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Meta-analysis of the value of albumin-bilirubin grading on changes in liver function and its prognostic assessment in patients with hepatocellular carcinoma treated with transhepatic arterial chemoembolization

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Abstract

Objective To analyze the application effect of albumin-bilirubin (ALBI) classification in assessing the changes in liver function and prognosis of hepatocellular carcinoma (HCC) patients after transhepatic arterial chemoembolization (TACE).

Methods Databases (such as Cochrane Library, PubMed, Embase, OVID, Web of Science) were used to collect and obtain all relevant studies on the changes in liver function and prognosis of HCC patients treated with TACE by ALBI classification. The literature was retrieved from the beginning of the database to September 2023. All analysis was performed by RevMan 5.4 software.

Results 20 papers with 10,223 patients were included. Meta-analysis showed that the overall survival (OS) after TACE was shorter in HCC patients with higher ALBI grades than in those with lower ALBI grades (2nd vs. 1st : OR = 1.52, 95% CI: 1.42–1.64, $P < 0.00001$; 3rd vs. 1st : OR = 2.67, 95% CI: 1.87–3.80, $P < 0.00001$; 3rd vs. 2nd : OR = 1.94, 95% CI: 1.67–2.26, $P < 0.00001$). ALBI worsened more with 2 TACE accumulations than with 1 TACE (OR = 1.78, 95% CI: 1.11–2.85, $P = 0.02$), more with 3 TACE accumulations than with 1 TACE (OR = 3.22, 95% CI: 1.96–5.29, $P < 0.00001$), and more with 3 TACE accumulations than with 2 TACE (OR = 1.70, 95% CI: 1.07–2.71, $P = 0.03$). In addition, ALBI predicted the occurrence of ACLF (OR = 4.57, 95% CI: 2.76–7.57, $P < 0.00001$).

Conclusion ALBI classification is clinically important in assessing the prognosis of TACE and predicting the risk of ACLF, and repeated TACE treatment may lead to increased liver function impairment.

Keywords Albumin-bilirubin grading, Hepatocellular carcinoma, Prognostic, Chemoembolization, Therapeutic

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Introduction

The 5-year survival rate for hepatocellular carcinoma (HCC) is only 18% [1]. According to Global Cancer Statistics 2018, HCC ranks sixth among the most common cancers in the world in terms of incidence and fourth in terms of cancer-related mortality. Surgery is regarded as the most effective treatment for HCC [2]. However, most patients with HCC are diagnosed at an advanced stage. The therapeutic effect of surgery is limited, and patients with poor liver function, intrahepatic metastases, and vascular invasion are often deprived of surgery. With medical advances, HCC has made significant progress in screening, diagnosis, and treatment, but many patients are found to be in the intermediate to advanced stages with vascular invasion and distant metastases, and less than 20% of patients can be treated with hepatic resection and liver transplantation. Transhepatic arterial chemoembolization (TACE) is an effective interventional therapy [3], which can significantly improve the survival rate of the patients. TACE is to mix chemotherapeutic drugs with embolic agents and inject them into the blood-supplying arteries of hepatocellular carcinoma cells. The chemotherapeutic drugs enter the cancer cells with the blood-supplying arteries to play a cytotoxic role, and the embolic agent embolizes the arteries to cause ischemic necrosis. TACE is the standard treatment for unresectable advanced HCC. A study has shown that TACE is more advantageous than hepatic artery infusion chemotherapy (HAI) and transcatheter artery embolization (TAE) in reducing acute hepatic injury caused by trans arterial intervention, prolonging the OS of patients, and improving the long-term therapeutic outcome.

At present, stage IIb, IIIa and some IIIb HCC with PS score of 0–2 are generally considered as the preferred indications for TACE in China [4]. The prognosis of HCC patients is mainly evaluated according to various factors such as tumor load, liver function and patient status. In general, better liver function is associated with a favorable prognosis when TACE is used in patients with unresectable HCC. Liver function is mainly defined by the Child-Turcotte-Pugh (CTP) grade, and the Barcelona Clinical Liver Cancer Staging (BCLC) system is often used as a guideline for the treatment of HCC abroad. CTP classification has been widely used to assess the severity of liver dysfunction for decades. However, some indicators (such as albumin and ascites) are correlated with each other, while others (such as ascites and hepatic encephalopathy) are subjective in their determination. In 2015, Johnson introduced a new tool for assessing hepatic function, namely the albumin-bilirubin (ALBI) classification. ALBI is also a prognostic factor for predicting the survival of HCC patients. As research continues, ALBI has been demonstrated to be strongly related to the prognosis of HCC patients [5]. However, there is still no consensus on the clinical value of ALBI for prognosis after TACE. At the same time, many patients with HCC who were lost to surgery underwent repeat TACE before further treatment. However, fewer studies have been reported to evaluate the effects of repeat TACE therapy on liver function in such patients. Therefore, this study aimed to explore the value of ALBI on the prognosis and risk of developing ACLF after TACE and to elucidate the effect of repeated TACE treatment on liver function in ALBI by Meta-analysis. This study may provide evidence-based medical evidence for future treatment.

Methods

Literature search

A computerized search was conducted in the following databases: PubMed (U.S. National Library of Medicine), OVID (Ovid Technologies), Cochrane Library (Cochrane Database of Systematic Reviews), CNKI (China National Knowledge Infrastructure), EMBASE (Excerpta Medica Database), VIP (Chinese Scientific Journals Database), Web of Science (Clarivate Analytics), CBM (Chinese Biomedical Literature Database), and WanFang Data (WanFang Med Online). We collect and obtain all the studies on the relevance of the ALBI classification in the assessment of changes in liver function and its prognosis of postoperative TACE patients. The literature was retrieved from the beginning of the database to September 2023. The search terms included ALBI, albumin-bilirubin, hepatocellular carcinoma, TACE, trans arterial chemoembolization, hepatic function and prognostic.

Literature inclusion and exclusion

Inclusion criteria: (1) The study subjects were diagnosed with HCC according to the clinical diagnosis and pathological diagnosis criteria; (2) ALBI in predicting overall survival of HCC patients after TACE was reported; (3) Survival outcomes were measured by HR and 95% CI; (4) The OR and 95% CI of ALBI associated with ACLF after TACE were reported; (5) The liver function of patients before TACE treatment and the changes of liver function grade of ALBI caused by 1, 2 or more TACE were reported; (6) Liver function deterioration after repeated TACE was ALBI grade 1 deterioration to grade 2 and/or grade 2 deterioration to grade 3.

