Clinics and Research in Hepatology and Gastroenterology (2016) xxx, xxx–xxx

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

ORIGINAL ARTICLE

ART score and hepatocellular carcinoma: An appraisal of its applicability

WeiLi Yin[a,1], Qi Ye[a,1], FengMei Wang[a], Jing Liang[a], BaiGuo Xu[a], Xu Zhang[a], Qian Zhang[a], Yi Liu[a], Ge Li[b,2], Tao Han[a,2,*]

[a] *Department of Gastroenterology and Hepatology, The Third Central clinical college of Tianjin Medical University, Tianjin Institute of Hepatobiliary Disease, Tianjin Key Laboratory of Artificial Cells, No. 83 Jintang Road, 300170 Hedong District, Tianjin, China*
[b] *Department of Public Health, Tianjin University of Traditional Chinese Medicine, 300193 Tianjin, China*

KEYWORDS
ART score;
TACE;
HCC;
Chinese patients

Summary
Background: Assessment for retreatment with TACE (ART) score evaluates whether hepatocellular carcinoma (HCC) patients can benefit from transcatheter arterial chemoembolization (TACE) retreatments. As previously reported, TACE has a good prognostic effect on patients with ART score of 0–1.5, while patients with ART score ≥ 2.5 might have minor or even no prognostic benefits. Our study verified whether ART score can guide multiple TACE retreatments in Chinese patients presenting with HCC.
Method: Nine hundred and thirty-four patients presenting with HCC and treated with TACE were recruited from January 2008 to June 2012, at which point 137 patients had been treated with TACE at least twice and could be assessed by ART score. Patients were assessed by ART score before the second, third, and fourth TACE treatment, and divided into 0–1.5 group and ≥ 2.5 group. Overall survival (OS) of both groups was compared, and patients were further evaluated on whether TACE retreatment was beneficial.
Results: Before the second, third, fourth TACE treatment, the median OS (95% CI) was respectively 25.0 (21.1–28.0) months, 29.0 (22.0–36.0) months and 24.3 (8.2–40.4) months for patients with ART score 0–1.5. 18.0 (14.5–21.5) months, 14.0 (6.4–21.6) months and 22.0 (11.8–32.3) months for patients with ART score ≥ 2.5. (*P* values were 0.036, 0.011 and 0.152 respectively).
Conclusion: Our results are consistent with previous study that before TACE treatment, patients should be assessed by ART score, and those with ART score 0–1.5 had superior prognosis as compared those with an ART score ≥ 2.5.

* Corresponding author.
E-mail address: hantaomd@126.com (T. Han).
[1] Both authors were the co-first authors and contributed equally to the work.
[2] Both authors were the co-corresponding authors and contributed equally to the work.

http://dx.doi.org/10.1016/j.clinre.2016.05.005
2210-7401/

Please cite this article in press as: Yin W, et al. ART score and hepatocellular carcinoma: An appraisal of its applicability. Clin Res Hepatol Gastroenterol (2016), http://dx.doi.org/10.1016/j.clinre.2016.05.005

Introduction

Hepatocellular carcinoma (HCC) is the most common malignant tumor in the clinic. More than 0.6 million HCC patients are diagnosed every year around the world, and HCC is recognized as the second leading cause of death among patients presenting with malignant tumors [1]. China is a high-prone area for HCC, and hepatitis B is an endemic disease for the whole country, which accounts for 54% [2] of all new and death cases for HCC globally.

At present, the Barcelona Clinic Liver Cancer (BCLC) staging system is most commonly used for HCC staging [3,4], as supported by the European Association for the Study of Liver (EASL) [5,6]. According to BCLC, HCC is divided into five stages, and distinguished anti-neoplastic protocols are chosen for different stages. Radical treatments for HCC currently include liver transplantation, hepatectomy, percutaneous ethanol injection (PEI), radiofrequency ablation, among others. These treatments are only applicable to early-stage HCC patients. However, most HCC patients are found at an advanced stage, without any opportunities for radical treatment [7].

According to a randomized controlled meta-analysis [8], TACE treatment is a recommended treatment protocol for intermediate-stage HCC (BCLC Stage B), which is asymptomatic, large, multiple and has no macrovascular invasion or extra-hepatic metastasis.

For most patients, HCC is merged with liver cirrhosis, thus both HCC and the extent of damage to liver function will influence the TACE prognosis. Some researchers [9] have indicated that the baseline characteristics of HCC, such as the size, tumor range, AFP value, and baseline Child-Pugh score and whether it is merged with ascites, are all related to the OS of HCC patients. TACE post-operative radiography and AFP response are also closely related to the prognosis of HCC patients [10—12].

Deterioration of liver function after TACE cannot be overlooked. If further deterioration of liver function occurs, the patient cannot conduct TACE retreatment, and might not even be considered for additional anti-tumor therapy. In this case, what is the criterion that can guide whether patients can be considered for TACE retreatments if they need it? The ART score can be used as a reference based on recent pertinent research [13,14], but patients studied in geographical areas of those published works were markedly different from patients that present in China in respect of disease pathogenesis, disparate regions, and other factors.

Our study will further discuss whether the ART score is applicable to patients with hepatitis B as the main presenting disease in China.

