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ORIGINAL ARTICLE

Remoteness of residence predicts tumor stage, receipt of treatment, and mortality in patients with hepatocellular carcinoma

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Key words
age at diagnosis, hepatocellular carcinoma, migration, mortality, remoteness of residence.

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Abstract

Background and Aim: Surveillance and early detection and curative treatment of hepatocellular carcinoma (HCC) are the mainstay of improving survival for patients, but there are several barriers to achieving this goal. We reported the impact of remoteness of residence on receipt of treatment, tumor stage, and survival in patients with HCC in Queensland.

Methods: We conducted a retrospective cohort study of 1651 HCC patients (147 migrants) from 1 January 2007 to 31 December 2016. We used Wilcoxon rank-sum test to compare the median age at the time of diagnosis and Bayesian Weibull accelerated failure time regression to identify independent predictors of time to death.

Results: The median survival time after HCC diagnosis was 9.0 months (interquartile range 2.0–24.0). Metropolitan residence ($P = 0.02$), non-English language ($P < 0.001$), foreign country of origin ($P < 0.001$), and HBV etiology ($P < 0.001$) were significantly associated with receiving surgical resection for HCC treatment. The strongest predictors of time to death were undifferentiated tumor at presentation (time ratio [TR] = 0.30, 95% credible interval (CrI) 0.23–0.39), age ≥70 years (TR = 0.42, 95% CrI 0.34–0.53), living in remote areas (TR = 0.67, 95% CrI 0.55–0.80), and presence of ≥1 comorbidity (TR = 0.69 95% CrI 0.54–0.90). All the other covariates adjusted, including country of birth (TR = 0.76, 95% CrI 0.49–1.06), did not predict survival time.

Conclusions: Patients living in rural and remote areas had late stage clinical presentation and poor survival. Remoteness of residence may limit access to HCC surveillance in at-risk patients such as those with cirrhosis, and timely curative treatment to improve survival in these patients.

Introduction

Globally, hepatocellular carcinoma (HCC) ranks as the fifth most prevalent cancer and the second most common cause of cancer-related mortality.[1,2] Asia and Africa had the highest incidence rates for HCC.[3] HCC occurs at a younger age in low- and middle-income countries such as sub-Saharan Africa, where hepatitis B (HBV) infection is more prevalent, and later in life in high-income countries.[4]

In Australia, the incidence of HCC has risen substantially in the past three decades, making HCC the cancer with the fastest growing incidence.[5] Importantly, more than half of the cases are in overseas born individuals, and a large part of increasing HCC incidence in Australia was attributed to migration from the Asia-Pacific region where HBV prevalence is high.[5,6] Upon immigration, migrants from high HBV burden countries carry that risk to new country and have a higher rate of HCC compared with other Australians (Taye B et al., unpublished data). Data are discrepant in terms of the impact that country of birth and environmental variables acquired in the country of birth add to outcomes and age at the time of diagnosis.[7,8]

Significant improvement in HCC survival can be achieved by increasing the rate of surveillance of patients at high risk for HCC, early detection, and high rate of uptake of curative therapy.[9] Access to early detection and timely treatment may be limited by several factors including patients' socioeconomic conditions and remoteness of their residence.[10] Many patients, including migrants, live in regional parts of Australia. Patients living in regional or remote areas may have lower rates of screening surveillance and treatment uptake for HCC, and may present with advanced stage of HCC.[11,12] In a retrospective cohort study of HCC patients in Southeast Queensland, we

