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The Effect of Hepatitis B and Alcohol Coexistence on the Development of Hepatocellular Carcinoma in Cirrhotic Patients

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ABSTRACT

Introduction: This study aimed to retrospectively compare the incidence of hepatocellular carcinoma (HCC), overall survival (OS), and HCC-free survival among patients with cirrhosis of different etiologies: alcohol-related, hepatitis B virus (HBV)-related, and combined HBV-alcohol-related. Additionally, the relationship between HBV viral load and HCC-free survival was evaluated in HBV-positive patients.

Methods: This retrospective single-center cohort study included 648 patients with cirrhosis followed for more than 6 months between July 2007 and April 2014. The patients were categorized into three etiological groups: alcohol-related cirrhosis (n=310), HBV-related cirrhosis (n=294), and HBV-alcohol-related cirrhosis (n=44). Clinical characteristics, HCC incidence, overall survival, and HCC-free survival were compared across these groups.

Results: During the follow-up period, HCC developed in 138 (21.3%) of the 648 patients. The prevalence of HCC differed significantly among the groups: 5.5% in the alcohol group, 34.7% in the HBV group, and 43.2% in the combined HBV-alcohol group ($p<0.001$). The 5-year cumulative HCC risk was 7% for the alcohol group, 40% for the HBV group, and 49% for the HBV-alcohol group. Despite these striking differences in HCC incidence, overall survival did not differ significantly among the etiological groups ($p=0.367$). Furthermore, in HBV-positive patients, baseline HBV DNA viral load ($<10^6$ vs. $\geq 10^6$ copies/mL) did not show a statistically significant difference in HCC-free survival ($p=0.408$).

Conclusion: HBV infection, particularly when combined with heavy alcohol use, significantly and synergistically increases the risk of HCC in patients with liver cirrhosis. The exceptionally high cumulative HCC incidence in the combined HBV-alcohol group, with 40% of patients developing HCC within the first year, underscores the critical need for close surveillance in this high-risk subgroup. Despite the differing HCC rates, overall survival remains similar across the groups, reflecting the complex and multifactorial determinants of cirrhosis-related mortality.

Keywords: Liver cirrhosis, hepatocellular carcinoma, hepatitis B virus, alcohol-related cirrhosis, survival analysis, synergistic effect

Introduction

Liver cirrhosis results from chronic inflammation and fibrosis of the liver, arising from numerous etiological factors. It causes 1.31 million deaths worldwide. The primary causes of cirrhosis include chronic viral hepatitis, alcohol, and non-alcoholic steatohepatitis (1,2). Liver damage from chronic viral hepatitis B (HBV) infection, when combined with heavy alcohol consumption, can lead to irreversible liver damage (3-5). Hepatocellular carcinoma (HCC) is the most significant complication of cirrhosis. It is the third leading cause of cancer-related deaths worldwide. Although some HCC cases can develop de novo, the vast majority (80%) develop in the setting of cirrhosis. The frequency of HCC development in the presence of cirrhosis varies according to the etiological cause of cirrhosis (4,6,7). HBV promotes carcinogenesis through integration of the viral genome into hepatocytes, causing chronic inflammation and inducing genetic instability via reactive oxygen species. In contrast, alcohol leads to HCC development by causing DNA damage through acetaldehyde, mitochondrial dysfunction, intestinal microbiota disruption, impairment of hepatic immune defense, and fibrosis secondary to hepatocyte damage (8,9). The co-occurrence of HBV and alcohol can elevate the risk of HCC to very high levels through a synergistic effect (10-12). Although the risk of HCC development, HCC-free survival, and cumulative HCC frequency in alcohol-related and HBV-related cirrhosis have been examined many times in the literature, large-scale studies demonstrating the synergistic effect of their coexistence are still needed. The outcomes of this synergistic effect are important for determining patient follow-up and surveillance intervals. International

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guidelines recommend six-month ultrasonographic follow-ups for all patients with cirrhosis, regardless of etiology. However, there is a need for etiologically individualized follow-up systems (13,14). Since the introduction of antiviral agents for HBV, their contribution to the risk of HCC development remains under active study. Many studies have shown that HBV viral load and high HBV DNA levels increase the population-based risk of HCC development. However, there is a need to demonstrate whether this effect continues at the same rate in a damaged hepatocyte environment, such as cirrhosis (15-17). Therefore, in this retrospective study, we compared the demographic, clinical, and laboratory values of patients with HBV-related cirrhosis, alcohol-related cirrhosis, and cirrhosis with HBV-alcohol co-occurrence. We evaluated overall survival, incidence of HCC development, and differences in HCC-free survival among these groups. Additionally, we examined the relationship between HBV viral load and HCC-free survival in the HBV-positive groups.

