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Hepatitis B related hepatocellular carcinoma: Screening, screening and more screening

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Abstract

Aim

Hepatocellular cancer (HCC) is the 4th leading cause of cancer-related death. Hepatitis B (HBV) related HCC represents a small fraction of HCC in western societies (<20%). No previous data on HBV related HCC in Ireland has been reported, thus our study aimed to describe this cohort.

Methods

Retrospective review of patients with HBV related HCC at the Irish National Liver Transplant Unit between January 2014 to August 2021.

Results

4.6% (39/847) of patients with HCC had chronic hepatitis B (CHB). Eighty-two percent were male and mean age was 54 years (SD±10.8; 31-78). 44% were Caucasian, 33% Asian and 23% African. 21.6% were diagnosed at early BCLC stage and being under ultrasound screening programme and having a previous diagnosis of CHB were the only associated factors. Patients on Nucleos(t)ides Analogues were more often within Milan criteria (56.5% vs 14.3%; p 0.01) and had less vascular invasion (4.5% vs 46.7%; p 0.02).

Discussion

Only a small proportion of HCC in Ireland are due to hepatitis B infection. However, prognosis can be improved by ultrasound screening and early detection of CHB. All persons born in regions of high or intermediate HBV endemicity (HBsAg prevalence>2%), such as Africa and Asia, should be screened for HBV.

Introduction

Hepatocellular cancer (HCC) is the 4th leading cause of cancer-related death worldwide[1]. Chronic infection with hepatitis B (CHB) is one of the most frequent causes of HCC. In the United States, Europe, Egypt and Japan hepatitis B (HBV) related HCC accounts for 20% of HCC, while in Africa and Asia it is around 60%. In 1981 Beasley et al.[2] reported for the first time the association with CHB and

HCC in a cohort of Taiwanese men. Since the discovery of the hepatitis B virus in 1965, multiple carcinogenic mechanisms have been documented[3]. In patients with hepatitis B related cirrhosis the annual incidence of HCC is particularly high in comparison with other aetiologies, up to 2% to 5%[4].

Despite the introduction of HBV vaccine in 1983, 350 million people are still chronically infected with HBV globally. HBV vaccine is known as the first anti-cancer vaccine, ever since universal infant vaccination in Taiwan demonstrated a significant reduction in HCC incidence in a cohort of children in the 1990s[5].

Interferon and Nucleos(t)ides Analogues (NA) are the current available treatments for CHB, but just a low fraction of patients achieve functional cure and as a result patients need to be on life-long treatment. The introduction in 1998 of first generation Nucleos(t)ides Analogues reduced the risk cirrhosis, hepatic decompensation, and HCC development. Lamivudine was initially described to reduce the risk of HCC recurrence after resection[6]. Later on, third generation Nucleos(t)ides Analogues (Entecavir and Tenofovir) showed a higher reduction in mortality and liver transplantation risk in comparison to Lamivudine, and a more effective reduction in HCC recurrence (7,8). Nonetheless, Entecavir and Tenofovir, despite its high potency in achieving viral suppression, do not act on HBV covalently closed circular DNA[9]; thus, they do not eliminate the risk of developing HCC (10). HBV covalently closed circular DNA resides in the hepatocyte's nuclei and is the template for transcription of viral RNAs, due to its location current available treatment can't interact with it[11].

HBV related HCC represents a small fraction of HCC in western societies. However, increasing migration from African and east Asian countries to Europe might change the epidemiological landscape. No data on HBV related HCC in Ireland has been reported to date. As a result, our study aimed to describe a cohort of patients diagnosed with hepatocellular carcinoma due to hepatitis B in Ireland, their staging, treatment, and survival outcomes.

Methods

Retrospective review of electronic data on all patients who had HBV related HCC referred to the Liver Unit in St Vincent's University Hospital from January 2014 to August 2021. St. Vincent's University Hospital hosts the Irish National Liver Transplant Program. Because of the volume of referrals, a dedicated HCC clinic was established in 2014. Chronic hepatitis B was defined by HBsAg positivity. Clinical notes were reviewed and demographic details, diagnostic test results, treatments received and outcomes were recorded.

Cirrhosis was diagnosed according radiological or pathological criteria when available. Diagnosis of HCC was based on biopsy results or radiological criteria using the Liver Imaging Reporting and Data

System (LIRADS) criteria[12]. All diagnoses and treatments were reviewed at a multi-disciplinary team meeting.

High alcohol intake was defined as the standard criteria: more than two drinks for females (>20g) and three drinks for males (30g) per day.

For statistical analysis demographic and clinical factors were compared across the 3 racial groups (Caucasians, Africans and Asians) and across BLCC stages using Chi-square tests for categorical variables and t tests or ANOVA for continuous variables. Data are expressed as mean ± SD unless otherwise stated. We used Kaplan-Meier curves to estimate survival between patients on hepatitis B treatment and those not on treatment, between different BCLC stages and between those attending ultrasound for HCC screening and those who were not on screening. All analysis were performed using SPSS statistics software version 28.0.

