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Transarterial radioembolization versus systemic treatment for hepatocellular carcinoma with macrovascular invasion: Analysis of the US National Cancer Database

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Author Contributions:

Ju Dong Yang devised the project and the main conceptual ideas for the study. Marie Lauzon and Michael Luu performed data extraction, statistical analysis, and generation of the tables and figures. All authors interpreted the results and Joseph C. Ahn drafted the manuscript under Ju Dong Yang's supervision. Marc L. Friedman, Kambiz Kosari, Nicholas Nissen, Shelly C. Lu, Lewis R. Roberts, and Amit G. Singal revised the manuscript critically for important intellectual content. All authors approved the final version to be published.

List of Abbreviations

AFP	alpha-fetoprotein
BCLC	Barcelona clinic liver cancer
CoC	commission on cancer
EASL	European Association for the Study of the Liver
HCC	hepatocellular carcinoma
HR	hazard ratio
IPTW	inverse probability of treatment weighting
KM	Kaplan-Meier
MELD	model for end-stage liver disease
MVI	macrovascular invasion
NCDB	national cancer database
OR	odds ratio
OS	overall survival
PVT	portal vein thrombosis
TACE	transarterial chemoembolization
TARE	transarterial radioembolization
WHO	World Health Organization
Y90	yttrium-90

ABSTRACT

Background and Aims: Systemic therapy remains the recommended first-line treatment for hepatocellular carcinoma (HCC) with macrovascular invasion (MVI). Transarterial radioembolization (TARE) is a promising alternative treatment given superior quality of life. The aims of this study were to 1) characterize trends and correlates for TARE as first-line treatment of HCC patients with MVI in the US and 2) compare survival after TARE versus systemic therapy.

Methods: We used the US National Cancer Database to identify patients with T3BN0M0 HCC during 2010-2017. We performed multivariable logistic regression to identify factors associated with use of TARE vs. systemic therapy and Cox proportional hazards regression to identify factors associated with overall survival.

Results: Of 11,259 patients with T3BN0M0 HCC, 1454 (12.9%) and 3915 (34.7%) patients were treated with TARE and systemic therapy, respectively. The proportion of patients who received TARE increased from 13.0% in 2010 to 37.0% in 2017. Older age, White race, and receiving care at an academic cancer program were associated with receipt of TARE, while lack of insurance, higher MELD score, Charlson comorbidity Index ≥3, and Northeast region were associated with receipt of systemic therapy. TARE was associated with reduced mortality compared to systemic therapy (adjusted hazard ratio: 0.74, 95%CI: 0.68-0.80), with consistent results observed in propensity weighted analysis and across all examined subgroups.

Conclusions: Use of TARE as first-line therapy for HCC with MVI has increased in the US. Patient characteristics, region, and medical center type affected the use of TARE.

TARE was associated with reduced mortality compared to systemic therapy for HCC patients with MVI.

Keywords: hepatocellular carcinoma; macrovascular invasion; transarterial radioembolization; systemic treatment

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, which typically occurs in the setting of chronic liver disease. It is among the leading causes of cancer incidence and mortality globally (*1*). Macrovascular invasion (MVI) of the portal vein and/or hepatic vein is one of the defining features for advanced-stage HCC (*2*). Traditionally, systemic therapy using the molecular targeted agent, sorafenib, has been the only treatment that increased median survival and time-to-progression in these patients (*3,4*). Recent advances in systemic therapy include the approval of lenvatinib and more recently, the combination of atezolizumab and bevacizumab (*5,6*).

Transarterial radioembolization (TARE) with yttrium-90 microspheres(Y90) is a form of locoregional therapy in HCC patients, which can be provided safely to patients with portal vein invasion and has been shown to provide superior time to progression compared to conventional transarterial chemoembolization (TACE) (*7*). TARE has been proposed as an alternative therapy for HCC patients with MVI given the potential for response and downstaging (*8*). Several retrospective studies (*9-11*) as well as randomized controlled trials (*12,13*) in HCC patients with MVI demonstrated that TARE was associated with comparable overall survival (OS) and fewer treatment-related adverse events compared to systemic therapy. While professional society guidelines continue to endorse systemic treatment as the first-line therapy for HCC with MVI (*14,15*), TARE has been widely adopted in clinical practice (*16*).

Trends in utilization of TARE and comparative effectiveness compared to systemic therapy in real-world clinical practice have not been well characterized. Therefore, the aim of this study was to characterize 1) temporal trends in the usage of TARE, 2) factors

associated with use of TARE and 3) overall survival after TARE as first-line treatment compared to systemic treatment for HCC with MVI in the US.

MATERIALS AND METHODS

Database

The National Cancer Database (NCDB) is a large, nationwide clinical oncology database jointly sponsored by the American College of Surgeons and the American Cancer Society. The NCDB contains hospital registry data from more than 1,500 Commission on Cancer-accredited facilities in the United States, representing more than 70 percent of newly diagnosed cancer cases and 34 million historical records.

Patients and Variables

All patients who were diagnosed with tumor stage T3BN0M0 HCC between January 2010 and December 2017 were identified from the NCDB. The diagnosis of HCC was based on the International Classification of Disease-Oncology-3rd Edition code C22.0 and the histology codes 8170-8175. T3BN0M0 HCC was defined as tumor involving a major branch of a large vein of the liver without lymph node involvement or extrahepatic metastasis. Patients with missing treatment information and those who did not receive TARE or systemic treatment were excluded.

TARE was defined using the variable “Phase I Radiation Treatment Modality” which records radiation modality administered during the first phase of radiation treatment delivered during the first course of cancer treatment. Patients with any of the following

codes were considered to have received TARE: brachytherapy not otherwise specified; brachytherapy, intracavitary, low dose rate; brachytherapy, intracavitary, high dose rate; brachytherapy, interstitial, low dose rate; brachytherapy, interstitial, high dose rate, or radioisotopes not otherwise specified. Systemic therapy was defined using variable “chemotherapy” or “immunotherapy” which record the type of chemotherapy or immunotherapy administered as the first-course treatment at any facility.

