

Effect of Alcohol Intake on Inflammatory Status and Prognosis in Cancer Patients

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Purpose: To explore the effect of alcohol on the inflammatory status and prognosis of patients with malignancy.

Patients and Methods: The clinical data of patients with malignant tumor who were admitted to the First Hospital of Jilin University from November 2011 to December 2018 were collected including basic clinical information, anthropometric indicators, body composition analysis, and serological indicators. Univariate and multivariate Cox proportional hazards models were performed to find predictors of survival. A nomogram was generated to indicate the interrelationships between the variables in the prediction model and the extent to which alcohol consumption affects prognosis. The C-index and calibration curves were used to verify the predictive accuracy of the scoring system.

Results: A total of 2929 cancer patients were included in this study, of which 552 (18.8%) patients had alcohol consumption habits and 2377 (81.2%) patients had no alcohol history. Patients in the Alcohol group had significantly shorter overall survival (OS) than the Non-Alcohol group, and further sub-analysis indicated alcohol consumption was significantly associated with prognosis of advanced breast cancer (HR = 4.617, 95% CI 1.361–15.664, $p=0.014$), and early stage hepatocellular carcinoma (HCC) without viral hepatitis (HR = 8.933, 95% CI 1.444–55.275, $p=0.019$). Multivariate Cox regression models also demonstrated that daily alcohol intake was a risk factor of survival benefits (HR = 1.256, 95% CI 1.016–1.554, $p=0.036$). Finally, a nomogram was constructed and the c-index of this scoring system is 0.751. The 3- and 5-year calibration curves of the model show a high agreement between the predicted probability and the actual observed survival rate.

Conclusion: Alcohol intake was demonstrated associates with patient outcomes. A human component-prognosis scoring system was established to predict the survival benefits of cancer patients.

Keywords: alcohol, inflammation, cancer, prognosis

Introduction

In 2020, the International Agency for Research on Cancer (IARC) led several research institutions to publish a significant study on alcohol drinking and cancer.¹ The study results that alcohol consumption is one of the critical risk factors for the global disease burden causally associated with various injuries and diseases, including cancer, and no safe dose exists.² The 2018 white paper “Moderate Drinking Status of Chinese Drinking Population” shows that the Chinese drinking population is as high as 600 million. Moreover, for about 36% of the East Asian people, there is a common loss-of-function variant in the ALDH2 gene on chromosome 12 (rs671), which significantly reduces the rate of acetaldehyde decomposition and aggravates the damage of acetaldehyde to various tissues and organs.³ At present, there is a lot of evidence indicating that alcohol consumption is strongly associated with the risk of the occurrence of multiple cancers,^{4,5} but the extent of harm of alcohol consumption in patients with different cancers remains to be explored, and there are many missing data, especially in China. Therefore, the aim of this large retrospective cohort study was to deeply investigate the effect of alcohol consumption on the prognosis of cancer patients.

Materials and Methods

Clinical Data Collection

We collected clinical data from November 2011 to December 2018 from the Department of Oncology, Cancer Center, First Hospital of Jilin University. Inclusion criteria: (1) Clear diagnosis of malignancy in pathological specimens. (2) Age ≥ 18 years. (3) No nutritional support treatment prior to nutritional assessment and laboratory testing. Exclusion criteria: (1) Death within 30 days of hospital admission. (2) Mixed types of tumor. (3) Patients who declined to participate. Finally, 2929 patients were involved. Patients with multiple hospitalizations were considered as one case, and data from the first investigation were analyzed. All patients were regularly followed up by telephone interviews or outpatient visits. All pathological staging was defined according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system. Overall survival (OS) was defined as the time period from diagnosis to mortality for any cause.

Research Methods

All patients received anthropometry, laboratory biochemical tests and nutritional assessment within 24 hours of hospital admission. Smoking history, alcohol consumption, comorbidities and diagnostic information were recorded. The nutritional assessment including the nutritional risk screening 2002 score (NRS 2002), patient-generated subjective global assessment (PG-SGA), Karnofsky performance status (KPS) and quality of life questionnaire-core 30 (QOL-C30). Patients were classified into Alcohol group once they had alcohol consumption habit and those who never drank were classified into Non-Alcohol group.

Drinking Volume of Alcohol Intake

Drinking volume of alcohol intake (g) = Drinking volume (mL) \times alcoholic concentration (%) \times 0.8 (alcohol density). The alcohol concentration of beer, wine, and liquor in China is calculated according to 4%, 12%, and 50% of the white paper “Moderate Drinking Status of Chinese Drinking Population”.

Hand Grip Strength (HGS)

HGS was examined by Jamar hydraulic grip dynamometer (Sammons Preston Rolyan, Illinois, USA). Patients seated upright with their elbows flexing at 90°, forearms and wrists in a neutral position. Then, patients were instructed to grip the dynamometer three times with their maximum strength and there was a 1-minute interval for rest each time. The maximum reading was recorded.

Body Composition

Visceral fat area (VFA) was assessed by the Inbody S10 equipment using bioelectrical impedance analysis technology. Electrode pads were attached to the ipsilateral upper and lower extremities in the supine position, and all procedures are performed according to the manufacturer's recommendations.

Laboratory Testing Indicators

Venous blood samples were collected on an empty stomach and sent to the hospital laboratory for testing. The parameters recorded included albumin, prealbumin, transferrin, total protein (TP), C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR).

