Comparison of albumin-bilirubin grade, platelet-albumin-bilirubin grade and Child-Turcotte-Pugh class for prediction of survival in patients with large hepatocellular carcinoma after transarterial chemoembolization combined with microwave ablation

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ABSTRACT

Purpose: To compare the predictive value of albumin-bilirubin (ALBI) grade, platelet-ALBI (PALBI) grade and Child-Turcotte-Pugh (CTP) class in patients with large hepatocellular carcinoma (HCC) after transarterial chemoembolization (TACE) combined with microwave ablation (TACE-MWA).

Methods: A total of 349 consecutive HCC patients (89.1% male; mean [± SD] age 53.4 ± 12.27 years) from three medical centers, who underwent TACE-MWA for up to 3 HCCs with maximum diameters of 5.1–8.0 cm between January 2000 and June 2018, were investigated. Overall survival (OS) and progression-free survival (PFS) were analyzed. The prognostic performances of ALBI grade, PALBI grade and CTP class were compared.

Results: TACE procedures were performed using lobaplatin (20–50 mg), epirubicin (30–60 mg), lipiodol (5–25 mL) and gelatin sponge particles (350–560 μm). Time point of the TACE procedure was stasis of blood flow in the feeder artery. The median follow-up duration was 28.0 months, the median OS was 28.0 months (95% confidence interval [CI] 23.55–32.45 months), and the median PFS was 4.8 months (95% CI 4.26–5.34 months). Patients with a ablation margin size of 11–15 mm experienced better PFS than those with a margin size of 6–10 or 0–5 mm (median, 6.5 versus [vs] 4.0 vs 2.3 months; p < .001). PALBI grade demonstrated significantly greater area under the curve values than ALBI grade or CTP class in predicting 1-, 3- and 5-year OS.

Conclusions: PALBI grade provided better predictive value than ALBI grade or CTP class in patients with large HCCs after TACE-MWA.

Introduction

Hepatocellular carcinoma (HCC) is a serious health problem, and ranks as the sixth most common cancer and the third leading cause of cancer-related death in the world [1,2]. More than 700,000 new cases of HCC are diagnosed annually. Transarterial chemoembolization (TACE) has long been recommended as a standard treatment for unresectable HCCs [3,4]. However, previous studies have reported that the incidence of complete tumor response to TACE was only 10–20% according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) guidelines [5–8]. Moreover, the median overall survival (OS) of HCC patients who underwent TACE ranged from 16 to 20 months [5–8].

As radical treatments, radiofrequency ablation (RFA) and microwave ablation (MWA) are the two most often performed thermal ablation procedures for liver tumors. Ablation margin size has been validated as an independent prognostic factor of local tumor progression after thermal ablation of liver tumors [9–11]. Wang et al. reported that the risk for local tumor progression decreased by 46% for each 5 mm increase in minimal margin size of RFA for hepatic metastatic disease from colorectal cancer [11]. Compared with RFA, MWA is associated with other advantages, such as...
more spherical and predictable ablation zones, less susceptibility to the heat sink effect, and is less dependent on tissue properties [12–16]. Nevertheless, when reviewing the performance of MWA in HCC patients, differences among available MWA devices should be considered [17,18].

Previous studies have shown that the combination of TACE and MWA (hereafter, TACE-MWA) can improve OS in patients with large HCCs, with better efficacy than either TACE or MWA alone [19–21]. Therefore, TACE-MWA was introduced as an important treatment strategy for patients with large HCCs. Maluccio et al. reported that bland arterial embolization combined with ablation was effective in treating solitary HCC lesions up to 7 cm in size, and achieved similar OS to surgical resection in selected patients. Moreover, their data indicated that the Okuda stage was associated with OS [22,23].

In HCC patients, OS is a composite clinical endpoint due to the mutual influence of prognostic factors. Hepatic function is an independent predictor of OS in patients with HCCs [24,25]. Unfortunately, the vast majority of HCC patients exhibit hepatic dysfunction, despite the absence of overt hepatic cirrhosis. In current clinical practice, the Child-Turcotte-Pugh (CTP) classification system is a widely used tool for assessing hepatic function in patients with HCC. However, the CTP classification was originally developed for patients with hepatic cirrhosis. The albumin-bilirubin (ALBI) grade is a prognostic nomogram that emerged from a multi-variate screen of routine clinicopathological variables in a grade is a prognostic nomogram that emerged from a multi-

Materials and methods

Patients and study design

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the Sun Yat-sen University Cancer Center, the Sun Yat-sen Memorial Hospital of Sun Yat-sen University (Guangdong, China) and the Fujian Provincial Hospital of Fujian Medical University (Fujian, China). Clinicopathological data from 641 patients, who underwent TACE-MWA for large HCCs between January 2000 and June 2018, were retrospectively reviewed. The follow-up was terminated on June 30, 2018. For patients who underwent TACE-MWA, TACE was performed first, followed by MWA 1–2 weeks later. MWA treatments were performed using local anesthesia and moderate intravenous sedation, and TACE treatments were performed using local anesthesia. If necessary, pethidine (60–75 mg) and valium (10 mg) were injected intramuscularly 5 min before either the MWA or TACE procedure to relieve pain and to achieve sedation. After the treatments, oxycodone hydrochloride controlled-release tablets or bonding transdermal fentanyl was used ‘on demand’ for management of abdominal pain. To avoid the occurrence of serious complications or adverse events, such as hepatic dysfunction, liver abscesses, or gastrointestinal hemorrhage, among others, the timing of MWA treatment depended on recovery after TACE. Among the 641 patients, approximately 75% (480/641) were treated with MWA within 2 weeks after undergoing TACE. The patients were discussed at multidisciplinary expert meetings, which included interventional radiologists, oncologists, hepatologists and pathologists, to determine therapeutic strategies for those with large HCCs.

