

Original Article

Alcohol consumption on liver function and its prognostic value in male patients with hepatocellular carcinoma: a retrospective cohort study

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Abstract: Background and Objective: Alcohol consumption has been proposed to be a main risk factor for hepatocellular carcinoma (HCC), especially in males. We aimed to investigate the effects of alcohol consumption on liver function in patients with HCC. We also explored the prognostic value of alcohol use in HCC. Methods: The medical records on 479 male HCC patients who underwent radical therapy between 2002 and 2012 were retrospectively reviewed. Kaplan-Meier curve, log-rank test, and Cox regression analysis were used to compare the overall survival (OS) and disease-free survival (DFS) between drinkers and non-drinkers. Results: A total of 138 patients had a habit of alcohol use. Compared with non-drinkers, drinkers tended to have a high prevalence of cirrhosis ($P = 0.004$), an elevated level of alanine aminotransferase (ALT) ($P = 0.007$) and γ -glutamyltranspeptidase (GGT) ($P < 0.001$). A potential dose response relationship was also indicated between alcohol consumption and levels of liver enzymes. When stratified according to etiology, log-rank test identified drinking as a significant factor for predicting poor OS as well as DFS in non-hepatitis B non-hepatitis C (NBNC) related HCC (both $P < 0.05$) but not in hepatitis B or C virus induced HCC (both $P > 0.05$). In addition, alcohol consumption was more likely to affect survival in the subgroups of patients with younger age, presence of cirrhosis, higher level of AFP, larger tumor diameter, and single neoplasm. Multivariate analysis showed that drinking, tumor size, and TNM stage were the three independent predictors for OS and DFS in NBNC-related HCC patients. Conclusions: Alcohol consumption significantly elevated the levels of liver enzymes, increased the risk of cirrhosis, and reduced the survival time in male HCC patients, especially in those without infection of hepatitis virus.

Keywords: Alcohol, hepatocellular carcinoma, survival, aspartate aminotransferase, γ -glutamyltranspeptidase

Introduction

Worldwide, hepatocellular carcinoma (HCC) is the fifth most common neoplasm with a poor prognosis and a rapidly increasing incidence [1]. Hepatic cirrhosis followed by infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) has been identified as a crucial etiology for HCC. Other established risk factors include obesity, excessive alcohol use, diabetes, cigarette smoking, aflatoxin exposure, and so forth [2]. It's worth noting that, due to the promotion of antiviral therapy, the population of hepatitis virus induced HCC has decreased over the past decade. However, recently, the proportion of non-hepatitis B non-hepatitis C (NBNC) related HCC is rising [3]. Moreover, the majority of

patients diagnosed with NBNC-related HCC are accompanied by alcoholic liver disease or non-alcoholic fatty liver disease.

In alcoholics, prolonged or excessive alcohol intake results in severe histological injury, rapid disease progression, and a high frequency of cirrhosis. Moreover, alcohol has been considered as a hepatic carcinogen in humans since 1988 [4]. A meta-analysis with 112 publications further confirms that excessive alcohol consumption significantly increases the risk of HCC, especially in individuals without infection of hepatitis virus [5]. Recently, excessive drinking has been indicated to be an independent determinant for poor postoperative survival in NBNC-HCC patients [6, 7].

Alcohol consumption and outcomes in HCC

Previous research also showed that alcohol use significantly elevated the levels of liver enzymes in the general population [8] and in individuals with hepatitis C [9]. However, to date, few studies have investigated the effects of alcohol consumption on liver function among HCC patients. In this study, we aimed to elucidate the associations between alcohol consumption and serum levels of liver enzymes as well as other clinical characteristics in HCC. In addition, we investigated the prognostic value of alcohol consumption in HCC patients stratified according to etiology.

Materials and methods

Study population

This study presented the analysis of HCC patients that were treated by either partial hepatectomy or radiofrequency ablation (RFA) between December 2002 and July 2012 in the First Affiliated Hospital of Medical College, Xi'an Jiaotong University. The information of the history and amount of alcohol consumption was extracted from electronic medical records. Patients who had no history of alcohol use based on the electronic medical records were defined as non-drinkers. Individuals who had incomplete information of alcohol intake, female patients, patients with previous treatment for HCC, with intrahepatic cholangio carcinoma or extrahepatic spread were all excluded. Finally, 479 patients were involved in the current study. Our research was in compliance with the Declaration of Helsinki [10] and the protocol was approved by the Ethics Committee of the institute. The STROBE statement was used to report this study.

Data collection

We used the electronic medical records to collect information including gender, age, etiology, information of alcohol consumption and cigarette smoking, status of cirrhosis, preoperative laboratory examinations (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ -glutamyltranspeptidase (GGT), and alpha-fetoprotein (AFP), tumor characteristics (number and diameter of the largest lesion), method of treatment, and pathologic results.

HCC diagnosis, treatment and follow-up

HCC and cirrhosis were firstly assessed by computed tomography (CT), magnetic resonance

imaging (MRI), abdominal ultrasound, and serologic results. For patients who underwent liver resection, HCC and cirrhosis were further confirmed by pathological examination of resected tissues.