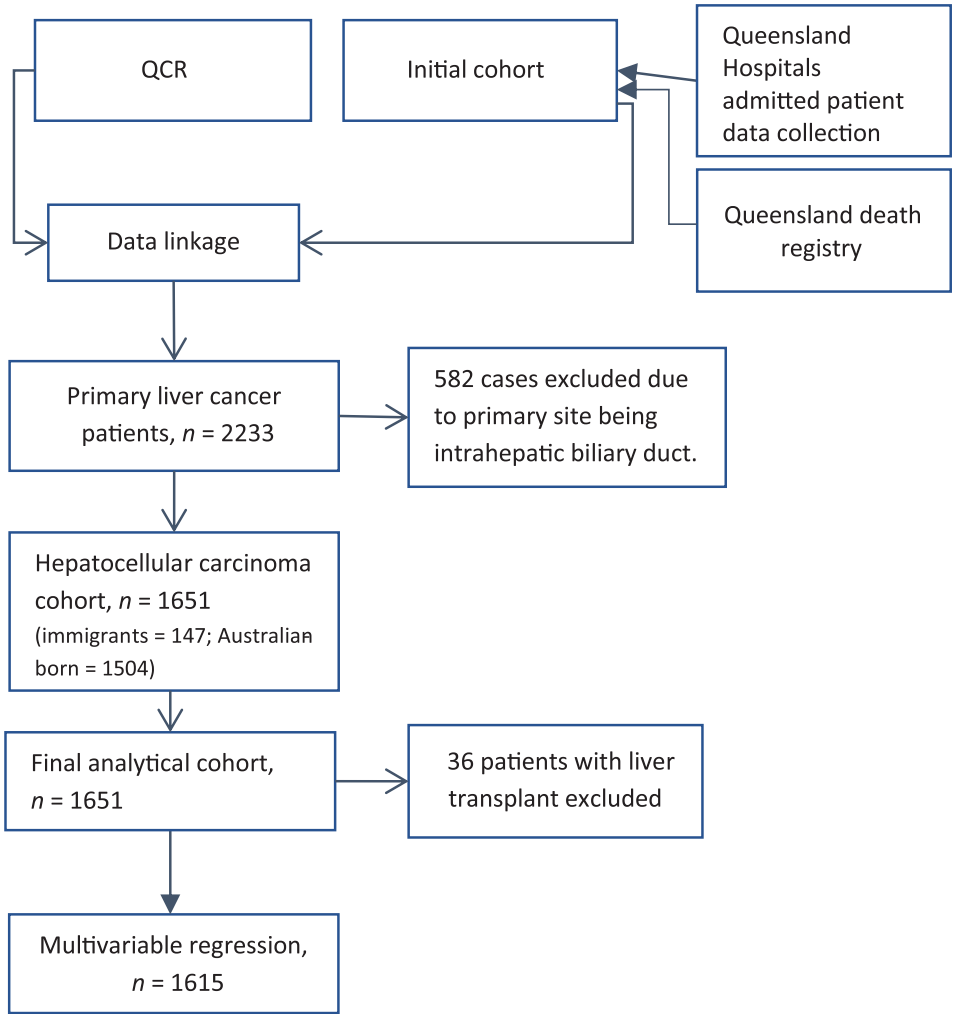

Figure 1 Study participant selection flowchart. Three data sources—Queensland cancer registry (QCR), Queensland hospitals admitted patient data collection, and Queensland death registry were used to obtain 2233 liver cancer patients and 1615 hepatocellular carcinoma cases were analyzed.

investigated the impact of migration, area of residence, preferred language, and tumor stage on receiving treatment and survival time in migrants born in Africa, Middle East, or Asian regions.

Methods

Study design and cohort. We conducted a retrospective cohort study of adults with a primary diagnosis of HCC from 1 January 2007 to 31 December 2016. Entry into the cohort was on the date of diagnosis of HCC and patients were followed until the date of death or 31 December 2016—the date of censoring.

Data sources. Data for 1651 HCC patients (147 migrants born in Africa, Middle East, or Asian regions) from the Queensland Cancer Registry, Queensland Hospitals Admitted Patient Data Collection (QHAPDC), and Queensland Death Registry were linked using deterministic data linkage by patient identifier and analyzed. We compared patients from Africa, Middle East, or Asian regions as one group (referred to here as migrants) to other Australians including those born in Europe and America (referred to here collectively as other Australians). This is because of the epidemiological similarities in viral hepatitis epidemiology between the Australian-born individuals and migrants from Western countries, where presumed cultural and linguistic barriers to engagement in healthcare may not be as limiting.[13] Analysis for significant differences between European and American migrants compared with Australian-born migrants showed no significant differences, and justified the incorporation of these two groups from an epidemiological perspective (Table S1). The data acquisition and participant selection processes are described in Figure 1.

Measurements and variables. We calculated Charlson Comorbidity Index (CCI) using validated coding algorithms.[14] Briefly, diseases were classified according to International Classification of Diseases 10th version and given weights following the methods by Charlson et al.[15] We excluded mild or severe liver disease in the CCI calculation because it is difficult to differentiate an isolated liver disease from HCC. HCC differentiation and recurrence were defined according to the standards.[16–18]

Table 1 Characteristics of hepatocellular carcinoma patients by country of birth, 2007–2016

Characteristic	Migrants, $n = 147$ (%)	Australian/EU/AM-born, $n = 1504$ (%)	Total, $n = 1651$ (%)	*P* value
Sex†				
Female	28 (19.2)	292 (19.7)	320 (19.6)	0.88
Male	118 (80.8)	1192 (80.3)	1310 (80.4)	
Marital status†				
Married/defacto	114 (80.3)	837 (58.5)	951 (60.5)	<0.001
Not married	28 (19.7)	593 (41.5)	621 (39.5)	
Remoteness of residence†				
Major city	124 (84.9)	823 (55.5)	947 (58.1)	
Outside major city	22 (15.1)	661 (44.5)	683 (41.9)	<0.001
SEIFA				
Q1 (most affluent)	32 (21.9)	141 (9.5)	173 (10.6)	<0.001
Q2	41 (28.1)	222 (15.0)	263 (16.1)	
Q3	18 (12.3)	259 (17.5)	277 (17.0)	
Q4	15 (10.3)	344 (23.2)	359 (22.0)	
Q5 (most disadvantaged)	40 (27.4)	517 (34.9)	557 (34.2)	
Preferred language†				
English	36 (24.7)	971 (65.4)	1007 (61.8)	<0.001
Other languages	63 (43.2)	41 (2.8)	104 (6.4)	
Not stated	47 (32.2)	472 (31.8)	519 (31.8)	

†Numbers may not add up to column total due to missing values.
AM, America; EU, Europe; SEIFA; socioeconomic index for areas.

Remoteness of residence was categorized using the Australian Standard Geographical Classification of areas based on Accessibility, Remoteness, Index of Australia indicators[19] and the relative socioeconomic advantage and disadvantage for participants was classified based on the socioeconomic index for areas classification system (SEIFA).[20] The primary outcome of interest was time-to-death in months. For patients who died on the same day as their date of diagnosis, we replaced the days between diagnosis and death by 0.5. Some variables had multiple responses and the numbers did not add up to 100%. This was indicated in the respective tables. In some cases, the totals were less than the overall total due to missing values in measurement of clinical variables—we highlighted the actual numbers in front of the variable.

