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Original Article

Key prognostic factors in transarterial chemoembolization combined with sorafenib treatment for hepatocellular carcinoma with portal vein tumor thrombosis

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Abstract: Background: Hepatocellular carcinoma (HCC) is a prevalent malignancy worldwide, with portal vein tumor thrombosis (PVTT) worsening its prognosis and complicating management. The combination of transarterial chemoembolization (TACE) and the targeted agent sorafenib has been proposed to improve treatment outcomes. This study investigates the prognostic factors influencing the effectiveness of this combined treatment in HCC patients with PVTT. Methods: A retrospective cohort study was conducted on 299 patients diagnosed with HCC and PVTT who underwent TACE and sorafenib treatment between January 2018 and December 2022. Patients were categorized into good-prognosis (n = 197) and poor-prognosis (n = 102) groups based on Response Evaluation Criteria in Solid Tumors (RECIST) assessed four weeks post-treatment. Prognostic factors were analyzed using univariate and multivariate analyses to identify significant determinants affecting therapeutic outcomes. Results: Key prognostic factors included tumor number, differentiation, size, PVTT extent, Child-Pugh class, ECOG performance status, hospitalization duration, and AFP levels. Patients with a single tumor had better outcomes (OR 0.358, P = 0.002), whereas poor differentiation (OR 4.561, P = 0.005) and larger tumor size (OR 0.347, P < 0.001) were associated with worse prognosis. A higher Child-Pugh class (OR 0.563, P = 0.035) and better ECOG performance (OR 2.710, P = 0.025) improved prognosis, while prolonged hospitalization and elevated AFP levels were linked to poorer outcomes. ASA classification and HCC morphology did not significantly impact prognosis. Conclusion: The prognosis of HCC with PVTT treated with TACE and sorafenib is significantly influenced by tumor characteristics, liver function, and overall patient health. Identifying these factors can aid in refining personalized treatment strategies to improve survival outcomes.

Keywords: Hepatocellular carcinoma, transarterial chemoembolization, portal vein tumor thrombosis, sorafenib, prognostic factors, therapeutic outcomes

Introduction

Hepatocellular carcinoma (HCC) is recognized as the sixth most common cancer globally and the third leading cause of cancer-related deaths. Its incidence is particularly high in regions such as Asia and sub-Saharan Africa [1, 2]. Its morbidity and mortality are closely associated with cirrhosis, predominantly resulting from chronic hepatitis B and C infections, as well as non-alcoholic fatty liver disease [3, 4]. In the clinical course of HCC, portal vein tumor thrombosis (PVTT) is a common and serious complication, occurring in approximately 44%-62% of patients [5, 6]. This condition significantly worsens prognosis by compromising liver function and reducing blood flow, further complicating treatment strategies. PVTT poses a major therapeutic challenge, limiting the effectiveness of surgical resection and restricting the safe application of other localized treatment modalities due to its propensity to accelerate intrahepatic and systemic spread [7].

The global burden of HCC underscores the urgent need for effective therapeutic strategies. Conventional treatments encompass surgical resection, liver transplantation, and radio-

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frequency ablation [8], whereas systemic therapies include chemotherapy and immunotherapy [9]. Despite advancements in diagnostic techniques and treatment modalities, managing HCC-particularly in the presence of PVTT-remains challenging due to the liver's unique microenvironment, tumor heterogeneity, and the limited applicability of these methods in complex cases.

Combined therapy with transarterial chemoembolization (TACE) and targeted molecular agents has emerged as a promising approach for HCC patients with PVTT [10]. TACE delivers localized chemotherapy while inducing ischemia, cutting off the tumor's blood supply, and reducing its metabolic activity [11]. It is a cornerstone treatment for intermediate-stage HCC, as outlined in the Barcelona Clinic Liver Cancer (BCLC) staging system, which is widely used for treatment decision-making [12]. However, in the presence of PVTT, TACE's efficacy is often diminished due to altered blood flow dynamics and the potential risk of ischemic damage to non-tumorous liver tissue [10]. This challenge supports the rationale for combining TACE with sorafenib, a multikinase inhibitor that targets pathways involved in tumor proliferation and angiogenesis, including vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptors [13]. This dual approach enhances therapeutic outcomes by complementing TACE's locoregional cytotoxic effects with the systemic antiangiogenic and antiproliferative actions of sorafenib.

Despite the theoretical advantages of this combination, the prognostic outlook for HCC patients with PVTT undergoing TACE combined with sorafenib remains complex and variable.

This study aimed to conduct an in-depth analysis of prognostic factors associated with TACE and sorafenib treatment in HCC patients with PVTT, using a large retrospective cohort from our institution. We introduced several innovative aspects that contributed to the fields of hepatology and oncology by providing a comprehensive evaluation of multiple prognostic factors in a well-defined patient cohort. By integrating clinical, pathological, and biochemical data, this study offered new insights into the intricate relationship between tumor biology and patient outcomes. The findings can aid in optimizing personalized treatment strategies, highlighting key prognostic factors that could help clinicians make informed decisions, thereby improving survival rates and quality of life.

The insights gained from this study can offer valuable guidance for clinical practice. By incorporating multiple prognostic factors into treatment decision-making, clinicians can develop more comprehensive and evidence-based strategies. This includes optimizing the timing and sequence of treatments, as well as enhancing the monitoring and management of potential complications.

Materials and methods

Patient selection

Study design: A retrospective study was conducted on 299 patients diagnosed with HCC and PVTT who received combined treatment with TACE and sorafenib at the First Affiliated Hospital of Chongqing Medical University between January 2018 and December 2022. These patients were categorized into two prognostic groups: the good-prognosis group (n = 197) included those who achieved complete response (CR), partial response (PR), or stable disease (SD), while the poor-prognosis group (n = 102) comprised patients with progressive disease (PD). This study was approved by the Institutional Review Board and Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

Prognosis was assessed four weeks post-treatment using imaging examinations performed with a dual-source computed tomography (CT) scanner (SOMATOM Force, Shanghai Siemens Medical Instruments Co., Ltd., China). Treatment efficacy was evaluated based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [14]. CR was defined as the complete disappearance of all measurable tumor lesions for at least four weeks. PR was characterized by a minimum 30% reduction in the sum of the longest diameter of target lesions from baseline, with no new lesions detected. SD was indicated when changes in the sum of the longest diameters of target lesions did not exceed a 20% increase or a 30% decrease, with no new lesions appearing. PD was diagnosed if there was an increase of more than 20% in the sum of the longest diameters of target lesions