The purpose of this study was to verify whether the ART score is applicable to HCC patients who need repeated TACE treatments at our hospital. The ART score (Table 1) [13] is recognized as an effective tool to predict whether a HCC patient can benefit from TACE retreatment.

In the pertinent studies [13,14], the selected patients were recruited mainly from non-Eastern Asian populations, while this research targeted Chinese patients at our hospital that presented with viral hepatitis, and especially with hepatitis B virus (76%) as the main pathogenesis. In this case, the population constitution was quite different from that previously published research [13,14]. As reported, the ART score could be applied to evaluate the feasibility of TACE retreatment for HCC patients. In line with the study, we also applied the ART score to patients before the second, third, and fourth TACE treatments, and further verified the applicability of the ART score to patients at our hospital for multiple TACE treatments, which was done by comparing the prognosis for two different groups, which were divided on the basis of ART score ranges.

Table 1 ART score sheet.

	Score
Radiological tumor response	
Absent	1
Present	0
AST increased by > 25%	
Present	4
Absent	0
Child—Pugh score increase	
1 point	1.5
≥ 2 points	3
Absent	0

AST: aspartate transaminase.

Patients and methods

Inclusion criteria

One hundred and thirty-seven patients were selected as those presenting with a diagnosis of HCC (all of these patients were complicated with cirrhosis) and were treated with TACE from January 2008 to June 2012 at The Third Central clinical college of Tianjin Medical University, with follow-up until June 2015. Before the first TACE treatment, all patients were above 18 years old and diagnosed with HCC by histology or dynamic image (CT or MRI). This meant that the patients met the EASL standard [15] for TACE treatment. The HCC patients were in the BCLC Stages A, B, and C, but patients in Stage C only included those that had branch portal vein tumor thrombus, and yet the main portal vein and other branches could maintain good blood supply and liver function and were Child-PughA or B. All selected patients had been treated with TACE at least twice and the time interval should not exceed more than 90 days.

Exclusion criteria

They are as follows:

- patients had received liver transplantation, hepatectomy, radiofrequency ablation, or PEI;
- liver function was at Child-Pugh C;
- the patient was BCLC Stage C and had main portal vein tumor thrombus or distant metastasis;
- ECOG score was > 1;
- patients had poor portal blood flow;
- patients were fully responsive to the first TACE treatment and TACE retreatment was not required.

Please cite this article in press as: Yin W, et al. ART score and hepatocellular carcinoma: An appraisal of its applicability. Clin Res Hepatol Gastroenterol (2016), http://dx.doi.org/10.1016/j.clinre.2016.05.005

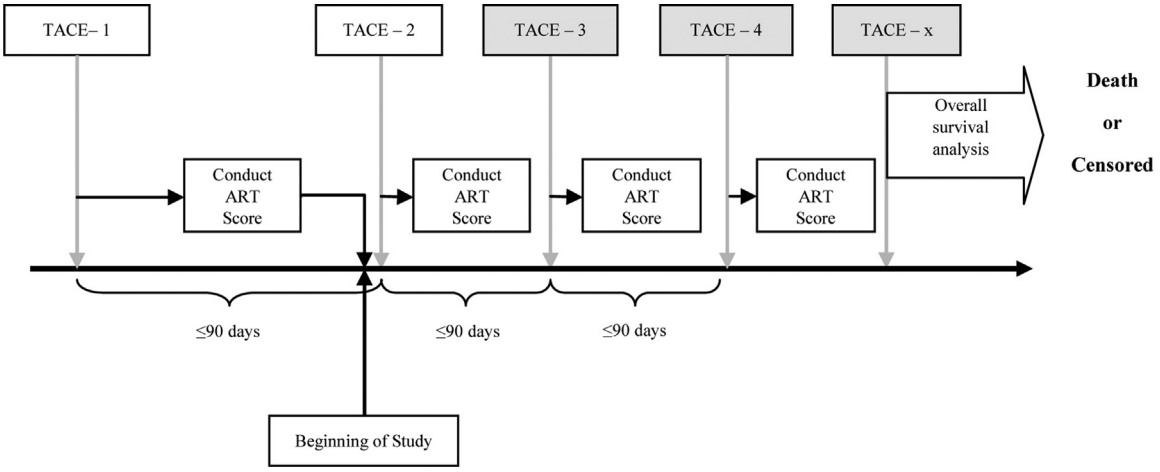

Figure 1 Study design roadmap.

ART score

The evaluation was combined with a radiographic response, deterioration of liver function. The patients were divided into two groups based on the ART score (Table 1). One group had an ART score between 0—1.5 and another group had an ART score $\geq$2.5. Differential prognosis could further indicate which group could not benefit from the next TACE treatment.

Data collection

This study was a retrospective analysis and was approved by The Third Central clinical college of Tianjin Medical University Ethics Committee and all individuals gave informed consent.

CT or MRI inspection was intensified 5—7 days before the first TACE treatment. HCC staging was based on the BCLC staging system [5,6], and the 6th version of UICC (TNM) (International Union against Cancer TNM Classification) [16].

Oncology response evaluations were based on the EASL standard [15] that resulted from CT or MRI inspection that was intensified before the second, third, and fourth TACE treatment (i.e., 90 days within the last TACE treatment). Objective oncological response was defined as the partial response of the last TACE treatment; however, stable or progressive lesions were recognized as ''no objective response''.

