Original Article

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Sorafenib combined with TACE improves survival in patients with hepatocellular carcinoma with vascular invasion

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SUMMARY Sorafenib is a recommended first-line therapy for advanced hepatocellular carcinoma (HCC). However, when used as monotherapy in patients in advanced stages, the prognosis remains suboptimal. This study aimed to evaluate the impact of transcatheter arterial chemoembolization (TACE) on survival outcomes in patients with advanced HCC treated with sorafenib, as well as to identify which subgroups may benefit most from the addition of TACE. This single-institution retrospective study included 92 patients diagnosed with Barcelona Clinic liver cancer (BCLC) stage C HCC who received sorafenib between August 2011 and December 2016. We assessed the influence of different treatment modalities on prognosis using multivariable regression analysis. Patients were categorized into three subgroups: those with vascular invasion, those with distant metastasis, and those with both risk factors. Baseline comparisons indicated no significant differences in clinical characteristics among the three groups. Survival analysis showed no statistically significant difference in overall survival (OS) between the subgroups. However, in the overall cohort of patients with BCLC stage C, multifactorial Cox regression analysis identified pre-treatment alpha-fetoprotein (AFP) levels (p = 0.020), alkaline phosphatase (ALP) levels (p = 0.034), and the absence of combination TACE therapy (p = 0.008) as independent risk factors affecting OS. Further subgroup Cox analyses revealed that the lack of combination TACE therapy was an independent risk factor for OS in both the vascular invasion group and the group with both risk factors. In conclusion, for patients with advanced HCC receiving sorafenib, the addition of TACE may enhance long-term survival, particularly in those with vascular invasion.

Keywords sorafenib, transcatheter arterial chemoembolization, hepatocellular carcinoma, cancer therapy

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent malignant tumors worldwide (*1*). Early-stage liver cancer can be effectively treated through radical surgery or liver transplantation (*2*). However, due to the insidious nature of liver cancer, most patients are diagnosed at an advanced stage, missing the optimal window for surgical intervention (*3,4*). The advanced stage, classified as Barcelona Clinic liver cancer (BCLC) stage C, encompasses patients with vascular invasion, metastasis, or both, which are associated with poor prognostic indicators (*5*). For patients with BCLC stage C, the introduction of the targeted therapeutic agent sorafenib represents a significant advancement in treatment (*6*). Sorafenib, recognized as the first targeted agent to improve the long-term prognosis of patients with advanced HCC, has demonstrated its efficacy in a multicenter phase 3 clinical trial (*7*). Consequently, it is considered a first-line treatment option for advanced liver cancer in many clinical guidelines (*5,8*).

However, the prognosis for patients with advanced HCC treated solely with sorafenib remains suboptimal (*9*). Consequently, several studies are exploring the use of sorafenib in combination with other therapies to enhance the prognosis of advanced liver cancer (*10,11*).

However, there is a paucity of research investigating the combination of sorafenib with interventional therapies. As a result, it remains controversial whether patients with advanced HCC are appropriate candidates for sorafenib combined with transcatheter arterial chemoembolization (TACE) therapy. This study aims to compare the efficacy of sorafenib combined with TACE therapy against sorafenib monotherapy, investigating whether the addition of TACE can improve outcomes for patients with advanced HCC.

Advanced HCC involves vascular invasion and distant metastasis, both of which significantly impact the prognosis. In large prospective cohorts of patients with BCLC stage C, survival rates vary significantly (*12*). The primary goal of the staging system is to classify patients into subgroups based on prognosis and tailor treatments accordingly. However, the current staging has limitations, and further subdivisions are needed for greater precision (*5*). This study aims to analyze patients with advanced HCC with varying risk factors to identify prognostic differences between subgroups and explore appropriate treatment options for each.

2. Materials and Methods

2.1. Patients

We retrospectively reviewed the records of 182 patients with BCLC stage C liver cancer who received sorafenib treatment between August 2011 and December 2016 at Tianjin Medical University Cancer Institute and Hospital (Figure 1). All patients were classified according to the BCLC staging system. The inclusion criteria were: (1) treatment with sorafenib and (2) availability of complete follow-up data and adequate clinical pathology information. Patients (n = 30) lacking adequate clinical information were excluded, as were those with BCLC stage B (n = 23) or Child-Pugh class C cirrhosis (n = 37). Ultimately, 92 patients met the inclusion criteria and were included in the analysis. To ensure objectivity, all researchers were blinded to clinical outcomes during data collection. This study followed the principles of the Declaration of Helsinki (revised in 2013) and was approved by the Ethical Committee of Tianjin Medical University Cancer Institute and Hospital, with the requirement for informed consent waived. All data were anonymized to protect patient identities before analysis.