Once discharge from wards, patients were regularly followed at outpatient clinics. The follow-up items included CT/MRI, ultrasound, and serologic tests. The same examinations were performed every 3 months for the first year, every 4 months for the second year, and every 6 months thereafter. Recurrent patients received salvage methods, including reoperation, percutaneous ablation, or transcatheter arterial chemoembolization, as appropriate.

Statistical analysis

All the statistical analyses were performed by using PASW version 18.0 software (SPSS Inc, Chicago, IL, USA). Continuous variables with normal distribution (Kolmogorov-Smirnov test, $P > 0.05$) were expressed as mean \pm standard deviation (SD), and otherwise, median (range) was adopted. Comparisons between subgroups were performed using *t* test or Wilcoxon test for continuous variables and χ^2 test for categorical data. The area under the receiver operating characteristic (ROC) curve was used for judging the discrimination ability of alcohol consumption in predicting the presence of cirrhosis.

The primary outcomes we observed included overall survival (OS) and disease-free survival (DFS), which were analyzed by the Kaplan-Meier method. Differences in survival were assessed by the log-rank test. To investigate the significance of drinking in various subgroups, additional survival analyses were performed after patients were stratified based on etiology, age, cirrhosis status, tumor characteristics, and treatment methods. In addition, all variables that were found to be significant in univariate analysis ($P < 0.05$) entered into a multivariate Cox regression analysis. A *P* value less than 0.05 was considered to be statistically significant.

Results

Patient characteristics

In total, our study population consisted of 479 patients, with the mean age of 52.4 ± 12.1 years. Amongst, 138 had a habit of alcohol use and 220 were smokers. 74.3% (356/479)

Alcohol consumption and outcomes in HCC

Table 1. Basic characteristics of HCC patients stratified according to the status of alcohol use

Variables	Total (n = 479)	Non-drinker (n = 341)	Drinker (n = 138)	p
Resection/RFA	331/148	230/111	101/37	0.218 ^a
Smoking/no	220/259	100/241	120/18	< 0.001 ^a
Age (yr)	53 (6-82)	53 (6-80)	50 (19-82)	0.214 ^b
HBV+HCV/NBNC	356/123	247/94	109/29	0.137
Cirrhosis/no	148/198	86/144	62/54	0.004 ^a
ALT (U/L)	45 (5-1519)	45 (5-1519)	54 (11-1436)	0.007 ^b
AST (U/L)	46 (14-1493)	45 (15-1442)	53 (14-1493)	0.059 ^b
ALP (U/L)	104 (4-1536)	103 (13-671)	111 (4-1536)	0.113 ^b
GGT (U/L)	75 (3-1830)	72 (3-1542)	111 (21-1830)	< 0.001 ^b
Platelets (10 ⁹ /L)	115 (13-729)	117 (13-729)	120 (17-430)	0.851 ^b
AFP ≥ 200/< 200 (ng/ml)	184/226	126/164	58/62	0.366 ^a
Tumor size ≥ 5/< 5 (cm)	246/193	167/144	79/49	0.124 ^a
Multiple/single	56/391	36/280	20/111	0.260 ^a
Child A/B+C	415/47	293/33	122/14	0.415 ^a
TNM I, II/III, IV	290/79	209/49	81/30	0.084 ^a
Drinking quantity (0/0-40/≥ 40 g/d)	341/79/59	341/0/0	0/79/59	< 0.001 ^a

Note: ^aχ² test; ^bWilcoxon test. The values are expressed as the median (range) or number. RFA: radiofrequency ablation; HBV: hepatitis B viral; HCV: hepatitis C viral; NBNC: non-hepatitis B non-hepatitis C; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: γ-glutamyltranspeptidase; AFP: alpha-fetoprotein.