In the laboratory, AFP and liver function parameters including Child-Pugh score [17] were all examined one day before every TACE treatment. In addition, dynamic changes of the Child-Pugh score were monitored before every TACE treatment. All changes for other relevant liver function parameters, between every TACE treatment were described in the statistics section. The AFP response was defined as an AFP > 200 ng/ml before TACE, and decreased by more than 50% after TACE. The AFP was divided into three groups when conducting univariate analysis:

- an AFP> 200 ng/ml and displayed a response after TACE;
- AFP > 200 ng/ml and displayed no response after TACE;
- an AFP < 200 ng/ml before TACE.

TACE procedure

Before conducting TACE treatment in The Third Central clinical college of Tianjin Medical University (the type of chemoembolisation of HCC were all cTACE, all patients could be performed superselective TACE), HCC was clearly diagnosed. All HCC patients were in BCLC stages A, B, and C. It should be noted that patients in stage C only included those that had branch portal vein tumor thrombus. By contrast, under situations where the main portal vein and other branches could maintain good blood supply and liver function, this was defined as Child-Pugh A or B. That said, all BCLC patients in stages A, B and C could be treated with TACE, and TACE retreatment could be further decided upon based on the radiographic results as to whether the tumor was active. The research design is shown in Fig. 1.

According to the differential diagnostic criteria, we applied ART score on patients before their second, third, and fourth TACE treatment. Overall death rates were defined from the time that patients were diagnosed with HCC to the time of death, or to the last follow-up. After a series of ART score, the prognosis for differential ART score before each TACE treatment was compared with the aim of analyzing whether there was a statistically significant difference.

Statistics analysis

Statistical descriptions were conducted before the first and second TACE treatment for the patients. The Kaplan-Meier method was applied to calculate the survival curves, and the median survival and 95% confidence intervals were reported. Log-rank test (timing inspection) was used to evaluate patient variable related to OS (before the first and second TACE treatment), tumor response variable, and liver function deterioration variable (between the first and second, second and third, third and fourth TACE treatment). These diagrams were the basis for selecting clinical sensitivity and appropriate conversions between each variable. All the reported *P* values were bilateral, and the significant differences were set at an alpha value of $P < 0.05$. The IBM SPSS statistics 21 software package was used for statistical analyses.

Please cite this article in press as: Yin W, et al. ART score and hepatocellular carcinoma: An appraisal of its applicability. Clin Res Hepatol Gastroenterol (2016), http://dx.doi.org/10.1016/j.clinre.2016.05.005

Table 2 Characteristics of the selected patients for ART score in The Third Central clinical college of Tianjin Medical University.

		N	%
Pre-TACE-1	137		
Age (years)	Mean ± SD	59.8 ± 8.7	
	Range	36–81	
Sex	Male	102	74
	Female	35	26
Etiology	HBV	104	76
	HCV	17	12
	Others	16	12
Child-Pugh stage[a]			
	A	69	50
	B 7 points	27	20
	≥ 8 points	41	30
Tumor size (cm)	Mean (P25, P75)	5.2 (3.4, 7.6)	
	Range	1.2–25.0	
Tumor extent	Unilobar	41	30
	Bilobar	96	70
Tumor number	Unifocal	27	20
	Multifocal	110	80
BCLC-stage	A	13	10
	B	97	71
	C	27	19
TNM stage	I	32	23
	II	45	33
	III	60	44
a-Fetoprotein (ng/ml)	< 200[b]	75	55
	≥ 200	61	45
Pre-TACE-2			
Child-Pugh stage	A	78	57
	B7 points	26	19
	≥ 8 points	33	24
a-Fetoprotein (ng/ml)[a]	< 200	81	59
	≥ 200	44	32

HBV: hepatitis B virus infection; HCV: hepatitis C virus infection; BCLC: Barcelona Clinic Liver Cancer; TNM: Tumor Nodes Metastasis.
[a] 12 missing values.
[b] One missing value.

Results

Characteristics of patients

The characteristics of all patients before the first and second TACE treatment were shown in Table 2. The detailed groups are in Fig. 2.

All the selected patients were treated with TACE at least twice. Between the first and second TACE treatments, there were 32 subjects that displayed a Child-Pugh score that increased by at least one score, 59 subjects that exhibited a Child-Pugh score that remained unchanged, and 46 subjects that had a Child-Pugh score that decreased at least one score. Before the second TACE treatment, 79 patients (57.6% of total patients) had a Child-PughA cirrhosis. Overall, patients were treated with TACE five times as the median (2–13 as the range), and the time interval between the first and second TACE treatments was 52 days as the median (31–90 as the range).

Univariate analysis of prognostic factors

It was determined that 86% of the selected 137 patients died during the follow-up period from January 2008 to June 2015 ($n = 118$), while 14%remained alive ($n = 19$). Overall, the median survival time (95%CI) was 23 (19.9–26.1) months.