Methods

Study Design and Ethical Approval

The study was conducted retrospectively among patients who received inpatient or outpatient treatment at the İzmir Katip Çelebi University Atatürk Training and Research Hospital Gastroenterology Clinic. Ethics committee approval for the study was obtained from Ethics Committee of İzmir Katip Çelebi University Atatürk Training and Research Hospital on April 16, 2015 (decision number: 63). The study was conducted in accordance with the principles of the Declaration of Helsinki. Data were collected using the hospital management system.

Patient Population and Eligibility Criteria

Patients with cirrhosis who were followed up for more than 6 months, both as inpatients and outpatients at the İzmir Katip Celebi University Atatürk Training and Research Hospital Gastroenterology Clinic between July 2007 and April 2014 were included. Patients with HBV-related cirrhosis, alcohol-related cirrhosis, and HBV-alcohol coexposure-related cirrhosis were included in the study. Patients with cirrhosis due to hepatitis C, autoimmune hepatitis, non-alcoholic steatohepatitis, cholestatic liver disease, hereditary disorders related to liver disease, and accompanying additional solid malignancies were excluded from the study. A total of 648 eligible patients were included: alcohol-related cirrhosis (n=310, 47.8%), HBV-related cirrhosis (n=294, 45.4%), and HBV-alcohol-related cirrhosis (n=44, 6.8%).

Definitions and Data Collection

The diagnosis of cirrhosis was made based on clinical, ultrasonographic, computed tomography (CT), and magnetic resonance imaging (MRI) features. For etiopathological classification, serological tests [Hepatitis B surface antigen (HBsAg), HBeAg, anti-HBc, and anti-HBs] and quantitative HBV DNA levels were evaluated. For the diagnosis of alcohol-related cirrhosis, the patient's years of alcohol consumption and daily alcohol intake were evaluated. Patients with a daily alcohol consumption >80 mg were classified as heavy alcohol users. Patients meeting both criteria were included as patients with HBV-related cirrhosis and alcohol-related cirrhosis. Patient age, gender, follow-up period (months), vital status at the last follow-up, dates of death (via the death notification system), HCC development during follow-up, Child-Pugh class, baseline HBV DNA level (copies/mL), and alpha-fetoprotein (AFP, ng/mL) were recorded. The diagnosis of HCC was determined by a nodule larger than 1 cm with a characteristic contrast enhancement pattern (arterial phase hypercontrast and venous phase washout) on contrast-enhanced CT or MRI according to the radiological criteria determined by the European Association for the Study of the Liver. Overall survival (OS) was calculated as the time from the date of diagnosis to death from all causes or, in surviving patients, to the date of last follow-up. HCC-free survival was calculated as the time from the date of diagnosis to HCC diagnosis, time to last follow-up in patients without HCC, or time to date of death in patients who did not receive an HCC diagnosis but died due to non-HCC causes. Patients without an HCC diagnosis at the end of the follow-up period were censored. In HBV-positive patients, the cut-off value separating high and low viral loads was determined to be 10^6 copies/mL.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics (version 27.0; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data and as median (minimum–maximum or interquartile range) for non-normally distributed data. Categorical variables were presented as frequencies and percentages. Normality of continuous variables was assessed using visual methods (histograms and probability plots) and the Kolmogorov-Smirnov and Shapiro-Wilk tests, as appropriate. Comparisons between two independent groups were performed using the Student's t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Comparisons among more than two groups were conducted using one-way analysis of variance or the Kruskal–Wallis test, depending on the data distribution. Categorical variables were compared using the chi-square test or Fisher's exact test, where appropriate. Adjusted residual analysis was additionally used to identify subgroup contributions to significant chi-square results in contingency tables. OS and HCC-free survival were analyzed using the Kaplan–Meier method, and differences between survival curves were evaluated using the log-rank test. Survival times were reported with 95% confidence intervals (CIs). Patients without an event during follow-up were censored at the date of the last clinical evaluation. Cumulative HCC incidence over time was evaluated using life-table analysis according to cirrhosis etiology. HBV viral load categories ($<10^6$ vs. $\geq 10^6$ copies/mL) were compared with respect to HCC-free survival using Kaplan–Meier survival analysis and the log-rank test. All tests were two-tailed, and a p value <0.05 was considered statistically significant.