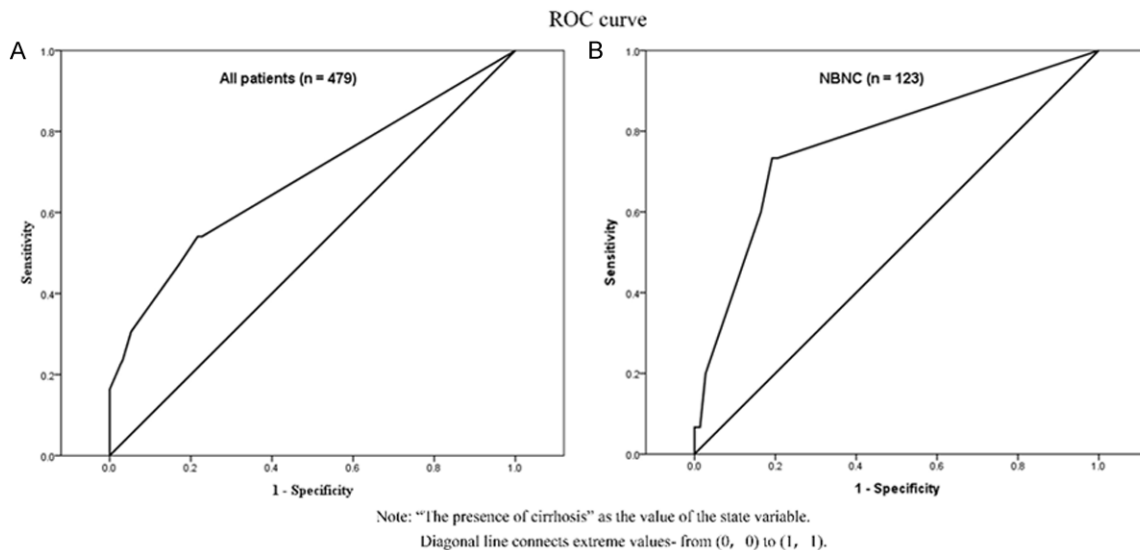


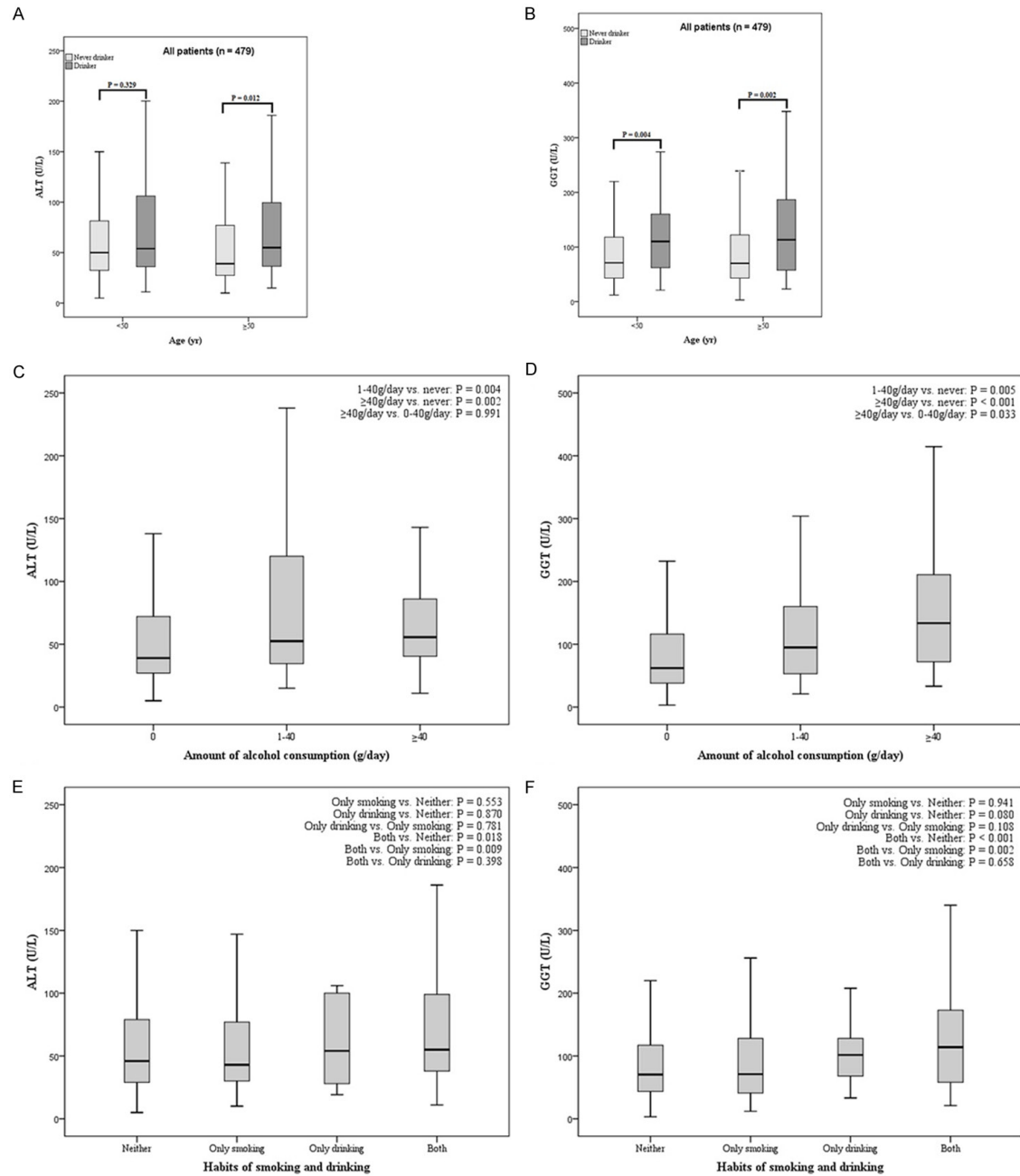
Figure 1. Diagnostic performance of alcohol use in detecting the presence of cirrhosis in all HCC patients (A) and in NBNC-related HCC patients (B).

patients had the infection of HBV or HCV and others were NBNC related HCC. During hospitalization, 331 patients received partial hepatectomy and 148 underwent RFA. Ultimately, 260 patients had a complete follow-up data. During a median follow-up time of 45 months, 51.5% (134/260) of patients died and 43.8% (114/260) experienced HCC recurrence.

