Hepatitis B virus-related hepatocellular carcinoma presenting at an advanced stage: is it preventable?

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ABSTRACT

AIM: Earlier diagnosis of hepatitis B virus (HBV) related hepatocellular carcinoma (HCC) increases treatment options and survival. The aim of this study is to evaluate which factors are associated with late presentation of HBV-related HCC.

METHOD: This is a retrospective review of all cases of HBV-related HCC diagnosed with late-stage/incurable HCC in New Zealand between 2003 and 2017. Cases were defined as patients with a positive hepatitis B surface antigen (HBsAg), and advanced (not amenable to potentially curable treatments) HCC at initial diagnosis. Patients were categorised into four groups according to potential reasons for late presentation: no previous diagnosis of HBV infection (Group A); known HBV diagnosis but not receiving HCC surveillance (Group B); known HBV diagnosis and receiving suboptimal HCC surveillance (Group C); and known HBV diagnosis and receiving optimised HCC surveillance (Group D).

RESULTS: A total of 368 patients were reviewed. The average age at death was 59 years, and the majority of patients were Māori (39%), Pacific (34%) or Asian (20%). The incidence of patients presenting with HBV-related advanced HCC increased from 4.5 cases to 6.3 cases per million people over the review period. Of the cases, 40% were categorised into Group A, 26% into Group B, 12% into Group C and 23% in Group D. Overall, the median survival was 138 days, and this did not change during the study period. Patients receiving optimised surveillance (Group D) survived longer (mean 469 days) than patients in Group A (90 days), Group B (145 days) or Group C (152 days) (p<0.05). Patients in Group D were more likely to be treated with transarterial chemoembolisation than patients in other groups (40% vs 15%, p<0.05).

CONCLUSION: This study has highlighted the need for improved rates of HBV diagnosis, better follow-up of those infected and the importance of optimal HCC surveillance. In New Zealand, HBV-related HCC disproportionately affects minority ethnic groups, and given the increasing incidence, provides a potential domain to reduce health inequities.

An estimated 248 million people worldwide have chronic hepatitis B virus (HBV) infection. The prevalence of HBV infection in New Zealand is approximately 3%, but is higher in Chinese (8.9%), South East Asian (8.1%), Pacific (7.3%) and Māori (5.6%) people. Although the introduction of universal neonatal vaccination in 1988 has almost eliminated childhood HBV infection in New Zealand, the high prevalence in adults has been maintained by increasing migration from Asian and South Pacific countries with endemic HBV infection. Up to 40% of people with HBV infection will develop chronic hepatitis B (CHB) which, if untreated, may progress to cirrhosis and the liver-related complications of decompensation and hepatocellular carcinoma (HCC). A particular challenge with diagnosing CHB is that symptoms do not develop until liver disease is advanced, at which point treatment options are limited and survival is poor. HCC is the second leading cause of cancer-related death worldwide and the leading cause in the Asia-Pacific region, where it accounts for over 500,000 deaths per annum, most
secondary to HBV. Only tobacco causes more cancer deaths than HBV.

Patients chronically infected with HBV have a 10–25% lifetime risk of developing HCC. Risk factors associated with an increased risk of HCC in patients with HBV infection include presence of cirrhosis, high HBV DNA level, a family history of HCC, childhood exposure to aflatoxin, older age, male gender, co-infection with HCV or HDV, and regular alcohol or tobacco use. However, HBV infection alone increases the lifetime risk of HCC more than 100 times, reflecting the direct carcinogenic effect of HBV integration into the host DNA.

Early diagnosis of HBV infection and recruitment into long-term monitoring improves patient outcomes, through early detection of CHB and HCC. Regular monitoring of serum ALT and HBV DNA levels will detect CHB prior to the onset of cirrhosis, when treatment with nucleoside analogues will prevent most liver-related complications, including HCC. Similarly, HCC surveillance will detect HCC at an earlier stage when curative treatment is still possible, resulting in improved survival. Recommended HCC surveillance is six-monthly measurements of serum alpha fetoprotein (AFP) in all patients with HBV infection. Six-monthly imaging of the liver with ultrasound (USS) is recommended in patients who are Asian and male aged 40 years or older or female aged 50 years or older, and at any age if there is either severe fibrosis or cirrhosis, or a family history of HCC.

