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ORIGINAL ARTICLE

Hepatic decompensation after transarterial radioembolization: A retrospective analysis of risk factors and outcome in patients with hepatocellular carcinoma

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Abstract

Transarterial radioembolization (TARE) is a well-established therapy for intermediate and advanced tumor stages of hepatocellular carcinoma (HCC). Treatment-associated toxicities are rare. Previous studies have outlined that the prognosis after TARE is determined primarily by tumor stage and liver function. The subset of patients benefiting from TARE remains to be defined. Sixty-one patients with HCC treated with TARE between 2015 and 2020 were retrospectively included in the study. Hepatic decompensation was defined as an increase of bilirubin or newly developed ascites that was not explained by tumor progression within 3 months after TARE. Predictive factors of hepatic decompensation and prognostic factors were assessed. Hepatic decompensation was observed in 27.9% (n = 17) of TARE-treated patients during follow-up. Albumin-bilirubin (ALBI) score at baseline and radiation dose on nontumor liver proved to be independent risk factors for the development of hepatic decompensation in multivariable regression models (ALBI score: odds ratio [OR] 6.425 [1.735;23.797], $p < 0.005$; radiation dose: OR 1.072 [1.016;1.131], $p < 0.011$). The occurrence of hepatic decompensation markedly impaired the prognosis of the patients. Survival was significantly worsened. Hepatic decompensation has shown to be an independent negative prognostic factor for death, adjusted for Barcelona Clinic Liver Cancer stage, age and ALBI grade (hazard ratio 5.694 [2.713;11.952], $p < 0.001$). *Conclusion*: Hepatic decompensation after TARE for HCC treatment is a highly relevant complication with major effects on the prognosis of patients. Main risk factors are the pretreatment ALBI score and radiation dose. There is an urgent need to define safe cutoff values and exclusion criteria for TARE to limit complications and improve patient outcomes.

Christian Goetz and Dominik Bettinger shared senior authorship.

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INTRODUCTION

Transarterial radioembolization (TARE) is an established treatment for patients with malignant liver tumors such as liver metastasis of solid tumors and primary liver cancer. In hepatocellular carcinoma (HCC), TARE is implemented as an alternative to transarterial chemoembolization (TACE) in intermediate and to systemic therapy in advanced stages (Barcelona Clinic Liver Cancer [BCLC] group classification B and C, respectively) and can be used as bridge to transplant or resection. The antitumoral effect of TARE is primarily ascribed to the dose of radiation emitted by yttrium-90 (90Y) resin or glass microspheres into the hepatic vasculature. Due to the small size of particles, there is less macro-embolic effect as in TACE; thus, TARE has been proven to be safe in patients with portal vein thrombosis (PVT).[1] Patients treated with TARE usually benefit from a mild toxicity profile and good quality of life during treatment.[2]

Several large randomized controlled studies have previously investigated the applicability and outcome of TARE in patients with HCC but failed to show superiority in overall survival (OS) compared with sorafenib[3,4] or TACE.[5] The main point of discussion remains the selection of patients benefiting from TARE. On the other hand, several questions regarding the applicability and indication of TARE and the treatment itself are unanswered. Notably, dosimetry planning has become the center of attention, as previous dosimetry approaches have been suspected to be insufficient to predict good tumor response while limiting treatment-related toxicity. Ongoing studies aim to analyze the effect of a personalized dosimetry approach in TARE,[6] and results are awaited eagerly.

Hepatic decompensation is a severe complication occurring after TARE. Underlying liver cirrhosis is a known risk factor for hepatic decompensation,[7] affecting most patients with HCC. Other risk factors for patients with HCC remain to be defined. In this single-center, retrospective study, we aimed to investigate the outcome of patients with intermediate and advanced HCC treated with TARE, focusing on the development of hepatic decompensation after treatment. This study should shed light on predictive factors for hepatic decompensation and help to define a subset of patients at highest risk.

METHODS

Patient selection and follow-up

This retrospective observational study included 154 patients treated with TARE between January 2015 and December 2020 at the University Medical Center Freiburg (Figure 1). All patients were bearing liver-exclusive or liver-dominant disease. None of the patients with HCC were eligible for liver transplantation before and after TARE, as they were outside the Milan criteria. Treatment decision for TARE in patients with extrahepatic metastasis was based on individual decisions discussed in and approved by the local tumor board. The hepatic manifestation was considered as the leading manifestation in these cases. PVT was not an exclusion criterion. Initial diagnostic imaging consisted of multiphase contrast-enhanced computed tomography or contrast-enhanced magnetic resonance imaging within 3 months before TARE. According to the manufacturer's specifications, all patients had bilirubin levels ≤2 mg/dl and tumor volume <50% of total liver volume in diagnostic imaging. Additional exclusion criteria were prior liver transplantation and any anti-cancer therapy between the first TARE treatment and 3-month imaging. All TARE procedures were conducted exclusively with resin 90Y microspheres (Sirtex Medical Europe GmbH). Administration to ≤2 segments or radiation segmentectomy patients were excluded to obtain a homogenous study population as described in the TARGET study.[8]

