


# Risk Stratification and Contemporary Predictors of Survival in Hepatocellular Carcinoma Treated With Transarterial Radioembolization

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## Abstract

**Background:** Identifying risk factors for poor outcomes in patients with hepatocellular carcinoma (HCC) treated with transarterial radioembolization (TARE) can aid in developing personalized management strategies, such as the early use of immune checkpoint inhibitors (ICIs).

**Methods:** In this retrospective review, we included HCC patients who received TARE at The Ohio State University Comprehensive Cancer Center from January 1, 2015, to August 30, 2022. The Kaplan-Meier method was used to estimate progression-free survival (PFS) and overall survival (OS). Cox proportional hazard analysis was conducted to find the independent predictors of PFS and OS.

**Results:** We included 141 patients (median age of 65 years; 80% Caucasian; 80% male). Better PFS was associated with higher albumin (alb) (hazard ratio (HR) = 0.58, P = 0.005) and lower total bilirubin (T bili) levels (HR = 0.70, P = 0.034). Better OS was associated with a history of ablation (HR = 0.35, P < 0.001) and higher pre-TARE alb (HR = 0.63, P = 0.01); OS was worse in those with hepatic encephalopathy (HR = 2.01, P = 0.006). There was a notable

trend toward worse OS in patients with ascites (HR = 1.71, P = 0.06) and metabolic-dysfunction-associated fatty liver disease (MAFLD)-associated HCC (HR = 1.86, P = 0.08). The receipt of ICI therapy was associated with a significantly better OS (P = 0.016), with a median OS of 1,102 days (95% confidence interval (CI): 884 - 1,509) compared to 614 days (95% CI: 493 - 829).

**Conclusion:** We present pretreatment risk factors (low alb, high T bili, MAFLD, hepatic encephalopathy, and ascites) that can predict poor outcomes in HCC patients treated with TARE. Preemptively treating such high-risk patients with ICI could improve their outcomes.

**Keywords:** Risk stratification; Hepatocellular carcinoma; Transarterial radioembolization; TARE; Liver function; Y90

## Introduction

Hepatocellular carcinoma (HCC) is the most common liver cancer, accounting for more than 80% of primary liver tumors with a poor 5-year survival rate (about 18%), making it the third leading cause of cancer-related deaths worldwide [1-4]. Managing HCC necessitates collaboration between various disciplines, including hepatology, radiation oncology, nuclear medicine medical oncology, surgery, and interventional radiology. Many societies propose risk stratification guidelines for HCC treatment, primarily using those from the Barcelona Clinic Liver Cancer (BCLC) and the American Association for the Study of Liver Diseases (AASLD) [5, 6]. Clear guidelines for choosing the best locoregional therapies (LRTs) among transarterial chemoembolization (TACE), stereotactic body radiotherapy (SBRT), and transarterial radioembolization (TARE) for intermediate and non-metastatic advanced HCCs are lacking. It is often dependent on available expertise at the institution where the patient is treated.

TARE or selective internal radiation therapy (SIRT) refers to the deployment of <sup>90</sup>Yttrium (Y90)-labeled microspheres directly into the tumor through the hepatic artery via a catheter [7, 8]. Microspheres used for TARE can be glass (TheraSphere, BTG International Group, London, UK) or resin (SIR-Spheres, Sirtex Medical Ltd, New South Wales, Australia) [9]. TARE was part of the AASLD guidelines (2018) and the National Com-

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prehensive Cancer Network (NCCN) guidelines for quite some time but was featured in the BCLC guidelines only in the latest update (2022) [6, 10]. The economic burden limits its use in Asian countries even though it is part of the recommended guidelines [11]. In recent years, TARE has become a good option for LRT in the United States, supported by increasing evidence of its benefits and acceptable toxicity profiles for patients with early-to-intermediate-stage HCC with adequate liver function [12-14]. It is used with curative intent (segmentectomy) to deliver ablative doses to smaller tumors or for local disease control (lobectomy). However, its benefit over systemic therapy, such as tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs), remains unclear in advanced tumors, as demonstrated in trials (SORAMIC, SARAH, and SIRveNIB) and limited retrospective studies [15-19].

In a recent study by Chen et al involving 413 patients with unresectable HCC, TARE microspheres achieved a median overall survival (OS) of 20.9 months (95% confidence interval (CI): 18.2 - 24.0). Notably, 17% of patients (n = 70) were able to undergo curative treatments following successful tumor downstaging. This subgroup exhibited a markedly improved median OS of 79.7 months (95% CI: 40.4 to not estimable), highlighting the potential of TARE as a bridge to curative therapy [20]. Additionally, recently published limited real-world data reported clinicopathological risk factors such as poor liver function (Child-Pugh B or C, low albumin, high total bilirubin (T bili), albumin-bilirubin (ALBI) grade 2 or higher), large tumor size, portal vein tumor thrombus (PVTT), high alfa-fetoprotein (AFP), and ascites as predictors of poor outcomes in patients with HCC treated with TARE [21-34]. The majority of these studies predated the era of ICI use in HCC. Furthermore, there are limited real-world data in the contemporary treatment era that integrate these risk factors with emerging systemic therapies involving ICIs.

In this retrospective study, we aimed to characterize pre-treatment clinical predictors of outcomes (progression-free survival (PFS) and OS) in a contemporary cohort of patients with HCC treated with TARE at a large academic medical center. We also explored the impact of subsequent ICI therapy on survival outcomes and evaluated less commonly studied etiologies such as metabolic-dysfunction-associated fatty liver disease (MAFLD). Our findings offer new insights into risk stratification and raise the possibility that early ICI integration in select high-risk patients may improve outcomes.

## Materials and Methods

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of The Ohio State University (OSU) (protocol number 2022C0177, approval date 12/11/2022). The requirement for informed consent was waived due to the retrospective nature of the study, which ensures no compromise to patient welfare or rights.

### Patient selection and chart review

Patient electronic medical records (EMRs) from the OSU

Wexner Medical Center (OSUWMC) from January 1, 2015, to August 30, 2022, were identified using the HCC diagnosis code from the International Statistical Classification of Diseases (ICD) (versions 9 and 10) and the current procedural terminology (CPT) procedure code for TARE. All eligible patients were discussed in our institutional multidisciplinary liver tumor board (LTB) meeting, and a unanimous decision was made to offer TARE. Patients included in this study were diagnosed with HCC based on imaging or biopsy and received at least one session of TARE during the study period. We excluded patients with HCC who underwent TARE and then received liver transplants to avoid competing risks. Planned staged procedures (without any disease progression after the first TARE session) were taken as one procedure for analysis.

Data extracted from the EMR included demographics (age, race, and gender), tumor-related clinicopathological data (etiology of cirrhosis such as MAFLD, viral hepatitis, autoimmune liver disease, etc.), smoking history, alcohol use history, ascites, hepatic encephalopathy (HE), and prior and post-progression therapy received including LRTs and systemic therapy. We also recorded HCC characteristics, including location, size and number of lesions, PVTT, and relevant laboratory data (T bili, albumin, AFP at the time of diagnosis, and international normalized ratio (INR)). Other treatments received (LRTs and systemic therapy) before and after TARE were also retrieved.

### Outcomes

The primary outcomes were PFS, OS, and OS specific to TARE (OS-TARE). PFS was defined as the time between the TARE procedure (the first, if the patient had multiple procedures) and disease progression noted on the scans, death, or the last date of follow-up. OS was defined as the interval from the date of diagnosis to the date of death or the last follow-up date. OS-TARE was defined as the interval from the date of the first TARE procedure to the date of death or the last date of follow-up. This distinction between OS and OS-TARE was made to isolate the survival benefit attributable to TARE and subsequent therapies (OS-TARE), while also accounting for the influence of prior treatments on overall survival from diagnosis (OS).

Post-TARE contrast-enhanced imaging results, in the form of either computed tomography (CT) or magnetic resonance imaging (MRI) reports available after the procedure, were reviewed in the LTB meeting to assess the response to the procedure using modified Response Evaluation Criteria in Solid Tumors (mRECIST). Most patients underwent CT scans, and few had MRIs. We also reported the impact of TARE on albumin, T bili, and Child-Pugh score (during follow-up to assess treatment response).