In this study, HCC patients were diagnosed according to the criteria defined by the American Association for the Study of Liver Disease and the European Association for the Study of Liver. The clinical stage was confirmed according to the Barcelona Clinic Liver Cancer guidelines. The presence of hepatic cirrhosis was confirmed based on hepatitis B virus (HBV)/hepatitis C virus (HCV) infection and the findings from computed tomography (CT)/magnetic resonance imaging (MRI) examinations. Inclusion criteria for the present study were as follows: ≥18 years of age; Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1; hepatic function of CTP class A or B; ≤3 HCC lesions that were 5.1–8.0 cm in maximum diameter; absence of evidence of intrahepatic vascular invasion and extrahepatic metastasis; absence of a history of surgical resection or other interventional treatments (e.g., 125I seed implantation, RFA, cryoablation, or percutaneous ethanol injection); absence of severe coagulation dysfunction (e.g., prothrombin activity <40%, international normalized ratio >1.26 and/or platelet count <50 × 10^3/L); absence of general infection, serious dysfunction of the heart or kidney, chronic obstructive pulmonary disease, recent stroke, or other uncontrolled comorbidities; absence of a combination of other malignancies; no previous targeted therapy (e.g., sorafenib) or immunotherapy (e.g., PD-1/PD-L1 antibody); and complete treatment and follow-up data.

Equipment

The Allura Xper FD 20 (Philips Healthcare, Best, Amsterdam, the Netherlands) digital subtraction angiography (DSA)
instrument was used for the TACE procedures. A 64-slice spiral CT scanner (SOMATOM 64 Sensation, Siemens, Munich, Germany) was used for MWA puncture guidance and image acquisition. The microwave ablation system was a water-cooled microwave apparatus (Kangyou Institute, Nanjing, China) equipped with a monopole microwave antenna (16–18 G). Consumables included the puncture needle, the artery catheter sheath, the angiography catheter (Terumo, Tokyo, Japan), and the micro-catheter (Terumo, Tokyo, Japan), lipiodol (Lipiodol Ultrafluide; Guerbet, Aulnay-Sous-Bois, France), gelatin sponge particles (Alicon, Hangzhou, China), and chemotherapeutics including lobaplatin and epirubicin.

**TACE procedure**

TACE was performed under DSA guidance. Hepatic artery angiography was performed using a 5 Fr catheter (RH or Yashiro) to assess location, number, size and blood supply of the target tumors. Subsequently, a 2.7/2.8 Fr micro-catheter was super-selectively inserted into the tumor-feeding arteries. A solution of lobaplatin (20–50 mg [0.5 mg/mL]) was infused into the tumor-feeding arteries via micro-catheter, followed by slow injection of an emulsion of epirubicin (30–60 mg) mixed with lipiodol (5–25 mL). The dosages of chemotherapeutics and embolization emulsion were dependent on body weight and tumor status. Finally, gelatin sponge particles (350–560 μm) mixed with contrast agent were administered into the tumor-feeding vessels. The endpoint of the TACE procedure was defined as static flow in the tumor arteries and full saturation of the feeding arteries. Postoperative treatments, including recovery of hepatic function, prevention of infection and symptomatic treatment(s), were performed. Liver and kidney function, and tumor marker levels were evaluated 3–7 days after TACE and before MWA.

**MWA procedure**

Before the MWA procedure, a fine metal marker was placed on the body surface over the target tumor with the patient in a supine position. If the target tumor was located in challenging segments of the liver, such as segment I, patients were positioned prone or on their left side to obtain an effective path for puncture, and to avoid damage to important vessels or other normal organs. After routine preparation before the procedure, patients were put into deep sedation. A plain CT scan was first taken to confirm the puncture path and location of the target lesion. The puncture site was anesthetized using 2% lidocaine, and an MWA electrode probe was then inserted along the path to reach the opposite edge of the tumor lesion through its center. After confirming the location of the MWA electrode probe, MWA treatment was performed. Microwave power was set to 55–70 W and the procedure lasted for 10–20 min. Subsequently, the MWA electrode probe was removed, and a final CT scan was taken to reexamine the ablation zone and to determine whether serious complications, such as abdominal bleeding or massive pneumothorax, occurred. During the MWA procedure, vital signs, such as heart rate, blood pressure and oxygen saturation, were monitored. After MWA treatment, liver protective, anti-inflammatory and symptomatic treatments were prescribed.

**Assessment of clinical efficacy and safety**

In the present study, the primary endpoint was OS, and the secondary endpoint was progression-free survival (PFS). OS was defined as the date of the first TACE session to the date of death or last date of follow-up. PFS was measured from the date of treatment initiation to tumor progression, death, or last follow-up, whichever came first. Tumor progression was defined as the occurrence of new lesions or local tumor recurrence diagnosed based on imaging, and cytological analysis or biopsy (if necessary). Local tumor response and recurrence, or new lesions, were assessed using contrast-enhanced CT/MRI examinations. According to the mRECIST guidelines, an objective response (OR) was defined as a complete response (CR) and partial response (PR), and disease control (DC) included CR, PR and stable disease (SD). Ablation margin size was evaluated by registration of post- and pre-MWA CT images. During the registration process, unenhanced, arterial phase, and portal phase images of the pre-MWA CT were first used for creating a color map. Then, portal phase CT images of post-MWA and pre-MWA were registered to assess the ablation size. Treatment-related complications were recorded. Major complications were defined as events that caused substantial morbidity or led to hospital admission or prolonged hospital stay. Furthermore, complications related to the TACE-MWA procedures were evaluated according to the criteria defined by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) classification system of complications [32].

