

# P-ART Score is a New Modification to Improve ART Score Predictive Accuracy for Patients with HCC Undergoing TACE

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**Background:** Predicting the prognosis of patients with HCC is challenging.

**Aim:** To evaluate the Assessment for Retreatment with TACE (ART) score in predicting survival after TACE retreatment and the value of adding post-TACE thrombocytopenia in improving its accuracy (P-ART).

**Methods:** Barcelona Clinic Liver Cancer (BCLC) stages A and B patients underwent TACE retreatment, and records were reviewed. Radiologic tumor response (RTR) after the first TACE was considered a partial response, while the absence of response is a stable or progressive disease. The one year overall survival (OS) from the second TACE was determined.

**Results:** One hundred and sixty patients included 88.1% men, age 60.7±7.2 years, Child-Pugh class A&B cirrhosis (n=133 and 27, respectively), mostly hepatitis C (96.3%), with BCLC-A&B (n=74 and 86, respectively). RTR was present in 82 patients. Variables associated with poor OS: baseline lower serum albumin and platelet count, besides follow-up absent radiologic tumor response, an increase in AST >25%, an increase in Child-Pugh score, and a fall in platelet count fall  $\geq 10,000/\text{mL}^3$  before TACE2. By multivariate analysis, ART score parameters and platelet count fall were independent predictors of poor survival. RTR absence had the higher risk of mortality by 3.12 times than responding tumors. ART score subgroups ( $\leq 1.5$  and  $\geq 2.5$  points, 81 and 79 patients, respectively) had no significant relation to OS (22.3 vs 16.7 months;  $P=0.07$ ). On modifying the ART score by adding 3 points for fallen platelet count  $\geq 10,000/\text{mL}^3$  (ART-P score), 113 patients scored 0–5 and 47 scored  $\geq 5.5$  with a median OS of 22 vs 11.2 months, respectively ( $P=0.01$ ).

**Conclusion:** ART score could not identify patients who will benefit from TACE retreatment in intermediate-stage HCC patients, and the addition of platelet count reduction (P-ART) could improve its prognostic ability.

**Keywords:** hepatocellular carcinoma, TACE, ART score, platelets

## Introduction

Hepatocellular carcinoma (HCC) accounts for 75% of primary liver cancers and is the third most prevalent cause of cancer death worldwide.<sup>1</sup> Unfortunately, most HCC patients are diagnosed at the intermediate and late stages of the Barcelona Clinic Liver Cancer (BCLC) staging system,<sup>2</sup> and accordingly, only palliative rather than curative therapies can be considered.

Trans-arterial chemoembolization (TACE) is currently the preferred therapy for HCC unresectable lesions as a palliative, usually or in some cases as a bridging treatment to liver transplantation, with better survival and favorable outcome.<sup>3</sup> More than one session may be needed; otherwise, alternative therapy should be considered.<sup>4</sup>

Several prognostic models have been developed to guide retreatment with TACE in HCC, including the Assessment for Retreatment with TACE (ART) score,<sup>5</sup> the Alpha-Fetoprotein, Barcelona Clinic Liver Cancer, Child-Pugh, and Radiological Response (ABCR) score,<sup>6</sup> and the Size, Number, Alpha-fetoprotein, Child-Pugh, and Objective Radiological Response (SNACOR) score.<sup>7</sup> These models combine clinical, biochemical, and radiological variables to

predict prognosis. To date, no meta-analysis or systematic review has directly compared these scores; however, an individual clinical study<sup>8</sup> has suggested that the SNACOR score may outperform ART and ABCR. Despite this, we chose to focus on evaluating the ART score because it was the first and most widely proposed model specifically designed for retreatment decision-making after TACE, and thus serves as the benchmark against which subsequent scores, including ABCR and SNACOR, have been developed.

The ART score was proposed to predict survival benefit of retreatment, based on three parameters measured just before the second TACE session; i.e., Child-Pugh score, AST, and the radiologic evidence of tumor response after the previous TACE session. Since its release, concerns about its prognostic ability were raised, and the need for additional quantifiable laboratory parameters was urged to improve its assessment.<sup>9,10</sup>

As thrombocytopenia is a common complication in liver cirrhosis<sup>11</sup> and because most HCC patients also suffer from liver cirrhosis, thrombocytopenia was studied as a potential prognostic marker for HCC survival, with results proving its association with worse overall survival.<sup>10,12</sup> This study aimed to investigate the prognostic effect of low platelet count as an additional tool to improve the ART score prognostic ability.