### Statistical analysis

A statistical analysis evaluated the potential association between the exposures of interest (gender, race, baseline laboratory values, and clinical data) and different survival outcomes such as PFS, OS, and OS-TARE. Patients who did not die were

censored at the date of the last follow-up.

The Kaplan-Meier method was employed to estimate PFS, OS, and OS-TARE. Univariate and Cox proportional hazard analyses assessed the association between exposures and various survival outcomes (PFS, OS, and OS-TARE). The log-rank test was utilized for categorical variables, and the Cox proportional hazard was used for continuous variables. A paired *t*-test was used to compare the pre- and post-TARE changes in serum albumin, T bili, and Child-Pugh scores.

## Results

### Baseline characteristics

Our initial EMR search resulted in 175 patients; we excluded 20 patients with colorectal metastasis in the liver and 14 patients with HCC who proceeded to have liver transplants, leaving 141 patients eligible for this study. Baseline characteristics are shown in Table 1. Most of our patients were Caucasian (80%), and males (80%) dominated the study population. The group's median age was 65 (range 49 - 88) years. Ascites (25%) and HE (29%) were the two most common decompensations of cirrhosis. The majority ( $n = 122$ ; 87%) of the patients had one session of TARE followed by two sessions ( $n = 17$ ; 12%) and three sessions ( $n = 2$ ; 1%). TARE was the initial therapy in 50 patients (35.46%). However, the rest of the patients received other LRTs, including TACE ( $n = 59$ ; 41.84%), ablation (35; 24.82%), surgery ( $n = 18$ ; 12.77%), SBRT ( $n = 7$ ; 4.97%), and systemic therapy (12; 8.52%) prior to TARE. Most of the study patients had one HCC lesion ( $n = 65$ ; 46.10%) followed by two lesions ( $n = 30$ ; 21.28%). Interestingly, HCC tumor sizes were  $\leq 3$  cm and  $> 3$  cm in 56 (40%) and 79 (56%) patients, respectively, with PVTT in 24 patients and the majority having Child-Pugh score A ( $n = 105$ ; 74.47%).

Among those who underwent TARE, only 39 patients were on ICIs. Five patients received TARE after HCC progression while on ICIs (pre-TARE ICI group), and 34 received ICIs after HCC progression on TARE (post-TARE ICI group). One patient in the pre-TARE group continued ICI treatment after TARE. Around 65% of the study population had TARE as the second or third line of management. The most common ICI used was a combination of atezolizumab and bevacizumab in 20 (51%) patients, followed by nivolumab alone in 19 (49%).

### Factors impacting PFS

The median PFS of our patients was 129 days (CI: 105 - 171 days). Table 2 outlines the unadjusted (univariate) and adjusted (multivariate) hazard ratios (HRs) for various factors influencing PFS in the study population.

Lower serum bilirubin (HR = 0.70, CI: 0.50 - 0.97,  $P = 0.034$ ) and higher serum albumin (HR: 0.58, CI: 0.40 - 0.85,  $P = 0.005$ ) were the independent predictors of PFS among patients treated with TARE. Patients with MAFLD (HR = 2.13, CI: 1.10 - 4.13,  $P = 0.06$ ) and prior TACE (HR = 1.38,  $P = 0.08$ ) had an increased risk of progression, though these trends did not reach

statistical significance in multivariate analysis. Similarly, ascites and HE suggested an increased progression risk but lacked statistical significance in the adjusted model. Notably, HCC with left PVTT was associated with a significant reduction in progression risk in univariate analysis (HR = 0.22,  $P = 0.038$ ). It is important to note that we studied the impact of the specific location of PVTT (left, right, and main portal vein) for univariate analysis only for PFS, OS, and OS-TARE. The presence of PVTT (yes vs. no) was used for multivariate analysis.

### Impact of ICI on PFS

Most patients in our study did not receive ICI before TARE. Their PFS was worse than that of the small pre-TARE ICI group (median PFS of 128 days (95% CI: 106 - 171 days) vs. (393 days (95% CI: 100 to not evaluable (NE))), suggesting that ICI use before TARE might delay disease progression significantly. However, the wide CI and the lower bound starting at 100 days suggest substantial variability among patients. The impact of ICI before TARE had no significant impact on PFS in univariate analysis (HR = 0.64, 95% CI: 0.26 - 1.58,  $P = 0.3$ ) or multivariate analysis (HR = 0.90, 95% CI: 0.32 - 2.51,  $P = 0.8$ ).

### Factors impacting OS-TARE

The group's median OS-TARE is 311 days (CI: 248 - 438 days). We outlined the factors influencing TARE (unadjusted (univariate) and adjusted (multivariate) HRs) (Table 3).

Higher albumin levels pre-TARE were significantly correlated with improved OS-TARE in both analyses. Conversely, a history of MAFLD or HE were associated with worse OS-TARE outcomes in both analyses. Additional findings revealed that a history of left PVTT was associated with improved OS-TARE in univariate analysis. While ascites at the time of TARE appeared to impact OS-TARE in univariate analysis negatively, this association was not statistically significant in the multivariate model when controlling for other factors.

### The influence of ICI on OS-TARE

Patients who received ICI treatment (pre- or post-TARE groups) had a better ( $P = 0.0005$ ) OS-TARE than those who did not receive ICIs (697 days (95% CI: 609 - 1,022 days) vs. 226 days (95% CI: 200 - 308 days)) (Fig. 1a). The post-TARE ICI group had a significantly ( $P = 0.0026$ ) better OS-TARE than the pre-TARE ICI group (703 days (95% CI: 609 - 1,022 days) vs. 678 days (95% CI: 393 - NE)) (Fig. 1b). ICI post-TARE was associated with improved OS-TARE in both univariate and multivariate analyses.

### Factors impacting OS

The study population's OS was 765 days (CI: 614 - 941 days). Table 4 provides a comprehensive overview of both univariate

**Table 1.** Baseline Characteristics of the Study Population (N = 141)

| Characteristic                       | n (%)                    |
|--------------------------------------|--------------------------|
| Median age of diagnosis              | 65 years (range 49 - 88) |
| Race                                 |                          |
| White                                | 113 (80.14%)             |
| African American                     | 22 (15.60%)              |
| Other                                | 6 (4.26%)                |
| Sex                                  |                          |
| Male                                 | 113 (80.14%)             |
| Female                               | 28 (19.86%)              |
| History of hepatitis B infection     | 8 (5.67%)                |
| History of hepatitis C infection     | 72 (51.06%)              |
| History of alcoholic liver cirrhosis | 110 (78.01%)             |
| History of MAFLD                     | 17 (12.06%)              |
| History of DM                        | 50 (35.46%)              |
| Ascites at diagnosis                 | 35 (24.82%)              |
| HE at diagnosis                      | 41 (29.08%)              |
| Smoking history                      |                          |
| Active                               | 52 (37%)                 |
| Former                               | 53 (38%)                 |
| Never                                | 36 (25%)                 |
| Alcohol use                          |                          |
| Active                               | 52 (37%)                 |
| Never                                | 65 (46%)                 |
| Former                               | 24 (17%)                 |
| Number of TARE procedures            |                          |
| 1                                    | 122 (87%) <sup>a</sup>   |
| 2                                    | 17 (12%)                 |
| 3                                    | 2 (1%)                   |
| Therapy before TARE                  |                          |
| None                                 | 50 (35.46%)              |
| TACE                                 | 59 (41.84%)              |
| Ablation                             | 35 (24.82%)              |
| Surgery                              | 18 (12.77%)              |
| SBRT                                 | 7 (4.97%)                |
| Systemic therapy                     | 12 (8.52%)               |
| Number of HCC lesions                |                          |
| 1                                    | 65 (46.10%)              |
| 2                                    | 30 (21.28%)              |
| 3                                    | 16 (11.35%)              |
| > 3                                  | 30 (21.28%)              |
| Size of HCC lesions                  |                          |
| ≤ 3 cm                               | 56 (40%)                 |
| > 3 cm                               | 79 (56%)                 |
| Not measurable                       | 6 (4%)                   |

