Increasing burden of advanced hepatocellular carcinoma in New Zealand—the need for better surveillance

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ABSTRACT

BACKGROUND: Regular surveillance for hepatocellular carcinoma (HCC) in patients with chronic hepatitis B viral (HBV) infection and hepatitis C (HCV) cirrhosis improves survival by earlier detection of the cancer at an earlier stage when curative intervention may still be possible. We compared patient characteristics, surveillance history and outcomes in patients presenting with advanced HCC secondary to HBV and HCV.

METHOD: In this retrospective study, clinical databases and notes were reviewed in all cases of advanced HCC related to HBV or HCV referred to the tertiary HCC service in Auckland, New Zealand between 1 January 2003 and 31 December 2017.

RESULTS: Over the 15-year period, 368 patients were referred with advanced HCC secondary to HBV (HBV-HCC) and 278 secondary to HCV (HCV-HCC), representing over 50% of all cases of HCC cases secondary to viral hepatitis. Of these 646 patients with advanced HCC, 75% of patients were not receiving guideline-recommended surveillance. More patients with advanced HBV-HCC were diagnosed with HCC prior to the diagnosis of HBV, compared to patients with advanced HCV-HCC (40% vs 28%, $p<0.01$). Fewer patients with previously diagnosed HBV infection were undergoing HCC surveillance than patients with previously diagnosed HCV infection (26% vs 42%, $p<0.01$). Late diagnosed patients had the worst outcomes, with 88% receiving palliative care and surviving on average only seven months (HBV five months vs HCV eight months, $p=0.05$).

CONCLUSION: Survival in New Zealanders with hepatocellular carcinoma remains poor because the cancer is incurable in most patients at the time of detection. Because most cases are secondary to chronic hepatitis B and C infections, improved screening and linkage to antiviral therapy and HCC surveillance should improve outcomes.

Viral hepatitis accounts for the vast majority of newly diagnosed hepatocellular carcinoma (HCC) worldwide.[1] In 2012, there were 770,000 cases of HCC, of which 56% were attributable to hepatitis B virus (HBV) and 20% to hepatitis C virus (HCV).[2] In New Zealand, of the 2,601 HCC cases recorded at the tertiary HCC database in Auckland City Hospital between 1998 and 2019, 51% and 34% were due to HBV and HCV respectively.[3] The bulk of the remainder of aetiologies are split between alcoholic liver disease and non-alcoholic steatohepatitis. In Australia, 22% of HCC is attributed to HBV and 41% to HCV.[4] The American, Asian and European liver societies[5–7] recommend surveillance with six-monthly liver imaging and alfa fetoprotein (AFP) in patients with viral hepatitis at high risk for development of HCC, as it is known to improve survival through earlier detection of tumours potentially amenable to curable treatments.[3,8]

Unfortunately, many cases of viral hepatitis either remain undiagnosed or without appropriate HCC surveillance, contributing

to advanced presentations. In New Zealand, it is estimated in 2019 that 50% of the estimated 100,000 patients living with chronic HBV infection and 40% of the estimated 45,000 patients living with chronic HCV infection remain either undiagnosed or lost to follow-up (Gane, personal communication). In Australia, 43% of the estimated 218,567 patients with chronic HBV infection and an estimated 25% of the over 230,000 patients with chronic HCV infection are undiagnosed.[9,10] Despite the introduction of universal neonatal vaccination in New Zealand in 1988, the prevalence of HBV is still increasing due to high rates of adults migrating from countries with endemic HBV, in particular Asia and the Pacific. Over the next two decades, the proportion of Asian ethnicities in New Zealand is projected to increase from 12% to 22% and Pacific Island ethnicity from 8% to 10%.[11]

Antiviral treatment in HBV and HCV viral eradication confers up to a 75% decrease in risk of HCC.[12,13] Although recent unrestricted funding of safe and effective direct acting antiviral therapy will rapidly reduce the prevalence of HCV, the number of HCV-HCCs will continue to increase until 2030 due to the large number of at-risk patients who had established cirrhosis prior to treatment.[14]

Compared to patients with HCV-HCC, those with HBV-HCC are younger, have less advanced fibrosis and often have a family history of HBV-HCC.[15] There are many other clinical and molecular differences between the two groups. However, few studies have compared the outcomes of patients with HBV-HCC and those with HCV-HCC.[16]

