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*Retrospective Cohort Study*

**Standards of liver cirrhosis care in Central Australia**

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Standards of liver cirrhosis care in Central Australia

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## **Abstract**

### **BACKGROUND**

Liver cirrhosis and hepatocellular carcinoma (HCC) are highly prevalent in Australia's Northern Territory (NT). Contributing factors include high levels of alcohol consumption, viral hepatitis and metabolic syndrome. Rural Aboriginal residents form a significant proportion of the Central Australian population and present a challenge to traditional models of liver care. HCC surveillance and variceal screening are core components of liver cirrhosis management.

### **AIM**

Our study assessed participation in HCC and variceal surveillance programmes in a Central Australian liver cirrhosis patient cohort.

### **METHODS**

Retrospective cohort study of patients with liver cirrhosis presenting to Alice Springs Hospital, Australia between 1.1.2012 and 31.12.2017. Demographic data, disease severity, attendance at hepatology clinics, participation in variceal and/or HCC surveillance programmes was recorded. Regression analyses were conducted to assess factors associated with two independent outcomes: participation in HCC and variceal surveillance.

### **RESULTS**

193 patients were identified. 82 patients (42.4%) were female. 154 patients (80%) identified as Aboriginal. Median Model for End-stage Liver Disease (MELD) Score at diagnosis was 11. Alcohol was the most common cause of cirrhosis. Aboriginal patients were younger than non-Aboriginal patients (48.4 *vs* 59.9 years,  $p$  value < 0.001). There were similar rates of excess alcohol intake (72.6% *vs* 66.7%,  $P = 0.468$ ) and obesity (34.5% *vs* 38.4%,  $P = 0.573$ ) across non-Aboriginal and Aboriginal cohorts. 20.1% of patients took part in HCC surveillance and 42.1% of patients completed variceal screening.

Aboriginal patients were less likely to engage with either HCC surveillance (OR 0.38, 95%CI 0.16-0.9, p 0.025) or undergo variceal screening (OR 0.31, 0.14-0.65,  $P = 0.002$ ).

## CONCLUSION

HCC or variceal surveillance programmes had less uptake amongst Aboriginal patients. Greater emphasis needs to be placed on eliminating cultural obstacles to accessing hepatology services.

**Key Words:** Viral hepatitis; cirrhosis; hepatocellular carcinoma; alcoholic liver disease; central australia

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**Core Tip:** Liver cirrhosis is prevalent in Australia's Northern Territory. Liver disease is a contributor to the mortality gap between Aboriginal and non-Aboriginal Australians. 20.1% of patients included in our study participated in hepatocellular carcinoma surveillance and 42.1% of patients underwent screening endoscopy in a rural Australian centre. Aboriginal patients were less likely to engage with screening programs despite their predominance in our study cohort.

## INTRODUCTION

Liver cirrhosis and hepatocellular carcinoma (HCC) constitute end-stage manifestations for a diverse range of pathological processes affecting the liver. Medical care of patients with cirrhosis is centred on treating underlying causative pathology, screening for HCC and preventing decompensation of liver disease (1). Standards of care in liver cirrhosis are well established in hepatological literature and national guidelines(2,3). The core measurable components of cirrhosis care pertain to surveillance programmes for gastro-

oesophageal varices and hepatocellular carcinoma. These have been shown to improve survival and ameliorate healthcare costs of liver disease(4–6).

Escalating morbidity and mortality rates from liver disease in Australia are widely recognized(2). This rising tide of liver disease has been fuelled by hazardous alcohol consumption, viral hepatitis and obesity(7). The healthcare costs of liver disease were estimated at \$50 billion per annum across Australia in 2012 (2). Geographical and socio-economic disparities in liver-related health service provision are a reality in Australia. The Northern Territory of Australia is afflicted by the highest per capita alcohol intake in Australia and one of the highest in the world(8). Furthermore, liver disease has been identified as one of the major diseases contributing to the well cited mortality gap between Aboriginal and non-Aboriginal Australians(9–11). Cross-sectional studies have demonstrated significantly higher prevalence of Hepatitis B in Aboriginal NT residents(12).