**Table 1.** Baseline Characteristics of the Study Population (N = 141) - (continued)

| Characteristic                                    | n (%)                      |
|---|----------------------------|
| HCC in liver lobes                                |                            |
| Right lobe  | 66 (46.81%)                |
| Both lobes  | 47 (33.33%)                |
| Left lobe   | 23 (16.31%)                |
| Undefined   | 5 (3.55%)                  |
| PVTT  |                            |
| None  | 107 (75.89%)               |
| Main portal vein                                  | 14 (9.93%)                 |
| Right portal vein                                 | 9 (6.38%)                  |
| Present but location is unclear                   | 7 (4.97%)                  |
| Left portal vein                                  | 4 (2.84%)                  |
| Child-Pugh score                                  |                            |
| A   | 105 (74.47%)               |
| B   | 34 (24.11%)                |
| C   | 2 (1.42%)                  |
| Baseline <sup>b</sup> T bili (mg/dL; median/mean) | 1/1.05                     |
| Baseline <sup>b</sup> albumin (g/dL; median/mean) | 4/3.76                     |
| Baseline <sup>b</sup> INR (median/mean)           | 1/1.09                     |
| Baseline <sup>b</sup> AFP (ng/dL; median/mean)    | 26.5 (1 - 78,314)/1,688.10 |
| TKI use   |                            |
| No  | 107 (76%)                  |
| Post-TARE   | 29 (21%)                   |
| Pre-TARE  | 5 (3%)                     |
| TKI drugs used                                    |                            |
| Sorafenib   | 21 (14.89%)                |
| Lenvatinib  | 16 (11.35%)                |
| Cabozantinib                                      | 2 (1.42%)                  |
| ICI use   |                            |
| No-ICI group                                      | 102 (72.34%)               |
| Post-TARE ICI group                               | 34 (24.11%)                |
| Pre-TARE ICI group                                | 5 (3.55%)                  |
| ICI drugs used                                    |                            |
| Nivolumab   | 19 (49%)                   |
| Atezolizumab and bevacizumab                      | 20 (51%)                   |

<sup>a</sup>24 patients had two-staged TAREs. <sup>b</sup>Before first TARE. AFP: alpha-fetoprotein; DM: diabetes mellitus; HCC: hepatocellular carcinoma; HE: hepatic encephalopathy; ICI: immune checkpoint inhibitor; INR: international normalized ratio; MAFLD: metabolic-dysfunction-associated fatty liver disease; PVTT: portal vein tumor thrombus; SBRT: stereotactic body radiotherapy; TACE: transarterial chemoembolization; TARE: transarterial radioembolization; T bili: total bilirubin; TKI: tyrosine kinase inhibitor.

and multivariate HRs for various factors affecting OS.

Demographic factors such as age and race did not significantly influence OS in adjusted models. MAFLD substantially increased mortality risk in the univariate model (HR = 2.23, P = 0.004) and remained a strong risk factor in the adjusted model (HR = 1.86, P = 0.082). HE significantly increased mortality risk in both univariate (HR = 1.61, P = 0.016) and multivariate

(HR = 2.01, P = 0.006) analyses, indicating a critical impact on survival. Ascites increased mortality risk, with multivariate analysis showing HR = 1.71 (P = 0.065), approaching statistical significance. TARE used in patients with a history of ablation had a better outcome (univariate HR = 0.50, P < 0.001; multivariate HR = 0.35, P < 0.001), highlighting its benefit in this population. Higher albumin levels were significantly asso-

**Table 2.** Factors Impacting PFS in the Study Population Treated With TARE

| Factor                                | Univariate |             |         | Multivariate |             |         |
|---------------------------------------|------------|-------------|---------|--------------|-------------|---------|
|                                       | HR         | 95% CI      | P-value | Adjusted HR  | 95% CI      | P-value |
| ICI used before TARE                  |            |             |         |              |             |         |
| No                                    | -          | -           | -       | -            | -           | -       |
| Yes                                   | 0.64       | 0.26 - 1.58 | 0.3     | 0.90         | 0.32 - 2.51 | 0.8     |
| Age at diagnosis                      | 0.99       | 0.97 - 1.02 | 0.6     | 0.99         | 0.97 - 1.02 | 0.7     |
| Race                                  |            |             |         |              |             |         |
| White                                 | -          | -           | -       | -            | -           | -       |
| African American/Black                | 0.86       | 0.53 - 1.39 | 0.5     | 0.94         | 0.54 - 1.65 | 0.8     |
| Other                                 | 0.59       | 0.22 - 1.61 | 0.3     | 0.45         | 0.15 - 1.34 | 0.2     |
| Hepatitis C                           |            |             |         |              |             |         |
| No                                    | -          | -           | -       | -            | -           | -       |
| Yes                                   | 0.91       | 0.65 - 1.29 | 0.6     | 0.98         | 0.62 - 1.55 | >0.9    |
| MAFLD                                 |            |             |         |              |             |         |
| No                                    | -          | -           | -       | -            | -           | -       |
| Yes                                   | 1.64       | 0.98 - 2.76 | 0.061   | 1.56         | 0.84 - 2.89 | 0.2     |
| SBRT                                  |            |             |         |              |             |         |
| No                                    | -          | -           | -       | -            | -           | -       |
| Yes                                   | 1.05       | 0.59 - 1.87 | 0.9     | 0.97         | 0.52 - 1.82 | > 0.9   |
| TACE                                  |            |             |         |              |             |         |
| No                                    | -          | -           | -       | -            | -           | -       |
| Yes                                   | 1.38       | 0.96 - 2.00 | 0.081   | 1.40         | 0.91 - 2.15 | 0.13    |
| Number of lesions                     |            |             |         |              |             |         |
| Single                                | -          | -           | -       | -            | -           | -       |
| > 1                                   | 1.24       | 0.87 - 1.75 | 0.2     | 1.12         | 0.76 - 1.64 | 0.6     |
| Size of the lesions                   |            |             |         |              |             |         |
| ≤ 3 cm                                | -          | -           | -       | -            | -           | -       |
| > 3 cm or not measurable              | 1.20       | 0.84 - 1.71 | 0.3     | 1.22         | 0.82 - 1.79 | 0.3     |
| Baseline <sup>a</sup> total bilirubin | 0.97       | 0.75 - 1.25 | 0.8     | 0.70         | 0.50 - 0.97 | 0.034*  |
| Baseline <sup>a</sup> albumin         | 0.63       | 0.48 - 0.84 | 0.002*  | 0.58         | 0.40 - 0.85 | 0.005*  |
| Active smoking                        |            |             |         |              |             |         |
| No                                    | -          | -           | -       | -            | -           | -       |
| Yes                                   | 0.97       | 0.68 - 1.39 | 0.9     | 0.89         | 0.59 - 1.33 | 0.6     |
| Active alcohol                        |            |             |         |              |             |         |
| No                                    | -          | -           | -       | -            | -           | -       |
| Yes                                   | 1.15       | 0.80 - 1.64 | 0.5     | 1.28         | 0.85 - 1.91 | 0.2     |
| Ascites                               |            |             |         |              |             |         |
| No                                    | -          | -           | -       | -            | -           | -       |
| Yes                                   | 1.54       | 1.03 - 2.28 | 0.034*  | 1.36         | 0.82 - 2.24 | 0.2     |
| HE                                    |            |             |         |              |             |         |
| No                                    | -          | -           | -       | -            | -           | -       |
| Yes                                   | 1.46       | 1.00 - 2.12 | 0.048*  | 1.29         | 0.84 - 1.96 | 0.2     |
| PVTT - absent vs. present             |            |             |         |              |             |         |
| Absent                                | -          | -           | -       | -            | -           | -       |

**Table 2.** Factors Impacting PFS in the Study Population Treated With TARE - (continued)

| Factor                               | Univariate |             |         | Multivariate |             |         |
|--------------------------------------|------------|-------------|---------|--------------|-------------|---------|
|                                      | HR         | 95% CI      | P-value | Adjusted HR  | 95% CI      | P-value |
| Present                              | 0.72       | 0.47 - 1.09 | 0.12    | 0.83         | 0.51 - 1.35 | 0.4     |
| PVTT - specific                      |            |             |         |              |             |         |
| None                                 | -          | -           | -       | -            | -           | -       |
| Left portal vein                     | 0.22       | 0.05 - 0.92 | 0.038*  | -            | -           | -       |
| Main portal vein                     | 0.87       | 0.48 - 1.55 | 0.6     | -            | -           | -       |
| Present, but the location is unclear | 1.29       | 0.57 - 2.96 | 0.5     | -            | -           | -       |
| Right portal vein                    | 0.66       | 0.32 - 1.36 | 0.3     | -            | -           | -       |

<sup>a</sup>Baseline: before TARE. \*Significant P values. CI: confidence interval; HE: hepatic encephalopathy; HR: hazard ratio; ICI: immune checkpoint inhibitor; MAFLD: metabolic-dysfunction-associated fatty liver disease; PVTT: portal vein tumor thrombus; SBRT: stereotactic body radiotherapy; TACE: transarterial chemoembolization; TARE: transarterial radioembolization.