Statistical Analysis

Data were analyzed by SPSS for Windows version 26.0 (IBM SPSS Statistics, IBM Corp., Armonk, NY) and R version 4.0 (R Foundation for Statistical Computing, Vienna, Austria). The Kolmogorov–Smirnov test was used to confirm normal distributions of continuous data. Independent *t*-tests were used for normally distributed data. Counting data were examined by using the chi-square test. Univariate Cox proportional hazards models were performed for all potential baseline predictors to calculate hazard ratios (HR) and their 95% confidence intervals (CI). Variables that were significant in univariate analysis ($P < 0.05$) and those with known prognostic values were selected to build multivariate Cox proportional models with a stepwise forward selection of variables. A nomogram was generated to indicate the interrelationships

between the variables in the prediction model and the extent to which alcohol consumption affects prognosis. Then, the C-index and calibration curves were adopted to verify the predictive accuracy of the scoring system.

Results

A total of 2929 cancer patients were included in this study, including 1271 (43.4%) male and 1658 (56.6%) female. There were cancers of lung 898 (30.7%) cases, digestive tract 539 (18.4%) cases, biliary tract and pancreas 77 (2.6%) cases, leukemia 315 (10.8%) cases, breast 701 (23.9%) cases, liver 100 (3.4%) cases, esophageal 58 (2.0%) and others 241 (8.2%) cases. 552 (18.8%) patients had previous alcohol history and 2377 (81.2%) patients had no alcohol history.

Characteristics of Involved Patients Stratified by Alcohol Intake

According to the statistics displayed in [Table 1](#), it was men drank much more prevalent than women ($P < 0.001$). And a person who drank was more possible being a smoker ($P < 0.001$). No statistical significance was revealed in comorbidities between Non-Alcohol group and Alcohol group ($P = 0.025$). The proportion of patients with alcohol consumption history was higher in lung cancer (43.5% vs 27.7%, $P < 0.05$), digestive tract cancer (25.9% vs 16.7%, $P < 0.05$) and esophageal cancer (6.5% vs 0.9%, $P < 0.05$). Besides, TNM stages were more advanced in Alcohol group, which was 30.5% vs 25.0% of the III stage and 24.1% vs 19.2% of the IV stage ($P < 0.05$).

Relationship Between Alcohol Consumption and Inflammatory Factors

KPS scores were higher in the Alcohol group (90.67 vs 88.8, $P = 0.003$) than patients in the Non-Alcohol group in lung cancer. TP was higher patients without alcohol consumption than those with alcohol consumption in lung cancer (68.05g/L vs 67.13g/L, $P = 0.050$), biliary tract and pancreas cancer (65.23g/L vs 60.36g/L, $P = 0.017$) and breast cancer (69.33g/L vs 66.45g/L, $P = 0.026$). Prealbumin in Alcohol group was higher in leukemia (0.23g/L vs 0.21g/L, $P = 0.041$) and breast cancer (0.25g/L vs 0.25g/L, $P = 0.037$) than those in Non-Alcohol group. In digestive tract tumors, CRP was significantly higher in Alcohol group patients compared with the Non-Alcohol group (31.91 mg/L vs 21.80 mg/L, $P = 0.041$). Notably, patients in the Alcohol group had higher HGS in lung cancer (30.66kg vs 24.53kg, $P < 0.001$), digestive tract cancer (30.74kg vs 23.53kg, $P < 0.001$), biliary tract and pancreas cancer (30.71kg vs 22.19kg, $P = 0.006$) and leukemia (31.20kg vs 24.51kg, $P < 0.001$) than those in the Non-Alcohol group ([Table 2](#)).

Effect of Alcohol Consumption on the Prognosis of Different Cancer Types Stratified by Stage

[Table 3](#) and [Figure 1](#) showed the relationship between alcohol consumption and specific cancer types stratified by stage. Patients in the Alcohol group had significantly shorter OS than those in the Non-Alcohol group no matter the stages were. And patients in the advanced stage had a relatively lower HR (HR = 1.445, 95% CI 1.147–1.821, $P = 0.002$) than that in the early stage (HR = 1.705, 95% CI 1.329–2.187, $P < 0.001$). Subgroup analysis found that alcohol consumption was significantly associated with prognosis of advanced breast cancer (HR = 4.617, 95% CI 1.361–15.664, $P = 0.014$). Moreover, there seemed a correlation between alcohol consumption and prognosis of hepatocellular carcinoma (HCC) in early stage (HR = 2.367, 95% CI 0.886–6.318, $P = 0.086$) although the results were not statistically significant.

Further Study on the Combination of Viral Hepatitis in HCC Patients

Given that viral hepatitis was a main cause of HCC in China, we further stratified HCC patients by viral hepatitis. The results were surprising. Alcohol consumption was significantly associated with prognosis of early HCC patients without viral hepatitis (HR = 8.933, 95% CI 1.444–55.275, $P = 0.019$). However, the relation was not observed neither in HCC with viral hepatitis nor advanced HCC without viral hepatitis ($P > 0.05$) ([Table 4](#), [Figure 2](#)).