## Patients and Methods

This Cohort retrospective study was conducted at our hospital's multidisciplinary HCC clinic and the Department of Gastroenterology and Hepatology – National Liver Institute – Menoufia University, for all eligible patients with unresectable HCC underwent TACE from January 2017 to January 2021, after approval by the National Liver Institute's institutional review board (IRB).

This study used existing medical records, for which obtaining individual patient consent was impractical. Measures were taken to ensure data confidentiality and security. In accordance with ethical guidelines (eg, the Declaration of Helsinki, ICH-GCP, and applicable local regulations), the requirement for informed consent was waived.

Patients were included if  $\geq 18$  years old, HCC diagnosed by dynamic imaging according to the European Association for the Study of the Liver (EASL) diagnostic criteria,<sup>13</sup> at BCLC stage A or B, with preserved liver function, Child-Pugh class A or B, and received within 90 days two or more TACE sessions.

## Data Collection

The following data were collected within one week of TACE1 (baseline) and TACE2 (follow-up), using the medical records, radiological images, the discharge summaries, and HCC clinic follow-up notes: demographic and clinical information (including Child-Pugh class, and BCLC staging), laboratory data: including alanine transaminase (ALT), aspartate transaminase (AST), serum albumin, total bilirubin, serum alpha-fetoprotein (AFP), and platelet count.

Patients were excluded if received the TACE2 session before liver transplantation as a bridging therapy or after HCC recurrence. In addition, patients were excluded if they showed extrahepatic metastases, the presence of Child-Pugh class C cirrhosis, main portal vein thrombosis, or incomplete data records.

Our triple-phase liver evaluation CT protocol used quad-phasic multidetector CT (Siemens definition A, 20 slices) with no contrast image, then after contrast arterial phase, portal phase, and lastly delayed phase images. According to our TACE preparation protocol, baseline imaging was done within one week before TACE1 for tumor evaluation, including nodules number, uni or bi-lobe, and the nodule(s) size if single (or their diameters sum). Another follow-up image was done one month after TACE1 to evaluate the tumor radiologic response according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST).<sup>14,15</sup> Viable tumors were considered if there was an arterial enhancement with early wash-out, and their size was measured at the delayed phase. As patients with complete response (defined as a complete vanishing of previously measurable tumors after the 1st TACE session) did not need TACE retreatment, the presence of tumor radiologic response was considered in this study if partial response occurred (defined as at least 30% decrease in the summation of target lesions diameters compared to their baseline); while the absent response was considered if there was progressive disease (at least 20% increase of this summation) or stable disease (if summation is between those of partial response and progressive disease).

ART score points were calculated by adding the points of its three parameters, ie, one point if radiological tumor response was absent, 4 points if  $> 25\%$  AST level increased from baseline, and 1.5 or 3 points if 1 or 2 points increased

in Child-Pugh score, respectively,<sup>5</sup> then the patients were classified into 2 groups from 0 to 1.5 points and from 2.5 to 8 points.

The main study outcome was the overall survival (OS), which was determined from the day of the second TACE session until the patient's death or date of data collection (ie, March 2022) for surviving patients.

## Transarterial Chemoembolization (TACE)

The conventional Transarterial chemoembolization (cTACE) was only used for this study population. The technique at our hospital angiography unit was performed percutaneously under conscious sedation by experienced interventional radiologists. Identification of the HCC nodules' feeding vessels was performed first via angiographic study of the coeliac trunk, superior mesenteric, and common hepatic arteries, and then selective cannulation of these vessels was done by microcatheters as far as possible in each tumor lesion.

A lipiodol-doxorubicin emulsion (doxorubicin 20–50 mg with lipiodol 6–20 mL; according to the tumor lesion size and vascularity) was slowly injected; the injected amount was also determined according to the tumor uptake. Lastly, gel foam embolization of the feeding artery was done, and the procedure was finished when the complete block of the feeding branch was achieved.