Statistical analyses. We used Stata 15.1 software (Stata Corp, 4905 Lakeway Drive, College Station, TX, USA). Two-sample Wilcoxon rank-sum test was used to compare the age at the time of diagnosis of HCC between migrants and other Australian patients. We calculated attributable fraction to estimate the contribution of HBV, hepatitis C virus (HCV), and alcohol misuse on an indication for listing for liver transplantation and surgical resection. We calculated attributable risk (AR) as the difference between those with the risk factor (I_e) and those without (I_o) as $AR = I_e - I_o$ and population attributable risk (PAR) as $AR \times P_e$ or $PAR = P_e\ (RR - 1)/[1 + P_e\ (RR - 1)]$; where P_e is the prevalence of the risk factors in the population.

We used Weibull survival curve to compare the cumulative probability of survival in HCC patients based on country of origin and HCC treatment status. We fitted Bayesian–Weibull accelerated failure time model to identify independent predictors of time to death for patients with HCC because the hazard rates of mortality from HCC increase monotonously over time, and we measured the multiplicative effect of the covariates on the time-scale.[21,22] We reported the effect sizes in time ratios—a clinically meaningful estimate that describes the magnitude of increase or decrease in survival time among patients with the covariate of interest compared with those without.[21,22] Time ratio tells the relative survival time in an exposed group compared with nonexposed group, and can be used to directly compare the impact of intervention in terms of increasing the time survived. Default normal priors with mean of zero and standard deviation 100 were used. Using the Bayesian inference of Markov Chain Monte Carlo (MCMC) algorithm, we used 10 000 MCMC samples and a burn-in state at 2500. The model diagnosis was made using a trace diagram. Time ratios (TR) and 95% credible intervals (CrI) were reported.

Human Research Ethics Committee of QIMR Berghofer Medical Research Institute (P2209) and Queensland Health (HREC/17/QPAH/23; HREC/2018/QMS/43571) approved the conduct of this study.

Results

Cohort characteristics. We retrospectively followed 1651 HCC patients (147 were migrants born in Africa, Middle East, or Asian regions) from 1 January 2007, to 31 December 2016, with a total person-months of observation of 28 018. Most migrants (84.9%) lived in major cities compared with just above half of other Australian (55.5%) patients ($P < 0.001$). A higher proportion of migrants than other Australian patients were in the most affluent SEIFA category ($P < 0.001$) (Table 1).

Etiology and clinical presentation. Table 2 presents the epidemiology of underlying etiologies of HCC. Chronic HBV (54.8%) was the leading underlying etiology for HCC in

Table 2 Clinical presentation and treatment of hepatocellular carcinoma in migrants and Australian-born patients, 2007–2016

	Migrants, $n = 147$ (%)	Australian/EU/AM-born, $n = 1504$ (%)	Total, $n = 1651$ (%)	*P* value
Etiology†				
Chronic hepatitis B	80 (54.8)	130 (8.8)	210 (12.9)	<0.001
Chronic hepatitis C	50 (34.2)	517 (34.8)	567 (34.8)	0.89
Alcohol misuse	12 (8.2)	648 (43.7)	660 (40.5)	<0.001
Non-alcoholic fatty liver disease	6 (4.1)	82 (5.5)	88 (5.4)	0.47
Non-alcoholic steatohepatitis	6 (4.1)	86 (5.8)	92 (5.6)	0.40
Drug use	2 (1.4)	78 (5.3)	80 (4.9)	0.038
Obesity	1 (0.7)	97 (6.5)	98 (6.0)	0.005
Other causes	6 (4.1)	82 (5.6)	88 (5.5)	<0.49
Age at diagnosis of HCC				
Median (IQR)‡	66.7 (54.9–74.5)	65.5 (57.3–75.2)	65.6 (57.0–75.0)	0.36
HCC differentiation				
Well differentiated	2 (1.4)	76 (5.1)	78 (4.7)	<0.001
Moderately differentiated	30 (20.4)	163 (10.8)	193 (11.7)	
Poorly differentiated	14 (9.5)	69 (4.6)	83 (5.0)	
Undifferentiated	0 (0.0)	8 (0.5)	8 (0.5)	
Not stated/unknown	101 (68.7)	1188 (79.0)	1289 (78.1)	
HCC recurrence§	34 (23.1)	328 (21.8)	362 (21.9)	0.71
Cancer metastasis§	142 (97.3)	1426 (96.1)	1568 (96.2)	0.48
Treatment for liver disease§				
Band	11 (7.5)	177 (11.9)	188 (11.5)	0.11
Tap	36 (24.7)	470 (31.7)	506 (31.0)	0.081
TIPS	0 (0.0)	4 (0.3)	4 (0.2)	0.53
Treatment for HCC§				
RFA	15 (10.3)	102 (6.9)	117 (7.2)	0.13
Surgical resection	41 (28.1)	143 (9.6)	184 (11.3)	<0.001
TACE	41 (28.1)	426 (28.7)	467 (28.7)	0.87
Liver transplant	5 (3.4)	31 (2.1)	36 (2.2)	0.37

†Multiple responses. Percentage totals may be above 100% due to overlap between etiologies.

‡Wilcoxon rank-sum test ($z = -1.17$, $P = 0.36$).

§Numbers represent patients who had outcome of interest.