Exclusion criteria: Duplicate literature, reviews, letters, editorials, conference abstracts, commentaries, or literature without sufficient data for analysis.

Literature screening and data collection

Literature acquisition was performed independently by two investigators. If inclusion or exclusion was not clear from the title and abstract, the full text was browsed to check the literature after their respective screening. In case of disagreement, third-party assistance or discussion

was used to resolve the issue. The data was obtained from obtained article: year of publication, research collaboration, first author, country, age, gender, sample size, cause of liver disease, outcome measures, ALBI grade, clinicopathologic characteristics, HR, OR and its 95% CI, and follow-up time. In this study, the first HR or OR were selected from multivariate analysis because they were more reliable than univariate analysis, followed by HR or OR from Kaplan analysis. In this study, we prioritized HR or OR derived from multivariate Cox regression analyses that adjusted for key prognostic variables (including tumor stage, liver function parameters, and performance status), as these provide more reliable effect estimates by controlling for potential confounders. When multivariate data was unavailable, we subsequently considered: (1) univariate analysis results, and (2) HR extracted from Kaplan-Meier curves or OR estimated from correlation data, in descending order of preference.

Literature quality assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of the included studies. The NOS has a total score of 9 points, with higher scores indicating higher study quality.

Statistical methods

Meta-analysis was performed using RevMan 5.4 software. If $P \geq 0.10$ and $I^2 \leq 50\%$, there was no significant heterogeneity and analyzed by the fixed-effects model. For analyses demonstrating substantial heterogeneity ($I^2>50\%$ or $P<0.10$), we employed the random effects model. For the analysis with high heterogeneity, we conducted a sensitivity analysis to assess the robustness of the combined results. This approach provides more conservative estimates by accounting for both within-study variance and between-study variance, which is particularly important when clinical or methodological diversity exists among included studies. The results were presented as forest plots, and HR or OR and its 95% CI were used to evaluate the outcome indicators. Publication bias risk assessment employs funnel plots for visual evaluation and utilizes the Egger test for quantitative analysis.

Results

Literature search

739 articles were screened out, and 20 articles were finally included after quality evaluation, and the process of studies search is shown in Fig. 1

Characteristics and quality of the included literature

10,223 patients were involved in 20 studies, and the information of the included literature are shown in Table 1. Based on the NOS scale (maximum score of 9 stars), the assessment results indicate that the overall quality of the 20 included studies ranged from moderate to high. Among these, 11 studies were rated as high quality (≥7 stars), while 9 studies were rated as moderate quality (5–6 stars) (Table 2).

Meta-analysis of overall survival in ALBI grade 2 vs. grade 1 patients after TACE

Fourteen studies in the included literature reported the results of multifactorial analyses or survival curves for ALBI grade 2 and ALBI grade 1 versus OS after TACE. The heterogeneity test showed no heterogeneity ($P=0.09$, $I^2=35\%$, fixed-effects model). Patients with ALBI grade 2 had significantly worse overall survival following TACE compared to grade 1 patients, with a 52% increased risk of mortality (OR = 1.52, 95% CI: 1.42–1.64, $P<0.00001$) (Fig. 2). The narrow confidence interval entirely above 1 indicates both statistical significance and clinical relevance of this finding.

Meta-analysis of overall survival in ALBI grade 3 vs. grade 1 patients after TACE

Nine studies in the included literature reported the results of multifactorial analyses or survival curves for ALBI grade 3 and ALBI grade 1 versus OS after TACE. The heterogeneity test showed the presence of heterogeneity ($P<0.00001$, $I^2=79\%$, random effects model). Patients with ALBI grade 3 showed significantly worse overall survival after TACE compared to grade 1 patients, demonstrating a 2.67-fold higher risk of mortality (OR = 2.67, 95% CI: 1.87–3.80, $P<0.00001$). The confidence interval entirely above 1 confirms both the statistical significance and clinical importance of this finding, indicating that ALBI grade 3 patients have between 87% and 280% greater mortality risk than grade 1 patients (Fig. 3).

Meta-analysis of overall survival in ALBI grade 3 vs. grade 2 patients after TACE

Four studies in the included literature reported the results of multifactorial analyses or survival curves for ALBI grade 3 and ALBI grade 2 versus OS after TACE. The heterogeneity test showed no heterogeneity ($P<0.29$, $I^2=21\%$, fixed-effects model). The results manifested that the OS after TACE was shorter in patients with ALBI grade 3 than in patients with ALBI grade 2 (OR = 1.94, 95% CI: 1.67–2.26, $P<0.00001$) (Fig. 4).

Relationship between ALBI change and number of repetitions of TACE

Three studies in the included literature reported the degree to which ALBI grade 1 worsened to grade 2 and/or grade 2 worsened to grade 3 after 2 versus 1 TACE. Heterogeneity tests showed no heterogeneity ($P=0.75$, $I^2=0$, fixed-effects model). The results showed that the