Regular six-monthly surveillance of high-risk patients should help enable detection of HCC at an early stage when curative treatment is possible. Therefore, higher rates of diagnosis, assessment and recruitment into HCC surveillance programmes of patients living with HBV or HCV is needed to improve outcomes. However, population data on uptake of appropriate surveillance is not readily available due to scale and logistical issues.[9] Understanding which steps in the process are failing is fundamental to inform public health, medical professionals and patients alike as to where improvement efforts can be focused. For example, a previous study noted 38% of patients with HCC missed surveillance due to a lack of surveillance orders from the provider, with only 3% due to patient non-compliance.[17] The aim of this study was therefore to review cases of advanced HCC secondary to HBV and HCV to examine differences in demographics, focusing on surveillance method of detection, but also subsequent treatments and survival.

Methods

We completed a retrospective cohort study of all cases of advanced HCC referred to the tertiary New Zealand HCC service over a 15-year period between 1 January 2003 to 31 December 2017. During this period, the total number of HCC reported was 1,818, of which 540 (30%) were HCV-related and 705 (39%) HBV-related. This service was introduced in 1998, where new HCC cases are requested to be referred by the responsible secondary care service through videoconferencing to a weekly multidisciplinary meeting at the New Zealand Liver Transplant Unit based in Auckland. Confirmation of diagnosis, treatment and management plans are then decided.

Advanced was defined as patients who were not eligible for curative therapy and who were treated with trans-arterial chemoembolisation (TACE), sorafenib (non-funded in New Zealand), or novel antitumour therapies through a clinical trial, or who received best supportive palliative care.

The HBV cohort included patients with positive hepatitis B surface antigen (HBsAg) at the time of advanced HCC diagnosis. The HCV cohort included those with current or previous Hepatitis C infection.

Patients were excluded if they had had a prior diagnosis of HCC, were not New Zealand residents, or if they were diagnosed with HCC prior to migrating to New Zealand.

A complete list of all patients with HCC from the prospectively maintained clinical database was obtained and only those meeting inclusion criteria retained. Patient demographics, dates of definitive HCC diagnosis, treatment modality and date of death, if applicable, was collected and abstracted in a standardised fashion. For detailed assessment of method of HCC surveillance, patients were grouped into four categories:

1. No known diagnosis of HBV/HCV infection prior to the diagnosis of HCC. This definition includes 'late hepatitis notification', defined as diagnosis as at the time or within two years before HCC diagnosis.[18]
2. Known HBV/HCV and met criteria for HCC surveillance but did not receive this (defined as not having had liver imaging for >2 years). For HBV, we included patients who were either cirrhotic or had a positive family history of HCC. For HCV, we only included patients who were cirrhotic (as stated on clinical correspondence, not inferred from investigation).
3. Known HBV/HCV diagnosis and receiving suboptimal HCC surveillance (defined as; for HBV: AFP without liver USS in patients who are cirrhotic or have a positive family history of HCC; or received their surveillance outside the recommended time-period). For HCV: receiving intermittent imaging only outside the recommended 6 monthly interval.
4. Known HBV/HCV diagnosis and receiving optimised HCC surveillance.

If the above information was not explicit from the referring physician, patient records were retrieved from the hospital and reviewed. These records included general practitioner referral letters and secondary care clinic letters. For patients with HBV, this also included review via the New Zealand national hepatitis foundation.

Patient and disease characteristics were summarised using descriptive statistics, including means or 95% Confidence Intervals (CI) for continuous measurements and frequencies or percentages for categorical measurements. Comparative analysis between groups was performed using the chi-square test for categorical variables. When values were smaller than 5 the Fisher's exact test was used. For normally distributed continuous variables the Student t-test was used to determine significance. Stepwise multivariable logistic regression was used to estimate Odds Ratios (ORs) and 95% CIs for surveillance. Survival from the time of HCC diagnosis was estimated by the Kaplan-Meier method and difference between groups assessed by the log-rank test. The Cox proportional hazards model was for multi-variate survival analysis. Statistical significance was defined as a two-tailed p value <0.05. Data analysis was performed using IBM SPSS Version 23.0. Armonk, NY: IBM Corp.

