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ORIGINAL RESEARCH

High-Volume Dilution of Drug-Eluting Beads Reduces Severe Pain After DEB-TACE: A Single-Center Retrospective Study

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Background: Abdominal pain is the most frequent consequence of postembolization syndrome (PES) after drug-eluting bead transarterial chemoembolization (DEB-TACE). The analgesic impact of an easily modifiable intraprocedural factor—microsphere suspension dilution, remains unclear. We evaluated whether high-fold dilution during DEB-TACE reduces early postprocedural pain and severe pain risk without compromising short-term response and safety.

Methods: This single-center retrospective cohort study included 362 patients with hepatocellular carcinoma who underwent DEB-TACE. The patients were divided into conventional dilution (Group A, n = 103), 30–50-fold dilution (Group B, n = 127), and > 50-fold dilution (Group C, n = 132). The outcomes included a maximum visual analog scale (VAS) pain score within 72 hours and moderate-to-severe (VAS score ≥ 4) and severe (VAS score ≥ 7) pain scores. Associations were tested through Spearman correlation and trend tests. Univariable and multivariable logistic regression were used to estimate adjusted odds ratios (ORs) for severe pain. Short-term tumor response was also assessed according to mRECIST at 1–3 months after the index procedure.

Results: The maximum 72-hour VAS score decreased with increasing dilution (median [interquartile range]: 6.0 [4.0–10.0] vs. 4.0 [2.0–5.0] vs. 0.0 [0.0–4.0]; $P < 0.001$). The prevalence of moderate-to-severe pain decreased from 77.7% to 56.7% and 28.8%, respectively, and that of severe pain decreased from 48.5% to 10.2% and 6.8%, respectively (Groups A–C). Dilution correlated with lower pain severity ($\rho = -0.636$; $P < 0.001$). Multivariate analysis revealed that compared with Group A, Groups B and C had lower odds of severe pain (OR 0.12 and 0.07; both $P < 0.001$). Subsegmental superselective catheterization (OR 0.45; $P = 0.024$) and intra-arterial lidocaine (OR 0.53; $P = 0.041$) were protective, whereas tumor proximity to the liver capsule increased the risk (OR 1.99; $P = 0.024$). Short-term tumor response also differed across groups, with the objective response rate increasing from 40.8% in Group A to 56.7% in Group B and 58.3% in Group C ($P = 0.015$).

Conclusion: High-fold microsphere suspension dilution during DEB-TACE was associated with reduced early postprocedural abdominal pain without compromising short-term laboratory safety.

Keywords: hepatocellular carcinoma, drug-eluting bead transarterial chemoembolization, DEB-TACE, postembolization syndrome, abdominal pain, visual analog scale, microsphere suspension dilution, high-fold dilution

Introduction

Liver cancer is the sixth most common cancer and the third leading cause of cancer-related mortality globally.[1] For patients with unresectable hepatocellular carcinoma (HCC), transarterial chemoembolization (TACE) remains an important locoregional treatment option.[2,3] Nevertheless, postembolization syndrome (PES) occurs frequently after TACE and may adversely

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affect postprocedural recovery.[4–6] Abdominal pain is among the most prevalent adverse events (AEs) reported after TACE and remains a major driver of periprocedural supportive care needs.[6–8] This clinical burden highlights the importance of identifying practical strategies to reduce postprocedural pain and improve tolerability. Evidence suggests that pharmacologic prophylaxis, particularly dexamethasone-based regimens, can reduce PES[9]. In addition, procedural and disease-related factors contribute to pain severity, suggesting that technical optimization improves tolerability.[10]

Drug-eluting bead TACE (DEB-TACE) enables sustained intratumoral chemotherapy delivery while achieving embolic ischemia, yet clinically meaningful abdominal pain remains common after DEB-TACE.[11] Beyond pharmacologic prophylaxis, intraprocedural technical factors may modulate tolerability by shaping bead dispersion and the embolization pattern. Microsphere suspension dilution can influence bead flowability and embolization distribution; a more diluted suspension promotes more homogeneous and distal embolization, which may reduce postprocedural pain by mitigating abrupt ischemic insult and focal tissue irritation. In routine practice, the bead mixture is often prepared in a total volume of 5–10 mL per 1 mL; hereafter, we refer to this as the conventional dilution. In this context, the expert recommendations from the Korean Liver Cancer Association suggest diluting the bead mixture to 30–50 mL to facilitate homogeneous embolization,[12] which may allow for effective DEB-TACE by limiting particle clumping and occlusion of the proximal artery. In clinical practice, increasing the dilution volume beyond conventional recommendations (ie., > 50-fold dilution) might provide additional analgesic benefits. However, it remains unclear whether higher-fold dilution can reduce postprocedural abdominal pain without compromising short-term safety and tumor response.

Therefore, we investigated whether a high dilution volume during DEB-TACE reduces postprocedural pain while maintaining procedural safety and short-term tumor response.

Methods

Study Design and Population

This retrospective cohort study was conducted at our institution. Consecutive patients with HCC who underwent DEB-TACE between January 2020 and December 2022 were screened. This study was approved by the institutional review board of Central Hospital, Tianjin University (IRB No. [2022–039-01]), and the requirement for informed consent was waived because of the retrospective design. All patient data were handled in a de-identified and confidential manner throughout data collection and analysis. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Patients were eligible if they 1) were ≥ 18 years old; 2) had HCC confirmed by histopathology or clinically diagnosed according to the Primary Liver Cancer Diagnosis and Treatment Guidelines[13] and/or the diagnostic criteria of the European Association for the Study of the Liver (EASL);[14] and 3) underwent DEB-TACE during the study period as the index procedure. For patients who underwent multiple DEB-TACE procedures, only the initial procedure was included in the analysis. Patients were excluded if they 1) had missing key data (n = 31); 2) received other concurrent locoregional therapies during the same session (eg., ablation) or emergent procedures (n = 28); 3) had a history of major abdominal surgery or other causes of acute abdominal pain around the time of the procedure that were deemed to confound pain assessment (n = 22); 4) had concomitantly used lipiodol during the DEB-TACE procedure (n = 157); and 5) had preprocedural liver function of Child–Pugh class C or main portal vein tumor thrombus (PVTT) (n = 53). The details are shown in Figure 1.

