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Analysis of factors affecting the prognosis of transcatheter arterial chemoembolization for hepatitis B-related hepatocellular carcinoma

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ABSTRACT

Objectives: The purpose of this study was to investigate the prognostic factors for transcatheter arterial chemoembolization (TACE) for hepatitis B-related hepatocellular carcinoma (HCC).

Materials and methods: The variables that may affect overall survival (OS), such as age, gender, AFP, Child Pugh classification, body mass index, HBV-DNA, HbeAg, tumor number, tumor diameter, BCLC stage, embolization method, ablation therapy, and targeted therapy, were analyzed by single factor and many factor COX regression. In addition, predictive factors of OS were stratified and a Kaplan-Meier survival curve was drawn.

Results: Among the 136 patients, the median follow-up time was 14.5 months (range: 2–72 months). HCC patients with the tumor diameter <3 cm had the highest survival rate, followed by patients with a tumor diameter of 3–5 cm; the survival rate of patients with the tumor diameter (greater than 5 cm) was the lowest. Among the BCLC stages, stage A patients had the highest survival rate, followed by stage B and stage C patients, which had the lowest survival rate.

The survival rate of Child Pugh grade A patients was higher than those with Child Pugh grade B. Compared with patients who did not undergo ablation treatment, the survival rate of patients with combined ablation treatment was relatively high. The survival rate of patients receiving drug-eluting beads transarterial chemoembolization (DEB-TACE) treatment was higher than those receiving conventional transarterial chemoembolization (cTACE) treatment. Additionally, repeated TACE treatment improved the OS rate of patients. These six factors were related to patient prognosis and the differences were statistically significant ($P < 0.05$).

Conclusions: Tumor diameter, BCLC stage, TACE repetition, and TACE combined with ablation were independent prognostic factors of OS.

1. Introduction

Hepatocellular carcinoma (HCC) accounts for more than 80% of all primary liver cancers and is the second leading cause of cancer-related deaths.[1] Greater than 85% of HCC patients are infected with hepatitis B virus (HBV), which is an important risk factor for HCC development.[2] Transarterial chemoembolization (TACE) is the first-line treatment for patients with HCC who are not appropriate candidates for surgical intervention.[3] Conventional TACE (cTACE) includes a super selective injection of iodized oil and chemotherapeutic drugs into the artery supplying blood to the tumor, which causes tumor necrosis through cellular ischemia and cytotoxicity. With the continuous improvement of embolization materials, CalliSpheres microspheres have attracted increasing attention from many scholars as new chemotherapeutic drug delivery carriers. Compared with cTACE, drug-eluting bead TACE (DEB-TACE) has the advantages of permanent embolization of the tumor blood supply and sustained slow release of chemotherapeutic drugs. This helps maintain the local concentration of chemotherapeutic drugs for a longer time, thereby achieving a higher objective response rate.[4,5]

However, in HCC patients who received TACE treatment alone, the complete tumor necrosis rate has been low and the residual tumor and recurrence rates have been high. One possible reason for this is that it is difficult to embolize all of the tumor's arteries, especially small branch vessels. Another treatment option, Percutaneous thermal ablation is considered the best local treatment option for focal unresectable lesions. Radiofrequency ablation (RFA) and microwave ablation (MWA) are the two main types of ablation treatments. The basic principle of these treatments is the use of thermal energy to destroy tumor cells or tissues, resulting in their coagulative necrosis. They have potential as important treatment strategies for HCC recurrence after TACE.[6–8] Percutaneous

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thermal ablation does achieve a significant curative effect; however, it is also plagued by a high incidence of local recurrence and intrahepatic metastasis. In addition, the local ischemic and hypoxic environment that occurs after TACE can stimulate the expression of vascular endothelial growth factor, leading to neovascularization of the tumor and the formation of collateral circulation, which promotes tumor recurrence and metastasis. If TACE treatment is combined with targeted therapy, it can prevent the neovascularization of tumor tissues and completely block the blood supply. In short, a large number of clinical studies have confirmed that combined multimodal treatment can effectively control disease progression and improve the overall survival (OS) of HCC patients.[9,10]

