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Early-Stage Australian HCC Patients Treated at Tertiary Centres Show Comparable Survival Across Metropolitan and Non-Metropolitan Residency

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Abstract

Background: Hepatocellular carcinoma (HCC) poses a significant public health challenge in Australia, with poorer survival observed in non-metropolitan populations. This study investigated whether survival disparities persist between non-metropolitan and metropolitan patients if only those with early-stage HCC treated at metropolitan tertiary referral centres

are considered. Methods: We performed a retrospective cohort study across ten Australian tertiary centres involving patients with a new diagnosis of Barcelona Clinic Liver Cancer (BCLC) stage 0 or A, recorded from 1 January 2016 to 31 December 2020. Residential postcodes were entered using the Modified Monash (MM) model to define metropolitan versus non-metropolitan residence. The primary endpoint was adjusted for all-cause mortality. Results: Our study included 854 patients (metropolitan n = 612, and non-metropolitan n = 242) with a median follow-up of 42.6 months. We found no significant survival or mortality differences between the two groups with the unadjusted Kaplan–Meier survival analysis (log-rank test p = 0.612) and with the Cox proportional hazards regression analysis (adjusted HR 0.93, 95% CI 0.64–1.34, p = 0.690). As expected, tumour burden, Child–Pugh Score, and Charlson Comorbidity Index (CCI) were significant predictors of mortality. Conclusions: Our findings suggest that previously observed survival disparities may stem from delayed diagnosis and reduced access to tertiary care in non-metropolitan regions and highlight the need for improved HCC surveillance and referral pathways, particularly for rural and Indigenous communities, to mitigate geographic inequities.

Keywords: hepatocellular carcinoma; HCC; metropolitan; rural; regional; remote; non-metropolitan; survival; mortality; outcomes

1. Introduction

Hepatocellular carcinoma (HCC) is a significant public health challenge in Australia, with rising incidence and poor survival rates despite advancements in treatment [1]. In Australia, access to healthcare and health-related outcomes are known to differ based on geographic location, with those residing in rural and remote areas, farthest from the large population centres, facing disadvantage across a broad range of health outcomes [2]. Residence in non-metropolitan areas of Australia has been shown to be associated with poorer HCC survival [3,4] however the reasons for this remain undefined.

The primary determinant of survival in HCC is the stage of disease at diagnosis, with median survival greater than 5 years in very-early and early-stage HCC where curative treatment can be offered, compared to the advanced and terminal stages, where the disease is universally fatal [5]. HCC is generally asymptomatic in the very-early and early-stages and therefore surveillance in at-risk patients is relied on for early diagnosis [6]. Indeed, HCC surveillance uptake has been shown to reduce mortality [7].

Furthermore, across all HCC stages, specialised multidisciplinary tertiary-level care is known to improve survival outcomes [8]. Management of HCC exclusively through multidisciplinary team meetings has recently been recommended by both the American and Australian panels of experts as an important quality indicator [9–11] and is recommended in international guidelines [12–14] due to the strong evidence for its positive impact on outcomes. In Australia, multidisciplinary teams directing HCC management are concentrated in tertiary centres in the large cities.

On this basis, it could be expected that the two primary reasons for the observed survival difference between Australian patients with HCC residing in non-metropolitan and metropolitan areas are systematic differences in stage at diagnosis due to differences in surveillance uptake [15] and differences in access to multidisciplinary tertiary care [16]. Non-metropolitan patients face unique challenges in accessing HCC surveillance, with underdiagnosis of chronic liver disease and individual patient, clinician, and system factors limiting regular access to semi-annual ultrasound [6]. Similarly, geographic distance and

clinical care pathways in their current form may pose a significant impediment to non-metropolitan HCC patients' access to multidisciplinary tertiary care.

We therefore hypothesised that in our existing retrospective cohort of very-early and early-stage HCC patients managed at tertiary centres [17–19], there would be no significant differences in survival, as this cohort would only include non-metropolitan patients who had been diagnosed early and had access to tertiary multidisciplinary care. We performed this study to test this hypothesis, in order to better understand the underlying reasons for the survival differences previously observed and to add to the national call for action in correcting systematic inequities [15,20].