DEB-TACE Procedure

DEB-TACE procedures were performed in a dedicated angiographic suite under local anesthesia (2% lidocaine). Access was obtained via the common femoral artery, after which catheter-based angiography of the celiac trunk and superior mesenteric artery was performed to map the hepatic arterial anatomy, identify tumor-feeding vessels, and verify patency of the portal vein. When helpful, intraprocedural cone-beam CT was performed to assist in superselective catheterization and to assess tumor vascularization. Target feeders were then catheterized with a microcatheter, and chemoembolization was performed using CalliSphere drug-eluting beads (100–300 μm) or DCBeads (300–500 μm) preloaded with epirubicin (40 mg per vial). The intended treatment endpoint was near stasis in the superselective tumor-supplying artery after microsphere delivery.[15] If near stasis was not achieved after microsphere administration, adjunctive bland embolization was used until the endpoint was reached.

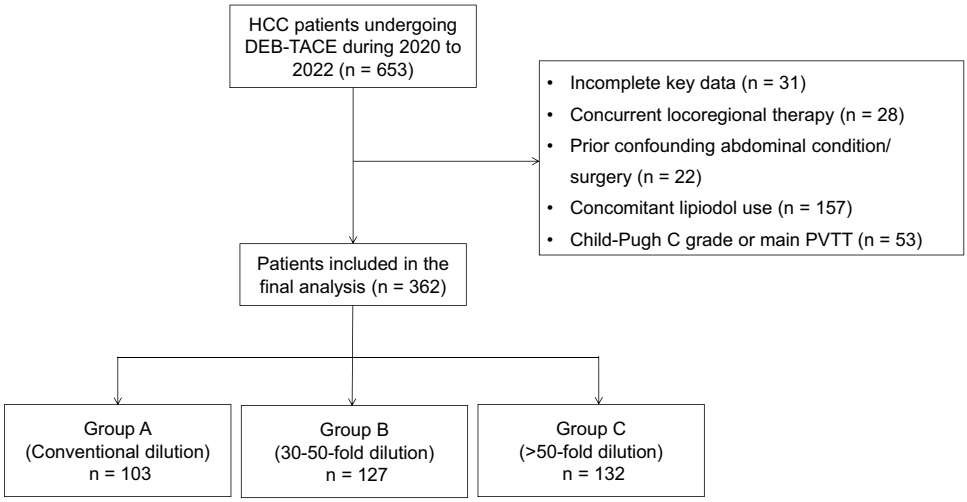

Figure 1 Flowchart of the study.

Dilution Protocol and Group Definition

To prepare the microspheres, first, the storage solution was completely aspirated to obtain the packing solution. Preprepared epirubicin was subsequently loaded into the microspheres gently. The injectate was then prepared by adding a mixture of normal saline and nonionic contrast medium at a 1.5:1 (saline:contrast) ratio to achieve the intended total suspension volume. The suspension was homogenized through gentle manual agitation immediately before delivery and intermittently during delivery to minimize sedimentation and ensure uniform dispersion. Injection was administered slowly with brief pauses and intermittent angiographic checks to avoid reflux and reassess antegrade flow.

The dilution factor was defined as the total suspension volume divided by the number of epirubicin-loaded beads. For all analyses, the patients were categorized according to the calculated dilution factor for each index procedure: Group A (conventional 5–10-fold dilution), Group B (30–50-fold), and Group C (> 50-fold). The observed dilution range in Group C was 50–80-fold. The three categories are illustrated in Figure 2.

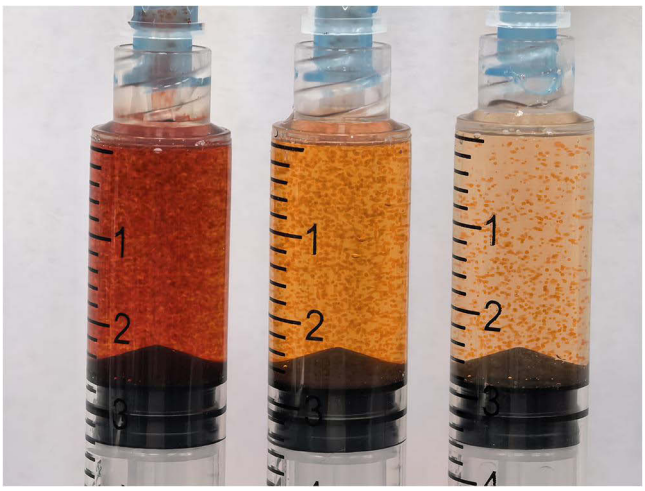

Figure 2 Representative macroscopic appearance of microsphere suspensions prepared with different dilution strategies. From left to right: Group A, conventional (5–10-fold) dilution; Group B, 30–50-fold dilution; and Group C, > 50-fold dilution. The image illustrates the progressively lower bead concentration and more dispersed microsphere distribution with increasing dilution.

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Intra-arterial lidocaine was administered for pain prophylaxis at the operator's discretion. The periprocedural analgesic regimen remained relatively stable throughout the study period and followed a stepwise, as-needed approach. Postprocedurally, nonopioid analgesics were used as first-line treatment for mild-to-moderate pain (eg., intramuscular bucinnazine 50–100 mg or intravenous flurbiprofen axetil 50 mg) on demand rather than routinely. If pain progressed to severe intensity or was inadequately controlled with first-line agents, second-line opioid analgesics were initiated (eg., intramuscular pethidine 50–100 mg or intravenous morphine 5–10 mg). Prophylactic corticosteroids were not routinely administered.

Data Collection

The clinical data collected included patient demographics and baseline clinical status. The tumor-related variables included the Barcelona Clinic Liver Cancer (BCLC) stage, largest tumor diameter, total tumor number, tumor proximity to the liver capsule, and the presence of PVTT. PES was assessed during hospitalization and was defined as the occurrence of fever, nausea, vomiting, fatigue, or diarrhea documented in the medical records. Pain was analyzed separately. Procedural variables included superselective catheterization (subsegmental level), microsphere size (100–-300 μm and 300–500 μm), and injected bead volume. Laboratory parameters, including liver function tests, renal function, and inflammatory markers, were collected at baseline and within 3 days after DEB-TACE.