**Follow-up**

Contrast-enhanced CT/MRI scans were performed 1–2 weeks before the initial TACE treatment to record and evaluate tumor status in the included patients. After TACE-MWA treatment, follow-up was performed at clinical visits at monthly intervals. Physical examination, laboratory tests (e.g., total bilirubin, serum albumin, prothrombin time and serum tumor marker levels) and contrast-enhanced CT/MRI were performed. Tumor response to TACE-MWA was evaluated using contrast-enhanced CT/MRI every 4–6 weeks after treatment. Local tumor control was assessed by the multidisciplinary team of radiologists and oncologists. If there was no residual tumor and tumor progression, the follow-up tests were prolonged to every 3 months. If residual tumor and/or tumor progression were observed, repeat MWA or TACE, 125I seed implantation, cryoablation, percutaneous ethanol injection, or sorafenib therapy were performed based on a consensus decision made by the multidisciplinary team in accordance with the evaluation of tumor status based on CT/MR imaging.
Definition of ALBI grade and PALBI grade

The ALBI score was calculated before interventional treatment using appropriate clinical parameters and recommended methods. The ALBI score was calculated using the following equation: ALBI score = (log_{10} bilirubin [µ mol/L] × 0.66) + (albumin [g/L] × −0.085). The ALBI grade was defined as follows: grade 1 (ALBI score ≤−2.60); grade 2 (−2.60 < ALBI score ≤−1.39); and grade 3 (ALBI score >−1.39) [27]. The PALBI score was calculated using the following equation: PALBI score = 2.02 × log_{10} bilirubin − 0.37 × (log_{10} bilirubin)^2 − 0.04 × albumin − 3.48 × log_{10} platelets + 1.01 × (log_{10} platelets)^2. The PALBI grade was defined as follows: grade 1 (PALBI score ≤−2.53); grade 2 (−2.53 < PALBI score ≤−2.09); and grade 3 (PALBI score >−2.09) [30,33].

Statistical analysis

All statistical analyses were performed using SPSS version 22.0 (IBM Corporation, Armonk, NY, USA). Quantitative data are expressed as frequency, mean ± standard deviation (SD), or median with corresponding 95% confidence interval (CI). The Mann-Whitney U test was used to compare continuous variables, and either Pearson’s χ2 test or Fisher’s exact test was used to compare categorical data. Cumulative survival curves of OS and PFS were generated using the Kaplan-Meier method. For OS analyses, patients who remained alive at the date of last follow-up were considered to be ‘censored.’ In terms of PFS, time was censored at the date of death or last follow-up without progression. The cumulative survival curves of the factors assessed using univariable analysis were compared using the log-rank test. Statistically significant (p < .1) factors identified in the univariate analysis were entered into a Cox proportion hazards regression model to identify independent predictors of survival. In the multivariable analyses, CTP class, ALBI grade and PALBI grade were included in three separate models. The area under the receiver operating characteristic curve (AUC), equivalent to concordance index, was calculated to test discriminatory powers for predicting 1-, 3- and 5-year mortality rates. For all tests, p < .05 was considered to be statistically significant.

Results

Patient characteristics

A total of 349 patients were ultimately enrolled (89.1% male; mean ± SD age, 53.4 ± 12.27 years range, 19–79 years). Ninety (25.8%) and 259 (74.2%) patients had an ECOG performance status score of 0 and 1, respectively, 273 (78.2%) had a history of HBV/HCV infection, and 156 (44.7%) developed hepatic cirrhosis. There were 86 (24.6%), 182 (52.1%) and 81 (23.3%) patients with ALBI grade 1, grade 2 and grade 3, respectively. There were 135 (38.7%), 106 (30.4%) and 108 (30.9%) patients with PALBI grade 1, grade 2 and grade 3, respectively. There were 261 (74.8%) and 88 (25.2%) patients with the CTP class A and B. In terms of tumor factors, HCCs in all included patients were 5.1–8.0 cm in maximum diameter, and 45% (159/349) exhibited multiple tumor lesions. When stratified according to ablation margin size, there were 90 (25.8%), 119 (34.1%) and 140 (40.1%) patients with a minimal margin size of 0–5, 6–10 and 11–15 mm, respectively. Baseline patient characteristics are summarized in Table 1.

Tumor response to TACE-MWA

The local tumor response to TACE-MWA was assessed according to the mRECIST guidelines. Analysis revealed that CR, PR, SD and progressive disease (PD) were noted in 58 (16.6%), 211 (60.5%), 41 (11.7%) and 39 (11.2%) patients, respectively. The DC and OR rates were 88.8% and 77.1%, respectively. Among 79 patients who experienced PD, 58 (73.4%) experienced local tumor recurrences and 21 (26.6%) experienced new tumor lesions.

OS and PFS

Over an 18-year follow-up period, the median follow-up duration was 28.0 months (range, 4.0–221 months), 253 patients died, and 96 survived at their last visit. The median OS was 28.0 months (95% CI 23.55–32.45 months), and the cumulative 1-, 3-, 5- and 10-year OS rates were 85.2%, 43.4%, 24.5% and 8.6%, respectively (Figure 1). The median PFS was 4.8 months (95% CI 4.26–5.34 months), and the cumulative 1-, 2-, 3- and 5-year PFS rates were 21.8%, 9.7%, 3.7% and 0.3%, respectively (Figure 2(A)).

Stratified according to ablation margin size, patients with a margin size of 11–15 mm experienced better median PFS than those with a margin size of 6–10 or 0–5 mm (6.5 versus [vs] 4.0 vs 2.3 months; p < .001). For patients with a margin size of 11–15, 6–10 and 0–5 mm, the respective cumulative 1-, 3- and 5-year PFS rates were 33.6%, 9.3% and 3.6%; 22.7%, 0% and 0%; and 1.1%, 0% and 0% (p < .001) (Figure 2B).

