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IMPACT OF VIRAL HEPATITIS ETIOLOGY ON SURVIVAL OUTCOMES IN HEPATOCELLULAR CARCINOMA: A LARGE MULTI-CENTER COHORT STUDY

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Acknowledgements: Nil**Abstract**

Background and Aims: 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 non-viral HCC, and evaluated whether the presence of HBV and HCV predicts patient outcomes.
Methods: We conducted a multi-center study of HCC cases diagnosed at six Melbourne tertiary hospitals between Jan 2000-Dec 2014. Patient demographics, liver disease and tumor characteristics, and patient outcomes were obtained from hospital databases, computer records and the Victorian Death Registry. Survival outcomes

were compared between HBV, HCV and non-viral hepatitis cases and predictors of survival determined using Cox proportional hazards regression.

Results: There were 1436 new HCC cases identified including 776 due to viral hepatitis (HBV 235, HCV 511, HBV-HCV 30) and 660 from non-viral causes. The median survival of HBV, HCV and non-viral HCC patients was 59.1, 28.4 and 20.9 months respectively (P<0.0001). On multivariate analysis, independent risk factors for survival included HCC etiology, 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 non-viral (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).

Conclusions: In this large multicenter study, HBV is independently associated with improved overall survival compared with HCV and non-viral related HCC. Further studies are needed to determine the underlying factor(s) responsible.

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[1-4], with an estimated incidence rate of 2.7 per 100,000 in developed countries and 6.6 per 100,000 in developing countries[1]. Most HCC arises in the setting of cirrhosis, with the most common underlying etiologies 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[5]. While previous studies reported that both viral infections account for an estimated 19% of HCC cases in developed countries,[1] 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[6].

While the overall 5-year survival with HCC is poor at 10-20% [7] 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[8]. Established prognostic factors associated with survival include severity of liver disease, tumor stage, performance status, alpha-fetoprotein level and treatment response[9-12]. However, it is unclear whether the etiology of the underlying liver disease has

prognostic significance, and in particular, whether survival differs between patients with viral hepatitis B and C and non-viral hepatitis-related HCC. Moreover, data is 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 multi-center observational study to compare the overall survival of patients with HBV-, HCV-, and non-viral hepatitis-related HCC.

Methods

Study design

This was a multicenter 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 center's database of HCC cases diagnosed at the respective tertiary hospital, the management of which was undertaken either at the one center or across centers 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 Amercian Association of the Study of the Liver (AASLD) clinico-radiologic diagnostic criteria[13] 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[14].

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, etiology and severity of underlying liver disease, laboratory results at diagnosis, method of diagnosis, radiological tumor 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 etiology of the underlying HCC, namely a) HBV-related HCC comprising patients with HBV infection only; b) HCV-related HCC comprising patients with HCV infection only; and c) non-viral liver disease related HCC comprising patients with an etiology 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.

Statistical analysis

Continuous variables were assessed for normality and expressed as mean ± standard deviation (SD) or median (inter-quartile range) depending on the underlying data distribution. Categorical variables were summarized using frequencies or proportions. Baseline comparisons between groups (HBV, HCV and non-viral) 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 $P < 0.05$ 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, alfa-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 $P < 0.05$ indicated statistical significance. Analyses were performed with SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Results

Study population

From January 2000 to December 2013 there were 1549 new cases of HCC diagnosed across the six centers. We excluded 113 patients who had no documented etiology 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 non-viral 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 loco-regional therapy (transarterial chemoembolisation [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).

Patient characteristics according to HCC etiology

There was a significant difference in age but not gender between the HCV, HBV and non-viral hepatitis groups with the non-viral 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 non-viral HCC. In comparison, the prevalence of diabetes was higher in the non-viral group compared to those with viral hepatitis (Table 1).

Although the presence of cirrhosis was less frequent in the non-viral 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 tumor 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 non-viral hepatitis related groups (Table 1). In addition, diagnosis via screening was more common in both viral hepatitis groups compared to the non-viral group (Table 1).