Due to the mutual influence of different prognostic factors, such as the general condition of the patient, the baseline characteristics of the tumor, and treatment options, OS in HCC patients is a composite clinical end point. However, with the continuous improvement of embolization materials and an increase in treatment methods, the weight of these influencing factors on the OS of HCC patients may shift. Therefore, this study includes patient nutritional status, Child-Pugh grade, preoperative serum alpha-fetoprotein (AFP) level, baseline tumor characteristics, and different treatment options in a prognostic risk assessment to explore the influential factors of OS in patients with hepatitis B-related HCC.

2. Methods

2.1. Patients

HBV-related HCC was diagnosed according to the standard of "Primary Liver Cancer Diagnosis and Treatment." Data from patients (N = 136) who were treated with TACE in our hospital from February 2014 to March 2020 were collected. Patients had not received any treatment other than antiviral therapy before TACE treatment. Inclusion criteria were: (1) Child-Pugh grade A or B; (2) HBV-related HCC; (3) complete relevant examinations before treatment, including serum AFP, hepatitis etiology, hepatitis B virus deoxyribonucleic acid (HBV-DNA), and (computed tomography) CT/magnetic resonance imaging (MRI); and (4) repeated TACE treatment that was consistent with the first TACE method. Exclusion criteria were: (1) malignant tumors at other sites; (2) received other treatments before TACE; (3) repeated TACE treatment that was inconsistent with the first treatment method; and (4) unstable systemic disease or uncontrolled infection. This study was approved by the Research Ethics Committee of the Second Affiliated Hospital of Kunming Medical University, Kunming City, China. Because the study was retrospective, informed consent was not required.

2.2. Data collection

General data from patients were collected before TACE treatment, including age, sex, height, and weight. Body mass index (BMI) was calculated by dividing the body weight (kg) by the height squared (m^2). According to the BMI classification standard of the "Chinese Obesity Surgical Treatment Guidelines",[11] patients were divided into low body weight (BMI $<$ 18.5 kg/m^2), normal body weight (BMI 18.5–23.9 kg/m^2), and overweight (BMI 24.0–27.9 kg/m^2). Routine imaging included liver dynamic contrast-enhanced CT or MRI. Two physicians with more than 5 years of experience in abdominal imaging blindly evaluated the baseline characteristics of the tumors (tumor number, tumor diameter, and Barcelona clinic liver cancer [BCLC] stage). When disagreements occurred, an agreement was reached after consultation. In addition, relevant laboratory tests were completed, including liver function, serum AFP, and HBV-DNA. The specific embolization method used during TACE was recorded and included either cTACE or DEB-TACE (CalliSpheres, Suzhou Hengrui Jialisheng Biomedical Technology Co., Ltd., Jiangsu, China) Follow-up assessments were performed every 3 to 4 months following treatment, and re-examination was performed via contrast-enhanced CT or MRI of the abdomen and laboratory examinations. The patient imaging data (CT or MRI) were evaluated according to the solid tumor remission assessment standard (modified response evaluation criteria in solid tumors, MRECIST). After determination of tumor recurrence during the follow-up process, repeat TACE or RFA/MWA alone or combined with targeted therapy was carried out based on liver function status, BCLC stage, and HCC recurrence location. The number of TACE treatments and specific combination treatments were recorded. OS was defined as the time from the date of the first TACE to death or the last follow-up.