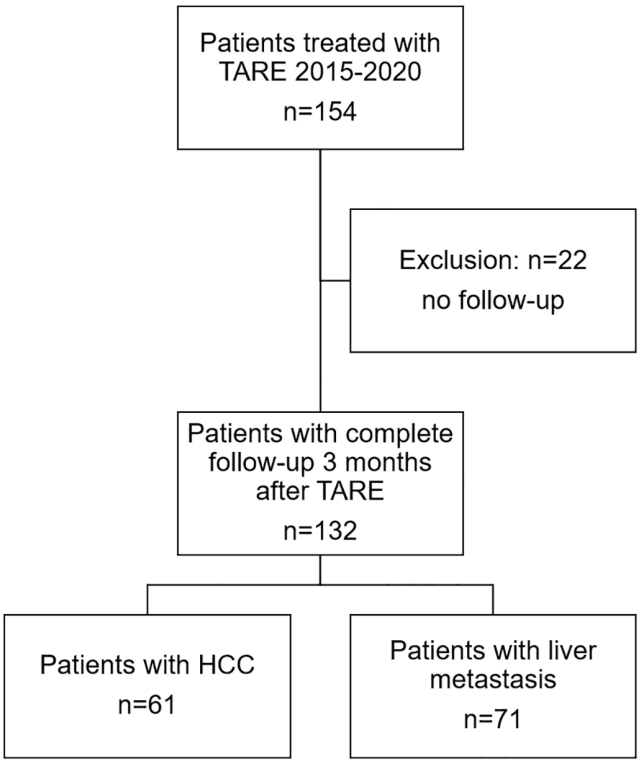

FIGURE 1 Flow chart of all patients included and excluded in the study

Seventy-one patients were treated for HCC. As a comparison group, 83 patients treated for liver metastasis of solid tumors were included (Table S1). Patients with no follow-up 3 months after TARE were excluded from the study (n = 10 in the HCC group, n = 12 in the metastasis group). From the remaining

132 patients, the demographic data were reviewed at baseline. The clinical, laboratory, and treatment-related data were assessed at different time points (baseline, 4 weeks, and 3 months after last treatment). The radiological response was assessed 3 months after TARE (second treatment, if applicable). All included patients were scheduled for therapy by the multidisciplinary tumor board.

Definitions

HCC was diagnosed by typical radiological or histological features, as recommended by current European Association for the Study of the Liver and American Association for the Study of Liver Diseases guidelines.[9,10] Tumor stage was graded according to BCLC. Response to treatment was assessed by modified Response Evaluation Criteria in Solid Tumors (mRECIST1.1).[11] The diagnosis of liver cirrhosis was confirmed by clinical, radiological, and laboratory findings. In individual cases, liver biopsy was performed to confirm the diagnosis. Liver function was assessed using the Child-Pugh score, Model of End-Stage Liver Disease (MELD) score and albumin-bilirubin (ALBI) score. Treatment-associated adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE).[12] Eastern Cooperative Oncology Group (ECOG) performance status was used to assess quality of life at baseline.

Hepatic decompensation was defined as an increase of bilirubin at least grade 3 according to CTCAE (at least 3-fold increase to baseline or upper limit of normal) or newly developed ascites at follow-up. Patients with ascites but no increase of bilirubin according to CTCAE grade 3, who had progressive disease (PD) at follow-up, were excluded from the hepatic decompensation group (n = 5).

TARE procedure and dosimetry

A detailed description of the pretreatment workup, therapy planning, and dosimetric approach is provided in the Supporting Information.

The dosimetry was calculated conventionally using the standard body surface area (BSA) method recommended by the manufacturer.[13,14] The activity to be implanted was adjusted according to the tumor size within the treated portion of the liver and the size of the patient.[13–15]

Following treatment, the applied radiation dose on the nontumor liver volume was calculated with two different dosimetry models (homogenous model/single-compartment approach and partition model/multi-compartment approach) using the PMOD software (version 3.8; PMOD Technologies Ltd.). Figure 2 illustrates the process preceding and following a single TARE application in a patient bearing tumors in the right liver lobe. The single-compartment and multiple-compartment approaches are shown.

Statistical analyses

The study was performed as an observational study. Patient data were analyzed from the day of pre-TARE planning (within 4 weeks before first TARE treatment). All patients were followed up until death or last contact. The primary endpoint was the development of hepatic decompensation 3 months after TARE. The secondary endpoint was OS after TARE. OS was calculated from the day of first TARE treatment. The cutoff point of survival data was June 29, 2021.

Categorical variables were expressed as frequencies and percentages, and continuous variables as median with interquartile range (IQR). Patients were stratified according to the occurrence of hepatic decompensation after TARE. Statistical differences were determined by chi-square test or Fisher's exact test for categorical variables and by Wilcoxon rank-sum test for continuous variables (no Gaussian distribution of the data). p values < 0.05 were considered significant.

OS was calculated using Kaplan–Meier analyses with death recorded as event. Differences in survival were calculated using log-rank tests. Predictive factors for the development of hepatic decompensation after TARE were analyzed by calculation of univariable and multivariable logistic regression models. After univariable analyses of possible predictive factors parameters with a p value < 0.05 (p-in) and p-out value of 0.1 entered the multivariable, bidirectional stepwise regression model starting with an empty model. Statistical analyses were performed with SPSS (version 27.0; IBM) and GraphPad Prism (version 8; GraphPad Software).