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 non-viral (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 non-viral hepatitis HCC (P<0.0001).

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 etiology of HCC was associated with improved overall survival compared to HCV (P<0.0001) and non-viral (P<0.0001) related HCC. Similarly, HCV-related HCC was associated with improved overall survival compared to non-viral HCC (P=0.001) (Table 2).

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 non-viral (P=0.03) and HCV-related HCC (P=0.01) (Table 2,

Figure 2). However, the differences in overall survival on univariate analysis were no longer significant between HCV and non-viral HCC (P=0.94) (Table 2).

In view of the differential frequency of diagnosis by screening among the viral hepatitis B and C and non-viral 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=0.009).

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 non-viral related HCC groups with P<0.001 (Figure 2).

Impact of HBV etiology 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=0.04) and non-viral related HCC (HR 0.44, 95%CI 0.28-0.70; P=0.001) (Figure 3A). However, the survival advantage of HBV over both HCV and non-viral HCC was not maintained among those with more advanced disease including BCLC stage B (HR 0.91, 95%CI 0.47-1.74, P=0.77 *vs* HCV; and HR 0.90, 95%CI 0.49-1.65, P=0.74 *vs* non-viral) (Figure 3B) and BCLC stage C (HR 0.85, 95%CI 0.51-1.41, P=0.53 *vs* HCV; and HR 0.74, 95%CI 0.46-1.21, P=0.24 *vs* non-viral) (Figure 3C) HCC.

Discussion

Our study provides additional insights into the potential impact of etiology on the outcome of HCC patients. In this large multicenter study of 1406 HCC cases diagnosed across six tertiary centers over 15 years, we found patients with HBV-related HCC had a longer overall survival compared to patients with non-viral and HCV-related HCC. Moreover, HBV was an independent predictor of survival even after adjusting for established predictors of survival including tumor 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 non-viral groups being 28 months and 21 months respectively. More importantly, HBV was an independent predictor of lower mortality versus non-viral

(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[15,16]. However, results across studies are not uniform with others finding no difference in survival between HBV-related HCC and other etiologies[17-18], 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 non-viral 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 favorable disease characteristics at diagnosis that portend to a better outcome. In our study, the HBV group did have several favorable 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, tumor 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 non-cirrhotic, and to have greater tumor 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 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 non-viral group, although the proportion was similar to the HCV group. Several cohort studies[14,24-28] including our own, a recent large prospective study from the Netherlands[15], and one randomized controlled trial[29] 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 non-viral and HCV groups.

In contrast to HCV infection, effective oral anti-viral 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 anti-viral 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 etiology, we identified BCLC stage, AFP level, tumour size and number, creatinine, and albumin as independent predictors of survival similar to what others have shown[10]. Interestingly, recent data suggests that the most robust predictors of death in HCC are portal vein thrombosis, tumor size, AFP level and Child–Pugh class, two of which we identified in our study.

Our study while large and multi-centered, has important limitations. Firstly, being retrospective in nature, data capture was incomplete in relation to baseline characteristics particularly on performance status that was not routinely captured across all centers until the last decade when the BCLC staging system became widely accepted. In addition, the BCLC staging system used was the only tumor classification system routinely employed across all sites. Finally, survival status was known in only 80% of cohort, with the remainder of subjects lost to follow up or survival status unable to be clarified from the Death Registry. However, there were no clinically significant differences in the baseline demographics, liver disease (ie. Child-Pugh class and score) and tumor characteristics including tumour stage and etiology of HCC between those in whom survival status was known and not known (data not shown).

In conclusion, this large multicenter cohort study examining prognostic factors in HCC found that HBV is independently associated with improved survival compared to HCV and non-viral 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.

Figure legend

Figure 1. Flow chart of patients included in the analysis and grouping of patients

Figure 2. Kaplan-Meier curve comparing overall survival between HBV, HCV and non-viral hepatitis related HCC

Figure 3. Kaplan-Meier curve comparing overall survival between HBV, HCV and non-viral hepatitis related HCC according to a) BCLC stage 0/A (Fig. 3A), b) BCLC stage B (Fig. 3B), and c) BCLC stage C (Fig. 3C) disease.