## Statistical Analysis

Collected data was entered in Microsoft Excel software and then imported into Statistical Package for the Social Sciences (SPSS; version 22.0). Quantitative variables were represented by mean  $\pm$  SD, while qualitative variables were expressed as numbers and percentages. To test differences for significance, the chi-square test ( $X^2$ ) was used for qualitative variables, while the *t*-test was used for quantitative independent groups and ANOVA for multiple groups. P value  $<0.05$  was set for a significant result.

## Study Design

All eligible consecutive patients with unresectable HCC underwent two or more TACE sessions within 90 days were included. The Log rank test was used to assess the effects of all available patient variables (pre-TACE 1 and pre-TACE 2) on OS, to screen for survival risk factors. If significant, a spline-based approach was applied to assess the functional form of the variable on OS. Variables with  $P < 0.05$  in the univariate analysis were entered as candidate variables into stepwise backward Cox regression analysis (coefficients of the Cox regression model were multiplied by 2 and rounded to obtain easy-to-use point numbers facilitating the bedside calculation). The identified risk factors will be used, in addition to the ART score, to establish a modified ART score model (integrated by addition). Survival curves were calculated using the Kaplan–Meier method. Median survival times (OS), and their 95% confidence intervals (CIs) were reported.

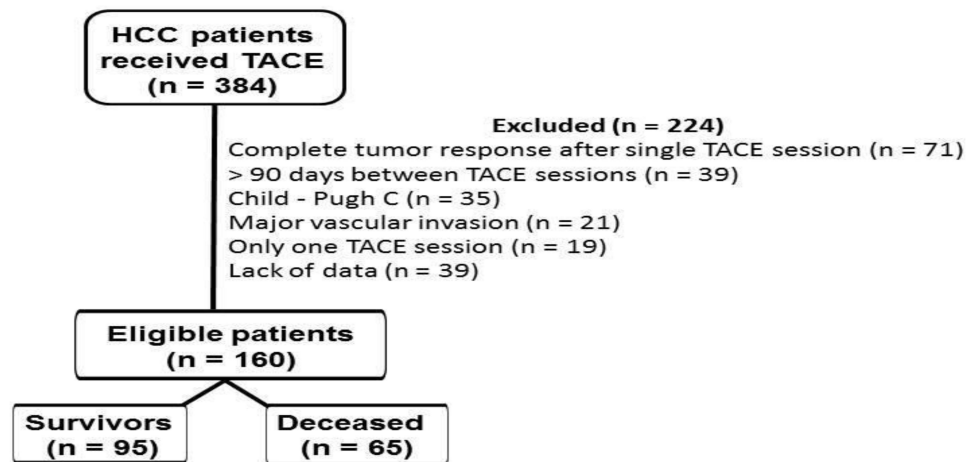
## Result

Out of the 384 screened patients, only 160 patients had received more than one TACE session and met the required inclusion criteria (Figure 1).

No patient received more than two TACE sessions (the mean-time interval between TACE1 and TACE2 was 66 days; range 52–89). There were 141 men and 19 women, with a mean age of  $60.74 \pm 7.18$  years. The vast majority ( $n=154$  patients; 96.3%) were hepatitis C antibody positive, with 83.1% Child-Pugh class A cirrhosis ( $n=133$ ). Ascites were detected in 20 patients (22.5%) at initial diagnosis and were controlled before the initial TACE.

Most of the patients ( $n=97$ ; 60.7%) had multiple focal lesions located in one lobe ( $n=108$ ; 67.5%), with 74 patients (46.3%) BCLC stage A; while 86 patients (53.7%) were BCLC stage B (Table 1).

ART score was calculated for all patients before TACE2: 81 patients (50.6%) scored 0–1.5, while 79 patients (49.4%) scored 2.5–8. Regarding tumor response: 82 patients (51.3%) had a partial response, 42 (26.2%) had stable disease, and 36 (22.5%) had progressive disease, therefore we had 82 and 78 patients with positive and negative radiologic tumor response; respectively (it is worth mentioning that 19.6% of the screened patients had a complete tumor response after the TACE1 session, therefore they were not included in the study).



