Predictive value of the albumin-bilirubin grade on long-term outcomes of CT-guided percutaneous microwave ablation in intrahepatic cholangiocarcinoma

Jia-Yan Ni, Chao An, Tian-Qi Zhang, Zhi-Mei Huang, Xiong-Ying Jiang and Jin-Hua Huang

Department of Minimally Invasive Interventional Radiology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, PR China; Department of Interventional Radiology, Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, PR China; Department of Interventional Ultrasound, Chinese PLA General Hospital, Beijing, PR China

ABSTRACT

Purpose: To assess the efficacy of the albumin-bilirubin (ALBI) grade on assessing long-term outcomes of computed tomography (CT)-guided percutaneous microwave ablation (CT-PMWA) in the treatment of patients with intrahepatic cholangiocarcinoma (ICC).

Methods: Between April 2011 and March 2018, 78 patients who underwent CT-PMWA were enrolled in this study. Overall survival (OS) and recurrence-free survival (RFS) were compared in the groups stratified by the ALBI grade and Child–Pugh score. Cox proportional hazard regression analyses were performed to determine independent predictors of OS and RFS.

Results: After a median follow-up of 22.7 months (range 1–86.7 months), 67 patients had died. The cumulative 1-, 3-, and 5-year OS rates were 89.5%, 52.2%, and 35.0%, respectively. Stratified by the ALBI grade, the cumulative 1-, 3-, and 5-year OS rates were 100%, 69.2%, and 25.8% for patients with the grade 1, respectively. For patients with the ALBI grade 2, the cumulative 1-, 3-, and 5-year OS rates were 41.0%, 10.3%, and 10.3%, respectively. Patients with a hepatic function of the ALBI grade 1 had significantly higher OS rates than patients with the ALBI grade 2 (p < .001). The multivariate analysis showed tumor size (Hazard Ratio [HR] 95% Confidence Interval [CI]: 9.03[1.01–80.52], p = .049), and the ALBI grade (HR[95%CI]:9.56[5.80–15.80], p = .014) were associated with OS, and tumor size (HR: 2.03[0.69–8.04], p = .049) was associated with RFS.

Conclusions: The preliminary data of this study showed the ALBI grade was effective to predict long-term outcomes of CT-PMWA in ICCs. Further study is necessary to validate our results by a large, multi-center patient cohort.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a kind of primary hepatic malignancies, which is considered as a subtype of cholangiocarcinomas (CCAs). ICC is still a rare tumor, representing about 3% of gastrointestinal malignancies [1]. As a highly malignant neoplasm, ICC often occurs sporadically without any apparent cause [2,3]. Currently, the incidence and mortality rate of ICC are rising despite to the advances of diagnostic and therapeutic efforts [4]. Although surgery remains the best treatment option for early-stage ICC, the majority of ICCs patients are diagnosed as intermediate-advanced stage which are not the indication of surgery [5]. Gemcitabine combined with cisplatin is the standardized systemic treatment strategy for advanced ICCs, but the efficacy of this combined therapy is not satisfactory [6].

Image-guided local ablation therapy was introduced as a radical treatment, which was useful to improve overall survival (OS) of patients [7–9]. Radiofrequency ablation (RFA) and microwave ablation (MWA) are two most often performed ablative treatments. Comparing to RFA, MWA was associated with several advantages, such as larger ablation zone, higher intratumoral temperature, less procedure time, and less dependence on electrical conductivities of tumor tissue [10–13]. Computed tomography (CT)-guided percutaneous MWA (CT-PMWA) has been confirmed as a safe and effective treatment for hepatocellular carcinoma (HCC) patients. Additionally, CT-PMWA was also performed for early-stage lung cancer, thyroid carcinoma, renal cell carcinoma, and liver metastatic cancer. However, a limited number of studies were designed to investigate the OS of ICC patients who underwent CT-PMWA.