Patient demographics, socioeconomic status, medical comorbidities, treatment facility, and treatment region were extracted from the NCDB. Demographic information included patient`s age, sex, and race/ethnicity. Socioeconomic status was characterized using insurance coverage, median income, educational attainment, and living environment. Patient medical comorbidities were described in terms of Charlson/Deyo comorbidity index (0, 1, 2, ≥3). Liver and HCC-specific clinical data including MELD score, method of diagnosis, tumor burden, and alpha-fetoprotein (AFP) level were captured for all patients. Treating facilities were classified into four categories: academic (>500 new cancer diagnoses annually and at least four postgraduate training programs), comprehensive community (>500 new cancer diagnoses annually), integrated network (no minimum caseload, joint venture with multiple facilities at least one of which is a hospital and a Commission on Cancer-accredited cancer program), and community (100 to 500 new cancer diagnoses annually). The facilities were also categorized according to their geographic regions within the US (Northeast, Midwest, South, West).

Statistical Analysis

Bivariate comparison of TARE vs. systemic treatment for continuous and categorical variables was performed using the Welch’s t-test, Wilcoxon-Mann-Whitney

test, or Pearson's chi-squared test where appropriate. Univariate and multivariable logistic regression was used to identify factors associated with use of TARE vs. systemic therapy. Kaplan-Meier analysis was used to estimate survival probabilities and the log-rank test was used to compare Kaplan-Meier curves. Time-to-event was defined as the time from HCC diagnosis to last follow-up or death. Furthermore, univariate and multivariable Cox proportional hazards regression was used to identify factors associated with overall survival. To adjust for potential confounders, propensity score matching and inverse probability of treatment weighted (IPTW) analyses were performed (*17*). Propensity score-matched cohorts were constructed by performing a 1:1 match using a caliper of 0.20 and the nearest neighbor method (*18*). A multivariable logistic regression model was used to construct the propensity scores including age, sex, race, ethnicity, insurance, comorbidity, AFP level, MELD score, facility type, and geographic region. IPTW was constructed based on the propensity scores and included in the Cox-proportional hazard regression model as case weights. The proportional hazards assumption among all survival models was assessed by the scaled Schoenfeld residuals as well as the goodness-of-fit test as proposed by Grambsch and Therneau (*19*). To account for missing data in the NCDB, the chained equation approach for multiple imputations was used prior to performing regression analyses (*20*). All statistical analyses were performed using R statistical software (version 4.0.3; R Foundation, Vienna, Austria) with two-sided tests and a significance level of 0.05.

RESULTS

Patient Characteristics

Of 11,259 patients diagnosed with T3BN0M0 HCC during 2010-2017, 1454

(12.9%) and 3915 (34.8%) patients were treated with TARE and systemic therapy, respectively, and included in the study (Supplemental Figure 1). The proportion of patients receiving TARE increased from 13.0% in 2010 to 37.0% in 2017 (Figure 1). The median age of patients was 63.0 years, with 80.7% being male (Table 1). The cohort consisted of 64% non-Hispanic Whites, 16.3% Blacks, and 10.2% Hispanics. Over half of the patients had government (Medicare or Medicaid) insurance coverage, although 34.5% had private insurance and 5.4% of patients were uninsured. Over three-fourths (76.0%) had a comorbidity score of 0-1, and median MELD score was 11. Median tumor diameter was 7.1 cm, and 85% had an elevated AFP level at diagnosis. Nearly two-thirds (61.7%) of patients were treated at an academic center, 22.2% at a comprehensive community cancer center, and 12.2% at an integrated network.

Factors Associated with Receipt of TARE

In multivariable logistic regression analysis (Table 2), independent predictors of receiving TARE included: older age (OR: 1.17, 95% CI: 1.09-1.27), having private insurance (OR: 2.04, 95% CI: 1.38-2.95) or Medicaid/Medicare (OR: 1.89, 95% CI: 1.28-2.72) vs. being uninsured, treatment in the Midwest (OR: 1.64, 95% CI: 1.36-2.08), South (OR: 1.27, 95% CI: 1.07-1.56), and West (OR: 1.74, 95% CI: 1.42-2.20) regions vs. Northeast region. Factors associated with decreased odds of TARE included: Hispanic ethnicity (OR: 0.69, 95% CI: 0.54-0.88) or Asian/other (OR: 0.74, 95% CI: 0.60-0.97) vs. White race/ethnicity, receiving treatment in a community cancer program (OR: 0.42, 95% CI: 0.27-0.68) or comprehensive community cancer program (OR: 0.73, 95% CI: 0.61-0.86) vs. academic program, Charlson index ≥3 vs. Charlson index of 0 or 1 (OR: 0.82, 95% CI: 0.68-0.98), and higher MELD score (OR: 0.76, 95% CI: 0.66-0.80).

Factors Associated with Overall Survival

Over a median follow-up of 8.18 months, the median overall survival for the entire cohort was 8.64 months. One- and three-year survival estimates were 37.3% and 9.6%, respectively. Patients who received TARE had higher OS compared to patients who received systemic treatment at 1 year (46.5% vs. 34.2%), 2 years (21.8% vs. 16.4%), and 3 years (10.4% vs. 9.3%) (Figure 2A). After propensity score matching, patients who received TARE continued to demonstrate higher OS compared to those who received systemic treatment at 1 year (45.6% vs. 34.2%), 2 years (20.8% vs. 16.7%), and 3 years (12.3% vs. 8.6%) (Figure 2B).

