Article published online: 2024-05-13

Predictors of Hepatic Decompensation after Yttrium90 Transarterial Radioembolization—Optimizing Patient Selection

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J Clin Interv Radiol ISVIR

Abstract

Objective Yttrium 90 (Y90) transarterial radioembolization (TARE) is effective for unresectable hepatocellular carcinoma (HCC) or to bridge/downstage before transplant; however, optimal patient selection is not well-described. This study aims to identify factors that increase risk of liver decompensation resulting in hospital admissions after TARE.

Methods Patients who received Y90 as their first treatment during 2012 to 2022 were identified from a prospectively collected database of 1675 HCC patients. Clinically significant hepatic decompensation was defined as total bilirubin more than or equal to 3 mg/dL or any increase in Model for End-stage Liver Disease (MELD) score resulting in readmission within 60 days or death.

Results Of 137 patients, 7 (5.1%) developed hepatic decompensation requiring admission within 30 days and an additional 8 (10.9%) within 60 days. Two of these patients (1.4%) died and two (1.4%) required urgent transplant within 2 months. Preprocedure albumin less than 3.5 gm/dL ($p = 0.0207$), international normalized ratio more than 1.2 ($p = 0.017$), ascites ($p = 0.036$), elevated MELD ($p = 0.012$), and Child-Pugh ($p = 0.007$) scores were significant predictors of decompensation, while creatinine and sodium were not. Patients with Child-Pugh B score were three to four times more likely to decompensate (28 vs. 8%) compared to Child-Pugh A. For every unit increase in Child-Pugh score more than 6, odds of decompensation increased by a factor of 2.15.

Conclusion Y90 TARE is safe and effective; however, 10.9% patients require readmission for worsened liver function. Because ascites is a significant factor in predicting decompensation and all patients require adequate renal function to receive Y90 TARE, Child-Pugh score may be more useful than MELD for patient selection. Further risk stratification may be required for those with a Child-Pugh score more than or equal to 7.

Keywords

- hepatocellular carcinoma
- yttrium 90
- transarterial radioembolization

DOI https://doi.org/10.1055/s-0044-1786711.
ISSN 2457-0214.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Liver cancer is the sixth most commonly diagnosed cancer worldwide, of which 75 to 85% of cases are hepatocellular carcinoma (HCC). While advances in hepatitis B virus (HBV) and hepatitis C virus (HCV) treatment and screening for HCC have improved the incidence and mortality of HCC, it remains the third leading cause of cancer death globally.[1] The rising incidence of steatosis-related liver disease may be driving the continued burden of HCC. Current practice standards for HCC management are guided by the Barcelona Clinic Liver Center (BCLC) staging system.[2] While transarterial chemoembolization (TACE) has traditionally been the standard of care for unresectable or intermediate-stage HCC (BCLC B), transarterial radioembolization (TARE) with yttrium90 (Y90) microspheres has gained recognition in recent years as an excellent choice for patients with single nodules less than or equal to 8 cm who are poor candidates or have previously failed TACE, ablation, resection, or transplant with life expectancy more than 5 years. TARE can also be used in patients with portal vein thrombosis while TACE is still considered a relative contraindication in select patients.[3–5]

Y90 is a pure beta-emitter that achieves its therapeutic effect by inducing DNA damage and subsequent tissue necrosis.[6] HCC receives 80 to 90% of its blood supply from the heaptic artery while normal liver parenchyma is primarily from the portal venous system. TARE takes advantage of the tumor's predominant arterial supply to selectively deliver treatment to targeted areas adn spare normal parenchyma.[7] The dosing varies (100–400 Gy) based on the type of microsphere used, extent of tumor involvement, liver mass size, lung shunt fraction, and total lung dose. Desired therapeutic goal and optimal dosimetry is an ongoing area of research; however, care is trending toward a personalized dosimetry approach.[8–12] Absolute contraindications to TARE include functional liver reserve less than 700 cc and uncorrectable liver shunt to gastrointestinal (GI) tract or lungs with potential for more than 30 Gy radiation exposure, decompensated liver function, hepatic encephalopathy, and pregnancy. Relative contraindications include more than 20% pulmonary shunt, elevated total bilirubin more than 2 mg/dL, abdominal ascites, severe portal hypertension, and prior external beam radiotherapy.[7,13]

The growing interest in TARE is due in part to its low-risk safety profile as an outpatient procedure. While the adverse effects after TARE are widely documented, current knowledge is primarily derived from small-to-moderate-sized cohort studies. Moreover, there is limited data regarding the rates of complications requiring hospitalization and the precipitating factors.[14,15] This study aims to address this knowledge gap and add to the current fund of literature by studying those treated with Y90 in a unique population where HCC is prevalent within its Asian-Pacific Islander dominant population. If factors such as MELD, Child-Pugh class, bilirubinemia, international normalized ratio (INR), creatinine, transaminase levels, underlying cirrhosis, tumor burden, or BCLC staging are found to influence the risk of readmission or liver decompensation, providers can better select patients to enhance outcomes with Y90-TARE.