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Table 1. Clinical characteristics of patients with viral and non-viral hepatitis related HCC

Parameter	Viral-hepatitis HCC			Non-viral HCC	P value[b]
	Overall *N* = 776[a]	**HBV** *N* = 235	**HCV** *N* = 511	*N*=660	
Demographics					
Age (years), Mn (SD)	59.2 (11.4)	57.9 (12.7)	60.1 (10.6)	67.0 (11.2)	<0.0001
Male, *n* (%)	618 (79.6)	186 (79.2)	406 (79.5)	540 (81.8)	0.51
Australian born, *n* (%)	148 (30.5) (n=485)	4 (2.6) (n=155)	139 (44.4) (n=313)	178 (47.3) (n=376)	<0.0001
Race/ethnicity, *n* (%)					
Caucasian	407 (63.7) (n=639)	60 (30.2) (n=199)	337 (80.6) (n=418)	453 (86.1) (n=526)	<0.001
Asian	188 (29.4) (n=639)	121 (60.8) (n=199)	57 (13.6) (n=418)	41 (7.8) (n=526)	<0.001
Diabetes, *n* (%)	99 (31.8) (n=311)	31 (31) (n=100)	66 (32.7) (n=202)	148 (47.7) (n=310)	0.0004
Alcohol, *n* (%)	202 (31.3) (n=646)	24 (12.4) (n=194)	170 (39.7) (n=428)	302 (56.5 (n=535)	<0.0001
Liver disease					
Cirrhosis, *n* (%)	596 (88.7) (n=672)	176 (83.8) (n=210)	399 (91.3) (n=437)	461 (78.8) (n=585)	<0.0001
Portal HTN, *n* (%)	283 (47.6) (n=595)	71 (42.3) (n=168)	200 (49.9) (n=401)	216 (42.9) (n=504)	0.07
Child-Pugh score[#], Mn (SD)	6.9 (1.9) (n=547)	6.4 (1.7) (n=162)	7.0 (1.9) (n=367)	7.1 (2.1) (n=425)	<0.001
Child-Pugh class A/B/C, *n*	439/244/66	160/54/13	264/181/48	384/179/79	
Platelets (x10^9/L), Mn (SD)	142 (88) (n=607)	173 (95) (n=181)	128 (80) (n=404)	173 (102) (n=528)	<0.001
Bilirubin (μmol/L), Mn (SD)	32 (47) (n=658)	27 (47) (n=197)	34 (47) (n=434)	35 (51) (n=557)	0.15
Creatinine (μmol/L), Mn (SD)	79 (28) (n=632)	82 (35) (n=186)	77 (25) (n=418)	83 (34) (n=547)	0.02
Albumin (g/L), Mn (SD)	33 (6.8) (n=658)	35 (7.3) (n=197)	32 (6) (n=434)	33 (7.0) (n=557)	<0.001
INR, Mn (SD)	1.2 (0.3) (n=620)	1.2 (0.3) (n=182)	1.2 (0.3) (n=412)	1.3 (0.3) (n=529)	0.006
HCC characteristics					
Detection method, *n* (%)					
Screening	374 (56.3) (n=664)	119 (59.5) (n=200)	247 (56) (n=441)	204 (37.4) (n=545)	<0.0001