Outcomes

Pain intensity was assessed using a 0–10 visual analog scale (VAS) recorded in routine postoperative nursing documentation. VAS assessments were performed at 0 h, 4 h, 8 h, 24 h, 48 h, and 72 h after the procedure.[16] In addition, any patient-reported pain at any time point triggered an immediate assessment. The primary pain outcome was the maximum VAS score within 72 hours after DEB-TACE. Moderate-to-severe pain and severe pain were defined as a VAS score ≥ 4 and ≥ 7, respectively. Safety outcomes were evaluated on the basis of changes in liver and renal function parameters (eg., Δalanine aminotransferase (ALT), Δaspartate aminotransferase (AST), Δalbumin (ALB), Δtotal bilirubin (TBIL), Δcreatinine, and Δblood urea nitrogen (BUN)), which were calculated as postprocedure values within 3 days minus baseline. Short-term tumor response was assessed on contrast-enhanced CT/MRI performed 1–3 months after the index procedure according to modified Response Evaluation Criteria in Solid Tumors (mRECIST), categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The objective response rate (ORR) was defined as CR+PR, and the disease control rate (DCR) was defined as CR+PR+ SD.

Statistical Analysis

Continuous variables were tested for normality using the Shapiro–Wilk test and are presented as the mean ± standard deviation for normally distributed data or median [interquartile range (IQR)] for nonnormally distributed data. Categorical variables are reported as counts (percentages). Comparisons among the three dilution groups (A, B, and C) were performed using one-way analysis of variance for normally distributed continuous variables, with the Bonferroni correction for multiple comparisons and the Kruskal–Wallis test with Dunn's test for nonnormally distributed variables. Categorical variables were compared using the χ^2-test or Fisher's exact test, as appropriate. The dilution strategy (A = 1, B = 2, C = 3) was treated as an ordinal variable and correlated with the maximum VAS score using Spearman's rank correlation; the trend in categorical pain outcomes was assessed using the Cochran–Armitage trend test. To identify independent predictors of severe pain, prespecified covariates were first examined in univariable logistic regression analyses. Covariates with $P < 0.05$ were then entered into a multivariable logistic regression model to estimate adjusted odds ratios (ORs) with 95% confidence intervals (CIs).

Subgroup analyses were performed to assess the consistency of the association between the dilution strategy and pain outcomes across clinically relevant strata, including sex, age (< 65 vs. ≥ 65 years), intra-arterial lidocaine use (yes vs. no), tumor proximity to the liver capsule (yes vs. no), maximum tumor diameter (< 5 cm vs. ≥ 5 cm), injected bead volume (< 1 mL vs. ≥ 1 mL), microsphere size (100–300 μm vs. 300–500 μm), number of prior TACE sessions (≤ 2 vs. > 2 times), Child–Pugh grade, and PVTT (yes vs. no). To assess whether the association between the high-fold group (Group C vs. Group A+B) and the outcome differed across prespecified subgroups, interaction terms between group and each subgroup variable were included in logistic regression models, and *P* values for interaction were derived from the corresponding group × subgroup terms.

All tests were two-sided, and a P value < 0.05 was considered to indicate statistical significance. Statistical analyses were performed using R (version 4.4.3, R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline and Procedural Characteristics

A total of 362 patients with 906 tumors were included (Group A, n = 103; Group B, n = 127; Group C, n = 132). Overall, 67.1% of the patients were male, and the mean age was 62 ± 10 years. Baseline demographic, tumor-related, and procedural characteristics were similar across the three groups (Table 1). There were no significant between-group differences in sex, age, maximum tumor diameter, tumor number, Child–Pugh class, PVTT status, or BCLC stage (all P > 0.05). Procedural characteristics did not differ significantly, including the number of prior TACE sessions, tumor proximity to the liver capsule, rate of subsegmental superselective catheterization, microsphere size, injected bead volume, or intra-arterial lidocaine use (all P > 0.05).

Clinical Efficacy

Among the 362 patients, the distribution of mRECIST responses differed significantly across groups (P = 0.006). The proportions of CR, PR, SD, and PD were 2.9%, 37.9%, 41.7%, and 17.5%, respectively, in Group A; 3.9%, 52.8%, 33.9%, and 9.4% in Group B; and 6.8%, 51.5%, 33.3%, and 8.3% in Group C. Accordingly, the ORR (CR+PR) increased from 40.8% (Group A) to 56.7% (Group B) and 58.3% (Group C) (overall P = 0.015); pairwise comparisons indicated a higher ORR in Groups B and C than in Group A (A vs. B, P = 0.025; A vs. C, P = 0.023), with a difference between Groups B and C (P = 0.792). The disease control rates (DCR; CR+PR+SD) were 82.5%, 90.6%, and 91.7% in Groups A, B, and C, respectively (P = 0.064) (Figure 3).