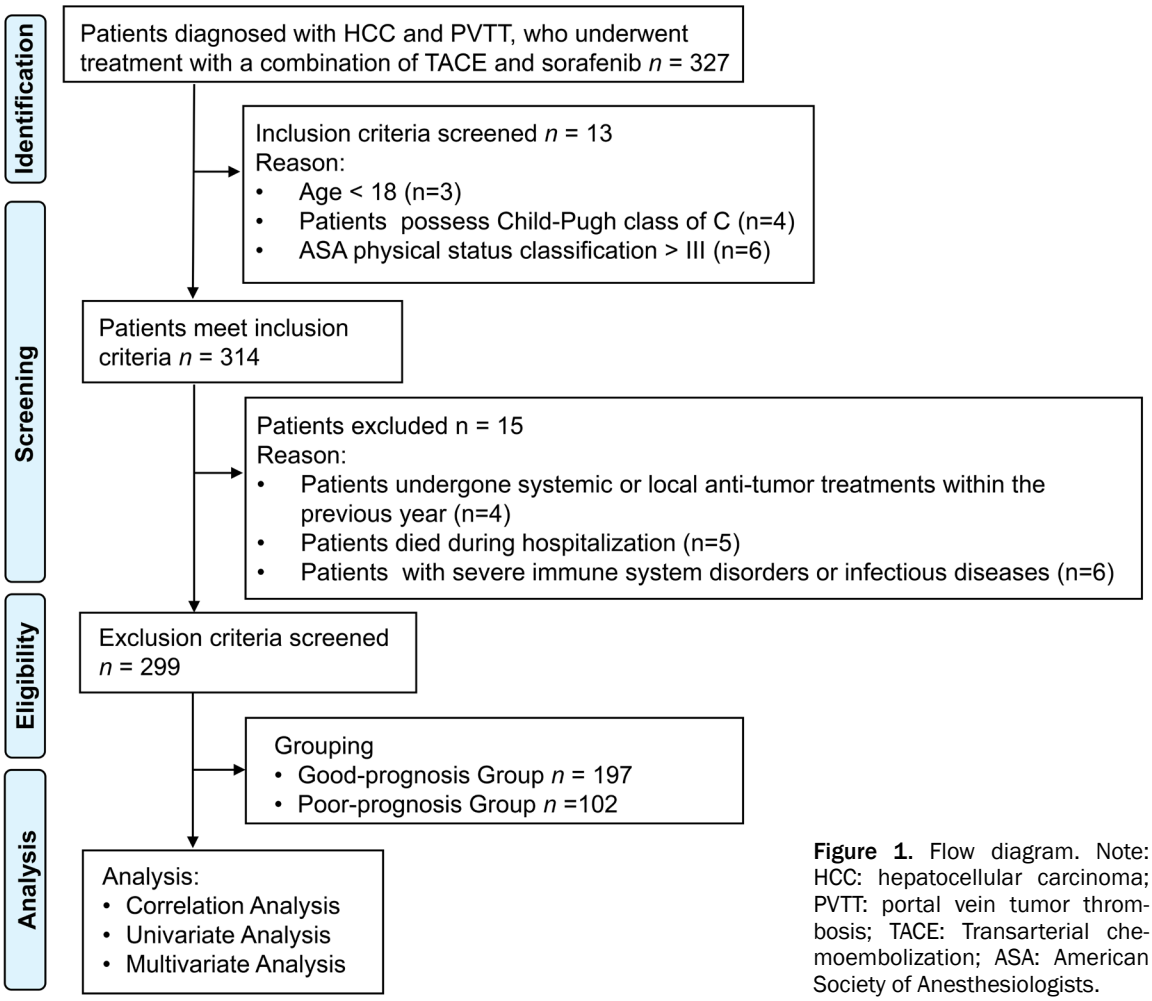

Figure 1. Flow diagram. Note: HCC: hepatocellular carcinoma; PVTT: portal vein tumor thrombosis; TACE: Transarterial chemoembolization; ASA: American Society of Anesthesiologists.

compared to the previous evaluation, with an absolute increase of at least 5 millimeters, or if new lesions were observed.

Inclusion and exclusion criteria: Inclusion criteria: Patients were eligible if there were 18 years or older, were diagnosed with HCC based on the AGA Clinical Practice Guideline [15] and PVTT as defined by the Guidelines for Diagnosis and Treatment of HCC with Portal Vein Tumor Thrombus in China (2021 Edition) [16], underwent treatment with TACE combined with sorafenib, had a Child-Pugh class of A or B, an Eastern Cooperative Oncology Group (ECOG) performance status [17] of 2 or lower, and an American Society of Anesthesiologists (ASA) physical status classification of III or lower. Additionally, they were required to have complete medical records with no missing data.

Exclusion Criteria: Individuals were excluded if they had a current or recent (within the past 5 years) history of other malignancies, had undergone systemic or local anti-tumor treatments (including surgery or radiation therapy) within the past year, or had severe immune system disorders or infectious diseases. Additionally, those who died during hospitalization, had coagulation disorders, or were pregnant or breastfeeding were excluded from the study (**Figure 1**).

Treatment approach: All patients received a combined treatment regimen of TACE and sorafenib. Initially, the patency of the portal vein and the adequacy of liver blood supply were assessed. The TACE procedure involved distal superselective 5-F catheterization of the hepatic arteries supplying the tumor, using Embosphere microspheres (Biosphere Medical

Inc., USA), lipiodol, and epirubicin. Specifically, a mixture of 50 mg epirubicin (Pharmorubicin, Pfizer Inc., USA) and 5-20 mL lipiodol (Lipiodol Ultra-Fluide; Guerbet S.A., France) was employed for chemoembolization. The embolization utilized absorbable Embosphere microspheres, sized between 300 and 500 micrometers, to target the entire tumor burden within the liver.

Upon admission, sorafenib (Bayer AG, Germany) was administered orally at a dose of 400 mg twice daily. Sorafenib administration was temporarily halted on the day of the TACE procedure and resumed within 4 to 7 days post-procedure [18].

Data extraction

Patient data were collected from the medical record system, including demographic information, baseline disease characteristics, disease severity, routine blood indicators, surgical details, liver function, and levels of serum tumor markers. The Child-Pugh classification was employed to assess liver function, categorizing patients into three grades (A, B, C) based on severity, with scores ranging from 1 to 3 points. Child-Pugh Class A (5-6 points) indicates relatively well-preserved liver function and a favorable prognosis, whereas Class C (10-15 points) signifies severe liver dysfunction and a poor prognosis, where more aggressive treatments, including potential liver transplantation, may be necessary as the condition worsens. The Child-Pugh score was considered a reliable predictor of postoperative mortality [19].

The ECOG performance status was used to evaluate patients' general health and treatment tolerance based on their level of physical activity. It ranges from 0, indicating a fully active individual with no restrictions in daily activities, to 5, which denotes death [20].

The ASA classification assessed the overall health status of patients prior to surgery, ranging from ASA I (Class 1) for healthy individuals with no significant systemic disease, to ASA VI (Class 6) for brain-dead patients, applicable only for organ donation procedures. Higher ASA scores correlate with poorer health conditions. The ASA classification has demonstrated moderate inter-rater reliability, with a kappa (κ) value of 0.61 [21].

