Impact of viral hepatitis aetiology on survival outcomes in hepatocellular carcinoma: A large multicentre cohort study

S. Mgaieth | W. Kemp | P. Gow | M. Fink | J. Lubel | A. Nicoll
A. Gazzola | T. Hong | M. Ryan | V. Knight | A. T. Dev | S. Sood
S. Bell | E. Paul | S. K. Roberts

1Department of Gastroenterology, Alfred Hospital, Melbourne, Vic., Australia
2Department of Gastroenterology, Austin Hospital, Heidelberg, Vic., Australia
3Department of Surgery, Austin Hospital, Heidelberg, Vic., Australia
4Department of Gastroenterology, Box Hill Hospital, Box Hill, Vic., Australia
5Department of Gastroenterology, Royal Melbourne Hospital, Parkville, Vic., Australia
6Department of Gastroenterology, St Vincent’s Hospital, Fitzroy, Vic., Australia
7Department of Gastroenterology, Monash Medical Centre, Clayton, Vic., Australia
8Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Vic., Australia

Summary

While HBV and HCV are risk factors for HCC, uncertainty exists as to whether these viral infections have prognostic significance in HCC. Thus, we compared the overall survival of patients with HBV, HCV and nonviral HCC, and evaluated whether the presence of HBV and HCV predicts patient outcomes. We conducted a multicentre study of HCC cases diagnosed at six Melbourne tertiary hospitals between Jan 2000-Dec 2014. Patient demographics, liver disease and tumour characteristics and patient outcomes were obtained from hospital databases, computer records and the Victorian Death Registry. Survival outcomes were compared between HBV, HCV and nonviral hepatitis cases and predictors of survival determined using Cox proportional hazards regression. There were 1436 new HCC cases identified including 776 due to viral hepatitis (HBV 235, HCV 511, HBV-HCV 30) and 660 from nonviral causes. The median survival of HBV, HCV and nonviral HCC patients was 59.1, 28.4 and 20.9 months, respectively ($P<.0001$). On multivariate analysis, independent risk factors for survival included HCC aetiology, gender, BCLC stage, serum AFP, total number and size of lesions, and serum creatinine and albumin. After adjusting for these and method of detection, HBV remained an independent predictor of improved overall survival when compared to both nonviral (HR 0.60%, 95% CI 0.35-0.98; $P=0.03$) and HCV-related HCC (HR 0.51%, 95% CI 0.30-0.85; $P=0.01$). In this large multicentre study, HBV is independently associated with improved overall survival compared with HCV and nonviral-related HCC. Further studies are needed to determine the underlying factor(s) responsible.

KEYWORDS
hepatitis B, hepatitis C, hepatocellular carcinoma, survival

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second leading cause of cancer death worldwide. It accounts for 70%-90% of primary liver cancers, and is more common in men than women. The incidence of HCC is increasing globally, particularly in the western world, with an estimated incidence rate of 2.7 per 100 000 in developed countries and 6.6 per 100 000 in developing countries. Most HCC arises in the setting of cirrhosis, with the most common underlying aetiologies being hepatitis B and C, and alcohol.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are both major risk factors for HCC, with an associated 5-100 fold
increased risk of HCC in patients with chronic HBV infection, and a 15-20 fold increased risk for HCV infection. While previous studies reported that both viral infections account for an estimated 19% of HCC cases in developed countries, a recent prospective epidemiological study from our group indicates that as many as 41% of cases are associated with HCV and 22% of cases are due to HBV infection.

While the overall 5-year survival with HCC is poor at 10%-20% this varies from 6.9% at 2 years in cases of advanced disease to 50%-90% at 5 years in earlier stages of disease that are amenable to curative treatment strategies. Established prognostic factors associated with survival include severity of liver disease, tumour stage, performance status, alpha-fetoprotein level and treatment response. However, it is unclear whether the aetiology of the underlying liver disease has prognostic significance, and in particular, whether survival differs between patients with viral hepatitis B and C and nonviral hepatitis-related HCC. Moreover, data are limited as to whether survival differences exist between those with viral hepatitis B and C given the differential availability of effective oral antiviral therapy over the past two decades for these chronic viral infections. Thus, we aimed in this multicentre observational study to compare the overall survival of patients with HBV-, HCV- and nonviral hepatitis-related HCC.

2 | METHODS

2.1 | Study design

This was a multicentre study of all cases of HCC diagnosed at six large Melbourne tertiary referral academic hospitals over the period between Jan 2000 and Dec 2013. Data were extracted from each academic centre’s database of HCC cases diagnosed at the respective tertiary hospital, the management of which was undertaken either at the one centre or across centres when specific services such as liver transplantation were required. Patients who were managed at more than one hospital were only included once, and data were captured across sites for the same patient. The diagnosis of HCC was based according to American Association of the Study of the Liver (AASLD) clinico-radiologic diagnostic criteria and/or histology. Cirrhosis was established in patients either by liver biopsy and/or on the basis of results of clinical, laboratory and imaging studies.

