Analysis of Hepatic Failure Risk after Transcatheter Arterial Chemoembolization in Advanced Hepatocelluar Carcinoma Patients

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Abstract: The purpose of this study was to investigate the effectiveness of ICG-R 15 and Child-Pugh classification in predicting the probability of liver failure after TACE in patients with advanced HCC. Seventy-four advanced HCC patients underwent TACE were enrolled into this study. Before TACE, to evaluate the liver function of patients, the Child-Pugh classification, ICG-R15 and other factors were recorded. Univariate and multivariate analyses assessing the risk factors for the occurrence of hepatic failure after TACE were performed. Twelve patients (16.2%, 12/74) suffered hepatic failure after TACE. The incidence of post-TACE hepatic failure is 90%(9/10) in the patients with Child-Pugh classification B and only 4.7%(3/61) in the patients with Child-Pugh classification A. Univariate analysis on the factors between patients with and without hepatic failure after TACE revealed that Child-Pugh classification A/B (P<0.0001), ICG-R15 (P<0.0001), albumin (P=0.0002), and serum total bilirubin (P=0.0152) showed statistical significance. In the multivariate analysis, Child-Pugh classification B (P=0.0001, OR=171.750) and ICG-R15 ≥20% (P=0.0187, OR=1.095) were the independent predictors associated with hepatic failure, and when used in combination, the specificity and accuracy Child-Pugh classification B and ICG-R 15 minutes test ≥ 20% in predicting liver failure after TACE reached 100% and 93.2%. Candidates with BCLC stage C HCC for TACE should undergo Child-Pugh classification as a screening test. ICG R15 minutes test should be further used for patients with Child-Pugh classification B. Patients with hepatocellular carcinoma (BCLC-C), if their liver functions are classified in Child-Pugh classification B, cannot get benefit of longer survival time from transcatheter arterial chemoembolization.
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1. Introduction

Hepatocellular carcinoma (HCC) is one of the most commonly diagnosed malignancies especially in Asia [1]. Many HCC patients present at an advanced stage at their initial diagnosis, for which curative resection is not feasible [2]. Transcatheter arterial chemoembolization (TACE) is considered one of the standard options for the management of advanced and unresectable HCC [3]. Although TACE is not recommended for patients with advanced HCC by the American Association for the Study of Liver Diseases (AASLD) and Barcelona Clinic Liver Cancer (BCLC) group [4] due to, at least in part, the potential risk of hepatic insufficiency after the procedure. However, some researchers [5-11] have already reported a survival benefit in patients with extrahepatic metastasis or vascular involvement who performed TACE instead of receiving the best supportive care. In a recently reported study, it was suggested that TACE could benefit a select group of patients with more limited BCLC stage C HCC [12]. Despite of its efficacy, hepatic failure after TACE in patients with HCC is a concern even in patients with relatively good hepatic reserve [13-15], and sufficient hepatic reserve must be confirmed prior to TACE for HCC patients with more limited hepatic reserve.

In addition to the commonly used Child-Pugh classificationification, ICG-R15 is a commonly used study before liver surgery. Both tests are currently required before surgical resection for HCC [16, 17]. Despite its extensive use as a pre-surgery clearance test and is considered superior than Child-Pugh classificationification for evaluating liver function reserve and predicting liver failure after surgery [18, 19, 20], the use of ICG-R 15 prior to TACE in BCLC stage C patients remains imperfect because of its dependency on hepatic blood flow and functional capacity of the liver [21]. The total hepatic blood flow, and regional variations of unit-by-unit flow within the hepatic parenchyma can markedly alter the retention value [22]. In a retrospective study of 142 HCC patients largely with BCLC stage A and B [14], the usefulness of conventional liver function tests and clinical parameters were questioned. The aim

of this study is to evaluate the effectiveness of ICG-R 15 and Child-Pugh classificationification in predicting the probability of liver failure after TACE in patients with BCLC stage C HCC.