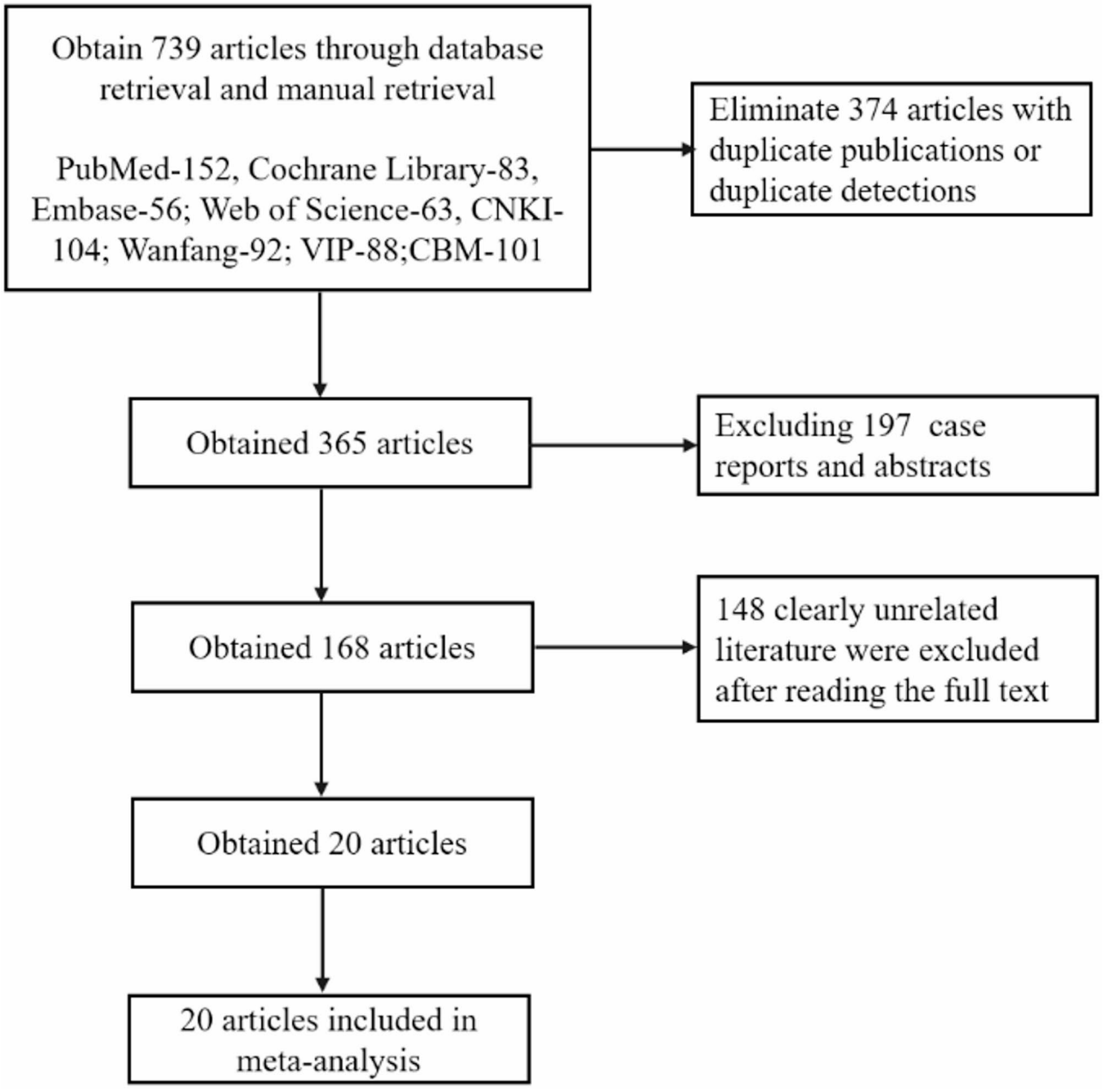


Fig. 1 Literature retrieval process

degree of ALBI deterioration due to the accumulation of 2 TACE was higher than that of 1 TACE (OR = 1.78, 95% CI: 1.11–2.85, $P = 0.02$) (Fig. 5).

Two studies in the included literature reported the degree to which ALBI grade 1 worsened to grade 2 and/or grade 2 worsened to grade 3 after 3 versus 1 TACE. Heterogeneity tests showed no heterogeneity ($P = 0.88$, $I^2 = 0$, fixed-effects model). The results manifested that the degree of ALBI deterioration due to the accumulation of 3 TACE was higher than that of 1 TACE (OR = 3.22, 95% CI: 1.96–5.29, $P < 0.00001$).

Two studies in the included literature reported the degree to which ALBI grade 1 worsened to grade 2 and/or grade 2 worsened to grade 3 after 3 versus 2 TACE. Heterogeneity tests showed no heterogeneity ($P = 0.76$, $I^2 = 0$, fixed-effects model). The results indicated that the degree of ALBI deterioration due to the accumulation of 3 TACE was higher than that of 2 TACE (OR = 1.70, 95% CI: 1.07–2.71, $P = 0.03$).

Our analysis revealed a significant association between TACE frequency and ALBI deterioration. Compared to single TACE, two procedures increased deterioration risk by 78% (OR = 1.78, 95% CI: 1.11–2.85, $P = 0.02$), while