Prognostic factors of OS and PFS

Univariate analyses revealed that ALBI grade (p < .001), PALBI grade (p < .001), CTP class (p < .001), ECOG performance status (p < .001), tumor number (p < .001), albumin level (p < .001), total bilirubin (p < .001) and alpha-fetoprotein level (p < .001) were significantly associated with OS (Table 2). Multivariate analyses revealed that ALBI grade (ALBI grade 2, hazard ratio [HR] 0.18 [95% CI 0.11–0.29; p < .001], ALBI grade 3, HR 0.41 [95% CI 0.29–0.57; p < .001]) and PALBI grade (PALBI grade 2, HR 0.35 [95% CI 0.23–0.53; p < .001], PALBI grade 3, HR 0.46 [95% CI 0.32–0.67; p < .001]; CTP class, HR 2.16 [95% CI 1.49–3.15; p < .001]; ECOG performance status; and alpha-fetoprotein level were independent predictors of OS (Table 2).

In terms of PFS, univariate analyses revealed that ALBI grade (p < .001), PALBI grade (p < .001), CTP class (p < .001), patient age (p = .085), ECOG performance status (p < .001), tumor number (p < .001), albumin level (p < .001), total bilirubin (p = .017), alpha-fetoprotein level (p = .088), TACE session (p = .001), MWA session (p = .001) and ablation margin size
Multivariate analyses revealed that ALBI grade (ALBI grade 2, HR 0.30 [95% CI 0.19–0.47; \( p < .001 \]), ALBI grade 3, HR 0.57 [95% CI 0.43–0.78; \( p < .001 \]); PALBI grade 2, HR 0.24 [95% CI 0.42–0.71; \( p < .001 \]), PALBI grade 3, HR 0.61 [95% CI 0.47–0.82; \( p < .001 \]); ECOG performance status, tumor number and ablation margin size were independent predictors of PFS (Table 3).

**Predictive value of the ALBI grade, PALBI grade and CTP class in OS**

Patients with ALBI grade 1 experienced better median OS than those with ALBI grade 2 or grade 3 (69.0 vs 29.0 vs 11.0 months; \( p < .001 \)) (Figure 3(A) and Table 3). Similarly, the median OS of patients with PALBI grade 1 was significantly better than those with PALBI grade 2 or grade 3 (52.0 vs 37.0 vs 14.0 months; \( p < .001 \)) (Figure 3(B) and Table 3). Patients with CTP class A experienced better median OS than those with the CTP class B (40.0 vs 13.0 months; \( p < .001 \)) (Figure 3(C) and Table 3).

**Relationship between ALBI grade, PALBI grade and CTP class in OS and PFS**

In the subgroup of those with CTP class A, patients with the ALBI grade 1 experienced better median OS (69.0 vs 35.0 vs 10.0 months; \( p < .001 \)) (Figure 4(A)) and PFS (15.5 vs 5.5 vs 2.1 months; \( p < .001 \)) (Figure 4(B)) than those with ALBI grade 2 or grade 3. In the subgroup analysis of CTP class B,
patients with ALBI grade 2 demonstrated better PFS than those with ALBI grade 3 (3.0 vs 2.5 months; \( p = 0.029 \)) (Figure 4(C)). However, there were no significant differences in OS (\( p = 0.246 \)) (Figure 4(D)).

Regarding PALBI grade, in the subgroup analysis of those with CTP class A, patients with PALBI grade 1 experienced better median OS (54.0 vs 40.0 vs 18.0 months; \( p < 0.001 \)) (Figure 5(A)) and PFS (6.5 vs 6.0 vs 2.5 months; \( p = 0.001 \)) (Figure 5(B)) than those with PALBI grade 2 or grade 3. In the subgroup analysis of patients with CTP class B, there were no significant differences in OS (\( p = 0.132 \)) (Figure 5(C)) and PFS (\( p = 0.531 \)) (Figure 5(D)). A summary of the relationships between ALBI grade, PALBI grade and CTP class in assessing survival is presented in Table 4.

**Comparison of ALBI grade, PALBI grade and CTP class in predicting OS**

The discriminatory capabilities of PALBI grade, ALBI grade and CTP class were quantified using AUC values. PALBI grade had higher AUC values than ALBI grade or CTP class in predicting 1-, 3- and 5-year OS (Figure 6(A–C)). The 1-, 3- and 5-year AUC values for PALBI grade were 0.81 (95% CI 0.76–0.86), 0.74 (95% CI 0.68–0.79) and 0.74 (95% CI 0.66–0.81), respectively. The 1-, 3- and 5-year AUC values for ALBI grade were 0.73 (95% CI 0.66–0.79), 0.69 (95% CI 0.63–0.75) and 0.67 (95% CI 0.59–0.74), respectively. The 1-, 3- and 5-year AUC values for CTP class were 0.67 (95% CI 0.60–0.74), 0.63 (95% CI 0.57–0.69) and 0.61 (95% CI 0.54–0.69), respectively.

**Complications**

There were no treatment-related deaths. Hepatic dysfunction was the most common complication, including elevation of biochemical test results and manifestations of ascites or icterus during the follow-up period. Among all patients, major complications related to TACE-MWA procedures were observed in 9 (2.6%), including liver abscess (\( n = 2 \)), subcapsular hematoma (\( n = 1 \)), intercostal artery hemorrhage (\( n = 1 \)), intrahepatic artery hemorrhage (\( n = 2 \)), refractory pleural effusion (\( n = 1 \)) and biloma (\( n = 2 \)). Minor complications were observed in 77 (22.1%) patients, including mild abdominal pain, fever, nausea, vomiting, fatigue and elevated liver enzyme levels. All minor complications were transient and resolved within 3–7 days. According to the CIRSE classification system of complications, the incidence of grade 1, grade 2, grade 3 and grade 4 complications were 18.6% (65/349), 3.7% (13/349), 2.0% (7/349) and 0.6% (2/349), respectively. There were no grade 5 or grade 6 complications.