In multivariable Cox regression analysis, receipt of TARE was independently associated with reduced mortality (HR: 0.74, 95% CI: 0.68-0.80). Results were consistent in propensity score matching (HR: 0.72, 95% CI: 0.63-0.82) and IPTW (HR: 0.74, 95% CI: 0.66-0.83) analyses. Similarly, results were consistent across examined subgroup analyses (Figure 3). Other factors associated with reduced mortality included female sex (HR: 0.91, 95% CI: 0.84-0.99) and Hispanic ethnicity (HR: 0.85, 95% CI: 0.75-0.96) (Table 3). Treatment at a community cancer program (HR: 1.38, 95% CI: 1.16-1.63), comprehensive community cancer program (HR: 1.23, 95% CI: 1.14-1.34), or integrated network (HR: 1.15, 95% CI: 1.04-1.28), receiving care at the Midwest vs. Northeast regions, (HR: 1.17, 95% CI: 1.06-1.29), elevated AFP level (HR: 1.36, 95% CI: 1.22-1.51), and higher MELD (HR: 1.11, 95% CI: 1.06-1.17) were independently associated with shorter OS.

DISCUSSION

Our study highlighted several important findings regarding patients with T3BN0M0 HCC treated with TARE or systemic therapy in the US. While systemic therapy continues to be the most common first-line treatment for patients diagnosed with T3BN0M0 HCC, the proportion of patients receiving TARE nearly tripled from 13.0% to 37.0% between 2010 and 2017. Second, we found significant variation in the receipt of TARE versus systemic therapy according to race/ethnicity, socioeconomic status, treating facility types, and geographic region. Lastly, treatment with TARE was associated with significantly improved survival compared to systemic treatment.

TARE's role in the treatment of HCC has evolved over several decades. After establishment of TARE's efficacy and safety profiles, its long-term treatment outcomes were examined across HCC tumor stages (*21-23*). Recent clinical trials have evaluated TARE's relative efficacy and tolerability compared to sorafenib in patients with advanced HCC. The SARAH trial found no significant difference in the median OS between patients who received TARE versus sorafenib; however, tolerability and quality of life were significantly better in the TARE group (*12*). Similarly, the SIRveNIB trial also reported no significant difference in median OS but fewer patients in the TARE group experiencing grade ≥3 adverse effects (*13*). A recent meta-analysis of these two comparative trials (SARAH and SIRveNIB) plus the SORAMIC study where TARE was followed by sorafenib showed that median OS with TARE was non-inferior to sorafenib (HR: 0.91, 95% confidence interval: 0.78-1.05) with significantly lower rates of severe adverse effects (28.9% vs. 43.3%, $p<0.01$) (*24*).

While the phase 3 trials did not reach their primary end-points of difference in OS,

it should be noted that both trials reported the dose of injected radiation but did not measure the actual radiation dose delivered to the tumor, as the latter has been shown to predict treatment response (*25*). The recently published phase 2 study DOSISPHERE-01 trial attempted to address this issue by comparing the efficacy of a personalized versus standard dosimetry approach in 60 patients with locally advanced HCC (*26*). The authors found a significant difference between the two groups, with 71% of patients in the personalized dosimetry group compared to 36% of patients in the standard dosimetry group having objective responses (p=0.0074) (*26*). Therefore, additional trials incorporating personalized dosimetry may help better elucidate outcomes of patients treated with TARE (*27*).

The findings of our study have important implications in the context of the above studies evaluating TARE's role in patients with advanced HCC. Decades of research have shown that TARE is a safe and effective form of treatment for patients with advanced HCC with or without MVI. Moreover, multiple studies have consistently shown that TARE is better tolerated with fewer serious adverse effects and higher quality of life compared to sorafenib. Given such advantages, it is not surprising that the overall proportion of patients with advanced HCC receiving TARE over systemic treatment has significantly increased between 2010 and 2017 despite the society guidelines not yet formally endorsing TARE as first-line therapy. We have found significant variation in the likelihood of receiving TARE over systemic treatment according to race/ethnicity, socioeconomic status, treatment regions, and treating facility types. The historically underserved non-White racial/ethnic groups and those of lower socioeconomic status had lower likelihood of receiving TARE. Patients treated in the community cancer centers also had lower

likelihood of receiving TARE compared to patients treated in the academic institutions, reflecting the relative lack of access to advanced interventional procedures in the community. The recently published inaugural AACR cancer disparities progress report highlights adverse differences in numerous measures of cancer burden, access to care, and outcomes among various population groups in the US, and emphasizes the need for more collaboration between the various stakeholders and more cancer health disparities research (*28*).

Our results must be interpreted in light of the recent advances in immunotherapy for treatment of HCC. The IMbrave150 study, a global, multicenter, open-label, phase 3 randomized trial, reported significantly improved OS in patients with unresectable HCC receiving atezolizumab plus bevacizumab compared to patients receiving sorafenib (*9*). As our study period was from 2010 to 2017, patients received systemic treatment when sorafenib was the first-line treatment. Therefore, it would be misleading to conclude based on our study that TARE is superior to all forms of systemic treatment. Instead, the results of our study and recent developments in immunotherapy for HCC highlight the exciting new possibility of combining TARE and immunotherapy for patients with HCC. Besides its locoregional antitumor efficacy, ionizing radiation from TARE may induce immune-mediated antitumor responses distant to the targeted area (*29*). There is a growing body of evidence supporting the ability of ionizing radiation to activate an immune response via releasing a flood of tumor-associated antigens into circulation (*30*), facilitating tumor antigen manifestation to T cells (*31*), and modulating the tumor microenvironment for improved recognition and killing by CD8+ T cells (*32*). Such findings suggest that immune checkpoint blockade may further enhance the immune responses caused by TARE and

synergistically achieve improved antitumor effects, and there are a number of ongoing clinical trials to address this question (*33*).

Our study also has several limitations related to its design. First, this was a retrospective study of a large cancer-focused database and some pertinent data such as the exact type of systemic treatment and what patients received as second-line therapy. Second, we did not have data on the degree of portal vein invasion, which has been shown to correlate with overall survival.

CONCLUSION

In conclusion, TARE is associated with improved overall survival compared to systemic therapy in HCC patients with macrovascular invasion. Although we noted increasing use for HCC patients with MVI, there continues to be notable variation in its use across the United States. In light of improved systemic therapy options for advanced HCC, continued studies are needed to evaluate the role of TARE, including in combination with immuno-oncology agents.