Contemporary healthcare models focus on the provision of centralized specialist cirrhosis care at tertiary hospitals in metropolitan areas. The Central Australian region is centred around the town of Alice Springs and spans a vast area encompassing parts of Northern Territory (NT), South Australia (SA) and Western Australia (WA). Central Australia is distinct from other parts of Australia given its remoteness and high proportion of Aboriginal constituents. This posits significant challenges for service providers in providing easily accessible culturally appropriate liver-related healthcare surveillance and interventions. Adherence with nationally agreed standards of care in liver cirrhosis in Central Australia has hitherto not been formally assessed.

Our study intends to outline the demographical and epidemiological characteristics of patients presenting to Alice Springs Hospital with liver cirrhosis. We also examined the influence of these factors on participation in variceal and HCC surveillance programmes.

## **Study Setting**

The Central Australian healthcare model is best described as “hub and spoke” in nature. Alice Springs Hospital is 186-bed healthcare facility that serves as the sole referral centre for an area of approximately 577,000km squared with a population of just under 50,000. Thus, conducting our study at ASH provides an insight into the standards of liver cirrhosis care for the wider Central Australian region.

## **MATERIALS AND METHODS**

### **Case Ascertainment**

The primary data for this study includes information on all patients admitted to ASH with an underlying or new diagnosis of liver cirrhosis between 1<sup>st</sup> January 2012 and 31<sup>st</sup> December 2017. The study cohort was identified using ICD-10 codes. Lists of ICD-10 Codes used to identify potential cases included liver cirrhosis as Principal (98 episodes) or Additional diagnosis (789 episodes) and chronic liver disease as principal (246) or additional diagnosis (4,728) (Codes K70, K71, K72, K73, K74, K75, K76, K77).

Case episodes were screened using electronic and paper medical records to identify eligible patients. Our study inclusion criteria required a confirmed diagnosis of liver cirrhosis and permanent residence in the Central Australian region. Diagnosis of liver cirrhosis was confirmed through assessment of available histology, biochemistry, radiography and documented clinical findings. Importantly, patients with probable diagnosis of cirrhosis based on either radiology or biochemistry but without documented clinical confirmation were not included in the analysis.

Data collated from medical records included demographic data, time of initial diagnosis, risk factors, aetiology of liver cirrhosis, Child Pugh (CP) score, Model for

End-stage Liver Disease (MELD) score at time of diagnosis, mode of initial presentation, referral to specialist liver clinic, participation in variceal and/or HCC surveillance programmes and development of HCC. From a residential perspective, the majority of non-Aboriginal residents of Alice Springs reside in registered domiciles whilst a significant proportion of Aboriginal residents live in distinct camps in the fringes of the city (13). Residential status of participants was thus divided into three entities: Alice Springs town, Alice Springs camps or rural.

Aetiology of liver cirrhosis was confirmed retrospectively based on medical records. Case-notes of patients diagnosed with Alcohol related cirrhosis were reviewed to confirm current or previous hazardous alcohol intake. For the purposes of this study, hazardous alcohol intake was defined as >14 standard units per week in line with National Health and Medical Research Council recommendations (14). Presence of hepatitis C virus (HCV) and Hepatitis B was confirmed through analysis of HCV RNA levels and hepatitis B serological tests (HBsAg, HBsAb, HbcAb, HbeAg, HbeAb), retrospectively. Non-Alcoholic fatty liver disease (NAFLD) related cirrhosis was diagnosed in patients with metabolic risk factors (obesity, type 2 diabetes, hypercholesterolemia) in the absence of hazardous alcohol intake. Autoimmune and primary biliary cirrhosis were diagnosed on the basis of serological, histological and biochemical testing.

Our primary outcomes were participation in HCC and variceal surveillance programmes. Participation in HCC Surveillance was defined as undergoing 6-monthly ultrasound assessment over a minimum of 1 year. Completion of an index screening endoscopy at diagnosis was used as a surrogate marker for adherence with variceal surveillance. Internationally validated Baveno VI criteria only recommend screening in selected patients with cirrhosis based on platelet count and elevated liver stiffness measurements (4). However, the absence of transient elastography services at ASH prohibited the use of Baveno criteria as a discriminating tool. Regression analyses were

conducted to assess factors associated with two independent outcomes: participation in HCC and variceal surveillance.