This study received institutional ethics approval by the Auckland District Health Board research review committee.

Results

Over 15 years from 2003 to 2018, 368 patients were diagnosed with advanced HBV-HCC due to HBV and 278 with HCV-HCC. This represents over 50% of cases of HBV-HCC and 54% of cases of HCV-HCC who were diagnosed during the study period.

Table 1: Baseline characteristics for HBV and HCV patients.

	Diagnosis		**P value**
	HBV (n=368)	**HCV (n=278)**	
Age at death (mean), years	59.1	59.9	0.41
Sex, male	305 (82.9)	231 (83.1)	0.94
Ethnicity n, (%)			
Māori	164 (44.6)	65 (23.4)	<0.01
Pacific	119 (32.0)	7 (2.58)	
Asian	56 (15.2)	19 (6.8)	
NZ European	20 (5.4)	177 (63.7)	
Other	9 (2.4)	10 (3.6)	

HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; NZ: New Zealand.

Table 1 demonstrates the characteristics of the two groups. Gender and age at death were similar for both groups. The majority of patients with HBV were Māori, Pasifika or Asian (45%, 32% and 15% respectively), while the majority of HCV patients were NZ European (64%) or Māori (23%) (P<0.01).

Differences between patients with HBV and HCV in terms of surveillance, treatments and survival from time of HCC diagnosis is shown in Table 2. Overall only 74 out of 646 (11.5%) patients were alive at their last follow-up. In patients who had been diagnosed with chronic viral hepatitis before the development of HCC, those with HBV-HCC were less likely to have either never received surveillance (26% vs 42%), but more likely to have received suboptimal surveillance (12% vs 2.5%) when compared to those with HCV-HCC (p<0.01). Also, undiagnosed viral hepatitis was more common in patients with HBV-HCC than those with HCV-HCC (40% vs 28%).

More patients with HCV were eligible for TACE and survived a mean of 2.3 months longer, p=0.03.

Table 3 demonstrates the breakdown of surveillance factors. Overall, only 25% of patients received optimised, guideline-recommended surveillance. There were significant differences between groups in terms of non-curative treatments offered and overall survival (p<0.001) (Figure 1). Patients without a known diagnosis of viral hepatitis had the worst outcomes, with 88% receiving palliative care and surviving on average only seven months.

There were no significant predictors of patients receiving optimised surveillance on univariate or multivariate analysis (Table 4).

Discussion

This study highlights the disparate outcomes of patients with late diagnosis of HBV and HCV. The high rate of undiagnosed viral hepatitis in this cohort of advanced HCC for HBV (40%) and HCV (28%) is similar to that reported in an Australian study (38% and 22%) and a recent Canadian study (46% and 31%).[18,19] The importance of this data is magnified by the associated outcome analysis, which illuminates the extremely poor outcomes for this patient subgroup, with patients surviving a mean of only seven months after HCC detection. This study, which focused on patients with advanced HCC was warranted given viral hepatitis is the most common overall cause of HCC, and most cases of HBV-HCC and HCV-HCC are detected at a late stage when treatment options are few and survival is poor.

These findings highlight the need for earlier identification of New Zealanders living with HBV and HCV to enable effective antiviral therapy to prevent progression to cirrhosis and to institute appropriate HCC surveillance in patients with risk factors.

Table 2: Surveillance Factors for HBV and HCV patients with treatment and survival.

	Diagnosis		
	HBV (n=368), %	**HCV (n=278), %**	**P**
Surveillance group			
1	146 (39.7)	79 (28.4)	<0.01
2	95 (25.8)	116 (41.7)	
3	44 (12.0)	7 (2.5)	
4	83 (22.6)	76 (27.3)	
Treatment			
TACE	75 (20.4)	81 (29.1)	<0.001
Palliative	293 (79.6)	197 (70.9)	
Survival, median (months) (95% CI)	5.2 (4.0–6.4)	8.3 (6.3–10.2)	0.05

TACE: Transarterial chemoembolisation.