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Disclosures:

Dr. Yang provides a consulting service for Exact Sciences and Gilead. Dr. Singal has been on advisory boards and served as a consultant for Genentech, Bayer, Eisai, BMS, Exelixis, AstraZeneca, and TARGET RWE. No other potential conflicts of interest relevant to this article exist.

KEY POINTS

QUESTION: What are the utilization trend and outcome of transarterial radioembolization (TARE) in comparison to systemic treatment for hepatocellular carcinoma (HCC) patients with macrovascular invasion (MVI)?

PERTINENT FINDINGS: In a retrospective cohort study of 5369 HCC patients with MVI from the US National Cancer Database between 2010 to 2017, utilization of TARE increased rapidly and was independently associated with improved survival compared to systemic treatment.

IMPLICATIONS FOR PATIENT CARE: TARE might be an effective treatment for HCC patients with MVI, and additional studies evaluating TARE's role in combination with the newer immuno-oncology agents are needed.

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Table 1. Clinical features of patients before and after propensity score matching

	Before Propensity score matching				After Propensity score matching			
	[ALL]	**Systemic**	**TARE**	**p***	**[ALL]**	**Systemic**	**TARE**	**p***
Characteristics	*N=5369*	*N=3915*	*N=1454*		*N=1136*	*N=568*	*N=568*	
Patient Demographics								
Age (years) Mean (SD)	63.0 (9.73)	62.6 (9.84)	64.2 (9.33)	<0.001	63.9 (9.13)	63.7 (9.49)	64.1 (8.75)	0.420
Sex				0.720				0.880
Male	4331 (80.7%)	3153 (80.5%)	1178 (81.0%)		917 (80.7%)	460 (81.0%)	457 (80.5%)	
Female	1038 (19.3%)	762 (19.5%)	276 (19.0%)		219 (19.3%)	108 (19.0%)	111 (19.5%)	
Race				<0.001				0.587
White	3347 (64.0%)	2356 (61.8%)	991 (70.0%)		781 (68.8%)	385 (67.8%)	396 (69.7%)	
Hispanic	536 (10.2%)	426 (11.2%)	110 (7.77%)		87 (7.66%)	47 (8.27%)	40 (7.04%)	
Black	851 (16.3%)	660 (17.3%)	191 (13.5%)		168 (14.8%)	81 (14.3%)	87 (15.3%)	
Asian + Others	496 (9.48%)	373 (9.78%)	123 (8.69%)		100 (8.80%)	55 (9.68%)	45 (7.92%)	
Socioeconomic Factors								
Insurance Status				<0.001				0.933
Uninsured	285 (5.42%)	247 (6.46%)	38 (2.65%)		39 (3.43%)	21 (3.70%)	18 (3.17%)	
Private	1815 (34.5%)	1319 (34.5%)	496 (34.5%)		392 (34.5%)	197 (34.7%)	195 (34.3%)	
Medicaid/Medicare	3072 (58.4%)	2209 (57.8%)	863 (60.1%)		683 (60.1%)	340 (59.9%)	343 (60.4%)	
Other	88 (1.67%)	49 (1.28%)	39 (2.72%)		22 (1.94%)	10 (1.76%)	12 (2.11%)	
Median Income				0.025				0.716
< $40,227	1168 (23.7%)	882 (24.5%)	286 (21.6%)		246 (21.7%)	125 (22.0%)	121 (21.3%)	
$40,227 - $50,353	1103 (22.4%)	825 (22.9%)	278 (21.0%)		268 (23.6%)	135 (23.8%)	133 (23.4%)	
$50,354 - $63,332	1113 (22.6%)	790 (21.9%)	323 (24.4%)		279 (24.6%)	145 (25.5%)	134 (23.6%)	

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$63,333 +	1540 (31.3%)	1103 (30.6%)	437 (33.0%)		343 (30.2%)	163 (28.7%)	180 (31.7%)	
Without Highschool Degree				0.003				0.099
≥ 17.6%	1345 (27.3%)	1023 (28.4%)	322 (24.3%)		269 (23.7%)	152 (26.8%)	117 (20.6%)	
10.9%-17.5%	1360 (27.6%)	1007 (27.9%)	353 (26.6%)		310 (27.3%)	152 (26.8%)	158 (27.8%)	
6.3% - 10.8%	1305 (26.5%)	934 (25.9%)	371 (28.0%)		338 (29.8%)	162 (28.5%)	176 (31.0%)	
< 6.3%	922 (18.7%)	641 (17.8%)	281 (21.2%)		219 (19.3%)	102 (18.0%)	117 (20.6%)	
Urban/Rural				0.373				0.885
Metro	4554 (87.1%)	3338 (87.5%)	1216 (86.1%)		974 (85.7%)	489 (86.1%)	485 (85.4%)	
Urban	600 (11.5%)	424 (11.1%)	176 (12.5%)		142 (12.5%)	70 (12.3%)	72 (12.7%)	
Rural	73 (1.40%)	52 (1.36%)	21 (1.49%)		20 (1.76%)	9 (1.58%)	11 (1.94%)	
Medical Facility Factors								
Facility Type				<0.001				0.923
Academic	3268 (61.7%)	2318 (60.1%)	950 (65.9%)		832 (73.2%)	418 (73.6%)	414 (72.9%)	
Community Cancer Program	203 (3.83%)	178 (4.62%)	25 (1.73%)		12 (1.06%)	5 (0.88%)	7 (1.23%)	
Comprehensive cancer Program	1178 (22.2%)	899 (23.3%)	279 (19.3%)		166 (14.6%)	81 (14.3%)	85 (15.0%)	
Integrated Network	648 (12.2%)	460 (11.9%)	188 (13.0%)		126 (11.1%)	64 (11.3%)	62 (10.9%)	
Region				<0.001				0.969
Northeast	1137 (21.5%)	877 (22.7%)	260 (18.0%)		208 (18.3%)	102 (18.0%)	106 (18.7%)	
Midwest	1094 (20.7%)	732 (19.0%)	362 (25.1%)		285 (25.1%)	141 (24.8%)	144 (25.4%)	
South	2161 (40.8%)	1626 (42.2%)	535 (37.1%)		385 (33.9%)	193 (34.0%)	192 (33.8%)	
West	905 (17.1%)	620 (16.1%)	285 (19.8%)		258 (22.7%)	132 (23.2%)	126 (22.2%)	
Clinical Factors								
Charlson Comorbidity				0.013				0.800
0 or 1	4079 (76.0%)	2950 (75.4%)	1129 (77.6%)		860 (75.7%)	427 (75.2%)	433 (76.2%)	