2. Methods

As previously described [17–19], we performed a multicentre retrospective cohort study involving subjects with Barcelona Clinic Liver Cancer (BCLC) stage 0 or A HCC managed across ten metropolitan tertiary HCC referral centres in the two most populous states of Victoria and New South Wales, including two centres providing state-wide liver transplant services.

Inclusion criteria for the study were as follows: adult aged >18 years of age; first diagnosis of HCC through 1 January 2016–31 December 2020 with either imaging fulfilling LIRAD-5 criteria or a histological diagnosis; documented BCLC 0/A disease; Child–Pugh (CP) A or B; cancer-related performance status of Eastern Cooperative Oncology Group (ECOG) 0; absence of extrahepatic disease and vascular invasion; and residential postcode available in records. Exclusion criteria were as follows: past diagnosis of HCC; diagnosis of a different solid organ malignancy, excluding non-melanotic skin cancer; or insufficient data in the medical record to describe the stage of HCC.

Waiver of consent was sought, with all patient data entered in a de-identified form. Ethics for the study was approved by Monash Health Human Research Ethics Committee (Reference Number: HREC/80727/MonH−2022−302788(v3), 23 February 2022).

Retrospective data collection from available medical records was performed from the date of HCC diagnosis to the end of follow-up, which was either death or the last medical record entry available at the time of data collection. Data relating to key baseline demographic, clinical, and tumour characteristics, treatment, and outcomes were de-identified and inputted into a centralised REDCap electronic data capture tool hosted at Monash University. The Modified Monash Model [21] was used to categorise patients as either metropolitan (Modified Monash (MM) 1) or non-metropolitan (MM 2 to 7) based on their recorded residential postcode. The full data set, as collected on REDCap, can be seen in Supplementary File S1.

Categorical variables were summarised by frequency, non-parametric variables by median and interquartile range, and parametric variables by mean and standard deviation. Comparisons in patient characteristics were performed using the Chi-square test, Mann–Whitney U test, or independent samples *t*-test for categorical, non-parametric, and parametric continuous variables, respectively. Multivariable Cox proportional hazards analysis was used to assess the impact of metropolitan vs. non-metropolitan residence on all-cause mortality, together with selected clinical covariates known to influence outcomes, with calculation of adjusted hazard ratios with 95% confidence intervals and *p*-values. Unadjusted Kaplan–Meier survival analysis was also performed, with a log-rank test used to assess significance. For both forms of analysis, the date of diagnosis was used as the index date, and censoring was performed at the date of the last medical entry viewed for surviving patients. Liver transplant was accessed to a similar degree by both groups, and given that it is positioned as a real-world curative treatment for recurrent or refractory HCC, it was not considered a censoring or competing event for the purposes of the analysis in this

study. Variables used for adjustment in the Cox proportional hazards analysis were selected based on an *a priori* judgement of their clinical relevance in predicting survival outcomes. Variables that could be directly affected by residential status (such as choice of treatment modality) were not used for adjustment, as such differences may have been the mechanism through which non-metropolitan patients were subjected to disadvantage. Because of the differing treatments used, we limited our analysis to all-cause mortality/overall survival, as direct comparisons in other oncological outcomes (such as recurrence-free survival) could not be meaningfully made across differing treatment allocation.

A two-tailed $p < 0.05$ was considered statistically significant. All statistical analysis was performed using SPSS 29.0 (SPSS, Inc., Chicago, IL, USA).

3. Results

A total of 854 patients were included in this study, with 612 (72%) residing in metropolitan and 242 (18%) in non-metropolitan locations. Median follow-up time from diagnosis to death or censoring was 42.6 months.