Results

Baseline Characteristics

The final analysis cohort consisted of 648 patients (Table 1). The cohort was predominantly composed of males (566/648, 87.3%), which reflects the well-known gender bias of both heavy alcohol consumption and HBV-related chronic liver disease. However, gender distribution was significantly non-homogeneous across etiological groups ($p<0.001$): while male gender was nearly universal in the alcohol-related (97.4%)

and HBV-alcohol-related (95.5%) groups, the proportion of female patients was significantly higher in the HBV-related group (24.5%), which is consistent with broader demographic patterns of HBV-related liver disease. In the HBV-related cirrhosis group, the mean baseline age was 61.97±10.84 years, which was significantly higher than that in the alcohol-related cirrhosis (59.44±9.28 years; p=0.006) and HBV-alcohol-related cirrhosis (59.30±8.98 years) groups. Mean follow-up periods in the alcohol-related cirrhosis, HBV-related cirrhosis, and HBV-alcohol-related cirrhosis groups were found to be 39.0, 43.1, and 26.4 months (p=0.106). A significant difference was observed in Child-Pugh classification among the three groups (p=0.001). Patients with alcohol-related cirrhosis were more frequently identified as Child-Pugh A (31.0%), and this rate significantly exceeded the expected frequency (adjusted residual: +4.4), whereas Child-Pugh B was predominant in the HBV group (58.8%; adjusted residual: +2.2). The proportion of Child-Pugh A patients in the HBV group (15.6%) was significantly lower than expected (adjusted residual: -4.2). The distribution of Child-Pugh categories in the HBV-alcohol-related cirrhosis group did not show a significant deviation from the expected values. Neither daily alcohol consumption (alcohol group: median 140 g/day; combined group: 140 g/day; p=0.839) nor serum AFP levels (p=0.769) showed significant differences between the relevant subgroups. Median HBV DNA was generally similar between the HBV and HBV-alcohol-related groups (111.23 vs. 97.78 copies/mL; Mann-Whitney U, p=0.364). The distribution between the two HBV DNA categories ($<10^6$ vs. $\geq 10^6$ copies/mL) also showed no difference between the HBV and HBV-related cirrhosis subgroups (p=0.294).

HCC Incidence

During the follow-up period, HCC developed in 138 out of 648 patients (21.3%). HCC prevalence differed significantly among the etiological groups (chi-square test, p<0.001): 5.5% (n=17) in the alcohol group, 34.7% (n=102) in the HBV group, and 43.2% (n=19) in the HBV-alcohol-related group. These findings confirm that HBV is a strong trigger of hepatocarcinogenesis and that the combined etiology constitutes the highest absolute HCC burden.

Overall Survival Analysis

Kaplan-Meier analysis of OS (Table 2, Figure 1) showed that the mean OS was 76.06 months (95% CI: 70.54–81.58) in the alcohol group, 81.37 months (95% CI: 75.92–86.82) in the HBV group, and 74.54 months (95% CI: 59.81–89.27) in the HBV-alcohol-related group. The overall log-rank test did not reach statistical significance (χ^2: 2.005, df: 2, p=0.367). The absence of a statistically detectable difference in survival between the groups is discussed below.

Table 1. Baseline demographic, clinical and laboratory characteristics according to etiology of cirrhosis

Variable	Alcohol-related (n=310)	HBV-related (n=294)	HBV + alcohol (n=44)	p value
Sex, n (%)				<0.001
Male	302 (97.4%)	222 (75.5%)	42 (95.5%)	
Female	8 (2.6%)	72 (24.5%)	2 (4.5%)	
Age (years), mean ± SD	59.44 ± 9.28	61.97 ± 10.84	59.30 ± 8.98	0.006
Follow-up (months), median (range)*	39.0 (6–114)	43.1 (6–115)	26.4 (7–113)	0.106
Hepatocellular carcinoma, n (%)				<0.001*
Present	17 (5.5%)	102 (34.7%)	19 (43.2%)	
Absent	293 (94.5%)	192 (65.3%)	25 (56.8%)	
Alcohol consumption (g/day), median (range)*	140 (80–300)	NA	140 (80–280)	0.839
Duration of alcohol use (years), median (range)*	25 (15–45)	NA	23 (14–50)	0.003
HBV DNA (copies/mL), median*	NA	111.23	97.78	0.364
AFP (ng/mL), median**	56.25	57.80	64.03	0.769
Child-Pugh class, n (%)***				0.001
Class A	96 (31.0%)	46 (15.6%)	9 (20.5%)	
Class B	152 (49.0%)	173 (58.8%)	25 (56.8%)	
Class C	62 (20.0%)	75 (25.6%)	10 (22.7%)	

*Mann-Whitney U test applied. **Kruskal-Wallis test; n=115 with available AFP data (alcohol n=12, HBV n=87, combined n=16). ***Adjusted residuals used for cell-level post-hoc analysis. Bold p values indicate statistical significance (p<0.05). SD: Standard deviation, HBV: Hepatitis B virus, AFP: Alpha-fetoprotein, NA: Not applicable