Hepatic function reserve was significantly associated with the OS of patients who received surgical therapy or local thermal ablation [14–17]. Therefore, accurate assessment of hepatic function is crucial to predict OS of patients.
The Child–Pugh classification system is widespread used to assess hepatic function reserve [18–20], but the subjective factors such as severity of ascites and degree of hepatic encephalopathy usually affect the assessment ability. Comparing to the Child–Pugh class, the albumin-bilirubin (ALBI) grade is associated with two important characteristics, which are simple and objective. The ALBI grade had already been used to assess hepatic function of patients with HCCs [21]. The ALBI grade is a prognostic nomogram emerging from the multivariate screen of routine clinicopathologic variables in a large, international cohort of patients with HCC, further validated in a separate group of cirrhotic patients without cancer [22]. Pinato et al. have validated the ALBI grade in a large, multicenter and international study, and the ALBI grade was confirmed to provide objective hepatic reserve estimation across each Barcelona Clinic Liver Cancer (BCLC) stage of HCC [22]. In addition, the ALBI grade was suggested as a significant predictor for the OS of HCC patients who underwent surgical resection, transarterial chemoembolization (TACE), or sorafenib [22–26]. Kao et al. constructed a nomogram with ALBI grade to assess the OS of patients with early-stage HCCs after RFA, in which study the ALBI grade was classified depending on the different levels [21]. The ALBI grading system is a novel method to assess hepatic function of patients. Objective and precise are two most important characteristics of the ALBI grade. The ALBI score was calculated before interventional treatment using the appropriate clinical parameters (albumin and bilirubin). The ALBI grade was classified depending on the different levels of the ALBI score, and the ALBI score was calculated with the ALBI grade in a large, multicenter and international study, and the ALBI grade was confirmed to provide objective hepatic reserve estimation across each Barcelona Clinic Liver Cancer (BCLC) stage of HCC [22]. In addition, the ALBI grade was suggested as a significant predictor for the OS of HCC patients who underwent surgical resection, transarterial chemoembolization (TACE), or sorafenib [22–26]. Kao et al. constructed a nomogram with ALBI grade to assess the OS of patients with early-stage HCCs after RFA, in which study the ALBI grade was classified depending on the different levels [21]. The ALBI grading system is a novel method to assess hepatic function of patients. Objective and precise are two most important characteristics of the ALBI grade. The ALBI score was calculated before interventional treatment using the appropriate clinical parameters (albumin and bilirubin). The ALBI grade was classified depending on the different levels of the ALBI score, and the ALBI score was calculated with the

Materials and methods

Patients

This study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the ethics committee of Sun Yat-sen University Cancer Center. The clinical data of 78 patients with 106 ICCs were retrospectively collected and reviewed. All included patients were initially treated with CT-PMWA in our center between April 2011 and March 2018. All included patients were discussed at multidisciplinary experts’ meetings including interventional radiologists, oncologists, hepatologists, and pathologists for the determination of ICCs therapy strategy. The entry criteria were listed as following aspects: (a) patients with a definite diagnosis of ICCs based on the pathologic findings of needle biopsy samples, (b) patients had single tumor lesion with a maximum size smaller than 5 cm, (c) patients with a tumor number less than 3 according to the Milan criteria, (d) patients who were unwilling or unsuitable to receive surgical resection due to their own decision or medical comorbidities. The contraindications for surgical resection including serious dysfunction of heart, kidney or coagulation, and challenging location of tumor lesions (surface of liver, near to intrahepatic large vessels), (e) patients with platelet count no less than 50,000/mm³, (f) patients with the Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, (g) patients who underwent CT-PMWA monotherapy without undergoing surgical treatment, liver transplantation, or any other treatments, including ¹²⁵I seed implantation, radiofrequency ablation, cryoablation or percutaneous ethanol injection, (h) patients with continuous follow-up and integrated data for evaluating prognosis, (i) ICCs without major vascular invasion, and extrahepatic or lymphatic metastasis by CT or magnetic resonance imaging (MRI) test.

Equipment

Siemens 64-slice spiral CT machine (SOMATOM 64 Sensation, Muenchen, Germany) was used for PMWA puncture guidance and image acquisition. The apparatus for microwave ablation was ECO-100 water-cooled microwave apparatus (Qinghai Electric Manufacturing, Nanjing, China) and monopole microwave antenna (16-18G).