The management of HCC depends on the size, location and number of lesions, as well as the severity of underlying liver disease. Curative treatment options include liver resection, ablation (ethanol injection, radiofrequency, microwave, stereotactic body radiation therapy, irreversible electroporation) and liver transplantation. Non-curative treatment options include transarterial embolisation (TAE) or chemoembolisation (TACE), sorafenib (a kinase inhibitor which is approved for use but not funded in New Zealand), and best practice supportive care.

Since 1998, the New Zealand Liver Unit at Auckland City Hospital has provided a national service for the staging and management of HCC. At weekly multidisciplinary meetings, clinicians from around New Zealand present via video conferencing all new cases of HCC. Patient and tumour details are stored on the HCC Database, along with treatment modalities and outcomes.

The aim of this current study is to determine what factors contributed to the late presentation of HBV-related HCC, including the impact of late diagnosis of HBV, lack of treatment with antiviral therapy and failure to recruit into the community HCC surveillance programme.

Method

Study design and population

This is a retrospective review of all advanced (not amenable to potentially curable treatments) cases of HBV-related HCC referred to the New Zealand Liver Unit over a 15-year period from 1 January 2003 to 31 December 2017.

Inclusion criteria were all patients who were hepatitis B surface antigen (HBsAg) positive at the time of HCC diagnosis, who had advanced HCC at initial diagnosis and who subsequently were treated with TAE, TACE, sorafenib or best practice supportive care. Exclusion criteria were a prior diagnosis of HCC or non-resident status.

Data collection

Data were collected by reviewing patients’ medical records and the national death database, including gender, ethnicity, age at diagnosis, date of HCC diagnosis, age and date of death. The date of the magnetic resonance imaging (MRI) or computed tomography (CT) diagnostic for HCC was considered the date of HCC diagnosis. Whether the patient had a prior diagnosis of cirrhosis by a hepatologist or gastroenterologist was recorded, as well as the HCC treatment received and if the patient had a first-degree relative with HCC.

A search of hospital and community laboratory databases was performed to determine if the patient had a positive HBsAg result prior to HCC diagnosis. If a patient was HBsAg positive prior to HCC diagnosis, previous radiological liver imaging (USS/CT/MRI) and AFP results were reviewed to determine the time-period between surveillance and HCC diagnosis, and if the patient was receiving the appropriate surveillance method.
Patients were then categorised according to potential reasons for late presentation. Patients were categorised into one of four groups:

A. No previous diagnosis of HBV infection
B. Known HBV diagnosis but not receiving HCC surveillance (defined as not having had liver imaging or AFP for two or more years)
C. Known HBV diagnosis and receiving suboptimal HCC surveillance (defined as AFP without liver USS in patients who are cirrhotic or have a positive family history of HCC; or receiving surveillance outside the recommended time-period)
D. Known HBV diagnosis and receiving optimised HCC surveillance.

To allow for short delays in investigations being performed, HCC surveillance was considered optimised if performed less than 12 months prior to HCC diagnosis, and suboptimal if more than 12 months.

Statistical analysis

The 15-year study period was divided into three five-year periods to determine trends in incidence over time. Incidence rates were calculated using Statistics New Zealand mid-year population estimates as the denominators.

Comparison of Kaplan Meier survival curves were performed using the log-rank test. The chi-square test was used to compare parametric data. A p-value <0.05 was considered statistically significant.

Results

A total of 374 patients from the New Zealand Liver Unit’s database were identified as presenting with late-stage/incurable HBV-related HCC. Six patients were excluded from the study, four because they did not reside in New Zealand and two because their HCC was not initially diagnosed in New Zealand. The final number of patients included in the study was 368.

Patient demographics

Of the 368 patients, 305 were male. The median age of death was 59 years (range 24–88). The most common ethnic groups were Māori (143 patients), followed by Pacific (125), Asian (72) and New Zealand European (20). The ethnicity of study patients is shown in Table 1.

Table 1: Patient ethnicity.

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Number (%)</th>
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<tbody>
<tr>
<td>Māori</td>
<td>143 (39)</td>
</tr>
<tr>
<td>Pacific</td>
<td>125 (34)</td>
</tr>
<tr>
<td>Tongan</td>
<td>53 (14)</td>
</tr>
<tr>
<td>Samoan</td>
<td>40 (11)</td>
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<tr>
<td>Cook Island</td>
<td>24 (7)</td>
</tr>
<tr>
<td>Niuean</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Tokelauan</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>72 (20)</td>
</tr>
<tr>
<td>Chinese</td>
<td>14</td>
</tr>
<tr>
<td>SEA</td>
<td>16 (4)</td>
</tr>
<tr>
<td>Taiwanese</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Japanese</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Filipino</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Indian</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>NZ European</td>
<td>20 (5)</td>
</tr>
<tr>
<td>Other European</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Middle Eastern</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>African</td>
<td>2 (0.5)</td>
</tr>
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Incidence

The incidence of advanced HBV-related HCC increased during the 15-year study period from 4.5 cases per million people between 2003 and 2007, to 6.0 cases per million people between 2008 and 2012, to 6.3 cases per million people between 2013 and 2017.