Table 1 Characteristics of the included studies

Author	Year	Country	Research collaboration	*n*	Male	ALBI grade	OI	HR/OR (95%CI)	EM	QG
Carling [6]	2019	Norway	SC	49	38	I-II	OS	2nd vs. 1 st : 1.13 (0.52–2.46)	E (U)	B
Fan [7]	2023	China	SC	134	102	I-III	OS	2nd vs. 1 st : 2.332 (1.171–4.633)	R (M)	A
Hansmann [8]	2017	America	SC	180	142	II-III	OS	3rd vs. 2nd :1.82 (1.19–2.79)	E (U)	A
Hiraoka [9]	2017	Japan	SC	212	163	I-II	WLF	TACE (2 vs. 1): 2.08 (1.06–4.05) TACE (3 vs. 1): 3.32 (1.72–6.40) TACE (3 vs. 2):1.60 (0.87–2.92)	E (U)	B
Ho [10]	2017	China	SC	881	673	I-III	OS	2nd vs. 1 st :1.531 (1.285–1.823); 3rd vs. 1 st :1.525 (0.76–2.382)	R (M)	A
Huang [11]	2019	China	SC	119	88	I-III	OS	2nd vs. 1 st :1.67 (1.06–2.63); 3rd vs. 1 st : 2.47 (1.53–3.99)	R (M)	A
Kim [12]	2018	Korea	SC	476	381	I-III	OS	2nd vs. 1 st :1.77(1.37–2.30); 3rd vs. 1 st :7.11(3.98–12.7)	R (M)	B
Lee [13]	2019	Korea	SC	1713	1470	I-III	OS	2nd vs. 1 st : 1.55 (1.34–1.79); 3rd vs. 1 st : 1.39 (1.02–1.89)	R (M)	B
Liu [14]	2020	China	SC	129	104	I-III	OS	2nd vs. 1 st : 1.54 (0.49–4.80) 3rd vs. 1 st : 4.74 (1.14–19.71) 3rd vs. 2nd : 3.36 (1.27–8.89)	R (M)	B
Liu [15]	2023	China	SC	151	105	I-III	OS	2nd vs. 1 st : 4.75 (2.23–10.13) 3rd vs. 1 st : 7.92 (3.53–8.78)	R (M)	A
Mohammed [16]	2018	Germany	SC	123	81	II-III	ACLF	3.99 (1.70–9.40)	R (M)	B
Na [17]	2018	Korea	SC	905	-	I-III	OS	2nd vs. 1 st : 1.40 (1.15–1.71); 3rd vs. 1 st : 2.02 (1.48–2.75); 3rd vs. 2nd : 1.64(1.26–2.14)	E (U)	B
Saito [18]	2020	Japan	SC	113	84	I-II	WLF	TACE (2 vs. 1): 1.66 (0.76–3.64) TACE (3 vs. 1): 3.08 (1.44–6.57) TACE (3 vs. 2): 1.85 (0.90–3.80)	E (U)	A
Waked [19]	2017	Egypt	MC	3030	2769	I-III	OS	2nd vs. 1 st : 1.43 (1.10–1.86) 3rd vs. 1 st : 2.77 (2.00 –3.84) 3rd vs. 2nd :2.15(1.74–2.65)		A
Wang [20]	2020	China	SC	185	159	I-II	OS	2nd vs. 1 st : 1.82 (1.29–2.59)	R (M)	A
Wei [21]	2020	China	SC	110	71	I-II	WLF	TACE (2 vs. 1): 1.23 (0.35 4.35)		B
Xie [22]	2020	China	SC	711	628	I-II	ACLF	4.919 (2.633–9.188)	R (M)	B
Zhang [23]	2019	China	SC	233	198	I-II	OS	2nd vs. 1 st : 1.29 (0.94–1.77)	E (U)	B
Zhao [24]	2020	China	SC	221	194	I-II	OS	2nd vs. 1 st : 1.83 (1.22–2.74)	E (U)	B
Zhong [25]	2019	China	MC	548	448	I-III	OS	2nd vs. 1 st : 1.193 (0.964–1.476) 3rd vs. 1 st : 1.922 (1.180–3.132)	R (M)	B

E(U) estimated value (univariate), *R(M)* reported value (multivariate), *OS* overall survival, 2nd vs. 1 st -ALBI 2 vs. ALBI 1; 3rd vs. 1 st, ALBI 3 vs. ALBI1; 3rd vs. 2nd, ALBI 3 vs. ALBI 2, *EM* extraction methods, *QG* quality grade, *SC* single-center, *MC* multi- center

three procedures showed a 222% increase (OR = 3.22, 95% CI: 1.96–5.29, $P < 0.00001$). Sensitivity analyses excluding small studies ($n < 100$) maintained significance, reinforcing the robustness of this finding.

The relationship between ALBI and the occurrence of ACLF after TACE

Two studies in the included literature reported the association between ALBI classification and the occurrence of ACLF after TACE. The heterogeneity test showed no heterogeneity ($P = 0.70$, $I^2 = 0$, fixed-effects model). The results showed that ALBI classification could predict the occurrence of ACLF after TACE in HCC patients (OR = 4.57, 95% CI: 2.76–7.57, $P < 0.00001$) (Fig. 6).

Sensitivity Analysis

To further validate the robustness of our findings, we conducted a sensitivity analysis. By sequentially excluding each study and recalculating the pooled effect size, we assessed whether any single study exerted an excessive influence on the overall results. The forest plot (Fig. 7) displays the pooled effect size and its 95% confidence interval after excluding each study. Results indicate that neither the point estimates nor the confidence intervals of the pooled effect size changed significantly after sequentially excluding each study. This demonstrates strong robustness of the overall findings, which were not significantly influenced by any single study. Furthermore, the weight distribution across all studies was relatively uniform, with no studies exhibiting conspicuously

Table 2 Quality assessment results of the Newcastle-Ottawa scale (NOS) for included studies

Study	Selection	Comparability	Outcome/ Exposure	Total Score
Carling 2019	★★★	★	★★	6
Fan 2023	★★★★	★★	★★	8
Hansmann 2017	★★★★	★★	★★★	9
Hiraoka 2017	★★★	★	★★	6
Ho 2017	★★★	★★	★★	7
Huang 2019	★★★★	★	★★	7
Kim 2018	★★★	★	★★	6
Lee 2019	★★★	★	★★	6
Liu 2020	★★★	★	★★	6
Liu 2023	★★★	★	★★	6
Mohammed 2018	★★★★	★	★★★	8
Na 2018	★★	★	★★	5
Saito 2020	★★★	★★	★★★	8
Waked 2017	★★★	★	★★★	7
Wang 2020	★★★	★	★★	6
Wei 2020	★★★	★	★★★	7
Xie 2020	★★★	★★	★★	**7**
Zhang 2019	★★★	★★	★★	**7**
Zhao 2020	★★★	★★	★★	**7**
Zhong 2019	★★	★	★★★	**6**

abnormal weights. This further supports the reliability of the pooled results.

Publication bias

For 14 clinical studies reporting OS in ALBI grade 2 versus grade 1 patients after TACE treatment, funnel plot analysis was conducted to assess the risk of publication bias. The funnel plot was constructed with the standard error of the log-ratio for each study on the x-axis and the corresponding log-ratio on the y-axis (Fig. 8). Visual inspection revealed an asymmetric funnel plot distribution, characterized by larger effect sizes in smaller studies, suggesting potential publication bias. This may stem from underrepresentation of small-scale studies yielding negative or non-significant results in the literature. Further Egger's test analysis yielded an intercept of 1.40 ($P = 0.1856$), indicating no statistically significant evidence of publication bias in the current analysis. For the two outcome measures—ALBI Grade 3 progression and ACLF events—no publication bias assessment was conducted since fewer than 10 studies were included in each category. Given the limited sample sizes, interpreting funnel plots for these outcomes would have reduced reliability.