**Table 3.** Factors Impacting TARE-Specific OS in the Study Population

| Factor                   | Univariate |             |         | Multivariate |             |          |
|--------------------------|------------|-------------|---------|--------------|-------------|----------|
|                          | HR         | 95% CI      | P-value | Adjusted HR  | 95% CI      | P-value  |
| ICI use                  |            |             |         |              |             |          |
| No                       | -          | -           | -       | -            | -           | -        |
| Pre-TARE                 | 0.42       | 0.15 - 1.16 | 0.10    | 0.61         | 0.17 - 2.18 | 0.6      |
| Post-TARE                | 0.50       | 0.32 - 0.78 | 0.002*  | 0.37         | 0.23 - 0.61 | < 0.001* |
| Age at diagnosis         | 1.00       | 0.98 - 1.02 | > 0.9   | 1.01         | 0.98 - 1.04 | 0.6      |
| Race                     |            |             |         |              |             |          |
| White                    | -          | -           | -       | -            | -           | -        |
| African American/Black   | 0.78       | 0.47 - 1.30 | 0.3     | 0.84         | 0.47 - 1.50 | 0.6      |
| Other                    | 0.70       | 0.26 - 1.92 | 0.5     | 0.63         | 0.20 - 1.96 | 0.4      |
| Hepatitis C              |            |             |         |              |             |          |
| No                       | -          | -           | -       | -            | -           | -        |
| Yes                      | 0.93       | 0.65 - 1.34 | 0.7     | 1.03         | 0.64 - 1.67 | 0.9      |
| MAFLD                    |            |             |         |              |             |          |
| No                       | -          | -           | -       | -            | -           | -        |
| Yes                      | 1.86       | 1.09 - 3.19 | 0.023*  | 2.13         | 1.10 - 4.13 | 0.026*   |
| SBRT                     |            |             |         |              |             |          |
| No                       | -          | -           | -       | -            | -           | -        |
| Yes                      | 0.66       | 0.34 - 1.26 | 0.2     | 0.63         | 0.30 - 1.34 | 0.2      |
| TACE                     |            |             |         |              |             |          |
| No                       | -          | -           | -       | -            | -           | -        |
| Yes                      | 1.20       | 0.82 - 1.75 | 0.3     | 1.28         | 0.78 - 2.11 | 0.3      |
| Number of lesions        |            |             |         |              |             |          |
| Single                   | -          | -           | -       | -            | -           | -        |
| Multiple                 | 1.35       | 0.93 - 1.95 | 0.11    | 1.29         | 0.85 - 1.95 | 0.2      |
| Size of the lesions      |            |             |         |              |             |          |
| ≤ 3 cm                   | -          | -           | -       | -            | -           | -        |
| > 3 cm or not measurable | 0.98       | 0.88 - 1.42 | > 0.9   | 0.96         | 0.82 - 1.49 | 0.9      |

**Table 3.** Factors Impacting TARE-Specific OS in the Study Population - (continued)

| Factor                                | Univariate |             |          | Multivariate |             |          |
|---------------------------------------|------------|-------------|----------|--------------|-------------|----------|
|                                       | HR         | 95% CI      | P-value  | Adjusted HR  | 95% CI      | P-value  |
| Baseline <sup>a</sup> total bilirubin | 1.18       | 0.92 - 1.52 | 0.2      | 0.85         | 0.61 - 1.18 | 0.3      |
| Baseline <sup>a</sup> albumin         | 0.62       | 0.47 - 0.82 | < 0.001* | 0.55         | 0.38 - 0.80 | 0.002*   |
| Active smoking                        |            |             |          |              |             |          |
| No                                    | -          | -           | -        | -            | -           | -        |
| Yes                                   | 1.19       | 0.82 - 1.74 | 0.4      | 1.05         | 0.67 - 1.63 | 0.8      |
| Active alcohol                        |            |             |          |              |             |          |
| No                                    | -          | -           | -        | -            | -           | -        |
| Yes                                   | 1.04       | 0.71 - 1.53 | 0.8      | 1.28         | 0.83 - 1.96 | 0.3      |
| Ascites                               |            |             |          |              |             |          |
| No                                    | -          | -           | -        | -            | -           | -        |
| Yes                                   | 1.86       | 1.23 - 2.81 | 0.003*   | 1.54         | 0.89 - 2.66 | 0.13     |
| HE                                    |            |             |          |              |             |          |
| No                                    | -          | -           | -        | -            | -           | -        |
| Yes                                   | 2.10       | 1.43 - 3.09 | < 0.001* | 2.40         | 1.49 - 3.88 | < 0.001* |
| Surgery                               |            |             |          |              |             |          |
| No                                    | -          | -           | -        | -            | -           | -        |
| Yes                                   | 0.81       | 0.47 - 1.39 | 0.4      | 1.21         | 0.62 - 2.37 | 0.6      |
| Ablation                              |            |             |          |              |             |          |
| No                                    | -          | -           | -        | -            | -           | -        |
| Yes                                   | 1.00       | 0.67 - 1.48 | > 0.9    | 0.91         | 0.55 - 1.49 | 0.7      |
| PVTT - absent vs. present             |            |             |          |              |             |          |
| Absent                                | -          | -           | -        | -            | -           | -        |
| Present                               | 0.69       | 0.44 - 1.07 | 0.10     | 0.71         | 0.41 - 1.25 | 0.2      |
| PVTT - specific vein                  |            |             |          |              |             |          |
| None                                  | -          | -           | -        | -            | -           | -        |
| Left portal vein                      | 0.21       | 0.05 - 0.87 | 0.031*   | -            | -           | -        |
| Main portal vein                      | 1.22       | 0.66 - 2.19 | 0.5      | -            | -           | -        |
| Present, but location is unclear      | 0.53       | 0.17 - 1.67 | 0.3      | -            | -           | -        |
| Right portal Vein                     | 0.63       | 0.29 - 1.37 | 0.2      | -            | -           | -        |

<sup>a</sup>Baseline: before TARE. \*Significant P values. CI: confidence interval; HE: hepatic encephalopathy; HR: hazard ratio; ICI: immune checkpoint inhibitor; MAFLD: metabolic-dysfunction-associated fatty liver disease; PVTT: portal vein tumor thrombus; SBRT: stereotactic body radiotherapy; TACE: transarterial chemoembolization; TARE: transarterial radioembolization.

ciated with better survival outcomes (multivariate HR = 0.63, P = 0.019), emphasizing the importance of nutritional and liver function status in patient prognosis.