CT-guided PMWA

Before PMWA procedure, a fine metal marker was placed on body surface over target tumor with patients lying supine. If target tumor located in complicated segments of liver, such as segment I or VI, patients had to lie prostrate or on the left side in order to get an effective path for puncture, and to avoid damage to important vessels or normal organs. After routine preparation, a plain CT scan was first performed to confirm puncture path and location of target lesion. Then puncture site was anesthetized with 2% lidocaine, and a 20G guided needle was inserted into focus of target tumor via the puncture path. After that, a plain CT scan was performed again to ensure the location of the guided needle. If it was satisfactory, MWA electrode probe was then inserted along the path of the guided needle to reach the opposite edge of tumor lesion through its center. After confirmation of the location of MWA electrode probe, MWA treatment was performed. The microwave parameters were set at 60–70Watt and the procedure lasted for 10–20 min. The ablation area covering the tumor focus and its surrounding area measured at least 1 cm as “safety margin”, as measured by comparing the real-time image taken after the procedure with the enhanced scan image taken before treatment. After MWA procedure, the MWA electrode probe was removed, and a final CT scan was performed to reexamine the ablation zone of MWA, and to obverse whether there were serious complications, such as abdominal bleeding, thoracic cavities or a massive pneumothorax. During MWA procedure, vital signs such as heart rate, blood pressure, and oxygen saturation were monitored. After MWA treatment, liver protection, anti-inflammatory, and sedation therapies were prescribed.

Definition of the ALBI grade

The ALBI grading system is a novel method to assess hepatic function of patients. Objective and precise are two most important characteristics of the ALBI grade. The ALBI score was calculated before interventional treatment using the appropriate clinical parameters (albumin and bilirubin). The ALBI grade was classified depending on the different levels of the ALBI score, and the ALBI score was calculated with the
levels of albumin and bilirubin of each patient. The ALBI score was defined as following aspects: \((\log 10 \text{ bilirubin} [\mu \text{mol/L}] \times 0.66) + (\text{albumin} [\text{g/L}] \times (–0.085))\). The continuous linear predictor was further categorized into 3 different grades for prognostic stratification purposes: grade 1 (the ALBI score less than \(-2.60\)), grade 2 (the ALBI score between \(-2.60\) and \(-1.39\)), and grade 3 (the ALBI score above \(-1.39\)) [28].

### Treatment efficacy and safety

The primary end point of this study was OS, and the secondary end point of this study was recurrence-free survival (RFS). OS was calculated from the date of the first session of PMWA to the date of death or last date of follow-up (survival). Local tumor recurrence was defined based on the imaging findings of irregular nodular, scattered, or eccentric pattern of peripheral enhancement around the ablation zone after PMWA. RFS was calculated from the date of the first session of MWA to the date of local tumor recurrence or the last date of follow-up (no finding of recurrence). Major complications were defined as events which caused substantial morbidity or disability that increased the level of care, or led to hospital admission, or substantially prolonged the hospital stay. And the complications related to PMWA procedures were evaluated according to the criteria defined by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) classification system of complications [29].

### Follow-up

In this study, follow-up was done by clinical visits or telephone at monthly intervals. Physical examination, laboratory tests such as total bilirubin, serum albumin, prothrombin time and tumor marker levels, and contrast-enhanced CT or MRI scan were reexamined. The chest X-ray was also performed every 4 weeks. If complete tumor ablation was attained, follow-up abdominal CT or MR imaging and laboratory tests were conducted every 3 months. The tumor response, residual viable tumors, and new tumor lesions were reassessed by our multidisciplinary team of radiologists and oncologists in terms of CT or MRI image, hepatic function, and tumor marker.

### Statistical analysis

Statistical analyses were performed using the SPSS 20.0 (SPSS, Chicago, IL) software. The quantitative data was expressed as mean ± standard deviation, and qualitative data was expressed as frequency. The \(\chi^2\) test was used to compare qualitative variables. OS and RFS were assessed by the Kaplan–Meier method with log-rank test. The differences in the survival curves of different groups were detected using log-rank test. Univariate analysis was performed using the log-rank test with respect to the potential prognostic factors affecting OS or PFS. All statistically significant prognostic factors evaluated by univariate analysis were entered into a Cox proportion hazards regression model. The Cox proportion hazards regression model was used to identify independent predictors of OS and RFS. For all tests, \(p\) values of less than 0.05 were considered to be statistically significant.