Table I Characteristics of Involved Patients Stratified by Alcohol Intake

Characteristics	Groups*		Total	P-value
	Non-Alcohol(n%)	Alcohol(n%)		
Sex				
Male	764(32.1)	507(91.8)	1271(43.4)	<0.001
Female	1613(67.9)	45(8.2)	1658(56.6)	
Age (year)				
<65	1894(79.7)	431(78.1)	2325(79.4)	0.402
≥65	483(20.3)	121(21.9)	604(20.6)	
Smoking				
No	1681(70.7)	87(15.8)	1768(60.4)	<0.001
Yes	696(29.3)	465(84.2)	1161(39.6)	
Comorbidities				
No	1369(57.6)	330(59.8)	1699(58.0)	0.225
Hypertension	306(12.9)	85(15.4)	391(13.3)	
Diabetes	217(9.1)	47(8.5)	264(9.0)	
Stroke	7(0.3)	1(0.2)	8(0.3)	
Cirrhosis	41(1.7)	7(1.3)	48(1.6)	
Others	437(18.4)	82(14.9)	519(17.7)	
Tumor types				
Lung	658(27.7)a	240(43.5)b	898(30.7)	<0.001
Digestive tract	396(16.7)a	143(25.9)b	539(18.4)	
Biliary tract and Pancreas	61(2.6)a	16(2.9)a	77(2.6)	
Leukemia	259(10.9)a	56(10.1)a	315(10.8)	
Breast	682(28.7)a	19(3.4)b	701(23.9)	
HCC	80(3.4)a	20(3.6)a	100(3.4)	
Esophageal	22(0.9)a	36(6.5)b	58(2.0)	
Others	219(9.2)a	22(4.0)b	241(8.2)	
Stage				
I	434(19.1)a	65(12.6)b	499(17.9)	<0.001
II	544(23.9)a	111(21.6)a	655(23.5)	
III	568(25.0)a	157(30.5)b	725(26.0)	
IV	436(19.2)a	124(24.1)b	560(20.1)	
Leukemia	290(12.8)a	58(11.3)a	348(12.5)	
Metastasis				
No	2271(95.5)	537(97.3)	2808(95.9)	0.064
Yes	106(4.5)	15(2.7)	121(4.1)	
Recurrence				
No	1917(80.6)	447(81.0)	2364(80.7)	0.859
Yes	460(19.4)	105(19.0)	565(19.3)	

Notes: *Each subscript letter denotes a subset of group categories whose column proportions do not differ significantly from each other at the 0.05 level.

Abbreviations: BMI, body mass index; HCC, hepatocellular carcinoma.

Establish and Validate Nomogram for Prognosis-Related Influences

As the OS was the endpoint event, the univariate Cox regression model results showed that the following nine factors associated with the OS: Sex, age, BMI, TNM stage, daily alcohol intake, smoking packs per week, NLR, PLR, and VFA ($P < 0.05$). Multivariate Cox regression models further confirmed that daily alcohol intake more than 30g was a risk factor of prognosis of cancer patients among all the included variables (HR = 1.256, 95% CI 1.016–1.554, $P = 0.036$) (Table 5).

A nomogram was established based on the results of the multivariate regression model. Thus, a prognostic scoring system was developed as displayed in Figure 3, where the daily alcohol intake more than 30g got 1.1 points. The C-index

Table 2 Basic Clinical Information for Cancer Patients Stratified by Alcohol Intake