AM, America; EU, Europe; HCC, hepatocellular carcinoma; IQR, interquartile range; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TIPS, transjugular intrahepatic portosystemic shunt.

migrants while alcohol misuse (43.7%) was the most prevalent etiology in other Australians. Hepatitis C infection was the second most prevalent underlying etiology for HCC in both migrants (34.2%) and other Australian (34.8%) patients.

The median age at the time of diagnosis of HCC in migrants (66.7 years, interquartile range [IQR] 54.9–74.5) and Australian-born patients (65.5, IQR 57.3–75.2) was similar ($P = 0.36$). A higher proportion of migrants presented with more differentiated HCC than other Australians (well-differentiated and moderately differentiated HCC, 21.8 *vs* 15.9%). The most prevalent HCC treatments received by migrants and other Australians were liver resection and transarterial chemoembolization (TACE), respectively (Table 2). Epidemiologic description of liver disease complications and comorbidities for HCC patients is presented in detail in Table S2.

Attributable fractions of etiologies for listing for liver transplantation. Chronic HCV (77.8%) was the leading underlying etiology for an indication for liver transplantation;

Table 3 Attributable risk and population attributable risk of underlying causes for an indication for liver transplant and resection for hepatocellular carcinoma, 2007–2016

	Received liver transplant				Liver resection			
	$n = 36$ (%)	*P* value	AR	PAR	$n =$ (%)	*P* value	AR	PAR
Chronic hepatitis C	28 (77.8)	<0.001	0.85 (0.67–0.93)	0.66	60 (32.6)	0.51	0.09 (−0.21–0.32)	0.03
Alcoholic liver disease	18 (50.0)	0.24	0.32 (−0.30–0.64)	0.16	45 (24.5)	<0.001	0.52 (0.34–0.65)	0.21
NAFLD	4 (11.1)	0.13	0.54 (−0.26–0.83)	0.06	18 (9.8)	0.005	0.47 (0.19–0.66)	0.05
Chronic hepatitis B	7 (19.4)	0.23	0.39 (−0.39–0.73)	0.08	42 (22.8)	<0.001	0.50 (0.32–0.63)	0.11
NASH	5 (13.9)	0.03	0.63 (0.07–0.85)	0.09	12 (6.5)	0.58	0.14 (−0.48–0.50)	0.01

AR, attributable risk; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PAR, population attributable risk.

Table 4 Factors associated with receiving surgical section and radiofrequency ablation for treatment of hepatocellular carcinoma

	Surgical resection			Radiofrequency Ablation		
	No resection, $n = 1417$ (%)	Had surgical resection, $n = 177$ (%)	*P* value	No RFA, $n = 1481$ (%)	Had RFA, $n = 113$ (%)	*P* value
Rurality of residence						
Major city	808 (87.4)	117 (12.6)	0.021	850 (91.9)	75 (8.1)	0.062
Rural/remote	609 (91.0)	60 (9.0)		631 (94.3)	38 (5.7)	
Preferred language						
English	908 (92.7)	71 (7.3)	<0.001	918 (93.8)	61 (6.2)	0.24
Other languages	75 (73.5)	27 (26.5)		93 (91.2)	9 (8.8)	
Country of origin						
Africa/Middle East/Asia	102 (72.3)	39 (27.7)	<0.001	126 (89.4)	15 (10.6)	0.085
Australia/America/ Europe-born	1315 (90.5)	138 (9.5)		1355 (93.3)	98 (6.7)	
SEIFA						
Q1 (most affluent)	146 (85.4)	25 (14.6)	0.33	161 (94.2)	10 (5.8)	0.050
Q2	221 (86.7)	34 (13.3)		231 (90.6)	24 (9.4)	
Q3	244 (90.0)	27 (10.0)		244 (90.0)	27 (10.0)	
Q4	316 (90.0)	35 (10.0)		335 (95.4)	16 (4.6)	
Q5 (most disadvantaged)	489 (89.7)	56 (10.3)		509 (93.4)	36 (6.6)	
Hepatitis B infection						
Negative	1254 (90.2)	137 (9.8)	<0.001	1301 (93.5)	90 (6.5)	0.012
Positive	163 (80.3)	40 (19.7)		180 (88.7)	23 (11.3)	
Hepatitis C virus infection						
Negative	933 (88.4)	122 (11.6)	0.41	1003 (95.1)	52 (4.9)	<0.001
Positive	484 (89.8)	55 (10.2)		478 (88.7)	61 (11.3)	

RFA, radiofrequency ablation; SEIFA, socioeconomic index for areas.

then, alcohol-related liver disease (24.5%) followed by chronic HBV (22.8%) were the leading underlying etiologies for liver resection. The liver transplantation attributed to chronic HCV was 850 liver transplants per 1000 chronic HCV positive HCC patients (95% confidence interval [CI] 0.67–0.93). Liver resection attributable to alcoholic liver disease was 520 resections per 1000 HCC patients with alcoholic liver disease (95% CI 0.34–0.65) (Table 3).

Factors associated with receiving curative treatment. Patients living in rural and remote areas were significantly less likely to receive surgical resection for the treatment of HCC compared with patients living in metropolitan areas (9 *vs* 13%, $P = 0.021$). A higher proportion of patients with HBV positive test result received surgical resection (20 *vs* 10%, $P < 0.001$), while a proportionally more patients diagnosed with HCV received radiofrequency ablation (RFA) treatment compared with those tested negative (11 *vs* 5%) (Table 4).