Table 1 Baseline and Procedural Characteristics

Variables	Category	All (n = 362)	Group A (n = 103)	Group B (n = 127)	Group C (n = 132)	P
Sex (male)		243 (67.1%)	69 (67%)	92 (72.4%)	82 (62.1%)	0.210
Age		62 ± 10	62 ± 9	62 ± 10	62 ± 11	0.994
Maximum tumor diameter (cm)		5.4 [4.3, 8.1]	5.1 [4.1, 8.3]	4.8 [3.9, 7.7]	5.9 [4.6, 8.2]	0.108
Tumor number		2 [1, 4]	3 [1, 4]	2 [1, 3]	2 [1, 3]	0.166
Child–Pugh	A	158 (43.6%)	40 (38.8%)	61 (48%)	57 (43.2%)	0.373
	B	204 (56.4%)	63 (61.2%)	66 (52%)	75 (56.8%)	
PVTT		59 (16.3%)	14 (13.6%)	23 (18.1%)	22 (16.7%)	0.647
AFP (> 400 ng/mL)		269 (74.3%)	75 (72.8%)	98 (77.2%)	96 (72.7%)	0.658
BCLC	A	39 (10.8%)	12 (11.7%)	15 (11.8%)	12 (9.1%)	0.210
	B	225 (62.2%)	67 (65%)	69 (54.3%)	89 (67.4%)	
	C	98 (27.1%)	24 (23.3%)	43 (33.9%)	31 (23.5%)	
Prior TACE sessions (> 2 times)		178 (49.2%)	49 (47.6%)	70 (55.1%)	59 (44.7%)	0.228
Tumor proximity to the liver capsule		159 (43.9%)	50 (48.5%)	49 (38.6%)	60 (45.5%)	0.288
Subsegmental superselective catheterization		116 (32%)	33 (32%)	41 (32.3%)	42 (31.8%)	0.997
Microsphere size	100–300 μm	251 (69.3%)	67 (65%)	93 (73.2%)	91 (68.9%)	0.405
	300–500 μm	111 (30.7%)	36 (35%)	34 (26.8%)	41 (31.1%)	
Injected bead volume	< 1 mL	187 (51.7%)	57 (55.3%)	60 (47.2%)	70 (53%)	0.438
	≥ 1 mL	175 (48.3%)	46 (44.7%)	67 (52.8%)	62 (47%)	
Intra-arterial lidocaine use		171 (47.2%)	43 (41.7%)	62 (48.8%)	66 (50%)	0.411

Abbreviations: PVTT: portal vein tumor thrombosis; AFP: alpha-fetoprotein; BCLC: Barcelona Clinic Liver Cancer staging system.

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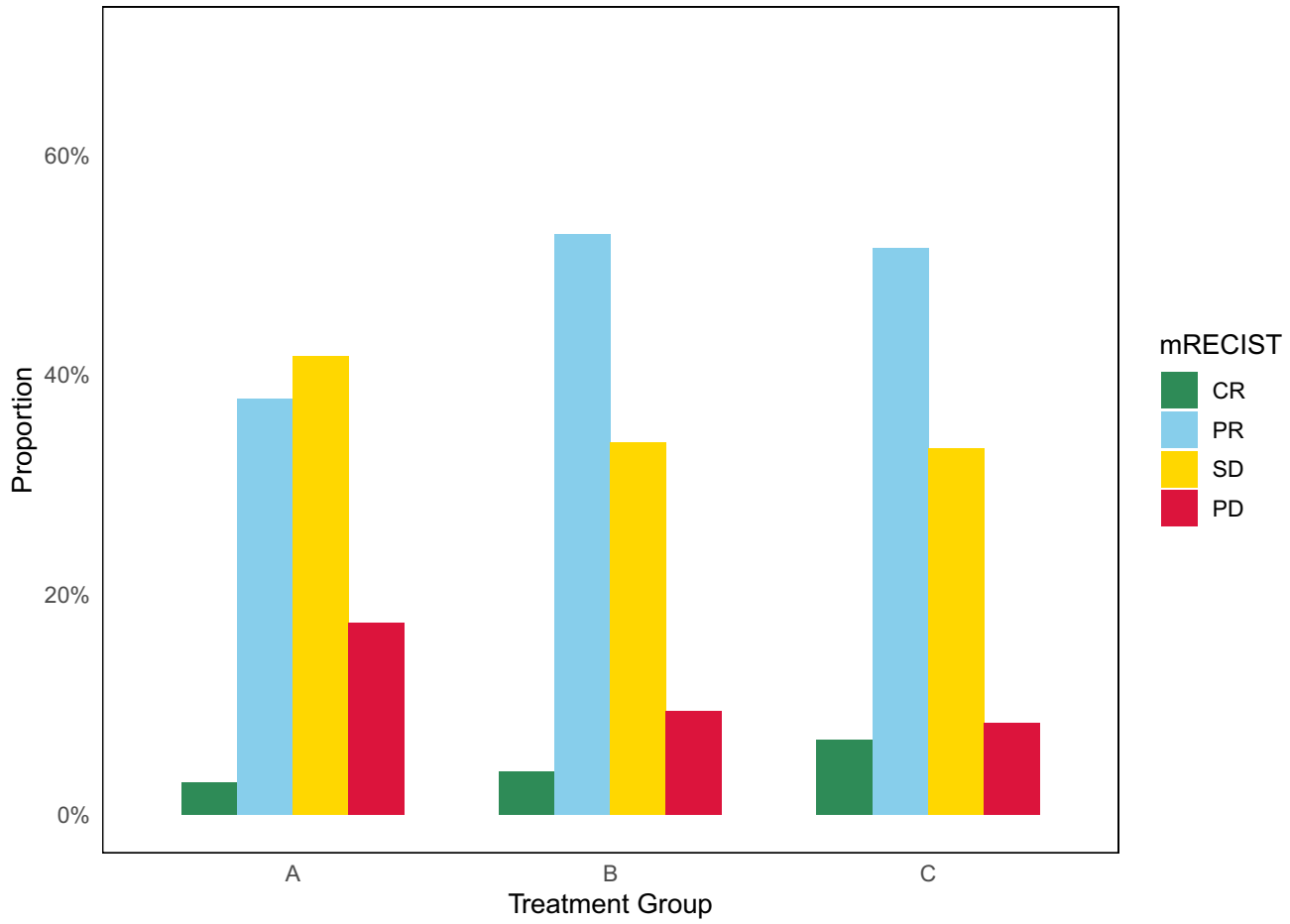

Figure 3 Distribution of tumor response by mRECIST across Groups A, B, and C; stacked bars represent the proportions of patients who achieved CR, PR, SD and PD, respectively, in each group.

Associations Between Dilution Level and Pain Severity

Postprocedural pain clearly decreased in a stepwise manner across the three dilution groups (Figure 4). The maximum 72-hour VAS score decreased from Group A to Group B and Group C (median [IQR]: 6.0 [4.0–10.0] vs. 4.0 [2.0–5.0] vs. 0.0 [0.0–4.0]; $P < 0.001$), and all pairwise comparisons remained significant (all adjusted $P < 0.001$). The overall proportion of patients who experienced moderate-to-severe pain (VAS score ≥ 4) was 52.5% and decreased across groups (77.7%, 56.7%, and 28.8%), whereas severe pain (VAS score ≥ 7) occurred in 19.9% of patients overall and decreased from 48.5% to 10.2% and 6.8% in Groups A, B, and C, respectively. Increased dilution was associated with decreased pain severity (Spearman's $\rho = -0.636$, $P < 0.001$; 95% CI, −0.702 to −0.552). The results of the Cochran–Armitage trend test further supported a significant linear trend in the incidence of moderate-to-severe pain across the ordered dilution groups ($P < 0.001$).

