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Retrospective Cohort Study

Impact of alcohol consumption on treatment outcome of hepatocellular carcinoma patients with viral hepatitis who underwent transarterial chemoembolization

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Abstract

BACKGROUND

Alcohol consumption increases the risk of hepatocellular carcinoma (HCC) in patients with pre-existing liver disease, including viral hepatitis. However, studies on the impact of alcohol consumption on the outcomes of HCC are limited. We hypothesized that alcohol had an additional effect with chronic viral hepatitis infection on treatment outcomes after transarterial chemoembolization (TACE) in patients with intermediate-stage HCC (Barcelona Clinical Liver Cancer [BCLC] -B).

AIM

To evaluate the additional effect of alcohol on treatment outcomes of TACE among HCC patients with viral hepatitis.

METHODS

This study, conducted at Hatyai Hospital in Thailand, included HCC patients over 18 years of age with chronic viral hepatitis. Records of HCC patients with viral hepatitis classified as BCLC-B who underwent TACE as the first treatment modality between

2014 and 2019 were retrospectively reviewed. Patients with chronic viral hepatitis only were categorized under group A, and those with chronic viral hepatitis and concurrent alcohol consumption were categorized under group B. Both groups were compared, and the Cox proportional-hazards model was used to identify the survival-influencing variables.

RESULTS

Of the 69 patients, 53 were categorized in group A and 16 in group B. There were no statistically significant differences in tumor characteristics between the two patient groups. However, Group A had a statistically significantly higher proportion of complete response (24.5% vs. 0%, P = 0.030) and a higher median survival rate (26.2 mo vs. 8.4 mo; log–rank P = 0.012) compared to group B. Factors associated with decreased survival in the proportional-hazards model included alcohol consumption (hazards ratio [HR], 2.377; 95% confidence interval [CI], 1.109–5.095; P = 0.026), presence of portal hypertension (HR, 2.578; 95%CI, 1.320–5.037; P = 0.006), largest tumor size >5 cm (HR, 3.558; 95%CI, 1.824–6.939; P < 0.001), and serum alpha-fetoprotein level >100 ng/mL (HR, 2.536; 95%CI, 1.377–4.670; P = 0.003).

CONCLUSION

In HCC BCLC B patients with chronic viral hepatitis, alcohol consumption is an independent risk factor for increased mortality and decreases the rate of complete response and survival after TACE.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide[1]. As the incidence of HCC is almost the same as the number of annual deaths caused by this malignancy, it is also the third leading cause of cancer-related mortality worldwide[2]. Most HCC patients are diagnosed late, subsequently leading to poor clinical outcomes

and often making palliative treatment their only option.[2, 3] For patients with intermediate-stage HCC (Barcelona Clinical Liver Cancer [BCLC] B), transarterial chemoembolization (TACE) with preserved liver function has been shown to improve survival.[2, 3]

Chronic viral hepatitis infection, in particular with hepatitis B virus (HBV) and hepatitis C virus (HCV), are important risk factors for HCC. In fact, HBV and HCV are estimated to be responsible for 50-90% of HCC cases worldwide.[4] Alcohol use disorder is associated with intravenous injections and bloodborne infections; heavy alcohol consumption has been reported to be much higher among individuals screened for chronic viral hepatitis than the general population.[5] Due to the strong association of alcohol misuse with alcohol-associated liver diseases, liver cirrhosis, and cancer,[6, 7] alcohol has been categorized as a human carcinogen.[8] Alcohol consumption enhances or accelerates hepatocarcinogenesis in patients with other pre-existing chronic liver diseases, especially chronic viral hepatitis infection.[9, 10] However, studies on the impact of alcohol consumption on HCC outcomes after treatment are limited.

The study's objective was to verify the additional effect of alcohol on treatment outcomes of TACE among intermediate-stage HCC (BCLC B) patients with viral hepatitis.