Parameters	Lung Cancer (N=898)			Digestive Tract Cancer (N=539)			Biliary Tract & Pancreas Cancer (N=77)			Leukemia (N=315)			Breast Cancer (N=701)		
	Non-Alcohol	Alcohol	P-value	Non-Alcohol	Alcohol	P-value	Non-Alcohol	Alcohol	P-value	Non-Alcohol	Alcohol	P-value	Non-Alcohol	Alcohol	P-value
NRS2002	0.72	0.57	0.084	0.84	0.49	0.008	0.92	1.17	0.568	0.35	0.04	<0.001	0.24	0.11	0.411
PG-SGA	4.67	4.36	0.232	6.73	6.45	0.434	8.59	8.80	0.866	4.37	4.11	0.635	3.09	3.53	0.500
KPS	88.88	90.67	0.003	86.60	85.73	0.513	85.41	87.50	0.593	89.58	89.11	0.755	92.04	90.00	0.297
QOL-C30	65.93	67.05	0.487	67.76	67.72	0.985	61.74	75.00	0.055	59.77	61.16	0.672	71.66	68.86	0.559
TP (g/L)	68.05	67.13	0.050	64.44	63.73	0.289	65.23	60.36	0.017	63.78	63.32	0.672	69.33	66.45	0.026
Albumin (g/L)	39.33	38.73	0.087	37.09	37.25	0.730	36.82	34.77	0.197	37.39	38.41	0.176	41.77	40.19	0.089
Prealbumin (g/L)	0.21	0.2174	0.145	0.19	0.19	0.373	0.18	0.19	0.641	0.21	0.23	0.041	0.23	0.25	0.037
Transferrin (g/L)	4.45	2.32	0.565	2.55	2.27	0.089	2.17	2.01	0.530	11.01	1.99	0.554	2.68	2.64	0.935
CRP (mg/L)	16.59	14.86	0.500	21.80	31.91	0.041	23.22	27.62	0.769	25.67	29.70	0.533	6.01	13.08	0.341
BMI (kg/m ²)	23.22	23.35	0.601	22.26	22.87	0.079	21.58	22.24	0.418	23.11	24.57	0.005	24.93	24.73	0.814
HGS (kg)	24.53	30.66	<0.001	23.53	30.74	<0.001	22.19	30.71	0.006	24.51	31.20	<0.001	20.11	21.59	0.290
VFA (cm ²)	92.88	88.49	0.095	82.98	80.75	0.539	73.49	70.11	0.683	78.66	85.20	0.183	100.91	100.83	0.992
NLR	3.31	4.41	0.284	5.12	4.29	0.521	4.31	5.32	0.485	2.80	3.31	0.433	2.64	1.93	0.696
PLR	175.98	160.68	0.124	192.17	173.82	0.275	197.18	184.11	0.719	177.02	169.16	0.798	149.48	111.64	0.053
Parameters	HCC (N=100)						Esophageal Cancer (N=58)			Others (N=241)					
	Non-Alcohol		Alcohol	P-value	Non-Alcohol		Alcohol	P-value	Non-Alcohol		Alcohol	P-value			
NRS2002	0.46		0.37	0.672	1.68		1.25	0.326	0.72		0.75	0.917			
PG-SGA	4.43		4.45	0.979	6.18		7.08	0.404	4.82		5.68	0.292			
KPS	90.13		91.00	0.723	89.55		89.44	0.968	89.31		86.36	0.238			
QOL-C30	70.52		72.08	0.777	58.33		72.45	0.016	67.35		57.58	0.048			
TP (g/L)	66.42		64.75	0.379	65.15		65.14	0.998	68.21		69.28	0.497			
Albumin (g/L)	36.98		35.04	0.159	37.01		38.14	0.297	39.34		39.84	0.674			
Prealbumin (g/L)	0.16		0.19	0.478	0.18		0.20	0.300	0.21		0.22	0.185			
Transferrin (g/L)	2.41		2.54	0.508	2.06		2.09	0.859	2.41		2.04	0.058			
CRP (mg/L)	4.62		19.85	0.398	17.66		11.82	0.374	22.84		39.80	0.395			
BMI (kg/m ²)	23.66		23.23	0.542	20.69		21.67	0.273	23.56		22.78	0.286			
HGS (kg)	27.75		27.46	0.913	25.29		28.67	0.123	20.49		26.57	<0.001			
VFA (cm ²)	98.07		86.13	0.163	77.63		69.69	0.392	93.02		76.61	0.035			
NLR	3.75		5.13	0.351	3.80		2.99	0.243	3.84		2.88	0.227			
PLR	122.35		144.03	0.388	202.09		152.20	0.106	192.88		124.03	0.045			

Abbreviations: HCC, hepatocellular carcinoma; PG-SGA, the patient-generated subjective global assessment; NRS2002, nutritional risk screening 2002 score; KPS, Karnofsky performance status; QOLC30, quality of life questionnaire-core 30; TP, total protein; CRP, C-reactive protein; BMI, body mass index; HGS, hand grip strength; VFA, visceral fat area; NLR, neutrophil to lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Table 3 Risk of Mortality in Drinking Patients Stratified by Stage

Specific Tumor Types	HR	95% CI	P-values
Total			
Early	1.705	1.329–2.187	<0.001
Advanced	1.445	1.147–1.821	0.002
Lung Cancer			
Early	0.955	0.641–1.423	0.822
Advanced	1.334	0.947–1.879	0.100
Digestive tract cancer			
Early	0.710	0.420–1.201	0.202
Advanced	0.985	0.488–1.990	0.967
Biliary tract and pancreas cancer			
Early	0.297	0.070–1.267	0.101
Advanced	1.780	0.724–4.375	0.209
Leukemia	1.200	0.761–1.892	0.433
Breast cancer			
Early	1.581	0.215–11.640	0.653
Advanced	4.617	1.361–15.664	0.014
HCC			
Early	2.367	0.886–6.318	0.086
Advanced	2.541	0.507–12.746	0.257
Esophageal Cancer			
Early	1.425	0.473–4.295	0.529
Advanced	0.304	0.089–1.039	0.058
Others			
Early	2.058	0.721–5.875	0.178
Advanced	1.561	0.444–5.488	0.487

Abbreviations: HR, hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma.

of this scoring system is 0.751. The 3- and 5-year calibration curves of the model showed a high agreement between the predicted probability and the actual observed survival rate (Figure 4A and B).

Discussion

Epidemiologic evidence has shown that alcohol is a risk factor of cancer occurrence and development. It is reported that approximately 4% of cancers worldwide are caused by alcohol consumption, and cancers of the esophagus (26%), liver (21%), and breast (13%) represent the most alcohol-attributable cases of cancer globally.⁶ Herein, the proportion of patients with alcohol consumption history was higher in lung cancer, digestive tract cancer and esophageal cancer, which agreed with previous studies.^{7,8} Although the mechanisms of alcohol inducing cancers are not totally clear, several aspects have been demonstrated interacted between alcohol consumption and cancer including genetic polymorphism, oxidative stress, retinoic acid metabolism and immune modulation.⁹

Alcohol mainly metabolites in liver through cytochrome P-450 2E1 (CYP2E1) systems. Alcohol consumption leads to oxidative stress.^{10,11} When ethanol administration in vivo, CYP2E1 is activated which generates large amounts of reactive oxygen species (ROS), and oxidizes to acetaldehyde. Acetaldehyde, in turn, stimulates specific white blood cells (monocytes and macrophages) to produce inflammatory cytokines and downstream ROS.⁶ This is consistent with the results that prealbumin and CRP were higher in the Alcohol group than in the Non-Alcohol group in the pan-cancerous patients included in our study. However, the elevated HGS of patients in the Alcohol group is not consistent with the poor prognosis because the number of males in the Alcohol group is as high as 507, accounting for 91.8% of the total alcohol consumption. Gender can behave a large impact on HGS¹² and bias the final results.