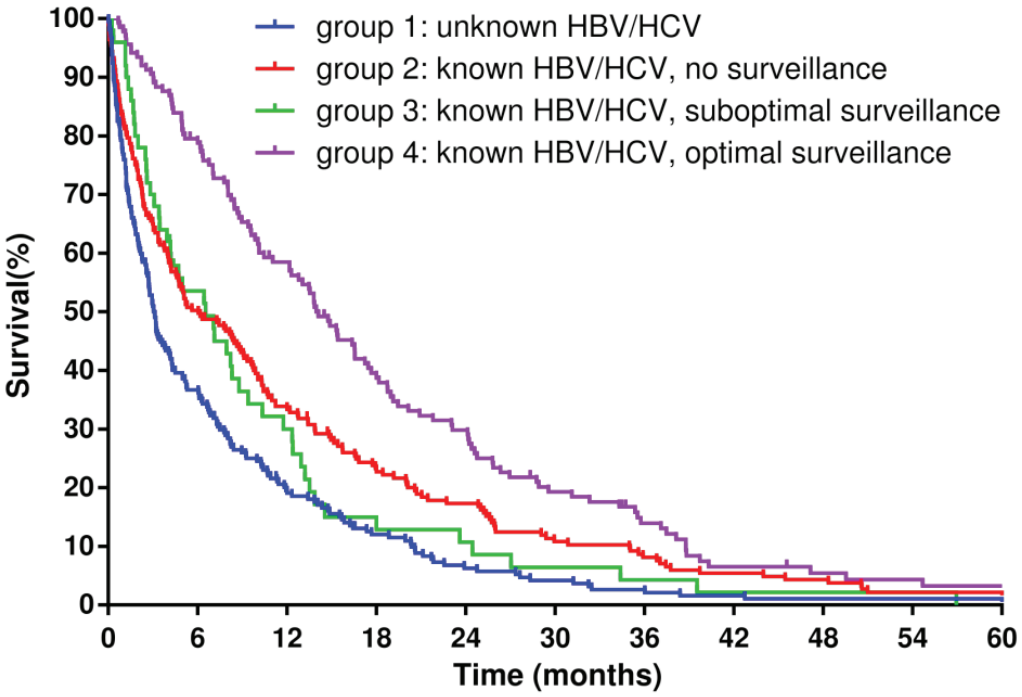
Table 3: Demographic and clinical characteristics of surveillance factors.

Surveillance factor, %	**1 (n=225) 34.8**	**2 (n=211) 32.7**	**3 (n=51) 7.89**	**4 (n=159) 24.6**	**P value**
Age at death (mean)	58.6	59.9	58	60.6	0.11
Gender					
Male, n (%)	185 (82.2)	177 (83.9)	42 (82.4)	132 (83.0)	0.77
Ethnicity, n (%)					
NZ European	51 (22.7)	85 (40.3)	8 (15.7)	53 (33.3)	0.003
Māori	81 (36.0)	67 (31.8)	22 (43.1)	59 (37.1)	
Asian	26 (11.6)	26 (12.3)	6 (11.8)	17 (10.7)	
Pacific	59 (26.2)	28 (13.3)	14 (27.5)	25 (15.7)	
Other	8 (3.6)	5 (2.4)	1 (2.0)	5 (3.1)	
Treatment, n (%)					
TACE	29 (12.9)	48 (22.7)	10 (19.6)	69 (43.4)	<0.001
Palliative	196 (87.9)	163 (77.3)	41 (80.4)	90 (56.6)	
Survival median, months (95% CI)	3.1 (2.5–3.6)	6.0 (3.6–8.5)	6.5 (3.0–10.0)	14.1 (11.3–16.8)	<0.001
Survival 25 percentile (SD)	9.3 (1.3)	16.6 (2.0)	13.0 (1.0)	25.8 (2.2)	
Survival 75 percentile (SD)	1.1 (0.2)	1.9 (0.3)	2.6 (0.6)	7.0 (1.1)	

Table 4: Analysis of predictors of surveillance (Groups 4 compared to 1,2,3).