Survival. The median survival time after HCC diagnosis for the entire cohort was 9.0 months (IQR 2.0–24.0 months). There was no statistically significant difference in the months survived after HCC diagnosis between migrants and other Australians. At 10 years, the survival probability was 1.2% for migrants and 0.7% in other Australians. Patients with HCC who presented with well-differentiated tumor had a significantly better probability of 12-month (55.9 *vs* 45.4%) and 120-month (2.4 *vs* 0.6%) survival compared with patients presented with poorly differentiated HCC (Fig. 2).

Predictors of time-to-death. After adjusting for age at diagnosis, remoteness of residence, and treatment for HCC, there was no statistically significant difference in the survival time between migrants and Australian-born patients (TR = 0.76, 95% CrI 0.49–1.06). Older age at diagnosis was associated with shorter survival time, patients in the age range of 60–69 years had 28% fewer months of survival compared with those <60 years (95% CrI 0.56–0.95), and being ≥70 years of age was associated with 58% fewer months of survival (95% CrI 0.34–0.53). HCC patients who lived outside of a major city had 33% fewer months of survival compared with those living in major cities (95% CrI 0.55–0.80). Patients who presented with undifferentiated HCC had significantly fewer months of survival (TR = 0.30, 95% CrI 0.23–0.39) compared with patients presented with well-differentiated tumor (Table 5).

Discussion

In the present study, we examined the impact of country of birth, rurality of residence, tumor stage at presentation, age at the time of diagnosis, and comorbidities on the survival of HCC in migrants in a cohort of 1651 patients. We found patients with HCC living outside of the major cities and in remote areas had poorer survival time compared with patients living in major cities. Living in rural, remote areas could be associated with lesser

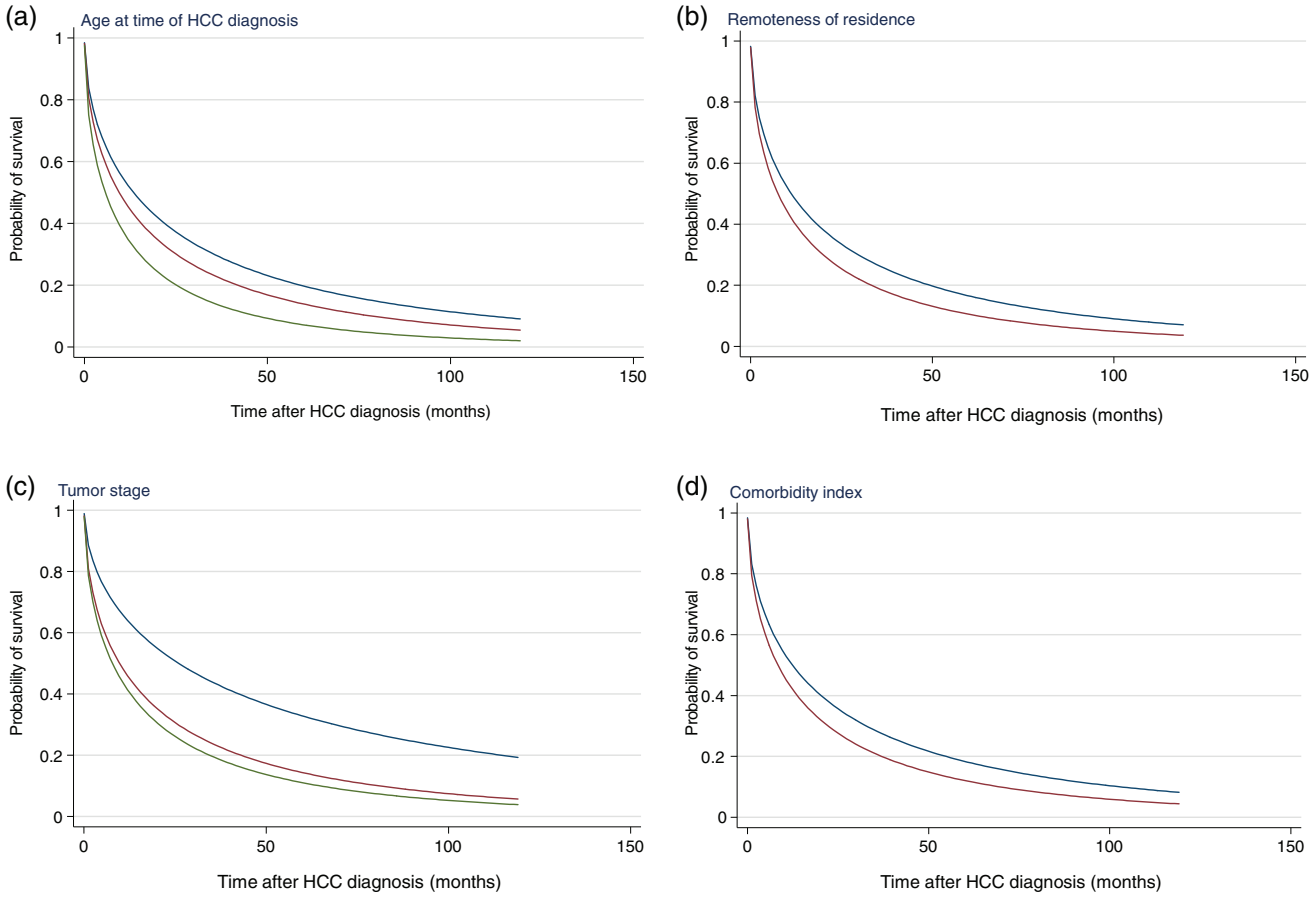

Figure 2 Weibull survival curves for hepatocellular carcinoma (HCC) by age at the time of HCC diagnosis (a), remoteness of residence (b), tumor stage at presentation (c), and medical comorbidities (d). The cumulative survival probability indicates survival time after diagnosis of HCC in months. The acronym HCC stands for hepatocellular carcinoma. (a): (——), <60 years; (——), 60–69 years; (——), ≥70 years. (b): (——), Major city; (——), remote areas. (c): (——), Well differentiated; (——), poorly differentiated; (——), undifferentiated. (d): (——), No comorbidity; (——), ≥1 comorbidity.