Alcohol consumption has negative effects on tumor patients of different stages as displayed in Table 3. Alcohol increases the metabolic burden of the liver and affects its health status.¹³ However, when we analyzed the patients with

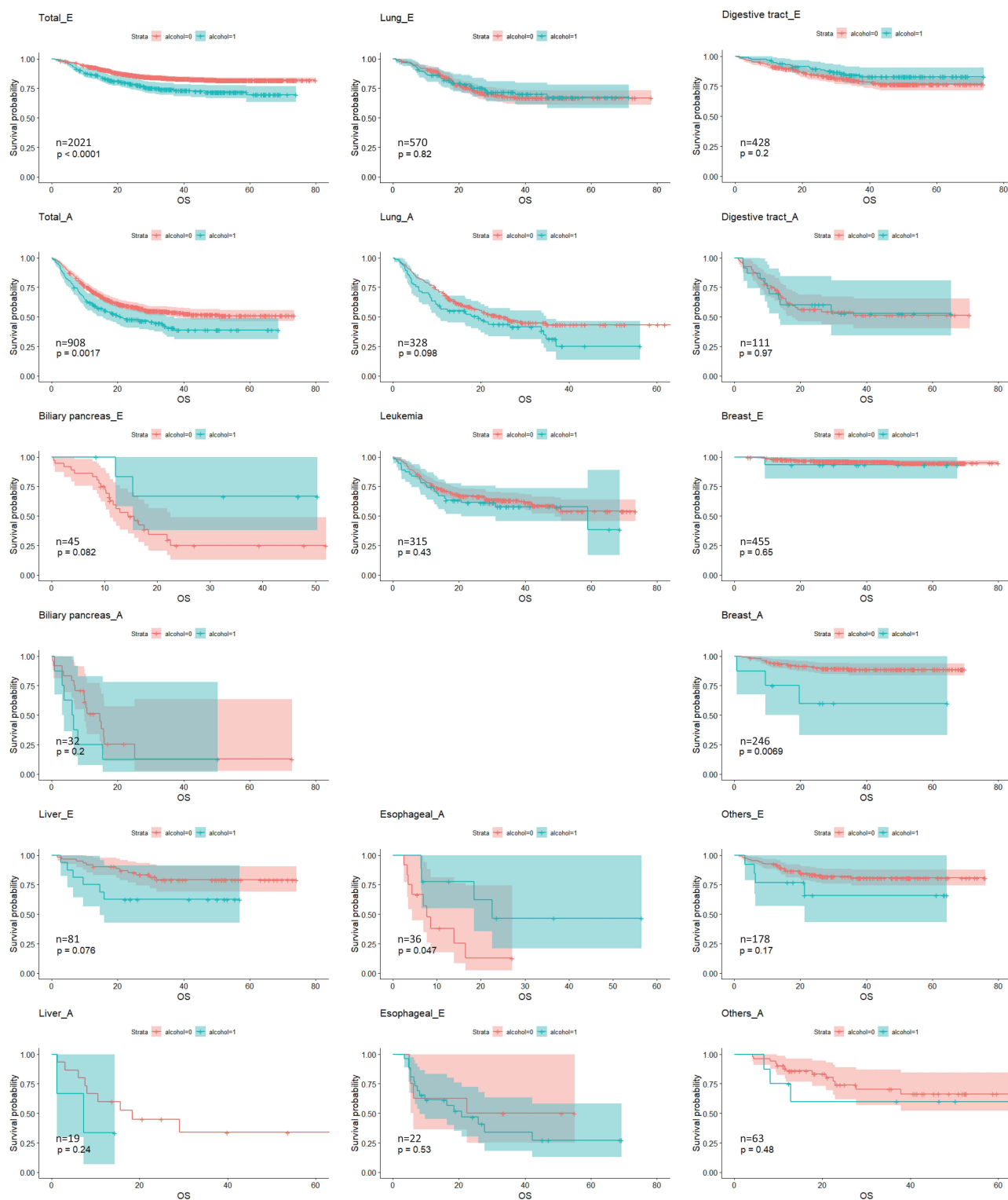


Figure 1 Kaplan-Meier curves of overall survival in different cancer types stratified by stage.

Note: E for early stage, A for advanced stage.