**Figure 1** Flow chart of patient selection for hepatocellular carcinoma patients who underwent TACE retreatment.

Four patients were changed from Child-Pugh class A stage to Child-Pugh class B, while an increased AST level  $\geq 25\%$  was noticed in 86 patients (53.7%).

Mortality within the study observational period was 71.9% (n = 115), 16.9% survival (n = 27), while 11.2% were lost from the follow-up (n = 18); mean OS was 19.1 months (95% CI: 15.7–23) and mean follow-up was 17.2 months.

**Table 1** Demographic, Clinical, Laboratory, and Tumor Characteristics of Included Patients

Baseline Variable	n (%) or Mean $\pm$ SD	p-value
<b>Male/Female</b>	141 (88.1%) / 19 (11.9%)	0.8
<b>Age (years)</b>	60.7 $\pm$ 7.2	0.7
<b>Tumor lesions:</b>		
$\leq 3$	63 (39.3%)	0.08
$> 3$	97 (60.7%)	
<b>Tumor location:</b>		
Right lobe	77 (48.1%)	0.3
Left lobe	31 (19.4%)	
Both	52 (32.5%)	
<b>Previous HCC treatment</b>		
No treatment	131 (81.9)	0.9
Ethanol injection	15 (9.4)	
Radiofrequency	13 (8.1)	
Microwave	1 (0.6)	
<b>Ascites</b>	20 (22.5%)	0.08
<b>Total bilirubin (mg/dL)</b>	1.09 $\pm$ 0.5	0.1
<b>Serum albumin (g/dL)</b>	3.53 $\pm$ 0.4	0.01
<b>PT-INR</b>	1.21 $\pm$ 0.2	0.05
<b>Hemoglobin (g/dL)</b>	12.45 $\pm$ 1.8	0.6
<b>Platelets (<math>\times 10^3/\text{mL}^3</math>)</b>	129.7 $\pm$ 78.5	0.03
<b>Serum creatinine (mg/dL)</b>	0.92 $\pm$ 0.2	0.1
<b>AST (IU/L)</b>	54.56 $\pm$ 32.6	0.07
<b>AFP (ng/mL)</b>	1620.3 $\pm$ 509.5	0.09
<b>Child-Pugh class: A/B</b>	133 (83.1%) / 27 (16.9%)	0.05
<b>DAA therapy: Yes/No</b>	32 (20%) / 128 (80%)	0.7
<b>BCLC stage: A/B</b>	74 (46.3%) / 86 (53.7%)	0.06

(Continued)

**Table 1** (Continued).

Follow-Up Variable	n (%)	p-value
<b>Tumor response</b>		
Yes (partial response)	82 (51.3%)	<0.001
No (stable & progressive)	78 (48.7%)	
<b>Child-Pugh score increase</b>		
Absent	125 (78.1%)	0.03
One point	31 (19.4%)	
≥ 2 points	4 (2.5%)	
<b>AST increase &gt;25%</b>		
No	74 (46.3%)	0.04
Yes	86 (53.7%)	
<b>Platelet count decrease ≥ 10,000/mL<sup>3</sup></b>		
No	86 (53.7%)	0.01
Yes	74 (46.3%)	
<b>ART score</b>		
0–1.5	81 (50.6%)	0.07
2.5–8	79 (49.4%)	

**Abbreviations:** n, number; SD, standard deviation; HCC, hepatocellular carcinoma; PT-INR, prothrombin time-international normalized ratio; AST, aspartate transaminase; AFP, alpha-fetoprotein; DAAs, direct-acting antivirals; BCLC, Barcelona clinic liver cancer; ART, Assessment for Retreatment with TACE.

Because the original endpoint of overall survival could not be reliably assessed owing to the high rate of loss to follow-up, the analysis was confined to the one-year overall survival rate from the second TACE, which was 59.4% (n = 95), with a mortality rate of 40.6% (n = 65), with no patient lost to follow-up within that one-year period.