opportunities to engage in surveillance for patients at risk of developing HCC such as those with cirrhosis.[23] These patients may not be as likely as those residing in major cities to regularly attend hepatology specialty clinics, which are mainly based in major cities because of the need to travel a long distance. This contributes to lack of access to good quality screening such as blood tests and ultrasound, loss to follow-up, and late diagnosis of HCC, when treatment at advanced stages may not be available or possible.[12] Patients in remote and rural areas are more likely to be exposed to environmental risk factors including aflatoxin known to accelerate the progression of HCC and cause earlier onset and higher mortality.[7]

We found no statistically significant difference in the median age at diagnosis of HCC between migrants and other Australian patients, similar to findings by Ashhab *et al.*[8] This could be due to selection bias of migrant populations compared with nonmigrant populations in countries endemic for HBV or differential exposures to environmental factors such as aflatoxin, which accelerate HCC progression.[7] Chronic exposure to aflatoxin causes mutation of the *TP53* tumor suppressor gene in hepatocytes, and increases HCC risk in persons with chronic HBV infection.[24,25] Most migrants lived in major cities and a significant proportion lived in higher socioeconomic locales, thus these individuals may differ from refugee and low-income migrants, and might be less likely to be exposed to factors that accelerate the progression of HCC. This may explain why HCC may occur at a younger age more commonly in developing countries, but it is not seen in our study's migrant participants. Although migrants may be likely to acquire HBV infection in early life,[26] the opportunities for a better access to HBV screening, surveillance in Australia may also have impacted risk by treatment of underlying risks and engagement in screening for HCC, and have contributed to HCC diagnosis at an early stage of the tumor.

A greater proportion of migrants presented with early-stage HCC compared with other Australians, and the higher proportion of HBV infection in migrants with HCC compared with other Australians may explain this. Hepatitis B-related HCC can

Table 5 Predictors of time-to-death for migrants and other Australian patients with hepatocellular carcinoma, 2007–2016

Predictor	Median survival months (IQR)	Time ratio	95% credible interval
Sex			
Male (*vs* female)	9.9 (2.0–25.0)	1.03	0.82–1.26
Age at diagnosis of HCC (*vs* <60 years)			
60–69 years	9.9 (2.9–25.0)	0.72	0.56–0.95
≥70 years	6.1 (1.9–18.4)	0.42	0.34–0.53
Country of birth			
Australian/America/Europe born (*vs* migrants)	8.1 (2.0–23.0)	0.76	0.49–1.06
Remoteness of residence			
Outside major city (*vs* major city)	7.0 (2.0–24.0)	0.67	0.55–0.80
Preferred language (*vs* English)			
Other language	8.1 (2.0–23.0)	1.56	1.26–2.00
SEIFA (*vs* most affluent)			
Q2	9.7 (2.0–26.0)	0.91	0.60–1.34
Q3	11.0 (2.9–24.9)	1.13	0.77–1.62
Q4	8.0 (2.0–24.5)	0.93	0.63–1.39
Q5 (most disadvantaged)	8.1 (2.0–23.0)	0.96	0.75–1.24
Charlson Comorbidity Index			
≥1 comorbidity (*vs* none)	8.0 (2.0–23.0)	0.69	0.54–0.90
Type of HCC			
Recurrent HCC (*vs* no recurrence)	6.0 (2.0–19.1)	0.60	0.46–0.77
Tumor stage at presentation (*vs* differentiated)			
Poorly differentiated	10.5 (2.0–25.0)	0.42	0.27–0.60
Undifferentiated	7.0 (2.0–21.0)	0.30	0.23–0.39

HCC, hepatocellular carcinoma; IQR, interquartile range; SEIFA, socioeconomic index for areas.

occur without cirrhosis, and is known to be associated with the occurrence of early-stage HCC.[27,28] While the data were unable to control for MELD score or Child–Pugh stage, migrant patients were less likely to have had treatment for portal hypertension complications of decompensation such as ascetic tap or variceal banding, which may suggest a lower rate of decompensation. HCC, occurring in the absence of cirrhosis, opens more curative treatment opportunities and may explain the observed difference in higher proportion of curative treatments in migrants, particularly higher rates of surgical resection (Table 2). Migrant patients with HCC had markedly lower rates of alcohol misuse (8% compared with 44% in other Australians with HCC). Therefore, the differences in the clinical presentation of HCC between migrants and other Australians is likely related to the epidemiological differences in viral hepatitis, alcohol misuse, rather than environmental determinants related to the country of birth.[13] Concomitant alcohol and drug use in the presence of HCC accelerates the progression of liver disease, causing presentation at later stages of HCC in other Australian patients than migrants.[28] Lastly, early-stage of HCC at the presentation in migrants could be explained by the fact that most migrants lived in major cities and provides them with better opportunities to be screened and diagnosed at an earlier stage of HCC.[11,28]