HCC based on alcohol consumption, the results were not ideal. This alerts us to - viral hepatitis, another major interference factor affecting HCC.^{14,15} According to a comparative risk study led by the National Cancer Center/ Peking Union Medical College Cancer Hospital of the Chinese Academy of Medical Sciences, approximately 76.3%

Table 4 Risk of Mortality Stratified by Stage and Viral Hepatitis in Drinking Patients Suffering HCC

	HR	95% CI	P-values
Non-Viral Hepatitis			
Early	8.933	1.444–55.275	0.019
Advanced	0.988	0.109–8.954	0.991
Viral Hepatitis			
Early	1.493	0.404–5.519	0.548
Advanced	3.972	0.359–43.929	0.261

Abbreviations: HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval.

and 65.9% of HCC among males and females over 20 years old in Jilin Province were attributable to viral hepatitis.⁸ Among the 100 cases of HCC included, 78 cases combined viral hepatitis, accounting for 78% of the total HCC patients. Therefore, we further stratified the discussion and found that alcohol consumption was significantly associated with the prognosis of early HCC without viral hepatitis but not with the prognosis of advanced HCC without viral hepatitis and HCC with viral hepatitis. This reflects the impact of viral hepatitis on the prognosis of HCC and also confirms that the larger impact of alcohol consumption on the prognosis of early-stage patients than that of advanced patients, which is

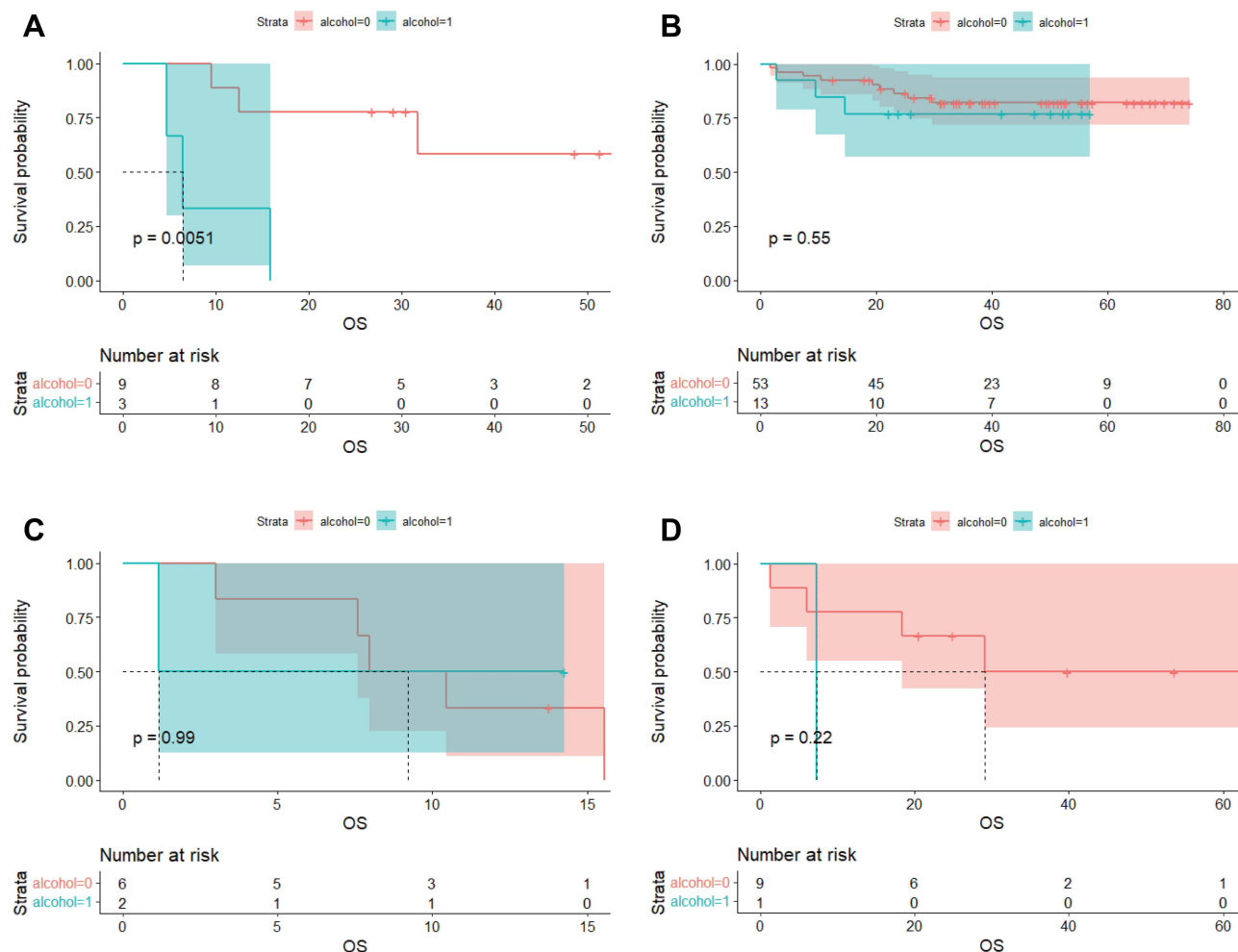


Figure 2 Kaplan–Meier curves of HCC stratified by stage and viral hepatitis. (A) HCC without viral hepatitis in early stage; (B) HCC with viral hepatitis in early stage; (C) HCC without viral hepatitis in advanced stage; (D) HCC with viral hepatitis in advanced stage.

Abbreviation: HCC, hepatocellular carcinoma.