2.2. Classification of vascular invasion and metastasis

Patients were classified into three groups based on tumor characteristics: (1) vascular invasion only (n = 24), (2) metastasis only (n = 48), and (3) both vascular invasion and metastasis (n = 20). Vascular invasion was further subdivided into four categories: involvement of the branch portal vein alone (n = 21), the left, right, or main portal trunk (n = 9), the hepatic vein (n = 4), and combined involvement of the portal and hepatic veins (n = 10). Metastasis was categorized into three groups: lymph node metastasis alone (n = 25), distant organ metastasis alone (n = 7), and both types (n = 36). It is important to differentiate vascular invasion from vascular thrombosis, which is characterized by arterial enhancement, portal vein dilation, or the formation of

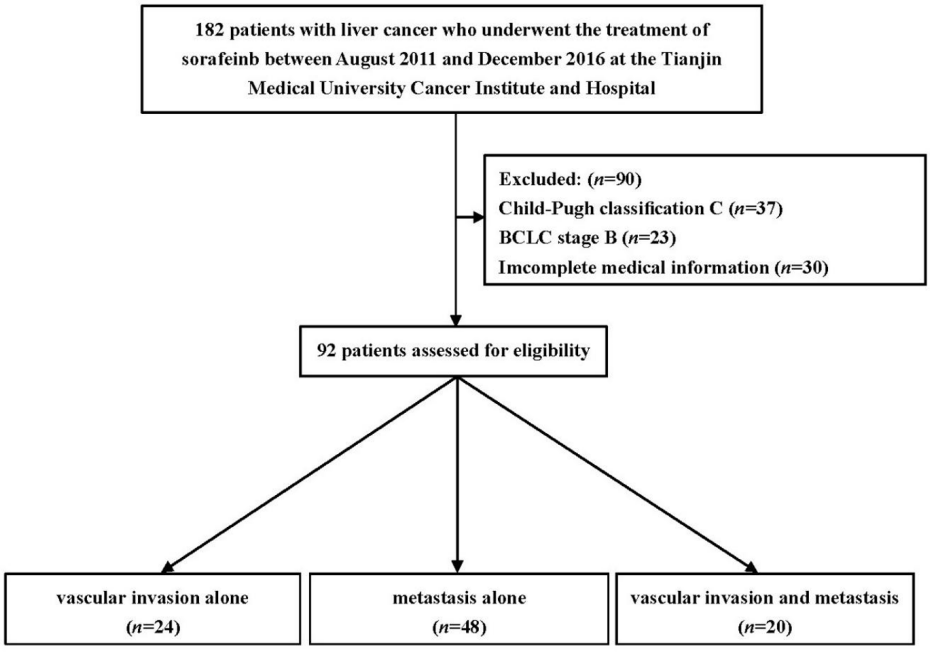

Figure 1. Flowchart of patient selection. BCLC, Barcelona Clinic Liver Cancer.

new thrombi adjacent to the tumor. Metastatic lymph nodes were diagnosed through histological examination or radiographic evidence of enlarged nodes.

2.3. Clinical characteristics of patients with BCLC stage C liver cancer

The data collected included demographic information (sex) and clinical history, such as pre-treatment alpha-fetoprotein (AFP), total bilirubin (TBIL), alkaline phosphatase (ALP), albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT) levels, hepatitis B virus/hepatitis C virus (HBV/HCV) status, liver cirrhosis, and ascites. Additionally, information regarding adjuvant therapies, including TACE and surgical history, was documented.

2.4. Postoperative management

Patients were followed up every three months with serum AFP measurements and imaging studies, which included magnetic resonance imaging (MRI), computed tomography (CT), or ultrasound. Overall survival (OS) was calculated from the initiation of sorafenib treatment; both clinical data and follow-up outcomes were meticulously recorded. We considered follow-up periods shorter than three months to be lost to follow-up. For patients who survived the follow-up period, the date of the last follow-up was recorded.