Table 1 describes the patient characteristics of each group. Non-metropolitan patients, in comparison to metropolitan patients, were significantly more likely to be Indigenous (5% vs. 2%, $p = 0.001$), have cirrhosis (89% vs. 81%, $p = 0.009$), have lower platelet counts (median 119 $\times$ 10^9/L vs. 136 $\times$ 10^9/L, $p < 0.001$), less likely to be diagnosed on surveillance (74% vs. 82%, $p = 0.017$, remaining patients diagnosed incidentally on imaging performed for other indications), and more likely to be managed at a liver transplant centre (66% vs. 45%, $p < 0.001$) with corresponding differences in initial treatment strategy, as previously described [17], with greater use of initial transarterial chemoembolization [TACE] (50% vs. 39%) and less use of upfront ablation (16% vs. 24%). Metropolitan patients were much more likely to have chronic hepatitis B as an underlying cause of liver disease (16% vs. 2%, $p < 0.001$). Age, sex, smoking, Charlson Comorbidity Index (CCI), Child–Pugh Score, tumour burden, and use of transplant over the course of follow-up did not significantly differ between the two groups. Median follow-up was 44.5 months (interquartile range (IQR) of 28.3 to 62.2 months) in the metropolitan group and 39.9 months (IQR 27.0 to 58.1 months) in the non-metropolitan group.

Table 1. Patient characteristics in metropolitan and non-metropolitan cohorts.

	Metropolitan ***n*** **= 612**	**Non-Metropolitan** ***n*** **= 242**	***p*-Value**
Age at diagnosis	64.7 ± 11.5	64.4 ± 9.4	0.759
Sex			
Female	124 (20%)	39 (16%)	0.165
Aboriginal and Torres Strait Islander status			
Not documented	16 (3%)	14 (6%)	0.001
Yes	10 (2%)	12 (5%)	
No	586 (96%)	216 (89%)	
Modified Monash Model Classification			
MM1 Metropolitan	612 (100%)	-	-
MM2 Regional centre	-	51 (21%)	
MM3 Large rural town	-	34 (14%)	
MM4 Medium rural town	-	23 (10%)	
MM5 Small rural town	-	129 (53%)	
MM6 Remote community	-	2 (1%)	
MM7 Very remote community	-	3 (1%)	

Table 1. *Cont.*

	Metropolitan ***n*** **= 612**	**Non-Metropolitan** ***n*** **= 242**	***p*-Value**
Aetiology			
Alcohol	76 (12%)	48 (20%)	
HBV	99 (16%)	6 (2%)	
HCV	100 (16%)	37 (15%)	
MASLD	81 (13%)	31 (13%)	
Other	32 (5%)	15 (6%)	<0.001
metALD	36 (6%)	19 (8%)	
HBV/HCV	23 (4%)	7 (3%)	
HCV + SLD	132 (22%)	77 (32%)	
HBV + SLD	33 (5%)	2 (1%)	
Smoking			
Yes	158 (26%)	77 (32%)	0.077
CCI	4 (3 to 6)	5 (3 to 6)	0.086
Cirrhosis			
Yes	502 (82%)	216 (89%)	0.009
Platelet count ($\times 10^9$/L)	136 (89 to 189.5)	119 (80 to 158)	0.001
Child–Pugh Score			
5	335 (55%)	134 (55%)	
6	166 (27%)	57 (24%)	
7	63 (10%)	27 (11%)	0.709
8	27 (4%)	15 (6%)	
9	21 (3%)	9 (4%)	
Diagnosed due to surveillance			
Yes	495 (82%)	175 (74%)	0.017
Tumour Burden			
Single lesion $\leq$ 2 cm	187 (31%)	66 (27%)	
Single lesion > 2 cm, $\leq$3 cm	153 (25%)	61 (25%)	
Single lesion > 3 cm, $\leq$5 cm	99 (16%)	36 (15%)	0.520
Single lesion > 5 cm	58 (9%)	21 (9%)	
Multinodular, $\leq$3 nodules, all $\leq$3 cm	115 (19%)	58 (24%)	
Managing Centre			
Transplant Centre	273 (45%)	159 (66%)	<0.001
Initial Treatment			
Resection	146 (24%)	39 (16%)	
Ablation	175 (29%)	70 (29%)	0.008
TACE	241 (39%)	121 (50%)	
Other	50 (8%)	12 (5%)	
Transplantation during follow-up period			
Yes	31 (5%)	11 (5%)	0.752

HBV, hepatitis B virus; HCV, hepatitis C virus; MASLD, metabolic associated steatotic liver disease; metALD, metabolic dysfunction and alcohol-associated liver disease; SLD, steatotic liver disease; CCI, Charlson Comorbidity Index; TACE, trans-arterial chemo-embolisation.