2.3. Treatments

All of the TACE treatments were performed using a digital subtraction angiography machine (Philips FD-20, Netherlands). After a successful puncture of the femoral artery using the Seldinger technique, abdominal cavity angiography was used to identify the tumor supply artery, and the 2.7-F microcatheter (Progreat; Terumo, Japan) was advanced to the artery using the coaxial catheter method. In the DEB-TACE group, CalliSpheres embolization microspheres (100–300 μm) were used, and 50 mg of epirubicin was loaded into the microspheres. After confirming the adsorption of epirubicin by the CalliSpheres microspheres, a high concentration of non-ionic contrast agent (iophorol, 33.9 g iodine/mL) was added at a volume ratio of 1: 1. The microspheres were shaken gently and allowed to stand for 5 min before use. A 1-ml or 2-ml syringe was used to extract the drug-loaded microspheres, and the embolization agent was slowly inserted into the lesion through the microcatheter (pulse injection was used; injection speed was 1–2 mL/min). The end point of embolism was the stagnation of contrast agent flow in the tumor blood supply artery during angiography. In the cTACE group, iodized oil and epirubicin were fully mixed and emulsified. The procedure and end point of embolization were the same as those in the DEB-TACE group. If the artery was abnormally slender and could not be completely embolized, RFA (RFA-1315 multipolar RFA electrode, Beijing Blacklight Optoelectronic Technology Co., Ltd., Beijing, China) or MWA (EC0-100AL8, Nanjing Yigao Microwave System Engineering Co., Ltd., Nanjing, China) were combined within one week following TACE treatment. The ablation treatment was completed under CT guidance, and the ablation range was at least 0.5 cm larger than the entire tumor range. Patients treated with TACE combined with targeted therapy were administered apatinib orally (500 mg/day) within two weeks of TACE treatment. If intolerable side effects occurred, the dose was reduced to 250 mg/day. If the patient still could not tolerate the side effects or disease progression was confirmed, apatinib treatment was discontinued.

2.4. Factor analysis

Univariate and multivariate Cox regression analyses were used to analyze the relationship between the general patient condition, baseline tumor characteristics, treatment methods, and other variables related to OS. General relevant variables included: age ($\geq$60 or $<$ 60 years), sex (male or female), AFP level ($\geq$200 or $<$ 200 ng/mL), liver function Child-Pugh classification (grade A or B), BMI ($<$18.5, or 18.5–23.9, or $\geq$ 24 kg/m^2), HBV DNA level ($\geq 10^5$ or $< 10^5$ IU/mL), and hepatitis B e-antigen (positive or negative). Variables related to tumor baseline characteristics included tumor number (single or multiple), tumor diameter ($<$3, 3–5, or $>$ 5 cm), and BCLC stage (stage A, B, or C). Treatment-related variables included embolization method (DEB-TACE or cTACE), whether the treatment was combined with targeted therapy (yes or no), whether it was combined with ablation therapy (yes or no), and the number of repeated TACE treatments during follow-up (1–2, 3–4, or $\geq$ 5 times).

2.5. Statistical analyses

The count data and grade data in this study are expressed as frequency (percentage). Univariate and multivariate Cox regression analyses were used to evaluate the factors influencing OS following TACE. The potential risk factors with a $P \leq 0.05$ in the univariate analysis were

Table 1
The characteristics of the 136 HCC patients.

Features	No. of cases (%)
Age (≧60/<60 years)	48 (35.3%)/88 (64.7%)
Gender (Male/Female)	116 (85.3%)/20 (14.7%)
Tumor number (solitary/multiple)	50 (36.8%)/86 (63.2%)
Child-Pugh class (A/B)	105 (77.2%)/31 (22.8%)
Targeted therapy (yes/no)	18 (13.2%)/118(86.8%)
TACE (DEB-TACE/c-TACE)	56 (41.2%)/80 (58.8%)
Ablation (yes/no)	42 (30.9%)/94 (69.1%)
TACE repetition	
1–2	64 (47.1%)
3–4	46 (33.8%)
≧5	26 (19.1%)
Serum AFP level (ng/ml)	
≧200	49 (36.0%)
<200	87 (64.0%)
Tumor diameter (cm)	
<3	26 (19.1%)
3–5	21 (15.4%)
>5	89 (65.4%)
HBeAg (serum)	
Negative	125 (91.9%)
Positive	11 (8.1%)
HBV DNA (IU/mL)	
$\geq 10^5$	14 (10.3%)
$<10^5$	122 (89.7%)
BCLC stages	
A	34 (25.0%)
B	46 (33.8%)
C	56 (41.2%)
BMI (kg/m2)	
<18.5	13 (9.6%)
18.5–23.9	101 (74.3%)
≧24	22 (16.2%)

