ORIGINAL ARTICLE

ROLE OF ASSESSMENT FOR RETREATMENT WITH TRANSARTERIAL CHEMOEMBOLIZATION SCORE IN DECISION OF RETREATMENT WITH TRANS-ARTERIAL CHEMO-EMBOLIZATION SESSIONS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Background: The objective behind this study was to determine that Assessment for Re-treatment with Transarterial chemoembolization (ART) score is really applicable in patients with hepatocellular carcinoma. **Methods:** A cross sectional observational study was conducted on all patients with hepatocellular carcinoma of intermediate stage and undergone ≥2 Transarterial chemoembolization. ART score was assessed before and after each session of Transarterial chemoembolization. Multi-logistic regression analysis was performed to compare the final outcome of patients with ART score of ≥2.5 into groups with two and more than two Trans-arterial chemo-embolization sessions. **Results:** A total of 100 HCC patients were recruited for final analysis. Our study participants consisted of total 100 HCC patients. Mean Child Pugh score was 6.1±0.95. In our study, most of the study participants (n=63) had ART score of less than 1.5 as compared to ART score >2.5 (n=37). A significant proportion of patients with ART score of <1.5 prior to second Trans-arterial chemo-embolization had better median survival as compared to patients with ART score of >2.5, *p*-value<0.001. Patients with ART score of more than 2.5 did not show any survival benefit after having 3rd or 4th Trans-arterial chemo-embolization session, *p*=0.47. **Conclusions:** Our study findings suggest that those HCC patients who receive multiple sessions of TACE with a low ART score have more favourable outcomes with increased survival rate.

Keywords: Hepatocellular carcinoma; Child Pugh Classification; MELD score; ART score
J Ayub Med Coll Abbottabad 2017;29(3):378–83

INTRODUCTION

Hepatitis C virus infection is the single most common cause of end stage sequelae of chronic liver disease called hepatocellular carcinoma (HCC).[1] Hepatocellular carcinoma is now the 5th most common cancer among all worldwide.[2] Because of long infective course of HCV infection majority of the patients with underlying HCC diagnosed at their 5th or 6th decade of life.[3] The treatment of patients with HCC varies from medical therapy to surgical procedures. As per Barcelona Clinic Liver Cancer (BCLC) guidelines for HCC, various options can be adapted after assessing liver function and tumour characteristics.[4–6]

Mainly population affected with HCC present at their advance stage of disease where treatment -options become limited and only symptomatic treatment can be offered because survival of such kind patients not more than 11-20 months.[7–8] Those patients who fall under category of intermediate stage HCC and BCLC stage B (asymptomatic patients with large or multifocal HCC and no extrahepatic extension) are treated with Transarterial chemoembolization (TACE).[9–11] On the other hand, TACE can also be used in patients who are awaiting for liver transplantation as a bridging therapy.[12]

Most of the previously conducted studies have determined several factors which may affect the overall prognosis of TACE such as extent of liver dysfunction, tumour size and characteristics, levels of alpha-fetoprotein (AFP), child-pugh classification, and liver function test. [9–15]

If liver function gets worse after taking TACE sessions so these kinds of patients cannot take further TACE sessions or any other antitumor treatment. [9,11,16]

Sieghart and his colleagues made a scoring system named as ART used to predict survival of HCC patients after having first TACE session.[17] This score can only be calculated using variables like presence or absence of radiologic tumour response, increase in Child score or AST (Aspartate transaminase). The methods used to calculate ART score is by selecting two separate groups of patients who do not share similar prognostic value. The ART score cannot be accurately calculated in patients who experienced more than one sessions of TACE.[17] Although, majority of HCC patients who are in intermediate stage require more than two sessions in a sequential manner.[11,17,18] That is why prognostic

value of repeated TACE session is scientifically need to be determine which has not been observed in our population and very few international literatures are available. So, this study will be conducted to determine that ART score is really applicable in patients with hepatocellular carcinoma at a tertiary care hospital in Pakistan.

MATERIAL AND METHODS

This cross-sectional hospital based study was conducted at Aga Khan University, Karachi for a period of fourteen years (January 2001 to 31st December 2014) in all patients admitted in a gastroenterology unit for TACE procedure through a consecutive sampling technique.