The incidence of PES excluding pain decreased from Group A to Group B and Group C (29.1% vs. 19.7% vs. 12.9%; overall $P = 0.008$), with a significant difference between Group A and Group C in pairwise comparisons (adjusted $P = 0.003$). By contrast, the differences between Group A and Group B and between Group B and Group C were not statistically significant (adjusted $P = 0.12$ and 0.177, respectively). The length of stay was similar across groups (median [IQR]: 5 [4–6] vs. 5 [4–5] vs. 4 [4–5] days; $P = 0.26$).

Laboratory Safety Outcomes

Baseline liver and renal function parameters were comparable across the three dilution groups, and postprocedural changes in laboratory values were observed (Table 2). No significant differences were observed across groups in ΔALT,

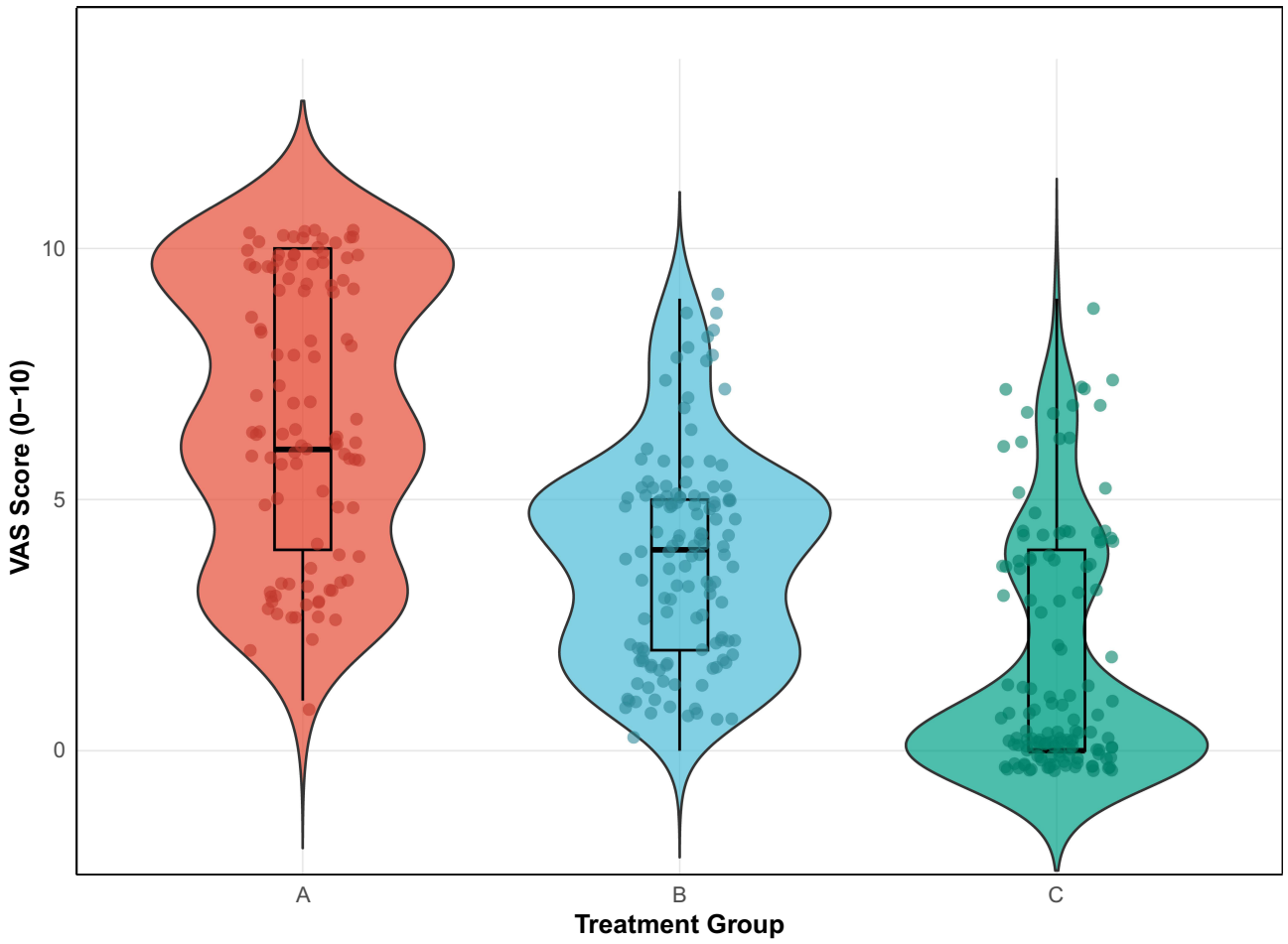

Figure 4 Distribution of maximum 72-hour VAS pain scores across dilution groups. Violin plots with overlaid boxplots show the distribution of maximum VAS scores within 72 hours after DEB-TACE in Groups A, B, and C. Overall between-group comparison was significant (Kruskal–Wallis test, $P < 0.001$), and all pairwise comparisons were significant after adjustment (all adjusted $P < 0.001$).

ΔAST, ΔALB, Δcreatinine, or ΔBUN (all $P > 0.05$). The ΔTBIL slightly increased in the higher-dilution group, although this difference did not reach statistical significance ($P = 0.092$). Overall, these findings indicate that the dilution strategy primarily influenced postprocedural pain outcomes without compromising short-term hepatic or renal safety, as reflected by routine laboratory tests.