### Results

#### Patient characteristics

The demographic characteristics of included patients are shown in Table 1. The laboratory tests were examined, which mainly included the following aspects: the median CA-199 was 43.1 U/ml (9.8–236.9 U/ml), the median \(\gamma\)-gamma-glutamyl transpeptidase (GGT) was 35.6 U/L (11.3–452.6 U/L), the mean albumin was 39.6 ± 4.6 g/L (31.3–48.1 g/L), and the median bilirubin was 20.2 g/L (5.0–41.9 g/L). According to the Milan criteria, all included patients were associated with early-stage ICCs, and with a hepatic function of Child–Pugh class A. Among all included patients, 55 (70.5%) patients had a Child–Pugh score of 5, and 23 (29.5%) patients had a Child–Pugh score of 6. Moreover, 39 (50.0%) patients with a hepatic function of the ALBI grade 1, and 39 (50.0%) patients with a hepatic function of the ALBI grade 2. No patient was associated with ALBI grade 3. The background characteristics

#### Table 1. Baseline characteristics of the patients.

| Characteristics                  | Number |
|----------------------------------|--------|
| Total                            | 78     |
| Age (years), Mean ± SD (range)   |        |
| <65                              | 59.6 ± 10 (40–77) |
| ≥65                              | 60 (76.9) |
| Gender                           | 18 (23.1) |
| Male                             | 57 (73.0) |
| Female                           | 21 (27.0) |
| Etiology                         |        |
| HBV/HCV                          | 16 (20.5) |
| No hepatitis                     | 62 (79.5) |
| Comorbidities                    | 35 (44.9) |
| Yes                              | 43 (55.1) |
| No                               | 3 (3.9) |
| Hepatic cirrhosis                |        |
| Yes                              | 24 (30.8) |
| No                               | 54 (69.2) |
| Tumor size (cm), mean ± SD (range)|   |
| <3                               | 36 (46.2) |
| ≥3                               | 42 (53.8) |
| Tumor number, total (range)      | 106 (1–3) |
| Single                           | 50 (64.1) |
| Multiple                         | 28 (35.9) |
| Differentiation                  |        |
| Low                              | 31 (39.7) |
| Moderate                         | 47 (60.3) |
| CA-199 (U/ml)*                   | 43.1 (9.8–236.9) |
| GGT (U/L)*                       | 35.6 (11.3–452.6) |
| Albumin (g/L), mean ± SD (range) | 39.6 ± 4.6 (31.3–48.1) |
| Bilirubin (g/L)*                 | 20.2 (5.0–41.9) |
| Platelet count (10^9)*           | 212.3 (60–296) |
| INR, mean ± SD (range)           | 1.1 ± 0.2 (0.8–1.4) |
| Child–Pugh score                 |        |
| 5                                | 55 (70.5) |
| 6                                | 23 (29.5) |
| ALBI grade                       |        |
| 1                                | 39 (50.0) |
| 2                                | 39 (50.0) |
| Follow-up (months)*              | 22.7 (1–86.7) |

Unless otherwise indicated data are number of patients, with percentage in parentheses.

*Data are medians, with interquartile range in parentheses.
SD: standard deviation; ALBI: albumin-bilirubin; HBV: hepatitis B virus; HCV: hepatitis C virus; cm: centimeter; GGT: \(\gamma\)-gamma-glutamyl transpeptidase; INR: international normalized ratio.
of the patients with the ALBI grade 1 and grade 2 were listed in Table 2. And there was no significant difference on background between those two groups. Among those 55 patients with Child–Pugh score of 5, 34 (61.8%) patients were categorized as the ALBI grade 1, and 21 (38.2%) patients were categorized as the ALBI grade 2. For patients with Child–Pugh score of 6, 5 (21.7%) patients were categorized as the ALBI grade 1, and 18 (78.3%) patients were categorized as the ALBI grade 2.