Table 5 Univariable and Multivariable Cox Regression of Factors Related to Overall Survival of Cancer Patients

Relevant Factors	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	P-values	HR	95% CI	P-values
Sex						
Male	Reference			Reference		
Female	0.458	0.397–0.528	<0.001	0.769	0.639–0.924	0.005
Age (year)						
<45	Reference			Reference		
45–75	1.595	1.294–1.966	<0.001	1.547	1.230–1.947	<0.001
>75	3.325	2.395–4.616	<0.001	2.402	1.687–3.421	<0.001
BMI (kg/m ²)						
<18	Reference			Reference		
18–24	0.614	0.473–0.797	<0.001	0.645	0.491–0.846	0.002
24–28	0.441	0.333–0.582	<0.001	0.500	0.373–0.671	<0.001
>28	0.272	0.185–0.399	<0.001	0.347	0.229–0.527	<0.001
Stage						
I	Reference			Reference		
II	1.942	1.311–2.877	0.001	1.76	1.187–2.610	0.005
III	4.765	3.329–6.821	<0.001	3.956	2.758–5.675	<0.001
IV	11.098	7.794–15.804	<0.001	9.191	6.440–13.117	<0.001
Leukemia	6.938	4.773–10.087	<0.001	6.907	4.710–10.131	<0.001
Drinking type						
None	Reference					
Liquor	1.738	1.460–2.070	<0.001			
Beer	3.455	0.486–24.582	0.215			
Liquor+Wine	1.035	0.570–1.878	0.911			
Liquor+Beer	1.244	0.840–1.843	0.275			
Daily Alcohol intake (g)						
<30	Reference			Reference		
≥30	1.774	1.487–2.117	<0.001	1.256	1.016–1.554	0.036
Weekly Smoking Pack						
≤1	Reference			Reference		
>1	1.999	1.738–2.299	<0.001	1.254	1.049–1.498	0.013
NLR						
<4	Reference			Reference		
≥4	1.882	1.620–2.187	<0.001	1.590	1.354–1.868	<0.001
PLR						
<140	Reference			Reference		
≥140	1.336	1.159–1.539	<0.001	1.101	0.934–1.298	0.253
VFA (cm ²)						
<90	Reference			Reference		
≥90	0.828	0.720–0.953	0.008	1.109	0.929–1.324	0.252

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; NLR, neutrophil-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; VFA, visceral fat area.

consistent with the hazard ratio of pan-cancer patients (Advanced: HR = 1.445 vs Early: HR = 1.705). This may be due to the fact that advanced patients often have metastases, combined with multiple organ failures and a shorter survival period,¹⁶ thus concealing the effect of alcohol consumption on prognosis. For advanced breast cancer patients, alcohol consumption often predicts a poor prognosis and a higher risk, which can be explained by two aspects: 1. Breast cancer is closely related to hormone levels in the body and is thus more susceptible to alcohol;¹⁷ 2. Fewer early breast cancer people with alcohol consumption were included in the study (2.2% of total early breast cancer patients).

In addition, we also establish a nomogram for patient basic clinical information and inflammatory factors to further study the influence of alcohol consumption on patient prognosis. We found that when the patients with daily alcohol

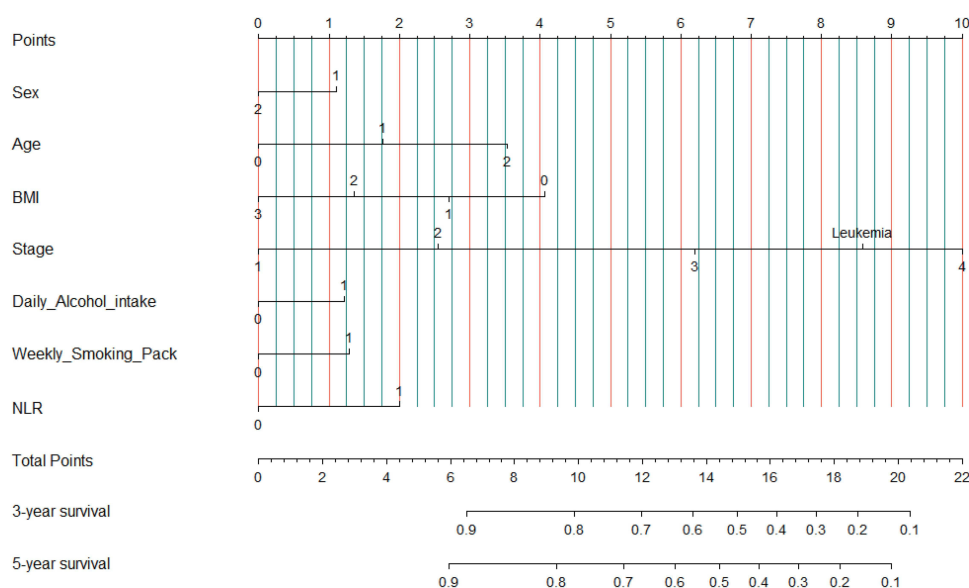


Figure 3 The scored marker system by nomogram used to quantize the prognosis-related markers.

Notes: Tumor stage: 1 = I; 2 = II; 3 = III; 4 = IV. NLR: 0 = NLR < 4; 1 = NLR ≥ 4. Age: 0 = Age < 45; 1 = Age ≥ 45 and Age < 75; 2 = Age ≥ 75. Daily Alcohol intake: 0 = Daily Alcohol intake < 30; 1 = Daily Alcohol intake ≥ 30. Weekly Smoking Pack: 0 = Weekly Smoking Pack ≤ 1; 1 = Weekly Smoking Pack > 1. BMI: 0 = BMI < 18; 1 = BMI ≥ 18 and Age < 24; 2 = BMI ≥ 24 and BMI < 28; 3 = BMI ≥ 28. Sex: 1 = Male; 2 = Female.