We could determine from the univariate analysis in Table 3 that long-term survival was significantly affected by the number of tumors ($P = 0.044$), BCLC Stage ($P = 0.008$), AFP value ($P = 0.002$), AFP response ($P < 0.0001$) and radiographic response ($P = 0.001$). Improved prognosis was obtained if variables of the tumor response, such as radiographic response (median survival (95%CI): response/no response was 31/12.3 (25.6–36.4/9.9–14.7) months, $P = 0.001$), or AFP response (response is defined as > 50% decrease of AFP) (median survival 95%CI): response/no response/base line for AFP < 200 ng/ml was 22/13.5/30.6 (16.4–27.6/10.3–16.7/26.6–34.6) months respectively, $P < 0.001$ had response as compared with

Please cite this article in press as: Yin W, et al. ART score and hepatocellular carcinoma: An appraisal of its applicability. Clin Res Hepatol Gastroenterol (2016), http://dx.doi.org/10.1016/j.clinre.2016.05.005

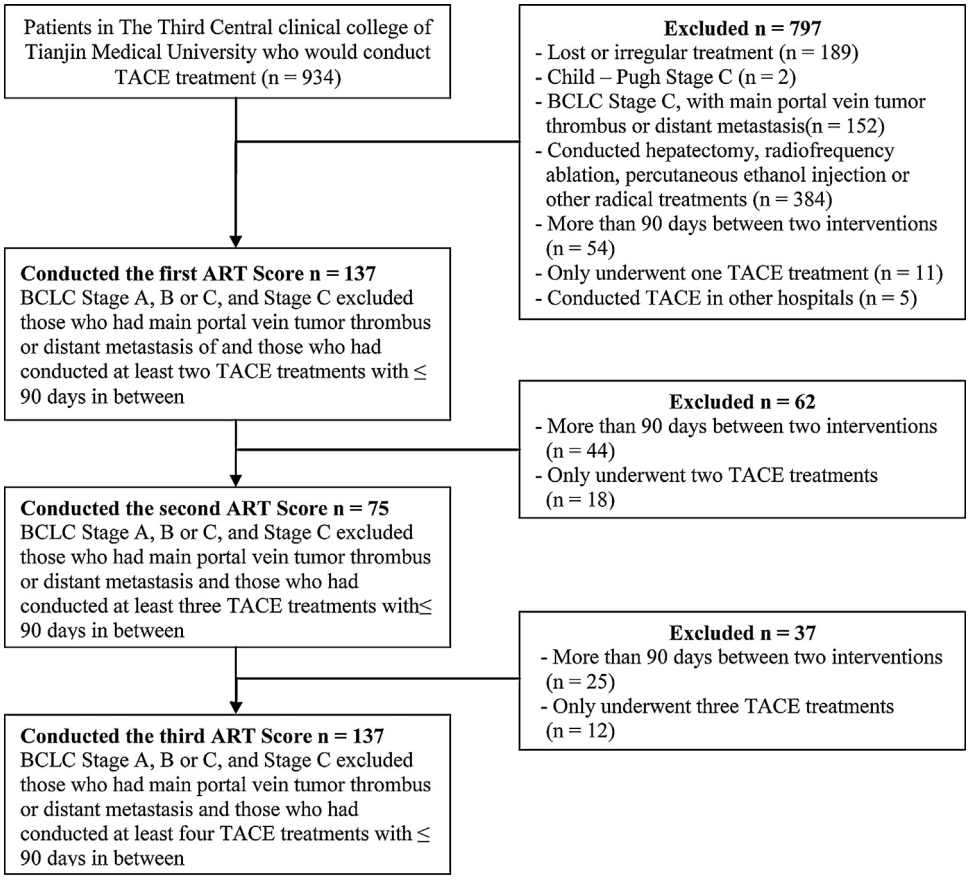

Figure 2 Situations for patients selected for ART score in The Third Central clinical college of Tianjin Medical University.

no response, and significant statistical difference was observed.

The effect of deterioration of liver function to patients before the second TACE treatments as compared with before the first TACE treatments was evaluated next. In relevant studies [13,14], it was indicated that patients would have a poorer prognosis if their AST increased by >25% and the Child-Pugh score increased ≥1 score. In our study, patients also had a poorer prognosis with increased AST and a poorer Child-Pugh score. More specifically, patients with or without >25% increase in AST had a median survival time (95%CI) of 24.0/18.5 (20.9—27.1/14.5—22.5) months respectively (P = 0.070). Patients with no increase, 1 score increase or ≥2 score in the Child-Pugh score had a median survival time (95%CI) of 24.0/22.0/18.0 (20.1—27.9/18.6—25.4/0—40.2) months respectively (P = 0.646). Thus, there was no significant difference.

Predictor for overall survival and univariate analysis

In our study, the survival rates for more than 1, 3 or 5 years were 76.6, 26.3 and 4.4%, respectively.

In univariate analysis (Table 3), the significant parameters tumor numbers, AFP value, AFP response and radiographic response before the second TACE were entered into a Cox regression analysis.

After the stepwise removal of variables which were not significant, only BCLC stages, radiologic tumor response, AFP response (Table 4) remained significant predictors of OS.