Symptoms	112 (16.9) (n=664)	33 (16.5) (n=200)	74 (16.8) (n=441)	146 (26.8) (n=545)	<0.001
Incidental	178 (26.8) (n=664)	48 (24) (n=200)	120 (27.2) (n=441)	195 (35.8) (n=545)	0.001
AFP (ng/L), Median (IQR)	27(6-216) (n=666)	14 (5-383) (n=202)	27 (7-132) (n=436)	9 (4-126)	<0.0001
BCLC stage, Median (IQR)	2 (1-3) (n=525)	1 (1-2) (n=155)	2 (1-3) (n=349)	2 (1-3) (n=452)	<0.0001
BCLC 0, n (%)	56 (10.7)	18 (11.6)	37 (10.6)	20 (4.4)	
BCLC A, n (%)	188 (35.8)	68 (43.9)	117 (33.5)	142 (31.4)	
BCLC B, n (%)	96 (18.3)	33 (21.3)	61 (17.5)	94 (20.8)	
BCLC C, n (%)	130 (24.8)	28 (18.1)	94 (26.9)	128 (28.3)	
BCLC D, n (%)	55 (10.5)	8 (5.2)	40 (11.5)	68 (15.1)	
Lesion Size (cm), Mn (SD)	3.9 (3.1) (n=727)	4.2 (3.4) (n=215)	3.7 (2.9) (n=486)	5.0 (3.6) (n=617)	<0.001
Number of lesions, Mn (SD)	1.6 (0.8) (n=750)	1.6 (0.8) (n=228)	1.6 (0.8) (n=494)	1.7 (0.8) (n=645)	0.66
Vascular Invasion, n (%)	60 (11.5) (n=522)	18 (11.9) (n=151)	37 (10.5) (n=352)	58 (13.7) (n=423)	0.40
Extrahepatic spread, n (%)	23 (6.7) (n=345)	4 (3.9) (n=102)	18 (7.8) (n=232)	22 (7.6) (n=291)	0.40
Deceased, n (%)	423 (54.5)	98 (41.7)	306 (59.9)	433 (65.6)	<0.001

Mn = mean, SD = standard deviation, IQR = interquartile range

[#]Determined in cirrhosis patients

[a]includes 30 patients with HBV-HCV co-infection

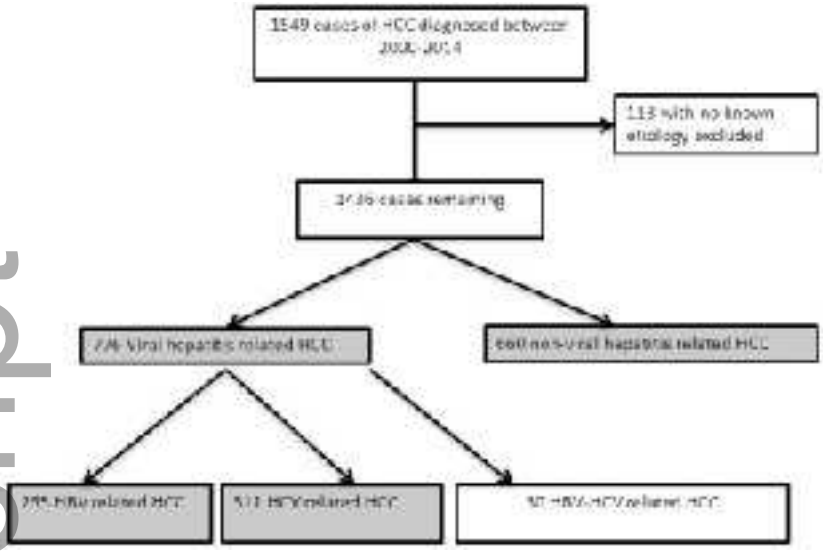
[b]P value comparing HBV vs HCV vs non-viral

Table 2. Relationship between clinical characteristics and overall survival: univariate and multivariate analysis