MATERIALS AND METHODS
Study design and patient population

This retrospective cohort study was conducted at Hatyai Hospital (a regional referral tertiary center in southern Thailand). The study protocol was approved by the Institutional Review Board of Hatyai Hospital (protocol number HYH EC 105-64-01) and conducted in accordance with the Declaration of Helsinki. The need for informed consent was waived because patient information was de-identified before analysis.

The inclusion criterion was HCC patients > 18 years of age with chronic viral hepatitis classified as BCLC B who underwent TACE as the first treatment modality between January 2014 and December 2019. The exclusion criteria were as follows: 1)

received any curative treatment for HCC; 2) infiltrative tumor or extrahepatic metastasis; 3) renal, cerebral, or cardiopulmonary dysfunction; 4) presence of other concurrent malignancy; and 5) insufficient data for analysis.

Data collection

A retrospective review of the medical records of each patient was performed manually by two independent investigators (with at least five years of experience in the field of hepatology), and a third investigator (senior consultant who had an experience of more than ten years) was consulted to resolve disagreements or discrepancies. For each patient, data were extracted from the demographic and clinical variables (including age, sex, body mass index, comorbidities, clinical presentation, and laboratory results), tumor characteristics (including the number of tumors and the size and stage of the tumors) at the time of diagnosis. Data on clinical outcomes included the number of total sessions of TACE and responses after all treatments were completed.

Treatment and evaluation of response

After discussion by a multidisciplinary team, TACE treatment was offered to patients and conducted after a consensus was reached between doctors and patients. Written informed consent was obtained from all the patients before the procedure. Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) was performed to evaluate tumor status prior to TACE. Conventional TACE was performed by experienced interventional radiologists. A single intravenous dose of antibiotic prophylaxis with third-generation cephalosporin was routinely administered, except in patients who were prescribed antibiotics for other indications. After assessment of feeding vessels to the segment where the tumor was located, a mixture of a cytotoxic drug (such as doxorubicin or mitomycin C) and iodized oil (Lipiodol; Guerbet, Milan, Italy) was injected, followed by embolization using gelatin sponge particles under fluoroscopic monitoring. We routinely assessed the treatment response at 4–6 wk after the procedure using dynamic contrast-enhanced CT or MRI.

Definitions and outcomes

HCC was diagnosed based on the American Association for the Study of Liver Disease (AASLD) criteria as previously described, and the BCLC system was used for tumor staging.[2] We stratified patients into two groups, namely "group A" consisting of patients with chronic viral hepatitis only and "group B" consisting of patients with concurrent chronic viral hepatitis and alcohol consumption. Viral hepatitis was defined as infection with either HBV or HCV as confirmed by a history of positive serological results (hepatitis B virus surface antigen and hepatitis C virus antibody) accompanied by the presence of HBV DNA or HCV RNA. Alcohol consumption was defined as daily alcohol consumption of at least 40 g.[11] The diagnosis of cirrhosis was based on clinical features, imaging, and histology. The presence of portal hypertension was confirmed if the patients had any of the following: 1) ascites; 2) esophageal or gastric varices; 3) splenomegaly accompanied by a platelet count <100,000/mm³.[2] Hepatic function was assessed using the Child–Turcotte–Pugh score [12] and the model of end-stage liver disease (MELD).[13] The patient's performance status was classified according to the Eastern Cooperative Oncology Group (ECOG) Performance Status scale.[14]

Complete response (CR) after treatment was defined as the disappearance of any intra-tumor enhancement in all target lesions, as demonstrated by dynamic enhanced cross-sectional imaging based on the modified Response Evaluation Criteria in Solid Tumors.[15] Overall survival (OS) was calculated from the date of diagnosis of HCC until either death (using data from the Thailand civil registrations) or the last follow-up date. The censored survival time was January 1, 2021.