Outcome measures

Blood test and liver function indicators: Fasting venous blood samples (5 mL each) were collected from patients in the early morning, one day after admission. These samples were then centrifuged at 3000 r/min for 10 minutes using a low-temperature high-speed centrifuge (TLD 12A, Hunan Xiangxi Scientific Instrument Factory, China). The separated plasma was stored at -80°C. Hematological parameters, including hemoglobin level, red blood cell count (RBC), white blood cell count (WBC), and platelet count (PLT), were measured using an automated hematology analyzer (SYSMEX-2100, SYSMEX Corporation, Japan). Baseline liver function parameters, such as total bilirubin (TB), albumin (ALB), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), were assessed using an automated biochemical analyzer (Mindray BC6800, Shenzhen Mindray Bio-Medical Electronics Co., Ltd., China).

Serum tumor markers: Fasting venous blood samples (5 mL each) were collected from patients in the early morning, one day after the TACE combined with sorafenib treatment. The samples underwent the same centrifugation procedure as described above. The obtained plasma was then analyzed to measure the levels of carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), and carbohydrate antigen 199 (CA199) using a chemiluminescent immunoassay (CLIA). The analysis was performed with a chemiluminescent immunoassay analyzer (CL-6000i, Shenzhen Mindray Bio-Medical Electronics Co., Ltd., China).

Statistical analysis

To ensure sufficient statistical power and identify a clinically significant effect size, the sample size for this study was determined using G*Power. The calculation incorporated assumptions of a medium effect size ($d = 0.5$) and a two-tailed significance level ($\alpha = 0.05$). It was estimated that 88 participants per group would be necessary to achieve a 95% power in rejecting the null hypothesis of equal means, using a 2-sided, 2-sample t-test assuming equal variance.

Data analysis was conducted using SPSS 29.0 statistical software (SPSS Inc., Chicago, IL, USA). Categorical data were expressed as [n (%)] and analyzed using Chi-square tests. Continuous variables underwent normality testing using the Shapiro-Wilk test. Variables that followed a normal distribution were expressed as mean ± standard deviation. Statistical significance was defined by a *P*-value of less than 0.05. For correlation analysis, Pearson's method was used for continuous variables, while Spearman's method was applied to categorical data. Both univariate and multivariate analyses, along with ROC analyses, were performed to identify factors affecting the prognosis of the patients.

Results

Basic data

The mean age was 56.44 ± 15.46 years in the good-prognosis group and 58.12 ± 14.65 years in the poor-prognosis group (P = 0.366) (**Table 1**). Body mass index was similarly distributed between the two groups, with means of 23.66 ± 2.16 kg/m^2 in the good-prognosis group and 23.75 ± 2.95 kg/m^2 in the poor-prognosis group (P = 0.786). Gender distribution was also comparable, with males comprising 73.6% of the good-prognosis group and 78.43% of the poor-prognosis group (P = 0.359). In addition, other factors, including smoking status (never: 72.59% vs 65.69%, P = 0.216), drinking history (23.86% vs 27.45%, P = 0.497), hypertension (24.87% vs 26.47%, P = 0.764), and diabetes prevalence (15.74% vs 18.63%, P = 0.525), showed no significant differences between the groups. Educational level distribution and marital status were similarly aligned across groups (educational level, P = 0.652; marital status, P = 0.303), suggesting that these demographic factors did not significantly influence prognosis in the cohort studied.

Patients in the good-prognosis group were more likely to have single tumors (85.79%) compared to those in the poor-prognosis group (71.57%) (P = 0.003) (**Table 1**). Tumor differentiation varied significantly, with the good-prognosis group exhibiting more poorly differentiated tumors (23.86%) than the poor-prognosis group (11.76%), while the poor-prognosis group had a larger proportion of well-differentiated tumors (45.1% vs 28.43%) (P = 0.005). Tumor size distribution also differed significantly, with smaller tumors (< 5 cm) being more common in the good-prognosis group (64.97% vs 73.53% in the poor-prognosis group) (P = 0.017). Morphologically, mass-type tumors were more prevalent in the good-prognosis group (11.68%) than in the poor-prognosis group (7.84%) (P = 0.033). There was also a significant difference in PVTT extension, with unilateral and bilateral branch involvement being more common in the poor-prognosis group (P = 0.039). HBV infection rates did not differ significantly between the groups (62.94% in the good-prognosis group vs 63.73% in the poor-prognosis group, P = 0.894).

Patients in the good-prognosis group were more frequently classified as Child-Pugh class A (56.85%) compared to those in the poor-prognosis group (40.2%) (P = 0.006) (**Table 1**). ECOG performance status scores showed significant variation, with the good-prognosis group having a higher proportion of patients with scores of 0 (36.55% vs 31.37%) and fewer with scores of 2 (11.68% vs 25.49%) compared to the poor-prognosis group (P = 0.009). The ASA classifications also differed significantly, with the good-prognosis group having more patients in ASA class 1 (22.84%) compared to the poor-prognosis group (18.63%), and fewer in ASA class 3 (2.54% vs 9.8%) (P = 0.021). These findings highlight the correlation between better disease severity measures and a more favorable prognosis.

Blood routine indicators

The RBC count was 4.75 ± 1.34 × 10^{12}/L in the good-prognosis group and 4.53 ± 1.33 × 10^{12}/L in the poor-prognosis group (P = 0.173) (**Figure 2A**). Hemoglobin levels were similar between the two groups, with values of 112.54 ± 21.44 g/L and 110.66 ± 27.86 g/L, respectively (P = 0.551) (**Figure 2B**). WBC counts were 10.66 ± 1.68 × 10^9/L for the good-prognosis group and 10.54 ± 1.36 × 10^9/L for the poor-prognosis group (P = 0.484) (**Figure 2C**). PLT counts also showed no significant difference, with the good-prognosis group having 122.45 ± 23.56 × 10^9/L and the poor-prognosis group having 125.36 ± 25.76 × 10^9/L (P = 0.328) (**Figure**