The associations between alcohol consumption and cirrhosis

Demographic data, serologic tests, and tumor characteristics of the 479 patients stratified by the habit of alcohol consumption are summarized in **Table 1**. Previous study showed that drinking significantly increased the incident risk

Alcohol consumption and outcomes in HCC



Alcohol consumption and outcomes in HCC

Figure 2. Boxplots comparing alcohol use with liver enzymes. Boxplots comparing alcohol use with preoperative serum levels of ALT (A) and GGT (B) in HCC patients stratified according to age, reflecting the dose-response relationships between alcohol use and ALT (C) and GGT (D), and comparing the effects of cigarette smoking and alcohol use in ALT (E) and GGT (F).

of cirrhosis. Consistently, we found that the probability of cirrhosis was much greater in drinkers than that in non-drinkers in HCC patients (53.4% vs. 37.4%, $P = 0.004$). Furthermore, the area under the ROC curve of alcohol consumption was 0.682 (95% CI: 0.613-0.751, $P < 0.001$) for predicting the presence of cirrhosis (**Figure 1A**). When stratified according to etiology, the area under the ROC curve in the NBNC-HCC group was significantly higher (**Figure 1B**, 0.772 95% CI: 0.632-0.916, $P = 0.001$) than that in the virus infection group (0.662 95% CI: 0.582-0.741, $P < 0.001$).

The associations between alcohol consumption and liver enzymes

Previous research indicated an elevated level of liver enzymes in drinkers in individuals with chronic hepatitis. In our current study, levels of ALT and GGT were both found to be significantly different between drinkers and non-drinkers in HCC patients ($P = 0.007$ and < 0.001 , respectively). **Figure 2A, 2B** were the box plots that further compared the levels of ALT and GGT between the two groups stratified according to age. Obviously, alcohol consumption was significantly related to an elevated level of GGT, independent of age. We also showed that alcohol consumption significantly increased ALT level in elder but not in young patients.

Furthermore, potential dose response relationships between drinking and liver enzymes, especially GGT, were identified (**Figure 2C, 2D**). Specifically, patients with preoperative intake of alcohol more than 40 g per day had a more severe liver injury compared with control group.

Cigarette smoking and alcohol consumption were the two most common unhealthy lifestyles that often coexist. We recently indicated that smoking was significantly associated with poor liver function in HCC [11]. Thus, smoking might be a confounding factor that influence the role of drinking. To eliminate this influence, patients were divided into four groups: neither smoking nor drinking, only smoking, only drinking, and both smoking and drinking. The results showed that patients with the habit of drinking alone, but not smoking alone, had significantly elevated ALT as well as increased GGT compared with individuals without the two habits (**Figure 2E,**

2F). It's indicated that the true unhealthy habit that deteriorates liver function might be alcohol consumption but not cigarette smoking.

The effects of alcohol consumption in the prognosis of HCC

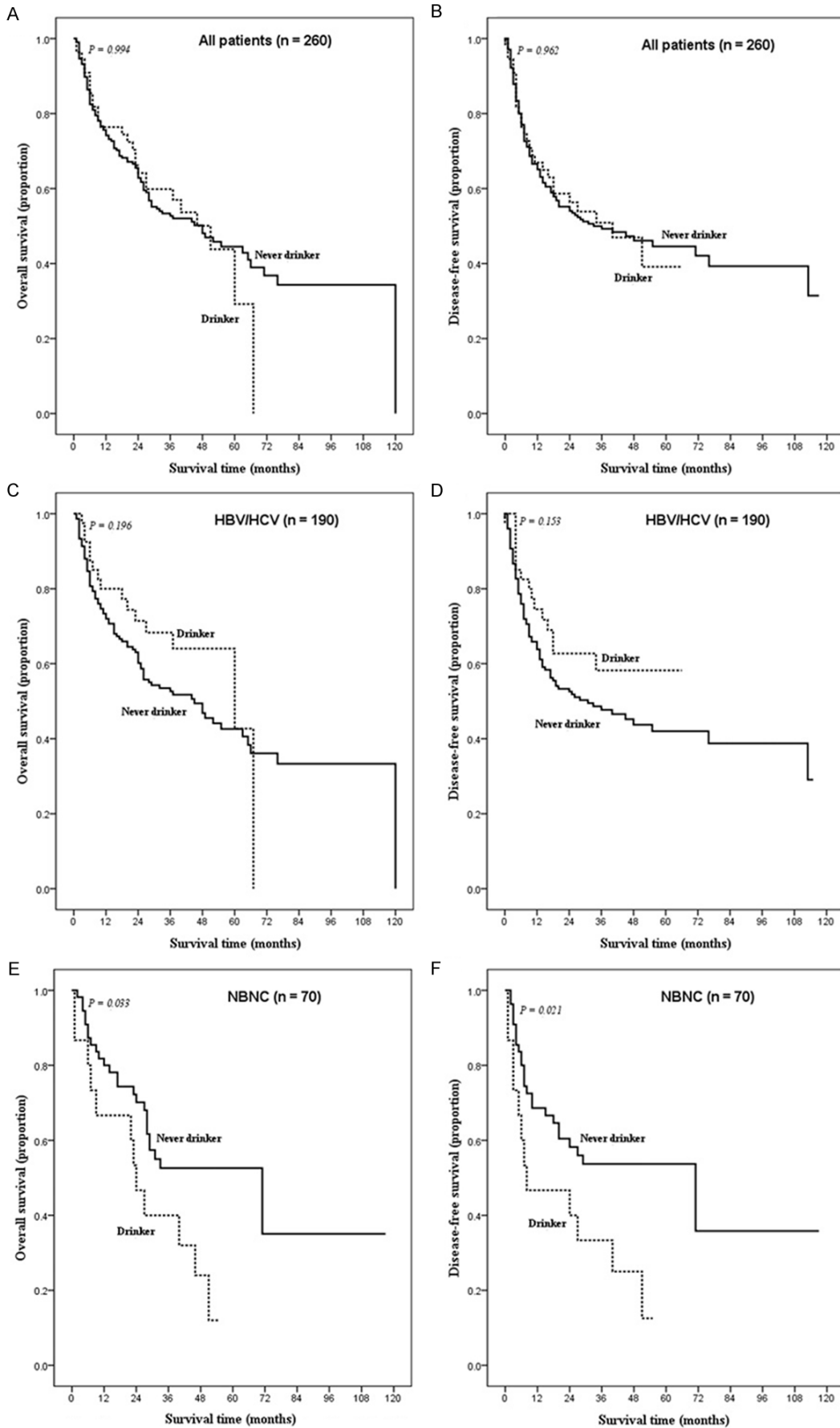
The clinical characteristics of the 260 HCC patients, who had a complete follow-up data, were shown in Supplementary Table 1. Compared with non-drinkers, drinkers had a higher probability of smoking and a higher level of ALT. There were no significant differences in other clinical characteristics between drinkers and non-drinkers.