Cox proportional hazards logistic regression, with an overall median follow-up time of 42.6 months (27.8 to 61.0 months), demonstrated no significant association between residence and all-cause mortality (adjusted HR 0.93 95% CI 0.64 to 1.34, $p = 0.690$) after adjusting for age, sex, managing centre, diabetes, smoking, alcohol, hepatitis B, cirrhosis, Child-Pugh Score (CPS), CCI, platelets, and tumour burden category. Hazard function curves are presented in Figure 1. Adjusted hazard ratios for variables included in the model

are shown in detail in Table 2. The statistically significant predictors of all-cause mortality were CPS (adjusted HR 1.42, 95% CI 1.25 to 1.62, $p < 0.001$), CCI (adjusted HR 1.18, 95% CI 1.08 to 1.28, $p < 0.001$), and single tumour > 5 cm (adjusted HR 2.15, 95% CI 1.17 to 3.98, $p = 0.014$, reference category single tumour ≤ 2 cm). The only predictor of reduced mortality was management at a centre with an integrated liver transplant program (adjusted HR 0.68, 95% CI 0.49 to 0.95, $p = 0.023$). The remaining variables were not significant predictors after multivariable adjustment.

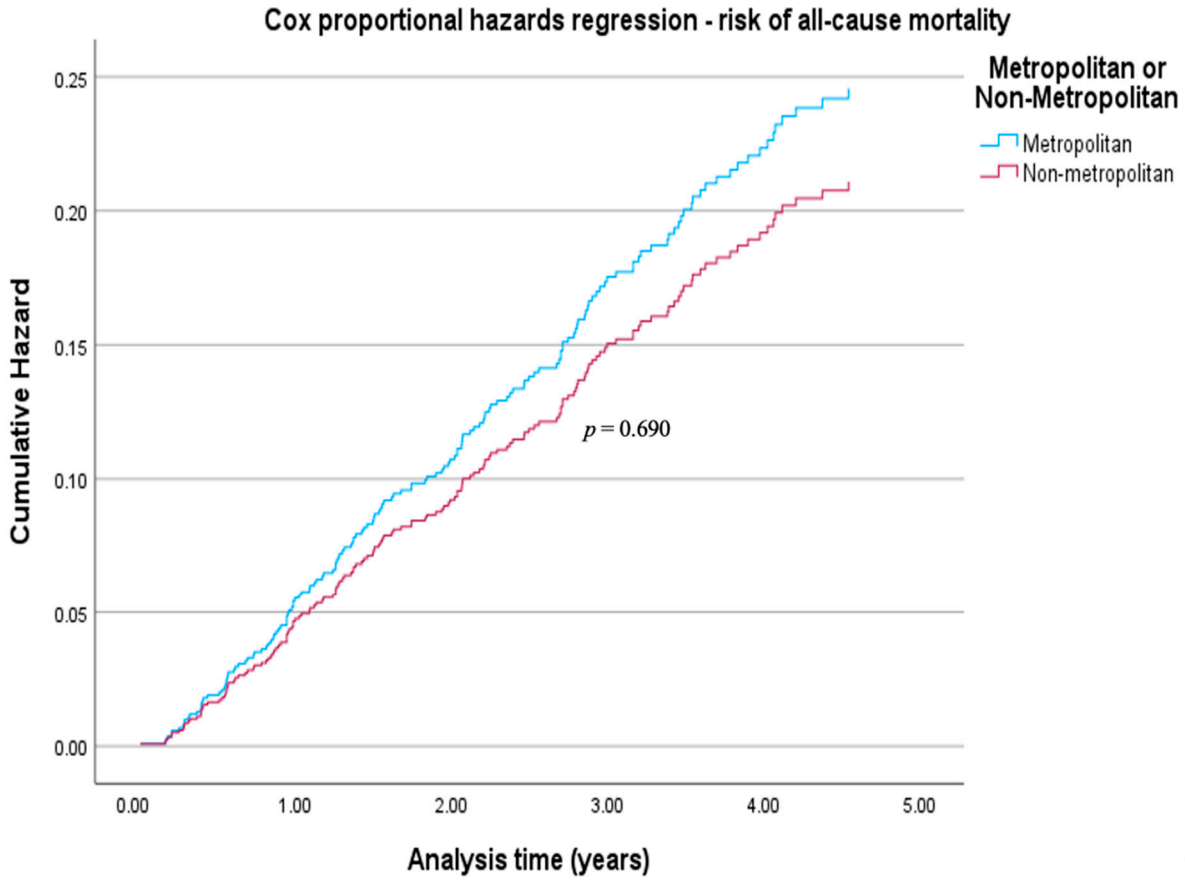


Figure 1. Cox proportional hazards regression—cumulative risk of all-cause mortality over time by metropolitan vs. non-metropolitan residence.