TACE = transarterial Chemoembolization, AFP = alpha-fetoprotein, HBV-DNA = hepatitis B virus deoxyribonucleic acid, BCLC= Barcelona Clinic Liver Cancer, BMI = Body Mass Index.

input into the multivariate Cox model to evaluate the independent prognostic factors of OS. To study the factors affecting OS rate, stratified analysis was carried out using the Kaplan-Meier method. All statistical analyses were performed using SPSS 17.0 software (IBM, Armonk, NY, USA). The test level was set to $\alpha = 0.05$, and variables with $P < 0.05$ were defined as statistically significant.

3. Results

3.1. Baseline statistics

Patients (N = 136) with hepatitis B-related HCC who met the inclusion criteria were selected for TACE treatment; baseline characteristics and treatment methods are shown in Table 1. The mean patient age was 55.1 ± 11.7 years, the majority were males (85.3%), and 122 (89.7%) patients had HBV DNA levels $< 10^5$ IU/mL. Almost all of the patients had acceptable liver function (Child-Pugh A/B: 105/31). Among the tumor markers, serum AFP was increased ≥200 μg/L in 49 (36.0%) cases. The mean diameter of the tumors was 6.75 ± 3.87 cm, and multiple tumors were detected in 86 (63.2%) patients. In terms of embolization methods, 56 (41.2%) patients received DEB-TACE and 80 (58.8%) patients received cTACE treatment. Most patients (80.1%) underwent repeated TACE treatment. In addition, some patients received TACE combined with targeted therapy (13.2%) and ablation therapy (30.9%). Regarding BCLC staging, 34 (25.0%) patients were stage A, 46(33.8%) were stage B, and 56(41.2%) were stage C. BMI results showed 13(9.6%), 101(74.3%), and 22(16.2%) cases were underweight, normal, and overweight patients, respectively.

3.2. Prognostic factors

Single factor analysis showed that tumor diameter ($P = 0.000$), BCLC stage ($P = 0.000$), Child-Pugh classification ($P = 0.041$), embolization method ($P = 0.048$), TACE repeat ($P = 0.000$), and ablation therapy ($P = 0.001$) were the influencing factors of OS. These six factors were selected as candidates for multivariate analysis. Multivariate Cox regression analysis showed that tumor diameter (Hazard ratio [HR] = 1.631, $P = 0.001$), BCLC stage (HR = 1.734, $P = 0.000$), TACE repeat (HR = 0.408, $P = 0.000$), and combined ablation (HR = 1.630, $P = 0.024$) were independent prognostic factors for OS (Table 2).

3.3. Survival rate of patients following TACE

Among 136 patients, the median follow-up time was 14.5 months (range: 2–72 months). Altogether, 13 (9.5%) patients were lost to follow-up. Factors with statistically significant differences in the univariate analysis were stratified, and the Kaplan-Meier survival curve of patient OS was drawn (Fig. 1). The results showed that the survival rate of HCC patients with a tumor diameter <3 cm before treatment was the highest, followed by the patients with a tumor diameter of 3–5 cm, and subsequently by patients with a tumor diameter (>5 cm) (Fig. 1A). For BCLC staging, the survival rate of patients with stage A was the highest, followed by stage B, and subsequently by patients with stage C (Fig. 1B). The survival rate of patients with Child-Pugh grade A was higher than those with Child-Pugh grade B (Fig. 1C). Fig. 1D shows the survival rate of patients with combined ablation treatment was relatively higher compared with patients who did not receive ablation treatment ($P = 0.001$). In addition, Fig. 1E shows the survival rate of patients following

Table 2
Prognostic factors for overall survival in patients with HCC by univariate and multivariate analysis.