Methods

Medical records from patients diagnosed with HCC who underwent Y90 TARE between January 1, 2012 through January 1, 2022 at the Queen's Medical Center (QMC) in Honolulu, Hawaii were retrospectively reviewed. This medical center is the tertiary referral center for complex hepatobiliary problems and has the state's only dedicated liver center and liver transplant program. All cases are discussed in a multidisciplinary hepatobiliary conference to decide on optimal care. Y90 TARE therapy was offered to patients with inoperable tumors as a salvage therapy, prior failed therapies, large solitary tumors with inadequate future liver remnant for upfront resection, and those requiring bridging or downstaging to transplant or resection. In this particular study, only patients who underwent Y90 TARE as their first treatment were included, and patients who underwent Y90 TARE as a secondary treatment for recurrence were excluded. A total of 137 patients met this criterion. Patient data was extracted from a single surgical practice and supplemented by electronic medical records from the medical center. All data was deidentified before analysis and in compliance with HIPAA standards. This study was approved by the Institutional Review Board of The Queen's Medical Center and complies with ethical regulations.

Y90 TARE was performed by a group of seven interventional radiologists at this medical center. All candidates for TARE therapy must undergo extensive workup, or "simulation," prior to treatment to assess anatomy and estimated shunt fraction. Hepatic angiography is performed to identify and prophylactically embolize vessels that increase the risk of microsphere migration into the GI tract. Technetium-99mm labeled macroaggregated albumin, which is similar in size to the Y90 microspheres, is administered to the proposed treatment site, and a single-photon emission computed tomography image is performed to determine hepatopulmonary shunting. Complications after radioembolization are primarily classified within the following groups: postradioembolization syndrome, nontarget deposition of microspheres (radiation pneumonitis, pancreatitis, dermatitis, biliary, or GI sequelae), and liver dysfunction secondary to radiation-induced parenchymal damage. Complications largely arise due to radiation-induced tissue or microembolic effects.[16,17] Patients who had a shunt fraction greater than 10 to 20% were not offered Y90 TARE. The actual Y90 TARE procedure was performed 3 to 4 weeks after the arterial mapping study. All Y90 TARE treatments were administered to either the right or left liver lobe; no segmental or subsegmental treatments were performed.

The following data was extracted: age, gender, ethnicity, comorbidities (diabetes mellitus, hypertension, hyperlipidemia, personal or family history of malignancy), risk factors for HCC (cirrhosis, HBV, HCV, nonalcoholic steatohepatitis (NASH), alcohol abuse, current tobacco, or alcohol use). Clinical records were used to identify the presence of ascites,

encephalopathy, height and weight to calculate body mass index (BMI), and tumor characteristics (size, number of nodules, laterality, BCLC staging, within Milan or UCSF transplant criteria). Laboratory data collected included bilirubin, albumin, protime INR, creatinine in order to calculate Child-Turcotte-Pugh score and Model for End-stage Liver Disease (MELD). These laboratory studies were measured just prior to Y90 arterial mapping and within 3 months after the actual Y90 TARE administration. Patients were categorized into Child-Pugh class (A, B, or C) based upon Child-Turcotte-Pugh score (5–6, 7–8, or >9 respectively). Any subsequent locoregional therapy or surgical intervention (resection, transplant) following the initial Y90 TARE was also recorded.