Table 2. Cox proportional hazards model—risk of all-cause mortality.

	Adjusted HR	**95% CI**	***p*-Value**
Residence			
Metropolitan	Reference	-	-
Non-metropolitan	0.93	0.64 to 1.34	0.690
Age	1.01	0.99 to 1.02	0.574
Sex			
Male	Reference	-	-
Female	0.66	0.42 to 1.03	0.067
Diabetes			
No	Reference	-	-
Yes	0.92	0.65 to 1.32	0.662

Table 2. *Cont.*

	Adjusted HR	95% CI	*p*-Value
Tumour Burden			
Single ≤ 2 cm	Reference	-	-
Single > 2 cm, ≤3 cm	1.26	0.82 to 1.95	0.293
Single > 3 cm, ≤5 cm	1.41	0.87 to 2.30	0.166
Single > 5 cm	2.15	1.17 to 3.98	0.014
Multinodular, ≤3 cm	1.15	0.73 to 1.81	0.551
Child–Pugh Score	1.42	1.25 to 1.62	<0.001
Cirrhosis			
No	Reference	-	-
Yes	1.33	0.74 to 2.39	0.335
CCI	1.18	1.08 to 1.28	<0.001
Platelet count	1	1.00 to 1.00	0.426
Alcohol			
No	Reference	-	-
Yes	0.9	0.63 to 1.28	0.548
HBV			
No	Reference	-	-
Yes	0.93	0.60 to 1.44	0.740
Smoking			-
No	Reference	-	0.819
Yes	0.96	0.65 to 1.40	
Managing Centre			
Non-transplant centre	Reference	-	-
Transplant centre	0.68	0.49 to 0.95	0.023

Unadjusted Kaplan–Meier survival analysis similarly demonstrated comparable survival between metropolitan and non-metropolitan residence (log-rank test $p = 0.612$) over the entire course of follow-up, with survival curves presented in Figure 2.