Factors associated with late diagnosis

Of the total patient cohort, 146 patients (40%) did not have a previous diagnosis of HBV infection prior to HCC diagnosis (Group A). Ninety-five patients (26%) were known to be infected with HBV but were not receiving any HCC surveillance (Group B).

The remaining 127 patients (35%) were in an HCC surveillance programme at the time of diagnosis. Forty-four (12%) were having suboptimal surveillance (Group C) and 83 (23%) were having optimised surveillance (Group D). This is shown in Figure 1.
Suboptimal surveillance (Group C)

Forty-four patients were receiving suboptimal surveillance. In 27 patients this was considered suboptimal because HCC surveillance was not performed within 12 months of HCC diagnosis. Eleven patients should have been receiving liver USS in addition to AFP due to having known cirrhosis, and six due to having a first-degree relative with HCC.

Survival

The median overall survival was 138 days (range: 2 to 3,191 days). There was no significant difference in survival between the three five-year periods. This is shown in Figure 2.

Figure 2: Overall survival for each five-year period.

The median survival in patients receiving optimised surveillance (Group D) was 469 days, which was significantly longer compared with Group A (90 days), Group B (145 days), and Group C (152 days) (p<0.05). This is shown in Table 2 and Figure 3.

Proportion of patients receiving TACE

Patients receiving optimised surveillance (Group D) were significantly more likely to receive TACE (40% of patients) than patients in the other groups (Group A= 11%, Group B=22%, Group C=18%), p<0.05.
Discussion

This study evaluated factors associated with late presentation in patients with HBV-related HCC. Identification of modifiable factors could help reduce the high liver-related mortality rates in New Zealand and other countries with endemic HBV infection.

The incidence of HBV-related HCC is highest in Polynesian (Māori and Pacific) and Asian men, reflecting endemic HBV infection in these populations.\textsuperscript{2–4} The male predominance reflects the effect of androgens on promoting HBV replication.\textsuperscript{15} This study demonstrated a similar distribution in patients presenting with advanced HBV-related HCC. Also, most patients die in their 5\textsuperscript{th} and 6\textsuperscript{th} decades of life within three months of diagnosis. These factors have the highest impact on Māori and Pacific Island communities, as most patients represent the primary income earners for large families. This high disease burden when combined with poor access to healthcare contributes to the substantial health disparity between different ethnic groups within New Zealand.\textsuperscript{16} Hence better prevention and earlier diagnosis of HBV-related HCC would contribute to reduction in health inequities in New Zealand.

This study suggests that the incidence of HBV-related HCC presenting at an incurable stage is steadily increasing in New Zealand, despite the introduction of universal neonatal vaccination in 1987 and funded oral antiviral therapy in 2000. During the study period the incidence increased from 4.5 to 6.3 cases per million people. Although diagnosis and reporting rates may have increased, it is likely that there has also been an increased incidence of HCC in New Zealand over the last 15 years. Other Western countries have seen similar trends. For example, South Australia has recorded an annual 20% increase in incidence over a 15-year period from 1996 to 2010 and this is projected to continue.\textsuperscript{17}

Table 2: Median survival for each group and overall.

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
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<tbody>
<tr>
<td>Median survival (days)</td>
<td>138</td>
<td>90</td>
<td>145</td>
<td>152</td>
<td>469</td>
</tr>
</tbody>
</table>

Figure 3: Survival for each group.
Factors contributing to this increase include an ageing cohort effect of the pre-immunisation population, and increasing levels of migration to New Zealand from neighbouring countries with endemic HBV infection including China, and South East Asian and Pacific nations. In 2013, Asians and Polynesians made up 15% of New Zealand’s population. During the next 25 years, if migration trends continue, then this is projected to increase to 40%, resulting in a continued increase in incidence of HBV-related HCC until HBV prevalence rates fall in the countries of origin from universal neonatal vaccination.