Variables	Univariate analysis			Multivaiate analysis		
	HR	95%CI	*p*	HR	95%CI	*p*
Age	1.084	(0.747, 1.572)	0.672			
Gender	0.671	(0.401, 1.122)	0.128			
Tumor number	1.368	(0.940,1.990)	0.101			
Child-Pugh class	1.549	(1.019,2.355)	0.041			
Targeted therapy (yes/no)	0.977	(0.577,1.657)	0.977			
TACE(DEB-TACE/c-TACE)	1.446	(1.003,2.084)	0.048			
Abltion (yes/no)	2.031	(1.362,3.029)	0.001	1.630	(1.068, 2.487)	0.024
TACE repetition	0.474	(0.372,0.604)	0.000	0.408	(0.312, 0.532)	0.000
Serum AFP level	0.716	(0.496,1.033)	0.074			
Tumor diameter	1.761	(1.367, 2.267)	0.001	1.631	(1.221,2.117)	0.001
HBeAg	0.875	(0.457,1.672)	0.685			
HBV DNA	0.670	(0.383,1.171)	0.160			
BCLC stages	1.953	(1.528,2.497)	0.000	1.734	(1.294, 2.323)	0.000
BMI	0.693	(0.469,1.023)	0.065			

TACE = transarterial Chemoembolization, AFP = alpha-fetoprotein, HBV-DNA = hepatitis B virus deoxyribonucleic acid, BCLC= Barcelona Clinic Liver Cancer, BMI = Body Mass Index, HR = hazard ratio, 95%CI = 95% confidence interval.