Ethics approval was obtained by the institution review board and ethics committees at each clinical site prior to commencement of the study. The ethics approval also covered extraction of mortality data on HCC cases from the Victorian Registry of Births, Deaths and Marriages following submission of a written application to the Registry. Data from the individual hospitals were amalgamated into a centralized database that was designed to record information on population demographics, including age at diagnosis, country of birth, ethnic background, aetiology and severity of underlying liver disease, laboratory results at diagnosis, method of diagnosis, radiological tumour characteristics, management strategies, response to treatment, follow-up and overall survival.

Missing data were obtained from hospital medical records, with patient follow-up censored at the 30th June 2014. Patients that had a follow-up visit after the 1st June 2014 were considered alive on the 30th June 2014, while those who had a follow-up visit preceding the 1st June 2014, had mortality information obtained from the Victorian Registry of Births, Deaths and Marriages.

The study population was divided into three separate groups based on the aetiology of the underlying HCC, namely (i) HBV-related HCC comprising patients with HBV infection only; (ii) HCV-related HCC comprising patients with HCV infection only; and (iii) nonviral liver disease-related HCC comprising patients with an aetiology other than HBV and/or HCV. Patients were defined as having HCV-related HCC if they were HCV antibody and/or HCV RNA positive while HBV-related HCC was defined as subjects with hepatitis B surface antigen positive or hepatitis B core and surface antibody positive in the absence of other known risk factors.

2.2 | Statistical analysis

Continuous variables were assessed for normality and expressed as mean ± standard deviation (SD) or median (interquartile range) depending on the underlying data distribution. Categorical variables were summarized using frequencies or proportions. Baseline comparisons between groups (HBV, HCV and nonviral) were conducted using analysis of variance or Kruskal-Wallis test as appropriate for continuous variables and chi-square test for categorical variables. Overall survival was the main study endpoint. Univariate and multivariate analyses were performed using Cox proportional hazards regression, with results reported as hazard ratios (HR) and 95% confidence intervals (95%CI). Variables with $P<.05$ on univariate analyses and/or those judged to be clinically important were considered for inclusion in the multivariate models as potential predictor variables.

The following factors were entered into the multivariate regression models: age at diagnosis, gender, ethnicity, presence of cirrhosis, Child-Pugh Class, alpha-fetoprotein (AFP) level, portal hypertension, platelet count, creatinine, bilirubin, albumin, INR, BCLC stage, number of lesions, screening as a mode of diagnosis and size of largest lesion. To account for clustering by hospital, the analyses were further adjusted by calculating robust standard errors. The Kaplan-Meier method was used to plot overall survival as a function of time and comparisons between curves were made using the log-rank test. All reported $P$ values are two-tailed and $P<.05$ indicated statistical significance. Analyses were performed with SAS software version 9.4 (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Study population

From January 2000 to December 2013, there were 1549 new cases of HCC diagnosed across the six centres. We excluded 113 patients who had no documented aetiology of the underlying liver disease, leaving 1436 patients in the final analysis. In total, 776 (54%) cases had viral hepatitis including 235 (30%) with HBV mono-infection, 511 (66%) with HCV mono-infection and 30 (4%) with HBV-HCV co-infection (Figure 1); the co-infection group was excluded from comparisons between HBV, HCV and nonviral-related HCC outcomes. The study cohort comprised
mostly males of Caucasian race with a mean age of 63 years at diagnosis. Cirrhosis was present in 84%, with 59% having Child-Pugh A liver disease and 45% having portal hypertension (Table 1). Overall, 42% had BCLC stage 0/A HCC, 19% had stage B disease, 26% stage C and 13% stage D. HCC was diagnosed via screening in 48% while 21% were diagnosed incidentally and 31% via symptoms (Table 1). Treatment history was available for 1243 cases (87%) of the study cohort. Among these, 31% had potentially curative therapies including resection, liver transplantation, local ablation (radiofrequency [RFA], microwave [MWA], irreversible electroporation [IRE], percutaneous ethanol injection [PEI]), 34% had palliative locoregional therapy (transarterial chemoembolization [TACE], selective internal radiation therapy [SIRT]) and 8% palliative systemic therapy, with 13% having best supportive care. The median follow-up of the cohort was 1.3 years (range: 0-13.4).