ART score

Patients were divided into two groups before the second, third, and fourth TACE treatments based on the ART score (i.e., the ART score was 0—1.5 for the first group and ≥2.5 for the second group) [13,14]. In our studied population, before the second TACE treatment, 79 patients had ART score 0—1.5 and 58 had ART score ≥2.5 (median survival (95%CI) was 25.0/18.0 (21.2—28.8/14.5—21.5) months for 0—1.5/≥2.5 respectively; P = 0.036). As shown in Fig. 3A, both groups had significant differences. Before the third TACE treatment, 43 patients had ART score 0—1.5 and 32 had ART score≥2.5, where in median survival (95%CI) was 29.0/14.0 (22.0—36.0/6.4—21.6) months for the 0—1.5 and ≥2.5 scores respectively; P = 0.011. As shown in Fig. 3B, both groups displayed a statistically significant difference. Before the fourth TACE treatment, 27 patients had ART score of 0—1.5 and 11 had ART score ≥2.5, and the median survival (95%CI) was 24.3/22.0 (8.2—40.4/11.8—32.3) months for the 0—1.5 and ≥2.5 respectively (P = 0.152; Fig. 3C).

Please cite this article in press as: Yin W, et al. ART score and hepatocellular carcinoma: An appraisal of its applicability. Clin Res Hepatol Gastroenterol (2016), http://dx.doi.org/10.1016/j.clinre.2016.05.005

Table 3 Univariate analysis of prognostic factors in HCC patients treated with TACE.

Variable	*N* = 137	Overall Survival (months)		*P*-value (Log Rank)
		Median	95% CI	
Age				
< 65	102	22	19.1—24.9	
≥ 65	35	27	19.8—34.2	0.78
Child-Pugh stage[a]				
A	69	25	19.2—30.8	
B 7 point	27	27	15.1—38.9	
≥ B 8 point	41	18.5	12.6—24.4	0.103
Etiology				
HBV	104	22	18.8—25.2	
HCV	17	31	3.17—58.8	
Others	16	24	13.4—34.6	0.51
Tumor extent				
Unilobar	41	25	18.7—31.3	
Bilobar	96	22	18.9—25.1	0.273
Tumor number				
Unifocal	27	25	19.9—30.1	
Multifocal	110	22	18.9—25.1	0.044
Tumor size (cm)[c]				
< 7.5	99	23	20.6—25.4	
≥ 7.5	35	20	11.3—28.7	0.871
BCLC-stage				
A	13	27	10.6—43.4	
B	97	24	20.0—28.0	
C	27	13	8.8—17.2	0.008
TNM stage				
I	32	29.3	19.2—39.4	
II	45	24.3	19.7—28.9	
III	60	17.5	13.2—21.8	0.052
a-Fetoprotein (ng/ml)				
< 200	76	29.3	24.7—33.9	
≥ 200	61	16	11.7—20.3	0.002
AFP response (ng/ml)[b]				
AFP > 200: no response	38	13.5	10.3—16.7	
AFP > 200: response	18	22	16.4—27.6	
AFP < 200	68	30.6	26.6—34.6	< 0.001
Radiologic tumor Response				
Present	78	31	25.6—36.4	
Absent	59	12.3	9.9—14.7	0.001
AST increase > 25%				
Absent	86	24	20.9—27.1	
Present	51	18.5	14.5—22.5	0.07
Child-Pugh score				
Increase absent	102	24	20.1—27.9	
+1 point	27	22	18.6—25.4	
+≥ 2 point	8	18	0—40.2	0.646
ART_2 Score				
0∼1.5	79	25	21.2—28.8	
≥ 2.5	58	18	14.5—21.5	0.036
ART_3 Score				
0∼1.5	43	29	22.0—36.0	
≥ 2.5	32	14	6.4—21.6	0.011
ART_4 Score				
0∼1.5	27	24.3	8.2—40.4	
≥ 2.5	11	22	11.8—32.3	0.152

BCLC: Barcelona Clinic Liver Cancer; TNM: Tumor Nodes Metastasis; AST: aspartate aminotransferase; ALT: alanine aminotransferase;
[a] Pre-TACE 2.
[b] Thirteen patients had missing values, AFP response was defined by a decrease of > 50% from baseline levels.
[c] Three patients had missing values.

Please cite this article in press as: Yin W, et al. ART score and hepatocellular carcinoma: An appraisal of its applicability. Clin Res Hepatol Gastroenterol (2016), http://dx.doi.org/10.1016/j.clinre.2016.05.005

Table 4 Results of multivariate stepwise backward Cox regression analysis of prognostic factors in patients with HCC treated with TACE.

	Overall survival			*P*-value
Variable	HR	95% CI	B	(Cox regression)
BCLC-stage	1.468	1.013—20128	0.384	0.042—
Radiologic tumor response	0.301	0.203—0.444	—1.202	0.000
AFP response	0.817	0.691—0.966	—0.202	0.018—