The poor survival for HCC (9.0 months) in our study could be related to increasing age at diagnosis, a strong predictor of poor HCC survival,[10,29–31] and the late-stage presentation of HCC. Well-differentiated, early-stage tumors have a protracted course and may be treated by surgical resection.[32] However, patients presenting with late-stage HCC may be ineligible to curative treatments when survival is often poor.[23,29,31,33,34] A high rate of liver disease complications (hepatorenal syndrome, hepatic encephalopathy, and gastrointestinal bleeding) and comorbidities in our patients may partly explain the poor survival in this cohort.[10,23,33,35–37] Wong *et al.*[28] found a lower frequency of liver disease complications was related to better survival in patients with HCC, particularly for migrants. Maximizing early diagnosis and regular screening of patients with an underlying disease such as cirrhosis may offer most benefit, opening a variety of treatment options for HCC patients that may improve survival.[38]

Another interesting finding in this study is that despite HBV being the leading underlying etiology for HCC in migrants, chronic HCV infection is still the leading indication for listing for liver transplantation. Although direct-acting antiviral treatment for HCV has resulted in a significant decline in the incidence of HCV infection, the risk of developing HCC remains after a sustained virologic response.[39] Hepatitis C virus remains the second most prevalent underlying etiology for HCC.

In Australia, the most common cause of HCV is injecting drug use (IDU), though in migrants from the developing world, HCV transmission may occur more frequently iatrogenically through contaminated infusions, products, and medical equipment where sterilizing facilities or protocols may not be adequate. Continued screening, HCV prevention using injection safety and treatment is needed to reduce the incidence of HCC and the number of patients requiring a transplant.[4,10,40]

A key strength of this study was the use of a validated coding algorithm[14] for comorbidities from linked hospital data.

Nevertheless, the potential for misclassification bias of presumed underlying causes, comorbidities, complications of cirrhosis, and treatment for HCC is a potential limitation. A recognized limitation was that, the available data did not permit an assessment of the severity of cirrhosis (e.g. using the Child–Pugh or MELD scores) and exact staging of HCC with both factors limiting curative treatment options and tumor stage is a strong predictor of a patient's survival after the diagnosis of HCC.[32]

In conclusion, our data showed that patients who lived in rural and remote areas, presented with advanced tumor stage, and older age had poorer survival. Migrants proportionally presented with earlier-stage HCC, probably related to the non-cirrhotic HBV infection, and lower etiological contribution from alcohol. Older age at diagnosis, comorbidities, and poor survival suggest the significance of screening for viral hepatitis, conducting HCC surveillance in at-risk patients such as those with cirrhosis, and timely curative treatment to improving survival in these patients.