2.5. Statistical analysis

Patient data were analyzed using IBM SPSS Statistics for Windows (version 29.0; IBM Corp., Armonk, NY, USA). Continuous variables were compared using unpaired *t*-tests, while categorical variables were analyzed using Mann–Whitney *U* tests. OS was estimated using the Kaplan–Meier method, with significance between groups assessed using the log-rank test. Multivariable analyses for OS were conducted, incorporating all significant variables identified through univariate analysis and utilizing Cox proportional hazards regression analysis. All statistical tests were two-sided, with a significance level set at $p < 0.05$.

3. Results

3.1. Baseline clinical characteristics and prognostic factors of 92 patients with BCLC stage C HCC

The demographics, clinical characteristics, and adjuvant therapies of all patients with BCLC stage are summarized in Table 1. Among the 92 patients, 82 were male, and 31 received TACE. Additionally, 65 patients had a history of chronic hepatitis virus B infection, while three had chronic hepatitis C infection. The numbers of patients with vascular invasion, metastasis, and both conditions were 24, 48, and 20, respectively. No statistically significant difference in OS was observed among the three groups (vascular invasion *vs.* metastasis, $p = 0.678$; vascular invasion *vs*. both, $p = 0.637$; metastasis *vs.* both, $p = 0.995$; Figure 2A). Furthermore, the differences in baseline clinical characteristics among the vascular invasion group, the metastasis group, and the group with both risk factors were not statistically significant. We then incorporated these clinical characteristics into the subsequent survival analysis. Univariate analysis identified four clinical characteristics — pre-treatment AFP, ALP, non-co-application of TACE, and the surgical history — as risk factors related to the survival of patients with BCLC

Table 1. Baseline clinical characteristics in the 92 HCC patients with BCLC stage C

BCLC stage C HCC patients ($n = 92$)	Vascular invasion ($n = 24$)	Metastasis ($n = 48$)	Both ($n = 20$)	*p*-value
Sex male/female	22/2	42/6	18/2	0.859
HBV (Yes/No)	18/6	32/16	15/5	0.684
HCV (Yes/No)	1/23	2/46	0/20	0.653
Liver cirrhosis (Yes/No)	19/5	33/15	15/5	0.629
PT(sec) >13.7/≤13.7	1/23	3/45	1/19	0.931
Pre-medication AFP (ng/mL)				0.312
>20/≤20	17/7	32/16	17/3	
TBIL (μmol/L) >21/≤21	12/12	23/25	11/9	0.869
ALB(g/L) >40/≤40	13/11	22/26	9/11	0.771
ALP (U/L) >125/≤125	13/11	21/27	13/7	0.266
ALT(U/L) >40/≤40	16/8	24/24	11/9	0.410
AST(U/L) >40/≤40	17/7	25/23	15/5	0.123
Accompanied by TACE				0.069
Yes	4	21	6	
No	20	27	14	
History of surgery (Yes/No)	10/14	24/24	7/13	0.501

HBV, hepatitis B virus; HCV, hepatitis C virus; PT, prothrombin time; AFP, alpha fetoprotein; TBIL, total bilirubin; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TACE, transcatheter arterial chemoembolization; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic liver cancer.

stage C. Specifically, pre-treatment AFP (p = 0.020, hazard ratio [HR] = 1.9; 95% confidence interval [CI], 1.1–3.1), ALP (p = 0.034, HR = 1.6; 95% CI, 1.0–2.5), and non-co-application of TACE (p = 0.008, HR = 2.1; 95% CI, 1.2–3.5) emerged as independent risk factors associated with OS in all patients with BCLC stage C (Table 2 and Figures 2B, 2C, and 2D). Notably, patients who received TACE demonstrated a better OS rate compared to those who did not. As highlighted in the introduction, vascular invasion and metastasis were identified as key risk factors in patients with BCLC stage C. Consequently, we divided the patients into three subgroups: those with vascular invasion, those with metastasis, and those with both risk factors. Our research further analyzed the survival effects of sorafenib in combination with TACE on patients with BCLC stage C liver cancer across these different subgroups.