Results

Over the study period 847 patients with a diagnosis of HCC were evaluated at the HCC clinic. Of these 4.6% (n:39) were diagnosed with CHB. Most of the patients (89.7%) were referred from other centers. Demographic data for these patients is shown in table 1. Eighty-two percent of patients with HBV related HCC were male, mean age was 54 years (SD±10.8; 31-78) and mean follow-up was 569 days (7 days - 3.038 days). Forty-four percent were Caucasian, a third Asian and 23% African in origin. There were some notable differences between racial groups (Table 1). Alcohol was a co-factor in a third of the Caucasians but was not seen in the African or Asian patients and less than half the Asian patients were cirrhotic.

A third of patients (33.3%) were diagnosed with hepatitis B infection at the time of HCC diagnosis. In 12.8% of the cases, it was not recorded whether the patients were previously aware of chronic hepatitis B infection. Of those previously diagnosed with hepatitis B, 95.2% were receiving oral antiviral medications (66.7% on Entecavir, 19% on Tenofovir, and 14.3% on Lamivudine). Over half of the patients (52.4%) had DNA detectable at the first referral visit, with a median viral load 201IU/mL (<10-4053). Most patients (79.5%) had cirrhosis, 82.8% were Child-Pugh A, 13.8% Child-Pugh B and 3.4% Child-Pugh C liver disease. Median alfa fetoprotein level at diagnosis was 65kU/L (range 1-575) and 62.2% were unifocal HCC. Half of the patients (50%) were diagnosed during routine liver ultrasound screening.

According to Barcelona Clinic Liver Cancer staging classification (BCLC) (13) 2.6%, 20.5%, 43.6%, 28.2% and 5.1% of patients were diagnosed in stage 0, A, B, C and D, respectively. At the time of diagnosis, 38.5% were within Milan Criteria and potentially suitable for liver transplantation, 21.6% had vascular invasion and 10.5% had distant metastasis. Detection of HCC as part of an ultrasound

screening programme and having a previous diagnosis of CHB were the only factors associated with an early Barcelona Clinic Liver cancer stage (BCLC 0 and BCLC A) (Figure 2). Mean survival time of patients detected in an ultrasound screening program was 1.608 days compared to 353 days in those not on screening (p 0.001) (Figure 3). Thirty percent of patients on Nucleos(t)ides Analogues were diagnosed at an early stage, compared to 13.3% in the non-treatment group (p 0.226). Patients receiving oral anti-viral treatment were more often within Milan criteria (56.5% vs 14.3%; p 0.01), had less vascular invasion (4.5% vs 46.7%; p 0.02) and had longer mean survival times (1.367 days vs 250 days; p 0,000) (Figure 4).

Six patients received a liver transplant (15%), despite at the time of diagnosis 15 patients (38.5%) were within Milan criteria. The reasons for this included: disease progression in two cases, two other cases had liver resection, one case underwent radiofrequency ablation, and the remaining four cases it was due to different circumstances (age and background of metastatic prostate cancer, among others). Other treatments received included in 10.5% of patients surgical resection, 2.6% radiofrequency ablation, 41% transarterial chemoembolization, 5.1% selective internal radiation therapy and 18.4% were on sorafenib. Due to their advanced disease status 21.1% of the patients were treated with symptomatic palliative therapy. During the study period 71.8% of patients died.

Discussion

This is the first study to document HBV related HCC in Ireland. We found that only a small proportion of HCC (4.6%) are caused by chronic hepatitis B infection. During the seven years of analysis, there was no increase in the proportion of HCC secondary to HBV, despite an increase in net migration in Ireland (14). Ireland is a low-prevalence country for hepatitis B (<2 %), although prevalence data in the general population is lacking. An antenatal HBV screening programme from an Irish maternity hospital (15) reported a prevalence of CHB of 0.35% in the pregnant cohort. However, this most likely overestimates the real prevalence as migration from endemic countries is mainly during childbearing age.

An important finding of this study is that one third of patients were diagnosed with HBV at the same time of presenting with HCC related symptoms. HCC related symptoms do not typically develop until liver tumours are large and cause distension of Glisson's capsule and subsequent pain or liver decompensation. In New Zealand, Mules et al. described that 40% of their advanced HCC cohort were not aware of their HBV diagnosis[16]. Previous studies in the United States and Europe have showed low screening and treatment rates in patients at risk of CHB[17,18]. Ispas et al.[19] examined the barriers of CHB disease monitoring, treatment, and liver cancer surveillance and lack of patient and health provider knowledge was reported in both cases. It is clear, from this study and others, that the prognosis is better for patients previously diagnosed with hepatitis B, as a result of antiviral treatment and regular ultrasound screening.