RESULTS

Patient characteristics

Table 1 summarizes the baseline data of patients with HCC (n = 61) stratified according to the development of hepatic decompensation after TARE. Seventeen patients (27.9%) were female and the median age at TARE was 65 years (IQR 60–75). Forty-eight patients (78.8%) were diagnosed with liver cirrhosis. The leading causes of liver disease were alcohol-associated liver disease (n = 18; 29.5%) and chronic hepatitis C virus infection (HCV, n = 18; 29.5%), followed by nonalcoholic fatty liver disease (n = 11; 18.0%) and chronic hepatitis B virus infection (n = 9; 14.8%). The tumor stage was classified as BCLC B in 51 patients

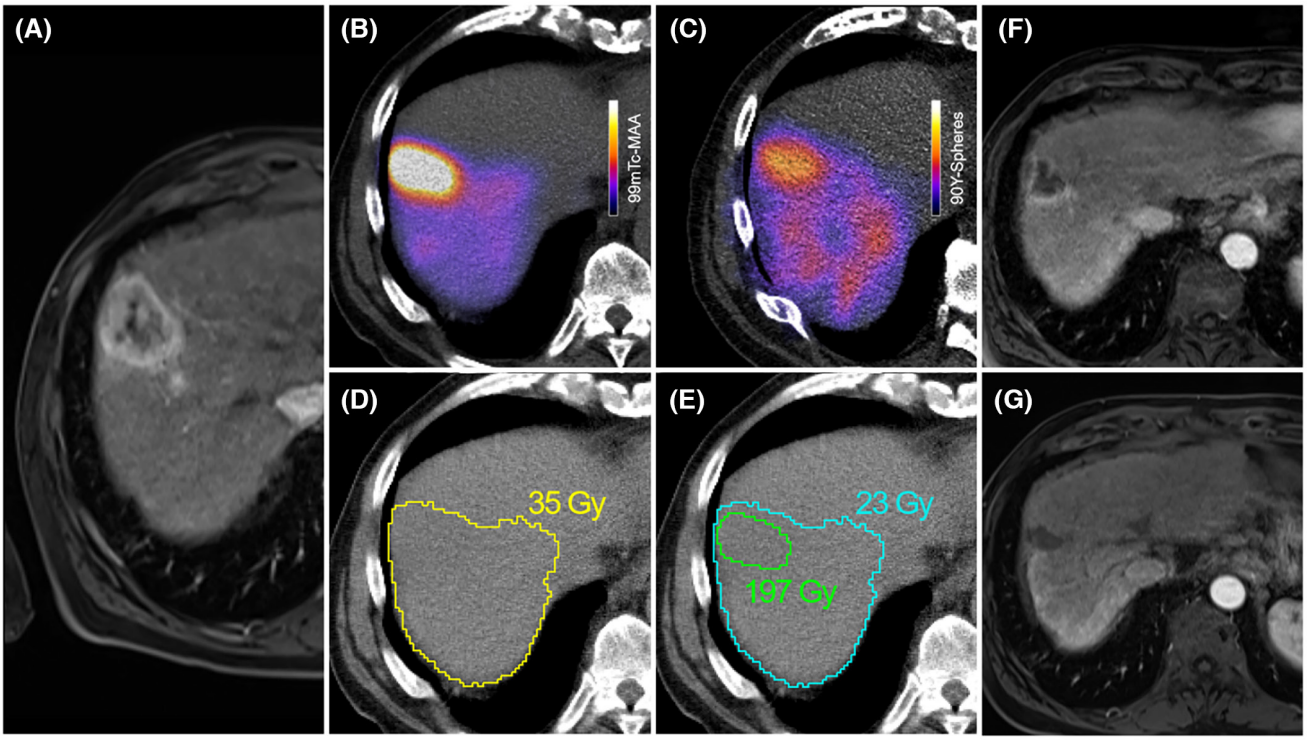

FIGURE 2 Therapy planning and outcome after a single transarterial radioembolization (TARE) application. (A) A 73-year-old male patient with multiple hepatocellular carcinoma (HCC) lesions in the right liver lobe was referred to TARE. The most prominent lesion (43 × 33 mm) laid subcapsular in Segment VIII and showed a pathognomonic contrast enhancement in the T_1-weighted gradient-echo acquisitions (VIBE) after intravenous administration of a Multihance bolus (Bracco Imaging Deutschland GmbH) (early arterial phase). (B) Following the workup process and the injection of 105 MBq 99mTc-MAA in the right hepatic artery, the SPECT/CT images showed a preponderant deposition of the tracer in the subcapsular lesion. During TARE application a few days later, a total of 1.15 GBq of 90Y microspheres (Sirtex Medical Europe GmbH) were infused selectively into the right hepatic artery after catheter repositioning. The post-therapy imaging (C) showed a similar distribution of the microspheres compared with the workup session. Dosimetry assessment was carried out both using a single-compartment approach (D) and a multicompartment model (E). Although the first model presumes homogeneous irradiation and identical dosimetry for both tumor and the healthy liver, the second approach defines not only multiple volumes and yields much higher absorbed doses for the subcapsular tumor, but also allocates a minored irradiation of healthy parenchyma (23 Gy vs. 35 Gy). The follow-up imaging 3 months (F) and 1 year (G) after TARE attest to the regress in size and contrast enhancement of the treated lesion. The left liver lobe developed hypertrophy. The patient presented no hepatic decompensation during follow-up

(84.5%) and BCLC C in 11 patients (15.5%). Six patients (9.8%) had extrahepatic metastasis, localized in the lung (n = 2), lymph nodes (n = 3), adrenal glands (n = 2), and bone (n = 1). PVT was present in 24.6% of patients (n = 15). Almost half of the patients (n = 28; 45.9%) were treatment-naïve, 14 patients (23.0%) were treated with prior resection, and 17 patients (27.0%) with TACE before TARE. The overall quality of life at baseline, assessed by ECOG performance status, was good (ECOG 0: n = 48 [78.7%], ECOG 1: n = 10 [16.4%], ECOG 2: n = 3 [4.9%]).