	Univariate analysis			Multivariate analysis					
				HBV *vs* HCV			HBV *vs* HCV *vs* non-viral		
	HR	95%CI	P	HR	95%CI	P	HR	95%CI	P
HBV vs. non-viral	0.47	0.37-0.60	<0.0001				0.60	0.38-0.95	0.031
HCV vs. non-viral	0.79	0.69-0.90	0.001				0.99	0.72-1.36	0.94
HBV vs. HCV	0.61	0.48-0.77	<0.0001	0.51	0.30-0.85	0.01			
Male	1.01	0.88-1.15	0.93	0.37	0.20-0.67	0.001	0.57	0.39-0.83	0.004
Age at diagnosis (yr)	1.015	1.01-1.02	0.001	0.98	0.96-1.001	0.07	1.01	0.99-1.02	0.44
Caucasian	1.11	0.85-1.45	0.44	1.07	0.51-2.25	0.85	0.88	0.54-1.43	0.60
Asian ethnicity	0.74	0.53-1.02	0.06	1.08	0.48-2.40	0.86	0.78	0.43-1.40	0.40
Other ethnicity	1.0[a]			1.0[a]			1.0[a]		
Child-Pugh Class	1.71	1.25-2.34	0.001	1.07	0.68-1.69	0.77	1.25	0.92-1.70	0.16
Cirrhosis	1.0	0.85-1.18	1.00	0.82	0.44-1.55	0.54	1.06	0.68-1.65	0.81
Bilirubin (µmol/L)	1.05	1.04-1.06	<0.0001	1.01	0.98-1.05	0.48	1.03	1.00-1.06	0.05
Creatinine (µmol/L)	1.05	1.02-1.08	<0.0001	1.17	1.07-1.29	0.001	1.08	1.03-1.13	0.002
Albumin (g/L)	0.94	0.92-0.95	<0.0001	0.96	0.91-0.998	0.043	0.97	0.94-0.996	0.024
INR	1.77	1.45-2.16	<0.0001	0.73	0.31-1.71	0.47	0.88	0.55-1.42	0.59
Platelet ($x10^9$/L)	1.02	1.01-1.03	<0.0001	1.002	0.97-1.04	0.92	1.00	0.98-1.02	0.75
BCLC	1.89	1.75-2.03	<0.0001	1.35	1.05-1.72	0.018	1.25	1.07-1.47	0.007
AFP (ng/L)	1.03	1.02-1.04	<0.0001	1.04	1.01-1.06	0.002	1.04	1.02-1.06	<0.0001

Total No. of lesions	1.43	1.29-1.59	<0.0001	1.45	1.14-1.84	0.002	1.46	1.25-1.72	<0.0001
Lesion size (cm)	1.14	1.12-1.16	<0.0001	1.18	1.1-1.28	<0.0001	1.13	1.08-1.18	<0.0001
Portal hypertension	1.27	1.05-1.53	0.013	1.51	0.95-2.42	0.08	1.22	0.89-1.66	0.22

[a]Reference category



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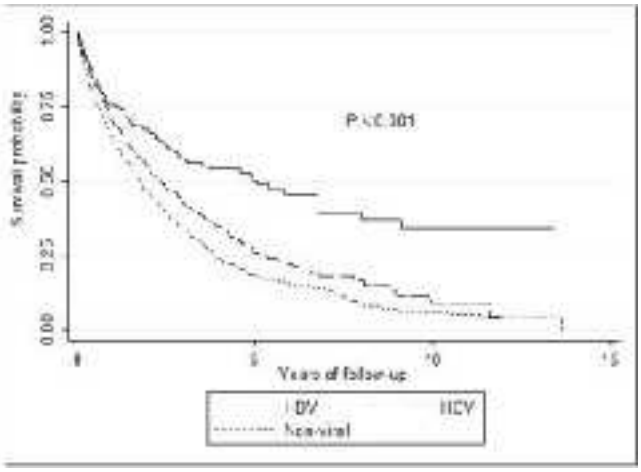

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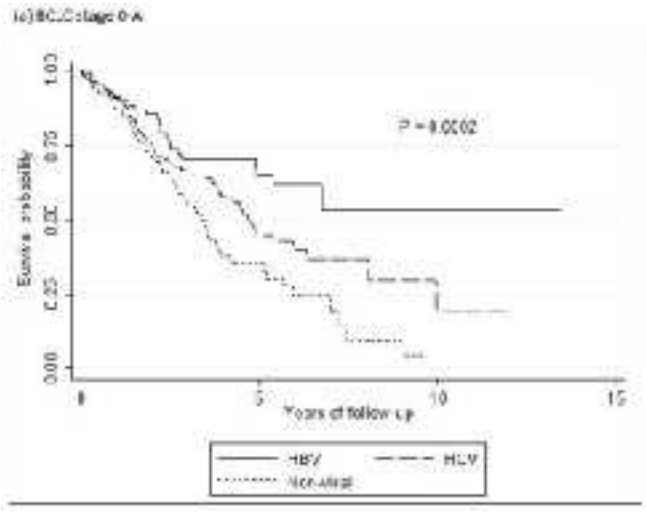