Table 2 Laboratory Safety Outcomes at Baseline and Within 3 days After DEB-TACE

Variable (Unit)	Group	Pre	*P* value (Pre Values Across Groups)	Post	*P* value (Post Values Across Groups)	Δ Post-Pre	*P* value (ΔAcross Groups)
CRP (mg/L)	All	6.3 ± 2.0	0.346	18.3 ± 11.1	0.571	12.1 ± 11.2	0.495
	A	6.3 ± 2.2		17.4 ± 10.7		11.2 ± 10.8	
	B	6.5 ± 2.3		18.4 ± 11.1		11.9 ± 11.2	
	C	6.1 ± 1.5		19.0 ± 11.5		12.9 ± 11.5	
TBIL (μmol/L)	All	27.9 [16.8, 40.5]	0.245	31.9 [18.3, 43.9]	0.159	2.55 [0.40, 6.18]	0.092
	A	27.2 [14.9, 39.3]		31.4 [15.9, 42.4]		1.70 [0.25, 5.20]	
	B	27.7 [15.0, 39.0]		30.9 [17.0, 45.2]		2.20 [0.15, 5.70]	
	C	28.4 [22.8, 41.0]		32.8 [25.3, 43.8]		3.90 [0.78, 6.62]	

(*Continued*)

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Table 2 (Continued).

Variable (Unit)	Group	Pre	*P* value (Pre Values Across Groups)	Post	*P* value (Post Values Across Groups)	Δ Post-Pre	*P* value (ΔAcross Groups)
ALT (U/L)	All	47 ± 15	0.332	54 ± 18	0.643	6.4 ± 5.6	0.590
	A	47 ± 15		54 ± 19		6.6 ± 5.5	
	B	46 ± 16		53 ± 19		6.7 ± 5.2	
	C	49 ± 14		55 ± 17		6.1 ± 6.0	
AST (U/L)	All	58 [23, 100]	0.910	66 [24, 111]	0.955	6.0 [1, 14]	0.549
	A	59 [22, 100]		66 [24, 110]		5.0 [1.5, 14.0]	
	B	57 [30, 100]		67 [34, 112]		6.0 [1.0, 14.0]	
	C	57 [17, 99]		62 [22, 113]		5.0 [0.75, 13.0]	
ALB (g/L)	All	36.0 ± 5.5	0.301	36.7 ± 5.4	0.342	0.71 ± 7.59	0.136
	A	36.6 ± 5.3		36.1 ± 5.6		−0.54 ± 7.60	
	B	35.5 ± 5.6		36.8 ± 5.3		1.35 ± 7.62	
	C	36.0 ± 5.4		37.1 ± 5.2		1.06 ± 7.49	
Creatinine (μmol/L)	All	79.63 ± 26.12	0.778	84.26 ± 28.85	0.440	4.63 ± 37.04	0.612
	A	80.90 ± 26.58		83.24 ± 30.44		2.34 ± 37.62	
	B	79.80 ± 25.56		86.88 ± 28.74		7.09 ± 36.67	
	C	78.48 ± 26.44		82.54 ± 27.69		4.05 ± 37.07	
BUN (mmol/L)	All	7.75 ± 3.21	0.165	8.34 ± 3.31	0.535	0.59 ± 4.55	0.110
	A	8.16 ± 3.31		8.04 ± 3.31		−0.12 ± 4.86	
	B	7.36 ± 3.24		8.50 ± 3.11		1.14 ± 4.12	
	C	7.80 ± 3.08		8.43 ± 3.51		0.63 ± 4.66	

Abbreviations: CRP, C-reactive protein; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; BUN, blood urea nitrogen.

Univariable and Multivariable Analyses for Severe Pain

According to the univariable logistic regression analysis, the dilution factor was significantly associated with severe pain (Group B: OR 0.12, 95% CI 0.06–0.24, $P < 0.001$; Group C: OR 0.08, 95% CI 0.03–0.16, $P < 0.001$). Subsegmental superselective catheterization (OR 0.54, 95% CI 0.29–0.98; $P = 0.048$) and intra-arterial lidocaine use (OR 0.53, 95% CI 0.30–0.89; $P = 0.019$) were associated with lower odds of severe pain, whereas tumor proximity to the liver capsule was associated with higher odds (OR 1.93, 95% CI 1.15–3.27; $P = 0.014$). Multivariate analysis revealed that the association between higher dilution and lower odds of severe pain remained significant (Group B: OR 0.12, 95% CI 0.06–0.24, $P < 0.001$; Group C: OR 0.07, 95% CI 0.03–0.15, $P < 0.001$). Subsegmental superselective catheterization (OR 0.45, 95% CI 0.22–0.88; $P = 0.024$) and intra-arterial lidocaine use (OR 0.53, 95% CI 0.28–0.97; $P = 0.041$) remained protective, whereas tumor proximity to the liver capsule remained an independent risk factor (OR 1.99, 95% CI 1.10–3.65; $P = 0.024$) (Table 3).

Subgroup Analyses

In the overall cohort, compared with Group A+B, Group C was associated with a significantly lower incidence of severe pain (6.8% vs. 27.4%), with an OR of 0.19 (95% CI 0.09–0.40; $P < 0.001$). This association was generally consistent across prespecified subgroups, with ORs mostly ranging from 0.10 to 0.45 and statistically significant *P* values in most strata. No significant interactions were detected for sex ($P = 0.989$), age (< 65 vs. ≥ 65; $P = 0.542$), intraprocedural lidocaine use ($P = 0.351$), tumor proximity to the liver capsule ($P = 0.292$), maximum tumor diameter ($P = 0.168$), injected bead volume (< 1 mL vs. ≥ 1 mL; $P = 0.502$), microsphere size (100–300 μm vs. 300–500 μm; $P = 0.273$), prior TACE session (≤ 2 vs. > 2 times; $P = 0.486$), or presence and absence of PVTT ($P = 0.582$), indicating that the treatment effect differed across these factors. A significant interaction was detected for the Child–Pugh class (P for interaction = 0.038): the pain relief effect was more significant in Child–Pugh B patients than in Child–Pugh A patients. The details are shown in Figure 5.