### **Statistical Analysis**

Descriptive statistics are presented for all patients in Table 1. Table 2 outlines a comparison of Aboriginal *vs* non-Aboriginal patients. <sup>3</sup> Categorical variables were compared using Chi square or Fisher's Exact Test. Normally distributed variables were analysed using Independent t-test while Wilcoxon Rank Sum Test was utilised for non-normally distributed variables. Our secondary outcomes focused on assessing the demographic and clinical variables influencing participation in HCC and variceal surveillance programmes. Unadjusted and adjusted binary logistic regressions were performed for both HCC and variceal surveillance (in separate models). These analyses are presented in Table 3 + 4. Confounders included in the adjusted models include age, gender, CP score.

### **RESULTS**

A total of 5,861 Case Episodes were identified using the coding criteria stated in our methodology. From a thorough analysis of these case episodes, we identified 193 patients with confirmed cirrhosis presenting to ASH from 1<sup>st</sup> Jan 2012 to 31<sup>st</sup> Dec 2017.

The discrepancy between case episodes and included patients was due to multiple factors. Firstly, the majority of case episodes identified with our extended search criteria involved non-cirrhotic patients. Secondly, most of our cohort presented to ASH on multiple occasions during the study period. Thirdly, patients with probable cirrhosis who had not undergone confirmatory testing were not included.



57.5% of the study cohort were male. 154 patients (80%) of the study cohort were Aboriginal. The average age at diagnosis was 50.7 years old (SD 11.9). The median MELD Score was 10 (IQR 8,18). 49% of the study cohort presented with CP Class A cirrhosis at the time of diagnosis. Of the remainder, 38% of patients initially presented with CP Class B cirrhosis and 12% with CP Class C. 31% of patients presented with decompensating events as the first clinical manifestation of liver cirrhosis. The most common decompensating events were acute on chronic liver failure and variceal haemorrhage. 54% of our cohort were residents of rural Central Australia. 30% of patients lived in Alice Springs whilst 16% were listed as residents of the surrounding town camps.

Alcohol related cirrhosis was the most common cause of cirrhosis in our study. Liver cirrhosis was attributed to alcohol in 71% of the study cohort. Viral hepatitis was also prevalent amongst our study cohort. 42 patients (22%) were identified as having chronic hepatitis B whilst 20 patients (10%) had hepatitis C. 11% of patients were deemed as having liver cirrhosis related to Non-Alcoholic Fatty Liver Disease (NAFLD). 5% of patients developed chronic congestive liver cirrhosis as a sequelae of underlying cardiac failure. Six patients had cryptogenic cirrhosis (*Table 1*). 29 patients developed hepatocellular carcinoma as a complication of liver cirrhosis. These patients were predominately male (72%) and Aboriginal (72%).

*Table 2* presents a comparison of epidemiological data between Aboriginal and non-Aboriginal patients. <sup>1</sup> Aboriginal patients were significantly younger than their non-Aboriginal counterparts (48.4 vs 59.9 years,  $p$  value < 0.001). Non-Aboriginal patients were predominately male (85%) while there was an equal gender split for the Aboriginal cohort. The average MELD score for Aboriginal patients was 11 (IQ 8,20) and 54% presented with CP Class B or C cirrhosis. The corresponding figures for non-Aboriginal patients were 10 (IQ 8,12) and 36%, respectively. <sup>2</sup> There were no observed differences in rates of hazardous alcohol intake (72.6% vs 66.7%,  $P = 0.468$ ) and obesity (34.5% vs

38.4%,  $P = 0.573$ ) between Aboriginal and non-Aboriginal cohorts. Our Aboriginal cohort had significantly lower rates of IVDU (1.3% vs 33.3%,  $p$  value  $<0.001$ ). From a geographical perspective, Aboriginal patients were significantly more likely to be residents of rural communities or town camps ( $p$  value  $<0.001$ ). Aboriginal patients were less likely to attend specialist liver clinics.

Given their association with Aboriginal ethnicity, place of residence and specialist clinic non-attendance were excluded from adjusted models examining factors influencing participation in surveillance programmes.