Statistical analysis

Categorical variables were expressed using descriptive statistics and assessed for statistically significant differences using Pearson's chi-square or Fisher's exact test. For continuous variables, data were presented as mean ± standard deviation (SD) or median and interquartile range (IQR) and tested for statistically significant differences using the Student's t-test and Wilcoxon rank-sum test. Survival analysis was performed using the Kaplan–Meier method, and the log-rank test was used to analyze statistical differences between the two groups. The Cox proportional hazards model was used to

identify variables influencing survival. After univariate analysis, sex, age, and other variables with probabilities (p-values) <0.2 were included in the multivariate analyses. All data analyses were performed using the statistical program Stata Version 15.1 (StataCorp LLC, College Station, TX, USA). Statistical significance was set at p <0.05.

RESULTS

Baseline characteristics

A total of 69 patients met the inclusion criteria and were enrolled in the study. The average age was 55.5 ± 9.9 years, and 51 (73.9%) were men. Of these patients, 53 were classified into group A (chronic viral hepatitis only) and 16 into group B (concurrent chronic viral hepatitis and alcohol consumption). Comparisons of demographic data are shown in Table 1. The proportion of female patients in group A was higher than that in group B (34.0% vs. 0%, $P = 0.007$). When compared between the two groups, serum albumin level in group A was significantly higher (mean ± SD = 3.6 ± 0.7 g/dL vs 3.2 ± 0.4 g/dL, $P = 0.017$), while serum aspartate aminotransferase (AST) level in group B was significantly higher (median [IQR] = 63.0 [42.0 to 116.0] mg/dL vs 96.5 [73.5 to 155.0] mg/dL). The proportion of patients with chronic hepatitis B tended to be higher in group A compared to group B (64.2% vs. 37.5%, $P = 0.058$), while the proportion of patients with chronic hepatitis C tended to be higher in group B compared to group A (37.7% vs. 62.5%, $P = 0.080$).

Tumor characteristics and response

There were no significant differences in tumor characteristics between these two patient groups (Table 2). The median number of TACE sessions was not significantly different between the two groups; the proportion of patients who achieved CR after treatment was statistically significantly higher in group A than in group B (24.5% vs. 0%, $P = 0.030$).

Impact of alcohol consumption on OS

Based on the Kaplan–Meier method, the survival rate of patients in group A was significantly higher than in group B (median OS was 26.2 mo in group A and 8.4 mo in group B; log-rank $P = 0.012$) (Fig. 1).

To identify the factors of OS after TACE in HCC patients with viral hepatitis, the Cox proportional-hazards model was used. In the multivariate analysis, factors associated with a decreased OS included alcohol consumption (hazards ratio [HR], 2.377; 95% confidence interval [CI], 1.109–5.095; $P = 0.026$), presence of portal hypertension (HR, 2.578; 95%CI, 1.320–5.037; $P = 0.006$), largest tumor size > 5 cm (HR, 3.558; 95%CI, 1.824–6.939; $P < 0.001$), and serum alpha-fetoprotein level > 100 ng/mL (HR, 2.536; 95%CI, 1.377–4.670; $P = 0.003$) (Table 3).

DISCUSSION

This retrospective cohort study was based on a series of patients with intermediate-stage HCC (BCLC B) who underwent TACE and reflects "real-life" outcome data from a Government Hospital in a middle-income country. The principal findings of this study were as follows: first, HCC BCLC B patients with chronic viral hepatitis concurrent with alcohol consumption showed a decreased rate of CR and survival after TACE than those who had chronic viral hepatitis alone; and second, after adjusting for confounding factors, alcohol consumption was observed as an independent risk factor of increased mortality after TACE in individuals with chronic viral hepatitis.

It has been well documented that regular alcohol consumption is associated with increased HCC risk, with a significant dose-dependent response relationship between the amount of alcohol intake and the risk of HCC.[16, 17] Recent meta-analysis demonstrated that consumption of even a small amount of alcohol is related to cancer risk.[18] The risk of HCC in alcohol consumption may differ depending on the severity of baseline liver status.[19] For patients with pre-existing chronic liver diseases, including HBV and HCV, alcohol consumption has a synergistic effect on the development of

HCC, although the risk threshold remains uncertain.[1, 20, 21] However, the data on the impact of alcohol consumption on HCC outcomes after treatment remains limited. To the best of our knowledge, this was the first study evaluating the impact of alcohol consumption on treatment outcomes among patients with intermediate-stage HCC after TACE in individuals with chronic viral hepatitis. According to the tumor characteristics, there were no significant differences in the number and size of tumors between the two groups. Patients with chronic viral hepatitis concurrent with alcohol consumption developed a lower rate of CR and had decreased survival rate after TACE than those who had chronic viral hepatitis alone. These results underscore that alcohol consumption provides worse outcomes after TACE when concomitant with chronic viral hepatitis. There are many possible reasons to explain this finding.