3.2. Prognostic factors related to OS rates in patients with BCLC stage C HCC and vascular invasion alone

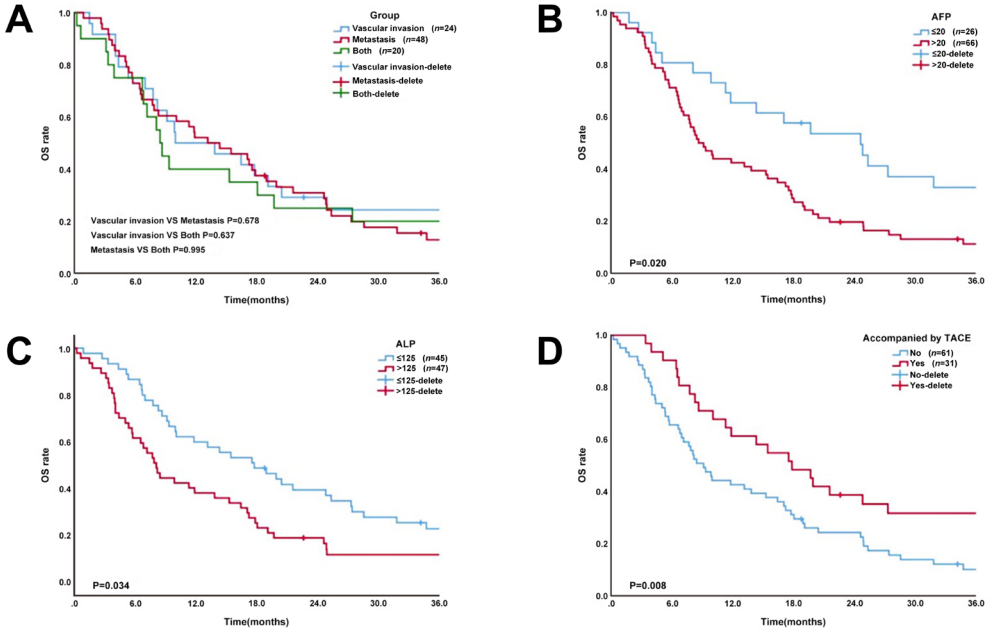

Figure 2. OS rates among patients with patients with BCLC stage C HCC. (A) Kaplan-Meier OS curves for subgroups of patients with advanced stage. **(B)** Kaplan-Meier OS curves based on AFP levels. **(C)** Kaplan-Meier OS curves based on ALP levels. **(D)** Kaplan-Meier OS curves comparing patients who received TACE with those who did not. (AFP, alpha fetoprotein; ALP, alkaline phosphatase; TACE, transcatheter arterial chemoembolization; OS, overall survival; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic liver cancer).

Table 2. Univariate and multivariate analysis of prognostic factors associated with OS in all 92 HCC patients with BCLC stage C

BCLC stage C HCC patients (n = 92)	Number	Univariate Analysis		Multivariate Analysis	
		three-year OS (%)	p-value	HR (95% CI)	p-value
Sex male/female	82/10	16.4/30.0	0.602		
HBV (Yes/No)	65/27	18.6/14.8	0.698		
HCV (Yes/No)	3/89	33.3/16.8	0.800		
Liver cirrhosis (Yes/No)	67/25	18.1/16.0	0.868		
PT(sec) >13.7/≤13.7	5/87	0.0/18.5	0.117		
Pre-medication AFP (ng/mL)			**0.007***		**0.020***
>20/≤20	66/26	11.3/33.0		1.9 (1.1,3.1)	
TBIL (μmol/L) >21/≤21	46/46	21.7/12.8	0.601		
ALB(g/L) >40/≤40	44/48	16.0/18.8	0.766		
ALP (U/L) >125/≤125	47/45	12.0/23.0	**0.040***	1.6 (1.0,2.5)	**0.034***
ALT(U/L) >40/≤40	51/41	22.7/10.3	0.137		
AST(U/L) >40/≤40	57/35	14.0/22.6	0.086		
Accompanied by TACE			**0.001***	2.1 (1.2,3.5)	**0.008***
Yes	31	31.7			
No	61	10.1			
History of surgery (Yes/No)	41/51	12.9/20.8	**0.046***		0.515

HBV, hepatitis B virus; HCV, hepatitis C virus; PT, prothrombin time; AFP, alpha fetoprotein; TBIL, total bilirubin; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TACE, transcatheter arterial chemoembolization; OS, overall survival; CI, confidence interval; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic liver cancer.

The variables included in the univariate and Cox multivariate analyses for patients with BCLC stage C and vascular invasion alone are summarized in Table 3. Following the univariate analysis for OS, the final multivariate model identified only one independent prognostic factor: the presence of TACE. The multivariate analysis indicated that patients in the TACE group had a significantly better OS rate compared to those in the non-TACE group (HR = 8.5; 95% CI, 1.1–65.3; $p = 0.040$; Figure 3A).