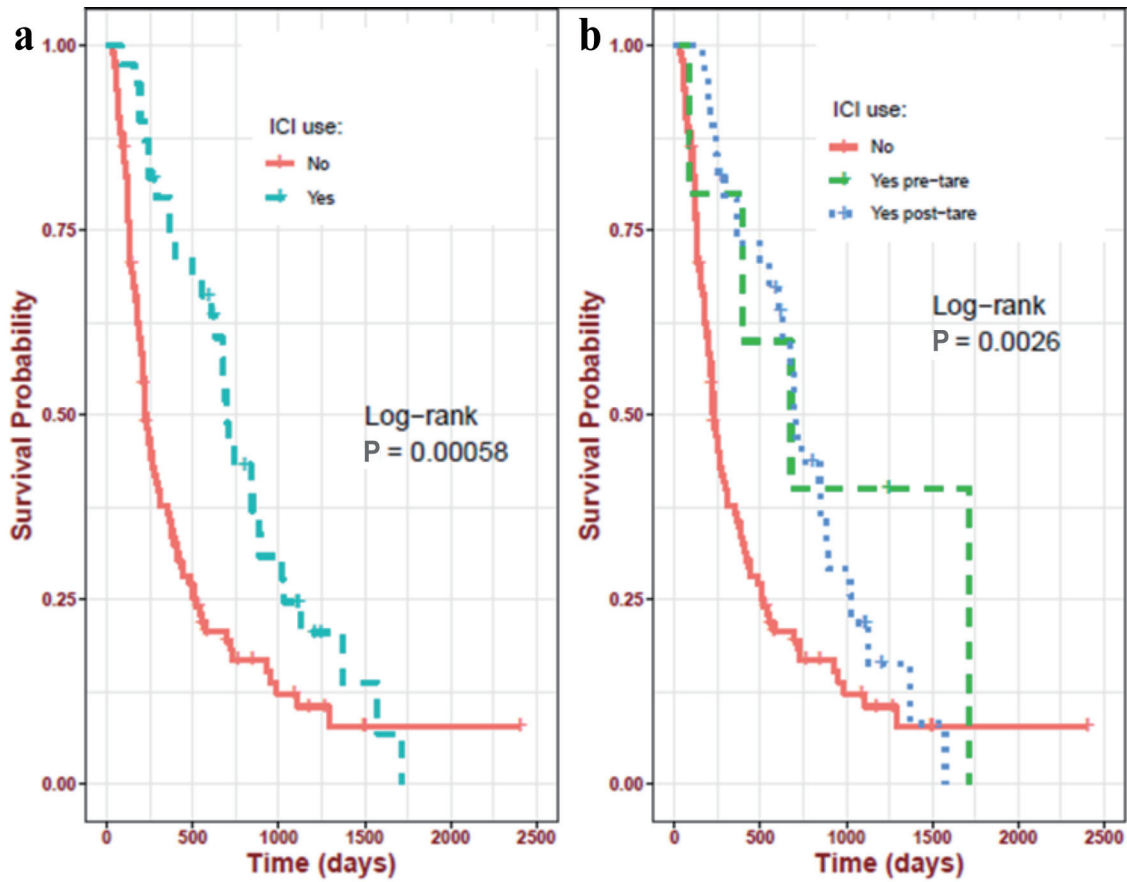
### The influence of ICI on OS

Median OS significantly (P = 0.016) improved (1,102 days (95% CI: 884 - 1,509 days) vs. 614 (95% CI: 493 - 829 days)) in patients treated with ICIs, suggesting a substantial OS benefit from ICI use (Fig. 2a). In the former group, the pre-TARE ICI group (1,959 days (95% CI: 1,557 - NE)) experienced better survival than the post-TARE ICI group (927 days (95% CI:

755 - 1,270 days)) as illustrated in Figure 2b, and the difference was significant (pre-TARE ICI > post-TARE ICI > no ICI groups, P = 0.038). This differs from OS-TARE (post-TARE ICI > pre-TARE ICI > vs. no ICI groups). ICI before or after TARE did not significantly impact univariate or multivariate analysis. However, on univariate analysis, there was a trend toward improving survival with ICI before (HR = 0.39, P = 0.067) and after (HR = 0.65, P = 0.059) TARE.

### Comparing the patients who received ICI therapy

We compared the ICI group (n = 39, pre-TARE + post-TARE



**Figure 1.** Impact of ICIs on the TARE-related OS in the study population. (a) ICI at any time in their lifetime (697 days) vs. never received ICI (226 days); (b) ICI before TARE (678 days) vs. ICI after TARE (703 days) vs. never received ICI (226 days). ICIs: immune checkpoint inhibitors; OS: overall survival; pre-TARE: ICI before TARE; post-TARE: ICI after TARE; TARE: transarterial radioembolization.

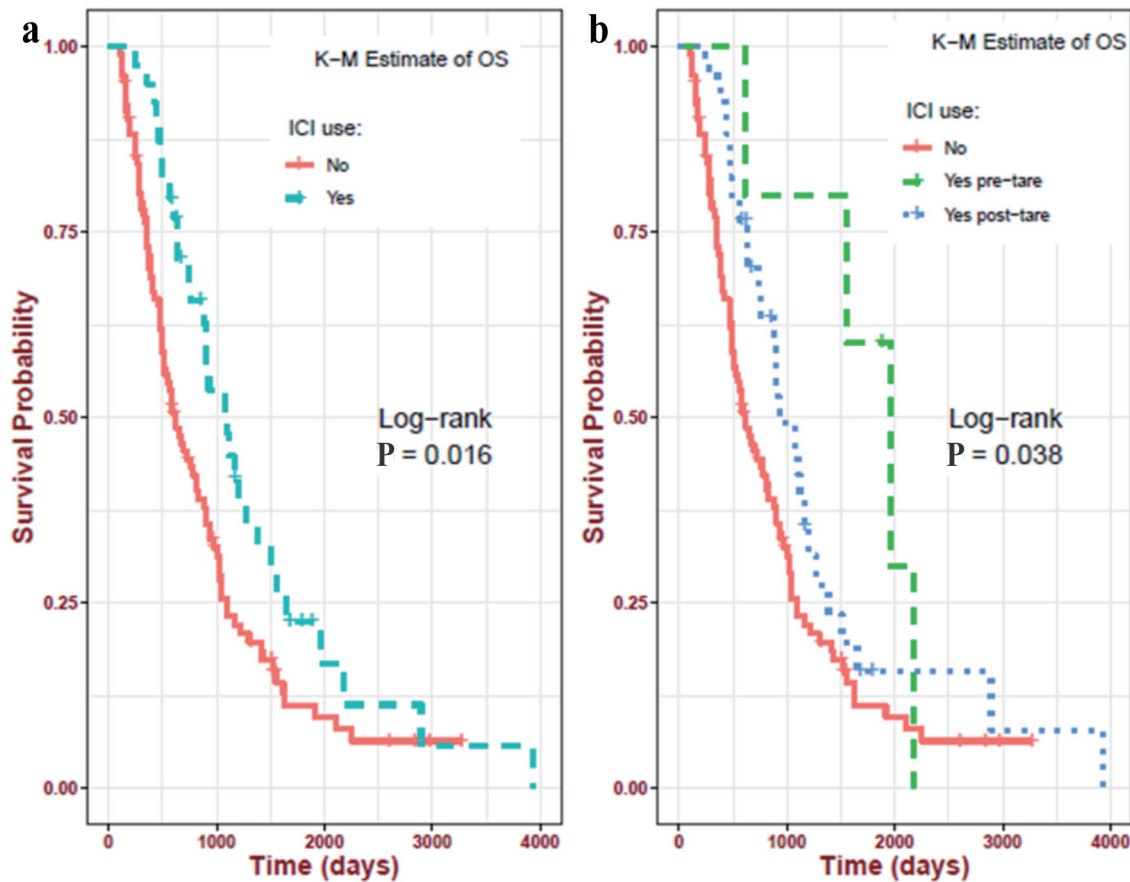
**Table 4.** Factors Impacting OS in the Study Population

| Factor                 | Univariate |             |         | Multivariate |             |         |
|------------------------|------------|-------------|---------|--------------|-------------|---------|
|                        | HR         | 95% CI      | P-value | Adjusted HR  | 95% CI      | P-value |
| ICI use                |            |             |         |              |             |         |
| No                     | -          | -           | -       | -            | -           | -       |
| Yes - pre-TARE         | 0.39       | 0.14 - 1.07 | 0.067   | 0.92         | 0.28 - 3.33 | > 0.9   |
| Yes - post-TARE        | 0.65       | 0.42 - 1.02 | 0.059   | 0.67         | 0.42 - 1.07 | 0.090   |
| Age of diagnosis       | 1.01       | 0.99 - 1.04 | 0.2     | 1.01         | 0.98 - 1.04 | 0.4     |
| Race                   |            |             |         |              |             |         |
| White                  | -          | -           | -       | -            | -           | -       |
| African American/Black | 0.71       | 0.43 - 1.18 | 0.2     | 0.81         | 0.44 - 1.48 | 0.5     |
| Other                  | 0.54       | 0.20 - 1.47 | 0.2     | 0.51         | 0.15 - 1.67 | 0.3     |
| Hepatitis C            |            |             |         |              |             |         |
| No                     | -          | -           | -       | -            | -           | -       |
| Yes                    | 0.68       | 0.47 - 0.99 | 0.043*  | 0.75         | 0.43 - 1.31 | 0.3     |
| MAFLD                  |            |             |         |              |             |         |
| No                     | -          | -           | -       | -            | -           | -       |
| Yes                    | 2.23       | 1.30 - 3.83 | 0.004   | 1.86         | 0.92 - 3.73 | 0.082*  |