	Univariate analysis		**Multivariate analysis**	
Variable of interest	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Age at death	1.01 (0.99–1.03)	0.18	1.01 (0.99–1.03)	0.22
Gender (Male)	1.00 (0.62–1.62)	0.99	1.04 (0.61–1.80)	0.88
HCV	1.29 (0.90–1.85)	0.16	1.09 (0.64–1.86)	0.75
NZ European	1.19 (0.81–1.75)	0.37	0.84 (0.27–2.61)	0.77
Māori	1.10 (0.76–1.60)	0.62	0.88 (0.29–2.66)	0.82
Asian	0.89 (0.50–1.57)	0.68	0.54 (0.16–1.87)	0.33
Pacific	0.71 (0.44–1.15)	0.17	0.76 (0.23–2.45)	0.64

Figure 1: Kaplan Meir survival curve of survival based on surveillance group.



High-quality population-level data on HCC is scarce. In particular, there is limited information on Pasifika population outcomes as no data is available from Oceania other than Australia.[20] This paper is designed to complement and combine data from our work to illuminate these issues with viral hepatitis in our country.[21,22] We have previously shown that for our total New Zealand HCV-HCC cohort, HCC is detected through routine surveillance in 44%.[21] This routine surveillance improved overall survival, OR 0.41 (95% CI [0.32, 0.53], p<0.0001), with an overall mean survival of 91.5 months (95% CI 76.4,106.6) compared to 43.0 (95% CI 34.2,51.9) for those patients not receiving regular surveillance. Patients who received regular surveillance had a significantly greater chance of receiving curative modality treatments than those who didn't, OR 5.68 (95% CI [3.80, 8.50], p<0.001). With such compelling figures, reinstituting the prematurely halted HBV national testing programme[23,24] and commencing a national HCV testing programme must be seriously considered.

In New Zealand, most patients presenting with advanced HBV-HCC and HCV-HCC are male and die in their late 50s, within one year of diagnosis. The majority of patients (92%) with HBV-related HCC were Māori, Pacific or Asian, with only 5% New Zealand European. Māori are overrepresented in advanced HCC due to both HBV and HCV at 45% and 23% respectively. Māori only represent 15% of the population and have an HBV prevalence of 5.8%, much lower than Chinese (9.1%) or Pasifika populations (8.5%).[24] Māori have a higher prevalence of HCV given increased frequency of risk factors for infection than non-Māori (Gane, personal communication). This over-representation must represent a huge gap in access to surveillance and treatment. Patients with HBV-HCC and HCV-HCC are often primary income earners for large families in low deciles[25] with far reaching impacts on not only family (whānau) but also communities.

As could be expected within this cohort of patients, the vast majority did not receive guideline recommended surveillance, including those with prior diagnosis of chronic viral hepatitis. Certainly, high deprivation index may be a barrier to appropriate medical care. In addition, poor awareness of the risks of HCC both in patients and healthcare workers may contribute to low

surveillance uptake. Previous studies both internationally and locally have noted that HCC surveillance is difficult to apply in practice.[9,26,27] Implementation in New Zealand of a national surveillance standard with clear criteria is needed. In the 1980s, the Japanese Ministry of Health implemented the world's first nationwide surveillance program because of increasing incidence of HBV-HCC and HCV-HCC cases. This initiative has resulted in significant improvements in outcomes in patients with HCC.[28]

Compared to patients with HBV-associated HCC, more patients with HCV-associated HCC were not receiving any surveillance at the time of HCC diagnosis (42% vs 26%) $p<0.01$. This difference may reflect the work of the New Zealand Hepatitis B Foundation, which aims to track, monitor and refer patients with HBV as necessary.

One quarter of cases of advanced HCC were in patients who were receiving recommended surveillance with a similar proportion from both HBV (23%) and HCV (27%) groups. This outcome reflects the limitations of our current techniques with insensitivity of AFP and imaging modalities, which is predominately ultrasound. Aggressive tumour biology may also be contributory. It is still important to note that within this group, 44% were still able to be offered TACE, and there was an additional average 12-months' survival compared to those patients who were newly diagnosed. Patients with HCV survived on average 2.3 months longer, likely secondary to the larger number who received TACE (29% vs 20%). In one series, patients with HBV-related HCC were less likely to be eligible for curative treatment (14% vs 34%, $p<0.05$)[15] compared to HCV patients, however our cohort was more even at 50% HBV, 46% HCV.