Table 2. Kaplan-Meier overall survival estimates by etiology of cirrhosis

Cirrhosis etiology	Total n	Events n	Censored n (%)	Mean survival (months)	p value
Alcohol-related	310	113	197 (63.5%)	76.06 (70.54-81.58)	
HBV-related	294	94	200 (68.0%)	81.37 (75.92-86.82)	
HBV + alcohol	44	15	29 (65.9%)	74.54 (59.81-89.27)	0.367
Overall	648	222	426 (65.7%)	78.41 (74.64-82.18)	

HBV: Hepatitis B virus

HCC- Free Survival Analysis

Kaplan-Meier analysis of HCC-free survival (Table 3, Figure 2) paralleled the OS analysis, and the log-rank test was statistically significant across all three groups (p=0.367). However, the event rates differed significantly: 5.5% of patients in the alcohol group, 34.7% of patients in the HBV group, and 43.2% of patients in the HBV-alcohol-related group experienced HCC events. The markedly higher censoring rate in the alcohol group (94.5%), reflecting both a low HCC rate and longer event-free periods, reduced the statistical power to detect differences within the Kaplan-Meier framework.

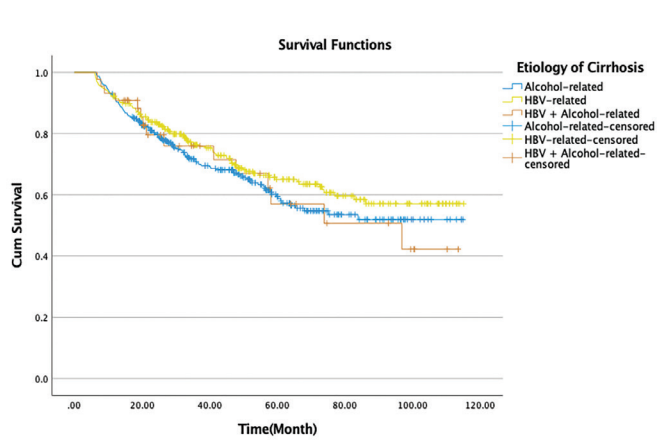

Figure 1. Kaplan-Meier overall survival estimates by etiology of cirrhosis. HBV: Hepatitis B virus

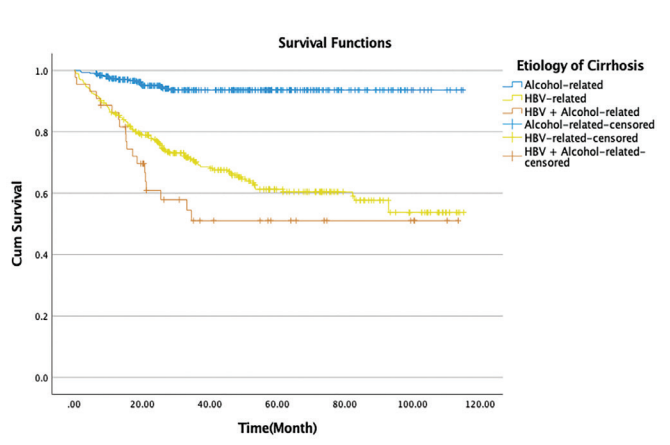

Figure 2. Kaplan-Meier HCC- free survival estimates by etiology of cirrhosis. HCC: Hepatocellular carcinoma, HBV: Hepatitis B virus

Cumulative HCC Incidence by Etiology

Life-table analysis revealed a progressive, etiology-dependent differentiation in cumulative HCC incidence rates (Table 4, Figure 3). In the alcohol group, the cumulative HCC risk was low and essentially plateaued after the first year: 5% at one year, 7% at three years, and 7% at five years. In contrast, a rapid early increase followed by continuous accumulation was observed in patients with HBV-related cirrhosis: 22% at one year, 34% at three years, and 40% at five years. The most prominent early increase in HCC risk was observed in the HBV-alcohol-related group: 40% at one year and 49% at both three and five years; this indicates that nearly half of the patients in this subgroup developed HCC and that most events occurred within the first year of the follow-up period.