Patients who had an increase in bilirubin more than or equal to 3 mg/dL or increase in MELD score were identified. Hepatic decompensation was defined as any hospital admission, urgent liver transplantation, or death within 60 days in which there was a bilirubin more than or equal to 3 mg/dL or an increase in MELD score. Any complications including abdominal pain, worsening ascites, encephalopathy, portal vein thrombus, GI or variceal bleeding, acute kidney injury, infection, or need for urgent liver transplant within 2 months were recorded. The primary outcome of this study was to determine risk factors for clinically significant hepatic decompensation within 60 days of Y90 TARE treatment. Statistical analysis was conducted by using SPSS 29.0.1. Continuous variables were compared using Wilcoxon rank sum tests and Kruskal–Wallis tests and categorical variables using Fisher's t-tests and Pearson's chi-squared tests. Statistical significance was set at level 0.05. Multivariate regression models were used to identified factors associated with hepatic decompensation. Factors analyzed included age, gender, ethnicity, history of HBV, HCV, MASH, alcohol abuse, tobacco use, Child-Pugh score, ascites, encephalopathy, total albumin, INR, creatinine, sodium, tumor number, tumor size, and tumor laterality, Y90 dosing, and liver radiation dosing.

Results

Of 137 patients identified, 31 were female (23%) and 106 were male (77%). Ethnic distribution was as follows: 64 Asian (46%), 33 (24%) Caucasian, 28 (21%) mixed race, 9 (7%) Native Hawaiian/Pacific Islander, and 3 (2%) Hispanic. The mean age at the time of diagnosis was 66.7 (standard deviation [SD] = 10.5) years. Most were Eastern Cooperative Oncology Group (ECOG) status 0 (48%) or ECOG 1 to 2 (47%), and a minority ECOG status 3 (5%). Risk factors for HCC included alcohol use (45%, $n = 61$), HCV (40%, $n = 55$), HBV (27%, $n = 37$), and nonalcoholic steatosis (26%, $n = 35$). Other comorbidities included smoking (66%, $n = 90$), diabetes (47%, $n = 64$), and obesity (31%, $n = 42$). Approximately 74% of patients had underlying cirrhosis. The majority of patients were Child-Pugh class A (84%, $n = 115$) with fewer being Child-Pugh class B (10%, $n = 14$). MELD scores ranged from 6 to 22, with a mean score of 9 (►**Table 1**).

Most patients were American Joint Committee on Cancer 7th edition stage 0 to 2 (78%, $n = 107$), and 30 (22%) patients were advanced stage 3 to 4. Solitary tumors were more common (69%, $n = 95$) and a minority had multiple (≥2) tumors (31%, $n = 42$). Most tumors (82 %, $n = 112$) were unilateral with a mean size of 5.9cm (SD = 3.5). The tumors of approximately half (53%, $n = 72$) were eligible for transplant: 45 patients were within Milan criteria and 27 were beyond Milan but within UCSF criteria (►**Table 2**). Most patients had Y90 TARE treatment to the right (78%) lobe, and a fewer (22%) to the left lobe. No segmental or sublobar treatments were performed in this study. The average Y90 dose was 59.8 mCi (SD = 28.5, range = 16.8–143.6) with average liver radiation dose of 114.7 Gy (SD = 11.1, range = 63.4–149.4).

In the 137 patients, 20 (15%) had an increase in bilirubin to more than or equal to 3 mg/dL and 54 (39%) patients had an increase in MELD score after the procedure. Of these, 15 patients (10.9%) developed clinically significant hepatic decompensation resulting in readmission or death after Y90 TARE treatment. Seven (5.1%) developed hepatic decompensation requiring admission within 30 days and an additional 8 (5.8%) patients within 60 days. Two of these patients (1.4%) died from hepatic decompensation after Y90 TARE. One patient died 21 days after Y90TARE for a 13 cm tumor with right portal vein invasion. The second patient died due to hepatorenal syndrome, severe encephalopathy, and respiratory failure 64 days after treatment of a 5.8 cm tumor. Of the patients with clinically significant hepatic decompensation, the majority (59%, $n = 10$) had an increased MELD score and fewer (41%, $n = 7$) had elevated total bilirubin of more than or equal to 3 mg/dL postprocedure. The most common complication was bleeding: GI (20%, $n = 3$), intraabdominal (20%, $n = 3$), and variceal (13.3%, $n = 2$). Less common complications included pulmonary congestion ($n = 3$), worsening ascites ($n = 2$), encephalopathy ($n = 2$), portal venous thrombus ($n = 2$), acute kidney injury, and spontaneous bacterial peritonitis. Two other patients (1.4%) who developed hepatic decompensation after Y90 treatment required urgent transplant within 2 months of their treatment. One patient was readmitted for portal venous thrombosis and acute kidney injury. This patient had a history of HCV, alcohol abuse, prior illicit drug use, and was classified as Child class B (score 8). Labs at the time of readmission were notable for a rise in total bilirubin of from 1.3 to 30.5 mg/dL and an increase in MELD score from 12 to 36. The second patient was readmitted for worsening ascites, pulmonary congestion, and spontaneous bacterial peritonitis. This patient had a history of HBV, alcohol abuse, obesity (BMI: 37.3) and was classified as Child class B (score 9). Labs at time of readmission were notable for a rise in total bilirubin of from 1.7 to 3.1 mg/dL and an increase in MELD score from 15 to 18. Both had sodium levels less than 130 and elevated mean prothrombin time (19.9) and INR (1.75) at the time of readmission.