### **Adherence with Variceal Surveillance**

Four patients were excluded as they died during their index admission and 11 patients were excluded on account of incomplete data. Thus, 178 patients were included in the primary analysis. Of the included patients, 75 (42.1%) received a screening endoscopy within six months of their diagnosis.

On univariate analysis, attendance at specialist liver clinics was associated with participation in variceal surveillance (OR 4.22, 95%CI 2.22-8.02,  $p$  value  $<0.0001$ ). Patients residing in Alice Springs were more likely to participate than patients from town camps or rural communities (AS vs AST, OR 4.03, 95%CI 1.5-10.5,  $p$  0.004; AS vs R, OR 3.05, CI 1.52 -6.13,  $p$  value 0.002). Conversely, Aboriginal ethnicity (OR 0.31, 95%CI 0.14-0.65  $p$  value 0.002) was associated with non-completion of screening endoscopy in both unadjusted and adjusted models. Neither age, gender nor disease severity were found to be associated with variceal surveillance in either model.

### **Adherence with HCC Surveillance**

Overall, 141 patients were included in the analysis of HCC surveillance participation. 29 patients (20.6%) participated with regular sonographic surveillance. Patients were excluded on the basis of Childs Pugh C disease severity (18 patients), concurrent diagnosis of HCC with cirrhosis (9), absence of follow up data (10) and death within 12 mo of cirrhosis diagnosis (15). In unadjusted models, review at specialist clinic was strongly associated with participation in HCC surveillance (OR 10.17, 95%CI 2.91-35.5  $p < 0.001$ ). Residence in Alice Springs was associated with better adherence to regular liver sonography in comparison to Alice Springs town camps and rural regions. Aboriginal patients were less likely to participate in both unadjusted (0.31, 95%CI 0.13-0.77,  $p$  value 0.01) and adjusted models (OR 0.29, 95%CI 0.10 -0.87  $p$  value 0.03). Neither age, gender nor disease severity were found to be associated with HCC surveillance in either model.

## **DISCUSSION**

With respect to overall participation in HCC surveillance, 20% of our cohort demonstrated sustained engagement with 6 moly ultrasound scans. Poor uptake limits the utility of surveillance as a means of ameliorating the morbidity, mortality and healthcare costs of HCC at a population level. This is rendered of greater significance by the heavy burden of HCC in the NT (15). It is important to note that poor uptake of HCC surveillance is not an issue specific to Central Australia. Participation is limited even in more urban and resource-rich settings. A retrospective study in Melbourne of patients diagnosed with HCC between 2012-2013 demonstrated a 41% compliance rate with surveillance (16). These statistics reflect the broader social and medical disenfranchisement of patients with cirrhosis as well as the demanding nature of regular surveillance sonography. Comparatively, variceal surveillance had greater uptake and this likely reflects the liberal definition used in our study as well as ease of access to endoscopy services during index admissions. In clinical practice, variceal surveillance requires further endoscopies with advancing severity of liver cirrhosis. However formal guidelines on screening intervals vary considerably and lack consensus.

Aboriginal ethnicity was strongly associated with non-participation in both HCC and variceal surveillance. This is rendered further significance as 80% of our study cohort was Aboriginal; a particularly noteworthy fact given that Aboriginal residents make up less than one quarter of the Central Australian population. This disproportionate prevalence of cirrhosis in Aboriginal patients correlates well with epidemiological data showing significantly higher incidence rates of HCC and liver disease in Aboriginal Territorians (17, 18). We demonstrated other points of departure between Aboriginal and non-Aboriginal cohorts. Aboriginal patients with cirrhosis presented at a younger age and with more advanced disease. This is in keeping with findings from a larger Australian retrospective cohort study comparing cirrhosis admissions between Aboriginal and non-Aboriginal populations over a 10-year period in Queensland (10). Additionally, half of our Aboriginal cohort were women. This contrasts with the male predominance of the non-Aboriginal cohort. Extrapolating further, these results are also out of keeping with national statistics that demonstrate distributions of premature liver deaths and liver related hospitalisations skewed towards men (2).

