namely alcohol, HBV, HCV, obesity, and diabetes increased the hazard ratio (adj-HR=1.54 95%CI 1.32–1.79). Adding aetiology (alcohol, HBV, HCV and NAFLD/NASH) did not alter the hazard ratio (adj-HR=1.44 95%CI 1.23–1.69). The final adjusted hazard ratio was 1.20 (95%CI 0.97–1.47; Table 5). Socioeconomic advantage and disadvantage was not associated with survival in both bivariable ($p$ = 0.414) and multivariable analyses ($p$ = 0.072 adjusted for all variables included in Table 5). The strongest predictors of mortality were higher comorbidity burden (CCI≥3 vs. CCI=0 adj-HR = 1.89, 95%CI 1.70–2.10) and remote/very remote place of residence (adj-HR = 1.26, 95%CI 1.01–1.56). Factors associated with improved survival following a HCC diagnosis included receipt of potentially curative procedures (adj-HR = 0.22, 95%CI 0.19–0.26), presence of cirrhosis (adj-HR=0.63, 95%CI 0.53–0.74), NAFLD/NASH (adj-HR = 0.69, 95%CI 0.59–0.82), obesity (adj-HR 0.73, 95%CI 0.59–0.91), diabetes (adj-HR 0.75, 95%CI 0.64–0.86), and HBV (adj-HR 0.82, 95%CI 0.70–0.97).

*Survival according to Aboriginal and Torres Strait Islander status*

Supplementary Figure 1 shows the Kaplan Meier survival curves for HCC cases comparing 'Aboriginal only', 'Torres Strait Islander only or both Aboriginal and Torres Strait Islander', and non-Indigenous Australians. The median time from diagnosis to death was 152 days(IQR 57–486) for Aboriginal only, 104 days (IQR 35–251) for Torres Strait Islander only/both Aboriginal and Torres Strait Islander, and 290 days for non-Indigenous cases (IQR 79–781;log rank $p < 0.001$). This disparity was reflected in the unadjusted hazard rate which was 36%higher for Aboriginal only cases (HR = 1.36 95%CI 1.15–1.61) and 81% higher for Torres Strait Islander only/both Aboriginal and Torres Strait Islander (HR = 1.81 95%CI 1.26–2.60;$p < 0.001$) compared to non-Indigenous Australians. In multivariable analysis, the disparity in survival between these three groups were no longer statistically significant, for Aboriginal only cases the adj-HR=1.16 (95%CI 0.93–1.46) and for Torres Strait Islander only/both Aboriginal and Torres Strait Islander adj-HR=1.36 (95%CI 0.92–2.00; $p$ = 0.160).

## Discussion

This study provides the first multi-jurisdictional, detailed epidemiological data concerning HCC in a large cohort of Indigenous Australians. Although broad details of HCC epidemiology in Indigenous Australian are known from national registry data [3], such as the younger onset and the more frequent presentation in women, more granular details are lacking. The significantly higher comorbidity burden, the more frequent remoteness and greater socioeconomic disadvantage in the Indigenous HCC cohort are novel findings that are likely to be drivers of survival disparity observed between Indigenous and non-Indigenous people with HCC. The study data also define important cofactors associated with HCC in Indigenous Australians, not previously identified.

Alcohol remains the most prevalent cofactor for HCC, with a history of alcohol misuse identified in 55% of Indigenous HCC patients, compared with 40% of non-Indigenous patients. Alcohol misuse may be a particularly potent cofactor for HCC in Indigenous Australians given the relatively higher rate of other cofactors, such as viral hepatitis and metabolic associated fatty liver disease. Therefore, identifying individuals at higher risk of harm from alcohol, such as those with cofactors, and addressing these risks in a targeted way at a community level, is likely to be an important intervention to reduce excess HCC incidence and mortality risk in Indigenous Australians.