Table 3 Univariate and Multivariate Logistic Regression Analyses of Factors Associated with Severe Pain

Variable	Univariable Analysis			Multivariable Analysis		
	Odds ratio	95% CI	*P*	Adjusted odds ratio	95% CI	*P*
Group A	Reference			Reference		
B	0.12	0.06–0.24	< 0.001	0.12	0.06–0.24	< 0.001
C	0.08	0.03–0.16	< 0.001	0.07	0.03–0.15	< 0.001
Child–Pugh B	1.37	0.81–2.36	0.241			
Age	1.01	0.99–1.04	0.415			
PVTT	1.03	0.50–2.02	0.925			
Subsegmental superselective catheterization	0.54	0.29–0.98	0.048	0.45	0.22–0.88	0.024
Intra-arterial lidocaine use	0.53	0.30–0.89	0.019	0.53	0.28–0.97	0.041
Tumor proximity to the liver capsule	1.93	1.15–3.27	0.014	1.99	1.10–3.65	0.024
Maximum tumor diameter	1.40	0.83–2.39	0.205			
Injected bead volume (≥ 1 mL)	0.88	0.52–1.48	0.634			
Larger microsphere size (300–500 μm)	1.36	0.78–2.33	0.264			
Prior TACE sessions (> 2 times)	1.04	0.62–1.75	0.875			

Abbreviations: PVTT, portal vein tumor thrombosis; CI, confidence interval.

Discussion

In this single-center retrospective cohort, higher microsphere dilution was associated with a marked, stepwise reduction in post-DEB-TACE pain. Increased dilution correlated strongly with lower maximum 72-hour VAS scores, and compared with conventional dilution, both the 30–50-fold and > 50-fold strategies were independently associated with substantially lower odds of severe pain after multivariable adjustment. Early postprocedural laboratory changes were comparable across groups, suggesting that greater dilution reduced pain without evident short-term hepatic or renal toxicity.

As locoregional treatment strategies for unresectable HCC continue to expand, both treatment efficacy and procedure-related tolerability remain important clinical considerations.[17] Prior syntheses have reported high PES rates,[18] and abdominal pain remains the most frequent symptom.[6–8] Although DEB-TACE enables sustained intratumoral drug delivery and may reduce systemic exposure, it is not consistently associated with a lower incidence of postprocedural abdominal pain than other approaches, and published results remain heterogeneous.[11,19] Beyond pain, overall postprocedural symptom burden may be influenced by regimen tolerability: anthracycline-based DEB-TACE can be accompanied by nausea, vomiting, or diarrhea,[20–23] and a lower doxorubicin dose is associated with fewer PES symptoms.[24] Several studies have identified DEB-TACE as an independent predictor of severe abdominal pain.[8,25,26] In our study, 52.5% of patients experienced moderate-to-severe pain, highlighting the importance of optimizing pain mitigation strategies specifically for this procedure.

This variability is likely driven in part by clinical and technical heterogeneity. Wang et al[10] reported that nonsuperselective chemoembolization and the presence of PVTT are crucial determinants of post-DEB-TACE abdominal pain. Other studies have shown that PES was more frequently observed with more extensive embolization, whereas microsphere size was not significantly associated,[27] which is consistent with our findings. Tumor anatomy may also increase pain vulnerability; evidence from ablation suggests that tumor distance to the capsule is an independent determinant of severe abdominal pain,[28] supporting the plausibility that capsule-adjacent lesions are more pain prone to locoregional therapies.

Mechanistically, post-TACE pain is believed to arise primarily from ischemia- and inflammation-related injury following embolization, including capsular irritation when lesions are subcapsular,[4,7] with a potential contribution from local chemical irritation due to high intra-arterial concentrations of the delivered agent.

Existing studies in this setting have mainly focused on pharmacologic prophylaxis, multimodal analgesia, and pain risk prediction, whereas relatively little attention has been paid to modifiable intraprocedural technical factors. Pharmacologic approaches, particularly dexamethasone- and lidocaine-based strategies, have shown benefit in reducing post-TACE pain and other PES-related symptoms.[9,29,30] While these studies support the effectiveness of drug-based strategies for alleviating PES, they also raise practical concerns: many patients with HCC have underlying cirrhosis, short-term post-TACE liver function fluctuations are common, and polypharmacy may increase hepatic metabolic burden