**Discussion**

In the present study, TACE-MWA procedures were performed in 349 patients with HCCs, which yielded acceptable 3-, 5- and 10-year OS rates of 43.4%, 24.5% and 8.6%, respectively. Prognostic analyses revealed that PALBI grade, ALBI grade, CTP class, ECOG performance status, and alpha-fetoprotein level were independent predictors of OS. Furthermore, our data revealed that PALBI grade was a better prognostic tool than ALBI grade or CTP class in predicting OS of patients with large HCCs after TACE-MWA.

TACE has long been recommended as the first-line treatment for unresectable HCCs. In attempts to improve the clinical efficacy of TACE, TACE-MWA has been validated as a better treatment strategy than TACE alone in several randomized controlled trials (RCTs) [34]. However, a limited number of studies reported the long-term outcomes of TACE-MWA for large HCCs. Zheng et al. reported medium-term outcomes of TACE-MWA in 92 patients with large HCCs, with a 3-year OS rate of 32.6% [35]. In that study, 44 (47.8%) patients exhibited HCC lesions with a maximum diameter >10 cm, and tumor size was confirmed as a significant predictor of OS. This may explain why the 3-year OS rate in our patients was higher than in their patients. Hu et al. reported a survival analysis involving 84 patients with large HCCs with maximum diameters of 5.0–10.0 cm who underwent TACE-
They found that alpha-fetoprotein level, hepatic function and tumor number were significant prognostic factors for OS. These findings are consistent with those of our study. Elnekave et al. compared the clinical efficacy of the combination of transarterial embolization (TAE) and ablation (TAE-ablation) with that of surgical resection for the treatment of solitary HCCs <7 cm [37]. The authors reported that patients who underwent TAE-ablation had a median OS of 54 months. However, approximately 70% of the patients in that study exhibited HCC lesions <5.5 cm, and all had CTP class A hepatic function. As such, it would be inappropriate to directly compare our results with those of their study.

### Table 2. Univariable and multivariable predictors of overall survival.

| Factor                  | Univariate analysis | Multivariate analysis |
|-------------------------|---------------------|----------------------|
|                         | No. of Pts (n = 349) |                      |
| Age (year)              | 0.95 (0.73–1.24)    | 0.95 (0.73–1.24)    |
| <60                     | 234                 | 0.95 (0.73–1.24)    |
| ≥60                     | 115                 | 0.95 (0.73–1.24)    |
| Gender                  | 0.85 (0.56–1.29)    | 0.85 (0.56–1.29)    |
| Male                    | 311                 | 0.85 (0.56–1.29)    |
| Female                  | 38                  | 0.85 (0.56–1.29)    |
| ECOG (score)            | 2.89 (2.09–4.00)    | 2.89 (2.09–4.00)    |
| 0                       | 90                  | 2.89 (2.09–4.00)    |
| 1                       | 259                 | 2.89 (2.09–4.00)    |
| Etiology                | 0.82 (0.64–1.05)    | 0.82 (0.64–1.05)    |
| HBV/HCV                 | 273                 | 0.82 (0.64–1.05)    |
| None                    | 76                  | 0.82 (0.64–1.05)    |
| Hepatic cirrhosis       | 0.82 (0.64–1.05)    | 0.82 (0.64–1.05)    |
| With                    | 156                 | 0.82 (0.64–1.05)    |
| Without                 | 193                 | 0.82 (0.64–1.05)    |
| Tumor number            | 1.82 (1.42–2.33)    | 1.82 (1.42–2.33)    |
| Single                  | 190                 | 1.82 (1.42–2.33)    |
| Multiple                | 159                 | 1.82 (1.42–2.33)    |
| Albumin level           | 0.45 (0.34–0.59)    | 0.45 (0.34–0.59)    |
| ≤3.5 mg/dL              | 112                 | 0.45 (0.34–0.59)    |
| >3.5 mg/dL              | 237                 | 0.45 (0.34–0.59)    |
| TBIL level              | 1.62 (1.26–2.08)    | 1.62 (1.26–2.08)    |
| ≤1.0 mg/dL              | 174                 | 1.62 (1.26–2.08)    |
| >1.0 mg/dL              | 175                 | 1.62 (1.26–2.08)    |
| ALT level               | 1.19 (0.93–1.52)    | 1.19 (0.93–1.52)    |
| ≤40 U/L                 | 172                 | 1.19 (0.93–1.52)    |
| >40 U/L                 | 177                 | 1.19 (0.93–1.52)    |
| PT INR                  | 1.07 (0.79–1.44)    | 1.07 (0.79–1.44)    |
| ≤1.0                    | 83                  | 1.07 (0.79–1.44)    |
| >1.0                    | 266                 | 1.07 (0.79–1.44)    |
| AFP level               | 1.76 (1.37–2.26)    | 1.76 (1.37–2.26)    |
| ≤400 ng/mL              | 208                 | 1.76 (1.37–2.26)    |
| >400 ng/mL              | 141                 | 1.76 (1.37–2.26)    |
| Platelet count          | 0.91 (0.68–1.20)    | 0.91 (0.68–1.20)    |
| ≤10 x 10^9 /L           | 85                  | 0.91 (0.68–1.20)    |
| >10 x 10^9 /L           | 264                 | 0.91 (0.68–1.20)    |
| CTP class               | 2.99 (2.27–3.96)    | 2.99 (2.27–3.96)    |
| A                       | 261                 | 2.99 (2.27–3.96)    |
| B                       | 88                  | 2.99 (2.27–3.96)    |
| ALBI grade              |                      |                      |
| 1                       | 1                   |                      |
| 2                       | 182                 |                      |
| 3                       | 81                  |                      |
| PALBI grade             |                      |                      |
| 1                       | 1                   |                      |
| 2                       | 106                 |                      |
| 3                       | 108                 |                      |
| TACE session            | 1.21 (0.94–1.56)    | 1.21 (0.94–1.56)    |
| ≤3                      | 220                 | 1.21 (0.94–1.56)    |
| >3                      | 129                 | 1.21 (0.94–1.56)    |
| MWA session             | 0.83 (0.61–1.13)    | 0.83 (0.61–1.13)    |
| ≤3                      | 278                 | 0.83 (0.61–1.13)    |
| >3                      | 71                  | 0.83 (0.61–1.13)    |
| Ablation margin size    |                      |                      |
| 0–5 mm                  | 0.98 (0.73–1.20)    | 0.98 (0.73–1.20)    |
| 6–10 mm                 | 0.88 (0.63–1.25)    | 0.88 (0.63–1.25)    |
| 11–15 mm                | 0.75 (0.51–1.13)    | 0.75 (0.51–1.13)    |

Data in parentheses are 95% confidence intervals.