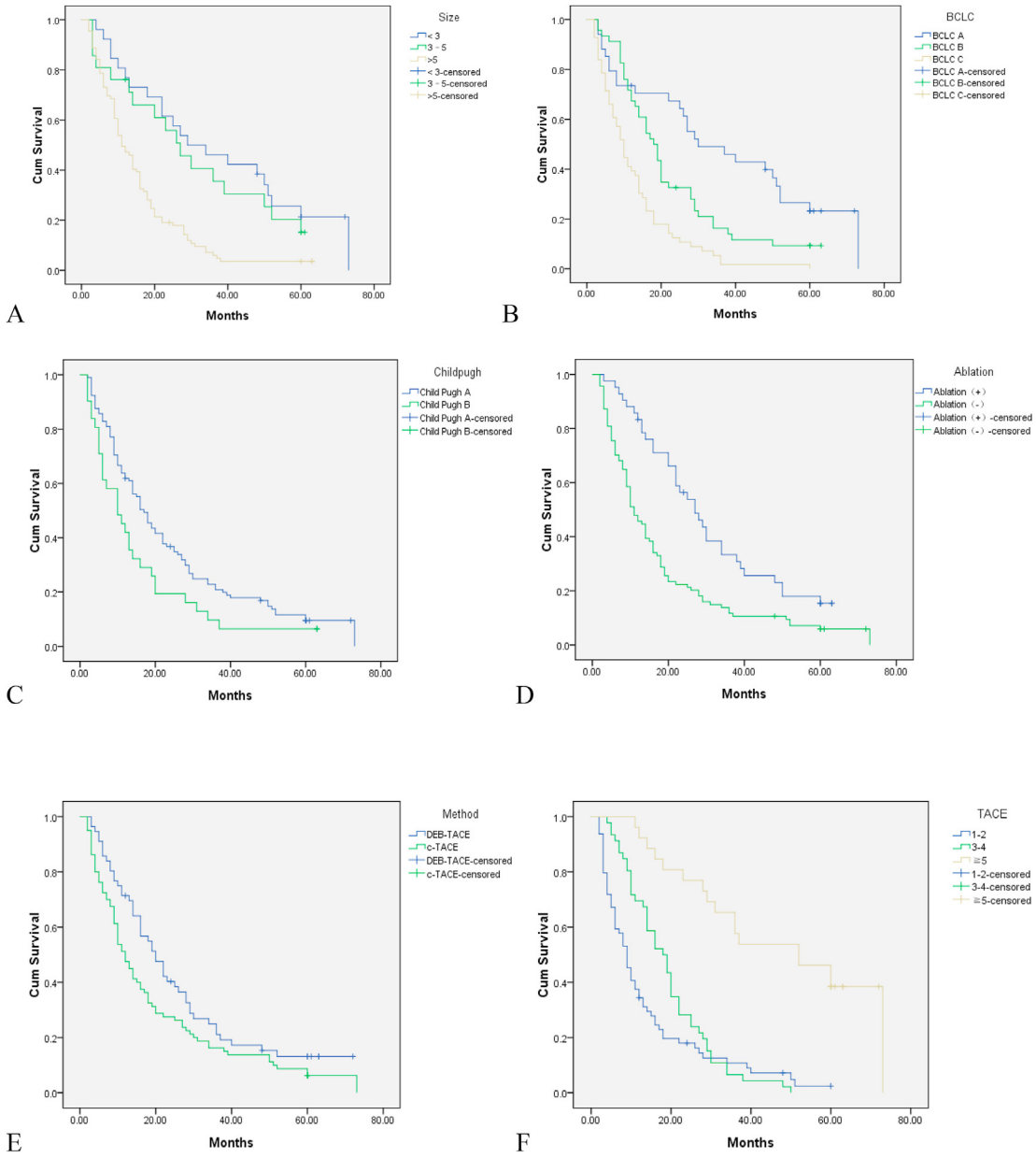

Fig. 1. Kaplan-Meier OS survival curve of 136 patients receiving TACE. The OS rate was stratified by the tumor diameter (A), BCLC stage (B), Child Pugh classification (C), ablation (D), embolization method (E) and repeated TACE treatment (F).

DEB-TACE treatment was higher than that of patients who received cTACE treatment ($P = 0.048$). Furthermore, repeated TACE treatment improved the OS rate of patients (Fig. 1F), and the differences were statistically significant ($P < 0.05$).

4. Discussion

The prognosis of patients with HBV-related HCC following TACE treatment is dependent not only on the characteristics of the tumor but also on the patient's general condition, liver function reserve, and subsequent treatments. Therefore, identification of the relevant prognostic factors and the appropriate quantification of the weight of each factor are essential for evaluating prognosis. This study retrospectively analyzed the correlation between baseline data, tumor characteristics, embolization schemes, and subsequent TACE treatment with OS in 136 HCC patients. The results showed that factors such as BCLC staging, tumor diameter, local ablation treatment, and repeated TACE were independent factors affecting the prognosis of patients. Among these factors, BCLC staging and repeated TACE treatment have a more significant impact on patient survival time.

BCLC staging is one of the most commonly used HCC staging systems. This staging involves multiple variables, such as tumor burden, liver function reserve, and tumor aggressiveness, is crucial for both prognosis and treatment decisions, and is now widely accepted in clinical practice.[12,13] In this study, univariate and multivariate Cox regression analyses showed that BCLC stage and tumor diameter determined the OS of patients following TACE treatment, independent of subsequent treatments.

With the development of new treatment methods, a growing number of treatment programs have been used clinically. CalliSpheres microspheres are network-structured microspheres that load drugs through ion exchange and hydrogen bonding. This is a reversible process. When the external environment changes, the adsorbed drug molecules are released from the microspheres due to their interaction with other ions. Compared with cTACE, DEB-TACE has the advantages of long-term embolization and a slow and stable drug release. In this study, the OS in the DEB-TACE

group was higher than that of the cTACE group ($P < 0.05$). Since the loaded drug is continuously and slowly released, it plays a greater role in inhibiting and killing tumor cells, causing toxic necrosis of the cells, increasing the anti-tumor effect, and prolonging the time to disease progression.