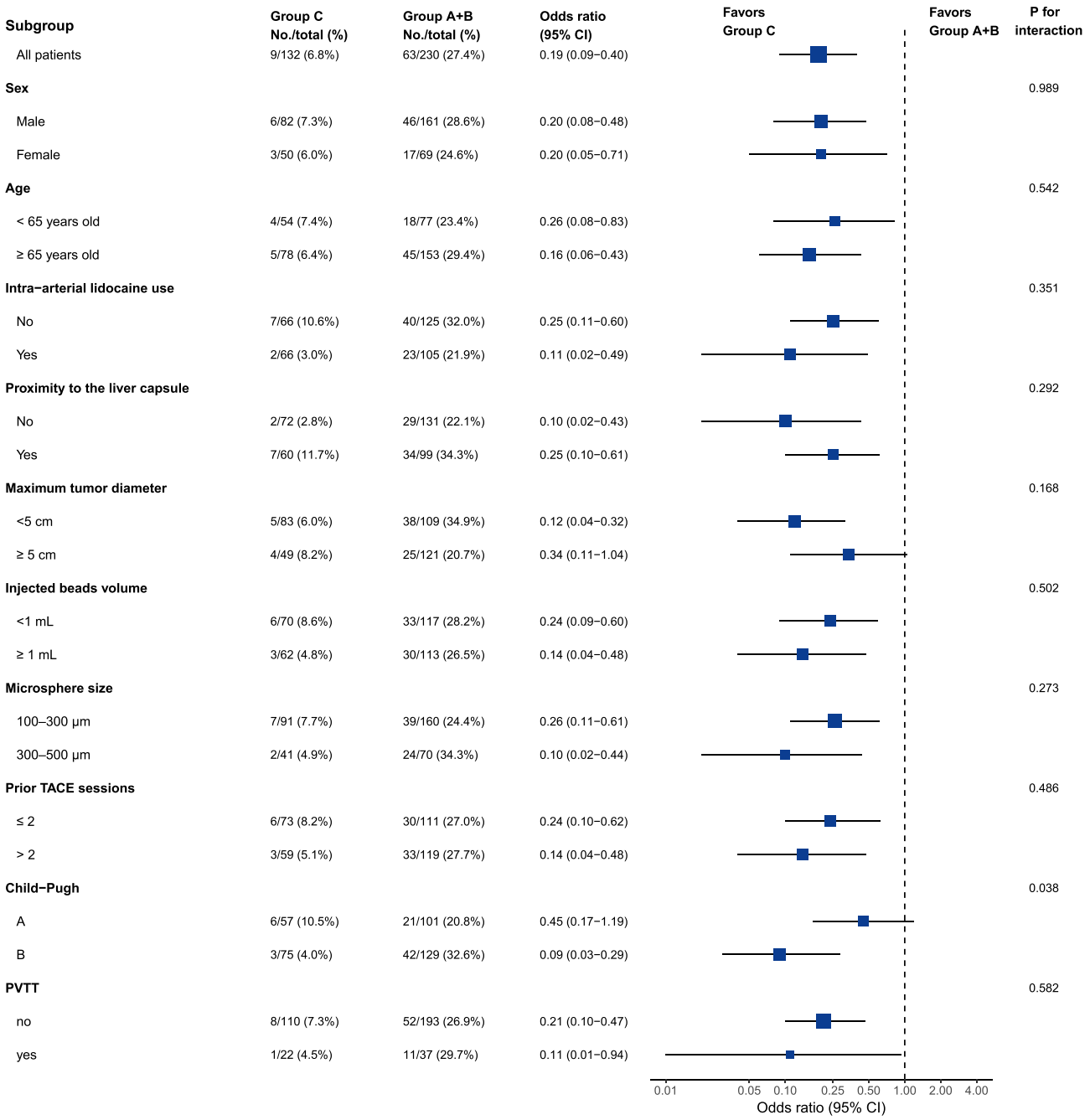

Figure 5 Forest plot of subgroup analyses comparing Group C versus Group A+B; points indicate odds ratios, and horizontal lines indicate 95% confidence intervals, with *P* values for interactions derived from group × subgroup terms in logistic regression models.

and medication-related risks. Moreover, glucocorticoids still warrant caution regarding hyperglycemia and infection.[9,29] In our cohort, intra-arterial lidocaine use was likewise associated with lower odds of severe pain after multivariable adjustment. Taken together, these findings support the importance of pain prevention in this setting, while also highlighting the potential value of complementary nonpharmacologic intraprocedural optimization.

A recent evidence summary on the prevention and treatment of post-TACE embolism syndrome further emphasized that optimal management should integrate preoperative preparation, intraoperative intervention, and postoperative symptom control, highlighting the importance of a more structured and individualized approach to symptom prevention.[31] In this context, this study also has several strengths. First, our study focused on a clinically relevant and potentially modifiable

intraprocedural technical factor, rather than on adjunctive pharmacologic pain control alone. Second, the study included a relatively large cohort with clearly defined dilution groups and demonstrated a consistent stepwise association across multiple pain outcomes, multivariable analyses, and prespecified subgroup analyses. These findings extend current knowledge by suggesting that microsphere suspension dilution is not merely a procedural preference, but a potentially modifiable technical determinant of early post-DEB-TACE pain. Several interrelated mechanisms may explain the analgesic effect of high-fold dilution: (1) a more dispersed and uniform microsphere distribution in the bloodstream, reducing focal aggregation that can cause abrupt increases in perfusion pressure and acute ischemic necrosis; (2) increased diluent volume improving microsphere flowability within feeding arteries, facilitating entry into smaller branches and thereby achieving a gentler, more progressive distal embolization—which may also contribute to improved early radiographic response,[32] although this observation should be interpreted cautiously and remains exploratory; and (3) a lower peak local drug concentration, which may lessen chemical irritation and vasospasm-related amplification of pain. Thus, high-volume dilution can be viewed as a technical counterpart to superselection, promoting a more tolerable ischemic insult by modulating the physical dynamics of the embolization process.

Several limitations should be acknowledged. First, this retrospective, nonrandomized study is susceptible to residual confounding; notably, dilution practices evolved over time, introducing potential temporal and practice-related bias. No formal a priori sample size calculation was performed because of the retrospective design. However, the number of severe pain events was adequate for the primary multivariable analysis, and the observed effect size supported the robustness of the primary findings. In addition, baseline demographic and tumor-related characteristics were well balanced across the three groups, and multivariable analysis was performed to adjust for potential confounders such as superselectivity and lidocaine use. Second, although the periprocedural analgesic regimens were relatively stable during the study period, analgesic exposure was not fully standardized at the individual-patient level. Outcomes relied primarily on routine nursing VAS documentation within 72 hours; longer-term and patient-reported measures of PES and quality of life were not available. Third, although early laboratory safety signals were comparable across groups, the present data are insufficient to determine whether differences in radiological response translate into durable tumor control or survival benefit. Prospective studies with standardized periprocedural management and longer follow-up periods are warranted to confirm these findings and to evaluate repeated TACE tolerance and long-term outcomes. In conclusion, patients with HCC who underwent DEB-TACE, increasing microsphere suspension dilution was associated with a marked, stepwise reduction in early postprocedural pain without evidence of short-term hepatic or renal toxicity on routine laboratory tests. Our findings add to current knowledge by identifying microsphere suspension dilution as a clinically relevant and potentially modifiable intraprocedural factor associated with lower early pain burden after DEB-TACE. This simple intraprocedural technical modification may improve patient comfort during the early postprocedural period.

Abbreviations

AE, adverse event; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; BUN, blood urea nitrogen; CBCT, cone-beam computed tomography; CI, confidence interval; CR, complete response; CRP, C-reactive protein; DCR, disease control rate; DEB-TACE, drug-eluting bead transarterial chemoembolization; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; IQR, interquartile range; IRB, institutional review board; mRECIST, modified Response Evaluation Criteria in Solid Tumors; OR, odds ratio; ORR, objective response rate; PD, progressive disease; PES, postembolization syndrome; PR, partial response; PVTT, portal vein tumor thrombosis; SD, stable disease; TACE, transarterial chemoembolization; TBIL, total bilirubin; VAS, visual analog scale.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All the authors report no relevant conflicts of interest for this article.

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