In 44.3% of patients, right and left liver lobe was treated in two separate procedures while 55.7% received treatment of one lobe only. The mean activity applied during TARE was 2.1 Giga Becquerel (GBq [IQR 1.53–2.30]). The most common treatment-related adverse events were nausea and fatigue, experienced by 14 (23.7%) and 13 patients (22%). Direct treatment-related adverse events were relatively mild and did not exceed grade 2 according to CTCAE (Table S3).

Incidence of hepatic decompensation after TARE

Seventeen patients with HCC (27.9%) developed hepatic decompensation after TARE. Compared with patients who were treated with TARE due to liver metastases of non-liver-related tumors (Tables S1 and S2), patients with HCC developed hepatic decompensation more frequently (27.9% vs. 15.5%, $p = 0.083$). Only 1 patient (1.4%) with non-primary liver cancer was diagnosed with liver cirrhosis, compared to 48 patients (78.7%) with HCC ($p < 0.001$), indicating liver cirrhosis as a main determinant of hepatic decompensation. Univariable and multivariable regression models confirmed that besides the radiation exposure of the non-tumor liver volume (in patients with and without HCC; Tables S4 and S5), the diagnosis of liver cirrhosis is an independent risk factor for hepatic decompensation after TARE adjusted for tumor entity and the presence of PVT (Table S4).

TABLE 1 Baseline data and characteristics of patients with HCC

	All patients (n = 61)	No hepatic decompensation (n = 44)	Hepatic decompensation (n = 17)	*p* value
Age (years)	65 (60; 75)	65.5 (60; 76.5)	64 (61; 72)	0.735
Female sex	17 (27.9%)	13 (29.5%)	4 (23.5%)	0.757
Liver cirrhosis	48 (78.8%)	33 (75.0%)	15 (88.2%)	0.319
Etiology of liver disease				
Alcohol	18 (29.5%)	12 (27.3%)	6 (35.3%)	0.538
HBV	9 (14.8%)	7 (15.9%)	2 (11.7%)	1
HCV	18 (29.5%)	12 (27.3%)	6 (35.3%)	0.538
NAFLD	11 (18.0%)	9 (20.5%)	2 (11.7%)	0.494
AIH	1 (1.6%)	1 (2.3%)	0	1
Other	2 (3.3%)	1 (2.3%)	1 (5.9%)	0.483
ECOG				
0	48 (78.7%)	38 (86.4%)	10 (58.8%)	0.038
1	10 (16.4%)	4 (9.1%)	6 (35.3%)	
2	3 (4.9%)	2 (4.7%)	1 (5.9%)	
Previous HCC treatment				
None	28 (45.9%)	19 (43.2%)	9 (52.9%)	0.493
Resection	14 (23.0%)	12 (27.3%)	2 (11.7%)	0.311
RFTA	3 (4.9%)	3 (6.8%)	0	0.553
TACE	17 (27.9%)	13 (29.5%)	4 (23.5%)	0.757
TKI	2 (3.3%)	1 (2.3%)	1 (5.9%)	0.483
SBRT	5 (8.5%)	4 (9.1%)	1 (5.9%)	1
Tumor characteristics				
BCLC stadium				
BCLC B	51 (83.6%)	35 (79.5%)	16 (94.1%)	0.257
BCLC C	10 (16.4%)	9 (20.5%)	1 (5.9%)	
Tumor volume (L)	0.31 (0.21; 0.42)	0.30 (0.19; 0.39)	0.35 (0.30; 0.53)	0.014
Tumor load (%)	20 (14; 27)	19 (11; 24)	23 (20; 30)	0.025
Max. tumor diameter (cm)	3.75 (2.50; 6.50)	3.35 (2.05; 6.25)	4.20 (3.25; 6.90)	0.184
Multifocal	51 (83.6%)	40 (90.9%)	11 (64.7%)	0.022
Extrahepatic metastasis	6 (9.8%)	6 (13.6%)	0	0.173
Portal vein thrombosis	15 (24.6%)	9 (20.5%)	6 (35.3%)	0.320
AFP > 400 ng/ml (n = 56)	15 (26.8%)	6 (15.0%)	9 (56.3%)	0.006
LogAFP baseline (n = 56)	1.36 (0.73; 2.64)	1.23 (0.65; 2.11)	2.70 (1.14; 3.23)	0.025
Laboratory data baseline				
Hemoglobin (g/dl)	12.8 (11.3; 14.1)	13 (11.9; 14.3)	11.7(9.5; 13.7)	0.071
WBC (Tsd/µl)	5.97 (4.69; 7.56)	6.05 (4.68; 7.36)	5.32 (4.72; 7.24)	0.676
Platelets (Tsd/µl)	179 (127; 260)	185 (117; 272)	151 (138; 212)	0.544
AST (U/L)	64 (41; 84)	55 (37; 76)	79 (71; 132)	<0.001
ALT (U/L)	37 (27; 54)	35 (26; 54)	42 (30; 54)	0.489
ALP (U/L)	157 (112; 217)	133 (102; 192)	211 (157; 319)	0.007
GGT (U/L)	247 (109; 420)	180 (95; 316)	436 (244; 505)	0.001
Bilirubin (mg/dl)	0.7 (0.5; 1.3)	0.6 (0.5; 1.1)	1.0 (0.7; 1.4)	0.018
Albumin (g/dl)	3.9 (3.4; 4.3)	4.1 (3.7; 4.4)	3.4 (3.0; 3.8)	<0.001
Creatinine (mg/dl)	0.85 (0.73; 1.12)	0.84 (0.75; 1.13)	0.86 (0.71; 1.12)	0.917