This significant burden of liver disease needs to be understood within broader socioeconomic context for Aboriginal Central Australians. Liver disease, similar to other highly prevalent chronic diseases, is a corollary of social, political and economic disenfranchisement (19). It is important for clinicians and policy makers to recognise the root causes for poor health and liver cirrhosis. Socioeconomic factors predisposing to high-risk behaviours such as hazardous alcoholic intake also play a role in the poor engagement of Aboriginal patients with formal liver services as demonstrated in our study.

Language and culture are additional factors that represent major obstacles to engagement with liver services for Aboriginal patients in Central Australia (20). In rural Central Australia, up to 80% of Aboriginal households predominately speak one of the

18 traditional languages. Proficiency in standard English is typically variable. This is in stark contrast with national census data showing that 83% of Aboriginal and Torres Strait Islanders speak English as a first language (19). Language barriers have significant repercussions for healthcare provision at ASH where most of the workforce are non-Aboriginal. Medical and follow-up information is often poorly disseminated and vulnerable to misinterpretation by patients. An ASH based study investigating recorded self-discharge rates found that up to 80% of patients were unaware of medical diagnosis or proposed length of stay (20). Similarly, achieving effective patient engagement is limited by other cultural factors. A study in nearby Mount Isa, Queensland found that patient perceptions of poor understanding or respect of Aboriginal culture on the part of medical practitioners was a major barrier to care (21). Communication barriers and failures in achieving patient trust clearly remain impediments in engaging Aboriginal patients with formal liver services in Central Australia.

Specialist review and residence in Alice Springs were both associated with completion of screening endoscopy and HCC surveillance in unadjusted models. This may reflect the fact that patients with sufficient motivation to attend outpatient appointments and located closer to central services are more likely to engage with surveillance programmes. It is also important to acknowledge the mediating effects of specialist review and place of residence on the causal pathway between Aboriginal status and reduced participation in liver surveillance programmes. Aboriginal patients were significantly less likely to attend specialist liver clinics and more likely to live either rurally or in town camps. This mediating effect is seen when considering the influence of place of residence on surveillance participation. Non-Aboriginal patients from Alice Springs were more likely to participate in both HCC and Variceal surveillance than the exclusively Aboriginal patients residing in Alice Springs town camps. Furthermore, there were no statistically significance difference in surveillance participation between rural and camp based Aboriginal patients.

From an aetiological perspective, alcohol and viral hepatitis were the main drivers of liver cirrhosis. Alcohol was implicated in the aetiology of more than two thirds of our study cohort either alone or in combination with viral hepatitis. Contextually, Northern Territory has been identified as having the highest per capita alcohol intake in Australia and one of the highest in the world. Similar proportions of Aboriginal and Non-Aboriginal patients exceeded recommended weekly limits of alcohol intake. Despite this, 75% of Aboriginal patients were classified as having alcohol related cirrhosis whilst only 25% of non-Aboriginal patients were labelled with this diagnosis. This discrepancy may be explained by the non-linear relationship between hazardous alcohol intake and development of cirrhosis (22). Data from the Australian Institute of Health And Welfare's (AIHW) National Drug Strategy Household Survey showed that while Aboriginal individuals were less likely to drink than non-Aboriginal counterparts, those that do are more likely to do so at hazardous levels (23).

However, it is impossible to discount potential elements of diagnostic bias especially when patients were not under the purview of specialists. The potential under-recognition of NAFLD in our study may support this view. Less than 10% of our cohort were deemed as having NAFLD as per available documentation. One would expect a higher prevalence of NAFLD in a Central Australian cohort given the above average rates of obesity and diabetes as well as the fact this condition is the most prevalent form of liver disease in Australia(2). Another point of concern for patients with cirrhosis who were not reviewed by liver specialists was a propensity to label alcohol as the primary aetiological factor without completion of the full battery of screening tests. This is clinically significant given that heavy alcohol intake has been shown to accelerate the progression of liver inflammation in underlying chronic hepatitis B and C (24). Furthermore, potentially erroneous labelling of alcohol related liver disease can perpetuate stigmatisation of Aboriginal patients. Several authors have highlighted



stigma as a major limiting factor in the engagement of Aboriginal patients with formal healthcare services (25).