**Table 4.** Factors Impacting OS in the Study Population - (continued)

| Factor                                | Univariate |             |          | Multivariate |             |          |
|---------------------------------------|------------|-------------|----------|--------------|-------------|----------|
|                                       | HR         | 95% CI      | P-value  | Adjusted HR  | 95% CI      | P-value  |
| SBRT                                  |            |             |          |              |             |          |
| No                                    | -          | -           | -        | -            | -           | -        |
| Yes                                   | 0.67       | 0.35 - 1.29 | 0.2      | 0.55         | 0.26 - 1.15 | 0.11     |
| TACE                                  |            |             |          |              |             |          |
| No                                    | -          | -           | -        | -            | -           | -        |
| Yes                                   | 0.77       | 0.53 - 1.13 | 0.2      | 1.13         | 0.70 - 1.81 | 0.6      |
| Number of lesions                     |            |             |          |              |             |          |
| Single                                | -          | -           | -        | -            | -           | -        |
| Multiple                              | 1.32       | 0.91 - 1.91 | 0.14     | 1.08         | 0.71 - 1.64 | 0.7      |
| Size of the lesions                   |            |             |          |              |             |          |
| ≤ 3 cm                                | -          | -           | -        | -            | -           | -        |
| > 3 cm or multiple                    | 1.27       | 0.87 - 1.85 | 0.2      | 1.08         | 0.68 - 1.72 | 0.7      |
| Baseline <sup>a</sup> total bilirubin | 1.17       | 0.88 - 1.55 | 0.3      | 0.90         | 0.65 - 1.25 | 0.5      |
| Baseline <sup>a</sup> albumin         | 0.71       | 0.54 - 0.94 | 0.016*   | 0.63         | 0.43 - 0.93 | 0.019*   |
| Active smoking                        |            |             |          |              |             |          |
| No                                    | -          | -           | -        | -            | -           | -        |
| Yes                                   | 0.95       | 0.65 - 1.38 | 0.8      | 1.09         | 0.69 - 1.74 | 0.7      |
| Active alcohol                        |            |             |          |              |             |          |
| No                                    | -          | -           | -        | -            | -           | -        |
| Yes                                   | 1.04       | 0.71 - 1.52 | 0.9      | 1.27         | 0.83 - 1.95 | 0.3      |
| Ascites                               |            |             |          |              |             |          |
| No                                    | -          | -           | -        | -            | -           | -        |
| Yes                                   | 1.75       | 1.16 - 2.64 | 0.008*   | 1.71         | 0.97 - 3.04 | 0.065*   |
| HE                                    |            |             |          |              |             |          |
| No                                    | -          | -           | -        | -            | -           | -        |
| Yes                                   | 1.61       | 1.09 - 2.36 | 0.016*   | 2.01         | 1.22 - 3.32 | 0.006*   |
| BMI                                   | 1.03       | 1.00 - 1.06 | 0.067    | 1.01         | 0.97 - 1.05 | 0.7      |
| Line of TARE used                     |            |             |          |              |             |          |
| First                                 | -          | -           | -        | -            | -           | -        |
| > 1                                   | 0.70       | 0.48 - 1.03 | 0.069    | 0.73         | 0.41 - 1.30 | 0.3      |
| Surgery                               |            |             |          |              |             |          |
| No                                    | -          | -           | -        | -            | -           | -        |
| Yes                                   | 0.56       | 0.32 - 0.97 | 0.038*   | 0.83         | 0.42 - 1.65 | 0.6      |
| Ablation                              |            |             |          |              |             |          |
| No                                    | -          | -           | -        | -            | -           | -        |
| Yes                                   | 0.50       | 0.33 - 0.75 | < 0.001* | 0.35         | 0.21 - 0.59 | < 0.001* |
| PVTT                                  |            |             |          |              |             |          |
| None                                  | -          | -           | -        | -            | -           | -        |
| Present                               | 1.06       | 0.70 - 1.69 | 0.7      | 0.72         | 0.39 - 1.35 | 0.3      |

<sup>a</sup>Baseline: before TARE. \*Significant P values. CI: confidence interval; HE: hepatic encephalopathy; HR: hazard ratio; ICI: immune checkpoint inhibitor; MAFLD: metabolic-dysfunction-associated fatty liver disease; OS: overall survival; PVTT: portal vein tumor thrombus; SBRT: stereotactic body radiotherapy; TACE: transarterial chemoembolization; TARE: transarterial radioembolization.



**Figure 2.** Impact of ICIs on the OS in the study population. (a) ICI at any time in their lifetime (1,102 days) vs. never received ICI (614 days); (b) ICI before TARE (1,959 days) vs. ICI after TARE (927 days) vs. never received ICI (614 days). ICIs: immune checkpoint inhibitors; OS: overall survival; pre-TARE: ICI before TARE; post-TARE: ICI after TARE; TARE: transarterial radioembolization.

ICI groups) and the no-ICI group (Supplementary Material 1, [gr.elmerpub.com](http://gr.elmerpub.com)). The ICI group tended to have a high fraction of patients pre-treated with surgery (23% vs. 9%,  $P = 0.04$ ) or SBRT (18% vs. 6%,  $P = 0.04$ ) and TKIs before or after TARE (47% vs. 17%,  $P < 0.001$ ) as compared to the no ICI group. The overall functional status of the liver of ICI group patients was better in the ICI post-TARE group, as demonstrated by significantly ( $P = 0.04$ ) higher BCLC A cases (56% vs. 35%) and fewer BCLC B (39% vs. 48%) and BCLC C (5% vs. 17%). This is supported by a strong trend ( $P = 0.05$ ) toward improvement in the mean T bili level (in mg/dL, 1 (standard deviation (SD) 1.7) vs. 2 (2.5),  $P = 0.02$ ) in the ICI group. The albumin levels were negligibly better in the ICI group, too (in mg/dL, 3 (0.6) vs. 3 (0.5),  $P = 0.002$ ). Similar results were seen when we compared the pre-TARE ICI, post-TARE ICI, and no ICI groups (Supplementary Material 2, [gr.elmerpub.com](http://gr.elmerpub.com)). Those in the pre-TARE ICI group tended to receive LRTs before TARE such as surgery (pre-TARE vs. post-TARE vs. no ICI = 80% vs. 15% vs. 9%, respectively,  $P < 0.01$ ) or SBRT (40% vs. 15% vs. 6%, respectively,  $P = 0.02$ ), and tended to receive TKIs before TARE (40% vs. 6% vs. 3%, respectively,  $P = 0.014$ ) or any time during their life (80% vs. 38% vs. 17%, respectively,  $P < 0.01$ ). The mean albumin levels in the post-

TARE ICI group were higher than in other groups.

**Impact of TARE on liver function**

We compared key indicators of liver function, albumin, total bilirubin, and Child-Pugh scores before and after TARE to study liver toxicity of the procedure (Table 5).