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References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 2018; **68**: 394–424.
2 World Health Organization. *Global Hepatitis Report, 2017*. Geneva: World Health Organization, 2018.
3 Sayiner M, Golabi P, Younossi ZM. Disease burden of hepatocellular carcinoma: a global perspective. *Dig. Dis. Sci.* 2019; **64**: 910–7.
4 Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nat. Rev. Gastroenterol. Hepatol.* 2019; **16**: 589–604.
5 Carville KS, MacLachlan JH, Thursfield V *et al*. Hepatocellular carcinoma over three decades in Victoria, Australia: epidemiology, diagnosis and trends, 1984-2013. *Intern. Med. J.* 2018; **48**: 835–44.
6 Zhu RX, Seto WK, Lai CL, Yuen MF. Epidemiology of hepatocellular carcinoma in the Asia-Pacific region. *Gut Liver*. 2016; **10**: 332–9.
7 Yang JD, Altekruse SF, Nguyen MH, Gores GJ, Roberts LR. Impact of country of birth on age at the time of diagnosis of hepatocellular carcinoma in the United States. *Cancer*. 2017; **123**: 81–9.
8 Ashhab AA, Rodin H, Powell J, Debes JD. Impact of immigration in presentation and outcomes of hepatocellular carcinoma in the USA. *Eur. J. Gastroenterol. Hepatol.* 2019; **31**: 24–8.
9 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**: e1001624.
10 Golabi P, Jeffers T, Younoszai Z *et al*. Independent predictors of mortality and resource utilization in viral hepatitis related hepatocellular carcinoma. *Ann. Hepatol.* 2017; **16**: 555–64.
11 Clark PJ, Stuart KA, Leggett BA *et al*. Remoteness, race and social disadvantage: disparities in hepatocellular carcinoma incidence and survival in Queensland, Australia. *Liver Int.* 2015; **35**: 2584–94.
12 Wong RJ, Kim D, Ahmed A, Singal AK. Patients with hepatocellular carcinoma from more rural and lower-income households have more advanced tumor stage at diagnosis and significantly higher mortality. *Cancer*. 2020; **127**: 45–55.
13 Jayaraman T, Lee YY, Chan WK, Mahadeva S. Epidemiological differences of common liver conditions between Asia and the West. *JGH Open*. 2020; **4**: 332–9.
14 Quan H, Sundararajan V, Halfon P *et al*. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med. Care*. 2005; **43**: 1130–9.
15 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**: 373–83.
16 World Health Organization. *World Health Organization Classification of Tumours by International Agency for Research on Cancer. WHO Classification of Tumours of the Digestive System*. Lyon: International Agency for Research on Cancer, 2010.
17 Martins-Filho SN, Paiva C, Azevedo RS, Alves VAF. Histological grading of hepatocellular carcinoma—a systematic review of literature. *Front. Med.* 2017; **4**(193). https://doi.org/10.3389/fmed.2017.00193.
18 Sherman M. Recurrence of hepatocellular carcinoma. *N. Engl. J. Med.* 2008; **359**: 2045–7.
19 Australian Institute of Health and Welfare. *Rural, Regional and Remote Health: A Guide to Remoteness Classifications*. Canberra: The Institute, 2004.
20 Australian Bureau of Statistics. *Census of Population and Housing: Socio-Economic Indexes for Areas (SEIFA), Australia, 2006*. Canberra: The Bureau, 2008.
21 Zhang Z. Parametric regression model for survival data: Weibull regression model as an example. *Ann. Transl. Med.* 2016; **4**: 484.
22 Lee ET, Go OT. Survival analysis in public health research. *Annu. Rev. Public Health*. 1997; **18**: 105–34.
23 Hong TP, Gow PJ, Fink M *et al*. Surveillance improves survival of patients with hepatocellular carcinoma: a prospective population-based study. *Med. J. Aust.* 2018; **209**: 348–54.
24 Liu Y, Wu F. Global burden of aflatoxin-induced hepatocellular carcinoma: a risk assessment. *Environ. Health Perspect.* 2010; **118**: 818–24.
25 Janevska D, Chaloska-Ivanova V, Janevski V. Hepatocellular carcinoma: risk factors, diagnosis and treatment. *Open Access Maced. J. Med. Sci.* 2015; **3**: 732–6.
26 Yang J, Gyedu A, Afihene M *et al*. Hepatocellular carcinoma occurs at an earlier age in Africans, particularly in association with chronic hepatitis B. *Am. J. Gastroenterol.* 2015; **110**: 1629–31.
27 Villanueva A. Hepatocellular Carcinoma. *N. Engl. J. Med.* 2019; **380**: 1450–62.
28 Wong PY, Xia V, Imagawa DK, Hoefs J, Hu KQ. Clinical presentation of hepatocellular carcinoma (HCC) in Asian-Americans versus non-Asian-Americans. *J. Immigr. Minor. Health*. 2011; **13**: 842–8.
29 Hale GA, Nurten SC, Derya OD *et al*. Predictors of Survival in Hepatocellular Carcinoma Patients. *Ann. Transplant.* 2015; **20**: 596–603.
30 Yuanyuan S, Yanhong W, Mengmeng L *et al*. Long-term trends of liver cancer mortality by gender in urban and rural areas in China: an age-period-cohort analysis. *BMJ Open*. 2018; **8**. https://doi.org/10.1136/bmjopen-2017-020490.
31 Njei B, Rotman Y, Ditah I, Lim JK. Emerging trends in hepatocellular carcinoma incidence and mortality. *Hepatology*. 2015; **61**: 191–9.
32 Okuda K, Musha H, Nakajima Y *et al*. Clinicopathologic features of encapsulated hepatocellular carcinoma: a study of 26 cases. *Cancer*. 1977; **40**: 1240–5.
33 Kulik L, El-Serag HB. Epidemiology and management of hepatocellular carcinoma. *Gastroenterology*. 2019; **156**: 477–91 e1.
34 Zhang G, Li R, Deng Y, Zhao L. Conditional survival of patients with hepatocellular carcinoma: results from the Surveillance, Epidemiology, and End Results registry. *Expert Rev. Gastroenterol. Hepatol.* 2018; **12**: 515–23.

35 Han ML, Chen CC, Kuo SH *et al*. Predictors of in-hospital mortality after acute variceal bleeding in patients with hepatocellular carcinoma and concurrent main portal vein thrombosis. *J. Gastroenterol. Hepatol.* 2014; **29**: 344–51.
36 Tao C, Zhongyuan Y, Choudhury AK *et al*. Complications constitute a major risk factor for mortality in hepatitis B virus-related acute-on-chronic liver failure patients: a multi-national study from the Asia–Pacific region. *Hepatol. Int.* 2019; **13**: 695–705.
37 Hassanien M, El-Talkawy MD, El-Ghannam M *et al*. Predictors of in-hospital mortality in patients with hepatocellular carcinoma and acute variceal bleeding. *Electron. Physician*. 2015; **7**: 1336–43.
38 Mak LY, Cruz-Ramon V, Chinchilla-Lopez P *et al*. Global epidemiology, prevention, and management of hepatocellular carcinoma. *Am. Soc. Clin. Oncol. Educ. Book*. 2018; **38**: 262–79.
39 Singal AK, Satapathy SK, Reau N, Wong R, Kuo YF. Hepatitis C remains leading indication for listings and receipt of liver transplantation for hepatocellular carcinoma. *Dig. Liver Dis.* 2020; **52**: 98–101.
40 Williams R, Alexander G, Armstrong I *et al*. Disease burden and costs from excess alcohol consumption, obesity, and viral hepatitis: fourth report of the Lancet Standing Commission on Liver Disease in the UK. *Lancet*. 2018; **391**: 1097–107.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. Similarities in demographic, underlying etiology, liver disease complication and comorbidity between patients with hepatocellular carcinoma born in Australia, Europe, and America.
Table S2. Liver diseases and comorbid conditions during the follow-up period in hepatocellular carcinoma patients, 2007–2016.