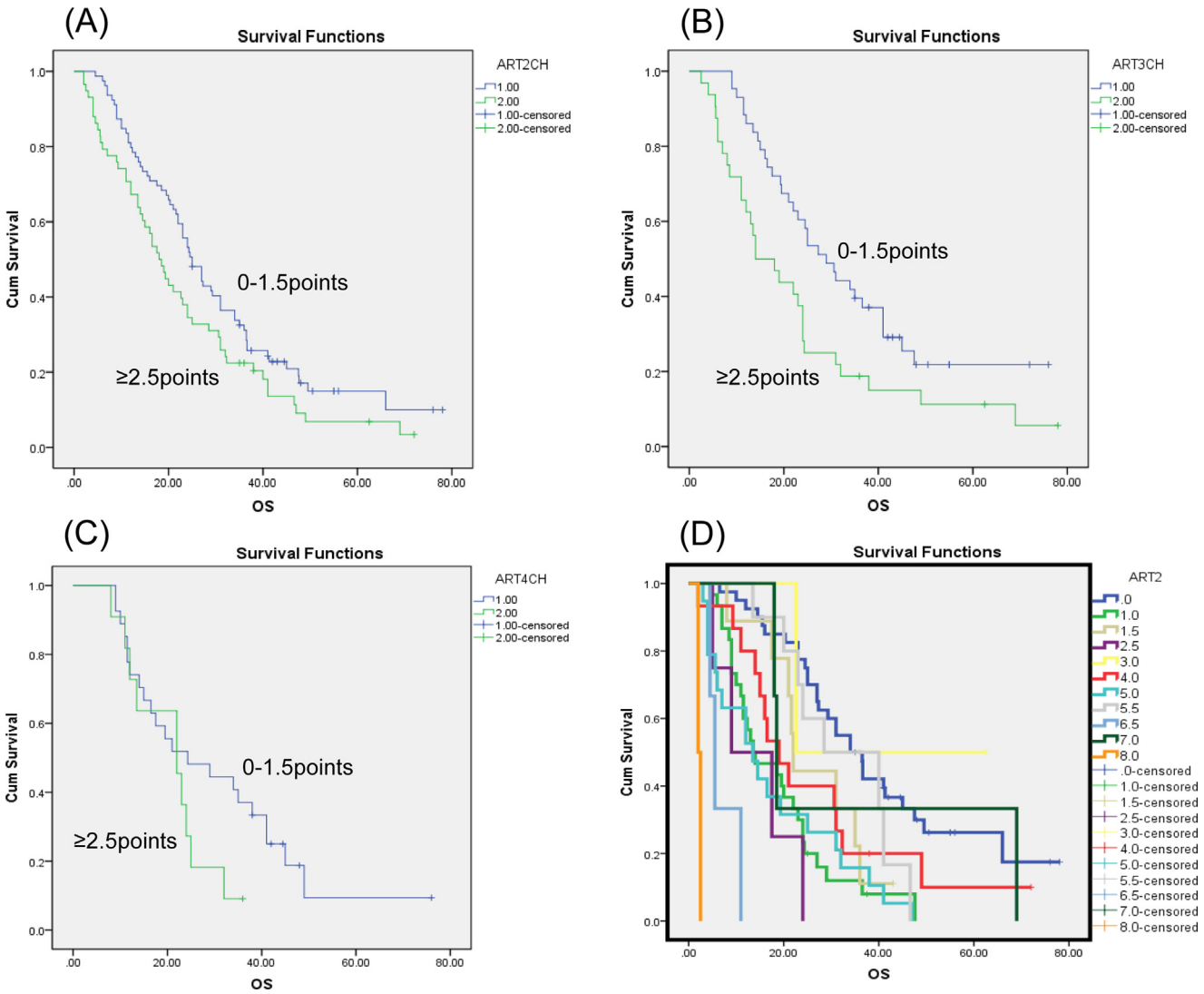

Figure 3 (1) In the following figures (A—C), ''1'' refers to a group with an ART score 0—1.5 and ''2'' refers to a group with an ART score ≥ 2.5. (2) All patients data were from The Third Central clinical college of Tianjin Medical University; (3) X-coordinate presents time (months), Y-coordinate presents probability. (A). The relationship between ART score and OS before the second TACE treatment for patients, the median OS (95%CI) was respectively 0—1.5 ($n = 79$), 25.0 (21.2—28.8) months; ≥ 2.5 ($n = 58$), 18.0 (14.5—21.5) months. $P = 0.036$. (B). The relationship between ART score and OS before the third TACE treatment for patients, the median OS (95% CI) was respectively 0—1.5 ($n = 43$), 29.0 (22.0—36.0) months; ≥ 2.5 ($n = 32$), 14.0 (6.4—21.6) months. $P = 0.011$. (C). The relationship between ART score and OS before the fourth TACE treatment for patients, the median OS (95% CI) was respectively 0—1.5 ($n = 27$), 24.3 (8.2—40.4) months; ≥ 2.5 ($n = 11$), 22.0 (11.8—32.3) months. $P = 0.152$. (D). The relationship between every ART score and OS before the second TACE treatment for patients.

Please cite this article in press as: Yin W, et al. ART score and hepatocellular carcinoma: An appraisal of its applicability. Clin Res Hepatol Gastroenterol (2016), http://dx.doi.org/10.1016/j.clinre.2016.05.005

Discussion

TACE has been widely applied in the clinical, and an international directory also points out that TACE can be used as a non-curative and first-line treatment [15] for patients that present with middle- or early-stage HCC but are otherwise unsuitable for surgery or radiofrequency ablation. Some studies have indicated that repeated TACE treatments may increase tumor response and survival [18], and typical HCC patients need to conduct more than three rounds of TACE treatments to obtain the best radiographic response [8,9,13,18,19]. However, some patients may not benefit from TACE retreatment under some situations, TACE retreatment may lead to deterioration of liver function or elicit a poorer prognosis. Moreover, most patients are diagnosed with HCC combined with liver cirrhosis, and thus have potential incentive for deterioration of liver function. Long-term survival or even the next treatment will be impacted if deterioration of liver function is evident after TACE treatment. As indicated by previous research studies [20], deterioration of liver function was identified as a key reason that hinders further TACE treatment after the first TACE for HCC patients; however, patients might also revert to other modes of therapy. In this case, it is crucial to understand how to best select patients for TACE retreatment after the first treatment had concluded. However, there are no specific standards for the degree of deterioration of liver function, and it fully depends on the diagnosing clinical physician as to whether TACE retreatment should be conducted.