Pts: patients; ECOG: Eastern Cooperative Oncology Group; HBV: hepatitis B virus; HCV: hepatitis C virus; cm: centimeter; TBIL: total bilirubin; ALT: alanine aminotransferase; PT INR: prothrombin time international normalized ratio; ALBI: albumin-bilirubin; PALBI: platelet-albumin-bilirubin; CTP: Child-Turcotte-Pugh; AFP: α-fetoprotein; TACE: transarterial chemoembolization; MWA: microwave ablation; mm: millimeter.
However, according to the previous studies, it is clear that TACE-MWA is superior to TACE alone for the treatment of solitary or a limited number of large HCCs.

In our study, we found that PALBI grade was superior to ALBI grade and CTP class in predicting OS of patients with large HCCs after TACE-MWA. These findings are consistent with those of previous studies [30,38]. The CTP classification was originally developed to assess hepatic function in patients with hepatic cirrhosis. However, in our study, 193 (55.3%) patients exhibited no evidence of hepatic cirrhosis, which may have decreased the predicted efficacy of CTP class. In addition, the clinical application of CTP class was

| Table 3. Univariable and multivariable predictors of progression-free survival. |
|-----------------------------------|------------------|------------------|------------------|------------------|------------------|
| **Factor**                        | **Univariate analysis** | **Multivariate analysis** |
|                                  | **No. of Pts (n = 349)** | **Hazard ratio** | **p Value** | **Hazard ratio** | **p Value** | **Hazard ratio** | **p Value** | **Hazard ratio** | **p Value** |
| Age (year)                        |                        |                  |            |                  |            |                  |            |                  |            |
| <60                               | 234                   | 1.21 (0.97–1.50) | .085       | 1.19 (0.96–1.49) | .119       | 2.20 (2.07–2.60) | .351       | 1.47 (1.05–1.77) | .209       |
| ≥60                               | 115                   |                  |            |                  |            |                  |            |                  |            |
| Gender                            |                        |                  |            |                  |            |                  |            |                  |            |
| Male                              | 311                   | 0.99 (0.69–1.42) | .978       |                  |            |                  |            |                  |            |
| Female                            | 38                    |                  |            |                  |            |                  |            |                  |            |
| ECOG (score)                      |                        |                  |            |                  |            |                  |            |                  |            |
| 0                                 | 90                    | 1.75 (1.38–2.23) | <.001      | 0.76 (0.58–1.00) | .047       | 1.09 (0.45–2.02) | <.001      | 3.62 (2.97–4.54) | <.001      |
| 1                                 | 259                   |                  |            |                  |            |                  |            |                  |            |
| Etiology                          |                        |                  |            |                  |            |                  |            |                  |            |
| With                              | 156                   | 0.90 (0.73–1.12) | .353       |                  |            |                  |            |                  |            |
| Without                           | 193                   |                  |            |                  |            |                  |            |                  |            |
| Tumor number                      |                        |                  |            |                  |            |                  |            |                  |            |
| Single                            | 190                   | 0.47 (0.35–0.63) | <.001      | 0.41 (0.21–0.71) | .006       | 0.21 (0.12–0.52) | .001       | 0.64 (0.34–1.02) | .021       |
| Multiple                          | 159                   |                  |            |                  |            |                  |            |                  |            |
| Albumin level                     |                        |                  |            |                  |            |                  |            |                  |            |
| ≤3.5 g/dL                         | 112                   | 0.64 (0.52–0.79) | <.001      | 1.02 (0.78–1.34) | .872       | 1.71 (1.54–1.99) | .140       | 1.87 (1.64–2.13) | .289       |
| >3.5 g/dL                         | 237                   |                  |            |                  |            |                  |            |                  |            |
| TBIL level                        |                        |                  |            |                  |            |                  |            |                  |            |
| ≤1.0 mg/dL                        | 174                   | 1.31 (1.05–1.63) | .017       | 0.85 (0.66–1.09) | .194       | 1.91 (1.74–2.62) | .306       | 1.18 (0.91–1.55) | .517       |
| >1.0 mg/dL                        | 175                   |                  |            |                  |            |                  |            |                  |            |
| ALT level                         |                        |                  |            |                  |            |                  |            |                  |            |
| ≤40 U/L                           | 172                   | 1.07 (0.87–1.33) | .526       |                  |            |                  |            |                  |            |
| >40 U/L                           | 177                   |                  |            |                  |            |                  |            |                  |            |
| PT INR                            |                        |                  |            |                  |            |                  |            |                  |            |
| ≤1.0                              | 83                    | 0.88 (0.67–1.16) | .354       |                  |            |                  |            |                  |            |
| >1.0                              | 266                   |                  |            |                  |            |                  |            |                  |            |
| AFP level                         |                        |                  |            |                  |            |                  |            |                  |            |
| ≤400 ng/mL                        | 208                   | 1.21 (0.97–1.49) | .088       | 0.88 (0.71–1.09) | .266       | 0.78 (0.37–1.28) | .315       | 0.64 (0.27–1.12) | .719       |
| >400 ng/mL                        | 141                   |                  |            |                  |            |                  |            |                  |            |
| Platelet count                    |                        |                  |            |                  |            |                  |            |                  |            |
| ≤100 x 10⁹ /L                     | 85                    | 1.13 (0.90–1.40) | .294       |                  |            |                  |            |                  |            |
| >100 x 10⁹ /L                     | 264                   |                  |            |                  |            |                  |            |                  |            |
| CTP class                          |                        |                  |            |                  |            |                  |            |                  |            |
| A                                 | 261                   | 1.89 (1.50–2.37) | <.001      |                  |            |                  |            | 0.46 (0.29–0.71) | .201       |
| B                                 | 88                    |                  |            |                  |            |                  |            |                  |            |
| ALBI grade                         |                        |                  |            |                  |            |                  |            |                  |            |
| 1                                 | 86                    | 1                  |            | 1                  |            |                  |            |                  |            |
| 2                                 | 182                   | 0.21 (0.14–0.31) | <.001      | 0.30 (0.19–0.47) | <.001      |                  |            |                  |            |
| 3                                 | 81                    | 0.46 (0.35–0.58) | <.001      | 0.57 (0.43–0.78) | <.001      |                  |            |                  |            |
| PALBI grade                        |                        |                  |            |                  |            |                  |            |                  |            |
| 1                                 | 135                   | 1                  |            | 1                  |            |                  |            |                  |            |
| 2                                 | 106                   | 0.56 (0.49–0.66) | <.001      | 0.24 (0.42–0.71) | <.001      |                  |            |                  |            |
| 3                                 | 108                   | 0.68 (0.58–0.82) | <.001      | 0.61 (0.47–0.82) | <.001      |                  |            |                  |            |
| TACE session                       |                        |                  |            |                  |            |                  |            |                  |            |
| ≤3                                | 220                   | 0.58 (0.43–0.79) | <.001      |                  |            |                  |            |                  |            |
| >3                                | 129                   |                  |            |                  |            |                  |            |                  |            |
| MWA session                        |                        |                  |            |                  |            |                  |            |                  |            |
| ≤3                                | 278                   | 0.67 (0.54–0.84) | .001       |                  |            |                  |            |                  |            |
| >3                                | 71                    |                  |            |                  |            |                  |            |                  |            |
| Ablation margin size               |                        |                  |            |                  |            |                  |            |                  |            |
| 0–5 mm                            | 90                    | 0.38 (0.13–0.60) | <.001      | 0.56 (0.31–0.85) | <.001      | 0.69 (0.44–0.98) | <.001      | 0.73 (0.49–1.02) | <.001      |
| 6–10 mm                           | 119                   |                  |            |                  |            |                  |            |                  |            |
| 11–15 mm                          | 140                   |                  |            |                  |            |                  |            |                  |            |