Screening for HBV should be performed on the basis of individual risk, which typically depends on the endemicity of HBV in the country of origin (low (<2%), intermediate (2-7%) and high (>8%) endemicity), sexual practices, use of injected drugs, and use of immunosuppressive drugs, among others[20]. In this presented cohort 56.4% of HCC cases were from Asian or African origin, and 40% of them were diagnosed with HBV at the same time of presenting with HCC related symptoms. Hence the importance of developing proactive strategies to diagnose and screen immigrants from moderate to high-risk endemic areas. Moreover, previous studies suggest that HBsAg screening of migrants from intermediate to high endemic countries, such as Eastern Europe, Asian and African countries, is likely cost effective[21].

This study also reflects and highlights the importance of race in HBV related HCC. Firstly, African and Asian patients were diagnosed with HCC at younger ages. This is related to HBV infection in early childhood, higher prevalence of HBV genotype C in Asian population and exposure to environmental co-carcinogens such as aflatoxin. In the Asian subgroup more than 50% of the cases developed HCC on a non-cirrhotic background; which represented almost all (except one) of the non-cirrhotic HCC in this study. This is a well-known effect[22,23] and is related to longer duration of HBV infection, chronic active hepatitis, higher HBV DNA level and genotype B and C. In this subgroup of patients 50% were HBVeAg+; which also translates in higher HBV DNA levels.
African origin is also associated with higher risk of non-cirrhotic HCC, consequently guidelines from the American Association for the Study of Liver Disease recommends screening this group independently of their age[20]. Despite these baseline differences between the racial groups in this study, no significant outcomes differences could be identified. A previous multi-centre study[24], including three US and one Spanish centre, described that non-Asians presented with more advanced liver cancer stage compared to Asians and that they were more likely to be listed for transplantation.

In relation to Barcelona Clinic Liver Cancer stage, 23.1% of the patients were diagnosed at an early-stage and the only associated factors were previous CHB diagnosis (38.1% vs 7.7%; p 0.05), and undergoing ultrasound screening program (44.4% vs 5.6%; p 0.007). As most of the patients were referred from other centers the compliance on screening practices could not be evaluated in further detail. Surprisingly, in this study Nucleos(t)ides Analogues treatment was not associated with early BCLC stage, which is likely due to the small sample size.

Limitations of the current study relate to its retrospective design and small size. Unfortunately, there was no data recorded on BMI, family history of HCC, length of hepatitis B treatment and genotype. HBV genotype analysis could not be performed since patients at the time of referral to the HCC clinic were already virally supressed or had low HBV DNA levels.

In summary, this study shows that HBV related HCC is relatively uncommon in Ireland, and despite significant immigration from higher HBV endemic regions, incidence has not increased in the recent

years. Nonetheless, it has a very high mortality rate and affects a young population with many years of life lost. Antiviral treatment and ultrasound screening are associated with improved survival. Therefore, efforts should focus on screening and identifying patients at risk of chronic hepatitis B whilst also providing linkage to care for treatment and HCC screening, when appropriated.

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Declarations of Conflicts of Interest:
None declared.

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Annex

	Cohort (n:39)	**Caucasian (n:17)**	**Asian (n:13)**	**African (n:9)**	**p**
Age	54 (SD±10.8)	61 (SD±9.4)	51.4 (SD±8.7)	44.7 (SD±8.3)	**0.000**
Gender (% male)	82%	81.3%	84.6%	77.9%	0.92
HbeAg +	15.4%	7.7%	30%	28.6%	0.428

NA treatment	64.1%	80%	69.2%	44.4%	0.2
T2DM	15.4%	18.8%	15.4%	11.1%	0.88
HCV/HDV	10.3%	12.5%	15.4%	0%	0.48
Alcohol co-factor	15.4%	31.3%	0%	0%	**0.019**
Cirrhosis	79.5%	100%	46.6%	88.9%	**0.001**