The association of chronic HBV with HCC in Indigenous Australians was confirmed by the study. HBV was found in approximately 25% of Indigenous HCC cases. The high prevalence of HBV in Indigenous Australians (2.5%) is well described, particularly in remotely living Indigenous Australians where the prevalence estimate of infection is 5.5% [13]. Clearly efforts to vaccinate, screen for infection and improve HBV antiviral treatment uptake will be critical and cost effective measures in reducing the incidence and mortality of HCC in Indigenous Australians and are likely to be cost effective. However, an exclusive focus on HBV and HCC surveillance in HBV patients is unlikely to reduce the overall HCC burden of disease in this population.

An important finding is the frequent association of markers of metabolic syndrome with HCC in Indigenous Australians. The knowledge of non-alcoholic fatty liver disease was evolving during the study period which commenced in 2000, so it is unsurprising that few patients received codes for this diagnosis. More reliable data were available for diabetes coding, an important marker of metabolic associated fatty liver disease. Diabetes was present in 48% of Indigenous HCC, significantly higher than the prevalence in non-Indigenous HCC (29%), again suggesting the relatively more important role of metabolic associated fatty liver disease in Indigenous HCC. The relatively higher prevalence of obesity (1.5-fold higher) and diabetes (3-fold higher) in Indigenous Australians have been previously well described [14,15] and our findings are consistent with this. However, the 48% prevalence of diabetes in Indigenous Australians with HCC far exceeds the age adjusted estimated diabetes prevalence in the overall Indigenous population (12.6%) [14]. Understanding the importance of obesity and metabolic syndrome as a cofactor for HCC in Indigenous Australians will therefore be critical in planning future interventions.

An important and novel finding from this study is the frequent presence of multiple HCC cofactors in Indigenous Australians. Over half of Indigenous Australians had multiple cofactors for HCC, significantly higher than for non-Indigenous Australians. The frequent clustering of HCC cofactors (in particular alcohol + viral hepatitis and alcohol + metabolic associated fatty liver disease) is a likely driver of earlier disease onset and poorer survival in Indigenous Australians. A thorough assessment of all HCC cofactors is likely to be critical for accurate assessment of HCC risk in Indigenous Australians with chronic liver disease.

The poorer survival of Indigenous Australians with HCC was confirmed by this study on unadjusted analysis. However, on multivariate analysis the strength of the association between Indigenous status and survival was weaker and statistically non-significant after adjusting for rurality, comorbidity burden and lack of curative therapy (adjusted-HR=1.20 95%CI 0.97–1.47). As only 6.4% of study patients were Indigenous, we therefore cannot exclude that a statistically significant association exists, and that a larger study, containing more Indigenous patients and greater statistical power, may find such an association. However, study findings suggest that other sociodemographic factors were important contributors to the survival in both Indigenous and non-Indigenous groups. Three variables, remoteness, comorbidity burden, and lack of curative therapy, were statistically significantly associated with poorer survival on multivariate analysis. Indeed the negative effects of rurality and higher comorbidity burden on many diseases are well known in all populations.

An important question arising from the study is how it informs HCC surveillance practice for Indigenous Australians living with HBV. Concerns about aggressiveness of HBV disease in Indigenous Australians relating to a unique C4 genotype, identified in some Indigenous populations have been raised, although the clinical relevance of this genotype across the entire heterogenous Indigenous Australian population has not been firmly established [16]. Recently developed Australian HCC guidelines [17] have suggested that non-cirrhotic Indigenous Australians living with CHB should commence HCC surveillance from age 50, on the basis of an estimated HCC incidence of 0.36 to 0.9% per year, derived from a small study of HCC in the Northern Territory [4]. and modelling data from other high risk populations, where cost effectiveness of HCC surveillance has been suggested when the incidence is >0.2%/year [18]. Data from this larger, multi-jurisdictional study suggest that HCC surveillance should be considered in males from age 40, on the basis of an annual HCC incidence rate of 0.23%. However, a limitation of such a recommendation is that all HBV-related HCC cases in patients less than 50 years occurred in cirrhotic individuals, where traditionally higher annual incidence rates of HCC (1.5%) are required for cost effectiveness of surveillance. Relatively small numbers of HBV-related HCC cases (58 in total) also limit conclusions. Further studies are required to provide local cost effectiveness data (particularly as costs of HCC surveillance in remote Indigenous communities are likely to be higher) and more precise estimates of HCC risk in Indigenous Australians living with HBV using multiple data inputs including fibrosis status, activity of HBV (viral load, hepatitis e antigen status, ALT), age, sex, family history of HCC and number of HCC cofactors.