The cause of one-year death: acute liver failure (n = 33), sepsis (n = 16), variceal or ulcerative gastrointestinal bleeding (n = 8), tumor rupture (n = 5), and pulmonary embolism (n = 3). ART group 0–1.5 points had 32.9% mortality (n = 29), while group ≥ 2.5 points had a mortality of 43.1% (n = 36); (p = 0.09).

Post-TACE2 complications were reported in 31 patients of the 95 surviving patients (32.6%): 19 patients suffered deterioration of their liver function in the form of jaundice and ascites, 10 patients developed portal vein thrombosis, and 2 patients developed bone metastases.

Because on Log rank test, platelet count decrease after the first TACE was significant, it was tested by spline analysis to investigate its influence on death hazard ratio, which revealed that a decrease of 10,000/mL<sup>3</sup> or more was associated with HR of 1.9 (compared to no platelet count similar decrease), and was associated with poor median OS (no decrease vs decrease: 21.2 vs 17.1 months [95% CI: 17.9–24.5 vs 13.4–20.9 months], P < 0.01) (Table 2).

Univariate analysis was done for all available variables, and results showed that only baseline lower serum albumin and platelet count, besides follow-up absent radiologic tumor response, increase in AST > 25%, increase in Child-Pugh score, and reduction of platelet count by ≥10,000 /mL<sup>3</sup> were associated with poor survival. By multivariate analysis, in addition to the ART score parameters, only platelet count reduction by ≥10,000 /mL<sup>3</sup> was the independent predictor of poor survival (Table 2). Absence of tumor response had the highest risk of survival reduction after TACE2 by 3.12 times than whose tumors responded to TACE, while platelets count reduction by ≥10,000 /mL<sup>3</sup>, Child-Pugh score increase by one or 2 points and AST increase ≥ 25% were at potential risks of 1.89, 1.76, 1.95 and 1.44 times those without similar changes; respectively.

Although the ART score by itself was not significantly associated with survival (p=0.07), all three parameters had a significant relation to survival. For this reason, platelet reduction ≥10,000 /mL<sup>3</sup> was tested in addition to the ART score to establish a modified ART score model, and results showed that the addition of 0 or 3 points for no decrease or decrease of platelets, respectively, produced a much better prognostic score (ART-P score). The new modified score validity for predicting poor survival across the study population was demonstrated by sensitivity and specificity of 75% and 84%,

**Table 2** Prognostic Factors, Univariate and Multivariate Analysis of Treated HCC Patients with TACE

Univariate Analysis				Multivariate Analysis				
Variable	OS (Months)		p	Variable	HR	95% CI	Points	P
	Mean	95% CI						
<b>Baseline albumin</b>				<b>Tumor response</b>				
3.5–5 (g/dL)	21.9	18.9–25.1	0.01	Yes	1		0	<0.001
< 3.5	16.1	12.5–19.7		No	3.12	1.85–5.26	1	
<b>Baseline platelets</b>				<b>AST increase</b>				
150 – 400 ( $\times 10^3/\text{mL}^3$ )	25	20.6–29.5	0.03	No	1		0	0.043
< 150	18.4	15.6–21.2		Yes	1.44	0.88–2.35	4	
<b>Tumor response</b>				<b>Child-Pugh score increase</b>				
Yes	21.8	18.9–24.7	<0.001	Absent	1		0	0.021
No	11	8.2–13.9		One point	1.76	0.97–3.19	1.5	
<b>AST increase</b>				$\geq 2$ points	1.95	0.46–8.14	3	
No	21.9	18.4–25.3	0.04	<b>Platelet count decrease</b>				
Yes	16.9	13.5–20.4		No	1		0	0.012
<b>Child-Pugh score increase</b>				Yes	1.89	1.15–3.12	3	
Absent	20.9	18.1–23.8	0.03					
One point	13.2	9.9–16.4						
$\geq 2$ points	8.6	5.4–11.7						
<b>Platelet count decrease</b>								
No	21.2	17.9–24.5	0.01					
Yes	17.1	13.4–20.9						

**Abbreviations:** OS, Overall survival; CI, confidence interval; HR, hazard ratio; AST, aspartate transaminase.

**Table 3** Area Under the Curve for Assessment for Retreatment with TACE - Platelet (ART-P) Score

Survival Predictor	Best Cutoff	AUC	95% CI	Sensitivity (%)	Specificity (%)	Accuracy (%)
P-ART score	5.38	0.78	0.72–0.85	73	84	76