TARE vs. Systemic for HCC with MVI

2	422 (7.86%)	298 (7.61%)	124 (8.53%)		100 (8.80%)	49 (8.63%)	51 (8.98%)	
≥ 3	868 (16.2%)	667 (17.0%)	201 (13.8%)		176 (15.5%)	92 (16.2%)	84 (14.8%)	
Diagnosis Method				<0.001				0.153
Cytology or Histology	2679 (49.9%)	2014 (51.4%)	665 (45.7%)		521 (45.9%)	273 (48.1%)	248 (43.7%)	
Clinical Diagnosis	2690 (50.1%)	1901 (48.6%)	789 (54.3%)		615 (54.1%)	295 (51.9%)	320 (56.3%)	
AFP				0.748				0.799
Negative	719 (15.0%)	518 (14.9%)	201 (15.3%)		162 (14.3%)	79 (13.9%)	83 (14.6%)	
Positive	4085 (85.0%)	2970 (85.1%)	1115 (84.7%)		974 (85.7%)	489 (86.1%)	485 (85.4%)	
MELD				<0.001				0.077
Median [IQR]	10.9 [8.47;16.5]	11.5 [8.47;17.6]	9.82 [7.50;13.4]		10.0 [7.94;13.6]	10.2 [8.44;14.1]	9.72 [7.50;13.2]	
Cirrhosis[#]				<0.001				
No cirrhosis	215 (19.1%)	167 (16.3%)	48 (46.6%)					
Cirrhosis	910 (80.9%)	855 (83.7%)	55 (53.4%)					
Tumor Size (cm)				0.111				0.016
Median [IQR]	7.10 [4.60;10.3]	7.20 [4.50;10.5]	7.00 [4.70;10.0]		7.00 [4.50;10.0]	7.30 [4.68;10.0]	6.70 [4.50;9.50]	

*NA: Not Applicable, [#]Cirrhosis status is available in only 24% of patients.
Abbreviations: AFP, alpha-fetoprotein; IQR, interquartile range; MELD, model for end-stage liver disease score; SD, standard deviation; TARE, transarterial radioembolization

Table 2. Factors predicting TARE treatment among patients with T3BN0M0 HCC

Characteristics	Univariate		Multivariate	
	HR (95%CI)	p	HR (95%CI)	p
Age (10 years change)	1.194 (1.122 to 1.272)	<0.001	1.174 (1.091 to 1.267)	<0.001
Sex_Male (Reference)	(reference)		(reference)	
Sex_Female	0.969 (0.831 to 1.129)	0.691	0.957 (0.802 to 1.122)	0.607
Race_White (Reference)	(reference)		(reference)	
Race_Hispanic	0.615 (0.496 to 0.768)	<0.001	0.685 (0.536 to 0.883)	0.003
Black	0.688 (0.576 to 0.817)	<0.001	0.829 (0.675 to 1.013)	0.070
Race_Asian + Others	0.796 (0.664 to 1.013)	0.034	0.735 (0.604 to 0.973)	0.012
Uninsured (Refence)	(reference)		(reference)	
Private Insurance	2.362 (1.648 to 3.318)	<0.001	2.038 (1.376 to 2.950)	<0.001
Medicaid/Medicare Insurance	2.470 (1.736 to 3.452)	<0.001	1.889 (1.276 to 2.716)	<0.001
Other Insurance	5.004 (2.913 to 8.547)	<0.001	3.225 (1.730 to 5.869)	<0.001
Median Income < $40,227 (Reference)	(reference)		(reference)	
Median Income $40,227 - $50,353	1.039 (0.850 to 1.221)	0.680	0.943 (0.742 to 1.144)	0.599
Median Income $50,354 - $63,332	1.252 (1.061 to 1.511)	0.013	1.095 (0.889 to 1.394)	0.430
Median Income $63,333 +	1.202 (1.025 to 1.429)	0.030	0.980 (0.761 to 1.258)	0.872
Without Highschool Degree ≥ 17.6% (Reference)	(reference)		(reference)	
Without Highschool Degree 10.9% - 17.5 %	1.100 (0.949 to 1.323)	0.262	0.976 (0.808 to 1.203)	0.811
Without Highschool Degree 6.3% - 10.8%	1.246 (1.057 to 1.471)	0.009	1.024 (0.815 to 1.264)	0.829
Without Highschool Degree < 6.3%	1.377 (1.151 to 1.652)	<0.001	1.181 (0.896 to 1.511)	0.212
Metro (Reference)	(reference)		(reference)	
Urban	1.125 (0.941 to 1.363)	0.212	1.161 (0.939 to 1.444)	0.174
Rural	1.085 (0.626 to 1.740)	0.753	1.134 (0.608 to 1.901)	0.663
Facility_Academic (Reference)	(reference)		(reference)	
Facility_Community Cancer Program	0.346 (0.231 to 0.534)	<0.001	0.424 (0.274 to 0.676)	<0.001
Facility_Comprehensive Community Cancer Program	0.762 (0.656 to 0.892)	<0.001	0.729 (0.612 to 0.864)	<0.001
Facility_Integrated Network	1.003 (0.826 to 1.196)	0.973	1.034 (0.845 to 1.274)	0.747
Region_Northeast (Reference)	(reference)		(reference)	
Region_Midwest	1.651 (1.390 to 2.017)	<0.001	1.640 (1.364 to 2.076)	<0.001
Region_South	1.110 (0.951 to 1.333)	0.225	1.268 (1.068 to 1.562)	0.014
Region_West	1.556 (1.287 to 1.906)	<0.001	1.740 (1.418 to 2.198)	<0.001
Charlson Index 0 or 1 (Reference)	(reference)		(reference)	
Charlson Index 2	1.087 (0.870 to 1.352)	0.457	1.117 (0.873 to 1.416)	0.371
Charlson Index 3	0.787 (0.662 to 0.934)	0.006	0.821 (0.676 to 0.984)	0.039
AFP_Normal (Reference)	(reference)		(reference)	
AFP_Elevated	0.992 (0.841 to 1.182)	0.928	1.123 (0.947 to 1.373)	0.223
MELD (10 units change)	0.736 (0.660 to 0.785)	<0.001	0.756 (0.663 to 0.801)	<0.001