3.3. Prognostic factors related to OS rates in patients with BCLC stage C HCC and metastasis alone

The variables included in the univariate and Cox multivariate analyses for patients with BCLC stage C and metastasis alone are summarized in Table 4. After conducting the univariate analysis for OS, the final multivariate model revealed that there were no independent prognostic factors. However, the univariate analysis indicated that ALP level was a significant

Table 3. Univariate and multivariate analysis of prognostic factors associated with OS in 24 patients with BCLC stage C HCC with vascular invasion

Patients with vascular invasion ($n = 24$)	Number	Univariate Analysis		Multivariate Analysis	
		three-year OS (%)	*p*-value	HR (95% CI)	*p*-value
Sex male/female	22/2	26.5/0.0	0.159		
HBV Yes/No	18/6	20.8/33.3	0.389		
HCV Yes/No	1/23	0.0/25.4	0.495		
Liver cirrhosis Yes/No	19/5	19.7/40.0	0.895		
PT(sec) >13.7/≤13.7	1/23	0.0/25.4	**0.042***	6.1(0.6,58.4)	0.119
Pre-medication AFP (ng/mL)					
>20/≤20	17/7	8.8/57.1	0.065		
TBIL (μmol/L) >21/≤21	12/12	25.0/22.2	0.885		
ALB(g/L) >40/≤40	13/11	20.5/27.3	0.858		
ALP (U/L) >125/≤125	13/11	20.5/27.3	0.991		
ALT(U/L) >40/≤40	16/8	25.0/25.0	0.601		
AST(U/L) >40/≤40	17/7	11.8/57.1	0.078		
Accompanied by TACE			**0.014***	8.5(1.1,65.3)	**0.040***
Yes	4	75.0			
No	20	15.0			
History of surgery Yes/No	10/14	10.0/35.7	0.259		

HBV, hepatitis B virus; HCV, hepatitis C virus; PT, prothrombin time; AFP, alpha fetoprotein; TBIL, total bilirubin; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TACE, transcatheter arterial chemoembolization; OS, overall survival; CI, confidence interval; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic liver cancer.

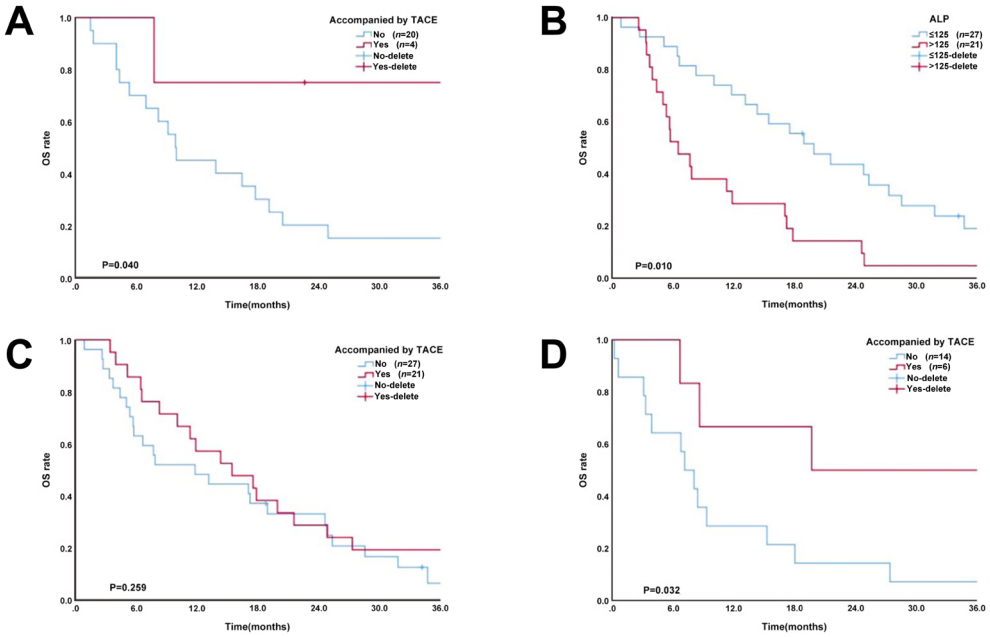

Figure 3. OS rates in subgroups of patients with BCLC stage C HCC. (A) Kaplan-Meier OS curves for the vascular invasion group, categorized by TACE treatment. **(B)** Kaplan-Meier OS curves for the metastasis group, based on ALP levels. **(C)** Kaplan-Meier OS curves for the metastasis group, categorized by TACE treatment. **(D)** Kaplan-Meier OS curves for patients with both risk factors categorized by TACE treatment. (TACE, transcatheter arterial chemoembolization; ALP, alkaline phosphatase; OS, overall survival; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic liver cancer).