(Continues)

TABLE 1 (Continued)

	All patients (n = 61)	No hepatic decompensation (n = 44)	Hepatic decompensation (n = 17)	*p* value
CRP (g/dl)	6.8 (4.0; 15.7)	6.0 (3.8; 12.1)	16.9 (7.1; 35.0)	0.007
INR	1.1 (1.04; 1.14)	1.08 (1.04; 1.12)	1.13 (1.09; 1.19)	0.014
Liver function tests Baseline				
Child-Pugh score (n = 59)				
A	56 (94.9%)	42 (97.7%)	14 (87.5%)	0.176
B	3 (5.1%)	1 (2.3%)	2 (12.5%)	
MELD score (n = 59)	8.45 (7.59; 10.23)	7.89 (7.08; 9.92)	9.08 (7.74; 11.43)	0.111
ALBI score				
Grade 1	29 (47.5%)	27 (61.4%)	2 (11.7%)	<0.001
Grade 2	32 (52.5%)	17 (38.6%)	15 (88.2%)	
TARE procedure				
Live-lung-shunt (%)	6.4 (4.3; 8.5)	6.4 (4.3; 8.6)	6.4 (4.9; 8.1)	0.942
Total activity (GBq)	2.1 (1.53; 2.30)	2.0 (1.4; 2.1)	2.3 (1.93; 2.39)	0.084
TARE application				
One lobe	34 (55.7%)	25 (56.8%)	9 (52.9%)	0.785
Both lobes	27 (44.3%)	19 (43.2%)	8 (47.1%)	
Total dose nontumor liver (Gy)				
Homogenous model	40 (34; 58)	40 (32; 53)	40 (34; 64)	0.717
Partition model	35 (25; 43)	33 (23; 39)	45 (31; 57)	0.011

Note: Baseline data of patients with HCC stratified to the development of hepatic decompensation after TARE. Data are presented in absolute numbers and percentages as well as median with IQR, respectively. Treatment decision for TARE in patients with extrahepatic metastasis was based on individual decisions discussed in and approved by the local tumor board. The hepatic manifestation was considered as the leading manifestation in these cases. A p value < 0.05 was considered statistically significant.

Abbreviations: AIH, autoimmune hepatitis; AFP alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Liver Cancer group classification; CRP, C-reactive protein; ECOG, Eastern Cooperative of Oncology Group; GBq, Giga Becquerel; GGT, gamma-glutamyl transferase; Gy, Gray; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; NAFLD, nonalcoholic fatty liver disease; RFTA radiofrequency-thermal ablation; SBRT, stereotactic body radiation therapy; TKI, tyrosine kinase inhibitor; WBC, white blood cells.

The liver function of patients with HCC with hepatic decompensation worsened within 3 months after TARE, while the liver function of patients with HCC without hepatic decompensation remained stable as shown in Figure S1. The median ALBI score 3 months after TARE was −0.943 (IQR −1.000; −0.812) in patients with hepatic decompensation, compared to −2.674 (IQR −2.955; −1.876) in patients without hepatic decompensation (p<0.001).

Predictive factors of hepatic decompensation after TARE in patients with HCC

Baseline data and tumor characteristics and procedure-related parameters were compared between patients with and without hepatic decompensation. Patients with hepatic decompensation had a larger tumor volume (350 ml [IQR 300–530] vs. 300 ml [IQR 190–390]; p = 0.014), a higher tumor load (ratio of tumor volume to total liver volume: 23% vs. 19%; p = 0.025), and higher alpha-fetoprotein (AFP) levels (>400 ng/ml: 56.3% vs. 15.0%; p = 0.006). In terms of liver function at baseline, patients with hepatic decompensation had higher levels of aspartate aminotransferase, alkaline phosphatase, bilirubin, gamma-glutamyltransferase, and international normalized ratio (INR), as well as lower levels of albumin (Table 1 and Figure S1). There was no significant difference in Child-Pugh score (hepatic decompensation: 5.5 [IQR 5–6]; no hepatic decompensation: 5 [IQR 5–6]; p = 0.082) or MELD score (hepatic decompensation: 9.089 [IQR 7.74–11.43]; no decompensation: 7.89 [IQR 7.08–9.92], p = 0.111). The ALBI score was significantly higher in patients with hepatic decompensation (−2.10 [IQR −2.48; −1.66] vs. −2.73 [IQR −3.12; −2.32]; p < 0.001). A total of 88.2% of patients with hepatic decompensation were grouped as ALBI grade 2 at baseline compared to 38.6% without hepatic decompensation (p < 0.001; Figure 3).

There was no difference in the mean activity applied during TARE (hepatic decompensation: 2.3 GBq [IQR 1.93–2.39]; no hepatic decompensation: 2.0 GBq [IQR 1.4–2.1], p = 0.084).

Regarding the median absorbed doses in the liver, the use of the homogenous dosimetry model (single-compartment approach) estimated an irradiation dose of 40 Gray (Gy [IQR 34–58]) for tumor as well as for nontumor liver within the treated lobes. According to this model, there was no difference between both groups (hepatic decompensation: 40 Gy [IQR 32–53]; no hepatic decompensation: 40 Gy [IQR 34–64]; $p = 0.717$). Using the multicompartment dosimetry approach or accordingly the "partition model," the mean radiation dose calculated for nontumor liver was lower with 35 Gy (IQR 25–43). Comparing both groups, patients with hepatic decompensation showed an irradiation of 45 Gy (IQR 31–57) for the nontumor liver, whereas the patients without decompensation revealed significantly lower irradiation with 33 Gy (IQR 23–38.5; $p = 0.011$).