### Treatment efficacy of CT-PMWA for ICCs

The median follow-up period was 22.7 months (range: 1–86.7 months). By the end of the follow-up, among the 78 patients who underwent CT-PMWA, 11 patients survived at their last visit. For treatment strategy, CT-PMWA procedure was repeated ‘on demand’ which depending on the local tumor response. By the end of this study, 45 patients underwent one treatment session, and 33 patients underwent two sessions. The cumulative OS rates at 1-, 3-, and 5-year were 89.5%, 52.2%, and 35.0%, respectively. And the cumulative RFS rates at 1-, 3-, and 5-year were 78.9%, 19.9%, and 0%, respectively. The representative MRI images during the follow-up period, and an example of the patient with ICC after CT-PMWA are depicted in Figure 1.

### Prognostic factors of patients with ICCs after CT-PMWA

Univariate and multivariate logistic regression analyses were performed to identify prognostic factors influencing the long-term OS of patients with ICCs after CT-PMWA. Univariate analysis revealed that tumor size (Hazard Ratio [HR] 95% Confidence Interval [95%CI] = 3.29 [1.07–10.1], p = .038), tumor number (HR [95%CI] = 3.60 [1.34–9.65], p = .011), and the ALBI grade (HR [95%CI] = 3.92 [1.37–11.23], p = .011) were significantly associated with OS. Multivariate analysis showed that the factors that significantly affected the OS were tumor size (HR [95%CI] = 9.03 [1.01–80.52], p = .049) and the ALBI grade (HR [95%CI] = 9.56 [1.58–58.00], p = .014) (Table 3). A total of 27 (34.6%) patients experienced local tumor recurrence during follow-up period. The univariate analysis showed statistically significant differences in term of RFS, which depending on tumor size (HR [95%CI] = 1.73 [0.65–4.63], p < .012), tumor number (HR [95%CI] = 3.60 [1.34–9.65], p = .011), and ALBI grade (HR [95%CI] = 1.01 [0.40–2.57], p = .003). The multivariate analysis showed the factor that significantly affected the RFS was tumor size (HR [95%CI] = 2.30 [0.69–8.04], p = .049) (Table 4).

### The ALBI grade and Child–Pugh score for long-term survival

The cumulative 1-, 3-, and 5-year OS rates in patients with Child–Pugh score 5 and Child–Pugh score 6 were 94.8%, 64.1%, and 56.4%; 92.3%, 38.5%, and 17.9%, respectively (Figure 2(A)). There were no significantly statistical differences between these two groups (p = .061). The cumulative 1-, 3-, and 5-year OS rates in patients with the ALBI grade 1 and grade 2 were 100%, 69.2%, and 25.6%; 41.0%, 10.3%, and 10.3%, respectively, which showing significantly statistical difference between these two groups (p < .001) (Figure 2(B)). According to the ALBI grade evaluation method, the patients with Child–Pugh score 5 could be divided into two groups of the ALBI grade 1 (n = 34) and the ALBI grade 2 (n = 21). The patients with the ALBI grade 1 had significantly higher OS rates than those patients with the ALBI grade 2 (p = .026) (Figure 3(A)). Similarly, the patients with Child–Pugh score 6 could be divided into two groups of the ALBI grade 1 (n = 18) and the ALBI grade 2 (n = 5), and the patients with the ALBI grade 1 were associated with significantly higher OS rates in comparison with the patients with the ALBI grade 2 (Figure 3(B)). The patients with hepatic function of the ALBI grade 1 had significantly higher OS rates than those patients with the ALBI grade 2 (p = .001). The patients with hepatic function of Child–Pugh score 5 and Child–Pugh score 6 were associated with a cumulative 1-, 3-, and 5-year OS rates of 76.9%, 15.4%, and 0%; 74.4%, 20.5%, and 0%, respectively, which showing no significantly statistical difference between these two groups (p = .371) (Figure 4(A)). For patients with hepatic function of the ALBI grade 1, the cumulative 1-, 3-, and 5-year OS rates were 76.9%, 20.5%, and 0%, respectively. And for patients with hepatic function of the ALBI grade 2, the cumulative 1-, 3-, and 5-year OS rates were 38.5%, 0%, and 0%, respectively. There were significantly statistical differences between these two groups (p = .003) (Figure 4(B)).
Complications