risk factor (p = 0.010; Figure 3B). Regarding TACE, no statistically significant difference was found in the metastasis subgroup (Figure 3C).

3.4. Prognostic factors related to OS rates in patients with BCLC stage C HCC with both vascular invasion and metastasis

The variables included in the univariate and Cox multivariate analyses for patients with BCLC stage C, vascular invasion, and metastasis are summarized in Table 5. Following the univariate analysis for OS, the final multivariate model again identified "presence of TACE," as an independent prognostic factor. The multivariate analysis demonstrated that patients in the non-TACE group had a significantly worse OS rate compared to those in the TACE group (HR = 4.1; 95% CI, 1.1–14.8; p = 0.032; Figure 3D).

4. Discussion

HCC is one of the most prevalent malignant tumors worldwide, ranking as the sixth most common cancer and the third leading cause of cancer-related

Table 4. Univariate and multivariate analysis of prognostic factors associated with OS in 48 patients with BCLC stage C HCC with metastasis

Patients with vascular invasion (n = 48)	Number	Univariate Analysis		Multivariate Analysis	
		three-year OS (%)	p-value	HR (95% CI)	p-value
Sex male/female	42/6	14.3/33.3	0.599		
HBV (Yes/No)	32/16	13.5/12.5	0.892		
HCV (Yes/No)	2/46	50.0/11.1	0.471		
Liver cirrhosis (Yes/No)	33/15	19.7/0.0	0.154		
PT(sec) >13.7/≤13.7	3/45	0.0/13.8	0.668		
Pre-medication AFP (ng/mL)					
>20/≤20	32/16	12.5/21.1	0.109		
TBIL (μmol/L) >21/≤21	23/25	13.0/13.5	0.721		
ALB(g/L) >40/≤40	22/26	10.4/15.4	0.392		
ALP (U/L) >125/≤125	21/27	4.8/19.0	**0.010***		
ALT(U/L) >40/≤40	24/24	23.1/0.0	0.105		
AST(U/L) >40/≤40	25/23	12.0/12.9	0.381		
Accompanied by TACE			0.259		
Yes	21	19.0			
No	27	6.2			
History of surgery (Yes/No)	24/24	13.0/12.5	0.512		

HBV, hepatitis B virus; HCV, hepatitis C virus; PT, prothrombin time; AFP, alpha fetoprotein; TBIL, total bilirubin; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TACE, transcatheter arterial chemoembolization; OS, overall survival; CI, confidence interval; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic liver cancer.

Table 5. Univariate and multivariate analysis of prognostic factors associated with OS in 20 patients with BCLC stage C HCC with vascular invasion and metastasis

Patients with vascular invasion (n = 20)	Number	Univariate Analysis		Multivariate Analysis	
		three-year OS (%)	p-value	HR (95% CI)	p-value
Sex male/female	18/2	16.7/50.0	0.432		
HBV (Yes/No)	15/5	26.7/0.0	0.200		
HCV (Yes/No)	0/20	20.0			
Liver cirrhosis (Yes/No)	15/5	13.3/40.0	0.234		
PT(sec) >13.7/≤13.7	1/19	0.0/21.1	**0.004***	14.0 (0.9,224.1)	0.063
Pre-medication AFP (ng/mL)					
>20/≤20	17/3	17.6/33.3	0.325		
TBIL (μmol/L) >21/≤21	11/9	36.4/0.0	0.202		
ALB(g/L) >40/≤40	9/11	22.2/18.2	0.735		
ALP (U/L) >125/≤125	13/7	15.4/28.6	0.535		
ALT(U/L) >40/≤40	11/9	18.2/22.2	0.970		
AST(U/L) >40/≤40	15/5				
Accompanied by TACE			**0.017***	4.1 (1.1,14.8)	**0.032***
Yes	6	50.0			
No	14	7.1			
History of surgery (Yes/No)	7/13	14.3/23.1	0.052		