All diagnosed admitted cases of HCC with age more than 18 years of either gender treated with more than two sessions of TACE (time between the TACE cycles each >90 days) and fall under BCLC category of stage A or B along with preserved liver functions (Child-Pugh class A or B) were enrolled under this study. The diagnosis of HCC was made using guideline based diagnostic criteria by European Association for the Study of the Liver Disease (EASL).[5]

Patients who were in child class C or BCLC stage C and those patients who received TACE prior to orthotopic liver transplantation (OLT) or resection, or if patient received TACE for HCC recurrence after OLT were excluded from the study. The study approved by the ethical review committee of Aga Khan University Hospital (ERC #3458-Med-ERC-15)

We have documented any adverse event that occurred within 30 days of any TACE session

The ART score has three variables (Table-1).

Table-1: Art score

ART score Points
Radiologic tumour response Absent 1 Present 0
AST increase > 25% Present 4 Absent 0
Child-Pugh score increase 1 point 1.5 ≥ 2 points 3 Absent 0

The ART score is calculated on the basis of sum of all three variables. As we have divided the patients into two groups based on their ART score as <1.5 and more than 2.5, the cut off value was set accordingly to determine the survival among these patients.

All data entered and analysed by using the Statistical package for social science SPSS (Release 16.0 and a p-value <0.05 were considered as statistically significant.

Quantitative variables were presented as means and SD such as age, AFP, child score, and MELD (Model for end stage liver disease) score and number (Percentage) for qualitative variables, such as gender and aetiology of cirrhosis. In our study, the survival of patients was calculated from the day of first ART score assessment until the patient died or till last visit. Those who lost follow-up were excluded from the study. Kaplan Meier analysis was performed to measure the in-hospital outcome in months. Multi-logistic regression analysis was performed to observe the effect of multiple variables on survival.

RESULTS

A total of 790 patients had TACE between January 2001 to December 2014. Two hundred fifty-six patients had ≥2 TACE sessions, 156 patients excluded due to missing variables. Total of 100 patients were included in the final analysis (Figure-1).

Out of 100 patients, 51 patients underwent 3 TACE sessions and 19 patients underwent 4 TACE sessions. Tumour response was present in 14 patients. Decompensation after TACE was seen in 15 patients, most common decompensation was ascites (14/15 patients). AST rise was seen in 23 patients after TACE. During follow-up period of average 48 months (range 20-74 months); overall mortality rate was observed out of 100 patients was 80% (n=80). A median of 27 months was observed as overall survival of patients in our study (95% CI, 11.4–32.7 months). The survival was calculated when the date patent was enrolled till his/her death. A significant association was observed in a univariate analysis among patients who underwent 1st TACE with 2nd, 3rd and 4th TACE after 27 vs. 25 vs. 12 months, *p* value 0.01 (Table-3).

On multivariate analysis, child class and ART score had prognostic significance (Table-4)

Overall, patients with an ART score of 0–1.5points (n=63) before TACE-2 had a median survival of 29 months [95% CI: 26.21-31.78] vs. those with some of ≥ 2.5 points (n=37) median survival 25months [95%CI: 11.10-22.89] *p*-value <0.001(Figure-2). Before TACE-3 and TACE-4 same results obtained (Figure-3,4). When a subgroup analysis was done in these patients, whether they had 2 TACE sessions or more than 2 TACE sessions, it was observed that there was no survival difference between both groups [18 months vs. 21 months, *p* value 0.47] (Figure-5).

There was no survival difference in patients with HCC size <5cm vs. >5cm (Figure-6) or AFP level <200 vs. >200 iu/ml (Figure-7).