Table 1. Comparison of demographic characteristics between two groups

Parameters	Good-prognosis group (n = 197)	Poor-prognosis group (n = 102)	t/χ^2	P
Age (years)	56.44 ± 15.46	58.12 ± 14.65	0.906	0.366
BMI (kg/m^2)	23.66 ± 2.16	23.75 ± 2.95	0.272	0.786
Gender (Male/Female) [n (%)]	145 (73.6%)/52 (26.4%)	80 (78.43%)/22 (21.57%)	0.841	0.359
Smoking status (never) [n (%)]	143 (72.59%)	67 (65.69%)	1.532	0.216
Drinking history [n (%)]	47 (23.86%)	28 (27.45%)	0.462	0.497
Hypertension [n (%)]	49 (24.87%)	27 (26.47%)	0.090	0.764
Diabetes [n (%)]	31 (15.74%)	19 (18.63%)	0.403	0.525
Educational level (high school or below/junior college or above) [n (%)]	37 (18.78%)/160 (81.22%)	17 (16.67%)/85 (83.33%)	0.203	0.652
Marital Status (Married/Unmarried or Divorced) [n (%)]	171 (86.8%)/26 (13.2%)	84 (82.35%)/18 (17.65%)	1.060	0.303
Tumor number (single/multiple) [n (%)]	169 (85.79%)/28 (14.21%)	73 (71.57%)/29 (28.43%)	8.805	0.003
Tumor differentiation (Poor/Medium/Well) [n (%)]	47 (23.86%)/94 (47.72%)/56 (28.43%)	12 (11.76%)/44 (43.14%)/46 (45.1%)	10.761	0.005
Tumor size (cm) (< 5/5-10/> 10) [n (%)]	128 (64.97%)/43 (21.83%)/26 (13.2%)	75 (73.53%)/9 (8.82%)/18 (17.65%)	8.163	0.017
HCC morphology (Mass type/Nodular type/Diffuse type) [n (%)]	23 (11.68%)/106 (53.81%)/68 (34.52%)	8 (7.84%)/43 (42.16%)/51 (50%)	6.830	0.033
PVTT extension (Main trunk/Main trunk + unilateral branch/Main trunk + bilateral branches) [n (%)]	61 (30.96%)/90 (45.69%)/46 (23.35%)	25 (24.51%)/39 (38.24%)/38 (37.25%)	6.463	0.039
HBV infection [n (%)]	124 (62.94%)	65 (63.73%)	0.018	0.894
Child–Pugh class (A/B) [n (%)]	112 (56.85%)/85 (43.15%)	41 (40.2%)/61 (59.8%)	7.462	0.006
ECOG performance status score (0/1/2/) [n (%)]	72 (36.55%)/102 (51.78%)/23 (11.68%)	32 (31.37%)/44 (43.14%)/26 (25.49%)	9.371	0.009
ASA (1/2/3) [n (%)]	45 (22.84%)/147 (74.62%)/5 (2.54%)	19 (18.63%)/73 (71.57%)/10 (9.8%)	7.715	0.021
TB (mg/dl)	1.45 ± 0.28	1.49 ± 0.36	0.838	0.403
ALB (g/l)	39.78 ± 11.55	38.76 ± 12.53	0.702	0.483
ALT (U/l)	46.23 ± 3.16	46.36 ± 4.25	0.279	0.781
AST (U/l)	62.03 ± 5.26	62.77 ± 5.55	1.126	0.261

Note: BMI: Body Mass Index; HCC: hepatocellular carcinoma; PVTT: portal vein tumor thrombosis; HBV: hepatitis B virus; ECOG: Eastern Cooperative Oncology Group; ASA: American Society of Anesthesiologists; TB: total bilirubin; ALB: albumin; ALT: alanine transaminase; AST: aspartate transaminase.

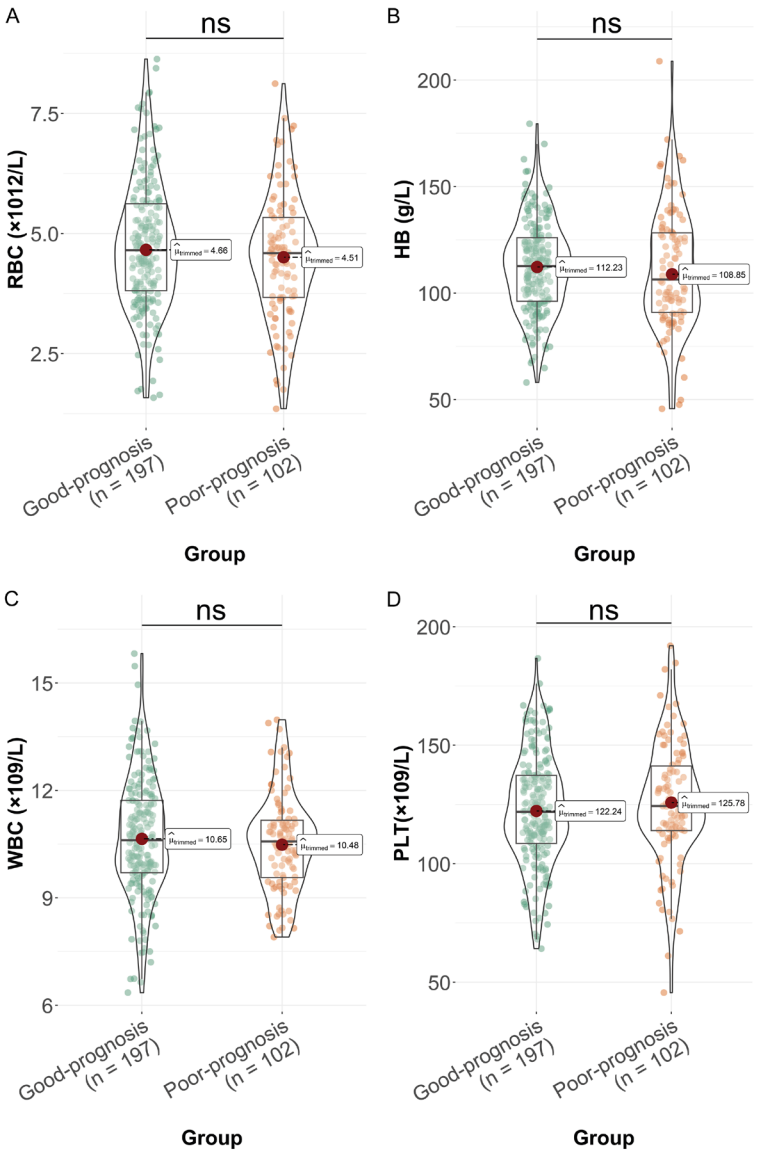

Figure 2. Comparison of blood routine indicators between two groups. A. RBC; B. HB; C. WBC; D. PLT. ns: no significant difference. Note: RBC: red blood cell; HB: hemoglobin; WBC: white blood cell; PLT: platelet.

2D). These results indicate that blood routine indicators did not significantly impact the prognosis in this cohort.

Surgical parameters

The duration of hospitalization was shorter in the good-prognosis group, with an average of 11.58 ± 3.15 days, compared to 12.53 ± 3.26 days in the poor-prognosis group (P = 0.015) (**Figure 3C**). In contrast, the operation time showed no significant difference between the groups, with means of 266.46 ± 68.53 minutes for the good-prognosis group and 261.67 ± 52.33 minutes for the poor-prognosis group (P = 0.502) (**Figure 3A**). Similarly, blood loss during the operation did not differ significantly, with 477.58 ± 157.85 mL in the good-prognosis group and 482.68 ± 154.89 mL in the poor-prognosis group (P = 0.790) (**Figure 3B**). These findings suggest that shorter hospitalization durations may be associated with a better prognosis for patients undergoing combined treatment.