Tumor Size	0.993 (0.983 to 1.002)	0.136	0.992 (0.982 to 1.001)	0.101

Abbreviations: AFP, alpha-fetoprotein; MELD, model for end-stage liver disease score; TARE, transarterial radioembolization

Table 3. Factors associated with overall survival among patients with T3BN0M0 HCC

Characteristics	Univariate		Multivariate	
	OR (95%CI)	p	OR (95%CI)	p
Age (10 years change)	1.022 (0.990 to 1.056)	0.184	1.035 (0.998 to 1.072)	0.063
Sex_Male (Reference)	(reference)		(reference)	
Sex_Female	0.925 (0.852 to 1.003)	0.060	0.912 (0.840 to 0.990)	0.029
Race_White (Reference)	(reference)		(reference)	
Race_Hispanic	0.830 (0.741 to 0.930)	0.001	0.850 (0.754 to 0.959)	0.008
Race_Black	0.947 (0.865 to 1.036)	0.232	0.933 (0.846 to 1.029)	0.164
Race_Asian + Others	0.887 (0.791 to 0.994)	0.040	0.894 (0.793 to 1.008)	0.066
Uninsured (Refence)	(reference)		(reference)	
Private Insurance	0.909 (0.787 to 1.051)	0.198	0.920 (0.793 to 1.067)	0.269
Medicaid/Medicare Insurance	0.970 (0.843 to 1.116)	0.672	0.956 (0.827 to 1.106)	0.547
Other Insurance	0.877 (0.659 to 1.167)	0.368	0.912 (0.685 to 1.215)	0.530
Median Income < $40,227 (Reference)	(reference)		(reference)	
Median Income $40,227 - $50,353	1.024 (0.927 to 1.131)	0.638	0.978 (0.878 to 1.089)	0.682
Median Income $50,354 - $63,332	0.923 (0.836 to 1.018)	0.107	0.884 (0.790 to 0.989)	0.032
Median Income $63,333 +	0.991 (0.907 to 1.083)	0.841	0.949 (0.839 to 1.073)	0.404
Without High School Degree ≥ 17.6% (Reference)	(reference)		(reference)	
Without High School Degree 10.9% - 17.5%	1.086 (0.993 to 1.189)	0.072	1.082 (0.981 to 1.193)	0.114
Without High School Degree 6.3% - 10.8%	1.098 (1.005 to 1.199)	0.038	1.117 (1.003 to 1.244)	0.044
Without High School Degree < 6.3%	1.088 (0.985 to 1.202)	0.097	1.131 (0.988 to 1.294)	0.073
Metro (Reference)	(reference)		(reference)	
Urban	1.134 (1.025 to 1.255)	0.014	1.106 (0.992 to 1.233)	0.070
Rural	1.276 (0.982 to 1.657)	0.068	1.171 (0.892 to 1.537)	0.255
Facility_Academic (Reference)	(reference)		(reference)	
Facility_Community Cancer Program	1.552 (1.311 to 1.838)	<0.001	1.376 (1.159 to 1.634)	<0.001
Facility_Comprehensive Community Cancer Program	1.247 (1.149 to 1.352)	<0.001	1.234 (1.135 to 1.342)	<0.001
Facility_Integrated Network	1.164 (1.055 to 1.285)	0.003	1.153 (1.043 to 1.275)	0.005
Region_Northeast (Reference)	(reference)		(reference)	
Region_Midwest	1.179 (1.069 to 1.301)	<0.001	1.167 (1.055 to 1.292)	0.003
Region_South	1.013 (0.929 to 1.105)	0.763	0.963 (0.879 to 1.054)	0.414
Region_West	1.000 (0.900 to 1.111)	0.996	0.987 (0.883 to 1.102)	0.813
Charlson Index 0 or 1 (Reference)	(reference)		(reference)	
Charlson Index 2	0.994 (0.878 to 1.126)	0.928	0.979 (0.863 to 1.109)	0.735
Charlson Index 3	1.082 (0.989 to 1.184)	0.087	1.073 (0.979 to 1.177)	0.131
AFP_Normal (Reference)	(reference)		(reference)	
AFP_Elevated	1.330 (1.202 to 1.473)	<0.001	1.356 (1.220 to 1.506)	<0.001

TARE vs. Systemic for HCC with MVI

MELD score (10-unit change)	1.134 (1.084 to 1.186)	<0.001	1.113 (1.061 to 1.167)	<0.001
Treatment_Systemic (Reference)	(reference)		(reference)	
Treatment_TARE	0.745 (0.691 to 0.803)	<0.001	0.739 (0.684 to 0.798)	<0.001

Abbreviations: AFP, alpha-fetoprotein; MELD, model for end-stage liver disease score; TARE, transarterial radioembolization

Figure 1. Proportion of patients who received TARE vs. systemic treatment for HCC with MVI between 2010 and 2017