In this study, all CT-PMWA procedures were performed with a success rate of 100%. There were no treatment-related deaths in the patients. The major complications related to MWA procedure were observed in three patients (3.8%), including two patients (2.6%) with liver abscess and one patient (1.3%) with pleural effusion. The minor complications were observed in 23 (29.5%) patients, including abdominal pain (14.1%), slight fever (12.8%), vomit (10.3%), and fatigue (23.1%). According to the CIRSE classification system of complications, the incidence of grade 1, grade 2, and grade 3 complications were 17.9% (14/78), 11.5% (9/78), and 3.8% (3/78), respectively. There were no complications of grade 4, grade 5 or grade 6 in this study.

Figure 1. Representative pictures of the patient with ICC after CT-PMWA. (a&b): Pre-PMWA MRI images (A: contrast-enhanced T1WI; B:T2WI); (c&d): Two images of plain CT scan during PMWA procedure show the well location of PMWA electrode probes; (e–g): Post-PMWA MRI images (contrast-enhanced TIWI) at 6-month(e), 1-year(f), and 3-year(g), respectively.
In clinical practice, a part of early-stage ICC patients were unwilling or unsuitable to receive surgical resection as their primary treatment due to some medical comorbidities or their own decision. CT-PMWA is an alternative treatment option for ICC patients without the chance to receive surgical resection. Nowadays, percutaneous local thermal ablation has widely been performed as an important treatment for ICC patients with early-stage ICCs [30]. Previous studies suggested that there were no significant differences on long-term OS between surgical resection and thermal ablation for early-stage HCCs. Regarding to ICC, Zhang et al. had reported that PMWA was a safe and effective treatment, and the Child–Pugh class was a protective factor that significantly influence the prognosis of patients [31].

In our study, the efficacy of the ALBI grade on predicting long-term survival of patients with ICCs after CT-PMWA was evaluated. The ALBI grade was validated as an independent factor associating the OS of included ICC patients. Although CT-PMWA is a kind of minimal invasive therapies, preoperative hepatic function reserve was significantly associated with the long-term prognosis of patients. Our findings were consistent with previous studies [18–26]. Therefore, the better patients’ hepatic function reserve was assessed, the better patients’ prognosis could be evaluated. In addition, we found the Child–Pugh score lost its independent attribute on patients’ OS. Our data indicated that the ALBI grade was associated with reliable discriminative ability to assess long-term OS of ICC patients after CT-PMWA. In this study, patients with a hepatic function of Child–Pugh score 5 were divided into two different groups of the ALBI grade 1 and grade 2. Our data revealed that the patients with a hepatic function of the ALBI grade 1 had significantly higher OS rates than those patients with the ALBI grade 2. Additionally, the different ALBI grades indicated different OS rates in patients with the same hepatic function of Child–Pugh score 6. We also studied whether the ALBI grade was associated with PFS of patients. Similarly, the univariate analysis revealed that the ALBI grade was significantly associated with PFS. These findings suggested that the ALBI grade could be a better stratifying biomarker which represented hepatic function reserve of patients with ICCs after CT-PMWA.

Many laboratory tests were associated with hepatic function reserve or tumor lesion, which include CA-199, GGT, serum albumin and total bilirubin levels. By studying the patients with high levels of GGT or CA-199, we found neither GGT nor CA-199 was associated with the long-term outcomes of OS or RFS. That might because all of the included