Liver function

TB levels were 1.45 ± 0.28 mg/dL in the good-prognosis group and 1.49 ± 0.36 mg/dL in the poor-prognosis group (P = 0.403) (**Table 1**). ALB levels were also comparable, with 39.78 ± 11.55 g/L in the good-prognosis group compared to 38.76 ± 12.53 g/L in the poor-prognosis group (P = 0.483). ALT levels showed negligible differences, reported as 46.23 ± 3.16 U/L in the good-prognosis group and 46.36 ± 4.25 U/L in the poor-prognosis group (P = 0.781). AST levels were also similar, at 62.03 ± 5.26 U/L for the good-prognosis group and 62.77 ± 5.55 U/L for the poor-prognosis group (P = 0.261). These results indicate that baseline liver function did not significantly differ between the two groups, suggesting that liver function indicators were not major determinants of prognosis in this cohort.

Serum tumor markers

The good-prognosis group exhibited lower AFP levels (154.67 ± 18.54 ng/mL) compared to the poor-prognosis group (160.63 ± 19.43 ng/mL) (P = 0.010) (**Figure 4A**). However, no significant differences were observed in other tumor markers. CEA levels were comparable between the groups, with values of 4.53 ± 1.65 ng/mL

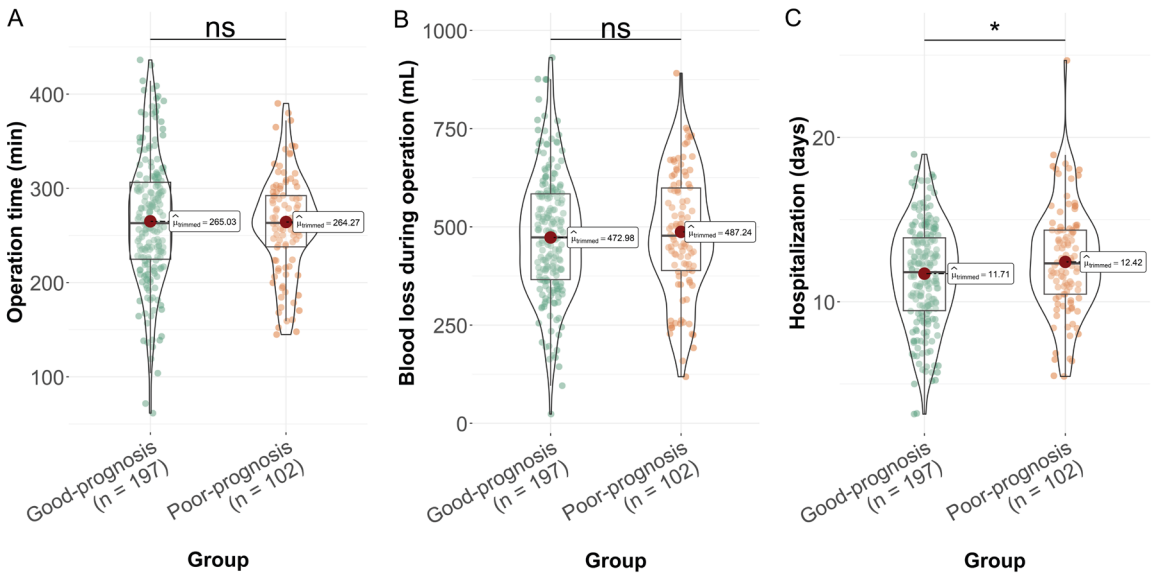

Figure 3. Comparison of surgical details between two groups. A. Operation time; B. Blood loss during operation; C. Hospitalization. *: $P < 0.05$; ns: no significant difference.

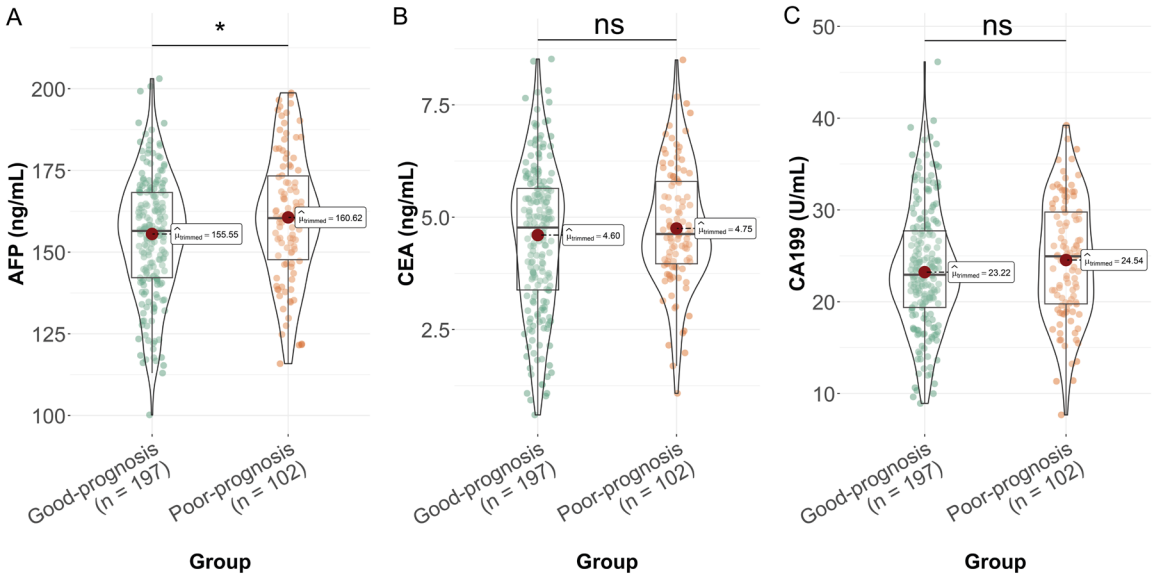

Figure 4. Comparison of serum tumor marker levels after treatment. A. AFP; B. CEA; C. CA199. *: $P < 0.05$; ns: no significant difference. Note: AFP: alpha fetoprotein; CEA: carcinoembryonic antigen; CA199: carbohydrate antigen 199.

in the good-prognosis group and 4.79 ± 1.35 ng/mL in the poor-prognosis group (P = 0.144) (**Figure 4B**). Similarly, CA199 levels showed no significant difference, with 23.55 ± 6.65 U/mL in the good-prognosis group and 24.56 ± 6.51 U/mL in the poor-prognosis group (P = 0.211) (**Figure 4C**). These findings suggest that while AFP levels may correlate with prognosis, CEA and CA199 levels did not significantly impact outcomes in this cohort.