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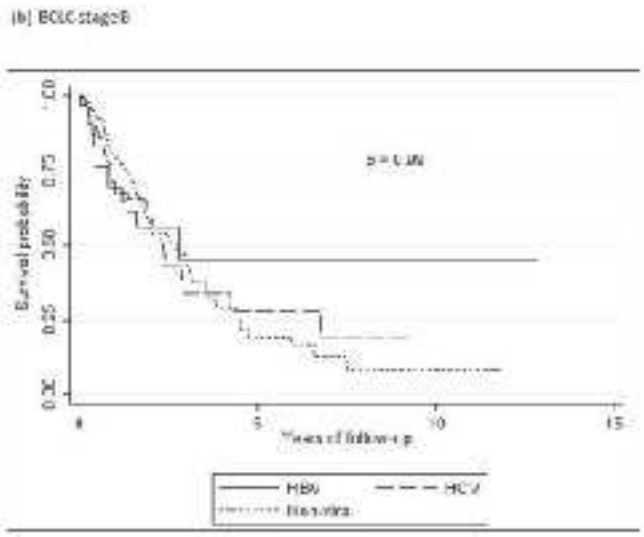

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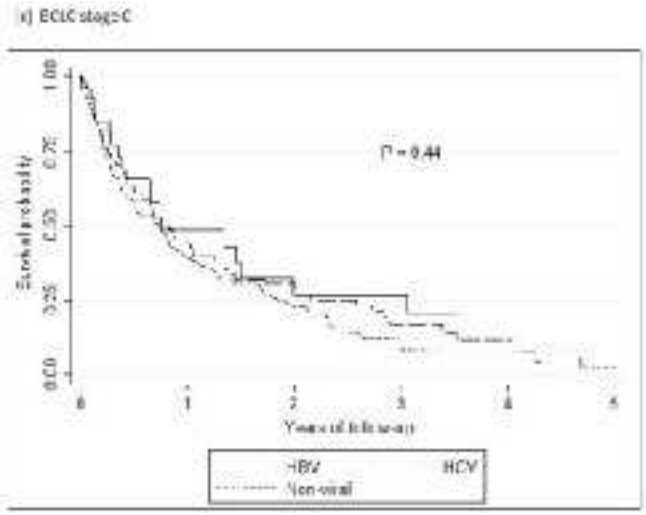

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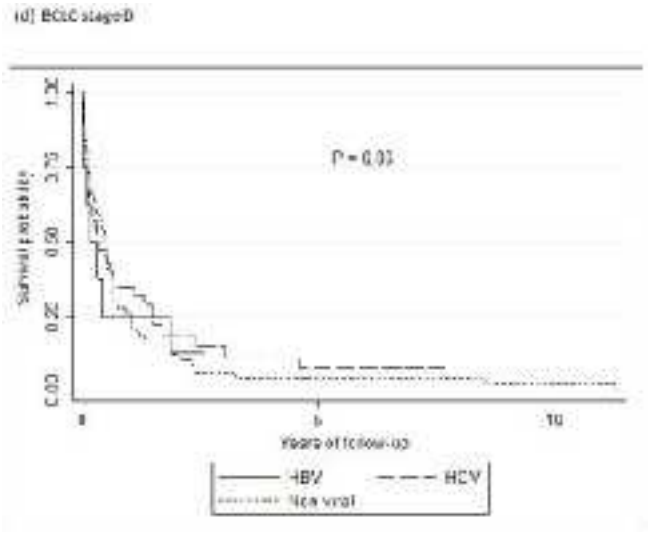

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