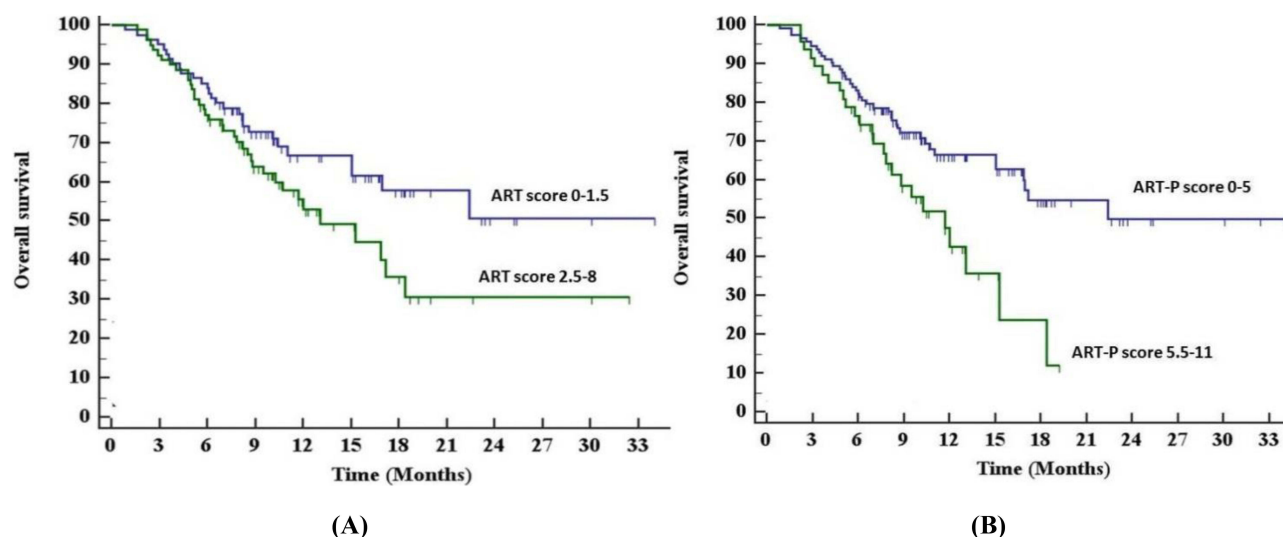
**Abbreviations:** AUC, area under the curve; CI, confidence interval; ART-P, Assessment for Retreatment with TACE – Platelet.

respectively, at a cutoff point of 5.38 points with the area under the ROC curve (95% confidence interval): 0.78 (0.72–0.85) (Table 3).

Next, the P-ART score was calculated for all patients in the cohort ( $n = 160$ ). Two subgroups were identified with recognizably different prognoses, from 0 to 5 points ( $n = 113$ ; 70.6%) and from 5.5 to 11 points (47 patients; 29.3%), with a median OS of 22 vs 11.2 months, respectively ( $P = 0.01$ ). It be noted that the two ART score subgroups (from 0 to 1.5 points and from 2.5 to 8 points) did not show a significant difference in survival (22.3 vs 16.7 months;  $P = 0.07$ ); the Kaplan-Meier survival curve showed that good prognostic subgroups of ART and ART-P scores have 1.76 and 2.09 times the median survival score compared to their poor prognostic subgroups, respectively (Figure 2).

## Discussion

Although TACE is the preferred treatment option for unresectable or intermediate-stage HCC patients, it is hard to embolize all the tumor-feeding vessels, and therefore, not all patients respond to the initial TACE session.<sup>16</sup> Determining the need for more sessions versus switching to other therapies is usually a subjective decision, and prognostic scores like ART were developed to guide this decision. The ART score was originally developed to predict survival for patients going to receive a second TACE session based on training and validation cohorts of Austrian patients. The authors concluded that patients with a score of 0–1.5 could continue to have TACE retreatment with a good prognosis (median