As shown in **Figure 3A, 3B**, when all included patients were analyzed, alcohol use seemingly showed no significant effects on OS and DFS (both $P > 0.05$). In similar, in HCC patients with infection of HBV or HCV, no statistically significant association was found between drinking and prognosis (**Figure 3C, 3D**, both $P > 0.05$). However, drinking was demonstrated to be significantly related to poor OS as well as DFS in the patients with NBNC related HCC (**Figure 3E, 3F**, both $P < 0.05$). More specifically, the 1-year, 3-year and 5-year OS rates were 81.6%, 49.6% and 49.6% vs. 61.5%, 38.5% and 19.2% for non-drinkers and drinkers, respectively, in NBNC-HCC patients.

As mentioned above, intake of alcohol ≥ 40 g/d caused a more severe hepatic injury. In order to investigate the effect of heavier alcohol consumption on HCC prognosis, we further excluded the patients with alcohol consumption < 40 g/d. We found that patients with alcohol ≥ 40 g/d had a significant worse OS and DFS compared with non-drinkers (**Figure 3G, 3H**, both $P < 0.05$).

Finally, we investigated the prognostic influence of alcohol consumption in various subgroups of NBNC-HCC patients. The covariates we analyzed included age, therapeutic methods, status of cirrhosis, level of AFP, tumor size and number. The results demonstrated that alcohol use might be more likely to affect survival in the subgroups of younger age, liver

Alcohol consumption and outcomes in HCC



Alcohol consumption and outcomes in HCC

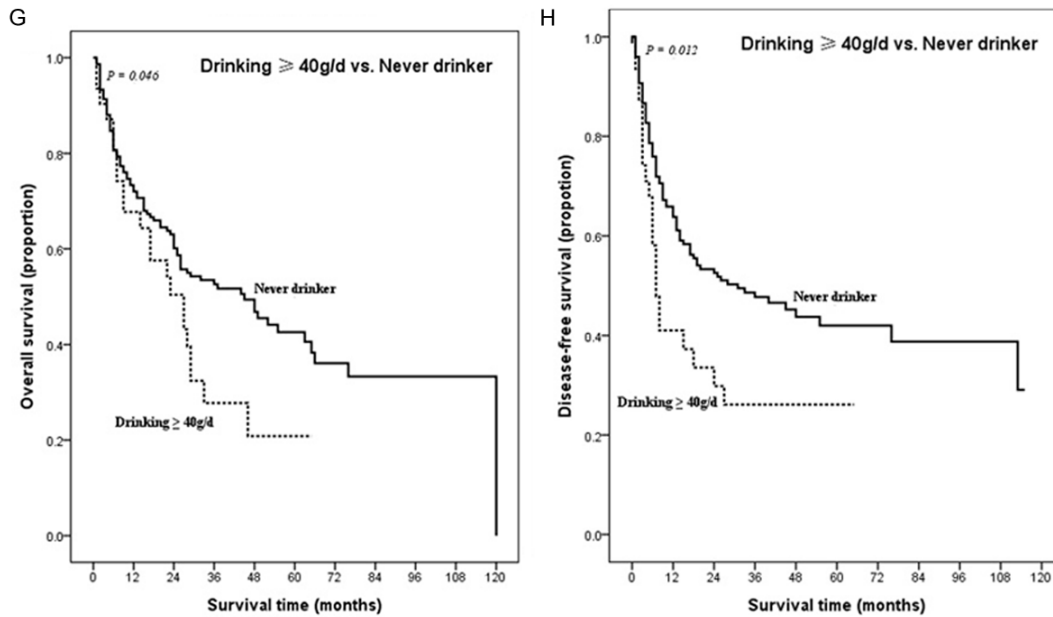


Figure 3. Kaplan-Meier cumulative overall survival (A) and disease-free survival (B) curves of the entire cohort, overall survival (C) and disease-free survival (D) curves of patients with infection of HBV or HCV, and overall survival (E) and disease-free survival (F) curves of NBNC related HCC patients, and overall survival (G) and disease-free survival (H) curves of the cohort that excluded patients with alcohol consumption 1-40 g/d, stratified according to the status of alcohol use.