First, patients with alcohol-related HCC are linked to poor general conditions, including performance status and hepatic reserve.[22] This is consistent with the results of our study demonstrating liver status in patients with viral hepatitis infection and alcohol consumption which was poorer in both synthesis (lower albumin level) and evidence of inflammation (higher AST level) than that in patients with viral hepatitis only. The impaired clinical status could be caused by the direct effect of ethanol on the liver, alcohol-associated malnutrition, or brain cognitive dysfunction occurring in chronic alcohol abuse.[23, 24] Poorer general conditions at the time of HCC detection were associated with a higher rate of non-HCC-related complications than viral-related-HCC, which resulted in shorter survival.[22, 25-28] In addition, continuing alcohol abuse precludes providing treatment options for best supportive care as a result of worsening survival.[29] In Thailand, most patients with HCC who abused alcohol still had concurrent alcohol consumption, leading to ongoing liver function deceleration and limited treatment options.[22, 28, 29] This could explain why patients with chronic viral hepatitis and alcohol abuse had a lower rate of CR and shorter OS than patients with chronic viral hepatitis alone in this study.

Second, alcohol can accelerate the progression of liver disease in patients with chronic viral hepatitis (B or C) by several mechanisms. Alcohol increases intestinal

permeability to various substances, especially bacteria-derived liposaccharides from the gut to the liver, stimulating Kupffer cell activity and promoting inflammatory cascade resulting in progression of fibrosis.[30, 31] Acetaldehyde, which is derived from the metabolism of ethanol, is a carcinogen and a highly toxic substance that plays a major role in the necroinflammation of hepatocytes.[1] Besides the direct biological impact of alcohol, the association between alcohol consumption and chronic viral hepatitis infection has been identified. Chronic alcohol consumption led to increased replication of viral hepatitis virus (both HBV and HCV) [32, 33] and altered immune response, which is associated with promoting hepatocyte injury resulting in hepatic deterioration.[34, 35] Heavy alcohol drinking was associated with rapid progression of fibrosis and development of cirrhosis in patients with HBV infection.[36] Among HCV patients, excessive alcohol consumption was strongly associated with decompensated cirrhosis.[37] In addition, HBV infection compromises the host function of antioxidant defense, which promotes alcoholic liver injury.[38] For these reasons, alcohol consumption and chronic viral hepatitis can synergize the lifetime risk of liver disease progression and ultimately increase the risk of death, as seen in our study.[37, 39]

Third, alcohol may alter the biological pattern of HCC in patients with viral hepatitis. Kubo *et al* demonstrated that the proportion of well-differentiated HCC was lower among those with massive alcohol consumption than those without alcohol use.[40] Undifferentiated HCC is more aggressive and metastatic. [41] Okada *et al* also reported that patients with excessive alcohol consumption had a short tumor-free and OS after treatment.[42]

Fourth, alcohol consumption is linked with different types of liver disease. Alcohol abuse, especially heavy alcohol consumption, cause changes in lipid metabolism resulting in aggravation of non-alcoholic liver disease (NASH), which affects treatment outcomes. NASH-related HCC is associated with poorer OS than HCC in patients with cirrhosis from other etiologies.[43]