Data in parentheses are 95% confidence intervals.
Pts: patients; ECOG: Eastern Cooperative Oncology Group; HBV: hepatitis B virus; HCV: hepatitis C virus; cm: centimeter; TBIL: total bilirubin; ALT: alanine aminotransferase; PT INR: prothrombin time international normalized ratio; ALBI: albumin-bilirubin; PALBI: platelet-albumin-bilirubin; CTP: Child-Turcotte-Pugh; AFP: α-fetoprotein; TACE: transarterial chemoembolization; MWA: microwave ablation.

limited by some constraints. Due to the challenges in assessing minimal ascites or encephalopathy, the subjective assessment of hepatic encephalopathy and ascites, and inter-relationships between serum albumin level and ascites by physicians, may decrease the accuracy of CTP class in evaluating hepatic function. It indicated that not all constituents of the CTP class have equal accessibility and reproducibility. The cutoff levels for albumin, bilirubin and pro-thrombin time are intrinsic drawbacks of CTP classification, which may have ultimately limited accurate prognostication. Furthermore, hepatic cirrhosis-related portal hypertension is a highly lethal factor affecting the long-term prognosis of HCC patients. However, the CTP classification does not include any biomarkers to assess portal hypertension.

To overcome the limitations of CTP classification, the ALBI grade is recommended as an important biomarker for assessment of hepatic function in patients with HCCs. Compared with CTP class, the ALBI grade is associated with three important features making it simple, objective, and accurate. Regarding ALBI grade, both serum albumin and bilirubin levels can offer an evidence-based, objective tool for assessment of hepatic function in patients with HCCs. The efficacy of the ALBI grade in assessing hepatic function of HCC patients has been validated in several studies. Kao et al. constructed a nomogram with ALBI grade to assess the OS of patients with early-stage HCCs after RFA, in which personalized long-term OS data were described [31]. Based on ALBI grade, PALBI grade was developed with platelet count acting as an evaluation tool to assess the severity of portal hypertension. Liu et al. also reported that ALBI grade was a good tool to assess hepatic dysfunction in patients with HCC [33]. In that study, the investigators examined HCC patients who underwent liver resection, RFA or TACE, and both ALBI and PALBI grades were validated as adequate models to assess hepatic dysfunction in HCC patients. Our data indicated that PALBI grade had better discriminatory power than ALBI grade and CTP class for prediction of 1-, 3- and 5-year OS. The findings of our study, therefore, were consistent with those of previous studies [33,38].