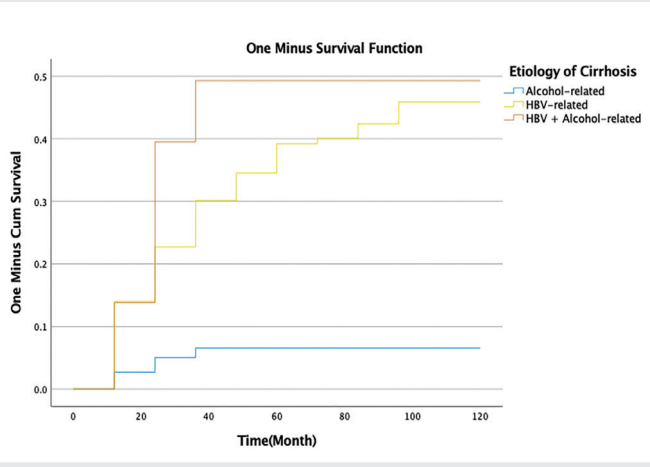

Figure 3. Cumulative HCC incidence by etiology of cirrhosis. HCC: Hepatocellular carcinoma, HBV: Hepatitis B virus

Table 3. Kaplan-Meier HCC- free survival estimates by etiology of cirrhosis

Cirrhosis etiology	n	HCC events n (%)	Censored n (%)	Mean HCC-free survival (months, 95% CI)	p value
Alcohol-related	310	17 (5.5%)	293 (94.5%)	76.06 (70.54–81.58)	
HBV-related	294	102 (34.7%)	192 (65.3%)	81.37 (75.92–86.82)	
HBV + alcohol	44	19 (43.2%)	25 (56.8%)	74.54 (59.81–89.27)	0.367

HCC: Hepatocellular carcinoma, HBV: Hepatitis B virus, CI: Confidence interval

Table 4. Cumulative HCC incidence at 1,3,5 years by etiology of cirrhosis

Etiology	1-year risk (%)	3-year risk (%)	5-year risk (%)
Alcohol-related cirrhosis	5%	7%	7%
HBV-related cirrhosis	22%	34%	40%
HBV + alcohol cirrhosis	40%	49%	49%

Cumulative risk: 1-cumulative survival, derived from life-table (actuarial) analysis at months 12, 36, and 60. HBV: Hepatitis B virus, HCC: Hepatocellular carcinoma

HBV Viral Load and HCC-Free Survival

Of the 221 HBV-positive patients with available DNA quantification data, 97 had HBV DNA $<10^6$ copies/mL and 124 had HBV DNA $\geq 10^6$ copies/mL (Table 5, Figure 4). HCC events occurred at rates of 20.6% and 28.2% in the low- and high-viral-load categories, respectively. Mean HCC-free survival was 89.85±4.66 months (95% CI: 80.70–98.99) in the low viral load group and 84.82±4.09 months (95% CI: 76.80–92.84) in the high viral load group. The log-rank test did not detect a statistically significant difference between the categories (p=0.408).

Discussion

This large, retrospective, single-center cohort study of 648 patients with HBV-, alcohol-, and combined HBV-alcohol-related cirrhosis demonstrates that etiology is a critical determinant of HCC risk; the combined HBV-alcohol group showed the highest cumulative incidence (49% at 5-years), followed by HBV-related (40%) and alcohol-related cirrhosis (7%). These findings are highly consistent with and substantially extend the existing evidence base on etiology-specific HCC risk in cirrhotic populations. The strikingly low HCC incidence in the alcohol-related group (5.5%) compared with the HBV-related (34.7%) and combined (43.2%) groups aligns with published meta-analytic estimates. Huang et al. (18) reported that the annual HCC incidence in alcohol-related cirrhosis is approximately 1.0–1.5% per year (19). In contrast, the corresponding figure for HBV-related cirrhosis ranges from 2.5% to 7.5% per year, depending on the viral replication status, geographic region, and use of antiviral therapy (4). In our HBV group, the observed five-year cumulative HCC incidence was 40%, corresponding to approximately 8% per year, which falls at the upper end of previously reported estimates.

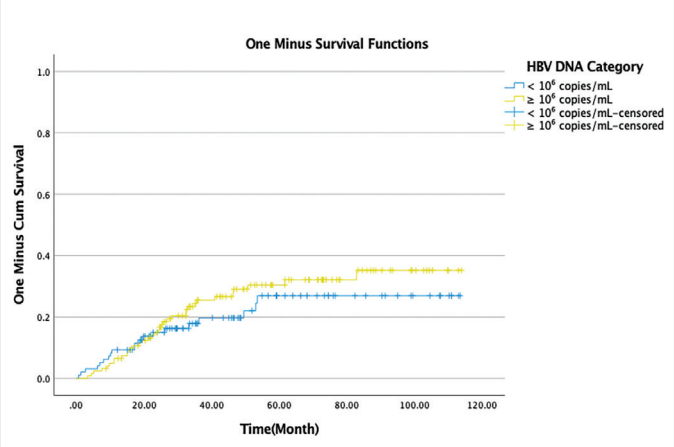

Figure 4. HCC free survival according to HBV DNA category in HBV-positive patients. HCC: Hepatocellular carcinoma, HBV: Hepatitis B virus