HBV, hepatitis B virus; HCV, hepatitis C virus; PT, prothrombin time; AFP, alpha fetoprotein; TBIL, total bilirubin; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TACE, transcatheter arterial chemoembolization; OS, overall survival; CI, confidence interval; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic liver cancer.

mortality globally (*1*). Due to its insidious onset and rapid progression, most patients are diagnosed with either locally advanced disease or distant metastasis, corresponding to advanced BCLC stage C, which includes portal vein thrombosis, lymph node involvement, or extrahepatic metastasis (*2*). This advanced stage accounts for a significant proportion of cases, with 50% to 60% of patients receiving their initial clinical diagnosis at this point, often when the disease has already reached a severe state. In the absence of effective intervention, OS is typically short, contributing to the stagnation of improvements in liver cancer prognosis in recent years (*13*).

Sorafenib is an oral multi-kinase inhibitor that targets several receptor tyrosine kinases, including vascular endothelial growth factor receptor-2, vascular endothelial growth factor receptor-3, platelet-derived growth factor beta, and members of the Raf family of serine or threonine kinases, thereby exerting its anti-tumor effects (*14,15*). It was the first targeted drug demonstrated to be effective in treating advanced HCC (*16*). Although newer therapies, such as lenvatinib and durvalumab, have emerged, they have yet to show significantly superior efficacy compared to sorafenib in phase III clinical trials (*5,17*). While studies indicate that combinations such as camrelizumab plus rivoceranib may yield better outcomes than sorafenib alone, this does not suggest that sorafenib cannot be enhanced when combined with other treatments (*18*). Consequently, sorafenib remains a key option in the treatment of liver cancer and continues to be recommended as a first-line therapy for advanced HCC in many clinical guidelines (*19*).

TACE involves injecting chemotherapeutic agents and embolic materials into the main artery supplying the tumor, leading to localized tumor necrosis (*20*). However, because this technique primarily induces ischemic necrosis, it may stimulate the upregulation of angiogenic factors such as vascular endothelial growth factor and platelet-derived growth factor beta, potentially contributing to tumor recurrence or metastasis (*21*). The ability of sorafenib to inhibit these pro-angiogenic effects following TACE suggests that combining sorafenib with TACE could enhance the anti-tumor effect (*22,23*). Recent studies have shown that this combination significantly improves the prognosis of patients with advanced HCC compared to TACE alone. However, since TACE is not typically recommended for patients in advanced stages, its efficacy in this setting remains uncertain. Therefore, it cannot be conclusively assumed that adding TACE to sorafenib therapy will yield better outcomes than sorafenib monotherapy (*24,25*).

Our study found that the combination of sorafenib and TACE significantly improved prognosis compared to sorafenib alone in all patients with advanced HCC. Multifactorial analysis indicated that not using TACE was an independent risk factor affecting OS. Therefore, combining TACE with sorafenib may lead to better outcomes for patients with advanced HCC.

To further identify the patient groups that may benefit most from TACE, we conducted a subgroup analysis. The results revealed no significant difference in prognosis between the vascular invasion group, the distant metastasis group, and the group with both risk factors. However, the absence of TACE was an independent risk factor for prognosis in both the vascular invasion group and the group with both risk factors, but not in the distant metastasis group. This suggests that TACE is particularly appropriate for patients with advanced HCC who exhibit vascular invasion.

Several limitations of our study should be acknowledged. First, it was a retrospective study, with data collected from 92 patients over a 10-year period. The small sample size is a common limitation in studies focusing on patients with BCLC stage C HCC treated with sorafenib, largely due to the rarity of the disease. Second, treatment plans and standards were influenced by physician experience and patient preferences, which could have affected the study outcomes. Consequently, randomized controlled trials are needed to provide more definitive comparisons. Finally, our analysis focused solely on short-term survival.

In conclusion, despite its limitations, this study offers valuable insights for clinical treatment, owing to the rigor of its experimental design. First, for patients with advanced HCC, there was no significant difference in prognosis among those vascular invasions, distant metastases, or both risk factors. Therefore, stratifying patients with advanced disease based on these risk factors may be unreliable. Secondly, for patients with advanced disease who have vascular invasion, combining TACE with sorafenib therapy may yield better efficacy.

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