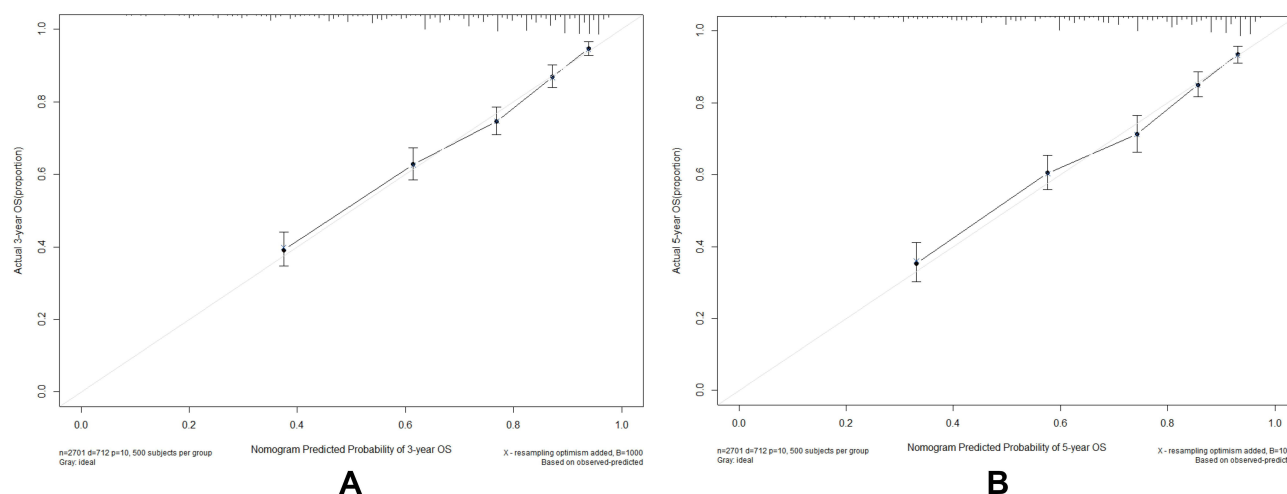


Figure 4 Calibration curves for the nomogram predictions of the 3- and 5-year overall survival. **(A)** Calibration curves for the nomogram predictions of the 3-year overall survival; **(B)** calibration curves for the nomogram predictions of the 5-year overall survival.

intake exceed 30g, the impact on the prognosis is equivalent to smoking more than one pack per week. Like smoking, drinking alcohol will not only increase the cancer rate but also affect the prognosis of patients,¹⁸ and this harm may not disappear with quitting smoking and drinking.

It is also noted that comorbidities may have an impact on prognosis as a confounding factor. Patients with cardiovascular diseases may have higher cardiac load and lower tolerance to cardiotoxicity of chemo- and immuno-therapeutic drugs,¹⁹ such as anthracycline and some immune check point inhibitors. This tends to limit patients' treatment options, and even cause death from treatment related cardiotoxicity. Long-term metformin administration has been shown to achieve inhibition of tumor growth through activation of AMP-activated protein kinase (AMPK) in some diabetic patients.²⁰ Besides, alcohol metabolites interrupt the balance of protein anabolism catabolism, cause inhibition of that protein's function and/or an immune response, and results in multi comorbidities and impairs nutrition status.^{21,22} However, some studies refer that light to moderate alcohol

consumption does have beneficial effects on cardiovascular system, diabetes, some autoimmune diseases and etc.²³ Rodrigues et al reported that types of alcohol beverage drinks also differ.²⁴ Similarly, it was liquor but not wine or beer found a risk factor of prognosis herein with HR 1.738 (95% CI 1.460–2.070, $P < 0.001$). However, no comorbidities or scores reflecting nutritional status were involved in the nomogram. The clue appeared where there no difference of comorbidities and nutritional status scores between Alcohol group and Non-Alcohol group in Tables 1 and 2. Although the debates are ongoing, what needs to be emphasize is that alcohol is definitely not recommended because the risk-benefit ratio of alcohol remains negative, particularly in the perspective of the carcinogenic effects.

There were limitations. As a real world study, 2929 cases is some kind of a large sample size. However, small case number of some cancer types limited the representation of conclusions. And, several cancer types are not listed and discussed separately whose case number less than 50. Therefore, perspectives need to be cautiously interpreted like “alcohol tends to affect prognosis of HCC in early stage” due to only 22 cases of HCC combined alcohol consumption habit.

In conclusion, we found that drinking patients tended to have poorer health status and higher levels of inflammation in overall tumor types. This may be due to acetaldehyde, a primary product of alcohol metabolism. Meanwhile, alcohol can also promote cancer development and metastasis by inhibiting DNA methylation.²⁵ Since there is a lot of evidence that alcohol consumption is closely related to the risk of cancer, researches are still in an initial stage on the effect of alcohol consumption on the prognosis of cancer patients. Therefore, we believe further investigation imperative.

Data Sharing Statement

Materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the first affiliated hospital of Jilin University (2017-362), and all the patient data in this research was approved by this committee. All study participants have filled out written informed consent for participation.

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Disclosure

Xiangliang Liu, Wenxin Zhang, and Wei Ji are co-first authors for this study. The authors report no conflicts of interest in this work.

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