**Figure 2** Kaplan-Meier survival curves comparing ART score (A) and ART-P score (B).

OS was 23.7 months), while patients with a score  $\geq 2.5$  had a poor survival chance (median OS was 6.6 months) which is not encouraging for TACE retreatment, therefore another therapeutic modality should be proposed.<sup>5</sup> On validation, there was a discrepancy between studies that demonstrate its prognostic impact<sup>9,17,18</sup> against those that failed to prove it.<sup>10,19</sup>

On screening for patients who had multiple TACE sessions, we excluded 71 patients (19.6%) who achieved complete tumor response after TACE1, which is against considering TACE as only a palliative treatment for those patients suffering unresectable HCC.

Our study investigated 160 Egyptian HCC cirrhotic patients, mostly due to hepatitis C virus, who received two TACE sessions within 3 months. Overall survival was determined from the day of the TACE2 session until reported death or date of data collection if they were still alive, with a mean follow-up of 17.2 months. One-year survival post-TACE retreatment was 59.4% ( $n = 95$ ), where 51 were from the ART score  $\leq 1.5$  points group (63%) while 44 patients were from the  $\geq 2.5$  points group (55.7%).

Although there was no significant difference between Child-Pugh grade A and grade B or between BCLC stage A and stage B, yet risk of mortality was higher in Child-Pugh grade B and BCLC stage B during analysis ( $p = 0.05$  and  $0.06$ , respectively), which necessitates careful selection for this group of patients. Also, neither previous HCC treatment nor the use of direct-acting antivirals for the eradication of the hepatitis C virus showed a significant relation to survival.

Multivariate analysis results showed that the individual parameters of the ART score were predictors of survival, although the score itself was not statistically significant. Among these, tumor response to the first TACE session was the most significant predictor of survival, OS in positive response vs no response was 21.8 and 11 months, respectively, which is consistent with what was noted before in many studies.<sup>5,6,20</sup>

The second significant predictor in our results was the decline in liver function, measured by the increase in Child-Pugh score (OS in stable score vs one point increase vs two points increase was 20.9, 13.2, and 8.6 months, respectively), which is again in agreement with what other studies reported.<sup>5,6,19</sup>

Regarding AST elevation after TACE1, which was previously commonly reported and was owed to the tumor necrosis and hepatic ischemia because of the high sensitivity of cirrhosis to ischemic changes,<sup>21,22</sup> which can reach up to 10 folds the baseline,<sup>23</sup> although our results showed a survival significant difference between those who had no elevated AST after TACE1 and who had (21.9 vs 16.9 months, respectively;  $p = 0.04$ ), yet its elevation has the least ability on multivariate analysis to independently predict poor survival compared to the other parameters ( $p = 0.043$  vs  $< 0.001$  for tumor response and  $0.021$  for Child-Pugh score increase).

ART score itself, as aforementioned, was not of prognostic value in our study. We explain that, while the score includes important measurable variables which assess the tumor response to the TACE1 and the liver function, in our

opinion, there were limitations that retard its prognostic ability. The used cut-off of 2.5 points to differentiate between good and poor prognostic groups is not suitable in the presence of the highest significance of the AST variable (4 points); ie, if this variable were alone positive, the patient score would be  $\geq 2.5$  points with a poor prognosis. The percentage of our patients with ART scores between 2.5 and 8 is higher compared to the original ART score study (49.4% vs 38%, respectively), which was secondary to the marked AST increase percentage at our study (53.7%) compared to 28.0% at the original study.

This discrepancy can be explained by the different underlying liver disease etiology in our cohort. The baseline mean AST in our cohort was relatively low ( $54.6 \pm 32.6$  U/L), making the ART threshold of a 25% increase easily achievable with only minor fluctuations ( $\sim 14$  U/L). Such rises may reflect expected biological or technical variability in HCV-related cirrhosis rather than true hepatic deterioration. In contrast, in alcohol-related cirrhosis – predominant in the original Austrian cohort – AST levels are usually higher and more stable,<sup>24</sup> so a 25% increase more reliably indicates significant functional decline. Consequently, the AST component of the ART score may lead to “false positive” risk classifications in HCV-predominant populations, as many patients with transient AST elevations regained their baseline liver function before undergoing a second TACE. This difference in disease etiology helps explain the limited prognostic utility of ART in our study compared with alcohol-predominant cohorts.