Improving outcomes of HCC for Indigenous Australians will be a significant challenge. The linkage of high HCC incidence and mortality with social determinants of health suggests that interventions are unlikely to be successful unless they also involve public health measures aimed at reducing social disadvantage and improving access to care. Anticipated beneficial effects from HBV vaccination and new HCV therapies on future HCC incidence may be diminished by the current obesity epidemic, which has disproportionately affected Indigenous Australians. Interventions will require substantial consultation and co-design with Indigenous communities to ensure cultural appropriateness. Early qualitative work has suggested that there are substantial educational barriers to address in order for often asymptomatic conditions to be prioritized by Indigenous Australians and to overcome common fears of cancer [19]. The use of educational tools in traditional language will also be critical in remote communities where English is often a second language [20]. Solving the “tyranny of distance” to deliver high quality liver ultrasound surveillance to at-risk individuals in remote communities represents another significant health challenge. However, the advent of simple serum based fibrosis tests, together with high quality mobile ultrasound devices, has already led to the development of mobile liver clinics to remote Indigenous communities in a number of Australian jurisdictions, with improved rates of HCC surveillance reported [21]. High quality studies evaluating the effectiveness and cost effectiveness of this model of care are an important research priority.

The study has a number of limitations. Firstly, it did not include all Australian jurisdictions. This in part relates to the difficulty of data linkage studies in Australia where there is no national or uniform data linkage process. However, the study was able to combine data for a significant time period and from three large jurisdictions, representing 43% of the Indigenous Australian population [22]. The poor coding for obesity and non-alcoholic fatty liver disease in hospital separations data made interpretation of the influence of metabolic associated fatty liver disease on HCC challenging. However, using the available data and a surrogate marker for obesity and diabetes, important findings emerged. Finally, our data were not able to provide information on prior performance of ultrasound that could indicate involvement in a surveillance program. Obtaining this data would be an important future study.

This study adds important data to better characterise HCC epidemiology and cofactors and their contribution to survival in Indigenous Australians. It highlights significant barriers and opportunities to address. It is hoped that such data will assist with a greater recognition of the burden of chronic liver disease in Indigenous Australians, the sixth leading cause of death in this population [23] and the third leading cause of the mortality gap between Indigenous and non-Indigenous Australians due to chronic disease [24]. These data will assist governments and Indigenous health care organizations to address this risk and design interventions to reduce the HCC mortality gap.

## Declaration of Competing Interest

Authors disclose the following interests related to this manuscript.

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## Author contributions

Alan Wigg-study design, data interpretation, manuscript writing

Sumudu Narayana-data collection, data analysis, ethics and governance approvals, manuscript review

Gunter Hartel-data analysis and manuscript review

Linda Medlin-manuscript review

Greg Pratt-manuscript review

Elizabeth Powell-manuscript review

Paul Clark-manuscript review

Jane Davies-manuscript review

Kirsty Campbell-manuscript review

Maree Toombs-manuscript review

Michael Larkin-manuscript review

Patricia Valery-study design, data collection, data analysis, ethics and governance approvals, manuscript writing, manuscript review

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## Data sharing statement

The final dataset used for all analyses used in this study is securely stored by the senior author Patricia Valery at QIMR Bergohoffer Medical Research Institute Queensland. The dataset can be accessed via request to the corresponding author of the manuscript, Professor Alan Wigg.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.100919.

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