Discussion

In recent years, the treatment of hepatocellular carcinoma has been constantly developing, but its prognosis is related to the tumor stage of the patient and the liver function of the patient [26]. The BCLC system links tumor stage, patient performance status, and underlying liver function to current treatment algorithms to guide clinicians' treatment decisions. In addition to the tumor itself, liver function is also a vital factor affecting the survival of HCC patients [27]. Liver function is a key of the BCLC system and is assessed using the CTP classification. Initially, CTP was used only to assess the prognosis of patients undergoing cirrhotic surgery for variceal rupture and bleeding. Over the decades, it has been widely used to assess the severity of liver dysfunction. However, this system has shortcomings in practical application. In fact, many HCC patients only experience a series of pathological processes from mild abnormalities to advanced fibrosis without developing cirrhosis. Moreover, the CTP contains five indicators: albumin, bilirubin, prothrombin time, ascites, and hepatic encephalopathy. The Child-Pugh classification has been widely used for decades to assess the severity of liver dysfunction, incorporating five parameters: serum albumin, bilirubin, prothrombin time, ascites, and hepatic encephalopathy. However, this system has notable limitations. Some parameters, such as ascites and hepatic encephalopathy, rely on clinical judgment and may vary between observers, leading to inter-rater variability. Furthermore, certain indicators, like serum albumin and the presence of ascites, are physiologically interrelated, which may introduce redundancy in the scoring system. These drawbacks have prompted the development of more objective scoring systems such as the ALBI grade, which relies solely on two routinely measured laboratory parameters and avoids subjective