In addition to the impact of alcohol on treatment outcome, our study revealed the other factors that affect the risk of mortality, including the presence of portal

hypertension, serum AFP > 100 ng/mL and larger tumor size. Consistent with the findings of a previous study, Scheiner *et al* demonstrated that portal hypertension was a significant poor prognostic factor in HCC patients undergoing TACE. After TACE, transient hepatic hypoxia enhanced the upregulation of vascular endothelial growth factor, which plays a significant role in cirrhosis progression and dysfunction.[44, 45] Tumor burden is another factor that affects the prognosis of HCC. A larger tumor size provides higher tumor volume resulting in a worse prognosis, which is consistent with the results of our study. A previous study reported that the elevation of serum AFP levels correlated with the tumor size in HCC.[46] In our study, patients with serum AFP levels of more than 100 ng/mL showed an increase in the risk of death with an odds ratio of 2.5. This supports that AFP is not only a diagnostic tool but also a prognostic tool of HCC.

Our study has several limitations. First, this was a single center study conducted in a tertiary care center in a developing country in Southeast Asia. According to a previous study by our group, the rate of adherence to the international guidelines of HCC treatment in developing Asian countries was decreased because of the regional culture in which the aggressive treatment options were not preferred extensively in patients with non-curative malignancies.[47] Second, this study was retrospective in nature. All variables were obtained from a review of medical records, which may have caused misclassification bias and missing data. Minimization of these errors was attempted using two independent reviewers, and a third reviewer made the final decision in case discrepancies were found. Third, some information that might affect survival (e.g., data on non-alcoholic fatty liver disease, viral status, and alcohol abstinence) was unavailable. Finally, the study population size was relatively small, and the number of patients among the two groups was disproportionate (53 in group A and 16 in group B). A future prospective study with a larger sample size and appropriately balanced heterogenous participants to eliminate bias and confirm the findings of this study is needed.

CONCLUSION

In HCC BCLC B, patients with chronic viral hepatitis concurrent with alcohol consumption had a decreased CR rate and survival post-TACE than those who had viral hepatitis infection only. Alcohol consumption was observed as an independent risk factor of increased mortality after TACE in individuals with viral hepatitis. The burden of alcohol is high globally and is avoidable, although difficult to prevent. The results of this study remind us that alcohol consumption will continue to be important, and strategies modified for these factors to limit their impact at the individual and population levels need to be continued.

ARTICLE HIGHLIGHTS

Research background

Alcohol consumption increases the risk of hepatocellular carcinoma (HCC) in patients with pre-existing liver disease, including viral hepatitis. However, the impact of alcohol consumption on the outcomes of HCC remained questionable

Research motivation

We hypothesized that alcohol had an additional effect with chronic viral hepatitis infection on treatment outcomes after transarterial chemoembolization (TACE) in patients with intermediate-stage HCC (Barcelona Clinical Liver Cancer [BCLC] -B).

Research objectives

We aims to evaluate the additional effect of alcohol on treatment outcomes of TACE among HCC patients with viral hepatitis.

Research methods

We conducted a retrospective review the records of 69 HCC patients with viral hepatitis classified as BCLC B who underwent TACE as the first-line treatment between 2014 and 2019 at Hatyai Hospital. Patients with chronic viral hepatitis only were categorized

under group A and those with chronic viral hepatitis and concurrent alcohol consumption were categorized under group B. Both groups were compared, and the Cox proportional hazards model was used to identify variables influencing survival.

Research results

We find that patients who had chronic viral hepatitis alone had a statistically significantly higher proportion of complete response (24.5% vs. 0%, P = 0.030) and a higher median survival rate (26.2 mo vs. 8.4 mo; log–rank P = 0.012) than those with chronic viral hepatitis concurrent with alcohol consumption. Alcohol consumption was an independent factor associated with decreased survival in the proportional hazards model included (hazards ratio [HR], 2.377; 95% confidence interval [CI], 1.109–5.095; P = 0.026).

Research conclusions

In HCC BCLC B patients with chronic viral hepatitis, alcohol consumption is an independent risk factor for increased mortality and decreases the rate of complete response and survival after TACE.

Research perspectives

This research underscore that alcohol consumption leads to worse outcomes after TACE in intermediate stage HCC patients with chronic viral hepatitis.

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