3.2 | Patient characteristics according to HCC aetiology

There was a significant difference in age but not gender between the HCV, HBV and nonviral hepatitis groups with the nonviral group being older than the viral hepatitis groups. Also, HBV-related cases were more likely to be born overseas, be of Asian background, and to be diagnosed before the age of 40 years, and less likely to have an alcohol history compared to those with HCV and nonviral HCC. In comparison, the prevalence of diabetes was higher in the nonviral group compared to those with viral hepatitis (Table 1).

Although the presence of cirrhosis was less frequent in the nonviral group, the severity of liver disease as measured by Child-Pugh score and serum albumin was lower in the HBV group with the groups otherwise similar with respect to the presence of portal hypertension and serum bilirubin levels (Table 1).

In addition, significant differences were observed between the groups in some baseline tumour characteristics including serum AFP and size of lesions, although the number of lesions, and presence of vascular invasion and extrahepatic spread were similar between groups. However, those in the HBV-related group were more likely to have a lower BCLC stage at diagnosis compared to subjects in the HCV, and nonviral hepatitis-related groups (Table 1). In addition, diagnosis via screening was more common in both viral hepatitis groups compared to the nonviral group (Table 1).

3.3 | Overall survival analysis

Overall survival data were available on 1197 (80%) of the patients. From January 2000 to June 2014, 857 (72%) patients had died, with deaths equally distributed among the nonviral (n=434) and viral hepatitis (n=423) groups. Among those with viral hepatitis, 26% of deaths had HBV infection and 74% had HCV infection. The median overall survival was 26.1 months. Patients with HBV had a median survival of 59.1 months, compared to 28.4 months in those with HCV and 20.9 months in those with nonviral hepatitis HCC (P<.0001).

3.4 | Univariate analysis of predictors of overall survival

On univariate analysis, BCLC stage, serum AFP, total number and size of lesions, serum creatinine, INR, platelet count, serum bilirubin, Child-Pugh class, age at diagnosis and presence of portal hypertension were associated with reduced overall survival. In contrast, having viral hepatitis B as the aetiology of HCC was associated with improved overall survival compared to HCV (P<.0001) and nonviral-related (P<.0001) HCC. Similarly, HCV-related HCC was associated with improved overall survival compared to nonviral HCC (P=.001) (Table 2).

3.5 | Multivariate analysis of predictors of overall survival

On multivariate analysis BCLC stage, serum AFP, total number and size of lesions, serum creatinine and albumin were independent
predictors of poor survival, whereas male gender was associated with improved overall survival (Table 2). Notably, HBV was an independent predictor of improved overall survival when compared to both nonviral ($P=.03$) and HCV-related HCC ($P=.01$) (Table 2). However, the differences in overall survival on univariate analysis were no longer significant between HCV and nonviral HCC ($P=.94$) (Table 2).

In view of the differential frequency of diagnosis by screening among the viral hepatitis B and C and nonviral groups, multivariate
analysis was further adjusted by including screening as the mode of HCC detection. In this analysis, HBV-related HCC remained independently associated with improved overall survival compared to HCV-related HCC (HR 0.51; 95%CI 0.31-0.85; \( P = .009 \)).

As shown in the Kaplan-Meier survival curves comparing overall survival between the three groups, the HBV-related HCC group had improved survival compared to the HCV and nonviral-related HCC groups with \( P < .001 \) (Figure 2).

### TABLE 2 Relationship between clinical characteristics and overall survival: univariate and multivariate analysis

<table>
<thead>
<tr>
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<th>Multivariate analysis</th>
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<tr>
<td></td>
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</tbody>
</table>

*Reference category.

#### 3.6 Impact of HBV aetiology on survival according to BCLC stage

Among those with early stage BCLC-0/A disease, subjects with HBV had better overall survival than those with HCV (HR 0.62, 95%CI 0.39-0.98; \( P = .04 \)) and nonviral-related HCC (HR 0.44, 95%CI 0.28-0.70; \( P = .001 \)) (Figure 3A). However, the survival advantage of HBV over both HCV and nonviral HCC was not maintained among those with more advanced disease including BCLC stage B (HR 0.91, 95%CI 0.47-1.74, \( P = .77 \) vs HCV; and HR 0.90, 95%CI 0.49-1.65, \( P = .74 \) vs nonviral) (Figure 3B) and BCLC stage C (HR 0.85, 95%CI 0.51-1.41, \( P = .53 \) vs HCV; and HR 0.74, 95%CI 0.46-1.21, \( P = .24 \) vs nonviral) (Figure 3C) HCC.

#### 4 Discussion

Our study provides additional insights into the potential impact of aetiology on the outcome of HCC patients. In this large multicentre study of 1406 HCC cases diagnosed across six tertiary centres over 15 years, we found patients with HBV-related HCC had a longer
overall survival compared to patients with nonviral and HCV-related HCC. Moreover, HBV was an independent predictor of survival even after adjusting for established predictors of survival including tumour stage, severity of liver disease, gender, AFP level and mode of diagnosis.