This likely reflects the relatively advanced disease stage at baseline in our cohort (predominance of Child-Pugh B), the inclusion of patients from the pre-antiviral era, and the Turkish epidemiological context, where HBV genotypes with high oncogenic potential are prevalent (20). The HBV-alcohol combination not only conferred the highest five-year HCC risk (49%) but also showed the steepest early accumulation; 40% of patients developed HCC within the first year. This finding is consistent with the mechanistic synergy between HBV and alcohol demonstrated in several large-scale studies. Lin et al. (21) showed that heavy alcohol use more than doubled HCC incidence in patients with HBV-related cirrhosis, and Tsai et al. (22) confirmed that the combination of heavy alcohol intake and *ALDH2* gene variants significantly increases HCC risk beyond that attributable to HBV alone. Mechanistically, alcohol accelerates HBV-mediated carcinogenesis by enhancing viral replication through acetaldehyde-induced epigenetic reprogramming, impairing HBV-specific T-cell immunity, increasing oxidative DNA damage, and pro moting fibrosis progression; together, these effects lower the threshold for malignant transformation in hepatocytes already destabilized by viral genome integration (10,16). Despite the marked differences in HCC risk, overall survival did not differ significantly among etiologic groups (log-rank p=0.367). Although it is somewhat unexpected that a four- to eightfold difference in HCC incidence does not translate into a statistically detectable difference in OS, several explanations are plausible. First, overall survival in cirrhosis is shaped by multiple complications: portal hypertensive events (bleeding, spontaneous bacterial peritonitis, hepatorenal syndrome), sepsis, hepatic decompensation, and comorbid conditions; none of these are systematically less severe in the alcohol group, despite its lower HCC risk. Second, the possibility cannot be excluded that antiviral therapy in HBV patients—systematically unrecorded in this dataset—may have improved overall survival in the HBV group while at the same time limiting HCC-related mortality (23,24). Third, the limited sample size of the HBV–alcohol group (n=44) reduces the statistical power to detect between-group differences in overall survival. Taken together, these factors suggest that while etiology strongly shapes HCC risk, its impact does not necessarily translate into discernible differences in OS (25). The lack of a statistically significant association between HBV viral load categories and HCC-free survival (p=0.408) warrants cautious interpretation. Large prospective studies, such as REVEAL, have identified HBV DNA levels as an independent dose–response determinant of HCC in asymptomatic HBsAg carriers (15,16). However, the relationship between HBV DNA and HCC has been established largely in populations without established cirrhosis. In patients with pre-existing cirrhosis, the hepatic microenvironment is already highly permissive to carcinogenesis. HCC may arise independently of current viral replication status, particularly after prolonged periods of persistently high-level viremia that may have occurred prior to the study

Table 5. HCC free survival according to HBV DNA category in HBV-positive patients

HBV DNA category	N	HCC events n (%)	Mean HCC-free survival (months ± SE)	p value
$<10^6$ copies/mL	97	20 (20.6%)	89.85±4.66 (80.70–98.99)	0.408
$\geq 10^6$ copies/mL	124	35 (28.2%)	84.82±4.09 (76.80–92.84)	
Total	221	55 (24.8%)	86.96±3.09 (80.89–93.03)	

Kaplan-Meier analysis with log-rank test. Only patients with available HBV DNA data (n = 221) are included. SE: Standard error, CI: Confidence interval, HCC: Hepatocellular carcinoma, HBV: Hepatitis B virus