Albumin levels increased significantly after the procedure, with a mean increase of 0.53 g/dL. The CI does not contain zero, reinforcing that the change is statistically significant. This suggests that the procedure has a positive effect on the albumin levels of patients, possibly indicating improved liver synthetic function. T bili levels decreased significantly after the procedure, with a mean decrease of 0.91 mg/dL. The CI, again not containing zero, confirms the statistical significance of this decrease. This indicates that the procedure effectively reduces T bili levels, suggesting improved liver function related to bilirubin processing. The Child-Pugh scores, which assess the prognosis of chronic liver disease, primarily cirrhosis, showed a significant decrease, with a mean reduction of 1.36 points. This substantial decrease indicates an overall improvement in liver function or reduced severity of liver disease fol-

**Table 5.** Impact of TARE on Liver Function

|                  | Mean difference | Lower | Upper | P-value  |
|------------------|-----------------|-------|-------|----------|
| Albumin          | 0.53            | 0.42  | 0.63  | < 0.0001 |
| Total bilirubin  | -0.91           | -1.29 | -0.53 | < 0.0001 |
| Child-Pugh score | -1.36           | -1.63 | -1.09 | < 0.0001 |

TARE: transarterial radioembolization.

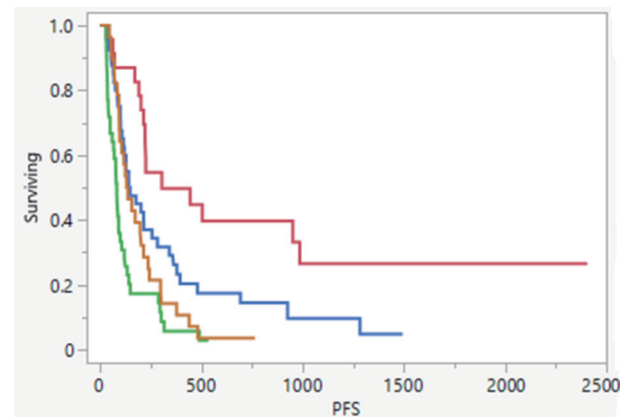
lowing the procedure.

**Imaging and outcome**

We did not have follow-up imaging reports for 11 patients (one died, and the reports were unavailable to verify response in 10 others). Among the 130 patients with imaging, the median follow-up imaging took place at 83 days after TARE (second TARE in patients who had two pre-planned procedures). Thirty-nine (39) patients (30%) had clear-cut progression of disease (PD), while 48% (n = 63) had an objective response, with complete response (CR) in 18% (n = 23) and partial response (PR) in 31% (n = 40). The reports were ambiguous (AR, no clear evidence of response or progression) in 22% (n = 28). The PFS was best among those with CR (median PFS of 303 days, 95% CI: 213 - 985) compared to those with PR (143 days, 95% CI: 106 - 254) or PD (80 days, 95% CI: 106 - 254). Patients with AR (132 days, 95% CI: 93 - 201) had PFS between PR and PD (AR < PR < PD). The difference among these groups (Fig. 3) was significant (P < 0.001).

**Discussion**

There is an urgent need to improve the dismal outcomes associated with HCC. The traditional approach of waiting for



**Figure 3.** Comparing PFS in patients based on the response noted in the first post-TARE imaging scan. Red indicates complete response, green indicates disease progression, blue indicates partial response, and yellow indicates ambiguous response. PFS: progression-free survival; TARE: transarterial radioembolization.

treatment failure with procedures such as TARE could lead to a worsening of the patient’s physical condition (ECOG performance status (PS)) or liver function (Child-Pugh B or C), deeming them ineligible for most LRTs or systemic therapy. The current approval for atezolizumab and bevacizumab is only for patients with good liver function (Child-Pugh A) based on the IMbrave 150 study [35]. Even though durvalumab and tremelimumab is approved irrespective of Child-Pugh score, its clinical benefit in Child-Pugh B and C patients is unknown [36]. Identifying patients at risk of TARE failure will enable treating physicians to implement effective strategies to improve outcomes.

Our study provides valuable insights into TARE’s real-world utilization and outcomes in managing HCC, particularly in the context of patients receiving both TARE and ICI, a treatment that is attracting much interest. The factors we incorporated in our multivariate analysis are more comprehensive than

**Table 6.** Factors Influencing Survival in HCC Patients Treated With TARE in Our Study

|                              | PFS                            | OS-TARE                                  | OS  |
|------------------------------|--------------------------------|--|---|
| <b>Multivariate analysis</b> |                                |  |   |
| Better survival              | High albumin                   | High albumin<br>Post-TARE ICI            | High albumin<br>Prior ablation                      |
| Poor survival                | Low total bilirubin            | HE<br>MAFLD                              | HE<br>MAFLD <sup>a</sup><br>Ascites <sup>a</sup>    |
| <b>Univariate analysis</b>   |                                |  |   |
| Better survival              | High albumin<br>Left vein PVTT | Post-TARE ICI<br>High albumin<br>No PVTT | Albumin<br>Prior surgery or ablation<br>Hepatitis C |
| Poor survival                | MAFLD <sup>a</sup><br>HE       | MAFLD<br>HE                              | Ascites<br>HE                                       |

<sup>a</sup>Has a trend toward significance with a P-value of 0.05 to 0.08. HE: hepatic encephalopathy; ICI: immune checkpoint inhibitor; MAFLD: metabolic-dysfunction-associated fatty liver disease; OS: overall survival; OS-TARE: TARE-specific OS; PFS: progression-free survival; PVTT: portal vein tumor thrombus; TARE: transarterial radioembolization.

most studies published. We intentionally avoided classifications such as BCLC in our analysis, as its definition is not uniform in all guidelines (AASLD vs. BCLC) and it is not strictly followed at most American institutes when selecting LRTs.

The impact of prior ICI on PFS was negligible. On the other hand, patients who received ICI at any time (pre- or post-TARE ICI groups) had significantly better outcomes (OS and OS-TARE) than the no-ICI group. Unlike typical cancer treatment analyses, interpreting OS-TARE and OS and their influencing factors is complex. Analyzing OS-TARE provides insight into the factors affecting outcomes following TARE. Traditional OS offers an understanding of influences before and after TARE. This dual perspective is essential since 65% of patients had undergone prior therapies, including various LRTs, ICI, and TKI. The median OS was significantly better in the pre-TARE ICI group by a large margin of 1,023 days (about 34 months or 3 years). In contrast, the median OS-TARE was negligibly (25 days) better in the post-TARE ICI group.

This underscores two major confounding factors that need to be considered: the intrinsic aggressiveness of HCC, which may be linked to genetic factors such as mutations or methylation along with clinicopathological factors, and the impact of LRTs and systemic therapies, specifically ICI, on TARE effectiveness. Although we lacked tissue or blood-based genomic correlatives to determine the impact of LRTs on survival, we explored the influence of clinicopathological features by including an extensive list of factors in our multivariate analysis. This included specific LRTs (surgery vs. TACE vs. SBRT vs. ablation) and systemic therapies (TKI, ICI). The ICI group (pre- or post-TARE) in our study had a higher fraction of patients who were pretreated with definitive procedures such as surgery or SBRT; received TKI (pre- or post-TARE); had improved T bili and albumin levels post-TARE; and whose disease was classified as BCLC A after TARE (Supplementary Materials 1 and 2, [gr.elmerpub.com](http://gr.elmerpub.com)). These findings suggest that careful patient selection is crucial for enhancing TARE outcomes, and incorporating ICI may play a significant role in this process.

Notably, ICI was not administered as part of standard-of-care (SOC) treatment before or after TARE; rather, it was given after disease progression post-TARE, or TARE was applied to patients who had progressed on ICIs. Nonetheless, this suggests that combining ICI with TARE may synergistically delay disease progression, potentially by enhancing the immune-mediated effects of TARE, as supported by translational evidence [37]. Chew et al showed that tumor-infiltrating lymphocytes (TILs) isolated post-TARE showed signs of immune activation (higher expression of granzyme B (GB) and infiltration of CD8<sup>+</sup> T cells, CD56<sup>+</sup> NK cells, and CD8<sup>+</sup> CD56<sup>+</sup> NKT cells), and next-generation sequencing showed up-regulation of relevant genes [37]. This is similar to the abscopal effect with combined SBRT and ICI, which we discussed at length in our previous publication [38]. There are encouraging data from early-phase clinical trials suggesting the safety and efficacy of this combination [39-43]. Multiple trials are currently underway to further investigate the benefit of adding ICI to TARE (EMERALD-Y90 or NCT06040099, NCT03099564, NCT04541173, NCT05063565) that could give us answers on the timing and sequencing of ICI to optimize clinical outcomes

[44].