2. Material and Methods

Patients and Characteristics

Between January 2009 and March 2010, 74 consecutive patients with advanced HCC (BCLC stage C) underwent TACE as the primary treatment in the First Affiliated Hospital of Zhengzhou University were enrolled and retrospectively analyzed in the study. The diagnostic criteria of hepatocelluar carcinoma are based on European Association for the Study of the Liver [17]. Advanced HCC (BCLC stage C) is characterized by an Eastern Cooperative Oncology Group (ECOG) performance status of 1-2, or the presence of MVI, or extrahepatic metastasis [23]. The baseline characteristics of 74 patients are shown in Table 1 and they fulfilled the following criteria: symptomatic tumors, ECOG 1-2; macrovascular invasion or extrahepatic spread (lymph node involvement or metastases); Child- Pugh (CP) functional classification A or B; platelet count >60,000/mm^3; absence of ongoing infection or spontaneous bacterial peritonitis. Exclusion criteria included: Coagulation function decreased seriously and could not be corrected; portal hypertension with hepatofugal flow or obstruction of main portal vein tumor thrombus without sufficient lateral portal vein branch; extensive transfer without the prolongation of survival in expectation; the volume of tumor more than 70% of the liver; history of a secondary malignancy.

Table 1. Summary of Baseline Characteristics

Parameter	Value	%
Age (years)	53.85±8.673	
Sex		
Male	61	82.4%
Female	13	17.6%
Viral marker		
HBsAg positive	66	89.2%
HBsAg negative	5	6.6%
Anti HCV positive	3	4.1%
Child-Pugh classification		
A	62	83.8%
B	12	16.2%
Albumin level g/l	34.68 ±4.193	
Bilirubin level	20.27±10.192	
ALT(U/L)	58.88±47.432	
Tumor diameter (cm)	7.98±4.125	

Pre-TACE preparation and studies

Before TACE, the results of following liver function or biochemical tests were collected: serum ALT, total bilirubin, albumin, PT, ICG-R15 minutes test, along with contrast-enhanced dynamic computed tomography or dynamic contrast-enhanced magnetic resonance. Risk factors including sex, age, ICG-R15 minutes test, serum albumin, total bilirubin, Child-Pugh classification, tumor size, A-V shunt, dose of Pirarubicin Hydronchloride, Cis-platin, Mitomycin and Lipiodol, were compared between patients with and without post-TACE hepatic failure.

A dose of 50 mg ICG dissolved in 10 ml of distilled water (5 mg/ml) was injected intravenously depending on the patient body weight (0.1 ml/kg), and the serum ICG-R15 concentrations were detected at every pulse interval by an optical probe adhered to the patient's dilator naris. The ICG-R15 result was calculated automatically from the blood ICG concentration time course.

TACE

The TACE procedure was performed according to Seldinger's technique of arterial catheterization. A 5F arterial catheter or 2.7F microarterial catheter which was necessary was introduced into the right of the segmental artery of the liver, or the left when appropriate. Hepatic arteriography was done and the feeding artery of the tumor was identified. Pirarubicin Hydronchloride (Main Luck Pharmaceuticals, Shenzhen, China), Cis-platin (Biovally, Yunnan, China), Mitomycin (Hisun, Zhejiang, China) and lipiodol (iodized oil, Guerbet Laboratories, Roissy, France) were emulsified by a pumping method at a ratio of 40mg:40mg:4mg:20ml. If the emulsion could not meet the requirements of tumor, lipiodol or embolism particles(Kelinas, Beijing, China) or gelatin sponge particles(Alicon, Hangzhou, China) had been used, the dose of various embolism materials basing on the size, number, and vascularity of the tumors and the amount of lipiodol less than 25ml. Under fluoroscopic detection, Pirarubicin Hydronchloride, Cisplatin, Mitomycin and lipiodol emulsion, lipiodol or/and embolism particles or/and gelatin sponge particles were injected into the segmental or subsegmental arteries until stagnation of blood flow of tumor-feeding arterial vessels was achieved. Significant arteriovenous shunts before TACE was firstly treated or 2.7F arterial catheter was introduced into the distal of arteriovenous shunts and then TACE procedure was done before this procedure.