Our study has a few limitations which our study design was unable to eliminate. Firstly, accurately quantifying the prevalence of liver cirrhosis in Central Australia is beyond the scope of this study. Secondly, our focus on hospital inpatients may not be reflective of the general cirrhosis population. This cohort of patients tend to be from more disadvantaged socio-economic backgrounds and present with more severe liver disease. A natural consequence of this is the presence of a selection bias that may render the study cohort less representative. However, our study does serve to determine whether the current model of liver care adequately meets the need of the most vulnerable subset of cirrhotic patients in Central Australia. We endeavour that this study can also be used as a foundation for further research in the area of liver cirrhosis in the Central Australian region.

## <sup>2</sup> **CONCLUSION**

Aboriginal patients were strongly overrepresented in our study and were less likely to engage with HCC or variceal surveillance. Strategies devised to address the issue of liver disease in Central Australia <sup>1</sup> will need to focus on eliminating cultural barriers to accessing care, expanding capacity for specialist review and ameliorating hazardous alcohol intake on a population level. We endeavour that this study can also be used as a foundation for further research in the area of liver cirrhosis in the Central Australian region.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

Northern Territory (NT), Australia has high rates of liver cirrhosis and hepatocellular carcinoma (HCC) as a consequence of harmful alcohol use, viral hepatitis and metabolic

syndrome. Aboriginal persons constitute a significant proportion of the population in the Central Australian region of NT. Several challenges are faced in providing culturally appropriate liver care to the diverse Central Australian population.

### ***Research motivation***

Liver disease has been identified as a significant contributor to the well cited mortality gap between Aboriginal and non-Aboriginal Australians. Central Australia is unique within Australia given its high proportion of Aboriginal residents. Formal adherence with hepatocellular carcinoma (HCC) or variceal screening programmes have not been specifically assessed in Central Australia.

### ***Research objectives***

Our first research objectives involves description of the baseline characteristics of inpatients presenting to a Central Australian hospital. Our second research objective involves assessment of adherence with HCC surveillance as well as analysis of the factors associated with participation. Our third research objective involves assessment of adherence with HCC surveillance as well as analysis of the factors associated with participation.

### ***Research methods***

Our study methodology involved performing a retrospective cohort study. All identified patients presenting to inpatient departments at Alice Springs Hospital, Northern Territory, Australia between 2012 to 2017 were included in the study. We collected data including demographics, disease causation and severity (Child Pugh Score), referral to hepatology clinics and adherence with <sup>1</sup>variceal and/or HCC surveillance programmes. Regression analyses were conducted to assess factors associated with two independent outcomes: adherence with HCC and variceal surveillance.



### ***Research results***

Aboriginal persons were over-represented and made up 80% of the study cohort. Aboriginal patients were younger and presented with more severe disease than non-Aboriginal counterparts. Overall 20.1% of our study cohort participated in HCC surveillance while 42.1% of patients underwent variceal screening. Aboriginal ethnicity was inversely associated with participation in HCC surveillance.

### ***Research conclusions***

This is the first study examining adherence with standards of liver cirrhosis care in Central Australia. Liver cirrhosis in Central Australia disproportionately affects Aboriginal communities as a corollary of adverse metabolic profiles, hazardous alcohol intake and viral hepatitis. The current centralised model of cirrhosis care does not adequately meet the need of Aboriginal Central Australians. Our study demonstrates the pressing need for interventions to improve participation of Aboriginal patients with cirrhosis in HCC screening in order to ameliorate the morbidity and mortality associated with delayed diagnosis. Language, geographical and cultural factors are important prisms through which to examine low participation rates among Aboriginal patients in Central Australia. This is compounded by limited utilisation of valuable primary care links. Correspondingly, interventions aimed at closing the gap in liver related health outcomes between Aboriginal and non-Aboriginal patients need to focus on addressing these factors.

### ***Research perspectives***

Future research should focus on piloting alternative models of cirrhosis care for Aboriginal patients with liver cirrhosis in Central Australia. Alternative care models should focus on expanding provision of telehealth services, enhancing utilisation of primary health care links and culturally tailoring care.

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