entry point (26). In our study, HBV DNA measurement reflected a cross-sectional value at the time of cirrhosis diagnosis. Regression analysis and dynamic monitoring of viral load after treatment could not be evaluated because of the study's retrospective design. Furthermore, HBV DNA data were available for only 221 of 338 HBV-positive patients, introducing potential selection bias that may have attenuated the observed association. Future studies incorporating serial HBV DNA measurem ents and detailed antiviral treatment data will be critical to fully charac terize this relationship in cirrhotic populations (27,28). The observed sex distribution across groups—near-universal male predominance in the alcohol and HBV–alcohol–related groups (97.4% and 95.5%, resp ectively) and a markedly higher proportion of women in the HBV group (24.5%)—is consistent with well-documented epidemiological data on heavy alcohol use disorder and HBV infection. Globally, the male-to-female ratio for alcohol-related cirrhosis ranges from approximately 4:1 to 10:1 (18,19). By contrast, HBV infection affects both sexes without a similarly pronounced imbalance, and in endemic settings, women with HBV-related cirrhosis may constitute a larger proportion of clinical cohorts. The higher mean age observed in the HBV group (61.97 years vs. approximately 59 years in the other groups) likely reflects the prolonged natural course of chronic HBV infection, in which cirrhosis typically develops after decades of subclinical disease. In contrast, liver disease related to heavy alcohol consumption tends to follow a more rapidly progressive course (3,4). The differing distribution of Child–Pugh classes between groups may be explained by earlier detection of alcohol-related cirrhosis at a compensated stage, resulting in a predominance of Child–Pugh A in the alcohol group. In contrast, the characteristically silent nature of HBV infection, with few early clinical symptoms, often leads to diagnosis at a more advanced stage, which likely underlies the predominance of Child–Pugh B in the HBV-related cirrhosis group (25). The extremely high HCC incidence in the HBV–alcohol-related cirrhosis group (40% within one year), irrespective of hepatic reserve, suggests that this subgroup requires imaging surveillance at intervals shorter than six months. International guidelines currently recommend ultrasonography surveillance every six months for all patients with c irrhosis; however, the dramatic early HCC burden in the combined group suggests that contrast-enhanced cross-sectional imaging (CT or MRI) ma y be necessary as the primary surveillance modality for these high-risk individuals (13,14). The lower five-year HCC risk in the alcohol-related cirrhosis group (7%) indicates that, even in the setting of established cirrhosis, alcohol abstinence may confer meaningful protection against HCC and underscores the importance of alcohol use disorder interventions as an integral component of cirrhosis management. The substantial HCC risk observed even in the low viral load group indicates that HBV-infected patients with cirrhosis should receive treatment with nucleos(t)ide analogs irrespective of the viral load.

Study Limitations

This study has several limitations. Its retrospective, single-center design limits generalizability and introduces risks of selection and information bias. Patients with missing baseline data were excluded, which may have shifted the analytic sample toward individuals with more complete medical records. HBV DNA measurement was cross-sectional rather than serial, and antiviral treatment data were not systematically captured; both factors constrain the interpretation of the viral load analysis. Alcohol use was assessed based on patient history and chart review rather than objective biomarkers (e.g., phosphatidylethanol). Moreover, assessment of additional comorbid factors such as body mass index, metabolic syndrome, and other coexisting conditions was incomplete due to the retrospective design.

Conclusion

This retrospective study demonstrates that HBV infection, particularly when combined with heavy alcohol use, significantly increases HCC risk in patients with liver cirrhosis. The HBV-alcohol combination group exhibited the highest five-year cumulative HCC incidence (49%), with 40% of patients developing HCC within the first year, underscoring the importance of close surveillance in this subgroup. Despite differing HCC rates, overall survival did not differ significantly among etiologic groups, reflecting the complex, multifactorial determinants of cirrhosis-related mortality. HBV viral load did not independently predict HCC-free survival in this cirrhotic cohort, a finding that warrants further investigation in prospective studies incorporating serial viral load assessments and comprehensive antiviral treatment data. These results support etiology-specific, risk-stratified approaches to HCC surveillance and highlight the critical importance of effective antiviral therapy for HBV-positive cirrhotic patients and of alcohol cessation counseling for all patients with alcohol-related or alcohol-concomitant liver disease.

Ethics

Ethics Committee Approval: Ethics committee approval for the study was obtained from Ethics Committee of İzmir Katip Çelebi University Atatürk Training and Research Hospital on April 16, 2015 (decision number: 63).

Informed Consent: Data were collected using the hospital management system.

Footnotes

Authorship Contributions: Surgical and Medical Practices - S.V.; Concept - S.V.; Design - T.A.C., S.V.; Data Collection or Processing - T.A.C.; Analysis or Interpretation - T.A.C., S.V.; Literature Search - T.A.C.; Writing - T.A.C.

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References

1. Juanola A, Pose E, Ginès P. Liver cirrhosis: ancient disease, new challenge. Med Clin (Barc). 2025; 164: 238-46.
2. Manthey J, Shield KD, Rylett M, Hasan OSM, Probst C, Rehm J. Global alcohol exposure between 1990 and 2017 and forecasts until 2030: a modelling study. Lancet. 2019; 393: 2493-502.
3. GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol. 2020; 5: 245-66.