Both RFA and MWA are thermal coagulation treatments that utilize the high temperature effect to induce necrosis of tumor cells.[14] Because HCC has multiple sources of blood supply, it is difficult to embolize all of the tumor supply arteries with TACE alone. Consequently, the establishment of collateral circulation after embolization results in residual tumor presence and disease recurrence. Therefore, TACE combined with RFA or MWA can compensate for the deficiencies of TACE alone. Through the heat deposition effect, the residual tumor is ablated and the small blood vessels around the tumor are occluded, reducing the chance of local tumor recurrence and prolonging OS. In this study, univariate and multivariate Cox regression analyses showed that TACE combined with RFA or MWA was an independent prognostic factor and was a positive factor in improving OS.

Apatinib mesylate is an oral tyrosine kinase inhibitor that inhibits tumor angiogenesis by inhibiting vascular endothelial growth factor receptor 2, thereby improving the prognosis of patients. For patients with advanced HCC, combined treatment with apatinib following TACE can prolong overall survival. Lu et al.[15] compared 44 patients treated with TACE alone to those treated with TACE combined with apatinib and found that apatinib prolonged the progression-free survival of patients with HCC. Chen et al.[16] showed that patients receiving TACE-apatinib had a longer OS than those treated with TACE alone. In this study, targeted therapy was not identified as an influencing factor of OS. It is worth noting that only 18 patients received targeted therapy and the sample size was small. Therefore, it is necessary to expand the sample size for further analysis.

Our data show that patients treated with repeated TACE treatments $\geq$5 had a relatively long OS and this was an independent prognostic factor of OS. This may be due to better local tumor control, leading to better OS. The results of the univariate analysis show that Child-Pugh classification is an important predictor of prognosis. Frequent TACE treatment aggravates the deterioration of liver function. This study only explored the effect of Child-Pugh classification on prognosis before TACE treatment. The relationship between repeated TACE treatment and postoperative liver function and prognosis requires further study.

The liver is the central organ of nutritional metabolism, and the risk of malnutrition is high in patients with cirrhosis. Malnutrition is closely related to shortened survival and increased mortality in patients with HCC.[17] In the univariate analysis from this study, the correlation between BMI and OS was almost statistically significant. Lee et al.[18] measured the cross-sectional area of skeletal muscle on the third lumbar vertebra (L3) by CT and analyzed the correlation between the L3 skeletal muscle index and OS. The results showed that muscle consumption is an independent prognostic factor for OS in patients with HCC. The current study only used BMI to assess nutritional status, which may be confused by edema and ascites caused by liver cirrhosis. Therefore, other more reliable quantitative indicators should be considered in further evaluations. In addition, a high level of HBV-DNA is a risk factor for OS. Preoperative standard antiviral treatment can reduce the risk of hepatitis episodes caused by viral activation, improve liver function, and reduce the risk of HCC recurrence. In this study, HBV-DNA levels were not an influencing factor of OS, which may be due to the radical antiviral therapy patients received prior to TACE treatment in most HBV-related HCC patients.

The main limitation of this study is that all of the data were collected retrospectively thus there may be selection bias. The sample size was small which can lead to an overinflation of any effect detected. A larger multi-center study assessing a wider range of influencing factors should be considered.

5. Conclusion

For patients with HBV-related HCC who received TACE as the initial treatment, factors such as tumor diameter, tumor BCLC stage, Child-Pugh classification, TACE embolization regimen, repeated TACE treatment, and ablation treatment, were related to OS. Among these factors, BCLC stage, tumor diameter, repeated TACE treatment, and ablation treatment were factors affecting OS.

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