Post-TACE Follow-up

The median follow-up time of all patients was 10.1 months (range 1-46 months). All patients were followed-up according to our institutional protocol after TACE, and received serum ALT, total bilirubin, albumin, PT, ICG-R15 minutes test, along with contrast-enhanced dynamic computed tomography or dynamic contrast-enhanced magnetic resonance every 1-3 months. The post-TACE hepatic failure was defined as elevation of the Child-Pugh score (≥2) and serum bilirubin level (≥2.0 mg/dl), newly developed ascites, or hepatic encephalopathy

within 2 weeks of TACE [14]. Survival time was documented from the date of TACE to death.

Statistics

Data were presented as means ± SDs. The Mann-Whitney U test, Fisher's exact test, and x^2 test with Yates'correction were used to compare the parameters between the hepatic failure and nonhepatic failure groups as appropriate. Stepwise logistic regression analysis was performed to evaluate the significant factors based on the results of multivariate analysis. We applied the receiver operating characteristic curve to decide the cutoff point of the significant parameters for the best predictive accuracy. Survival was estimated using the Kaplan-Meier method; differences in the survival rates between the groups were compared by the log-rank test. A *p* value of < 0.05 was considered significant. All statistical analyses were carried out using SAS for Windows version 9.1.

3. Results

At the time of this analysis, 68 patients (91.9%) had died. The median overall survival for the 74 patients was 8.1 months (range, 7-1380 days), and the survival curve is shown in Fig.1. The median overall survival for Child-Pugh classification A and Child-Pugh classification B was 8.5 months (95% CI:7.7, 9.3 months) and 2.5 months (95% CI: 2.4, 2.6months) (p=0.002). The corresponding 3, 6, 9, 12 and 24 month survival rates of two group were 85%, 32%, 60%, 17%, 11% and 33%, 17%, 17%, 8%, 0%, respectively.

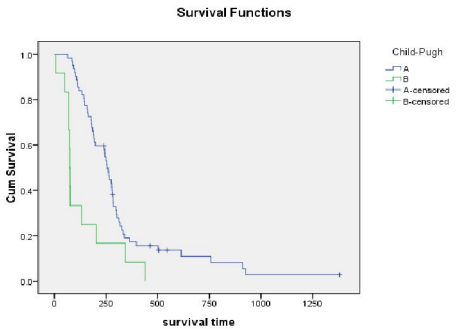

Figure 1. Kaplan-Meier survival for the patients with advanced HCC according Child-Pugh classification

Post-TACE liver failure occurred in 16.2% patients (12/74). The incidence of post-TACE hepatic failure in patients with Child-Pugh classification B is 90% (9/10), versus 4.7% (3/64) in patients with Child-Pugh classification A. The incidence of post-TACE hepatic failure in the advanced HCC patients with Child-Pugh classification B is the 19.1 times higher than in those of with Child-Pugh classification A (P<0.0001). Except for one case, all other patients with Child-Pugh classification B suffered liver failure, and the only one case without liver failure owned ICG-R15<15%. Among the 12 hepatic failure patients, one (8.3%) died of hepatic failure associated with TACE within 1 month after this procedure.

Univariate analysis revealed that Child-Pugh classification A/B, ICG-R15, albumin, and serum total bilirubin were significant prognostic factors to predict patients with and without hepatic failure after TACE (Table 2). Table 3 showed that Child-Pugh classification manifested higher sensitivity, specificity, and accuracy than other post-TACE predictors of hepatic failure. However, when used in combination, Child-Pugh classification B and ICG-R 15 minutes test ≥20% can substantially improve the specificity (100%) and accuracy (93.2%) of the predictive effeteness of liver failure after TACE. In multivariate analyses, Child-Pugh classification B and ICG-R15 were both independent predictors of post-TACE hepatic failure.

Table 2. Characteristics of Patients With or Without Hepatic Failure After TACE for the Treatment of advanced HCC patients.