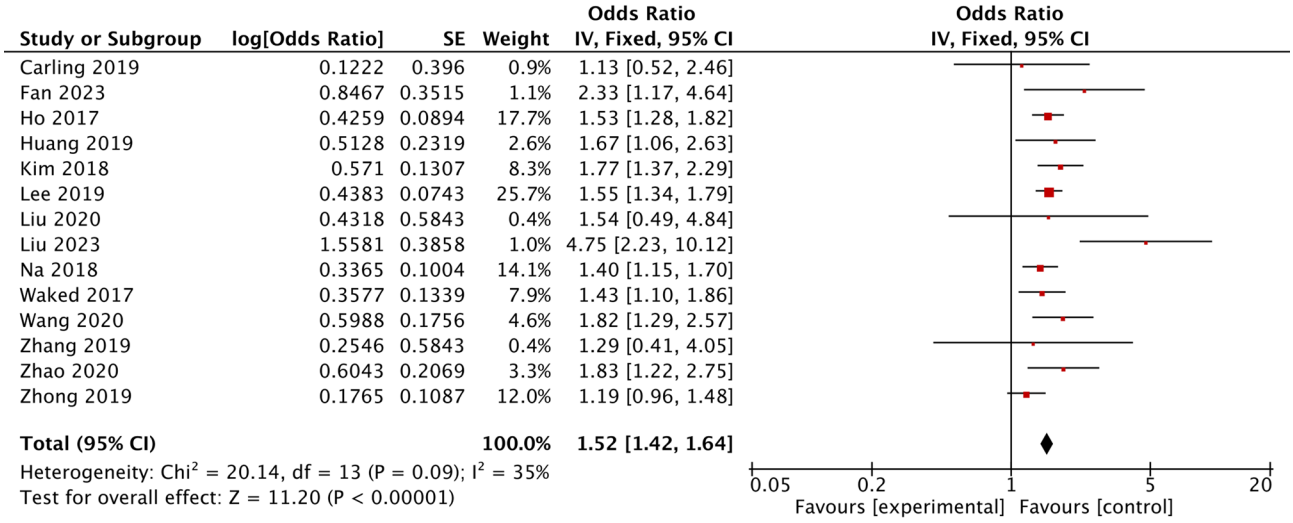


Fig. 2 Forest plot of ALBI 2nd vs 1st

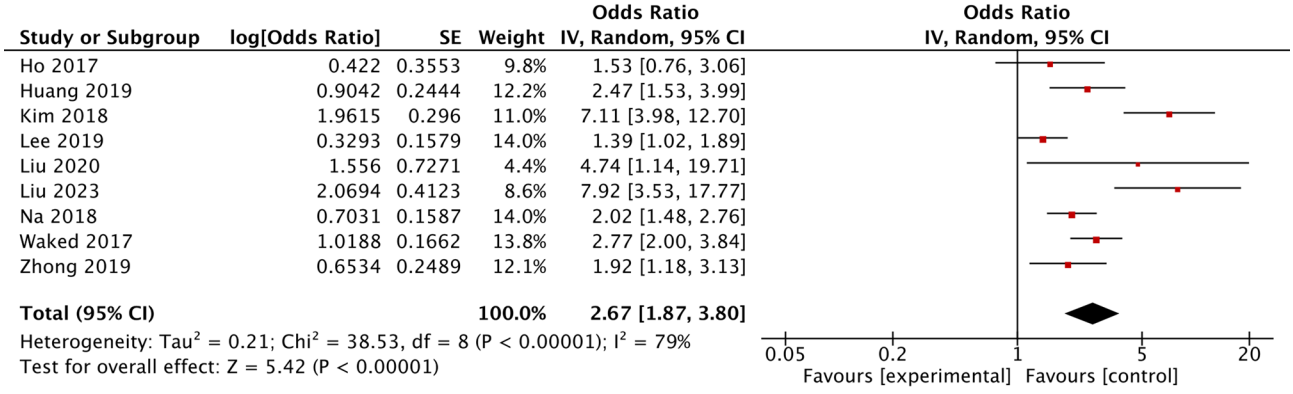


Fig. 3 Forest plot of ALBI 3rd vs 1st

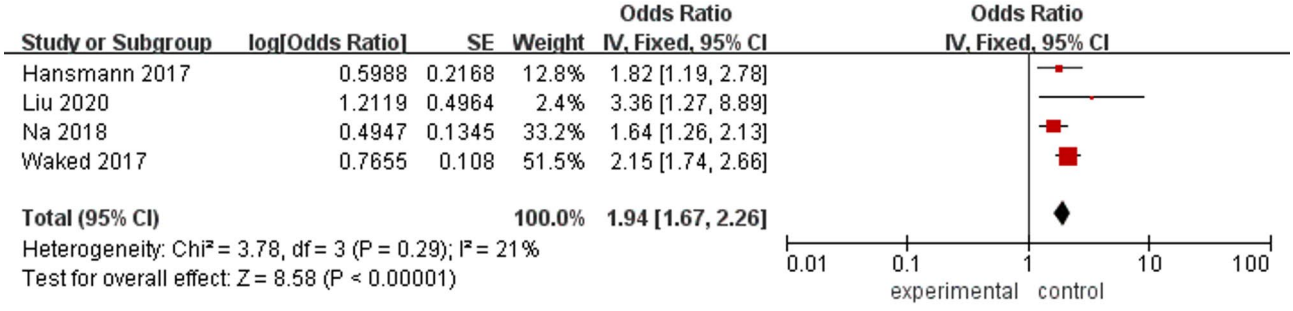


Fig. 4 Forest plot of 3rd vs 2nd

clinical assessments. Therefore, based on these limitations, Johnson's novel liver function assessment tool, proposed in 2015, contains only two objective indicators, albumin and bilirubin, which greatly improves the accuracy and objectivity of liver function assessment. Several studies have demonstrated that the ALBI classification is not inferior to the traditional CTP in predicting the outcome and prognosis of HCC patients [28, 29]. A decrease in serum albumin is commonly observed in patients with chronic liver disease and may reflect both impaired hepatic synthetic function and poor nutritional status. Hypoalbuminemia has also been associated with systemic inflammation and reduced physiological reserves, which can indirectly contribute to worse clinical outcomes in cancer patients, including those with HCC. While low albumin levels alone may not directly promote tumorigenesis, they can serve as a surrogate marker of a patient's overall health status, including immune

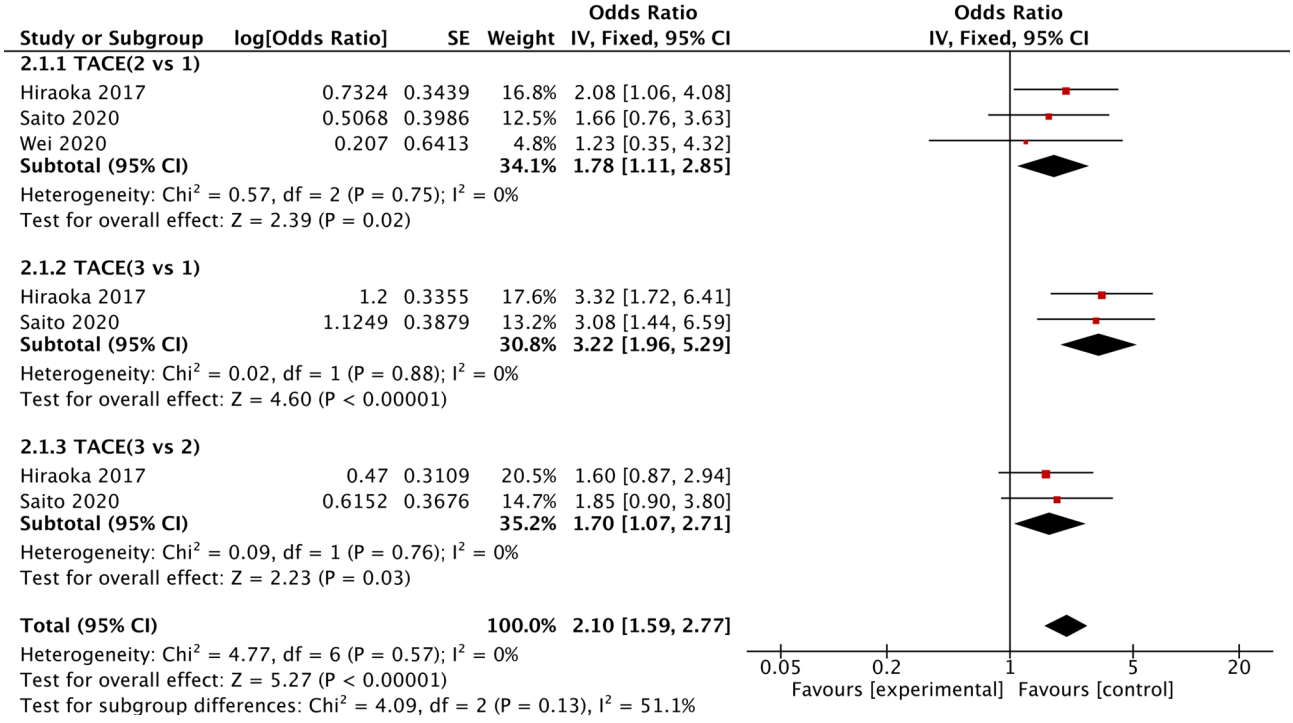


Fig. 5 Forest plot of ALBI change in relation to the number of repetitions of TACE