Our study also highlighted several other prognostic factors to consider when selecting patients for TARE (Table 6).

Some risk factors influencing OS, such as HE, ascites, lower T bili, and higher albumin levels at the time of TARE, are not surprising as they reflect overall liver health and are consistent with previous reports available in the literature [21, 23, 24, 31]. Patients with prior ablation are typically under active surveillance, which may lead to earlier detection of recurrence with favorable features, such as smaller tumor size and preserved liver function, making them suitable candidates for TARE. This underscores the critical role of maintaining hepatic reserve in HCC management, as patients with better liver function are more likely to tolerate and benefit from TARE and other therapeutic interventions. As reflected in Table 1 and Supplementary Materials 1 and 2 ([gr.elmerpub.com](http://gr.elmerpub.com)), most patients did not have concerning T bili or albumin levels. Therefore, we interpret this as patients with T bili levels at the higher end of normal or albumin levels at the lower end of normal are at the risk of having poor TARE-related outcomes.

The MAFLD population in our study is low (12%), but those who had it experienced lower OS and PFS; however, in another study, it did not negatively impact outcomes [45]. MAFLD has previously been associated with aggressive HCC biology, potentially due to an immune activation, impaired autophagy, and genetic mutations, including CTNNA1 and TP53, contribute to the progression of MAFLD to HCC, with dysregulated pathways such as Wnt/ $\beta$ -catenin and Ras/MAPK playing key roles [46, 47]. As the prevalence of MAFLD-related HCC continues to rise, identifying effective treatment strategies for this patient population will be important. The factors impacting OS-TARE (albumin levels, MAFLD, and HE) or PFS (total bilirubin and albumin) were not that different from the factors impacting OS. We did not see any convincing evidence of the negative impact of PVTT on outcomes as reported in other studies [26, 27, 31]. On univariate analysis, history of a main PVTT had a negative impact on OS (HR = 1.84, P = 0.041) while patients with left PVTT had a good OS-TARE (HR = 0.21, P = 0.031) or PFS (HR = 0.22, P = 0.038). The poor outcomes observed in patients with main PVTT in our study are consistent with existing literature and may be attributed to more severely compromised portal blood flow in this subgroup [22, 48]. However, the small number of patients with left PVTT (n = 4) limits our ability to draw definitive conclusions regarding outcome differences between left, right, and main PVTT. Larger studies incorporating detailed assessments of liver function, including markers of inflammation, fibrosis, and portal hypertension, are needed to validate these findings and better delineate the clinical implications of PVTT location on TARE outcomes.

Following TARE, the observed improvements in liver function parameters, such as increased albumin and decreased bilirubin levels, further highlight its clinical benefits. This may be attributed to the localized cytotoxic effect of TARE, which induces effective tumor cell death while sparing normal hepatic tissue, thereby preserving and, in some cases, enhancing liver function. This is important with regard to tolerability and maintaining treatment eligibility, especially with potential combinations with systemic agents. Finally, patients who do

not show clear evidence of response with TARE in the first post-procedural scans should be considered as having a PR and be treated accordingly. This approach may include initiating systemic therapy or pursuing other lines of treatment. We need to consider incorporating new tools to better assess early treatment response to TARE, such as evaluating enhancing tumor volume (ETV) in post-TARE MRI ( $\geq 65\%$  reduction in ETV is associated with improved survival) or tumor vascularity in contrast to enhanced ultrasound 2 weeks post-TARE (reduction associated with response) [49, 50].

Limitations of this study include its retrospective nature and the potential for selection bias in the patient population. Additionally, the various treatment approaches and the relatively small sample size for specific subgroup analyses may limit the generalizability of the findings. For most of the study period (2015 - 2022), ICI was not the SOC. Atezolizumab and bevacizumab were approved for use in the clinic in mid-2021, and durvalumab/tremelimumab was much later. Even though single-agent nivolumab and pembrolizumab were available in 2020, their use was not favored in most populations as sorafenib and lenvatinib were still SOC [51-53]. Hence, we need more recent real-world data to understand the benefit of ICI with TARE. We acknowledge several technical differences in TARE, including the doses of radiation delivered, the choice between lobectomy and segmentectomy, and the number of TAREs performed on each patient (staged and retreatment). Patient selection was typically through a multidisciplinary discussion. Physician bias could have played a role in selecting TARE for patients. Pre-TARE or post-TARE AFP levels were not available to us for most patients, so we could not study its impact on treatment response or survival, though it has been reported in some other studies [25, 30]. Similarly, though we had patient ECOG scores at diagnosis and post-TARE follow-up visits, we did not have them just before TARE, which would have enhanced our study. Finally, the study did not incorporate genomic or molecular biomarkers that dictate tumor biology and could provide insights into HCC aggressiveness or modulate therapeutic response to TARE and other treatment modalities. Nonetheless, these real-world data provide valuable insights that can inform clinical decision-making and help optimize patient selection for TARE in HCC management.

Future research should focus on several critical areas. First, prospective trials are needed to define the optimal timing and sequencing of ICIs with TARE, particularly considering our findings suggesting differential survival benefits based on treatment order. Second, translational studies integrating tissue and blood-based biomarkers (for example, immune gene expression profiles, circulating tumor DNA, and immune cell phenotyping) are essential to identify predictive markers of response to TARE-ICI combinations. Third, there is a need to evaluate functional imaging biomarkers, such as early changes in ETV on MRI or vascularity shifts on contrast-enhanced ultrasound, to refine early response assessment and identify patients at risk of treatment failure. Fourth, the differential impact of HCC etiology, especially MAFLD-associated HCC, which emerged as a potential negative prognostic factor in our cohort, warrants further investigation given its rising global incidence and possible implications for immune response and disease biology. Lastly, standardized protocols for TARE de-

livery, including dosing strategies, segmental vs. lobar administration, and retreatment criteria, should be systematically evaluated across real-world settings to better define their influence on outcomes and harmonize practice. As immunotherapy becomes increasingly central to HCC treatment paradigms, clarifying how LRTs like TARE can be integrated in a personalized, biomarker-driven framework will be essential for improving outcomes in this complex and heterogeneous disease.

## Conclusion

In this large real-world cohort, TARE demonstrated favorable safety and efficacy profiles in patients with HCC, particularly when integrated into a multimodal treatment approach that included ICIs. Our findings highlight the importance of preserved liver function and prior liver-directed therapies in shaping treatment outcomes and suggest that post-TARE immunotherapy (including ICI) may confer significant survival benefits. These results underscore the need for prospective studies to optimize sequencing strategies, incorporate molecular and functional biomarkers for better patient selection, and define the role of TARE in the evolving immunotherapy landscape of HCC.

## Supplementary Material

**Suppl 1.** Comparing groups that received immune checkpoint inhibitor therapy and transarterial radioembolization (TARE) in the study population.

**Suppl 2.** Comparing groups that received immune checkpoint inhibitor therapy before and after transarterial radioembolization (TARE) in the study population.

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No relevant financial disclosures.

## Conflict of Interest

The authors declare no conflict of interest.

## Informed Consent

Informed consent was obtained from all subjects involved in the study.

## Author Contributions

Conceptualization, methodology, data curation, supervision, and writing - draft supervision: Ashish Manne. Writing - original draft preparation: Deepak Sherpally. Data curation and writing- review and editing: Parthib Das. Data curation: Samuel Paul and Eric Min. Biostatistics/formal analysis: Fode Tounkara. Writing - review and editing: Fode Tounkara, Khalid Mumtaz, Mina Makary, Austin J. Sim, Anne Noonan, Pannaga Malalur, John Hays, Ning Jin, Arjun Mittra, Eric Miller, Dayssy Diaz Pardo, and Kenneth Pitter.

## Data Availability

The authors declare that data supporting the findings of this study are available within the article and its supplementary information files.

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