resection, cirrhosis, AFP \geq 200 ng/ml, tumor size \geq 5 cm, and single lesion (**Figure 4A, 4B**).

Predictors of OS and DFS by Cox regression

Univariate analysis revealed that drinking, AFP, tumor size, tumor number, and TNM stage were significantly associated with OS and DFS (**Table 2**).

Furthermore, multivariate analysis was performed and the results showed that drinking, tumor size, and TNM stage were the three independent predictors for OS as well as DFS (**Table 2**).

Discussion

On the whole, deaths from hepatic diseases are responsible for 70% of directly recorded mortality related to alcohol use [12]. To date, HCC remains the most horrible liver disease that threatens public health, and the incidence of this malignancy is rising year by year. Infection with certain hepatitis virus especially HBV or HCV and obesity have been recognized as main risk factors for HCC [13]. In addition, there were numerous literatures that reported the important associations between several

unhealthy lifestyle habits, cigarette smoking and alcohol use in particular, and the formation of HCC. Recently, drinking has been identified as an indisputable hazard factor of carcinogenesis in several sites of human body, including liver [14]. A large prospective cohort study conducted in eight European countries showed that, among men and women, 33% and 18% of the total HCC were caused by alcohol intake alone respectively [15]. However, it's worth noting that, the initiation and progression of HCC often result from the interaction between different carcinogenic agents [5]. The joint effects of alcohol consumption and other risk factors, such as viral hepatitis, diabetes, smoking, obesity, and aflatoxin exposure, have also been clearly verified [5, 16].

The population of alcohol use is increasing rapidly in many countries, such as China. According to the data from national surveys in China, between 2002 and 2007, alcohol use doubled for males (from 39.6% to 84.1%) and increased more than 6 times for females (from 4.5% to 29.3%). Generally, the normal quantity of alcohol use is less than 40 g per day for males and less than 20 g per day for females. Cirrhosis is considered as an intermediate disease that links several risk factors with HCC [17-21] and a