In the present study, the ablation margin size was evaluated by the registration of post- and pre-MWA CT images. Kim et al. [39] and Shin et al. [40] reported that the registration of post- and pre-ablation CT images was an accurate and useful technique for assessing the safety margin after ablation therapy. Therefore, the method we used in the present study to evaluate the ablation margin was supported by previous studies [39,40]. We found that patients with a minimum ablation margin size of 11–15 mm experienced
significantly better median PFS than those with a minimum ablation margin size of 0–5 or 6–10 mm (6.5 vs 4.0 vs 2.3 months). Our data demonstrated that the differences between the two groups were statistically significant ($p < .001$). Previous studies have shown that ablation margin size is independently associated with the outcomes of thermal ablation for HCCs or hepatic metastases with a maximum tumor size <5.0 cm [9–11]. Wang et al. reported that the risk for local tumor progression decreased by 46% for each 5 mm increase in minimal margin size of RFA for hepatic metastasis of colorectal cancer [11]. Shady et al. reported that an ablation margin <5 cm was a significant predictor of shorter local tumor PFS, and suggested that an ablation margin >5 cm was critical for local tumor control in patients with colorectal liver metastases who underwent RFA or MWA [16]. Few studies have investigated the predictive value of ablation margin in the assessment of outcomes of TACE-MWA for large HCCs.

To the best of our knowledge, this was the first investigation to examine and compare PALBI grade, ALBI grade and CTP class in a large, multi-center study involving patients with large HCCs after TACE-MWA. We confirmed that PALBI grade demonstrated better efficacy in predicting OS. Strengths of the present study included its multi-center design, large sample size, and long-term follow-up.

There were, however, some limitations to our study, the first of which was its retrospective design. Although the data regarding survival analyses were accurate and carefully recorded by the reviewers, prospective RCTs are still needed to confirm our proposal and hypothesis. Second, the included patients had large HCCs with a maximum diameter of 5.1–8.0 cm; therefore, our findings need to be validated by investigating patients with HCCs >8.0 cm in diameter. Third, the ablation margins were evaluated using traditional two-dimensional images of post- and pre-MWA CT scans. Recently, new volumetric three-dimensional methods for assessment of ablation completeness or ablation margin have been described [41,42]. Future studies may be needed to validate our results by using these recommended methods.

In conclusion, our multi-center data confirmed that PALBI grade was a better prognostic tool than ALBI grade or CTP class in predicting OS of patients with large HCCs after TACE-MWA.

**Ethical approval**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with

![Kaplan-Meier curves of overall survival (A&C) and progression-free survival (B&D) in patients with the CTP class A (A&B) and CTP class B (C&D) stratified by the ALBI grade. ALBI: albumin-bilirubin; CTP: Child-Turcotte-Pugh.](image-url)
Figure 5. Kaplan-Meier curves of overall survival (A&C) and progression-free survival (B&D) in patients with the CTP class A (A&B) and CTP class B (C&D) stratified by the PALBI grade. PALBI: platelet-albumin-bilirubin; CTP: Child-Turcotte-Pugh.

Table 4. Overall survival and progression-free survival stratified by ALBI grade, PALBI grade and CTP class.

| Subgroup | No. of Pts (n = 349) | Overall survival | Progression-free survival |
|----------|----------------------|------------------|---------------------------|
| ALBI grade | | Median (month) | $\chi^2$ | p Value | Median (month) | $\chi^2$ | p Value |
| 1 | 86 | 69.0 (10.0–221.0) |  | | 17.0 (1.0–96.0) |  | |
| 2 | 182 | 29.0 (5.0–121.0) |  | | 4.5 (0.5–51.0) |  | |
| 3 | 81 | 11.0 (4.0–90.0) |  | | 2.5 (0.5–31.0) |  | |
| PALBI grade | | | 85.2 | <.001 | 30.6 | <.001 |
| 1 | 136 | 52.0 (5.0–221.0) |  | | 5.5 (0.5–96.0) |  | |
| 2 | 105 | 37.0 (5.0–84.0) |  | | 5.0 (0.5–49.0) |  | |
| 3 | 108 | 14.0 (5.0–78.0) |  | | 2.5 (0.5–36.0) |  | |
| CTP class | | 67.3 | <.001 | | 33.1 | <.001 |
| A | 261 | 40.0 (5.0–221.0) |  | | 5.0 (0.5–96.0) |  | |
| B | 88 | 13.0 (4.0–90.0) |  | | 3.0 (0.5–39.0) |  | |
| CTP class A | | 102.8 | <.001 | | 44.1 | <.001 |
| ALBI grade 1 | 85 | 69.0 (10.0–221.0) |  | | 15.5 (1.0–96.0) |  | |
| ALBI grade 2 | 142 | 35.0 (5.0–121.0) |  | | 5.5 (1.0–51.0) |  | |
| ALBI grade 3 | 34 | 10.0 (5.0–75.0) |  | | 2.1 (0.5–31.0) |  | |
| CTP class B | | 1.3 | .246 | | 12.4 | .029 |
| ALBI grade 1 | 41 | 13.0 (5.0–73.0) |  | | 3.0 (0.5–39.0) |  | |
| ALBI grade 2 | 47 | 13.0 (4.0–90.0) |  | | 2.5 (0.5–26.0) |  | |
| CTP class A | | 34.9 | <.001 | | 13.4 | .001 |
| ALBI grade 1 | 128 | 54.0 (9.0–221.0) |  | | 6.5 (1.0–96.0) |  | |
| ALBI grade 2 | 87 | 40.0 (7.0–84.0) |  | | 6.0 (1.0–49.0) |  | |
| ALBI grade 3 | 46 | 18.0 (5.0–78.0) |  | | 2.5 (0.5–56.0) |  | |
| CTP class B | | 4.1 | .132 | | 1.27 | .531 |

Unless otherwise indicated data are medians, with interquartile range in parentheses.
ALBI: albumin-bilirubin; PALBI: platelet-albumin-bilirubin; CTP: Child-Turcotte-Pugh; Pts: patients.
the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent**

Written informed was obtained from all individual participants in the study.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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Figure 6. Receiver operating characteristic curves and corresponding AUC for 1-(A), 3-(B) and 5-year (C) OS. ALBI: albumin-bilirubin; APLBI: platelet-albumin-bilirubin; CI: confidence interval; AUC: area under the curve.
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