There has been controversy as to whether HCC surveillance confers any survival benefit in the overall population at risk for HCC.[29] Only one randomised controlled study has demonstrated survival benefit of HCC surveillance in the screened population, even when transplantation was not available and the resection rate in both groups was extremely low.[8] This was because most HCCs detected in the screening group were small and much more likely to be cured, while most HCCs in the control arm were advanced and only detected after the patient presented with symptoms such as pain, weight loss or complications of portal vein invasion. The only other randomised trial was stopped because of lack of recruitment.[30] However, a recent analysis of 38 observational studies of 10,904 patients with cirrhosis reported significant benefit of HCC surveillance on patient survival (51% vs 28%).[5] Although the incidence of HCC was similar, the proportion of HCCs that were detected at an early stage and offered curative therapy was higher in patients receiving HCC surveillance (62% vs 38%). The practice of HCC surveillance is also supported by multiple retrospective studies in patients with HCC, demonstrating superior survival in those patients receiving HCC surveillance that is maintained even after correction for a lead-time bias of up to four years.[31–33]

Limitations of this study include absence of important data regarding tumour stage or staging classifications, severity of underlying liver disease or co-morbidity. As this study focused on surveillance modality, possible additional important co-factors previously noted to be significant in HBV and HCV associated HCC such as mental illness, frequency of physician visits or rural or metropolitan residence was not recorded.[18,19] Additional possible missed cases of patients that were not referred to the tertiary HCC service and palliated locally are thought to be low, and will not be captured by this data.

Strengths of this study lie in the long-term follow-up and accuracy and completeness of the data because all cases were reviewed by a central HCC multidisciplinary meeting, which provided consistency of diagnosis, investigation and subsequent management and treatment plans with core staff, Individual case review, including inclusion of information from primary and secondary care allowed insight into surveillance practice that population-based studies do not allow. One designated tertiary referral service for the country afforded us consistency of diagnosis, investigation and subsequent management and treatment plans.

Better outcomes for patients with HCC can only be achieved through early detection when curative intervention is possible. Earlier diagnosis of HBV and HCV infection through public awareness and universal screening programmes would allow both

earlier detection of those at risk for HCC and also could prevent cirrhosis through improved linkage to antiviral therapy. All HBV patients should be offered enrolment in the community-based Hepatitis Foundation national surveillance programme. HCC surveillance in patients with HBV should be expanded from the current recommendations for those with cirrhosis or family history of HCC to include all HBsAg+ with severe fibrosis or cirrhosis (liver stiffness measurement >8 kPa); all HBsAg+ males over 40 years and all HBsAg+ females over 50 years as recommended by the American Association for the Study of Liver Diseases (AASLD) guidelines.[34] A pilot study should be conducted to determine the utility of the two HCC risk scores which have been validated in Asian populations—the REACH B predictive HCC risk score in patients not on nucleos(t)ide analogue (NUC) therapy and the REAL-B predictive HCC risk score in patients maintained on NUC therapy.[35,36] In addition, the New Zealand Society of Gastroenterology is currently preparing national HCC surveillance guidelines for all primary and secondary care.

New Zealand is one of the 194 member states to adopt the 2016 World Health Organization (WHO) strategy to eliminate viral hepatitis as a major public health threat by 2030. The current national HCV action plan and proposed HBV action plan will aim to find the remaining undiagnosed cases. If the current AASLD HCC surveillance recommendations are adopted (six-monthly AFP and ultrasound in all HBV cases over 40 years and all HCV cirrhotics), this would total almost 140,000 ultrasounds per annum. Surveillance has been shown to be cost effective compared to no surveillance, with a cost effectiveness ratio comparable to currently implemented screening strategies including colonoscopy and mammography.[37,38] Appropriate funding will need to be provided for this increased demand on secondary care radiology services.

Conclusion

More than half of new diagnoses of viral hepatitis related HCC in New Zealand are diagnosed at an advanced stage. Despite the many differences between HBV and HCV, patients with advanced HCC share similar challenges with regard to poor surveillance and rapid demise. The largest challenge lies in those patients who remain undiagnosed, highlighting the need for educating and reinforcing to practitioners the importance of surveillance in those with risk factors to help reduce the incidence of patients presenting with advanced HCC.

Competing interests:
Nil.

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