Alcohol consumption and outcomes in HCC

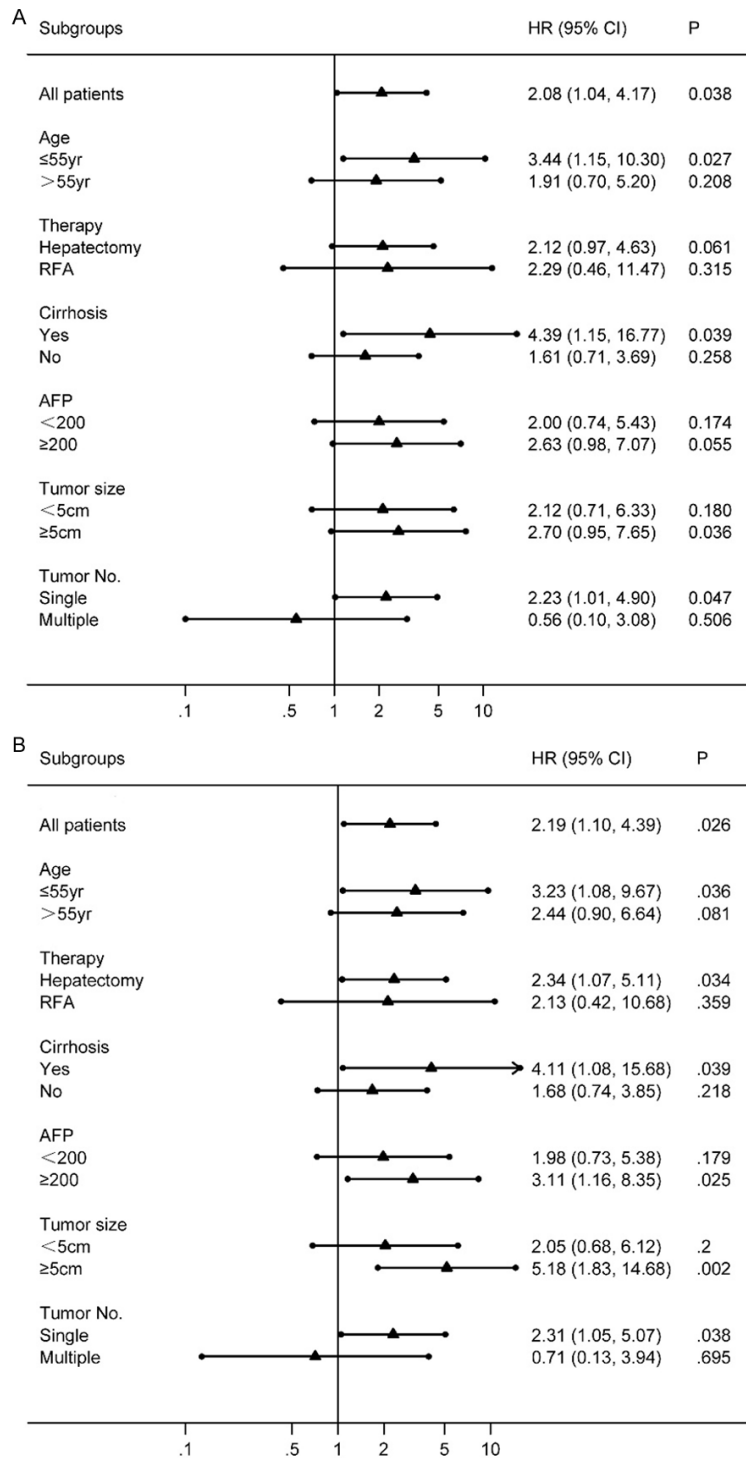


Figure 4. The effects of alcohol on overall survival (A) and disease-free survival (B) in NBNC related HCC patients, stratified according to age, therapeutic methods, status of cirrhosis, level of AFP, tumor size and number.

determinant that affects the prognosis of HCC whatever the underlying etiology [22]. Excessive, long-term alcohol consumption leads to alcoholic hepatitis and significantly increases

the risk of hepatic cirrhosis or HCC. According to previous study, 10% of HCC patients are caused by alcohol induced cirrhosis, and the proportion is almost identical to that of HCV infection [23]. In the current study, we firstly found that alcohol use was related to an increased risk of cirrhosis in HCC patients, especially in those without infection of hepatitis virus.

Previous data indicated that alcohol consumption elevated the serum levels of liver enzymes in individuals with hepatitis C [9]. Our current study further highlighted that alcohol consumption could increase the levels of ALT and GGT in HCC patients, independent of smoking. In addition, a recent study showed that alcohol consumption had a deleterious effect on HCC survival, especially in hepatitis virus carriers [24]. In our study, a statistically significant association between alcohol consumption and survival was identified only in NBNC-related but not in HBV or HCV-induced HCC. Moreover, the detriments of modest and heavy alcohol consumption may be different in HCC. Kudo et al showed that only severe alcoholic liver disease increased the risk of recurrence after hepatectomy in NBNC-derived HCC patients [7]. We found that patients with alcohol ≥ 40 g/d had a significant poorer prognosis compared with non-drinker.

At present, the exact mechanisms behind alcohol's effect on HCC formation and outcome are manifold and complicated. In addition to the indirect role of alcohol-induced cirrhosis and the synergistic effects with other risk factors, the carcinogenicity of acetal-

Alcohol consumption and outcomes in HCC

Table 2. Univariate and multivariate analyses of factors associated with overall survival and disease-free survival of NBNC related HCC patients

Variables	OS		DFS	
	HR	P	HR	P
Univariate analyses				
Resection/RFA	1.42 (0.67-2.99)	0.358	1.28 (0.60-2.72)	0.529
Smoking/no	1.06 (0.50-2.28)	0.875	0.82 (0.39-1.76)	0.617
Drinking/no	2.08 (1.04-4.17)	0.038	2.19 (1.10-4.39)	0.026
Age (> 55/≤ 55 ys)	1.24 (0.57-2.71)	0.582	1.28 (0.57-2.84)	0.550
Cirrhosis/no	1.29 (0.56-2.98)	0.556	1.31 (0.56-3.07)	0.536
ALT (≥ 80/< 80 U/L)	0.90 (0.42-1.92)	0.783	1.12 (0.51-2.45)	0.733
AST (≥ 80/< 80 U/L)	1.11 (0.52-2.38)	0.558	1.27 (0.51-3.16)	0.602
Platelets (≤ 100/> 100×10 ⁹ /L)	0.76 (0.35-1.66)	0.495	0.68 (0.31-1.52)	0.348
AFP (≥ 200/< 200 ng/ml)	2.47 (1.15-5.29)	0.020	2.62 (1.21-5.67)	0.014
Tumor size (≥ 5/< 5 cm)	2.68 (1.25-5.76)	0.011	2.91 (1.33-6.37)	0.008
Multiple/single	3.31 (1.38-7.94)	0.007	3.08 (1.29-7.34)	0.011
Child B+C/A	2.07 (0.77-5.58)	0.149	2.20 (0.76-6.38)	0.147
TNM III, IV/I, II	4.01 (1.73-9.31)	0.001	4.12 (1.82-9.32)	0.001
Multivariate analyses				
Drinking/no	2.28 (1.07-4.85)	0.033	2.64 (1.22-5.72)	0.014
AFP (≥ 200/< 200 ng/ml)	2.11 (0.89-5.03)	0.091	2.92 (0.92-9.30)	0.070
Tumor size (≥ 5/< 5 cm)	2.89 (1.12-7.44)	0.028	2.74 (1.06-7.08)	0.037
Multiple/single	2.50 (0.78-7.98)	0.294	1.89 (0.70-5.12)	0.212
TNM III, IV/I, II	3.29 (1.27-8.53)	0.015	3.13 (1.20-8.16)	0.020