### Table 3. Factors associating with the overall survival of patients.

| Factor                  | Univariate analysis | Multiple analysis |
|-------------------------|---------------------|-------------------|
| Age (years)             | HR (95% CI) p value | HR (95% CI) p value |
| <65                     | 0.65 (0.21–1.99) .446 |                     |
| ≥65                     | 60                  |                   |
| Gender                  | 1.48 (0.52–4.21) .467 |                     |
| Male                    | 57                  |                   |
| Female                  | 21                  |                   |
| Etiology                | 0.56 (0.21–1.49) .249 |                     |
| HBV/HCV                 | 35                  |                   |
| No hepatitis            | 43                  |                   |
| Comorbidities           | 1.23 (0.43–3.49) .704 |                     |
| Yes                     | 24                  |                   |
| No                      | 54                  |                   |
| Tumor size (cm)         | 3.60 (1.34–9.65) .111 | 4.73 (0.88–25.32) .156 |
| <3                      | 36                  |                   |
| ≥3                      | 42                  |                   |
| Tumor number            | 3.60 (1.34–9.65) .111 | 1.96 (0.49–7.82) .341 |
| Single                  | 50                  |                   |
| Multiple                | 28                  |                   |
| Differentiation         | 1.09 (0.78–1.65) .817 |                     |
| Low                     | 31                  |                   |
| Moderate                | 47                  |                   |
| CA-199 (U/ml) ≤37       | 1.42 (1.11–1.98) .414 |                     |
| >37                     | 37                  |                   |
| GGT (U/L) ≤50           | 2.03 (0.77–5.36) .155 |                     |
| >50                     | 29                  |                   |
| Child–Pugh score ≤3    | 0.38 (0.08–1.65) .575 |                     |
| >3                      | 49                  |                   |
| ALBI grade 1            | 3.92 (1.37–11.23) .011 | 9.56 (1.58–58.00) .104 |
| 2                       | 39                  |                   |
| 3                       | 23                  |                   |
| ALBI grade 2            | 1.01 (0.40–2.57) .003 | 1.38 (0.38–5.06) .624 |
| 1                       | 39                  |                   |
| 2                       | 39                  |                   |

ALBI: albumin-bilirubin; HBV: hepatitis B virus; HCV: hepatitis C virus; cm: centimeter; GGT: γ-gamma-glutamyl transpeptidase; HR: hazard ratio; CI: confidence interval.

### Table 4. Factors associating with the recurrence-free survival of patients.

| Factor                  | Univariate analysis | Multiple analysis |
|-------------------------|---------------------|-------------------|
| Age (years)             | HR (95% CI) p value | HR (95% CI) p value |
| <65                     | 0.81 (0.29–2.29) .696 |                     |
| ≥65                     | 60                  |                   |
| Gender                  | 0.30 (0.07–1.29) .105 |                     |
| Male                    | 57                  |                   |
| Female                  | 21                  |                   |
| Etiology                | 2.92 (0.38–22.28) .197 |                     |
| HBV/HCV                 | 16                  |                   |
| No hepatitis            | 62                  |                   |
| Comorbidities           | 0.75 (0.29–1.90) .541 |                     |
| Yes                     | 35                  |                   |
| No                      | 43                  |                   |
| Hepatic cirrhosis       | 1.98 (0.21–3.09) .871 |                     |
| Yes                     | 24                  |                   |
| No                      | 54                  |                   |
| Tumor size(cm) <3       | 1.73 (0.65–4.63) .012 | 2.30 (0.69–8.04) .049 |
| ≥3                      | 42                  |                   |
| Tumor number            | 3.60 (1.34–9.65) .111 | 1.96 (0.49–7.82) .341 |
| Single                  | 50                  |                   |
| Multiple                | 28                  |                   |
| Differentiation         | 1.09 (0.78–1.65) .817 |                     |
| Low                     | 31                  |                   |
| Moderate                | 47                  |                   |
| CA-199 (U/ml) ≤37       | 1.42 (1.11–1.98) .214 |                     |
| >37                     | 37                  |                   |
| GGT (U/L) ≤50           | 0.60 (0.20–1.83) .369 |                     |
| >50                     | 29                  |                   |
| Child–Pugh score ≤3    | 0.91 (0.30–2.75) .863 |                     |
| >3                      | 49                  |                   |
| ALBI grade 1            | 1.01 (0.40–2.57) .003 | 1.38 (0.38–5.06) .624 |
| 2                       | 39                  |                   |
| ALBI grade 2            | 39                  |                   |

ALBI: albumin-bilirubin; HBV: hepatitis B virus; HCV: hepatitis C virus; cm: centimeter; GGT: γ-gamma-glutamyl transpeptidase; HR: hazard ratio; CI: confidence interval.