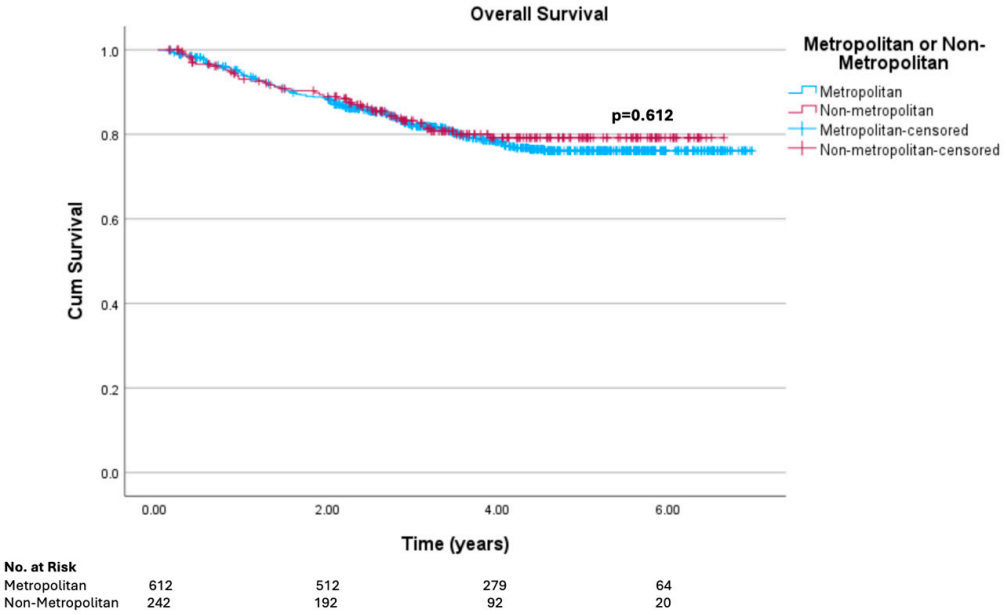


Figure 2. Kaplan–Meier survival analysis—by metropolitan vs. non-metropolitan residence.

Sensitivity analysis, using the same Cox proportional hazards analysis but stratifying for each MM classification individually, similarly found no significant differences in survival based on residence. Results are presented in Supplementary Figure S1 and Supplementary Table S1.

4. Discussion

Disparities in outcomes between non-metropolitan and metropolitan residing Australians with HCC represent a significant public health challenge. Similar geographic inequities have been observed in China [22], the USA [23,24], and the UK [25]. There is limited research focusing on delineating the causes of these disparities, with some postulated contributors including the following: later stage at diagnosis mediated by poorer surveillance uptake [26], differential access to post-treatment imaging surveillance to detect tumour recurrence [27], limited availability of aetiologic therapies such as direct acting antivirals for hepatitis C [28], and reduced access to tertiary-level care [26]. Our study is the first to show, in a real-world Australian context, that if only early-stage patients managed at a tertiary centre are considered, these disparities are not observed. Both groups in our study have similar unadjusted overall survival and all-cause mortality after adjusting for key clinical covariates. We believe that this lends significant weight to the notion that the primary reasons for the observed survival gap between metropolitan-living and non-metropolitan-living Australian patients relate to stage at diagnosis and access to tertiary care. This may be true internationally, and we encourage investigators from other nations to replicate our study.

Those living in rural and remote communities, especially First Nations Australians, are known to face systemic barriers to accessing HCC surveillance [29,30], reducing the likelihood that HCC will be diagnosed at an early-stage, where curative therapy is an option. HCC surveillance in Australia involves abdominal ultrasonography with or without serum alpha-fetoprotein testing and is clinician-driven, as no centralised surveillance program currently exists. HCC surveillance uptake in Australian primary care has historically been poor, with one study reporting less than a third of chronic hepatitis B patients receiving appropriate surveillance [31], in contrast to those receiving specialist care, where rates of uptake have been observed to be in excess of 80% [32]. Furthermore, patients at risk for HCC, particularly those with non-viral cirrhosis, often go entirely unrecognised, with one study demonstrating that up to a quarter of patients with HCC are only diagnosed with cirrhosis at the time of HCC diagnosis [33]. Improving identification of those at-risk for HCC and access to HCC surveillance across Australia and similar other multicultural countries is a clear and urgent need, and there has been a recent call for an increase in resources to identify those at-risk and for a national centralised surveillance program [20].

Furthermore, limited access to tertiary healthcare centres, compounded by socioeconomic, cultural, and ethnic factors, may further impede the delivery of curative therapy in otherwise eligible patients. Current referral pathways for those with a new diagnosis of HCC are not currently standardised across Australia, particularly in the more populous states of Victoria and New South Wales, and are also clinician-dependent. Inherent barriers, such as travel time and distrust of non-local services, continue to pose a significant impediment to access to care [34]. Streamlining of referral pathways and integration of local rural and remote services with metropolitan tertiary care, and utilising existing telehealth technologies, could reasonably be expected to enhance access to improved diagnostic accuracy of HCC and to delivery of curative therapies, such as liver resection, percutaneous ablation, and transplantation.