Table-2: Baseline characteristics of study patients (n=100)

Characteristics	Mean+SD/ %	Characteristics	MEAN +SD/ %
Age, in years (Mean and SD)	57.53±9.8	MELD score (mean and SD)	9.4±2.3
Male	82	Tumour size <5cm	62
Female	18	Tumour size >5 cm	62
Child score (Mean and SD)	6.1±0.95	BCLC stage	
Child class		A	61
A	71	B	39
B	29	∞- Fetoprotein	
Aetiology of cirrhosis		<200	65
HCV	67	≥200	35
HBV	17	Tumour response present	14
NBNC	11	Decompensating after TACE	15
HBV+HCV	3	AST >25%	23
BCS	1	Before TACE 2	
ALD	1	Child score	6.5 ± 1.05
Tumour size		Before TACE 3	
<5cm	62	Child score	6.4 ± 0.87
>5cm	38	Before TACE 4	
		Child score	6.3 ± 1.12

Table-3: Univariate analysis of prognostic factors

Variable	n=100	Median	95% CI	*p* value
Age				
<65 years	64	64	20.06–27.93	0.27
≥65	36	36	23.92–36.08	
Aetiology				
Viral	87	27	23.8–30.11	0.65
others	13	21	13.07–28.92	
∞- Fetoprotein				
<200	65	27	21.38–32.61	0.23
≥200	35	22	17.87–26.12	
Tumour size				
<5 cm	62	27	20.66–33.33	0.31
>5 cm	38	25	19.44-30.56	
BCLC stage				
A	61	25	18.81–31.19	0.37
B	39	25	19.34–30.65	
AST >25%				
No	84	27	23.91–30.08	0.19
Yes	16	14	6.51–21.48	
Tumour response				
No	88	25	20.07–29.92	0.70
Yes	12	28	24.91–31.08	
Child score increase				
0 points	66	27	23.20–30.79	
1 points	27	25	11.40–38.60	0.01
≥2 points	7	12	10.71–13.28	

Table-4: Multivariable cox regression of prognostic factors

Variable	Hazard Ratio	95% CI	*p* value
Child stage			
A	1.0		
B	3.19	1.58–6.44	0.001
ART score			
0-1.5 points	1.0		
≥2.5 points	2.56	1.17–5.59	0.01
AST >25%			
No	1.0		
Yes	0.37	0.16-1.33	0.12