Using clinically relevant parameters significantly different between patients with and without hepatic decompensation, univariable and multivariable regression models were calculated (Table 2). In univariable regression models, a higher ALBI score, higher C-reactive protein and higher radiation dose of nontumor liver emerged as risk factors for the development of hepatic decompensation. In the multivariable logistic regression model, ALBI score (odds ratio [OR]: 6.425 [confidence interval [CI] 1.735–23.797]; $p = 0.005$) and radiation dose on nontumor liver (OR: 1.072 [CI 1.016–1.131]; $p = 0.011$) remained independent risk factors for hepatic decompensation (Table 2). The high predictive value of the ALBI score is also mirrored in the fact that only 2 patients (11.7%) with ALBI grade 1 developed hepatic decompensation during follow-up (Figure 3).

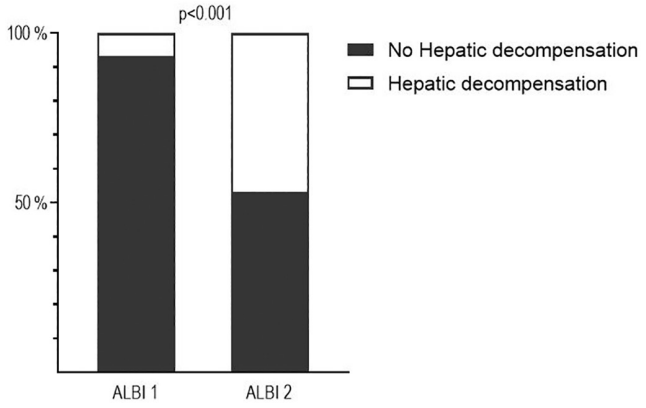

FIGURE 3 Fraction of patients with hepatic decompensation in relation to albumin-bilirubin (ALBI) grade. ALBI grade of patients with and without hepatic decompensation. Data are displayed as a fraction of the total

Hepatic decompensation after TARE significantly influences post-TARE treatment and OS

Treatment response was assessed according to mRECIST1.1. Seven patients had no radiologic follow-up. Patients who died within 3 months after TARE for any cause were counted as having PD (n = 6). A total of 14.8% of the patients (n = 9) received a partial remission (PR) and 11.5% (n = 7) stable disease. A total of 62.3% (n = 38) of the patients had radiologic tumor progression at follow-up or died within 3 months after TARE (hepatic decompensation: n = 5, no hepatic decompensation: n = 1). There was no difference in treatment response between patients with and without hepatic decompensation (Table S6). However, the prognosis of patients with hepatic decompensation may be determined primarily by death through liver failure and not by lacking treatment response.

The development of hepatic decompensation after TARE also affected further treatment. Indeed, only 27.3% of patients (n = 3) with hepatic decompensation received further treatment of HCC after TARE, compared to 78.9% of patients (n = 30) without decompensation ($p = 0.003$; Tables S6 and S8).

Kaplan–Meier analysis was performed to assess OS of patients after TARE. The occurrence of hepatic decompensation significantly influenced the prognosis. The median OS of patients with hepatic decompensation was 4 months (IQR 3–4). Patients without hepatic decompensation had a median OS of 15 months ([IQR 7–23], $p < 0.001$; Figure 4). The short-term survival of patients with hepatic decompensation was significantly

TABLE 2 Predictive factors for hepatic decompensation after TARE in patients with HCC

	Univariable regression			Multivariable regression		
Parameters	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Dose nontumor liver *(Partition model)*	1.063	1.016; 1.112	0.008	1.072	1.016; 1.131	0.011
ALBI score	5.454	1.802; 16.509	0.003	6.425	1.735; 23.797	0.005
CRP	1.035	1.002; 1.069	0.040			
Tumor load	79.988	0.746; 8574.618	0.066			
Tumor volume	13.883	0.948; 203.352	0.055			

Note: Univariable and multivariable regression models of factors predicting hepatic decompensation in patients with HCC after TARE. A p value < 0.05 was considered statistically significant.

Abbreviations: CI, confidence interval; OR, odds ratio.

reduced with a 90-day mortality of 23.5% (n = 4; no hepatic decompensation: n = 2 [4.5%], $p = 0.046$). The 1-year mortality was 82.4% in patients with hepatic decompensation compared to 34.1% in patients without hepatic decompensation ($p < 0.001$). Cox-regression analysis confirmed that hepatic decompensation after TARE is a highly relevant risk factor for death in patients with HCC. Adjusted for BCLC, ALBI grade and age, hepatic decompensation after TARE emerged as an independent negative prognostic factor (HR: 5.67 [CI 2.70–11.90], $p < 0.001$; Table 3).

DISCUSSION

In the last decade, TARE has emerged as an important treatment option for patients with HCC in the intermediate and advanced stages. TARE is a safe and effective transarterial treatment approach in patients with HCC.