**Discussion**

Discussion

In clinical practice, a part of early-stage ICC patients were unwilling or unsuitable to receive surgical resection as their primary treatment due to some medical comorbidities or their own decision. CT-PMWA is an alternative treatment option for ICC patients without the chance to receive surgical resection. Nowadays, percutaneous local thermal ablation has widely been performed as an important treatment for patients with early-stage ICCs [30]. Previous studies suggested that there were no significant differences on long-term OS between surgical resection and thermal ablation for early-stage HCCs. Regarding to ICC, Zhang et al. had reported that PMWA was a safe and effective treatment, and the Child–Pugh class was a protective factor that significantly influence the prognosis of patients [31].

In our study, the efficacy of the ALBI grade on predicting long-term survival of patients with ICCs after CT-PMWA was evaluated. The ALBI grade was validated as an independent factor associating the OS of included ICC patients. Although CT-PMWA is a kind of minimal invasive therapies, preoperative hepatic function reserve was significantly associated with the long-term prognosis of patients. Our findings were consistent with previous studies [18–26]. Therefore, the better patients’ hepatic function reserve was assessed, the...
patients had relatively early ICCs, and the levels of CA-199 and GGT were not directly associated with status of tumor growth and OS of the patients. However, on the basis of previous studies and our clinical practice, we suggest that the level of CA-199 is significantly associated with OS of the patients with intermediate-advanced stage ICCs. Because the serum albumin and total bilirubin levels could indicate hepatic function reverse of patients with liver disease. Hence, it suggested that the ABLI grade which includes albumin and total bilirubin levels could be an effective predictor for prognosis of patients with ICCs after CT-PMWA.

Currently, the Child–Pugh classification system is suggested as an important factor to assess prognosis of patients with liver cirrhosis and primary liver cancer. However, the system was originally developed for patients with cirrhosis, not liver cancer. The Child–Pugh score includes the following five parameters: serum albumin, bilirubin levels, prothrombin time, extent of ascites and degree of hepatic encephalopathy. Although, in clinical practice, the Child–Pugh class was widely accepted as a convenient, noninvasive indicator of liver function, it was limited by several constraints. Sometimes, the assessment of slight ascites or
minimal encephalopathy can be clinical challenge for physicians, which can only be judged subjectively [32]. Hence, it indicated that not all constituents of the Child–Pugh score have equal accessibility and reproducibility. Additionally, the score does not include platelet counts or other biomarkers to indicate portal hypertension, a highly lethal complication of cirrhosis that can coexist within each Child–Pugh classification [6]. However, there are some advantages of the ALBI score over the Child–Pugh score for assessment of prognosis in patients with ICCs. Firstly, as for the ALBI grade, both serum albumin and bilirubin levels can offer an evidence-based, objective tool for assessment of hepatic function in patients with ICCs. The ALBI grade can effectively avoid the subjective assessment of ascites and hepatic encephalopathy by different observers. Secondly, the Child–Pugh score was originally designed for assessing the hepatic function of patients with cirrhosis. Comparing to Child–Pugh class system, the ALBI grade was based on serum albumin and bilirubin levels, which could effectively evaluate hepatic function reserve of ICC patients without cirrhosis. Thirdly, the ALBI grade has more assessable accuracy for long-term OS in comparison with other prognostic factors. And the ALBI grade appeared to be an evidence-based, simple and objective assessment method with a good prognostic performance in patients with ICCs after CT-PMWA.

Some limitations may exist in this study. Firstly, this is a single-center retrospective study with a relatively small patient series. The limited sample size might reduce the statistical power of our analysis. As far as we know, ICC is a kind of rarely malignant tumor. In the future study, more patients will be included to provide further evidence. Secondly, all included patients were associated with a hepatic function of Child–Pugh class A, a control group such as patients with a hepatic of Child–Pugh class B might be needed to confirm our proposal and hypothesis.

In conclusion, CT-PMWA was safe and effective for patients with ICCs. The preliminary data of this study showed the ALBI grade was effective to predict long-term outcomes of CT-PMWA in ICCs. Further study is necessary to validate our results by a large, multi-center patient cohort.

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 the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants, and the written informed consent was provided by each patient included in the study.

Disclosure statement

No potential conflict of interest was reported by the authors.

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