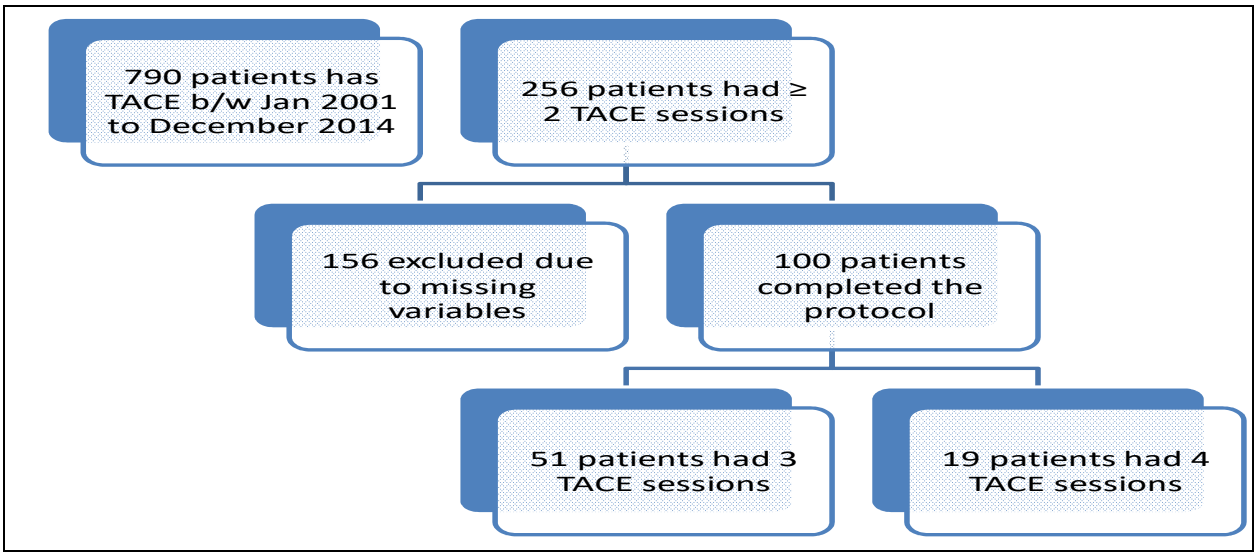

Figure-1: Flow diagram

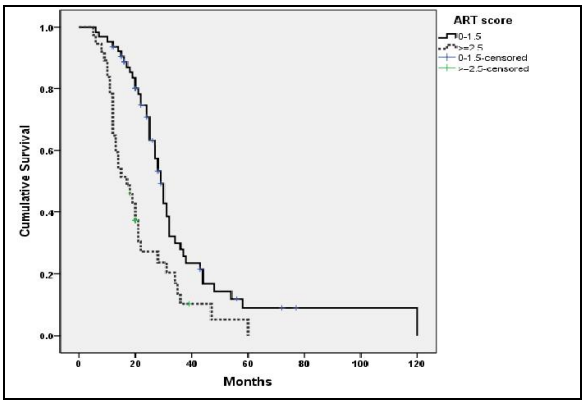

Figure-2: ART score before TACE 2

0-1.5 points (n=63): Median survival time: 29months [95% CI: 26.21-31.78], ≥2.5 points (n=37): Median survival time: 25months [95%CI: 11.10–22.89] *p* value <0.001

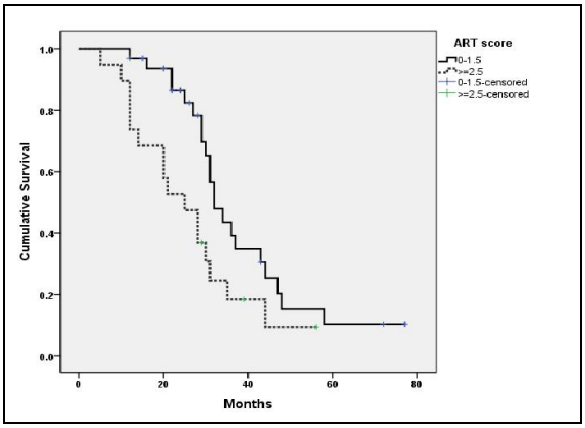

Figure-3: ART score before TACE 3

0-1.5 points (n=32): Median survival time: 32months [95% CI: 27.39–36.60], ≥2.5 points (n=19): Median survival time: 25months [95%CI: 16.46–33.53] *p* value= 0.02

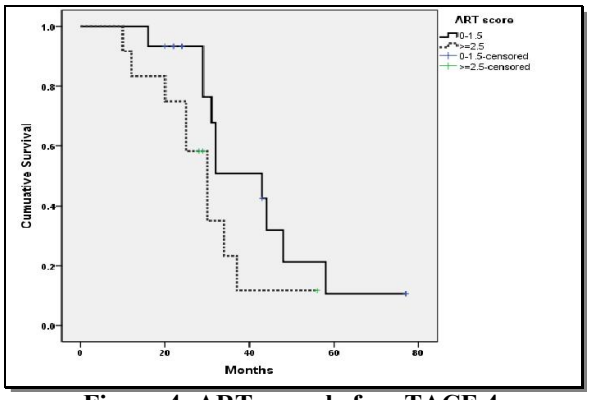

Figure-4: ART score before TACE 4

0–1.5 points (n=10): Median survival time: 43months [95% CI: 29.77–56.22], ≥2.5 points (n=9): Median survival time: 30months [95% CI: 23.54-36.54] *p* value= 0.1

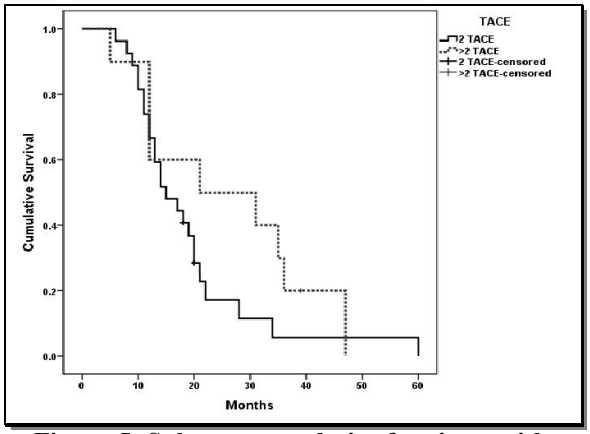

Figure-5: Sub-group analysis of patients with ART score >2.5

2 TACE (n=27): Median survival time: 18 months [95% CI: 9.91-20.08], >2 TACE (n=10): Median survival time: 21 months [95% CI: 1–50.44] *p* value=0.47