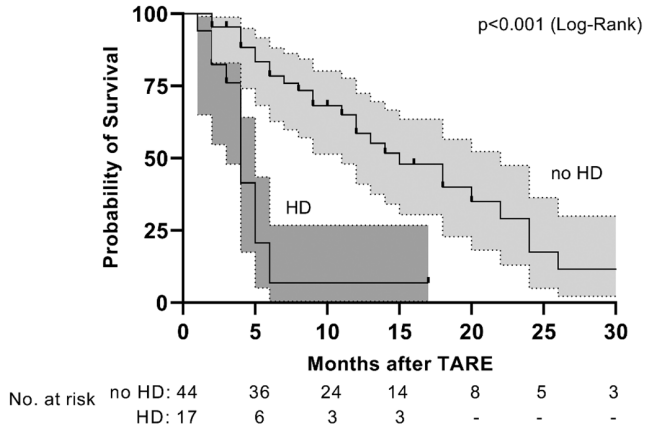

FIGURE 4 Kaplan-Meyer curves for overall survival of patients with HCC after TARE. Kaplan-Meyer curves for overall survival (OS) in months of patients with HCC stratified for the development of hepatic decompensation (HD) after TARE. Median OS in months and patients at risk are indicated in the numbers at the bottom

Complication rates are low; however, serious complications such as hepatic decompensation may develop and influence the prognosis of patients. Most patients with HCC have underlying liver cirrhosis or advanced liver disease and therefore are at risk of developing deterioration of liver function. Therefore, it is important to identify patients who are at high risk for the development of post-TARE hepatic decompensation to achieve an individualized approach for treatment allocation and planning of the radiation dose.

Beyond this background, we analyzed the incidence and predictive factors of hepatic decompensation after TARE in patients with HCC. First, we analyzed the incidence of post-TARE hepatic decompensation in patients with HCC compared to patients with hepatic metastases of extrahepatic cancer. It is well known that underlying liver disease, especially liver cirrhosis, is a main risk factor for hepatic decompensation.[7] As expected, the frequency of liver cirrhosis was much lower in patients with non-primary liver tumors, and consecutively these patients also developed post-TARE hepatic decompensation less often (15.5% vs. 27.9%, $p = 0.083$). In line with these findings, multivariable analysis confirmed liver cirrhosis as a major risk factor for post-TARE hepatic decompensation. Only 2 of the patients with HCC who developed hepatic decompensation had no diagnosis of liver cirrhosis. One had underlying chronic HCV infection, the other NASH, suggesting a chronic liver damage in these patients as well.

Importantly, preserved liver function is a major prognostic factor in patients with liver cirrhosis. Especially in patients with HCC, preservation of liver function is essential for further treatment allocations. Several reports show that deterioration of liver function in patients with HCC is associated with reduced treatment options and therefore significantly affects survival. With these observations in mind, a detailed and accurate assessment of liver function is essential. Apart from the Child-Pugh score and the MELD score, the ALBI score has been

TABLE 3 Cox regression model for the analysis of risk factors for death after TARE

	Cox single-variable regression			Cox multiple-variable regression		
Parameters	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Hepatic decompensation	5.383	2.589; 11.190	<0.001	5.694	2.713; 11.952	<0.001
Liver cirrhosis	1.292	0.641; 2.602	0.474			
Tumor load (%)	6.422	0.573; 71.963	0.131			
BCLC (B vs. C)	1.038	0.497; 2.169	0.920			
ALBI grade (1 vs. 2)	2.493	1.365; 4.552	0.003			
Age (years)	1.038	1.007; 1.069	0.014	1.036	1.004; 1.069	0.027
Portal vein thrombosis	1.641	0.842; 3.196	0.160			
Sex (male vs. female)	0.956	0.493; 1.855	0.895			

Note: Univariable and multivariable Cox regression model of prognostic factors after TARE in patients with HCC. A p value of < 0.05 was considered statistically significant.

Abbreviation: HR, hazard ratio.

established as an objective tool for assessment of liver function and prognosis in patients with HCC who have been treated with TACE and in patients with sorafenib therapy.[16–18] As the ALBI score can identify changes in liver function, we set out to analyze its use in predicting post-TARE hepatic decompensation. Importantly, we could confirm the ALBI score as a surrogate for liver function and thus a main determinant of hepatic decompensation after TARE. Only 2 patients with ALBI grade 1 developed hepatic decompensation during follow-up. Other scoring systems for liver function, such as the Child-Pugh score and MELD score, did not predict hepatic decompensation after TARE. This may be due to the low number of patients with Child-B and no patients with Child-C classification included in the study. Our results are in line with previous studies also showing the superiority of the ALBI score in predicting the prognosis of patients with HCC after TARE.[19–21] However, the results extend these studies by showing that the development of hepatic decompensation primarily determines the worsening prognosis in patients with higher ALBI score after TARE. The high risk for hepatic decompensation even for patients with ALBI grade 2 should be a strict indication for a close clinical follow-up.

Besides the ALBI score, we also found that radiation dose on the nontumor liver was an independent predictive factor for hepatic decompensation. In our patients, therapy planning and calculation of the activity to be applied in each liver lobe was based on the recommended BSA method postulating a homogeneous distribution of the microspheres in the treated liver areas. Our dosimetry assessment using single-compartment approaches delivered a fair, reproducible mean radiation dose in both patient groups, showing no difference between patients evolving toward hepatic decompensation and patients showing no complication in the follow-up. The use of a multi-compartment approach (partition model) allowed us to consider differences in the distribution of the microspheres between tumor and nontumor, reflecting the physiological differences in the tissue perfusion. In the partition model, the mean radiation dose on the nontumor liver was higher in patients with hepatic decompensation (45 Gy compared to 33 Gy in patients without decompensation). As previously suggested and currently recommended, the partition model should be preferred, as it allows a more accurate evaluation of the dosimetry.[13,22,23] The higher radiation dose in addition to an impaired liver function may be the tipping point triggering hepatic decompensation in patients with HCC. Recently, Villain et al. discussed for nontumor liver a cutoff >40 Gy for normal liver function and >30 Gy if liver function is impaired as an upper limit for the irradiation following TARE. This recommendation arose from an international panel of experts[23] and is congruent with our findings, but remains vague and lacks well-defined criteria for clinical practice. Further studies should aim to define clear cutoff values for dosimetry planning with a special remark on patients with limited liver function.