The purpose for this current study was to establish an objective tool to guide physicians on the best practices of choosing appropriate HCC patients for TACE retreatment. As shown in both Figs. 3A and B, patients were divided into two groups based on different ART score and distinct prognoses were obtained for both groups. The group with an ART score of 0—1.5 had a much better prognosis than those subjects with an ART score ≥ 2.5, and there was a distinct difference between them by statistical analysis. Thus, the ART score could be regarded as an important index to predict the OS, which was supported by pertinent studies [13,14]. Patients with an ART score of eight only had a median survival of two months, which indicated that patients with a high ART score (≥ 2.5) could not benefit much from TACE retreatment (Fig. 3D).

As reported in the research [13], an ART score inherently has a certain clinical practicality. Firstly, the ART score is robust and can be practiced at places where the medical conditions are relatively poor; Secondly, the ART score can protect patients by preventing them from further harm that might be caused by TACE retreatment due to an oversight of changes in laboratory tests; and third, inadequate TACE treatments can be avoided by carefully applying the ART score. An increase in the ART score means an increased risk of TACE retreatment (Fig. 3D) and a decreased OS. We can decide on the necessity of TACE retreatment based on the ART score before each TACE treatment to decrease both unnecessary treatment costs and potential side effects.

There were many differences between our results and relevant research [13,14] in univariate analysis. Although patients whose AST and Child-Pugh score increased had a poorer prognosis in our research, there was no significant difference statistically, and there are some differences in Cox regression analysis, which may be accounted for by any of the following reasons.

- the difference in etiology: the patients had mainly alcoholic liver disease in relevant research [13,14], while our patients had mainly viral hepatitis. For patients with viral hepatitis, their AST and Child-Pugh score would significantly increase when virus activity happened, but decrease quickly after the onset of antiviral drug therapy. In this case, the influence of AST and Child-Pugh score on long-term prognosis may not be distinct. However, for patients with alcoholic liver disease, which usually combining mitochondrial damage, AST increased more significantly than the patients with viral hepatitis, and the changes of liver function directly depended on whether they continued drinking alcohol. If patients abstained from drinking alcohol, AST and Child-Pugh score would not change much in the short-term. Thus, two groups of patients had different characteristics, which would directly impact the variance of both the AST and Child-Pugh score;
- the difference in basis of liver function: 57.6% of our patients were under Child-Pugh A cirrhosis before the second TACE treatment, while 67.0% of the patients in a relevant study [13] were under Child-Pugh A cirrhosis before the second TACE treatment;
- the difference in BCLC stages. All of the patients in relevant study were under BCLC Stage A or B, while part of our patients were under BCLC Stage C;
- an insufficient number of cases. In this situation, further research should be expanded.

In addition, our patients included some that were under BCLC StageC (excluding patients with main portal vein tumor thrombus, poor blood supply or distant metastasis), but the overall results were basically the same with previously published relevant studies [13,14]. Before the fourth TACE retreatment, there was no statistical difference between the results of both groups, but the median survival for the group with an ART score 0—1.5 was still greater than the other group with an ART score ≥ 2.5, which may be caused by the small number of patients in the group or the results excursion. Thus, further verification should be conducted by joining multi-center studies to effectively increase the overall assessable patient population. In terms of the comparison of survival for both groups with different ART score before the second TACE treatment, our results were not exactly the same as those previously reported [13] but had the same trend, considering the differences in patient population and pathogenesis.

According to another Italian report [21], ART score had no guidance on whether the patient should conduct TACE retreatment because there was no statistical difference on overall survival between patients with ART score of 0—1.5 and patients with ART scores ≥ 2.5 from their research population, which may be caused by the difference in research population and the relatively smaller number of patients (i.e., $n = 51$).

As previously reported [13], the ART score had its own shortage. Although the EASL standard for TACE prognosis

Please cite this article in press as: Yin W, et al. ART score and hepatocellular carcinoma: An appraisal of its applicability. Clin Res Hepatol Gastroenterol (2016), http://dx.doi.org/10.1016/j.clinre.2016.05.005

appears equal to the mRECIST standard [22], but mRECIST standard has more accurate and clearer judgment with respect to the prognosis of relatively stable lesion partial response [23]. This may be related to different definitions of the two standards for partial response. EASL standard is defined by > 50% decrease of tumor, while mRECIST standard is defined by > 30% decrease of tumor mass. Moreover, our patients were all recruited from our hospital, and presented predominantly with viral hepatitis, in which case there may be some limitations for the relevant and applicability of our results. The research population should be expanded and our hospital should cooperate with multiple centers to obtain more convincing results. In addition, patients in different countries have different pathogenesis and there will also be significant difference in univariate analysis.