Correlation analysis of prognostic factors affecting the outcome of TACE combined with sorafenib treatment in HCC patients with PVTT

The correlation analysis of prognostic factors impacting the outcome of TACE combined with sorafenib treatment in patients with HCC and PVTT identified several significant associations (**Table 2**). The number of tumors (single/multiple) showed a negative correlation (rho =

Table 2. Correlation analysis of prognostic factors affecting the outcomes

Parameters	rho	P
Tumor number (single/multiple) [n (%)]	-0.172	0.003
Tumor differentiation (Poor/Medium/Well) [n (%)]	0.190	*P* < 0.001
Tumor size (cm) (< 5/5-10/> 10) [n (%)]	-0.058	0.313
HCC morphology (Mass type/Nodular type/Diffuse type) [n (%)]	0.147	0.011
PVTT extension (Main trunk/Main trunk + unilateral branch/Main trunk + bilateral branches) [n (%)]	0.128	0.027
Child-Pugh class (A/B) [n (%)]	-0.158	0.006
ECOG performance status score (0/1/2/) [n (%)]	0.120	0.039
ASA (1/2/3) [n (%)]	0.104	0.073
Hospitalization (days)	0.115	0.046
AFP (ng/mL)	0.133	0.022

Note: TACE: Transarterial chemoembolization; HCC: hepatocellular carcinoma; PVTT: portal vein tumor thrombosis; ECOG: Eastern Cooperative Oncology Group; ASA: American Society of Anesthesiologists; AFP: serum tumor markers.

-0.172, P = 0.003), indicating that patients with multiple tumors had a poorer prognosis. Tumor differentiation demonstrated a positive correlation (rho = 0.190, P < 0.001), with better differentiation linked to improved outcomes. HCC morphology's correlation (rho = 0.147, P = 0.011) suggested that mass type was associated with favorable outcomes. PVTT extension also correlated positively (rho = 0.128, P = 0.027), indicating less extensive PVTT was preferable. Child–Pugh class (A/B) showed a negative correlation (rho = -0.158, P = 0.006), highlighting better liver function correlating with better prognosis. ECOG performance status (rho = 0.120, P = 0.039) and hospitalization duration (rho = 0.115, P = 0.046) were positively correlated, meaning worse performance status and longer hospitalization were linked to poor outcomes. AFP levels also showed a modest positive correlation (rho = 0.133, P = 0.022) with prognosis. Conversely, tumor size and ASA classification did not show statistically significant correlations, with tumor size (rho = -0.058, P = 0.313) and ASA (rho = 0.104, P = 0.073), indicating these factors were less impactful on outcomes in this cohort.

Univariate analysis of prognostic factors

The univariate analysis of prognostic factors affecting the outcomes of TACE combined with sorafenib in patients with HCC and PVTT identified several significant predictors (**Table 3**). A lower risk of poor prognosis was associated with having a single tumor, as indicated by a negative coefficient (-0.875) and an odds ratio (OR) of 0.417 (95% confidence interval (CI), 0.231-0.751; P = 0.004). Poor tumor differentiation was linked to worse outcomes, with a coefficient of 0.579 and an OR of 1.785 (95% CI, 1.263-2.554; P = 0.001). Tumor morphology, notably mass type, also emerged as a significant factor, with a positive coefficient (0.482) and an OR of 1.619 (95% CI, 1.105-2.402; P = 0.015). PVTT extension was associated with poor prognosis, with a coefficient of 0.362 and an OR of 1.436 (95% CI, 1.043-1.990; P = 0.028). The Child–Pugh class showed a protective effect with a negative coefficient (-0.673) and an OR of 0.510 (95% CI, 0.312-0.827; P = 0.007). Furthermore, a higher ECOG performance status score was linked to worse outcomes (coefficient of 0.398, OR of 1.489; P = 0.025). Hospitalization duration also correlated with prognosis, with a coefficient of 0.094 and an OR of 1.098 (95% CI, 1.018-1.188; P = 0.017). An increase in AFP levels slightly worsened prognosis (OR of 1.017; P = 0.011). ASA classification showed a trend towards significance (P = 0.055), but tumor size did not significantly influence the prognosis (P = 0.648).

Multivariate analysis of the prognostic factors

The multivariate analysis identified several independent prognostic factors affecting outcomes in patients with HCC and PVTT treated with TACE and sorafenib (**Table 4**). A single tumor presence was associated with a significantly better prognosis, as evidenced by a negative coefficient (-1.026) and an OR of 0.358 (95% CI, 0.186-0.691; P = 0.002). Poor tumor differentiation had a strong negative impact on prognosis (coefficient 1.518, OR 4.561; 95% CI, 1.574-13.216; P = 0.005). Larger tumor size

Table 3. Univariate analysis of prognostic factors affecting the outcomes

Parameters	Coefficient	Std. Error	Wald	P	OR	95% CI
Tumor number (single/multiple) [n (%)]	-0.875	0.300	2.918	0.004	0.417	0.231-0.751
Tumor differentiation (Poor/Medium/Well) [n (%)]	0.579	0.179	3.233	0.001	1.785	1.263-2.554
Tumor size (cm) (< 5/5-10/> 10) [n (%)]	-0.076	0.167	0.456	0.648	0.926	0.662-1.280
HCC morphology (Mass type/Nodular type/Diffuse type) [n (%)]	0.482	0.198	2.438	0.015	1.619	1.105-2.402
PVTT extension (Main trunk/Main trunk + unilateral branch/Main trunk + bilateral branches) [n (%)]	0.362	0.164	2.201	0.028	1.436	1.043-1.990
Child-Pugh class (A/B) [n (%)]	-0.673	0.248	2.715	0.007	0.510	0.312-0.827
ECOG performance status score (0/1/2/) [n (%)]	0.398	0.178	2.237	0.025	1.489	1.053-2.119
ASA (1/2/3) [n (%)]	0.498	0.260	1.916	0.055	1.646	0.997-2.778
Hospitalization (days)	0.094	0.039	2.395	0.017	1.098	1.018-1.188
AFP (ng/mL)	0.017	0.007	2.547	0.011	1.017	1.004-1.031

Note: TACE: Transarterial chemoembolization; HCC: hepatocellular carcinoma; PVTT: portal vein tumor thrombosis; ECOG: Eastern Cooperative Oncology Group; ASA: American Society of Anesthesiologists; AFP: serum tumor markers; OR: odds ratio; CI: confidence interval.