While mortality did not differ between non-metropolitan and metropolitan patients in our retrospective cohort study, we found that large tumour size, increasing Child–Pugh

Score, and increasing Charlson Comorbidity Index were clearly significant predictors of mortality, while management at a transplant centre (as compared to a non-transplant centre) was protective. These findings are in keeping with conventionally accepted prognostication in HCC, with tumour size and Child–Pugh Score forming two of the most important factors in the BCLC staging system [5]. Charlson Comorbidity Index, which captures age and non-liver comorbidities, is similarly well-validated in prognostication across a wide range of conditions and populations [35], including in liver disease [36,37]. Management at a transplant centre (as compared to a non-transplant centre) was protective against mortality, as previously observed [17], which may be confounded by selection bias given the retrospective nature of the study.

Our study demonstrating similar survival outcomes does have important limitations. Firstly, the retrospective design raises the possibility of information bias and direct and indirect selection bias in assessing differences in survival. We have attempted to mitigate this by using a multivariable model, but certain key clinical covariates, such as ongoing alcohol intake or adherence to medical therapy, have been unaccounted for. Secondly, statistical power is limited by the duration of follow-up and cohort size. Survival differences may have been observed with greater patient numbers or a longer duration of follow-up, particularly as non-metropolitan patients could be expected to receive systematically different longer-term care, such as future reduced surveillance uptake, which could theoretically delay the detection of late tumour recurrence and negatively affect long-term survival. Thirdly, the residential postcode was recorded at the time of data entry, and patients who moved residence between diagnosis and data entry may not have been captured, raising the possibility of misclassification bias. We would expect that only a small minority of patients may have moved during the study period, and it would be unlikely for this to have significantly affected the results.

Importantly, our results are specific to a cohort of patients with early-stage disease at diagnosis who were referred to a metropolitan tertiary centre for management and, therefore, should not be generalised to all non-metropolitan patients with HCC, many of whom are diagnosed with more advanced disease or have limited access to tertiary care. Regional and rural Australian patients with HCC managed at non-metropolitan centres are not represented by the unique cohort described in our study, and all available evidence suggests that they face inferior survival outcomes compared to those living and managed in metropolitan areas. The similarity in survival outcomes observed in our study suggests that early diagnosis and referral to expert multidisciplinary care are the two key factors needed in non-metropolitan cohorts to achieve parity with metropolitan patients in HCC outcomes.

While we believe that our study provides compelling indirect evidence for stage at diagnosis and access to tertiary care as the likely explanations for the survival gap between metropolitan and non-metropolitan patients, direct evidence should be sought prospectively to definitively assess this, including direct comparisons between metropolitan and non-metropolitan by BCLC stage and by assessing differences in care between those referred to tertiary centres and those not referred, which was not possible in our cohort.

5. Conclusions

We believe that our findings underscore the importance of surveillance uptake and streamlined referral pathways in maximising the outcomes of patients with HCC, particularly those living in non-metropolitan areas in Australia and other similar large nations. Community-based models of care, ideally within the framework of a national centralised screening program, to improve identification of patients at risk for HCC and encourage adherence with semi-annual ultrasound surveillance, are urgently needed and should be ex-

pected to reduce the gap in outcomes observed between Australians living in metropolitan and non-metropolitan areas.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/livers6010002/s1, Figure S1: Cox proportional hazards regression—cumulative risk of all-cause mortality over time by individual modified monash model classification; Table S1: Predictors of all-cause mortality by cox proportional hazards regression—residence by individual modified monash model classification; File S1: Minimum Dataset.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Human Research Ethics Committee of Monash Health (HREC Reference Number: HREC/80727/MonH−2022−302788(v3), 23 February 2022).

Informed Consent Statement: Waiver of consent was sought, with all patient data entered in a de-identified form. Patient consent was waived by the Human Research Ethics Committee of Monash Health for the following reasons: The study did not involve an intervention, it was low-risk in terms of data collection and participant burden, we did not anticipate any risk of harm associated with collecting de-identified data, a significant proportion of the population targeted for recruitment were likely to be unwell or deceased at the time of inclusion in the study, and there was sufficient protection of patient privacy as the data is de-identified.

Data Availability Statement: The data presented in this study are available on request from the corresponding author due to privacy restrictions.

Conflicts of Interest: The authors declare no conflicts of interest.

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