Since HCC is not a simple disease, ie, the underlying liver cirrhosis with portal hypertension could complicate its assessment and hence its treatment. For instance, thrombocytopenia, a common finding with liver cirrhosis and is known to be associated with poor liver condition and high mortality.<sup>25</sup> After TACE, platelet count fall was reported, which could be secondary to a portal hypertension increase, drug toxicity, or low-grade DIC with platelet consumption as reported before.<sup>26,27</sup> Our selection of an absolute reduction of  $> 10,000/\text{mL}^3$  in platelet count after TACE1 was selected because it was significantly associated with poorer survival (1.9-fold lower) in our analysis, consistent with previous studies.<sup>10,12</sup> This cutoff provided the best balance between sensitivity and specificity, avoided distortion at low platelet counts common in cirrhosis, and offers a uniform clinical floor for concern. As this was a retrospective study, we relied on our standard routine institutional laboratory procedures. Follow-up platelet counts were usually obtained in the morning to reduce diurnal variation and measured on automated analyzers subject to daily quality control and maintenance. Samples with analyzer flags (eg, platelet clumping) were repeated or excluded, thereby minimizing biological and technical variability as far as possible.

Based on this, we proposed a modified ART score (P-ART), incorporating platelet fall  $> 10,000/\text{mL}^3$  and using a higher cut-off value of 5 points instead of 1.5 in the original ART score.

Our proposed P-ART scoring system groups ( $\leq 5$  or  $\geq 5.5$  points) showed better differentiation results between good or poor prognosis compared to the original ART score groups ( $\leq 1.5$  or  $\geq 2.5$  points). Therefore, it could be used to decide if the patient should have a second TACE session or should another treatment modality should be offered.

Furthermore, some experts recommended giving the patient a chance for two TACE sessions at least before the treatment plan is modified.<sup>28</sup> If the decision for the 2nd TACE depended on ART score, in our study, half of our patients could be deprived of their chance for another TACE session, which would affect their response and lower their survival. Conversely, when the platelet count was included in the ART score, the majority of patients (70.6%) received a P-ART score of 0–5, while just 29.3% received a score of 5.5–11, with a substantially better OS (22 vs 11.2 months, respectively;  $p = 0.01$ ).

The strengths of the present study include the large sample size and the incorporation of post-TACE thrombocytopenia into the ART score, as thrombocytopenia is a well-recognized predictor of outcome in patients with liver cirrhosis in general and HCC in particular. The resulting P-ART score represents a modification of the original ART model by integrating platelet count, a simple and routinely available marker of liver reserve and portal hypertension. While the ABCR score expanded upon ART by adding AFP and BCLC stage, and the SNACOR score focused on tumor burden, AFP, and liver function, our P-ART score preserves the simplicity of ART while enhancing prognostic performance. It may therefore serve as a complementary tool to these existing models, especially in clinical settings where a practical and easily applicable retreatment score is required.

Many major limitations could be found: (1) Our cohort was almost entirely composed of patients with HCV-related cirrhosis (96.3%), which limits direct generalizability to other populations. Because the dynamics of AST and platelet changes differ across disease etiologies, the prognostic performance of the P-ART score may vary in alcohol-related,

HBV-related, or NASH-related cirrhosis. External validation in diverse cohorts is therefore necessary before applying the P-ART score broadly. (2) Conventional TACE was only administered to our patients, so our findings may not suit patients who received TACE-drug eluting beads. (3) This study is a single-center study; however, our study included a relatively large number of patients in a major tertiary referral center. (4) Reliability and generalizability should be further validated in independent, multicenter cohorts.

## Conclusion

Our proposed P-ART score could be an effective and simple tool in predicting survival for intermediate-stage HCC patients after their first TACE session, considering that patients who scored  $\leq 5$  points live double times long as those who scored  $\geq 5.5$  points. The score also supports the appropriate selection for the need to repeat TACE or switch to other therapeutic modalities, although it still needs further validation.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This research received no external funding.

## Disclosure

There are no conflicts of interest.

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