This study identified several factors associated with late presentation of HBV-related HCC, including lack of HBV diagnosis, lack of follow-up in diagnosed patients and suboptimal HCC surveillance in diagnosed patients receiving follow-up. Almost 40% of patients with advanced HBV-related HCC were not aware of their HBV status at the time of presentation. Many other patients with a prior diagnosis had never been recruited into long-term monitoring for the complications of CHB and HCC. Not surprisingly, these patients had the most advanced stage of HCC with the shortest survival. Early diagnosis and management of HBV will prevent cirrhosis and subsequent HCC, while early detection of HCC through optimal surveillance will improve survival in those patients who develop this complication.

Hepatitis B virus infection meets the World Health Organization’s criteria for screening in endemic countries with readily identifiable at-risk Asian and Polynesian populations; a safe, inexpensive and reliable HBsAg screening test which allows early diagnosis and treatment early in the natural history of chronic hepatitis B; straightforward recall procedures based on interval monitoring with serum ALT, HBV DNA, AFP and abdominal ultrasound; and safe and effective oral antiviral therapy treatment for active CHB. In 1998, the New Zealand Government funded a national HBV screening programme, targeting Asian, Pacific and Māori New Zealanders aged over 15 years (and therefore unlikely to be protected by universal neonatal vaccination). Over the next two years, more than 10,000 new cases of HBV infection were diagnosed. Unfortunately, the programme was halted early when only one quarter of the target population had been screened. Although an additional 10,000 new cases have since been identified through opportunistic screening in primary care, an estimated 80,000 remain undiagnosed. Urgent consideration should therefore be made to fund a second national HBV testing programme targeting the 800,000 untested adult Māori, Asian and Pacific New Zealanders at risk for HBV infection. This could be expected to identify almost 60,000 HBsAg+ New Zealanders for recruitment into the community-based surveillance programme.

A significant proportion (26%) of patients who presented with advanced HCC had previously been diagnosed with HBV infection but were not receiving HCC surveillance. Factors likely to be contributing to this high rate include lack of awareness of long-term HCC risk by both patient and health professional, poor access to healthcare, and unwillingness to engage in follow-up because of the stigma associated with HBV infection. Since 2002, the Hepatitis Foundation, a non-government organisation, has provided a community-based surveillance programme, focusing on improving HBV awareness and reducing stigmatisation in affected communities. Unfortunately to date, less than one quarter of the 120,000 HBV-infected New Zealanders have been recruited into this community-based programme.

Finally, some patients who are receiving recommended HCC surveillance may present with advanced HCC, highlighting the limitations of current surveillance methods. Serum alpha fetoprotein measurements lack sensitivity (almost one-third of HCCs do not produce AFP) and specificity (in a healthy HBV population, most AFP elevations are secondary to either pregnancy or active CHB). Abdominal ultrasound also lacks sensitivity (15% of HCCs are not visible on USS until very large) and specificity (multiphase CT or MRI are needed to distinguish HCC from benign lesions). Overall however, HCC surveillance improves survival by detecting HCC at an earlier stage when curative intervention is possible. The observation in this current study that
survival is also improved in patients who present with advanced HCC is explained by the higher proportion who receive TACE in this group.

The current APASL and AASLD recommendations state that all patient groups with an annual HCC incidence of at least 0.2% receive six-monthly liver USS in addition to AFP, including Asian females aged over 50 years and Asian males over 40 years who have CHB.9,14 Our results would support expansion of these recommendations to include Māori and Pacific people, given the similar age of HBV infection and HBV genotype distribution in Polynesian and Asian populations.

Limitations to this study include the likelihood that some cases of advanced HCC were discussed in regional multidisciplinary meetings and not referred to the New Zealand Liver Unit HCC multidisciplinary meeting, particularly patients with very advanced HCC requiring immediate palliative care. Secondly, a higher rate of referrals to the New Zealand Liver Unit may account for the increasing incidence found in this study. Lastly, the reasons why recommended HCC surveillance was not being performed on patients with previously diagnosed HBV infection are not known. Such data would inform action to improve access to HCC surveillance.

In summary, in New Zealand, a high-income country with endemic HBV infection, almost half of all cases of HBV-related HCC are diagnosed late when curative intervention is no longer possible. This study has identified factors contributing to patients with HBV infection presenting with advanced HCC. It has highlighted the need for improved rates of HBV diagnosis and better follow-up of those infected, and the importance of optimal HCC surveillance. Finally, in New Zealand, HBV-related HCC already disproportionately affects minority ethnic groups, and the increasing incidence suggests this as an area of focus to reduce health inequities.

Competing interests:
Nil.

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