The prognostic role of HBV in HCC is an important finding. The median overall survival in the HBV group was 59 months which was significantly longer than that in HCV and nonviral groups being 28 months and 21 months, respectively. More importantly, HBV was an independent predictor of lower mortality versus nonviral (HR 0.60, 95%CI 0.25-0.95) and HCV (HR 0.51, 95%CI 0.30-0.82) related HCC. These findings are similar to those recently reported by van Meer et al. who found in multivariate analysis of 1148 cases that HBV infection was associated with significantly improved survival compared to HCV-related HCC. However, results across studies are not uniform with others finding no difference in survival between HBV-related HCC and other aetiologies and/or that HBV is not an independent predictor of survival.19,20 In addition, other studies have suggested that the influence of HBV on outcome is dependent on tumour stage, reporting that HBV has no influence on survival in earlier stage HCC, but a negative survival impact in later stage disease.8,21 In contrast, we found that HBV seemed to have a protective effect on survival in those with early stage disease compared to those with HCV and nonviral HCC but had no beneficial survival impact in those with more advanced disease. How might these findings be explained? One obvious possibility is that HBV subjects had more favourable disease characteristics at diagnosis that portend to a better outcome. In our study, the HBV group did have several favourable characteristics including a higher frequency of age <40 years at diagnosis, Child-Pugh A liver disease and earlier BCLC stage. However, the groups were similar in several other important characteristics including gender, markers of severity of liver disease including cirrhosis status, tumour burden and frequency of macrovascular invasion. These findings contrast with other studies reporting a lower survival among HBV cases in which HBV patients were more likely to be noncirrhotic, and to have greater tumour burden at diagnosis.17,22,23 Still, the multivariate analysis adjusted for all these variables with HBV remaining an independent predictor of improved survival. Similarly, there were differences in

![FIGURE 3](image-url)  
**FIGURE 3** Kaplan-Meier curve comparing overall survival between HBV, HCV and nonviral hepatitis-related HCC according to (A) BCLC stage 0/A, (B) BCLC stage B, (C) BCLC stage C, and (D) BCLC stage D disease.
baseline characteristics between the HBV and HCV cohorts including BCLC stage, Child-Pugh class and history of excess alcohol; however, HBV remained a significant and independent predictor of survival on multivariate analysis after adjusting for these.

Comparative differences in the frequency of diagnosis by screening for HCC is another plausible reason for the improved survival of the HBV cohort. In our study, a greater proportion of the HBV group were diagnosed by screening compared to the nonviral group, although the proportion was similar to the HCV group. Several cohort studies14,24-28 including our own, a recent large prospective study from the Netherlands,15 and one randomized controlled trial29 have shown that detection by screening is an independent predictor of patient survival in HCC. Even so a comprehensive systematic review of this topic concluded that robust evidence demonstrating a survival benefit from screening is lacking, with most studies being of low quality.30 Nevertheless, we adjusted for mode of diagnosis on multivariate analysis finding that HBV remained an independent predictor of improved survival compared to the nonviral and HCV groups.

In contrast to HCV infection, effective oral antiviral therapy has been available for chronic hepatitis B for two decades. Long-term suppression of viral replication with oral nucleos(t)ide therapies (eg, entecavir, tenofovir) achieves multiple benefits including improvement in liver histology, liver function and clinical course, and a reduction in risk of severe complications of cirrhosis including HCC.31-38 In addition, adjuvant treatment with oral nucleos(t)ide analogues has been shown in several retrospective cohort studies and meta-analyses to reduce the rate of HCC recurrence in HBV-related HCC and to improve survival following a complete response to potentially curative therapies.39-43 Thus, the improved outcome of HBV-related HCC cases in our cohort could have been in part due to antiviral therapy with additional studies needed to explore this possibility.

The other findings from our study are consistent with what is known in the literature. In addition to disease aetiology, we identified BCLC stage, AFP level, tumour size and number, creatinine and albumin as independent predictors of survival similar to what others have shown.44-45 Interestingly, recent data suggest that the most robust predictors of death in HCC are portal vein thrombosis, tumour size, AFP level and Child-Pugh class, two of which we identified in our study.46

In conclusion, this large multicentre cohort study examining prognostic factors in HCC found that HBV is independently associated with improved survival compared to HCV and nonviral HCC and that most of this survival benefit appears to be in those with early stage disease. Further studies are needed to explore the underlying protective mechanism(s) involved including the role of viral suppression.

DISCLOSURES

None.

AUTHOR CONTRIBUTIONS

All authors contributed to the drafting and review of the manuscript.

REFERENCES