Parameter	Hepatic Failure (N=12)	Nonhepaticfailure (N=62)	p
Age (yr)	54.00±7.793	53.47 ±10.513	0.7453
M/F	9/3	52/10	1.0000
HBV/R Child-	11/1	55/7	1.0000
Pugh(A/B)	3/9	59/3	<0.0001
ICG-R15 (%)	30.94 ±16.456	14.30±9.405	<0.0001
Albumin (g/l)	32.63 ±4.128	37.75 ±4.214	0.0002
Bilirubin, total (g/l)	22.27 ±11.429	15.65±7.769	0.0152
Tumor diameter (cm)	9.78±4.336	7.21±3.751	0.0554
Significant arteriovenous shunts (with/without)	5/7	9/53	0.0726
Invasion of vascular (with/without)	11/1	37/25	0.0728
ALT (U/L)	70.33±55.683	50.80±37.209	0.2647
Dose of THP(mg)	22.75±11.177	31.45±10.173	0.0094
Dose of DDP (mg)	22.75±11.177	31.45±10.173	0.0094
Dose of MMC (mg)	2.275±11.177	3.145±10.173	0.0094
Dose of Lipiodol	13.25±6.797	17.19±7.211	0.0845

Table 3. The Predictive Value of Various Parameters and Multivariate Analysis of Predictors of Hepatic Failure in Advanced HCC Patients After TACE.

Parameters	Child-Pugh B	ICG-R15≥20%	Child-Pugh B ICG-R15≥20%
Sensitivity	75.0%（9/12）	66.7%（8/12）	58.3%（7/12）
Specificity	98.4%（61/62）	83.9%（52/62）	100%（62/62）
Accuracy	94.6%（70/74）	81.1%（60/74）	93.2%(69/74)
OR	171.750	1.095	
95% CI of OR	19.224-999.999	1.028-1.167	
P	0.000 1	0.0187	

4. Discussions

Patients with advanced HCC usually have limited liver function. As such, local treatment including surgical resection or TACE may cause substantial side effects including liver failure. Therefore, accurate prediction of liver failure after treatment is critical for treatment selection and predicting prognosis. Conventionally, patients with Child-Pugh classification A or B are accepted as candidates. However, a set of perfect index or an ideal liver function test used to predict the liver failure risk after TACE is still lacking especially for the patients with advanced HCC. In this study, we have found that Child-Pugh classification and ICG-R 15 are significant and independent predictive factors of post-procedural liver failure in patients with BCLC stage C HCC treated with TACE. Specifically, the specificity and sensitivity rates were 98.4% vs. 83.9%, and 75% vs. 66.7%, respectively for Child-Pugh classification and ICG-R 15. When used in combination, patients with Child-Pugh classification B and ICG ≥20% can substantially improve the specificity and accuracy of the predictive effectiveness for liver failure.

More than two-thirds of patients with advanced HCC died of liver failure or intrahepatic tumor progression rather than progression of metastatic disease [5, 24, 25]. Effective local treatment such as TACE is important in disease control and palliation for patients with advanced HCC especially when regional or systemic disease is limited [5-12]. However, liver failure after TACE significantly impairs outcome including patients' survival [13]. In our study, median overall survival time for patients with CP classification B was 2.5 months, significantly shorter than those with classification A. Thus it is important to provide the aggressive treatment to patients who can best tolerate the therapy. For HCC patients with BCLC stage A/B disease who undergo surgery, liver function is usually evaluated by Child-Pugh and ICG-R 15 minutes test, and patients with Child-Pugh A and ICG-R 15 < 20% are usually considered to tolerate major liver resection [26,27]. While TACE will significantly impair the function of treated region in the liver, reliable study for liver function that could accurately predict liver failure after the procedure is lacking especially in patients with BCLC stage C HCC.