Table 4. Multivariate analysis of prognostic factors affecting the outcomes

Parameters	Coefficient	Std. Error	Wald Stat	P	OR	OR CI Lower	OR CI Upper
Tumor number (single/multiple) [n (%)]	-1.026	0.335	-3.067	0.002	0.358	0.186	0.691
Tumor differentiation (Poor/Medium/Well) [n (%)]	1.518	0.543	2.796	0.005	4.561	1.574	13.216
Tumor size (cm) (< 5/5-10/> 10) [n (%)]	-1.057	0.301	-3.510	< 0.001	0.347	0.193	0.627
HCC morphology (Mass type/Nodular type/Diffuse type) [n (%)]	0.059	0.486	0.122	0.903	1.061	0.409	2.752
PVTT extension (Main trunk/Main trunk + unilateral branch/Main trunk + bilateral branches) [n (%)]	-0.805	0.463	-1.739	0.082	0.447	0.180	1.108
Child-Pugh class (A/B) [n (%)]	-0.574	0.272	-2.113	0.035	0.563	0.331	0.959
ECOG performance status score (0/1/2/) [n (%)]	0.997	0.444	2.245	0.025	2.710	1.135	6.472
ASA (1/2/3) [n (%)]	-0.335	0.458	-0.732	0.464	0.715	0.291	1.755
Hospitalization (days)	0.090	0.044	2.030	0.042	1.094	1.003	1.194
AFP (ng/mL)	0.016	0.007	2.167	0.030	1.016	1.002	1.031

Note: TACE: Transarterial chemoembolization; HCC: hepatocellular carcinoma; PVTT: portal vein tumor thrombosis; ECOG: Eastern Cooperative Oncology Group; ASA: American Society of Anesthesiologists; AFP: serum tumor markers; OR: odds ratio; CI: confidence interval.

was associated with worse outcomes (coefficient -1.057, OR 0.347; 95% CI, 0.193-0.627; P < 0.001). Although the morphology of HCC did not significantly affect outcomes (P = 0.903), the extent of PVTT showed a trend toward significance (P = 0.082). Besides, the Child-Pugh class remained a significant positive prognostic factor (coefficient -0.574, OR 0.563; 95% CI, 0.331-0.959; P = 0.035). Higher ECOG performance status scores were associated with poorer outcomes (coefficient 0.997, OR 2.710; 95% CI, 1.135-6.472; P = 0.025). The duration of hospitalization also correlated with prognosis, having a coefficient of 0.090 and an OR of 1.094 (95% CI, 1.003-1.194; P = 0.042). Increased AFP levels were independently associated with poorer prognosis (coefficient 0.016, OR 1.016; 95% CI, 1.002-1.031; P = 0.030). The ASA classification did not significantly affect the outcome (P = 0.464). These findings indicate that tumor characteristics, liver function, and patient performance status significantly influence the effectiveness of TACE combined with sorafenib in this patient population.

ROC analysis of the prognostic factors

The ROC analysis of prognostic factors affecting the outcome of TACE combined with sorafenib treatment in HCC patients with PVTT revealed the following (**Figure 5**): Tumor number did not yield a valid threshold. Tumor differentiation exhibited a sensitivity of 0.451 and specificity of 0.716, with an area under the curve (AUC) of 0.607. Tumor size demonstrated a sensitivity of 0.176 and specificity of 0.868, with an AUC of 0.471. HCC morphology showed a sensitivity of 0.5 and specificity of 0.655, with an AUC of 0.581. The extent of PVTT presented a sensitivity of 0.373 and specificity of 0.766, with an AUC of 0.573. Child-Pugh class indicated a sensitivity of 0.598 and specificity of 0.569, with an AUC of 0.583. ECOG performance status had a sensitivity of 0.255 and specificity of 0.883, with an AUC of 0.567. ASA classification featured a sensitivity of 0.098 and specificity of 0.975, with an AUC of 0.549. Hospitalization duration recorded a sensitivity of 0.431 and specificity of 0.685, with an AUC of 0.57. Lastly, AFP level was associated with a sensitivity of 0.569 and specificity of 0.584, with an AUC of 0.581.

Discussion

The prognosis of HCC with PVTT remains poor, making TACE combined with sorafenib a key focus in oncological treatment strategies. This study aimed to evaluate the prognostic factors influencing outcomes in patients receiving this combination therapy.

Key results from our analysis exhibited that the presence of a single tumor was associated with a significantly better prognosis compared to multifocal lesions. As shown in the study by Mazzotta et al. [22], patients with ≥ 5 HCC nodules had a significantly lower overall survival after liver transplantation compared to those with < 5 nodules. The pathophysiological basis for this could be attributed to the physiological burden and complexity of managing multiple lesions within the hepatic environment, which increases the likelihood of liver dysfunction, complicates the delivery of therapeutic agents, and diminishes the overall treatment effect.

Tumor differentiation played a decisive role, with poorly differentiated tumors adversely impacting prognosis [23]. This outcome likely reflects the aggressive biological behavior and resistance to therapy typically exhibited by poorly differentiated carcinomas. These tumors tend to be more angiogenically active and less responsive to anti-angiogenic treatments such as sorafenib, which targets VEGFRs. The increased cellular proliferation and reduced apoptosis resistance in poorly differentiated tumors may contribute to their suboptimal response to TACE, which relies on embolization to induce ischemia and selective cytotoxicity.

Interestingly, tumor size was another significant prognostic factor. Larger tumors, typically associated with poor outcomes, can impose substantial hemodynamic stress on the liver by exerting mechanical effects and increasing metabolic demands, often leading to compromised hepatic function [24-26]. Furthermore, larger tumors might possess necrotic cores, which reduce their responsiveness to embolization strategies used in TACE, thereby hindering effective treatment [27, 28]. It is plausible that larger tumors harbor a greater propensity for heterogeneity, conferring variable sensitivity to sorafenib and enabling resistant clones to evade therapeutic pressure [29].