Preprocedure albumin less than 3.5 mg/dL ($p = 0.027$), INR more than 1.2 ($p = 0.017$), bilirubin ($p = 0.009$), ascites ($p = 0.036$), and elevated MELD ($p = 0.012$) and Child-Pugh ($p = 0.007$) scores were significant predictors of decompensation within 60 days. Preprocedural creatinine ($p = 0.259$), sodium ($p = 0.082$), and platelets ($p = 0.497$) were not associated with hepatic decompensation (►**Table 1**). For every unit increase in total bilirubin greater than 0.95, the risk of

Table 1 Patient demographics, risk factors for hepatic decompensation within 60 days

			All patients	*p*-Value
Total number			137	
Mean age at diagnosis			66.7	0.971
Gender	Female		31 (23%)	0.656
	Male		106 (77%)	
Ethnicity	Asian		64 (46%)	0.389
	NHPI		9 (7%)	
	White		33 (24%)	
	Hispanic		3 (2%)	
	Mixed race		28 (21%)	
HCC risk factors	HBV		37 (27%)	0.688
	HCV		55 (40%)	0.491
	Cirrhosis		102 (74%)	0.732
	Tobacco abuse		90 (66%)	>0.999
	Alcohol abuse		61 (45%)	0.494
	NASH/NAFLD		35 (26%)	0.732
BMI			25.3	0.368
Ascites			26 (19%)	0.036
Preprocedure labs (mean)	Child-Pugh	A	115 (84%)	0.007
		B	14 (10%)	
	MELD		8	0.012
	Sodium		138	0.082
	Creatinine		0.99	0.259
	Bilirubin		0.89	0.009
	Albumin <3.5		23 (17%)	0.027
	Platelets		165	0.497
	INR		1.1	0.017
Bilateral tumor			27 (20%)	0.423
Tumor size ≥ 5cm			68 (50%)	>0.999
Y90 dose (mCi)			59.8	0.969
Liver radiation dose (Gy)			114.7	0.903

Abbreviations: BMI, body mass index; HBV hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; NASH, nonalcoholic steatohepatitis; NHPI, Native Hawaiian and Pacific Islander.

hepatic dysfunction increased by a factor of 3. Patients with Child-Pugh B score were three to four times more likely to have hepatic decompensation than those with Child-Pugh A (28 vs. 7.7%). For every unit increase in Child-Pugh score over 6, the odds of severe decompensation increased by a factor of 2.15 (►**Fig. 1**).

Patient demographics, tumor characteristics, and Y90 or liver radiation dosing did not influence the risk of decompensation; this included age, gender, ethnicity, ECOG status, history of HBV, HCV, NASH, alcohol abuse, former or active tobacco use, tumor size, tumor, laterality, Y90 dosing, or liver radiation dosing (►**Table 1**). There were no risk factors associated with mortality; however, this may have been due to the small sample size ($n = 9$).

Discussion

Y90 TARE is generally well tolerated and is now widely accepted as a therapy for those with unresectable HCC, or those who are poor responders or poor candidates for TACE. Notably, the 2021 Legacy study demonstrated the effectiveness of TARE as a primary treatment method for BCLC-0 patients with single nodules less than 8 cm.[2,18] The National Cancer Center Network (NCCN) also recommends locoregional therapies including TACE and TARE as neoadjuvant bridging or downstaging therapies for those with transplant wait list times exceeding 6 months.[19] Eligibility is generally limited to those with adequate renal function and bilirubin less than 2 to 3 mg/dL due to increased risk of liver failure;