It is suggested that Child-Pugh classification combined with indocyanine green retention ratio at 15 minutes test could evaluate the liver function for hepatic resection for hepatocellular carcinoma [28, 29, 30]. Child-Pugh classification is the most widely acceptable qualitative criterion on assessing liver function [31], and ICG-R15 is one of quantitative liver function tests (QLFTs) [21]. However, the use of clearance tests to predict liver failure after TACE has not been sufficiently reported especially for patients with advanced HCC. In a retrospective study published in 2002, 142 patients with unresectable HCC treated with TACE, conventional liver function tests including Child-Pugh classification and ICG were not significantly associated with liver failure after TACE. In that study, patients' stage of HCC was not mentioned. As such, these results may not be applicable to patients with more advanced HCC such as stage C disease whose liver function are usually substantially impaired as compare to patients with earlier stage disease. The incidence of post-TACE hepatic failure varied from 12.0% to 17% [13, 14, 32]. Huang et al reported that among 103 patients with Child-Pugh classification A, post-TACE hepatic failure occurred in 4% patients, compared with 38% of 39 patients with Child-Pugh classification B [14] .The former results coincide with our result (4.7%), but the latter is quite lower than 90% in this study. This variation may be mainly due to the BCLC stage difference of enrolled patients.

Three liver failure patients with Child-Pugh classification A in our study had main portal veins (MPV) invasion, and all of them had ICG-R15≥15%. We found that the MPV of one patient was completely occluded by tumor thrombus. Consequently, cavernous transformation of portal vein occurred. Other two cases had MPV stenosis which achieved 90% because of tumor thrombus, detected when selective arterial portography was performed. TACE making ischemic liver damage progress for preexisting MPV invasion might give rise to liver failure in Child-Pugh classification A patients [32, 33]. In addition, except one case, all other patients with Child-Pugh classification B suffered liver failure, and the only one case without liver failure owned ICG-R15<15%. Choi et al. reported that the median ICG-R 15 (preoperative status) of Child-Pugh classification A patients was 12.7% ranged from (1.0-22.7%) in his study [34]. Therefore, ICG-R15<15% was probably infrequent for the advanced HCC patients with Child-Pugh classification B. The dose of chemoembolization agents for TACE treatment, such as adriamycin and lipiodol, were suggested to be the risk factors of liver failure after TACE by Katsushima and Min-Shan Chen [35, 36]. However, this result was not reconfirmed by our study. The probable explanation of this discrepancy is that we used a smaller dose of chemoembolization agents than they used [34, 35, 36]. The lower dose of Pirarubicin Hydronchloride, Cis-platin, and Mitomycin which was applied to the patients with poorer liver function in the study contributed to the significance of difference between patients with or without hepatic failure. We cannot conclude that smaller dose of Pirarubicin Hydronchloride, Cis-platin, and Mitomycin could lead

to hepatic failure after TACE in patients with HCC at an advanced stage.

Although this is the first study that addresses the predictive factors of liver failure in BCLC stage C HCC, a number of limitations need to be mentioned. First, although this retrospective study included a relatively large number of subjects, the number of patients eventually developed liver failure is limited. Meaningful analyses might not be feasible for various combinations of Child-Pugh classification and ICG-R 15 although we have found that the specificity reached 100% for Child-Pugh classification B and ICG ≥ 20%. Second, we have tested most of the commonly used predictive factors for liver failures such as Child-Pugh classification, ICG retention test, albumin, serum total bilirubin and discovered two independent predictive factors. However, other potentially significant prognostic factors, although not widely used and reported, were not evaluated due to the retrospective nature of the study. For example, monoethylglycinexylidide was found to be useful for predicting liver failure after TACE in the study reported by Yi-Shin Huang et al [14]. The significance of monoethylglycinexylidide for BCLC stage C HCC should be further investigated.

In conclusion, Child-Pugh classification and ICG-R15 are two independent predictive factors for liver failure after TACE in patients with BCLC stage C HCC. Child-Pugh classification is highly sensitive for predicting liver failure, and when used in combination, the specificity and accuracy Child-Pugh classification and ICG-R 15 ≥ 20% in predicting liver failure after TACE reached 100% and 93.2%. As such, we would suggest that candidates with BCLC stage C HCC for TACE should undergo Child-Pugh as a screening test. ICG R15 minutes test should be further used for patients with Child-Pugh classification B. Patients with hepatocellular carcinoma (BCLC-C), if their liver functions are classified in Child-Pugh classification B, can not get benefit of longer survival time from transcatheter arterial chemoembolization, so the treatment with TACE for them must be cautious or given up. However, the use of such recommendation should be further tested in a prospective study before it can be routinely recommended.

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