OS: overall survival; DFS: disease-free survival; RFA: radiofrequency ablation; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AFP: alphafetoprotein.

dehyde and several potential biologic materials have also been proposed to be implicated in alcohol-related hepato carcinogenesis [25]. Amongst, a crucial mechanism is an increased release of oxidative stress, which is mainly derived from alcohol metabolism and inflammation in liver tissue [26]. Additionally, alcohol increases the production of cytochrome P-450 2E1, which ultimately accelerates the formation of lipid peroxides, impairs the antioxidant defense system, and decreases hepatic retinoic acid. In addition, chronic alcohol exposure and acetaldehyde could lead to direct DNA damage, alter gene expression, and promote tumor formation [26].

There are several noted limitations in our current study. First, it belonged to a small, single-center retrospective cohort study. The information of the history and amount of alcohol use and other variables was all obtained from electronic medical records, which might be inaccurate. In addition, as the study quality could not be effectively controlled, retrospective study may inevitably lead to confounding and bias. In

addition to smoking, there might be other confounding factors that influence liver function, such as other unhealthy life habits, obesity, diabetes, etc. However, these information can not be obtained and thus several potential confounding factors could not be controlled. Therefore, our finding should be validated by prospective cohort study. Second, therapeutic method is an important factor that affects HCC outcome. However, we included HCC patients both with curative resection and with RFA to obtain more individuals. Third, as the incidence of HCC and the use of alcohol are mostly males in China, we just analyzed the effects of alcohol use in men. Thus, the associations between alcohol use and liver function as well as survival in female HCC patients need to be further investigated. Lastly, the impact of white wine, red wine, and beer might be different [27], and a further research that subdivides wine is required.

Despite the above limitations, our study had several significant findings. It was the first time

to investigate the adverse effects of alcohol use in liver function and cirrhosis in HCC patients. We showed that the diagnostic capability of alcohol in predicting cirrhosis and the prognostic ability of drinking were both higher in NBNC induced HCC patients than in those with HBV or HCV infection.

Cigarette quitting and alcohol control are critical measures for preventing tumorigenesis and shutting down mortality. It is estimated that about 20% of cancer related deaths can be prevented by smoking cessation. As drinking produces more severe liver damage than smoking in HCC, we speculate that the prognosis of HCC could be improved by limiting alcohol.

Conclusions

In conclusion, our study supports that alcohol consumption significantly elevates the levels of liver enzymes, increases the risk of cirrhosis, and reduces the survival time in male HCC patients, especially in those without infection of hepatitis virus.

Disclosure of conflict of interest

None.

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Alcohol consumption and outcomes in HCC

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Alcohol consumption and outcomes in HCC

Supplementary Table 1. Basic characteristics of 260 HCC patients (with a complete follow-up data) stratified according to the status of alcohol use

Variables	Total (n = 260)	Non-drinker (n = 186)	Drinker (n = 74)	<i>p</i>
Resection/RFA	172/88	126/60	46/28	0.319 ^a
Smoking/no	111/149	49/137	62/12	< 0.001 ^a
Age (yr)	55 (24-82)	56 (24-81)	53 (29-82)	0.337 ^b
HBV+HCV/NBNC	190/70	140/46	50/24	0.206
Cirrhosis/no	96/153	65/114	31/39	0.245 ^a
ALT (U/L)	63 (7-1315)	58 (7-1315)	78 (13-867)	0.030 ^b
AST (U/L)	51 (11-1075)	48 (11-1075)	64 (14-623)	0.110 ^b
ALP (U/L)	110 (17-872)	113 (21-872)	101 (17-493)	0.254 ^b
GGT (U/L)	47 (12-1830)	44 (12-1830)	54 (24-914)	0.116 ^b
Platelets (10 ⁹ /L)	107 (3-486)	102 (3-486)	109 (31-354)	0.786 ^b
AFP ≥ 200/< 200 (ng/ml)	106/122	77/85	29/37	0.622 ^a
Tumor size ≥ 5/< 5 (cm)	147/97	101/75	46/22	0.142 ^a
Multiple/single	38/219	26/157	12/62	0.681 ^a
Child A/B+C	229/25	165/17	64/8	0.669 ^a
TNM I, II/III, IV	177/43	131/30	46/13	0.573 ^a
Drinking quantity (0/0-40/≥ 40 g/d)	186/43/31	186/0/0	0/43/31	< 0.001 ^a

Note: ^aχ² test; ^bWilcoxon test. The values are expressed as the median (range) or number. *RFA*: radiofrequency ablation; *HBV*: hepatitis B viral; *HCV*: hepatitis C viral; *NBNC*: non-hepatitis B non-hepatitis C; *ALT*: alanine aminotransferase; *AST*: aspartate aminotransferase; *ALP*: alkaline phosphatase; *GGT*: γ-glutamyl transpeptidase; *AFP*: alphafetoprotein.