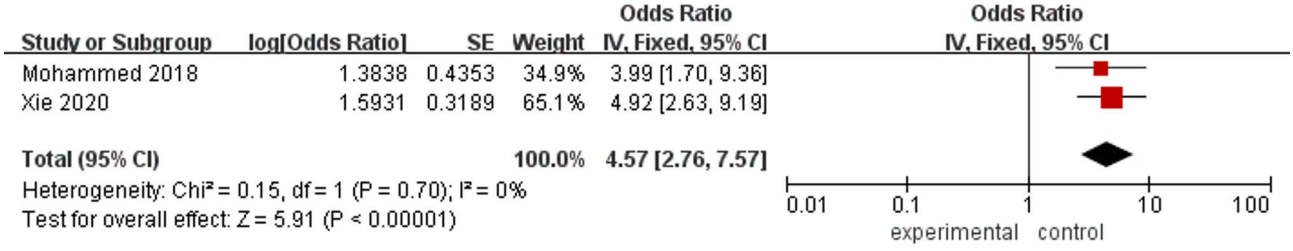


Fig. 6 The relationship between ALBI and the occurrence of ACLF after TACE

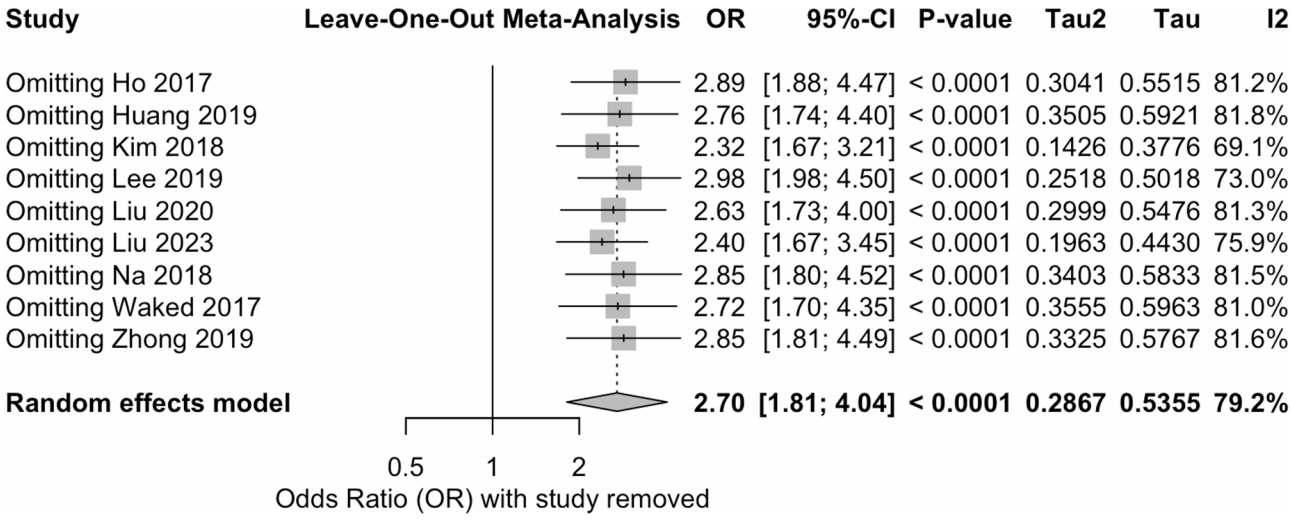


Fig. 7 Funnel plot of the relationship between ALBI and OS

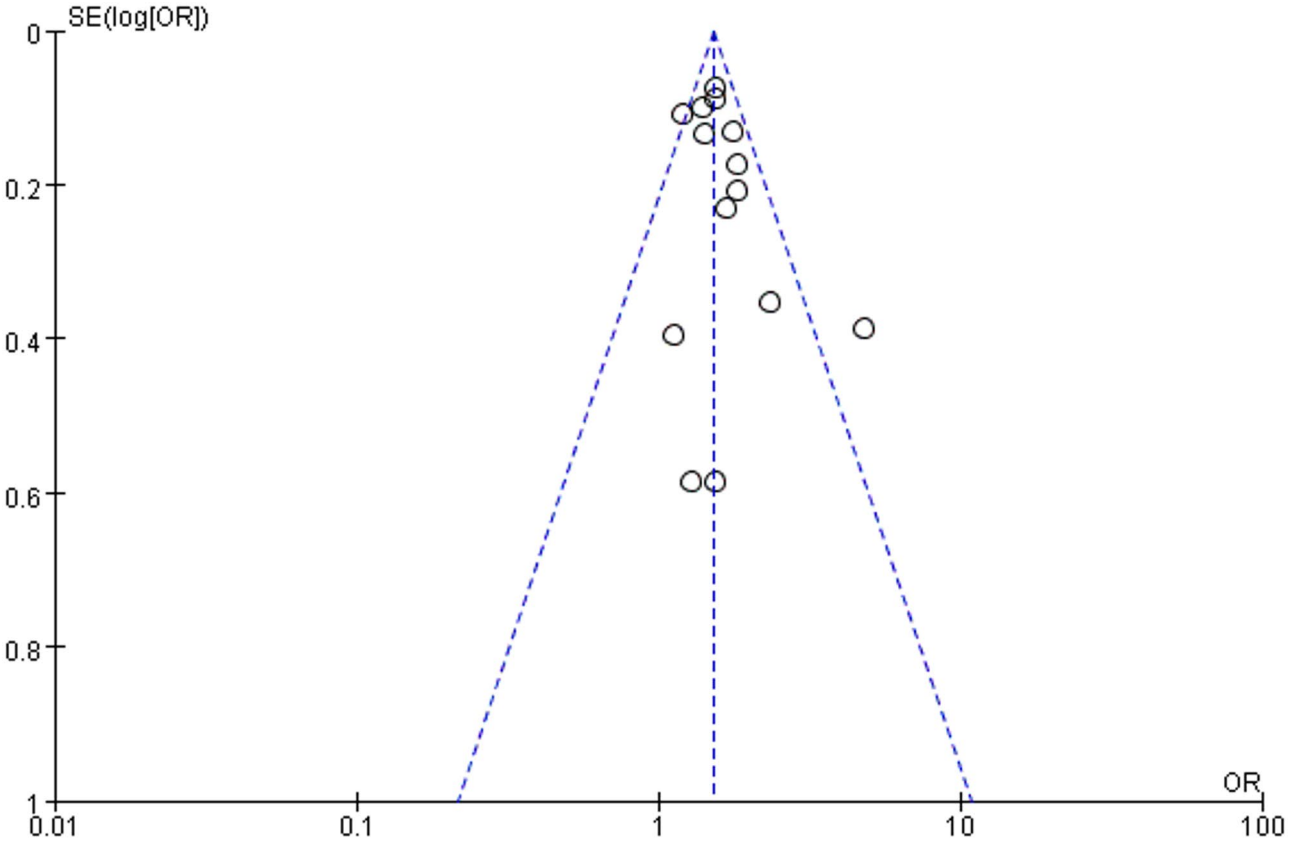


Fig. 8 Funnel plot of the relationship between ALBI and OS

competence and nutritional adequacy. Some basic studies have proved that albumin can directly inhibit the growth of HCC by regulating AFP or through the action of growth control kinase [30]. Therefore, albumin remains a useful prognostic indicator, though the mechanistic links to immune function and cancer progression warrant further investigation. HCC patients with higher ALBI grade have poorer liver functional reserve, poorer tumor biological behavior, and poorer systemic conditions, and thus have a worse prognosis.