The development of hepatic decompensation after TARE is a main determinant of prognosis in patients with HCC. The OS was significantly reduced by hepatic decompensation. A total of 23.5% of patients with hepatic decompensation died within the first 3 months and 82.4% of patients within the first year after TARE. Multivariable analysis confirmed that hepatic decompensation is an independent risk factor for death adjusted for BCLC stage, ALBI grade, and age. These results highlight the high relevance of prevention of hepatic decompensation, as the high short-term mortality is probably due to liver failure and not tumor progression or advanced stage in the first line. Survival rates after TARE have previously been studied primarily in the light of BCLC stage[24] and liver function scores, such as Child-Pugh[2] and ALBI score.[20,21] In this study, ALBI grade was a negative predictor factor for death solely in the univariable regression, but not in the multivariable analysis, including the parameters for hepatic decompensation, age, and BCLC. This suggests that ALBI score primarily predicts the development of liver toxicity and also affects the prognosis.

Besides the direct effect on prognosis by liver toxicity, patients with hepatic decompensation receive few additional treatments, which negatively affects their outcome. One could postulate that a higher radiation dose on targeted tumor volume leads to better tumor response. Indeed, the frequency of patients receiving partial remission or SD at follow-up was slightly higher in patients with hepatic decompensation, although not statistically significant. Still, the assumption of a higher response rate through a higher activity during TARE does not outweigh the risk of treatment toxicity in patients at risk.

The treatment response in our study was worse than reported from previous studies (Table S7). In addition to significant differences in BCLC stages, Child-Pugh classification, presence of extrahepatic metastasis and pretreatment, our patients had a higher tumor burden with a median tumor load of 20%. Moreover, 83.6% of the patients had multifocal liver lesions. Compared with previous trials, patients included in this study probably had further advanced disease stages, implying a palliative setting in many cases. We counted patients without radiologic follow-up and death for any cause within 3 months after TARE as PD, to exclude biasing. The differences in outcome and treatment response may limit the transferability to other patients. However, the main endpoint addressing risk factors for hepatic decompensation is less affected and may still be transferable to other patient cohorts.

The upcoming of immunotherapy now offers a safe and well-tolerated treatment for patients with advanced stages of HCC.[25] Supposedly, some of the patients treated with TARE in our study would now be treated

with immunotherapy instead. Still, at the time of inclusion, immunotherapy was not broadly available and alternative systemic therapies like sorafenib are less well tolerated, whereas TARE and other loco regional treatments were favored over systemic therapy.

In this study, we defined hepatic decompensation as an increase of bilirubin at least CTCAE grade 3 or the development of ascites within 3 months after TARE. Hepatic toxicity of TARE has been studied previously, and radioembolization-induced liver disease (REILD) has been described as a specific syndrome occurring in patients 4 to 8 weeks after treatment with TARE. It has been first studied in a cohort of patients without chronic liver disease.[26] Even though it is described as a distinct entity and the histological evidence of sinusoidal occlusion has been documented in some patients,[26] the supposed pathophysiological mechanism of REILD has never been confirmed in a large cohort. Clinically, REILD cannot be differentiated from hepatic decompensation of underlying liver disease, challenging the hypothesis of a distinct pathophysiological entity. Also, in patients with liver cirrhosis, the cutoff of bilirubin > 1.5 mg/dl might be too low, so we decided to use a more dynamic definition. Our study aimed to investigate the prognosis of patients with HCC after TARE in light of liver toxicity, to better understand factors contributing to decompensation and define parameters for individual treatment decisions. The course of liver function parameters, namely bilirubin, albumin and INR, in patients with and without hepatic decompensation in our study, and the highly demerging curves of the Kaplan-Meyer plot indicate that the applied definition of hepatic decompensation distinctively discriminated between two groups. Thus, the aim of our study was sufficiently met.

Our study has several limitations: First, this was a single-center study with a retrospective design. Patients classified as BCLC A were omitted, suggesting a possible selection bias, and making our results not transferable to patients treated as bridge to transplant or bridge to resection. Despite these limitations, this study underlines the importance of careful patient selection before treatment and highlights the relevance of hepatic decompensation after TARE for the prognosis and outcome of patients with HCC. There is a need for further studies, focusing on investigating safe dosimetry cutoff values in patients with limited liver function and cirrhosis.

AUTHOR CONTRIBUTIONS

Study concept and design: Marlene Reincke, Christian Goetz, and Dominik Bettinger. *Data acquisition*: Marlene Reincke and Christian Goetz. *Data analysis and interpretation*: Marlene Reincke, Christian Goetz, and Dominik Bettinger. *Manuscript draft*: Marlene Reincke, Christian Goetz, and Dominik Bettinger. *Critical revision of the manuscript for important intellectual content*: all authors. *Study supervision*: Christian Goetz and Dominik Bettinger. All authors approved the final version of the article, including the authorship.

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CONFLICT OF INTEREST

DB consults for Bayer Healthcare and is on the speakers' bureau of Falk Foundation, Boston Scientific, and W.L. Gore & Associates. MS consults for Roche Pharma AG, Falk Foundation e.V., and W.L. Gore & Associates, and advises Bayer.

ETHICS APPROVAL

The study was approved by the local ethics committee (no. EK 20–1154) and is in accordance with the Declaration of Helsinki.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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