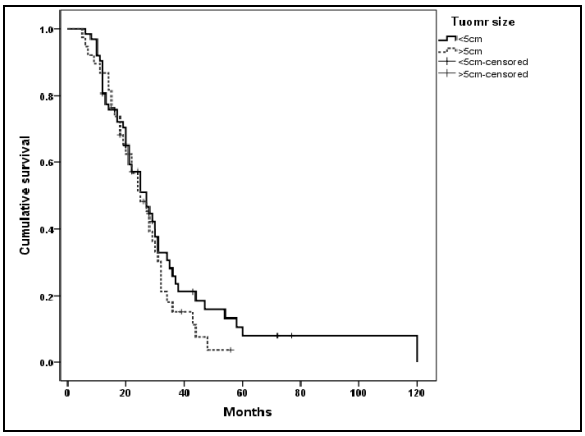

Figure-6: Survival difference between HCC patients with tumour size <5cm vs >5cm

<5 cm (n=62): Median survival = 27 months [20.66-33.33],n >5cm (n=38): Median survival = 25 months [19.44-30.56] *p* value=0.31

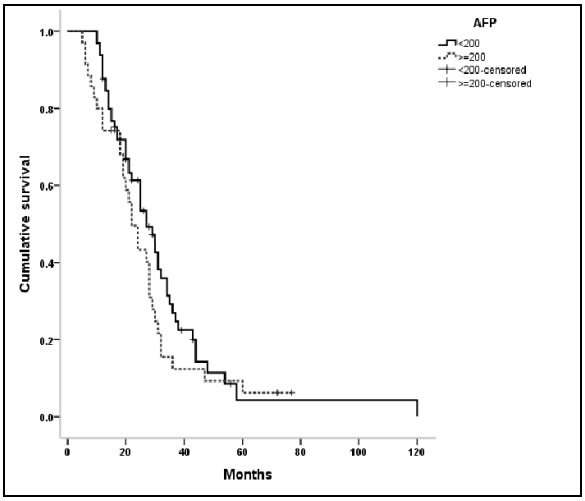

Figure-7: Survival difference between HCC patients with AFP <200 vs AFP >200

<200 (n=65) = Median survival = 27 months [21.38-32.61], >200 (n=35) = Median survival = 22 months [17.87-26.12] *p* value=0.23

DISCUSSION

HCC is the serious complication of liver cirrhosis.[1]There are various treatment options for advance stage HCC including TACE.[4–10] In some routine treatment procedure patients with HCC usually require more than two sessions of TACE to achieve desired outcome.[11,17]

Significantly favourable survival benefit of TACE was observed when comparing the patients with ART score of <1.5 with ART score >2.5 before going to TACE 2 and TACE 3 (29 months vs. 25months, *p* value <0.001 and 32 months vs. 25 months, *p* value 0.02, respectively).

These results are comparable with the results of Seighart study, in which patients with favourable ART score had better survival as compared to those with unfavourable ART score.[17,18]

In patients with a dismal ART score (≥2.5 points) prior to TACE-2, when we did subgroup analysis, we found that there is no survival benefit between patients who had only two TACE sessions or more than two TACE sessions (survival 18-month vs 21 months, *p* value 0.47). If we find ART score (≥2.5 points), then these patients should not be subjected to further TACE sessions and should be offered other treatment options like systemic therapy with sorafenib etc.[19,20]

Few limitations of the study include retrospective study design, missing variables of the patients with ≥2 TACE sessions so ART score before TACE 2 only be calculated in 100 patients. Still sample size was adequate to compare the groups with high and low ART score.

CONCLUSION

Our study findings suggest that those HCC patients who receive multiple sessions of TACE with a low ART score have more favourable outcomes with increased survival rate.

Acknowledgements:

We acknowledge the efforts of all the authors in this work.

Conflict of interest:

There is no conflict of interest related to this article.

AUTHORS' CONTRIBUTION

AH: Literature search, conceptualization of study design, data collection, write-up. SA: Conceptualization of study design, proof reading. SA: Data analysis, data interpretation. TUH: Data collection, proof reading.

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Received: 22 February, 2017	*Revised: 25 March, 2017*	*Accepted: 16 June, 2017*

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