4. Sankar K, Gong J, Osipov A, Miles SA, Kosari K, Nissen NN, et al. Recent advances in the management of hepatocellular carcinoma. Clin Mol Hepatol. 2024; 30: 1-15.
5. Seitz HK, Bataller R, Cortez-Pinto H, Gao B, Gual A, Lackner C, et al. Alcoholic liver disease. Nat Rev Dis Primers. 2018; 4: 16.
6. Mancebo A, González-Diéguez ML, Cadahía V, Varela M, Pérez R, Navascués CA, et al. Annual incidence of hepatocellular carcinoma among patients with alcoholic cirrhosis and identification of risk groups. Clin Gastroenterol Hepatol. 2013; 11: 95-101.
7. Jee SH, Ohrr H, Sull JW, Samet JM. Cigarette smoking, alcohol drinking, hepatitis B, and risk for hepatocellular carcinoma in Korea. J Natl Cancer Inst. 2004; 96: 1851-6.
8. Mackowiak B, Fu Y, Maccioni L, Gao B. Alcohol-associated liver disease. J Clin Invest. 2024; 134: e176345.
9. Rehm J, Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. J Hepatol. 2013; 59: 160-8.
10. Poorolajal J, Shadi Y, Heshmati B. Interaction between hepatitis B, hepatitis C and alcohol in the development of hepatocellular carcinoma: a systematic review and meta-analysis. J Viral Hepat. 2025; 31: e14042.
11. Ganesan M, Eikenberry A, Poluektova LY, Kharbanda KK, Osna NA. Role of alcohol in pathogenesis of hepatitis B virus infection. World J Gastroenterol. 2020; 26: 883-903.
12. Kulik L, El-Serag HB. Epidemiology and management of hepatocellular carcinoma. Gastroenterology. 2019; 156: 477-91.
13. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatocellular carcinoma. J Hepatol. 2025; 82: 315-74.
14. Hwang SY, Danpanichkul P, Agopian V, Mehta N, Parikh ND, Abou-Alfa GK, et al. Hepatocellular carcinoma: updates on epidemiology, surveillance, diagnosis and treatment. Clin Mol Hepatol. 2025; 31: S228-54.
15. Harputluoglu M, Carr BI. Hepatitis B before and after hepatocellular carcinoma. J Gastrointest Cancer. 2021; 52: 1206-10.
16. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology. 2012; 142: 1264-73.
17. Lyu X, Liu K, Chen Y, Wang Z, Yao J, Cai G, et al. Analysis of risk factors associated with the development of hepatocellular carcinoma in chronic HBV-infected Chinese: a meta-analysis. Int J Environ Res Public Health. 2016; 13: 604.
18. Huang DQ, Terrault NA, Tacke F, Gluud LL, Arrese M, Bugianesi E, et al. Global epidemiology of cirrhosis - aetiology, trends and predictions. Nat Rev Gastroenterol Hepatol. 2023; 20: 388-98.
19. Huang DQ, Mathurin P, Cortez-Pinto H, Loomba R. Global epidemiology of alcohol-associated cirrhosis and HCC: trends, projections and risk factors. Nat Rev Gastroenterol Hepatol. 2023; 20: 37-49.
20. Abassa KK, Wu XY, Xiao XP, Zhou HX, Guo YW, Wu B. Effect of alcohol on clinical complications of hepatitis virus-induced liver cirrhosis: a consecutive ten-year study. BMC Gastroenterol. 2022; 22: 140.
21. Lin CW, Lin CC, Mo LR, Chang CY, Perng DS, Hsu CC, et al. Heavy alcohol consumption increases the incidence of hepatocellular carcinoma in hepatitis B virus-related cirrhosis. J Hepatol. 2013; 58: 730-5.
22. Tsai MC, Yang SS, Lin CC, Wang WL, Hsu YC, Chen YS, et al. Association of Heavy Alcohol Intake and ALDH2 rs671 Polymorphism with hepatocellular carcinoma and mortality in patients with hepatitis B virus-related cirrhosis. JAMA Netw Open. 2022; 5: 2223511.
23. Sung JJY, Tsoi KKF, Wong VWS, Li KCT, Chan HLY. Meta-analysis: treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. Aliment Pharmacol Ther. 2008; 28: 1067-77.
24. Wong GL, Chan HL, Mak CW, Lee SK, Ip ZM, Lam AT, et al. Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients with liver cirrhosis. Hepatology. 2013; 58: 1537-47.
25. Morgan TR, Mandayam S, Jamal MM. Alcohol and hepatocellular carcinoma. Gastroenterology. 2004; 127: 87-96.
26. Ioannou GN, Green P, Kerr KF, Berry K. Models estimating risk of hepatocellular carcinoma in patients with alcohol or NAFLD-related cirrhosis for risk stratification. J Hepatol. 2019; 71: 523-33.
27. Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Risk for hepatocellular carcinoma in patients with alcoholic cirrhosis: a Danish nationwide cohort study. Ann Intern Med. 2012; 156: 841-7.
28. Huang DQ, Tan DJH, Ng CH, Amangurbanova M, Sutter N, Lin Tay PW, et al. Hepatocellular carcinoma incidence in alcohol-associated cirrhosis: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2023; 21: 1169-77.