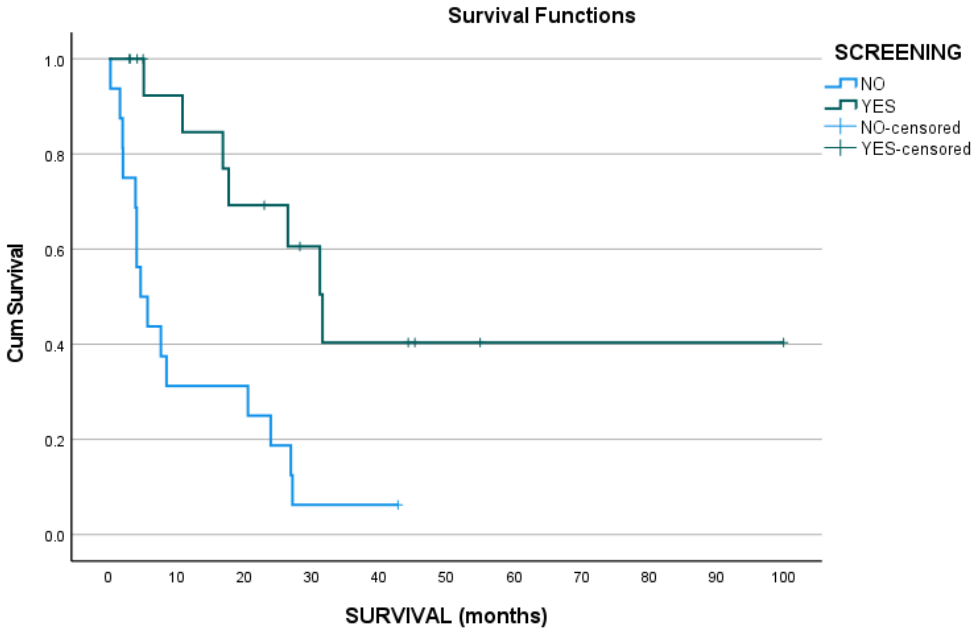
Table 1: Demographic data and clinical characteristics of patients with HBV related HCC and according their race.

Table 2: Demographic data and clinical characteristics according the BCLC stage

	Early BCLC stage (0+A) (n:9)	**Advanced BCLC stage (B,C,D) (n: 30)**	**p**
Age	55.8 (SD±9.6)	53.4 (SD±11.2)	0.88
Male	100%	76.7%	0.11

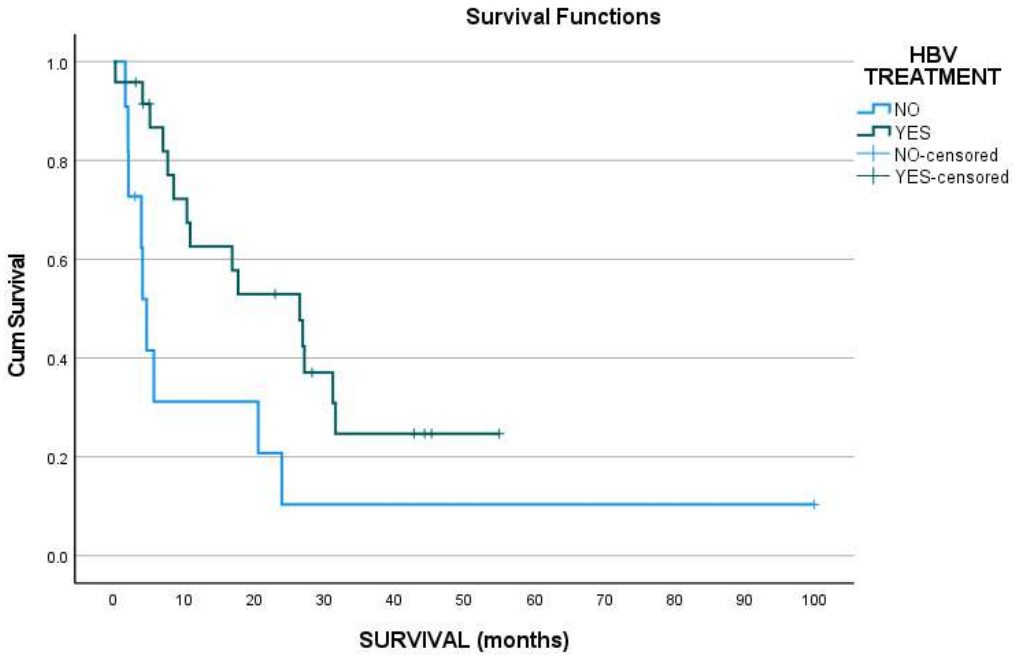
Asian	33.3%	34.5%	0.94
African	44.4%	17.2%	0.09
Caucasian	22.2%	48.3%	0.167
T2DM	22.2%	13.3%	0.51
HCV/HDV	0%	13.3%	0.24
ALD	0%	20%	0.145
Cirrhosis	77.8%	80%	0.88
AlfaFP (kU/L)	8.6 (1-522)	217 (2-575.274)	**0.046**
CHB at the time of HCC diagnosis	11.1%	48%	**0.05**
NA treatment	77.8%	55.2%	0.22
Ultrasound Screening	88.9%	37%	**0.007**
OLT	33.3% (100% within Milan)	6.9% (50% within Milan)	**0.07**
Survival	1.687,5	378,5	**0.000**

Figure 3:



P<0.001

Figure 4:


Survival Functions
HBV TREATMENT
NO
YES
NO-censored
YES-censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
70
80
90
100
SURVIVAL (months)

p 0.022