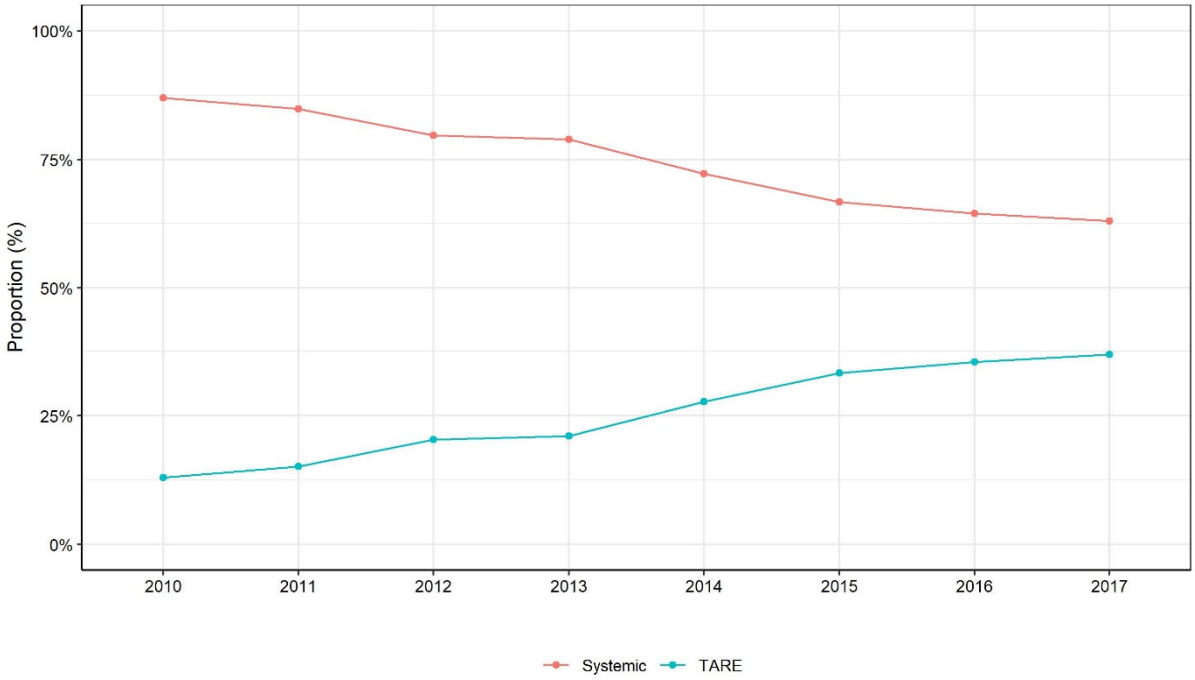


Figure 2. Overall survival estimates of patients treated with TARE vs. systemic treatment