The ART score will be more instructive if it can be formulated to be applicable to local regions based on the characteristics of different geographical or geo-coded regions, various pathogenesis and by univariate analysis. Overall, the ART score is a relatively novel, non-invasive, objective and widely applicable scoring system for TACE retreatment. Patients with ART scores $\geq$ 2.5 or even higher may not benefit any more significantly from TACE retreatment, and thus might need to choose other treatment options like Sorafenib treatment according to other standards. The ART score is a new system, and there are unsolved issues like whether other factors should be added to evaluate the effectiveness of the therapy together. It needs to be further perfected by verification on patient populations from different pathogeneses, different subjects and different regions in order to be applicable to every country and every patient population based on their unique characteristics and qualities.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

This study was supported by the National 12th 5-year Plan for Hepatitis Research to Tao Han, China (No. 2012ZX10002004-011) and Tianjin Science and Technology Fund to Tao Han, China (No. 13RCGFSY19200).

References

[1] McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. Clin Liver Dis 2015;19:223—38.
[2] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69—90.
[3] Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329—38.
[4] Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 2010;30:61—74.
[5] Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35:421—30.
[6] European Association For The Study Of The Liver. EASL- EORTC clinical practice guidelines. Management of hepatocellular carcinoma. J Hepatol 2012;56:908—43.
[7] Hucke F, Sieghart W, Schoniger- Hekele M, Peck-Radosavljevic M, Muller C. Clinical characteristics of patients with hepatocellular carcinoma in Austria is there a need for a structured screening program? Wien Klin Wochenschr 2011;123:542—51.
[8] Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 2003;37:429—42.
[9] Raoul JL, Sangro B, Forner A, Mazzaferro V, Piscaglia F, Bolondi L, et al. Evolving strategies for the management of intermediate- stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. Cancer Treat Rev 2011;37:212—20.
[10] Ebied OM, Federle MP, Carr BI, Pealer KM, Li W, Amesur N, et al. Evaluation of responses to chemoembolization in patients with unresectable hepatocellular carcinoma. Cancer 2003;97:1042—50.
[11] Vogl TJ, Trapp M, Schroeder H, Mack M, Schuster A, Schmitt J, et al. Transarterial chemoembolization for hepatocellular carcinoma: volumetric and morphologic CT criteria for assessment of prognosis and therapeutic success-results from a liver transplantation center. Radiology 2000;214:349—57.
[12] Memon K, Kulik L, Lewandowski RJ, Wang E, Ryu RK, Riaz A, et al. Alpha-fetoprotein response correlates with EASL response and survival in solitary hepatocellular carcinoma treated with transarterial therapies: a subgroup analysis. J Hepatol 2012;56:1112—20.
[13] Sieghart W, Hucke F, Pinter M, Graziadei I, Vogel W, Müller C, et al. The ART of decision making: re-treatment with TACE in patients with hepatocellular carcinoma. Hepatol 2013;57:2261—73.
[14] Hucke F, Sieghart W, Pinter M, Graziadei I, Vogel W, Müller C, et al. The ART-strategy: Sequential assessment of the ART score predicts outcome of patients with hepatocellular carcinoma re-treated with TACE. J Hepatol 2014;60:118—26.
[15] European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908—43.
[16] Sobin L, Wittekind C, editors. UICC (2002) TNM classification of malignant tumours. 6th ed. New York: Wiley-Liss; 2002. p. 81—3.
[17] Child CG, Turcotte JG. Surgery and portal hypertension. Major Probl Clin Surg 1964;1:1—85.
[18] Bolondi L, Burroughs A, Dufour JF, Galle PR, Mazzaferro V, Piscaglia F, et al. Heterogeneity of patients with intermediate (BCLC B) hepatocellular carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis 2012;32:348—59.
[19] Terzi E, Golfieri R, Piscaglia F, Galassi M, Dazzi A, Leoni S, et al. Response rate and clinical outcome of HCC after first and repeated cTACE performed ''on demand. J Hepatol 2012;57:1258—67.
[20] Raoul JL, Bruix J, Greten TF, Sherman M, Mazzaferro V, Hilgard P, et al. Relationship between baseline hepatic status and outcome, and effect of sorafenib on liver function: SHARP trial subanalyses. J Hepatol 2012;56:1080—8.
[21] Terzi E, Terenzi L, Venerandi L, Croci L, Renzulli M, Mosconi C, et al. The ART Score is not effective to select patients for transarterial chemoembolization retreatment in an Italian Series. Dig Dis 2014;32:711—6.

Please cite this article in press as: Yin W, et al. ART score and hepatocellular carcinoma: An appraisal of its applicability. Clin Res Hepatol Gastroenterol (2016), http://dx.doi.org/10.1016/j.clinre.2016.05.005

[22] Gillmore R, Stuart S, Kirkwood A, Hameeduddin A, Woodward N, Burroughs AK, et al. EASL and mRECIST responses are independent prognostic factors for survival in hepatocellular cancer patients treated with transarterial embolization. J Hepatol 2011;55:1309–16.

[23] Shim JH, Lee HC, Kim SO, Shin YM, Kim KM, Lim YS, et al. Which response criteria best help predict survival of patients with hepatocellular carcinoma following chemoembolization? A validation study of old and new models. Radiology 2012;262:708–18.

Please cite this article in press as: Yin W, et al. ART score and hepatocellular carcinoma: An appraisal of its applicability. Clin Res Hepatol Gastroenterol (2016), http://dx.doi.org/10.1016/j.clinre.2016.05.005