Table 2 Tumor/patient characteristics

		All patients ($n = 137$)
Median number of tumors		1
Average size (cm)		5.9
AJCC stage	0–2	107 (78%)
	3–4	30 (22%)
Location	Unilateral	112 (82%)
	Bilateral	25 (18%)
Transplant eligible	Milan	45
	UCSF, not Milan	27
Hepatic decompensation	Within 30 days	6 (4.3%)
	Within 60 days	13 (9.4%)
Death	Within 30 days	1
	Within 60 days	1

Abbreviations: AJCC, American Joint Committee on Cancer; UCSF, University of California, San Francisco.

however, there is limited literature that examines the prognostic factors that may predict success, failure, or complications from Y90 TARE.[20–22] As HCC is most prevalent in the Asian and Pacific Islander populations, evaluating outcomes in Hawaii, which has the highest relative populations of Asians (36.8 vs. 6.1%) nationwide, is critical.[23]

The current 2023 NCCN guidelines recommend restricting Y90 eligibility to those with preprocedural total bilirubin less than 2 mg/dL. This recommendation primarily arises from a single-center prospective study concuted by Salem et al in 2010.[20,21] Our study confirms that this recommendation is appropriate given our findings of a threefold greater risk of hepatic decompensation for every unit increase above 0.95. Our study, however, only evaluated lobar administration of Y90 TARE. As this treatment modality has the safety benefit of being able to be administered segmentally or subsegmentally, such as in the Legacy study, further studies evaluating hepatic decompensation in treating selective areas would be of interest, especially for those with more advanced disease or who have mild residual liver toxicity after their first treatment.

While most cases of liver toxicity after radioembolization are reversible, persistent toxicities of grade 3 or higher, as defined by the National Cancer Institute Common Terminology Criteria version 3.0, are reported in 9 to 19% of patients.[21,22] The most serious complication is radioembolization-induced liver disease that has a reported incidence of up to 6.7%.[10,24–26] It is characterized by elevated bilirubin and liver enzymes—specifically alkaline phosphatase, ascites, or jaundice approximately 2 weeks to 4 months after radiation. Risk increases with age, baseline bilirubin levels, whole-liver treatment, and use of the empiric method for dose calculation.[10,22] Unfortunately, evaluation of postprocedural hepatic dysfunction is complicated by the preexisting dysfunction inherent in many HCC patients especially those with cirrhosis. Sangro et al demonstrated that even in patients without chronic liver disease, 20% developed clinical hepatic dysfunction within 4 to 8 weeks of treatment, all of whom had received chemotherapy prior to radioembolization. This suggests that that decline in hepatic function may be largely attributed to preexisting liver dysfunction inherent to HCC itself in conjunction with sequela from prior

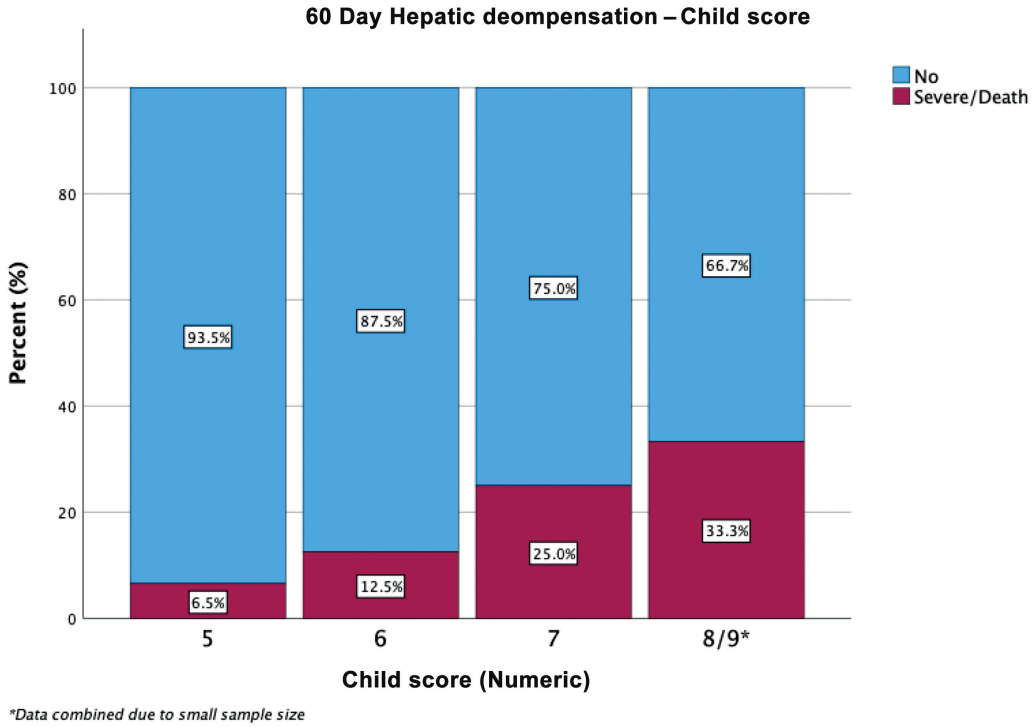

Fig. 1 Hepatic decompensation at 60 days by Child-Pugh score.