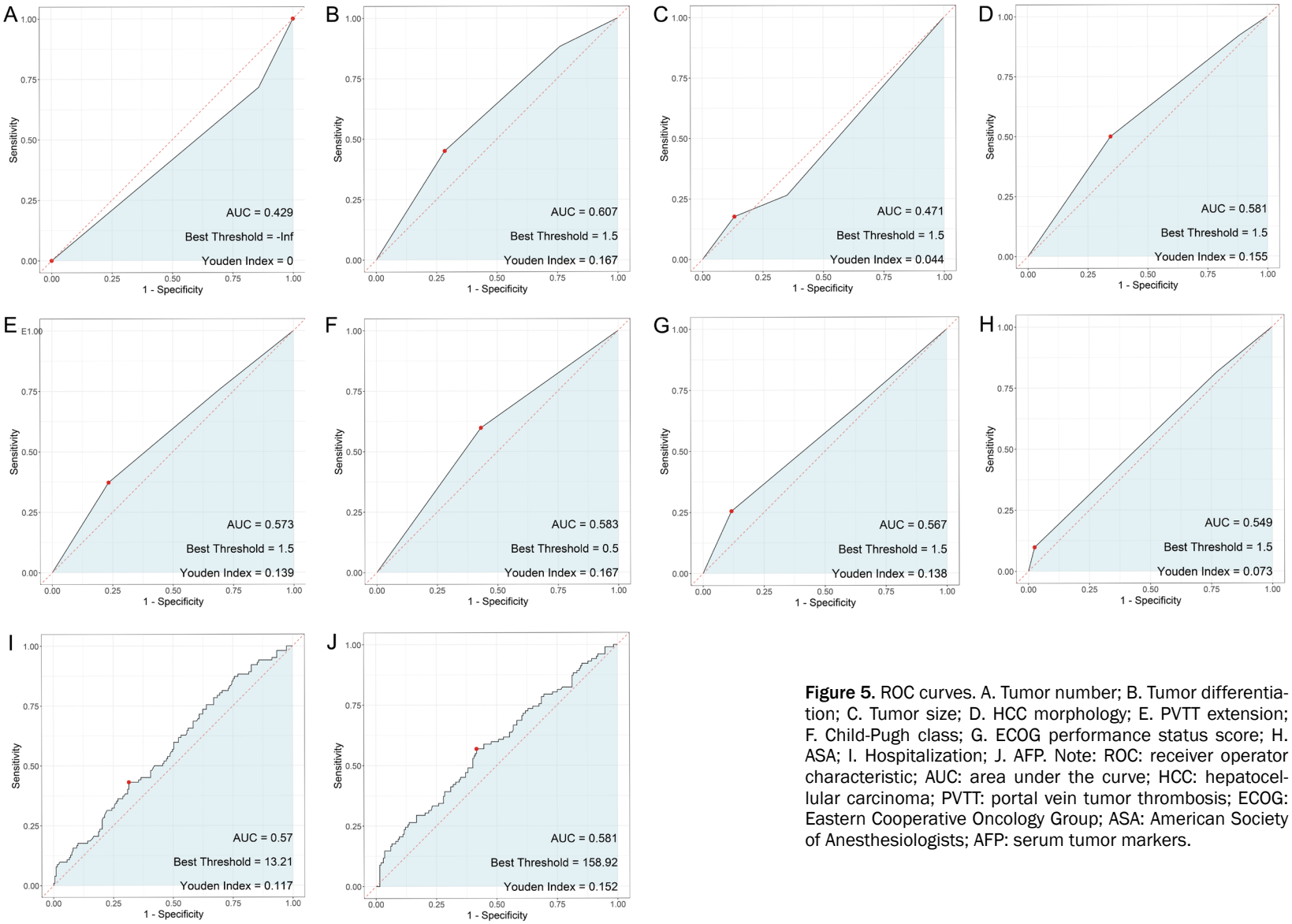

Figure 5. ROC curves. A. Tumor number; B. Tumor differentiation; C. Tumor size; D. HCC morphology; E. PVTT extension; F. Child-Pugh class; G. ECOG performance status score; H. ASA; I. Hospitalization; J. AFP. Note: ROC: receiver operator characteristic; AUC: area under the curve; HCC: hepatocellular carcinoma; PVTT: portal vein tumor thrombosis; ECOG: Eastern Cooperative Oncology Group; ASA: American Society of Anesthesiologists; AFP: serum tumor markers.

On the other hand, the extent of PVTT profoundly affects prognosis, with extensive thrombosis correlating with less favorable outcomes. Extensive PVTT can obstruct portal venous blood flow, precipitating portal hypertension and deteriorative liver function [30]. This condition can further limit the efficacy of TACE due to compromised nutrient supply and reduced accessibility of chemotherapeutic agents to the affected regions. Moreover, PVTT can serve as a conduit for metastatic spread, escalating disease progression and complicating therapeutic regimens.

The Child-Pugh classification, a well-established prognostic model in liver disease, significantly influenced outcomes, affirming that better-preserved liver function aids in more favorable treatment responses. This point highlights the importance of liver functional reserve in determining the feasibility and endurance of aggressive treatment modalities. A compromised liver function limits the body's ability to metabolize sorafenib and manage the ischemic stress induced by TACE, leading to increased susceptibility to treatment-related hepatotoxicity and adverse events.

Additionally, the ECOG performance status was another determinant of prognosis, with better performance scores correlating with improved outcomes. This aligns with expectations, as patient functional status was intimately tied to the capacity to endure and respond to aggressive therapeutic regimens. Patients with better baseline activity levels likely exhibit a more robust physiological reserve, enabling them to withstand treatment-induced stresses more effectively.

AFP levels emerged as an independent prognostic factor, reflective of tumor biology and burden [31]. Elevated AFP levels often indicate more aggressive tumor behavior and a greater tumor burden, factors that were generally associated with worse outcomes. While AFP was not solely a marker of tumor size, it was indicative of metabolic activity within the tumor, potentially correlating with higher vascularization and resistance to embolization strategies employed in TACE [32]. This finding is consistent with the study by Ma et al. [33], which reported that patients in the AFP ≤ 20 ng/mL group had a lower recurrence rate at 2 years post-surgery and higher survival rates at 18 and 24 months compared to those in the AFP 20-400 ng/mL and AFP > 400 ng/mL groups. Preoperative serum AFP levels are closely associated with the malignant characteristics and prognosis of HCC.

Hospitalization duration was shown to correlate with prognosis, likely reflecting treatment complications or comorbid conditions that impede recovery and necessitate prolonged care. Extended hospital stays could denote greater post-treatment complications or a less favorable response to therapy, signaling underlying vulnerabilities that impair patient recovery and overall outcomes.

Our study highlights the critical interplay between tumor burden, biological aggressiveness, and patient functional status in shaping therapeutic outcomes in HCC with PVTT. Observations in tumor number, differentiation, and size underscore the importance of comprehensive diagnostic evaluation in tailoring patient-specific treatment plans and prognostic assessments. These factors combine synergistically to dictate the dynamic landscape of HCC progression and response to treatment, emphasizing the need for a holistic approach in managing this complex disease.

Although our research offers important insights into the prognosis and influencing factors for treating HCC with PVTT using TACE and sorafenib, we acknowledge certain limitations. Primarily, the retrospective study design could result in selection bias, which might restrict the broader applicability of our conclusions. Additionally, the lack of randomization and uniform treatment protocols across the study cohort may have affected the homogeneity of treatment responses. Furthermore, we were unable to incorporate molecular and genetic analyses, which could provide a deeper understanding of tumor heterogeneity and therapeutic resistance. Lastly, our study's reliance on data from a single institution may not fully capture regional variability in patient demographics and healthcare delivery, suggesting the need for multicentric studies to validate our results and enhance their broader applicability.

One critical area for future investigation is the development of a predictive model to evaluate patient prognosis more accurately. Such a model could integrate multiple prognostic fac-

tors identified in this study, including tumor characteristics (number, differentiation, size), extent of PVTT, liver function status (Child-Pugh class), systemic health indicators (ECOG performance status), and serum tumor markers (AFP). By incorporating these variables into a comprehensive algorithm, clinicians could better predict individual patient outcomes, tailor treatment strategies, and improve patient management. To strengthen the generalizability and reliability of our findings, prospective validation studies involving larger and more diverse patient populations are warranted.

Conclusion

In conclusion, the interplay of tumor characteristics, liver function status, and systemic health significantly affects the prognosis for patients undergoing TACE combined with sorafenib for HCC with PVTT. Identifying these factors not only aids clinicians in decision-making but also underscores the need for personalized treatment strategies to optimize survival while minimizing risks. Ongoing advancements in understanding HCC pathogenesis and treatment response continue to refine therapeutic approaches, enabling tailored interventions that address the unique clinical profiles of afflicted patients.

Disclosure of conflict of interest

None.

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