A) Before propensity score matching B) After propensity score matching

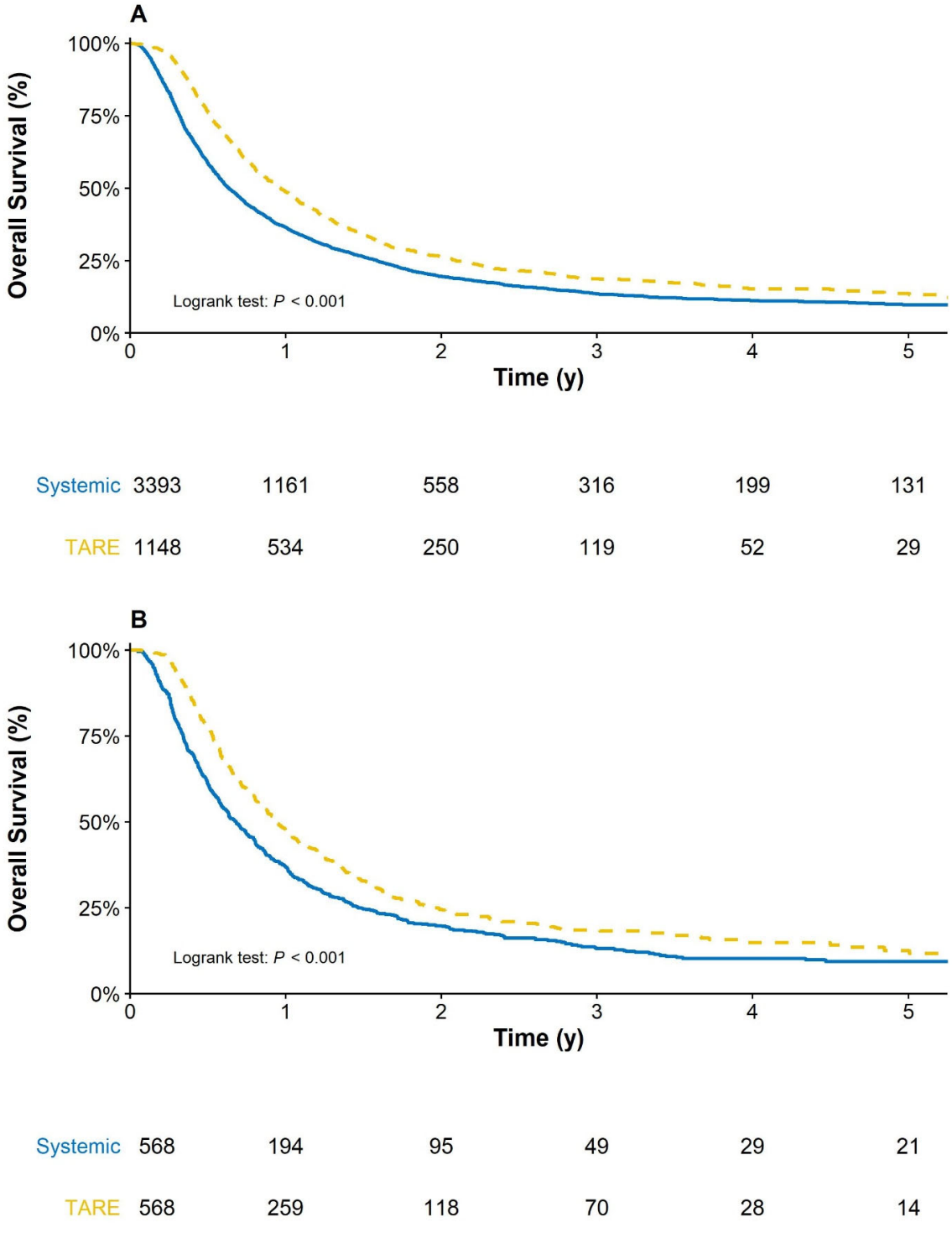
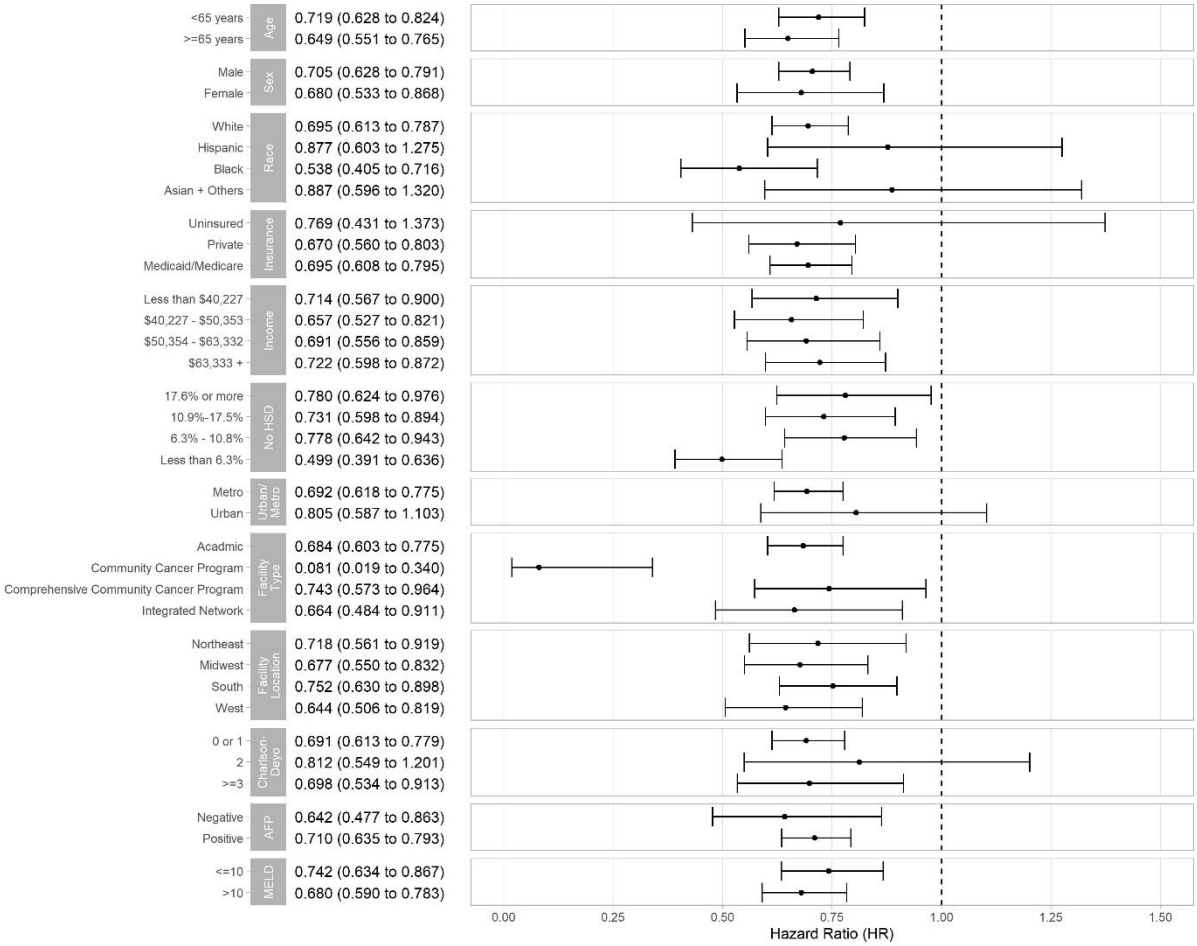
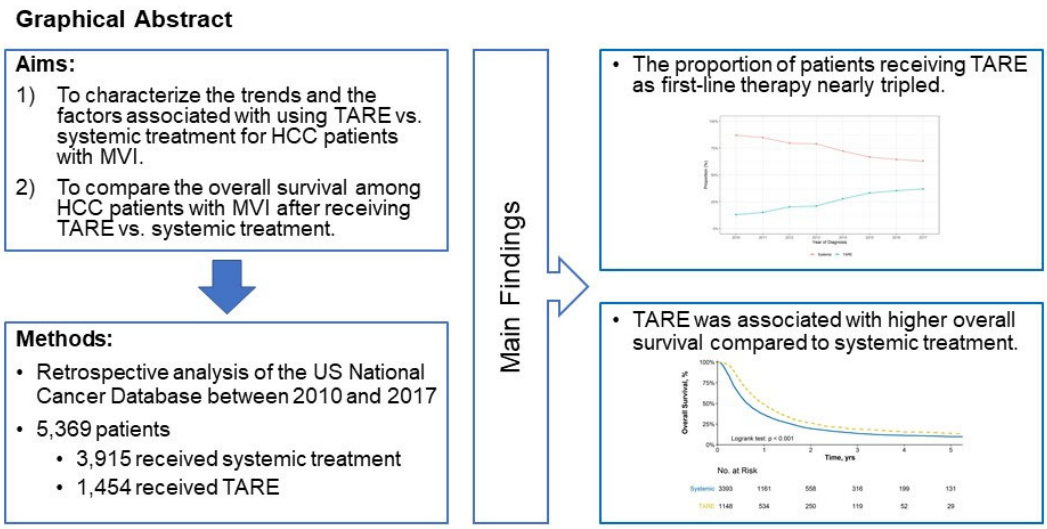


Figure 3. Comparison of survival in the various subgroup of patients treated with TARE vs. systemic treatment



Graphical Abstract



Supplemental Figure 1