therapies rather than Y90 treatment.[21,22,24] Our study eliminates this potential confounding variable by only evaluating patients who received Y90 treatment as their first treatment modality, thus excluding those with recurrent liver cancer who received Y90 as a salvage therapy. In doing so, this study demonstrates a similar to lower-risk safety profile of Y90 compared to prior studies with only 5.1% patients developing hepatic decompensation requiring readmission or death within 30 days after treatment and 10.9% within 60 days. Unfortunately, 2.8% still developed severe complications resulting in urgent transplant or death, thereby suggesting that current selection criteria should be improved upon.

Prior studies have also identified total delivered radiation dose, treatment of the right lobe, and increased number of prior liver treatments as risk factors for hepatic decompensation.[10,21,22] One recently published study in 2023 by Lee et al has now demonstrated lower overall survival and progression-free survival in patients with Child-Pugh class B compared to A, median score 6.[27] This in conjunction with our study's findings of three to fourfold elevated risk of hepatic decompensation with Child-Pugh class B and odds of severe decompensation increasing by a factor of 2.15 for every unit increase in score over 6 suggests that preprocedural evaluation of Child-Pugh score should be routine. While MELD score was also noted to be a significant predictor of decompensation within 60 days, each component of the Child-Pugh score was found to be a significant predictor of decompensation (albumin, INR, bilirubin, ascites) while creatinine, which is a component of MELD, was not. This may be due to the inherent selection bias created by the need for adequate renal function to tolerate intravenous contrast for these procedures. A similar study by Brown et al.[28] in patients undergoing TACE also demonstrated that Child-Pugh score, and specifically albumin level greater than 3.4 g/dL, was also a more useful predictor of survival than MELD. As such, our findings suggest that evaluating for Child-Pugh score A with further consideration for risk stratification for those with a score greater than 7 may be more useful in selecting candidates for TARE. Further studies evaluating the impact on overall survival will be paramount.

This study is limited in that it was retrospective and from a single center in Hawaii. Some procedural specifics including perfused volume and tumor/normal liver ratio were not consistently recorded in the interventional radiology reports and may limit characterization of hepatic decompensation. Furthermore, as mentioned previously, this study only evaluated patients who received Y90 TARE as their first treatment regimen; thus, it may have inherently biased our patient population to those with lower baseline liver dysfunction either secondary to less advance disease or fewer prior interventions.

Conclusions

Y90 TARE is a generally safe and effective treatment modality for unresectable HCC. With the current patient selection, 10.9% of patients experience a decline in liver function and 2.8% of patients experience severe decompensation resulting in death or need for urgent liver transplant. As the role of TARE continues to expand in the treatment of HCC, refining patient selection criteria will be paramount for optimizing patient selection and outcomes. Child-Pugh score may be a more useful metric for risk stratification than just bilirubin alone when selecting candidates for TARE as it incorporates multiple factors that contribute to hepatic decompensation.

Abbreviations

HCC	Hepatocellular Carcinoma
Y90	Yttrium90
TARE	Transarterial Radioembolization
TACE	Transarterial Chemoembolization
BCLC	Barcelona Clinic Liver Center
MELD	Model for End-Stage Liver Disease
INR	International Normalized Ratio
SPSS	Statistical Package for Social Sciences
HIPAA	Health Insurance Portability and Accountability Act
UCSF	University of California, San Francisco
MASH	metabolic dysfunction-associated steatohepatitis
NHPI	Native Hawaiian and Pacific Islander

Ethical approval

This study was approved by the Institutional Review Board of The Queen's Medical Center and complies with ethical regulations.

Acknowledgements

Linda Wong, MD, is affiliated with Astra-Zeneca's Speakers Bureau. All other authors have no financial disclosures or conflicts of interest to declare.

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