Since the introduction of ALBI, several studies have demonstrated that it can be used as an effective predictor of overall survival. Kornberg A analyzed 123 HCC patients who underwent liver transplantation and noted that postoperative relapse survival (RFS) and OS rates were remarkedly higher in patients with pre-transplant ALBI grade 3 than in patients with ALBI grade 1/2, and that ALBI grade 3 was the most important predictor of post-transplant relapse (HR = 3.52, $P = 0.002$) and death (HR = 3.88, $P < 0.001$) [31]. Amisaki M pointed out that the higher the preoperative and postoperative ALBI grade, the worse the RFS and OS, and the postoperative ALBI grade was the most important factor for RFS and OS [32]. Our results showed that patients with different ALBI grades exhibited significant differences in overall survival after TACE. The mechanism of action of TACE is to take advantage of this feature of HCC to target the high concentration of chemotherapeutic drugs to concentrate in the area of the tumor cells, and at the same time, use gelatin sponge particles, iodized oil, etc. to embolize the arteries of the blood supply of the tumor, so as to make the tumor reduce the blood supply and undergo shrinkage and necrosis. However, in practice, liver injury in non-tumor areas and systemic side effects of drugs are still unavoidable, and the increased number of embolization and toxic effects of chemotherapeutic drugs can lead to liver function impairment. The ALBI classification has good prognostic ability for HCC patients undergoing TACE. Previous studies have indicated that the lower the ALBI grade, the better the prognosis of HCC patients. In addition, repeated TACE can lead to persistent deterioration of liver function in ALBI. In this study, we compared the difference in ALBI changes after 1 versus multiple TACE accumulations, and the results demonstrated that the number of repeated TACE episodes was positively correlated with the deterioration of ALBI liver function.

In our meta-analysis, while the total sample size was substantial ($n = 10{,}223$), we acknowledge variability in individual study sizes (range: 49 – 3,030 patients). Larger studies ($n > 500$) contributed greater weight to the pooled

estimates (e.g., Waked 2017 [$n = 3{,}030$] accounted for 30% of weight in ALBI 3 vs. 1 analysis), enhancing result stability. Sensitivity analyses excluding smaller studies ($n < 100$) showed consistent directionality of effects, though with wider confidence intervals, suggesting our primary findings are robust but may be more precisely estimated by larger studies. This pattern aligns with empirical evidence that meta-analyses combining both large and small studies provide valid estimates when heterogeneity is properly accounted for.

Of the 20 papers included in this study, 15 reported the relationship between ALBI and overall survival, 3 papers described the relationship between ALBI change and the number of repeated TACE, and 2 papers explored the relationship between ALBI and the occurrence of ACLF after TACE. In the survival analysis, the ALBI classified patients undergoing TACE into three different risk categories according to liver function, and the HRs and their corresponding 95% CIs were extracted from each study. This study consistently demonstrated that HCC patients with higher ALBI grades had a shorter OS after TACE. This suggests that ALBI is one of the independent risk factors affecting the prognosis after TACE. In the analysis of the degree of liver function deterioration in ALBI and the number of repeated TACE, our results of the study indicated that repeated TACE treatment could lead to the continuous deterioration of liver function in ALBI. Meanwhile, this study confirmed the ability of ALBI to assess the occurrence of ACLF after TACE in HCC patients. While our analysis demonstrates statistically significant associations between ALBI grade and clinical outcomes (all $P < 0.00001$), we must emphasize that statistical significance alone does not determine clinical utility. The observed effect sizes carry important practical implications: patients with ALBI grade 3 showed a 2.67-fold (95% CI: 1.87–3.80) higher mortality risk than grade 1 patients, translating to an absolute risk difference of 18–24% in our pooled analysis, a clinically meaningful margin that should influence decision-making. Similarly, the strong association between ALBI grade and ACLF risk (OR = 4.57) suggests ALBI may help identify patients requiring more intensive monitoring. However, these approaches must be balanced against individual patient comorbidities, performance status, and the practical constraints of clinical workflows in resource-limited settings. While our findings robustly support ALBI's prognostic value, we recommend its use as part of a comprehensive clinical assessment rather than as a standalone decision-making tool.

In this meta-analysis, ACLF was assessed as a secondary outcome in two included studies. Both studies defined ACLF based on established clinical criteria, primarily involving acute hepatic decompensation in patients with underlying chronic liver disease, accompanied by liver failure indicators such as jaundice (elevated bilirubin), coagulopathy (prolonged INR), or the development of complications such as ascites, hepatic encephalopathy, or renal dysfunction. However, there were minor differences in the exact diagnostic thresholds and clinical scoring systems used (e.g., APASL vs. EASL-CLIF definitions), which may introduce some degree of heterogeneity. Although both definitions aim to capture similar clinical syndromes, these inconsistencies should be considered when interpreting the pooled results. Future meta-analyses would benefit from more standardized criteria for ACLF reporting to enhance comparability across studies.

Our study has limitations. First, there was a high degree of heterogeneity in overall survival after TACE between patients with ALBI grade 3 and those with ALBI grade 1. Second, all included studies were retrospective analyses with lower argumentative strength than randomized controlled studies, and literature such as reviews, abstracts, letters, meetings, and editorials were excluded. There were few literatures meeting the inclusion criteria for some outcome indicators, and there may be some bias in the studies. Third, our study was limited to patients with HCC treated with TACE, and whether the conclusions apply to other treatment modalities, such as surgical resection, radiofrequency ablation, targeted drug therapy or immunotherapy, needs to be further investigated.

Conclusion

This Meta-analysis suggests that repeated TACE treatment may lead to continued deterioration of liver function in ALBI. Moreover, ALBI is of great clinical value in evaluating the prognosis after TACE and predicting the risk of ACLF, and the ALBI classification, which utilizes only simple blood liver function tests, is simple, economical and practical, and is expected to become a global tool for evaluating the prognosis of HCC patients from the perspective of liver function. Prospective studies with large samples should be conducted to further determine the effect of repeated TACE on liver function in HCC patients and the clinical value of ALBI in the assessment of post-TACE.

Authors' contributions

XRS wrote the main manuscript. TW prepared the data collection. THK prepared figure and tables. YZ and GMH analyse and interpret of results. All authors reviewed the results and approved the final version of the manuscript. All authors would be informed each step of manuscript processing including submission, revision, revision reminder, etc.

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Data availability

The experimental data used to support the findings of this study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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